Comparison of neuromuscular block measured by compressomyography at the upper arm and electromyography at the adductor pollicis muscle in obese and non-obese patients: an observational study

Honing, G.H.M.; Torensma, B.; Martini, C.H.; Hoek, K.B.; Velzen, M. van; Olofsen, E.; ... ; Boon, M.

Journal of Clinical Anesthesia 78 (2022) 110673

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Original Contribution

Comparison of neuromuscular block measured by compressomyography at the upper arm and electromyography at the adductor pollicis muscle in obese and non-obese patients: An observational study

G.H.M. Honing, M.D. [a,*], B. Torensma, M.Sc. [a,b], C.H. Martini, M.D. Ph.D. [a], K.B. Hoek, M.D. [a], M. van Velzen, Ph.D. [a], E. Olofsen, Ph.D. [a], M. Niesters, M.D. Ph.D. [a], A. Dahan, M.D. Ph.D. [a], M. Boon, M.D. Ph.D. [a]

[a] Department of Anesthesiology LUMC, Albinusdreef 2, 2333, ZA, Leiden, the Netherlands
[b] Dutch Obesity Clinic West, Bordewijklaan 5, 2591, XR, The Hague, the Netherlands

ARTICLE INFO

Keywords:
Neuromuscular nondepolarizing agents
Electromyography
Neuromuscular monitoring

ABSTRACT

Study objective: Quantitative neuromuscular monitoring is traditionally evaluated at the adductor pollicis muscle. By contrast, the TOF-Cuff compressomyograph evaluates neuromuscular block (NMB) at the upper arm. However, compressomyography has not been fully validated against other monitoring entities. This study evaluates the agreement between NMB measured by compressomyography at the upper arm and electromyography at the adductor pollicis muscle during various levels of neuromuscular block in patients with and without obesity.
Interventions: NMB was measured at the upper arm by compressomyography (TOF-Cuff) and by electromyography (GE-NMT) at the adductor pollicis.
Design: Prospective, multicenter, observational study.
Setting: Secondary and tertiary care hospitals' operating theatres.
Patients: 200 non-obese and 50 obese patients.
Measurements: During onset and offset of deep (post-tetanic-count 1–15 twitches), moderate (Train-of-Four-count 1–3 twitches) and shallow (Train-of-Four-ratio 0.01–1.0) depths of NMB were measured in obese and non-obese patients. The bias and limits of agreement of both devices were calculated using a Bland-Altman analysis for repeated measurements. Data obtained during spontaneous recovery (i.e. without the use of reversal agents) were used in the primary analyses.
Main results: Data from enrolled patients yielded 942 paired post-tetanic-counts, 1175 paired train-of-four-counts and 1574 paired train-of-four ratios during spontaneous recovery. In non-obese patients, mean bias (95% CI) between the two devices was 3.405 (2.294 to 4.517) during deep NMB; −0.023 (−0.205 to 0.160) during moderate NMB and 0.312 (0.287 to 0.338) during shallow NMB. In obese patients, bias was −0.170 (−2.872 to 2.531); 0.178 (−0.202 to 0.558); 0.384 (0.299 to 0.469) for deep, moderate and shallow NMB respectively.
Conclusions: There is variable disagreement between the level of NMB measured at the upper arm by compressomyography and at the adductor pollicis muscle measured by electromyography, throughout the various stages of NMB in obese and non-obese patients. Recovery of NMB on compressomyography preceded recovery on electromyography, which may have consequences for reversal and extubation decisions in clinical practice.

1. Introduction

Neuromuscular blocking agents (NMBAs) are frequently used to facilitate intubation and optimize surgical conditions during general anesthesia, [1,2] but are also associated with postoperative respiratory complications. [3,4] To adequately titrate the depth of neuromuscular block (NMB) during a procedure, and to prevent residual effects after removal of the endotracheal tube, it is advised to use a quantitative neuromuscular monitoring device. [5] Unfortunately, cumbersome application and calibration procedures of many neuromuscular

* Corresponding author.
E-mail address: g.h.m.honing@lumc.nl (G.H.M. Honing).

https://doi.org/10.1016/j.jclinane.2022.110673
Received 12 August 2021; Received in revised form 6 January 2022; Accepted 28 January 2022
Available online 5 February 2022

monitoring devices frequently precludes correct use of these devices in clinical practice. [6]

The TOF-Cuff compressomyograph (CMG) is a neuromuscular monitoring device that was designed to provide anesthesiologists with a user-friendly alternative to the traditional monitors. It consists of modified blood pressure cuff with two built-in electrodes. NMB is determined by evaluation of pressure changes generated by muscular activity in the inner part of the cuff following peripheral nerve stimulation at the upper arm. [7] As such, the monitoring site and technique of the TOF-Cuff CMG differs from other monitors. However, results obtained with CMG may not be interchangeable with results obtained with traditional neuromuscular monitoring devices. Data from studies that compared CMG to traditional neuromuscular monitoring devices are limited and did not entail deeper levels of NMB or behavior in patients with obesity. [7–10] This observational study was designed to fill these gaps and compared CMG at the upper arm to electromyography (EMG) at the adductor pollicis muscle during deep, moderate and shallow levels of NMB in patients with and without obesity.

2. Materials & methods

This prospective, multicenter, observational study, with acronym TOCUFF, was performed between November 2017 and July 2020 at the Leiden University Medical Centre (LUMC, Leiden, The Netherlands) and the Dutch Obesity Clinic (The Hague, The Netherlands). Study procedures followed Good Clinical Practice (GCP) and Equator Standards for Reporting Diagnostic accuracy studies guidelines, Appendix 1. [11,12] The study protocol was approved by the Institutional Ethics Review Committee Leiden-Den Haag-Delft on April 6, 2017 (committee identifier: P17.050) and registered prior to patient enrollment at ClinicalTrials.gov (NCT03117387; principal investigator: A.D.; date of first registration: April 17, 2017).

Eligible patients received oral and written information one week before surgery, written informed consent was obtained from patients willing to participate. Patients needed to be ≥18 years old, American Society of Anesthesiologists class I-III and to be scheduled for elective, non-cardiac surgery with general anesthesia requiring NMBAs. Exclusion criteria included known neuromuscular disease, indication for rapid sequence induction, upper extremity deep vein thrombosis, pregnancy or breastfeeding and rocuronium or sugammadex contraindications.

