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ORIGINAL RESEARCH

The interest of 100 versus 200 Hz tetanic stimulations to quantify low levels of residual neuromuscular blockade with mechanomyography: a pilot study

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Abstract
A more sensitive method than the train-of-four ratio seems required to detect low levels of residual neuromuscular blockade before tracheal extubation. The goal of the study was to determine the potential benefit of 5 s of 100 versus 200 Hz tetanic stimulation to quantify the residual block with mechanomyography in anesthetised patients. Twenty informed and consenting 18- to 80-year-old patients undergoing nose surgery were included. On the left hand, neuromuscular transmission was continuously monitored by acceleromyography. On the right side, a new mecanomyographic device (Isometric Thumb Force©) recorded the force of thumb adduction (N) developed during 5 s of 100- and 200 Hz tetanic stimulations of the ulnar nerve at three consecutive times: baseline before inducing the neuromuscular blockade, at the time of contralateral train-of-four ratio 0.9 recovery, and 3 min after additional sugammadex reversal. Tetanic Fade Ratios (TFR = F residual/F max) were compared between 100 and 200 Hz stimulations using Student's t test. At the time of TOF ratio 0.9 recovery, both 100 and 200 Hz TFR were significantly decreased compared to baseline (0.61 and 0.16 on average, respectively, $p < 0.0001$). The 200 Hz TFR was significantly lower than the 100 Hz TFR ($p < 0.0001$). There were no differences between baseline and post-reversal TFR. The 200 Hz TFR has the potential to better describe low levels of residual neuromuscular blockade than the TOF ratio and 100 Hz TFR and would benefit from further investigations. Retrospectively registered in the Australian and New Zealand Clinical Trials Registry ACTRN12619000273189.

Keywords Neuromuscular transmission monitoring · Residual neuromuscular blockade · Mechanomyography · Tetanic stimulation · Train-of-four ratio

1 Introduction

Quantitative neuromuscular transmission monitoring (NMTM) is mandatory to manage the depth of neuromuscular blockade (NMB) during general anesthesia [1]. In every patient, it determines the individual onset time before tracheal intubation and provides the clinician with post-tetanic count (PTC) and train-of-four (TOF) count to maintain the NMB at the proper depth according to the surgical need [2, 3]. At the time of tracheal extubation, quantitative NMTM is the recommended method to reduce the risk of residual NMB [4, 5]. Among other techniques, acceleromyography (AMG) has been developed to provide the clinician with a simple quantitative NMTM. It has been demonstrated to be a valuable measurement tool in clinical practice [6, 7]. However, when using the TOF stimulation pattern, the threshold of safe recovery is close to the baseline (TOF ratio 0.9 or even 1.0), which could be a problem for reliably excluding low levels of residual NMB [8]. In clinical practice, the administration of neuromuscular blocking agents (NMBA) has recently been suggested to remain a risk factor for postoperative pulmonary complications even when using

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NMTM and reversal agents [9]. A more sensitive method seems required to detect low levels of residual NMB before tracheal extubation.

Since the early seventies, high-frequency tetanic stimulation was demonstrated to be valuable for quantifying the integrity of neuromuscular transmission with mechanomyography [10, 11]. Based on analogic paper recordings, the amplitude remaining at the end of contraction (residual or minimal force) was divided by the peak height obtained (maximal force) to provide a tetanic fade ratio [12, 13]. However, at a time when NMB recovery relied on various "clinical tests" requiring the patient's collaboration (maximal tidal volume, inspiratory force, or sustained head lift) and a TOF ratio of 0.7, it was considered misleading, as tetanic fade could be present in some studies even when the patient was considered to have recovered full muscular strength [13, 14].

In light of these challenges, this pilot study was designed to determine the potential benefit of 100 and 200 Hz tetanic stimulations to detect very low levels of residual NMB in patients receiving halogenated free anaesthesia. A new mechanomyographic device was developed to digitally record muscle responses in the clinical setting.

The primary outcome measures were the maximal force developed during the tetanic contraction and the residual force at the end of the 5 s of stimulation. The secondary outcome was to quantify and compare any fade occurring during the 100 and 200 Hz tetanic contraction. Tetanic Fade Ratios (TFRs) were obtained with both tetanic stimulations at three specific times: before muscle relaxant administration, at the time of contralateral accelerometric TOF ratio 0.9 recovery and, finally, 3 min after 2 mg/kg sugammadex additional administration.

2 Materials and methods

2.1 The Isometric Thumb Force monitoring system (Fig. 1)

The original Isometric Thumb Force (ITF©) handgrip[1] combined with its Visual/ITF© software was designed to be used in an anesthetised subject equipped with a peripheral nerve stimulator delivering, at the wrist, a trans-cutaneous electrical stimulation on the cubital nerve. This device allows a mono-axial measurement of the isometric contraction forces developed by the thumb muscles in stable conditions [15].

Practically, the thumb is first inserted inside a tunnelled compartment in which it rests without any significant preload. The other fingers surround a cylindrical handle containing the force transducer. A circular basis provides optimum support for either the left or right palm. A dome tops and protects the thumb from any external contacts. Five adjustable non-elastic straps allow for individual adjustment of the setup and ensure constant close contact of the palm and fingers with the handgrip. The ITF handgrip is produced by 3D printing in biocompatible PA 2200 nylon.

The thumb rest is mechanically connected to the handle force transducer by a stainless steel cylinder with a needle, movable in a single axis through sliding polytetrafluoroethylene (PTFE) bearings. The force transducer (FC2231-0000-0050-L, Connectivity Measurement Specialties, Mansfield, Texas) based on a piezo resistive gage bridge produces linear measurements in the range of 0.05 to 220 Newtons (N) for a maximum displacement of 100 microns. The force cell is connected by a shielded cable to the dedicated signal processing circuit (LMP90100 Front End Amplifier, Texas Instruments, Dallas, Texas). The 24-bit, amplified and filtered digitised signal is transmitted by an Inter-Integrated Circuit protocol (I2C) to an interface module (NI-8451, National-Instrument, Austin, Texas) communicating the data to a PC (Intel Core i5) via a USB connection. In this configuration, the force value acquisition sampling frequency is close to 200 Hz. Each data collection was recorded in a dedicated file for off-line analysis.

2.2 Patient management

The monocentric study protocol was approved before patients inclusion by the Institutional Ethical Committee (CHU UCL Namur, Yvoir, Belgium, OM 050 Prof P. Evrard, under registration numbers 54/2017 B039201732500). It was performed in accordance with the ethical standards of the Declaration of Helsinki and was retrospectively included in the Australian and New Zealand Clinical Trials Registry (ACTRN12619000273189).

After obtaining written informed consent from all participants, 20 patients with American Society of Anesthesiologists (ASA) grades I to II (aged 18 to 80 years), who were scheduled to undergo rhinoplasty or rhinoseptoplasty under general anaesthesia, were included in the study. The exclusion criteria were pregnant or breastfeeding women, patients with renal or hepatic insufficiency, patients with neurological disorders, and any patient with a suspected allergy to the drugs used in the protocol or receiving medications that could interfere with neuromuscular transmission. The patient's height, weight, age, and sex were recorded in the protocol to define the population investigated.

All patients received alprazolam 0.5 mg 60 min before arriving in the operating theatre. They were conventionally

[1] This prototype device stems from the Laboratory of Microengineering and Bioinstrumentation—HEPIA/inSTI—University of Applied Sciences Western Switzerland (HES-SO Geneva), Campus Biotech, Chemin des Mines 9, CH-1202 Geneva, Switzerland. philippe.passeraub@hesge.ch / fabien.moreillon@hesge.ch.