2.1. General anesthesia procedures

Since this was an observational study, dosing of anesthetics, NMBAs and reversal agents where at the attending anesthesiologists' discretion. In practice, all patients received rocuronium as NMBA. In all cases, routine monitoring (non-invasive blood pressure, heart rate, electrocardiography and pulse oximetry) was applied. Core temperature (measured at nasopharynx) was maintained at 36°-37° Celsius with forced warm air blankets. The protocol was amended to additionally measure peripheral skin temperature at the palmar surface of the hand. A dedicated unblinded researcher collected the study data (patient age, height, weight and dominant arm; location of EMG and CMG device; rocuronium and sugammadex dosing) in the operating room via an electronic clinical research form (eCRF; Castor EDC, CIWIT B.V., Amsterdam, The Netherlands). He or she did not advise about rocuronium or sugammadex dosing. At skin closure sugammadex was administered if the normalized EMG Train-of-Four (TOF)-ratio was <0.9; extubation was performed at TOF-ratio ≥ 0.9 as measured by EMG.

2.2. Neuromuscular monitoring

This study compares two currently available quantitative neuromuscular monitoring techniques; EMG and CMG. CMG was performed using the TOF-Cuff (RGB Medical Devices, Madrid, Spain). This device consists of a modified blood pressure cuff with two build-in electrodes that elicit muscle twitches at the upper arm by stimulating the nerves that run at the medial bicipital groove. The level of NMB is calculated by evaluating twitch-evoked pressure differences in the slightly inflated cuff. [7] In all patients an appropriately sized cuff was placed according to manufacturing recommendations. [7]

EMG was performed using the EMG-NMT module of the General Electric Healthcare neuromuscular monitor system, which was connected to a separate, standalone B450 monitor (General Electric Healthcare, Helsinki, Finland). The recording electrodes of the EMG were attached over the belly and insertion of the adductor pollicis muscle whilst the stimulating electrodes were positioned over the ulnar nerve.(Appendix 2) EMG measures depth of NMB by analyzing the compound action potentials of the (ulnar) innervated adductor pollicis muscle. [12] In all patients, five seven millimeter Ag/AgCl electrodes (ConMed, New York, USA) were positioned after degreasing the skin, according to manufacturing recommendations. The MechanoSensor hand adapter (General Electric Healthcare, Helsinki, Finland) was applied as stabilizer to prevent movement artefacts.

The EMG device was positioned ipsilateral of the CMG device in half of the patients and contralaterally in the other half (non-randomized). After induction of anesthesia, but before administration of rocuronium, the CMG and EMG devices were asynchronously calibrated in agreement with GCP, to ensure supramaximal stimulation. [12] Additionally, the calibration procedure followed the recommendations of the manufacturers of both devices. These recommendations however differed with regard to the setting of the pulse-width of the electrical stimulus in obese and non-obese patients. Briefly, EMG stimulus pulse width is recommended to be set at 200 μseconds in non-obese and at 300 μseconds in obese patients. In contrast, CMG stimulus pulse width is recommended to be set at 200 μseconds in both obese and non-obese patients. Should supramaximal stimulation not be achieved at this setting, the pulse-width may be increased to 300 μseconds.

Rocuronium was administered after stable recordings were verified, defined as a TOF-ratio difference < 5% averaged over three consecutive measurements.

At a TOF-count of zero twitches, a tetanic stimulus (five seconds of 50 Hz) was followed by a 3 s pause, which was succeeded by 15 one Hertz stimuli to obtain a post-tetanic count (PTC). Paired PTC measurements were performed and recorded at five-minute intervals; no TOF-count measurements were performed during this five-minute interval. Paired measurement sequence was alternated after each interval to prevent a systematic bias. If EMG and CMG were applied ipsilaterally, paired measurements were performed with 20 s intervals, to prevent device co-interference.

TOF stimulation consisted of four supramaximal stimuli of two Hertz, paired CMG and EMG measurements were recorded at five-minute intervals. At a TOF-count of four twitches, paired TOF-ratios were measured at 2.5-min intervals, all TOF-ratios were normalized to the baseline TOF-ratio of each device. The comparisons were made during deep NMB (defined as a post-tetanic-count of 1–15 twitches), moderate NMB (defined as a train-of-four-count of 1–3 twitches) and shallow NMB (defined as a train-of-four T4/T1 ratio of >0 to 1.0; which formally entails shallow and minimal NMB and full recovery of NMB [13]). Measurements ceased after both devices showed full recovery.

2.3. Sample size calculation

Two prior validation studies exist that compared the TOF-Cuff CMG to mechanomyography (MMG) at the adductor pollicis muscle. [7,10] These data were however obtained after pharmacologic antagonism (i.e. using neostigmine or sugammadex); no data on the agreement during spontaneous recovery of NMB were reported by these studies. As such, assumptions for a power calculation could not be made for this study. Since we anticipated that differences between the devices would be very small (as previously found by others [7,10]), we opted for a sufficiently

sized sample size of 100 non-obese patients to be included at the Leiden University Medical Center, and 100 obese patients, to be included at the Dutch Obesity Clinic. However, during the execution of the study at this center, it became apparent that nearly all patients were given sugammadex at the end of anesthesia. Since this was an observational study, the use of reversal agents was not protocolized. However, as we were primarily interested in data obtained during spontaneous recovery at the final stages of recovery of NMB (i.e. shallow and minimal NMB), we decided to restrict inclusion at the obesity clinic to half the original sample size, and include the other half at the LUMC, where spontaneous recovery was much more likely to be allowed. Finally, the protocol was amended to additionally investigate the effect of peripheral skin temperature on electromyographic measurements in a subset of 100 patients, which warranted the enrollment of an additional 50 patients. This amendment was approved by the local ethical committee. Data obtained during shallow and minimal NMB from the first 15 non-obese patients of this study were used for a prior publication. [8]