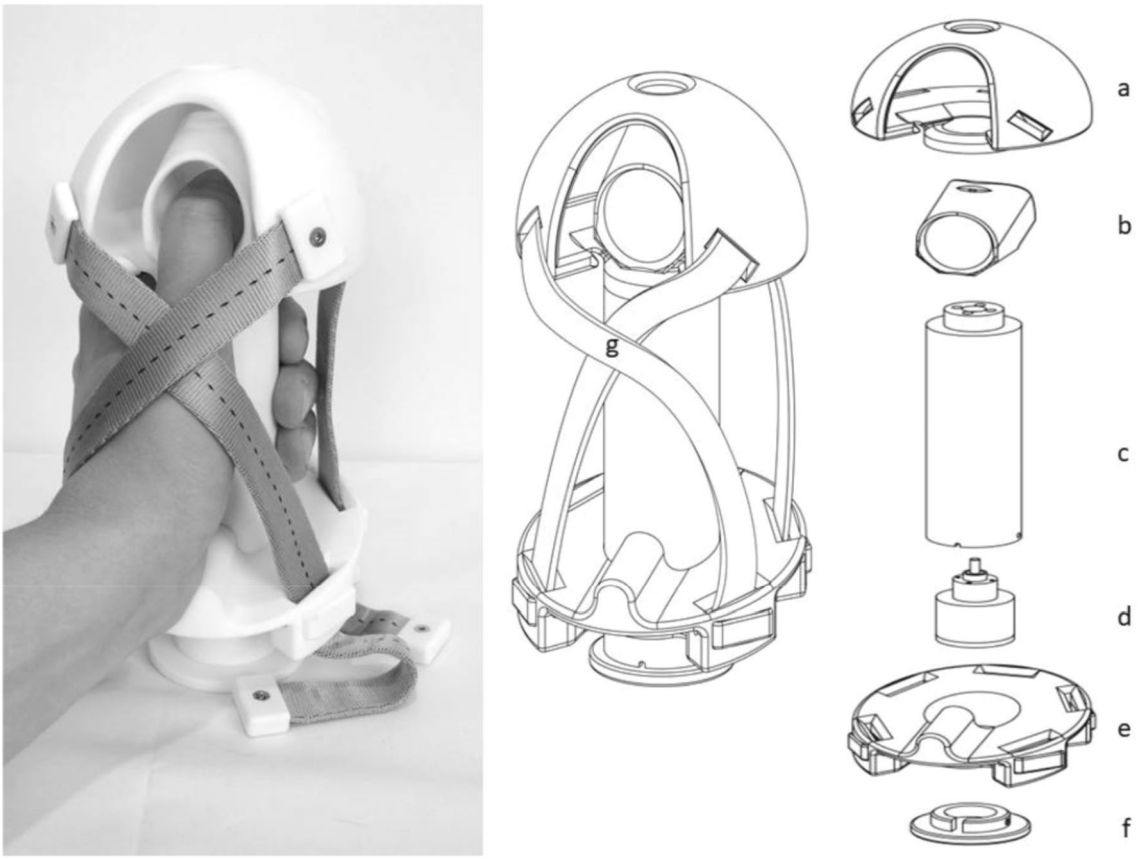

Fig. 1 Isometric Thumb Force handgrip. See Methods section for details. a: protective dome, b: thumb rest, c: handgrip, d: force transducer, e: support for the ulnar edge of the hand, f: closure plate, g: adjustable non-elastic straps

monitored with a pulse oximeter, a three-lead electrocardiogram and a noninvasive blood pressure monitor scheduled in automatic mode at 5-min intervals. An intravenous catheter was inserted into their forearm for crystalloid infusion (side at random). Neuromuscular monitoring was set up according to a specific protocol.

Anesthesia was induced with continuous intravenous infusion of remifentanil 0.25 µg/kg/min and continuous infusion of propofol 1% to obtain theoretical plasma concentrations ranging from 3 to 6 µg/mL (Diprifusor Cardinal Health, Basingstoke, UK). Lidocaine 1 mg/kg was also given as an intravenous bolus. After loss of consciousness, manual ventilation was provided during NMTM calibration and the initial NMBA-free baseline measurements. Then, rocuronium 0.45 mg/kg was administered. Non-invasive automatic blood pressure measurement was suspended during the neuromuscular onset to avoid dissimilar distribution of the rocuronium in the two arms. Tracheal intubation was performed when the TOF count reached zero with both monitors. Automatic non-invasive blood pressure measurement was reactivated. Mechanical ventilation (closed circuit, 40% oxygen in air) maintained end-tidal CO_2 within the normal range. Anesthesia was maintained with the continuous intravenous administration of remifentanil 0.15 µg/kg/min and propofol with a target plasma concentration of 2 to 4 µg/mL. Blankets prevented heat loss from the body, and the oropharyngeal temperature was kept stable.

2.3 Neuromuscular transmission monitoring

All recordings were performed during general anesthesia. The skin was cleaned with diethyl ether, and two electrodes were placed above the ulnar nerve on each wrist.

A TOF-Watch SX® (Alvesia Pharma, France) (TWSX) was set on the left hand. The accelerometric transducer was taped on the thumb's pulp, and the hand was inserted and held inside an SL TOF tube [16]. Another TOF-Watch® (Organon-Technika, Copenhagen, Denmark) designed to deliver high-frequency tetanic stimulation (including 100 and 200 Hz) was connected to the electrodes on the right arm, which was equipped with the ITF handgrip. Both arms were positioned alongside the body on soft padding to protect nerve structures from any extra focal pressure.

Supra-maximal stimulation and initial calibration were obtained using the TWSX internal automatic sequence, and the current intensity displayed was applied on both sides.