2.4. Statistical analyses

Paired measurements were compared using a Bland-Altman analysis modified for repeated measurements (*http://sec.lumc.nl/method_agreement_analysis, Leiden, the Netherlands*). [14] This Bland-Altman analysis corrects for between subject variability of repeated paired measurements in individual subjects. Bland-Altman analysis estimates bias and limits of agreement (LoA; 95% differences between compared devices) between CMG and EMG and evaluates instrumental imprecision by calculating the repeatability coefficient (RC), which is equal to the standard deviation of the within-subject variability of each device. For interpretation of the Bland-Altman bias during offset of NMB one can assume that a bias above zero indicates that CMG overestimates NMB recovery whilst a bias below zero indicates that CMG underestimates NMB recovery. Furthermore, to get an indication of the differences in bias in the various stages of recovery (i.e. deep, moderate and shallow NMB), the relative bias was calculated, with: Bias (R) = bias / maximal range. The maximal range corresponds to the maximal possible spread in PTC, TOF-count or TOF-ratio values between the two devices at these stages. For instance, for PTC, the maximal spread is 15, for TOF-count the maximal spread is 4 and for TOF-ratio the maximal spread is 1.0.

The time until full recovery of a single induction dose of rocuronium on both devices was also assessed. The recovery time was defined as the time-interval between administration of an induction dose rocuronium and full NMB recovery; full recovery was defined as a normalized TOF-ratio of $\geq$0.9 on the EMG *or* TOF-ratio $\geq$ 0.95 measured at three consecutive times with the TOF-Cuff CMG. The latter is based on the manufacturers' recommendation for safe extubation. Only data obtained in the absence of pharmacological NMB reversal were eligible for this analysis.

Post-hoc, data of moderate and deep NMB collected at the first five minutes after rocuronium administration were analyzed as onset of NMB and hereafter as offset of NMB. Data collected after NMB reversal were analyzed separately.

Beside the Bland-Altman analyses, parametric or non-parametric tests were used as appropriate for the other comparisons and were performed in R. (Version 4.0.3., 2020, R Foundation for Statistical Computing, Vienna, Austria). Normality was assessed with the Shapiro-Wilk test and Q-Q plot, continuous normally distributed variables are expressed by mean ± standard deviation (SD) whilst non-normally distributed variables are expressed by median ± interquartile range [IQR]. *P*-values <0.05 were considered significant.

Prior to inferential data analyses, the following data preprocessing was performed;

a) A TOF-count of >0 twitches was transformed to a PTC of 15 twitches, in case one of both devices measured a deep NMB (i.e. displayed a value of PTC 0–15 twitches)
b) A TOF-count of <4 twitches was transformed to a TOF-ratio of 0 in case one of both devices measured a shallow NMB (i.e. displayed a TOF-ratio > 0–1.0)

Incomplete measurement pairs and data collected after one of either devices reached full recovery were excluded from data analyses.

3. Results

In total, 300 patients were screened for eligibility of whom 200 were enrolled at the Leiden University Medical Center and 50 at the Dutch Obesity Clinic. Exclusion reasons were: not meeting inclusion criteria ($N = 2$), cancellation of the surgical procedure ($N = 27$) or declining to participate ($N = 21$). All enrolled patients were allocated and treated according to protocol and included in data analyses (Patient enrollment diagram; Fig. 1). Baseline characteristics differed significantly between participating centers as expected (Table 1). In the enrolled patients, device malfunction occurred in 35 patients with EMG and in 8 patients with CMG. The majority of malfunctions were caused by electrode disengagement. Data collection ceased after signal disruption.

3.1. Bias and limits of agreement during deep, moderate and shallow neuromuscular block

Data obtained during spontaneous recovery (offset) of NMB came from patients that had not received sugammadex, or from patients in which the NMB was reversed, whose data were only obtained prior to pharmacologic NMB antagonism. In total 3430 paired measurements in 198 non-obese patients, and 261 paired measurements in 46 obese patients were available. In 6 patients (4 obese and 2 non-obese) no data on spontaneous recovery was available due to device malfunctions or early pharmacological NMB reversal. In non-obese patients, bias (95% CI) between the two devices was 3.405 (2.294 to 4.517) during deep NMB; −0.023 (−0.205 to 0.160) during moderate NMB and 0.312 (0.287 to 0.338) during shallow NMB. In obese patients, bias was −0.170 (−2.872 to 2.531); 0.178 (−0.202 to 0.558); 0.384 (0.299 to 0.469) for deep, moderate and shallow NMB respectively. Limits of agreement of both obese and non-obese patients are reported in Fig. 2 and Tables 2 and 3.

To standardize the various biases, we calculated the relative biases at each level of NMB (i.e. deep, moderate and shallow), which are expressed as a percentage. The relative bias during offset of NMB in 198 non-obese patients was 23% during deep NMB; 1% during moderate NMB and 31% during shallow NMB. In 46 obese patients, relative biases were 1%, 6% and 38% for these levels respectively. Bias and relative bias were also calculated during the onset time frame for 43 obese and 153 non-obese patients (see Tables 2 and 3). Fig. 3 and Appendix 3 summarizes the relative biases during onset and offset of NMB and shows the direction of the bias throughout these stages.

3.2. Time to adequate recovery

On both devices, the time to reach adequate recovery was assessed in pooled data of 4 obese and 92 non-obese patients, that had received a single bolus dose rocuronium at induction and were allowed to recover from the NMB spontaneously. Adequate recovery was defined as a normalized TOF-ratio $\geq$ 0.9 on the EMG or a TOF-ratio $\geq$ 0.95 at three consecutive measurements by CMG. Rocuronium was dosed at 0.53 [0.45–0.62] mg/kg ideal body weight at induction. Median [IQR] recovery time to a normalized TOF-ratio $\geq$ 0.9 on the EMG was 65.0 [50.0–80.0] minutes versus 52.0 [44.5–65.0] minutes with CMG ($p <$ 0.01; overall median difference of 10.0 [range − 13.0 to 130.0] minutes.

Reversal of NMB with sugammadex was warranted in 133 patients (45 obese and 88 non-obese patients) because the normalized TOF-ratio

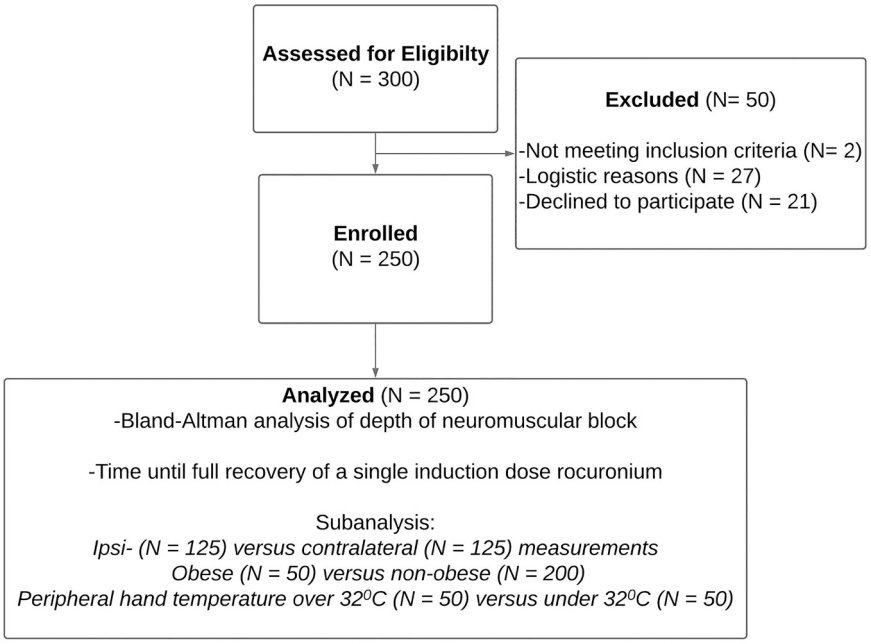

Fig. 1. Patient enrollment diagram.

Table 1
Subject baseline characteristics.

	Leiden University Medical Centre (N = 200)	Dutch Obesity Clinic (N = 50)
Sex (Male/Female)	89/111	15/35
Age (years, range)*	58 [19–83]	46 [23–65]
BMI (kg/m^2)*	25.6 [22.7–28.7]	40.2 [38.6–43.2]
ASA class physical status (n)* 1	60	0
2	114	1
3	26	49
Induction dosage rocuronium (mg/kg ideal body weight)*	0.62 [0.5–0.72]	0.49 [0.42–0.54]
Number of patients with the electromyograph at the ipsilateral / contralateral extremity of the compressomyograph (n)	128/72	0/50
Number of patients with compressomyograph at dominant / non-dominant extremity (n)	124/74†	1/49

Values are median [interquartile range] unless otherwise stated. *$P < 0.01$. BMI: Body Mass Index. † = missing data of 2 patients.

on the EMG was <0.9 at the end of the procedure (median TOF-ratio at reversal 0.59). Conversely, CMG signaled adequate recovery in 42 of these 133 patients at that time. After reversal, the median [IQR] time to reach a normalized TOF-ratio ≥ 0.9 on the EMG was 3.0 [2.0–3.0] minutes.

3.3. Effects of laterality of measurements and peripheral temperature

In both obese and non-obese patients, bias was not influenced by other variables. Bias was comparable when EMG monitoring was performed either ipsi- or contralateral to CMG (0.305 versus 0.336) and bias was not influenced by peripheral temperature (bias when peripheral temperature < 32^{0}C was 0.289 versus 0.319 in patients with peripheral temperature > 32^{0}C).

3.4. Instrumental precision

Instrumental precision of CMG and EMG, as reflected by the repeatability coefficient (RC), in both obese and non-obese patients, was not significantly different at deep, moderate and shallow NMB, albeit with considerable variability throughout the ranges (see Tables 2 and 3).

4. Discussion

This study evaluated the agreement between NMB measured at the upper arm by CMG and at the adductor pollicis muscle measured by EMG, during deep (PTC 1–15 twitches), moderate (TOF-count 1–3 twitches) and shallow (TOF-ratio 0.01 to 1.0) NMB. This was done in 50 obese and 199 non-obese patients. The results of this study show that, throughout onset and recovery, there was considerable bias (i.e. disagreement) between the two devices. In addition, the magnitude of the difference depended on the depth of NMB, onset or offset, and between obese and non-obese patients. By adjusting the bias for the level of NMB, we obtained a relative bias, which allows for easy comparison of the biases found at the various depths of NMB. Relative bias was lowest during offset moderate NMB, meaning that there was good agreement between both devices at this level of NMB. Bias was larger at early onset moderate NMB and at late offset shallow NMB, meaning that at these levels, agreement between the devices was lower.

The variation in the magnitude and the direction of the bias at the various depths of NMB, means that conclusions from these data are also heterogenous and depend on the clinical situation in which the devices are used. Should a deep NMB be desired for a certain type of surgery, inadequate depth of NMB will be noted earlier by CMG at the upper arm, than by EMG at the adductor pollicis, giving the anesthesiologist the opportunity to intervene before significant recovery has occurred. However, a consequence of the substantial disagreement at the final stages of recovery (i.e. offset shallow NMB), was that CMG signaled adequate recovery (defined by the manufacturer of the TOF-Cuff CMG as three consecutive TOF-ratios of ≥0.95) on average 10.0 min faster than EMG, measured in 96 patients that were allowed to spontaneously recover from a single induction dose of rocuronium. Half of these patients had a normalized TOF-ratio < 0.9 on the EMG at the end of anesthesia, potentially increasing the risk of postoperative respiratory