Then, TOF stimulations were applied at 15-s intervals during a short stabilisation period. The protocol included 3 consecutive periods of analysis:

- *Baseline* On the TWSX side, four T4/T1 ratios were recorded to determine the initial baseline before NMBA administration. We calculated 90% of the mean value to determine the normalised TOF ratio 0.9 recovery threshold using the following formula: normalised TOF ratio 0.9 = sum of 4 TOF ratio × 9/40, with the result rounded up [17]. On the ITF side, two consecutive tetanic stimulations (100 and 200 Hz at random) were applied for 5 s, with a two-minute interval to avoid any potentiation [18, 19]. The force applied on the mechanomyographic sensor was recorded by the ITF monitoring system for further analysis.
- *0.9 TOF Recovery* Consecutive TOF stimulations every 15 s were applied on both hands to monitor the NMB, from the onset and, during surgery, until the spontaneous recovery of a normalised TOF ratio of 0.9 on the TWSX side. At that moment, both tetanic stimulations (same order as previously) were applied with 2-min intervals, and the force developed was recorded by ITF.
- *Post Reversal* Then, to accelerate and to complete NMB final recovery, 2 mg/kg of sugammadex was additionally administered intravenously to encapsulate most of the remaining rocuronium. After 3 more minutes, the effects of the last two tetanic stimulations (ITF side) were recorded to determine a final level after the reversal.

2.4 Data collection and statistical analysis

A sample of 20 patients was arbitrarily determined and was expected to provide a significant ($p < 0.05$) difference between the TFRs recorded during baseline and recovery with both tetanic stimulations.

The force measurement profiles after 100 and 200 Hz stimulations were analysed in all patients to evaluate the overall quality of the recordings and to exclude any missing data and major artefacts from the analysis.

Off-line data analysis was based on the archived files. Each tetanic signal was described in a 5 s window starting from the 1 Newton value If this 1 N threshold was not reached, the recording was excluded from the analysis.

A Tetanic Fade Ratio (TFR) was determined to quantify any fade occurring during the muscle contraction: referring to the resting level just before the contraction, the residual force at the end of 5 s of stimulation was divided by the maximal force obtained during the contraction to provide a ratio [12, 13].

Using R software version 3.3.6 (R Project for Statistical Computing, Vienna, Austria), Student's t-tests were performed to compare the TFR obtained after 100- or 200-Hz stimulations in each period of analysis (Baseline, TOF Recovery and Post Reversal). $P < 0.05$ was considered significant.

Table 1 Maximal and residual forces

N	100 Hz		200 Hz	
	F maximum	F residual	F maximum	F residual
Baseline	18.79 ± 9.40	18.19 ± 9.34	18.66 ± 8.34	17.96 ± 7.83
TOF recovery	13.68 ± 5.81	8.60 ± 7.17	13.68 ± 6.09	2.03 ± 3.00
Post reversal	14.06 ± 6.49	13.51 ± 6.19	14.08 ± 6.12	13.08 ± 5.73

The maximal force developed during the contraction (F maximum) and the residual force at the end of 5 s of stimulation (F residual) before neuromuscular blockade (Baseline), at the time of contralateral acceleromyographic normalised TOF ratio 0.9 (TOF Recovery) and 3 min after 2 mg/kg sugammadex additional administration (Post Reversal). The results are expressed as the mean ± SD

3 Results

The patients included were 70% men, 54 ± 16 (mean ± SD) years old, 79 ± 13 kg in weight and 173 ± 9 cm in height. Supramaximal ulnar nerve stimulation was obtained with 56 ± 6 mA.

All recordings are available as supplemental digital content.

Four recordings were excluded from the analysis for the following reasons: significant displacement of the thumb in the tunnelled sensor during the tetanic contraction (n = 3) or missing data due to protocol error (n = 1). One patient presented a significant (> 1 N) spike before the contraction period, probably caused by an external disturbance; the acquisition window was manually adapted. Any signal occurring after the 5-s window was not considered (spike or baseline deviation). Two contractions were interrupted after 2.5 s because of a possible stimulator default (low battery). The method was applied to the available data.

The forces developed during the tetanic contractions are detailed in Table 1. The TFRs calculated for each contraction are presented and compared between the 100 and 200 Hz groups at baseline, TOF recovery and post reversal in Table 2 and illustrated in Fig. 2. At the time of normalised TOF ratio 0.9 recovery, both 100 and 200 Hz TFR were significantly decreased compared to baseline ($p < 0.0001$). The 200 Hz TFR was significantly lower than the 100 Hz TFR ($p < 0.0001$). There was no difference between baseline and post-reversal TFR.