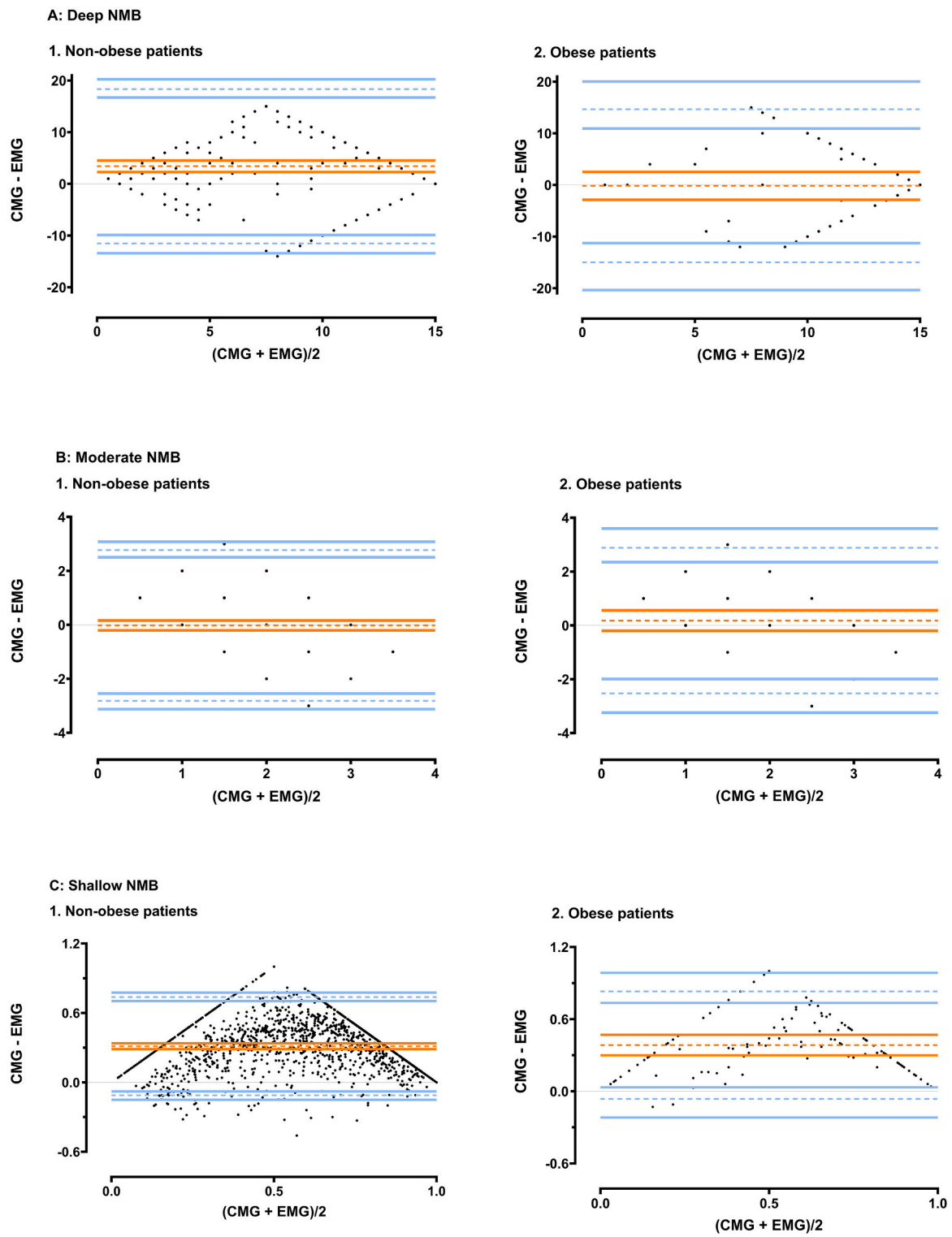

Fig. 2. Bland-Altman plots of the difference against the corresponding mean during offset of deep neuromuscular block (Post-Tetanic-Counts 1–15); moderate neuromuscular block (TOF-Counts 1–3) and shallow neuromuscular block (TOF-ratios 0.01–1.0) as measured by compressomyography (CMG) and electromyography (EMG) in obese and non-obese patients. Bias with 95% confidence intervals (95% CI) are plotted in orange, upper and lower limits of agreement (LoA) with corresponding 95% CIs are plotted in blue. Exact datapoints, represented with black dots, may comprise multiple unique measurements. A bias of zero indicates no difference between examined devices. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

complications if these patients' tracheas would have been extubated at that time. As such, a high index of suspicion for residual NMB is needed when CMG is used at the final stages of (spontaneous) recovery, *even* when CMG has indicated adequate recovery. In general, the risk of residual NMB is increased in patients who received a NMBA within two hours prior to extubation. [15]

In addition, the timing and dosing of sugammadex may be affected by the type of monitoring. CMG indicated a PTC of 1 or 2 twitches or a TOF-count of 2 twitches several minutes earlier than EMG. This is relevant as the dose sugammadex is based on these levels of NMB. In

Table 2
Bias and precision of compressomyograph versus electromyography during onset and offset of deep and moderate neuromuscular block and during offset of shallow neuromuscular block in non-obese patients.

Depth of NMB	Deep PTC 1–15		Moderate TOF count 1–3		Shallow TOF ratio 0.01–1.0				
	Onset	Offset	Onset	Offset	Offset				
Range					0.20 to 0.39	0.40 to 0.59	0.60 to 0.79	0.80 to 1.0	0.01 to 1.0
Number of patients	52	140	130	181	88	102	117	127	130
Number of measurements	53	880	160	1081	143	183	280	723	1469
Bias (95% CI)	0.167 (−1.551 to 1.884)	3.405 (2.294 to 4.517)	−1.468 (−1.703 to −1.232)	−0.023 (−0.205 to 0.160)	0.182 (0.152 to 0.211)	0.297 (0.262 to 0.332)	0.388 (0.357 to 0.418)	0.369 (0.336 to 0.401)	0.312 (0.287 to 0.338)
Upper LoA (95% CI)	12.184 (9.617 to 15.914)	18.328 (16.704 to 20.230)	1.255 (0.889 to 1.688)	2.771 (2.502 to 3.079)	0.475 (0.430 to 0.529)	0.673 (0.620 to 0.736)	0.740 (0.695 to 0.795)	0.782 (0.735 to 0.838)	0.737 (0.703 to 0.776)
Lower LoA (95% CI)	−11.851 (−15.581 to −9.284)	−11.518 (−13.419 to −9.893)	−4.191 (−4.624 to −3.825)	−2.816 (−3.125 to −2.547)	−0.116 (−0.166 to −0.067)	−0.078 (−0.142 to −0.026)	0.035 (−0.020 to 0.080)	−0.045 (−0.100 to 0.002)	−0.112 (−0.151 to −0.078)
TOF-Cuff RC (95% CI)	4.000 (2.083 to 25.139))	3.693 (3.514 to 3.891)	0.790 (0.633 to 1.050)	0.670 (0.640 to 0.702)	0.062 (0.052 to 0.076)	0.063 (0.055 to 0.074)	0.063 (0.057 to 0.071)	0.066 (0.062 to 0.070)	0.292 (0.281 to 0.303)
EMG-RC (95% CI)	7.762 (4.041 to 48.783)	3.626 (3.451 to 3.821)	0.916 (0.734 to 1.218)	0.780 (0.746 to 0.818)	0.095 (0.080 to 0.116)	0.126 (0.109 to 0.148)	0.122 (0.110 to 0.137)	0.149 (0.141 to 0.158)	0.243 (0.234 to 0.252)
WSV	16.250	24.460	0.882	0.750	0.012	0.016	0.012	0.013	0.028
BSV	21.345	33.510	1.048	1.282	0.011	0.021	0.021	0.031	−0.019

BSV: Between-Subject Variance, CI: Confidence Interval, LoA: Limits of Agreement, RC: Repeatability Coefficient, WSV: Within Subject Variance.

Table 3
Bias and precision of compressomyography versus electromyography during onset and offset of deep and moderate neuromuscular block and during offset of shallow neuromuscular block in obese patients.

Depth of NMB	Deep PTC 1–15		Moderate TOF count 1–3		Shallow TOF ratio 0.01–1.0
	Onset	Offset	Onset	Offset	Offset
Number of patients	22	29	22	43	14
Number of measurements	24	62	23	94	105
Bias (95% CI)	−5.772 (−8.324 to −3.221)	−0.170 (−2.872 to 2.531)	−0.841 (−1.537 to −0.145)	0.178 (−0.202 to 0.558)	0.384 (0.299 to 0.469)
Upper LoA (95% CI)	5.510 (1.968 to 10.914)	14.656 (10.931 to 20.028)	2.241 (1.277 to 6.624)	2.883 (2.351 to 3.598)	0.831 (0.735 to 0.986)
Lower LoA (95% CI)	−17.055 (−22.459 to −13.513)	−14.997 (−20.369 to −11.272)	−3.923 (−8.306 to −2.959)	−2.526 (−3.242 to −1.995)	−0.063 (−0.218 to 0.033)
TOF-Cuff RC (95% CI)	4.031 (2.099 to 25.335)	4.132 (3.333 to 5.439)	0.707 (0.315 to 22.565)	0.837 (0.702 to 1.038)	0.308 (0.269 to 0.360)
EMG RC (95% CI)	3.500 (1.822 to 21.997)	3.182 (2.567 to 4.189)	1.414 (0.631 to 45.130)	0.761 (0.638 to 0.944)	0.245 (0.214 to 0.287)
WSV	0.500	19.537	0.500	0.836	0.035
BSV	32.635	37.686	1.972	1.069	0.017

BSV: Between-Subject Variance, CI: Confidence Interval, LoA: Limits of Agreement, RC: Repeatability Coefficient, WSV: Within Subject Variance.

practice, this means that it may take longer to reach full recovery when sugammadex is dosed based on CMG readings. Finally, apart from these results we wish to highlight two beneficial features of CMG. Specifically, its easy application and lower operational failure rate make it stand out above EMG and possibly other neuromuscular monitoring devices. These aspects are important for any neuromuscular monitoring device to increase compliance in daily practice.

There may be several factors that contribute to the results we found in this study. In essence, the study has evaluated an outcome which is affected by two variables: both the mechanism *and* location to determine the level of NMB differ between CMG and EMG. These variables may both contribute to the disagreement that was found, albeit the relative contribution of each variable remains unknown. We will however review some hypothetical factors that could have contributed to differences that we found. First, CMG evaluates twitch-evoked pressure differences in the cuff to determine the level of NMB; EMG evaluates compound action potentials. These techniques may not yield interchangeable results, regardless of the testing location. Furthermore, the precise mechanism of CMG is currently unclear. The pressure differences that are generated in the cuff of the CMG may be caused by peripheral nerve stimulation but may also be caused by direct stimulation of the muscle, in which case the neuromuscular junction is bypassed. Both phenomena may also occur simultaneously, which could explain the faster recovery of NMB measured by the CMG. In addition, CMG evaluates neuromuscular function at the upper arm musculature, which consists of the biceps and triceps muscle, while EMG was applied to the adductor pollicis muscle. Thus, CMG interrogates multiple muscles, whereas EMG evaluates NMB at one peripheral muscle. We argue that more knowledge on the mechanism of measuring NMB by the CMG is needed to fully understand the merits of this neuromuscular monitoring modality.

In addition to these device related issues, physiological differences between the upper arm muscles and the adductor pollicis muscle regarding sensitivity for NMBAs may contribute to the results we found in this study. In general, various neuromuscular testing locations in the body have shown variable effects of NMBAs and NMB recovery, [16,17] indicating variations in sensitivity of muscles for NMBAs. This results in differences in onset and offset times of NMB between muscles. [18] For instance, applying the EMG monitor to the orbicularis oculi or flexor hallucis brevis will yield significantly different results than when it is