Table 2 Comparison of 100 and 200 Hz tetanic fade ratios

	TFR 100 Hz	TFR 200 Hz	TFR 100 Hz–TFR 200 Hz
Baseline	0.96 ± 0.08	0.97 ± 0.06	− 0.01 (95% CI − 0.14 to 0.12) $p = 0.91$
TOF recovery	0.61 ± 0.44	0.16 ± 0.25	0.46 (95% CI 0.27 to 0.64) $p < 0.0001$
Post reversal	0.97 ± 0.05	0.94 ± 0.11	0.03 (95% CI − 0.15 to 0.21) $p = 0.71$

The Tetanic Fade Ratios (TFR = F residual/F maximum) obtained before neuromuscular blockade (Baseline), at the time of contralateral acceleromyographic normalised TOF ratio 0.9 (TOF Recovery) and 3 min after 2 mg/kg sugammadex additional administration (Post Reversal). The results are expressed as the mean ± SD. The differences between 100 and 200 Hz TFR are expressed as the mean, 95% confidence intervals, and p values

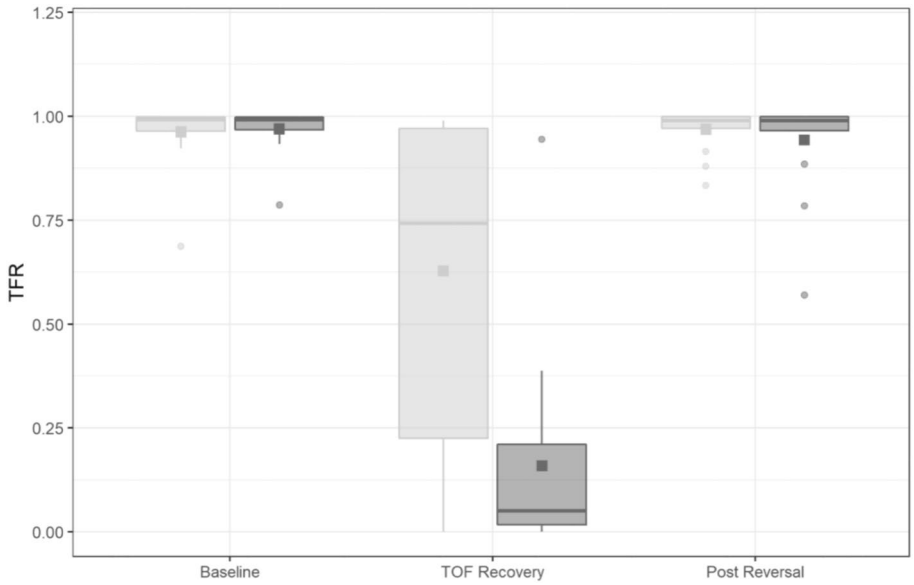

Fig. 2 Tetanic Fade Ratios at 100 and 200 Hz. The Tetanic Fade Ratios obtained before neuromuscular blockade (Baseline), at the time of contralateral acceleromyographic normalised TOF ratio 0.9 (TOF Recovery) and 3 min after 2 mg/kg sugammadex additional administration (Post Reversal). Boxplots present 100 Hz TFR in light grey and 200 Hz TFR in darker grey (means as squares, medians as lines, interquartile ranges, and outliers as dots)

4 Discussion

In patients anesthetised with no halogenated vapours, the new ITF© monitoring system has evidenced, for both 100 and 200 Hz tetanic stimulations, stable baseline contractions before rocuronium administration, significant fades concomitant with the contralateral spontaneous recovery of a normalized acceleromyographic TOF ratio 0.9 and the return to stable contractions after 2 mg/kg sugammadex additional administration. At the time of spontaneous normalised TOF ratio 0.9 recovery, the isometric mechanomyographic recordings showed that the 5-s 200 Hz tetanic stimulations induced significantly deeper fades than those recorded during the 100 Hz stimulations. These results emphasized that high-frequency tetanic fade ratios are very sensitive for quantifying very low levels of residual paralysis.

Various patterns of nerve stimulation have been described to assess muscle force recovery after NMBA administration. In addition to the classical low-frequency stimulation patterns, a single twitch (0.1–1 Hz) and the 2 Hz train-of-four (TOF), various tetanic frequencies were considered. The authors experimented with different durations (lasting from 0.5 to 10 s) and a wide range of frequencies (from 30 to 400 Hz); the high frequencies of stimulation (100–200 Hz) were considered a more sensitive index of neuromuscular transmission recovery than the single twitch or TOF [10, 11, 20].