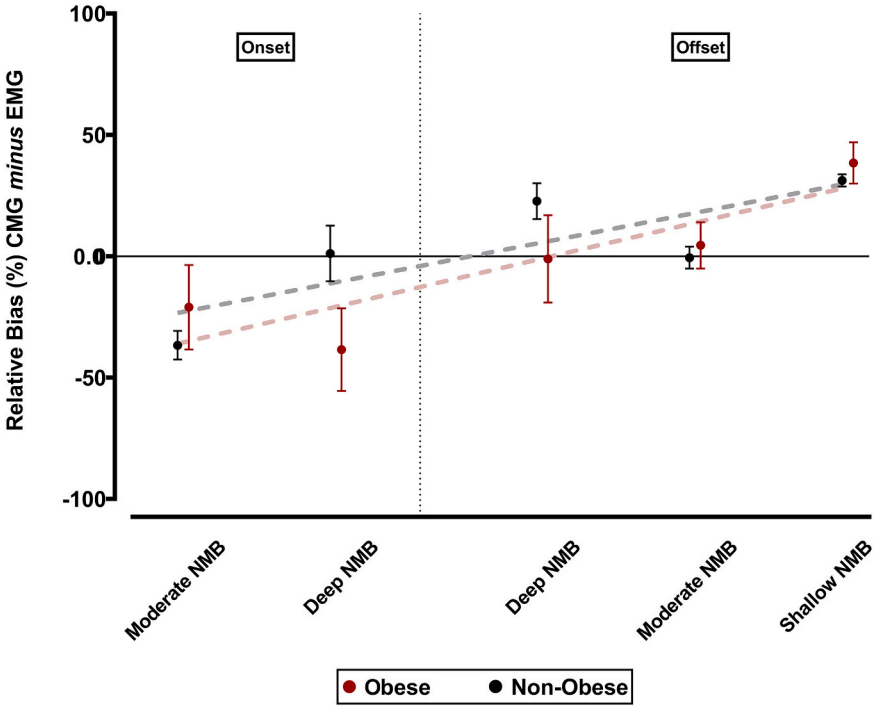

Fig. 3. Relative bias and 95% confidence interval during onset and offset of deep neuromuscular block (Post-Tetanic-Counts 1–15); moderate neuromuscular block (TOF-Counts 1–3) and shallow neuromuscular block (TOF-ratios 0.01–1.0) in obese (red dots and confidence interval) and non-obese (black dots and confidence interval) patients. A regression line (dashed line) was fitted for both groups to show the tendency of the bias at the various levels of NMB. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

applied to the adductor pollicis muscle. [16] Furthermore, the offset time of the diaphragm is shorter than the offset time of more sensitive muscles like the adductor pollicis muscle, [16] but also upper airway muscles and carotid body function. The latter two are critical systems to maintain adequate ventilation in the immediate postoperative period. [19–21]

The results of the current study are in agreement with a previous, small, multi-center study, that compared CMG at the upper arm to both EMG and acceleromyography of the adductor pollicis muscle. [8] However, the data from that study came from two separate protocols which were not preplanned to be published together. In addition, questions were raised as to whether temperature or laterality of measurements influenced the results. In the current study we took this into account, and we found that both variables did not significantly affect the results. Two other studies have compared CMG to MMG in the final stages of recovery (i.e. shallow and minimal NMB). [7,10] Rodiera et al. performed a pilot study in 40 adults and 20 children and found a bias of −0.04 at a TOF-ratio > 0.70. [7] This bias is significantly lower than the bias found in the current study. Another, more recent study by Veiga Ruiz et al. compared CMG to MMG in 32 adults. [10] The bias in that study was assessed when the MMG TOF-ratio was >0.7. This resulted in a low bias (0.047), [10] comparable to the bias found by Rodiera et al. There may be several explanations for the differences in the biases found by our study at shallow NMB and the studies by Rodiera and Veiga Ruiz. [7,10] First, in these studies, reversal agents were administered to all patients. Reversal speeds up the recovery of NMB which may attenuate bias compared to spontaneous recovery. Indeed, when we study the bias of the data in our study that was obtained *after* reversal, bias for shallow NMB was reduced to 0.198 (−0.255 to 0.650), compared to a bias of 0.320 (−0.108 to 0.747) obtained during spontaneous recovery. In addition, bias in the two former studies was assessed at TOF-ratio of 0.7, rather than the commonly accepted 0.9 threshold. Another difference was the reference monitor to which CMG was compared. We used EMG as reference monitor, whereas the studies by Rodiera and Veiga Ruiz et al. used MMG. [7,10] MMG has long been considered the gold standard in neuromuscular monitoring, however its set up is cumbersome and there are no commercially available devices. Therefore, EMG is increasingly used as an alternative comparator. [12] In addition, a recent study that compared EMG to MMG found a low bias, indicative of the validity of use for EMG as a reference monitor. [22]

This study has some limitations. First, there were local differences between the two participating centers that led to a discrepancies in the use of sugammadex. Especially in obese patients, sugammadex was frequently used to ensure full recovery of NMB at the end of anesthesia; this reduced the available data at shallow levels of NMB for the analyses in this subgroup and made us decide to include only half of the anticipated sample size in this center. Furthermore, we were unable to analyze the effect of arm dominance in obese patients, as most obese patients had CMG applied at the dominant arm.

We feel that the results obtained during shallow NMB in this group should be regarded as exploratory. Still, the overall picture that emerges from both groups is similar, being that CMG and EMG cannot be used interchangeably and show a dynamic disagreement throughout the stages of onset and offset of NMB. In addition, to facilitate pair-wise comparisons between the various levels of NMB with different integers and scales, we had to preprocess the data. This process may have led to an underestimation of the true biases as we had to round down some data (e.g. a TOF-count of 1 or more twitches was converted to a PTC of 15 twitches). In addition, we normalized TOF-ratios which complies to good research practice, but is often obviated in clinical practice. Nevertheless, the effect of normalization on EMG reading was generally very limited (0 to 3% difference). Additionally, properties of the electronic clinical research form software restricted the frequency of measurements which lead to a low number of measurements at onset of NMB. Furthermore, no formal power and sample size calculation was performed for this study, as there were limited data available on spontaneous recovery of NMB from previous studies. [7,10] We opted for a large sample size as we expected that differences in primary and secondary outcomes would be small. In addition, dosing of NMBAs and reversal agents was not protocolized, and we anticipated that many patients would not be allowed to recover spontaneously from the NMB. Still, in 96 out of the 250 patients, data on full spontaneous recovery was collected, which we believe is robust to provide a viable insight of the course of disagreement between the devices at onset and recovery of NMB. Finally, the amendments regarding the effects of peripheral temperature and (contra-)laterality of the device set-up were made after the

study had started. However, we were still able to collect sufficient data to answer these questions.

In conclusion, data from both obese and non-obese patients in this study show that there is variable disagreement between the level of NMB measured by CMG at the upper arm and EMG at the adductor pollicis muscle, throughout various stages of NMB. This may have consequences for the timing and dosing of reversal agents, and the decision to extubate the trachea. It is important that clinicians using these devices are aware of these differences. Adaptation of device algorithms may improve their dynamic performance at deep and shallow blockade.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2022.110673.

Disclosures

The Leiden University Medical Centre received an investigator-initiated trial grant of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Author statement

All authors discussed the results and contributed to the final manuscript.