Using mechanomyography with significant preload (500 g) and subcutaneous tetanic stimulations lasting 10 s, Stanec et al. demonstrated that tetanic fade appeared as soon as the frequency exceeded 50 Hz and increased regularly with higher frequencies. Reducing the stimulation duration to 5 s, the force was then maintained until 70 Hz [12]. This study, published in 1978, sustainably impacted the literature and anaesthesiology clinical practice from that time, avoiding the use of high stimulation frequencies of long duration because such patterns were suspected to evidence fade even in the absence of neuromuscular blockade [21]. However, it is notable that the Stanec et al. study was performed on patients receiving halothane, whereas halogenated vapours have been clearly associated with muscle fade even in the absence of NMB administration [22].

According to the data recorded with ITF isometric mecanomyography in the present study during total intravenous anesthesia, with no particular preload applied to the thumb resting simply on the sensor, no tetanic fade occurred in the absence of NMB (baseline) or after sugammadex complete reversal of the rocuronium block: these 100 and 200 Hz TFRs were both close to 1. Conversely, at the time of normalised TOF ratio 0.9 recovery, the 5 s 100 Hz TFR was 0.61 on average and was confirmed to be a sensitive index of residual NMB, as previously demonstrated [10, 11]. However, the 200 Hz TFR was significantly more affected by the residual block (TFR averaging 0.16), making this higher frequency TFR even more sensitive to investigations of low levels of NMB. These observations appeared to confirm the keystone experimental works of different authors, but more particularly those of D. Waud and B. Waud [11, 23]. In different in vitro and in vivo observations, these authors described the recovery of NMB according to a concept linked to the percentage of motor end-plate cholinergic receptors functioning normally ("free receptors"). Supposing that before muscle relaxant administration, 100% of end-plate receptors were free, the full recovery of a TOF signal—T4/T1 ratio of 1—was concomitant to only 30% of free receptors, whereas the absence of fade at the end of a 5-s 100 Hz tetanic stimulation indicated the return of 50% free receptors. Finally, the absence of fade at the end of a 5-s 200 Hz tetanic stimulation was observed in the presence of 75% free receptors. It was the goal of the additional sugammadex dose administered after TOF ratio 0.9 recovery to further reduce the rocuronium plasma concentration and to free rapidly more nicotinic receptors to assess if the 100 and 200 Hz TFR would recover the baseline value.

Our pilot study used a new mechanomyography device, allowing continuous digital acquisition of the force developed during thumb adduction. Some refinements should improve the stability of the hand around the handgrip as well as the position of the thumb in the tunnelled thumb rest during operation, and the force transducer should be sensitive in multiaxial (not only monoaxial vertical) directions. Some other artefacts observed in the data collected seemed linked to the nerve stimulator (few spikes at the beginning of and after the end of the stimulation and aborted stimulations). Consequently, four patients were excluded from the analysis, which further reduced the samples studied.

Unlike the TFR that recovered the baseline value after reversal (see Table 2), the maximal force remained lower after sugammadex administration (see Table 1). This difference has no obvious explanation and could be related to progressive modification of the thumb position on the MMG sensor during operation, to gradual neuromuscular transmission adaptation during repetitive nervous stimulations, or to any residual limitation of the neuromuscular transmission. Further studies should provide more information regarding the final NMB recovery when investigated with high-frequency tetanic stimulations.

In conclusion, the 200 Hz TFR has the potential to better describe low levels of residual NMB than the TOF ratio and the 100 Hz TFR and would benefit from further investigations. A more complete recovery could be documented after the TOF ratio returned to 0.9, which could improve NMB management in patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10877-021-00745-6.

Author contributions All authors contributed to the study conception and design. Material preparation was performed by PAP, FM and AAd'. Data collection was performed by PED and JM. Data analysis was performed by MR. The first draft of the manuscript was written by PED and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest Alain A D'Hollander is the President of the Fondation pour l'Anesthésie et la Réanimation (FAR) which granted this study. The authors have no relevant financial or non-financial interests to disclose.

Ethical approval Institutional Ethical Committee (CHU UCL Namur, Yvoir, Belgium, OM 050 Prof P. Evrard, under registration number 54/2017 B039201732500). Retrospectively included in the Australian and New Zealand Clinical Trials Registry (ACTRN12619000273189).

Informed consent All patients provided written informed consent to participate to the study and for results publication.

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