Declaration of Competing Interest

MB, AD and CM received consultancy and/or speaker fees from MSD.

Acknowledgements

The authors thank all involved anesthesiologists, residents and medical students for their contribution to this study.

References

[1] Mencke T, Echternach M, Kleinschmidt S, Lux P, Barth V, Plinkert PK, et al. Laryngeal morbidity and quality of tracheal intubation: a randomized controlled trial. Anesthesiology 2003;98:1049–56. https://doi.org/10.1097/00000542-200305000-00005.

[2] Martini CH, Boon M, Bevers RF, Aarts LP, Dahan A. Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs deep neuromuscular block. Br J Anaesth 2014;112:498–505. https://doi.org/10.1093/bja/aet377.

[3] Berg H, Roed J, Viby-Mogensen J, Mortensen CR, Engbaek J, Skovgaard LT, et al. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. Acta Anaesthesiol Scand 1997;41:1095–103.

[4] Grosse-Sundrup M, Henneman JP, Sandberg WS, Bateman BT, Uribe JV, Nguyen NT, et al. Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched cohort study. BMJ 2012;345:e6329. https://doi.org/10.1136/bmj.e6329.

[5] Eriksson LI. Evidence-based practice and neuromuscular monitoring: it's time for routine quantitative assessment. Anesthesiology 2003;98:1037–9. https://doi.org/10.1097/00000542-200305000-00002.

[6] Naguib M, Kopman AF, Lien CA, Hunter JM, Lopez A, Brull SJ. A survey of current management of neuromuscular block in the United States and Europe. Anesth Analg 2010;111:110–9. https://doi.org/10.1213/ANE.0b013e3181c07428.

[7] Rodiera J, Serradell A, Alvarez-Gomez JA, Aliaga L. The cuff method: a pilot study of a new method of monitoring neuromuscular function. Acta Anaesthesiol Scand 2005;49:1552–8. https://doi.org/10.1111/j.1399-6576.2005.00777.x.

[8] Krijtenburg P, Honing G, Martini C, Olofsen E, van Elst HJ, Scheffer GJ, et al. Comparison of the TOF-Cuff((R)) monitor with electromyography and acceleromyography during recovery from neuromuscular block. Br J Anaesth 2019;122. https://doi.org/10.1016/j.bja.2018.11.011. e22-e4.

[9] Sfeir Machado E, Keli-Barcelos G, Dupuis-Lozeron E, Tramer MR, Czarnetzki C. Assessment of spontaneous neuromuscular recovery: a comparison of the TOF-Cuff ((R)) with the TOF Watch SX((R)). Acta Anaesthesiol Scand 2020;64:173–9. https://doi.org/10.1111/aas.13487.

[10] Veiga Ruiz G, García Cayuela J, Orozco Montes J, Parreño Caparrós M, García Rojo B, Aguayo Albasini JL. Monitoring intraoperative neuromuscular blockade and blood pressure with one device (TOF-Cuff): a comparative study with mechanomyography and invasive blood pressure. Revista Española de Anestesiología y Reanimación (English Ed) 2017;64:560–7. https://doi.org/10.1016/j.redare.2017.09.002.

[11] Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. Bmj 2015;351:h5527. https://doi.org/10.1136/bmj.h5527.

[12] Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J, et al. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. Acta Anaesthesiol Scand 2007;51:789–808. https://doi.org/10.1111/j.1399-6576.2007.01352.x.

[13] Brull SJ, Kopman AF. Current status of neuromuscular reversal and monitoring: challenges and opportunities. Anesthesiology 2017;126:173–90. https://doi.org/10.1097/ALN.0000000000001409.

[14] Olofsen E, Dahan A, Borsboom G, Drummond G. Improvements in the application and reporting of advanced Bland-Altman methods of comparison. J Clin Monit Comput 2015;29:127–39. https://doi.org/10.1007/s10877-014-9577-3.

[15] Rudolph MI, Ng PY, Deng H, Scheffenbichler FT, Grabitz SD, Wanderer JP, et al. Comparison of a novel clinical score to estimate the risk of REsidual neuromuscular block prediction score and the last train-of-four count documented in the electronic anaesthesia record: a retrospective cohort study of electronic data on file. Eur J Anaesthesiol 2018;35:883–92. https://doi.org/10.1097/eja.0000000000000861.

[16] Donati F, Meistelman C, Plaud B. Vecuronium neuromuscular blockade at the diaphragm, the orbicularis oculi, and adductor pollicis muscles. Anesthesiology 1990;73:870–5.

[17] Larsen PB, Gatke MR, Fredensborg BB, Berg H, Engbaek J, Viby-Mogensen J. Acceleromyography of the orbicularis oculi muscle II: comparing the orbicularis oculi and adductor pollicis muscles. Acta Anaesthesiol Scand 2002;46:1131–6. https://doi.org/10.1034/j.1399-6576.2002.460912.x.

[18] Cantineau JP, Porte F, d'Honneur G, Duvaldestin P. Neuromuscular effects of rocuronium on the diaphragm and adductor pollicis muscles in anesthetized patients. Anesthesiology 1994;81:585–90.

[19] Eriksson LI, Sato M, Severinghaus JW. Effect of a vecuronium-induced partial neuromuscular block on hypoxic ventilatory response. Anesthesiology 1993;78:693–9.

[20] Broens SJL, Boon M, Martini CH, Niesters M, van Velzen M, Aarts L, et al. Reversal of partial neuromuscular block and the ventilatory response to hypoxia: a randomized controlled trial in healthy volunteers. Anesthesiology 2019;131:467–76. https://doi.org/10.1097/aln.0000000000002711.

[21] Eriksson LI, Sundman E, Olsson R, Nilsson L, Witt H. Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: simultaneous videomanometry and mechanomyography of awake human volunteers. Anesthesiology 1997;87:1035–43.

[22] Bowdle A, Bussey L, Michaelsen K, Jelacic S, Nair B, Togashi K, et al. A comparison of a prototype electromyograph vs. a mechanomyograph and an acceleromyograph for assessment of neuromuscular blockade. Anaesthesia 2020;75:187–95. https://doi.org/10.1111/anae.14872.