Pneumatomyography

A device for and a method of neuromuscular monitoring

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Pneumatomyographie

Ein Gerät und eine Methode für neuromuskuläres Monitoring

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unter der Betreuung von

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Graz, am …… …..

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Abstract

Current methods for neuromuscular monitors are facing several problems, including space requirements and reduced versatility in regards of the patients positioning. In our institution, we developed a new neuromuscular transmission monitor, the Pneumatomyograph (PMG, European patent number: EP 06018557.6, US patent number: US 60/824.541). It was designed to overcome these problems. The main idea behind is to measures the muscle force of the hand in response to electric stimulation of the ulnar nerve at the wrist *via* pressure changes in a balloon positioned in the hand and fixated by a fastener strap. In this thesis, we give a detailed description of this new technique, and present results of a study comparing it with the gold standard in neuromuscular monitoring, the Relaxometer mechanomyograph (MMG).

Methods: The two monitors were randomly allocated to the left or right hands of 16 patients. The first twitch of the train-of-four (TOF) expressed as percentage of control response (T1%), and the TOF ratio (T4:T1) were used to evaluate the neuromuscular block produced by rocuronium 0.6 $mg \cdot kg^{-1}$.

Results: The PMG monitor exhibited no pre-relaxation reverse fade (T4>T1) or T1 exceeding 100%. There was no significant difference in mean (SD) onset time, Dur_{25} (time to T1 25% recovery), or $Dur_{0.9}$ (time to 0.9 TOF ratio recovery) measured by the PMG. PMG showed 100% sensitivity and 75% specificity in indicating full relaxation for tracheal intubation, and 80% sensitivity with 86% specificity in predicting MMG 0.9 TOF ratio.

Conclusions: The PMG could be a reliable clinical monitor in the daily anesthesia practice that does not require time to set up or rigid support of the arm.

Zusammenfassung

Die zur Zeit verfügbaren Methoden des neuromuskulären Monitorings zeigen verschieden Einschränkungen, unter anderem einen großen Platzbedarf oder eine eingeschränkte Flexibilität in der Lagerung des Patienten. In unserer Klinik entwickelten wir einen neuen neuromuskulären Monitor, den Pneumatomyographen (PMG, Europäische Patent Nummer: EP 06018557.6, US Patent Nummer: US 60/824.541). Die zugrundeliegende Methode ist darauf ausgerichtet, diese Probleme zu umgehen. Sie besteht in der indirekten Messung der Muskelkraft der Hand nach einer Stimulation des Nervus ulnaris im Handgelenksbereich über die Veränderung des Drucks eines Ballons, der in der Hand positioniert und durch eine elastische Bandage fixiert wird. In dieser Dissertation wird eine detaillierte Beschreibung der Technik gegeben. Darüber hinaus präsentieren wir eine Studie, die die neue Technik mit dem Goldstandard im neuromuskulären Monitoring, der Relaxometer Mechanomyographie (MMG) vergleicht.

Methodik: Beide Monitore wurden zufällig entweder dem rechten oder dem linken Arm eines Patienten von insgesamt 16 Patienten zugeordnet. Die erste Antwort einer *train-of-four* (TOF) Serie als Prozentsatz einer Kontrollantwort (T1%) und die TOF Ratio (T4:T1) wurden verwendet um die neuromuskuläre Blockade bei einer Gabe von 0.6 $mg \cdot kg^{-1}$ Rocuronium zu beschreiben.

Resultate: Bei PMG konnte kein *reverse fade* (T4>T1) vor Gabe des Muskelrelaxants oder eine Überschreiten von 100% T1 gesehen werden. Es bestand kein signifikanter Unterschied in der durchschnittlichen onest-time, Dur_{25} (Zeit bis zu einer 25% Erholung von T1) oder der $Dur_{0.9}$ (Zeit bis zur Erholung auf 0.9 TOF Ratio), gemessen mit PMG im Vergleich mit MMG. PMG zeigte eine 100% Sensitivität und eine 75% Spezifität im Anzeigen einer vollen Relaxierung für die tracheale Intuba-

tion und eine 80% Sensitivität und eine 86% Spezifität für die Voraussage von MMG 0.9 TOF Ratio.

Schlussfolgerung: Die Pneumatomyographie stellt eine zuverlässige Methode zur Messung der neuromuskulären Funktion im klinischen Alltag dar, ohne dabei eine zeitkonsumierende und einschränkende Fixierung des Arms zu bedürfen.

1 Introduction

Neuromuscular blocking agents rank among the most frequently used drugs in general anesthesia. They are administrated to enhance intubation conditions, the avoid patients movements during surgery and to alleviate the conditions in the operating field. Since the first use of curare in anesthesia in the year 1942 (Griffith and Johnson 1942) there was a permanent development and a steady improvement in the used substances. Though, even today's generation of muscle relaxants shows a distinct interindividual variation in pharmacodynamics, whereby still neither onset time nor the time until full recovery is precisely predictable for a single patient. Thus, residual blockade of patients in the postoperative care still remains a problem. (Debaene, Plaud *et al.* 2003) Unfortunately, this problem is completely underestimated by many clinicians, as they feel safe when using short- and midlong acting neuromuscular blocking agents (NMBA). (Blobner 2009)

The risk for respiratory complications related to postoperative residual curarization (PORC) ranges between 1 and 13%. (Blobner 2009) In a prospective study, therapeutically intervention was necessary in 0.8% of the patients. (Murphy, Szokol *et al.* 2005) From this data it can be concluded that for a safe application of NMBAs appropriate monitoring of recovery is fundamental.

Neuromuscular monitoring offers several tools for quantifying the effect of neuromuscular blocking agents. In the recent edition of *Miller's Anesthesia*, Jørgen Viby-Mogensen recommends objective neuromuscular monitoring for every patient receiving neuromuscular blocking agents. (Viby-Mogensen 2004) Still, according to a survey in German hospitals it is only used in a minority of the operating rooms on a regular basis. (Fuchs-Buder, Hofmockel *et al.* 2003) Even worse are the data from a recent survey in the United Kingdom. More than 60% of the anesthet-

ists stated never to use neuromuscular monitoring at all. In addition, they found limited knowledge about the recommended TOF ratio for safe extubation. (Grayling and Sweeney 2007)

Mechanomyography (MMG) is regarded as the gold standard in quantifying neuromuscular relaxation. (Fuchs-Buder, Claudius *et al.* 2007) Detecting the force of the muscle contraction caused by nerve stimulation directly through a force transducer is the most reliable method; though the required equipment is rather bulky und the setup is time-consuming. Even more, the method needs a rigid fixation of one arm on a board, which is sometimes not accomplishable in regards of an often overcrowded operating room and special positions. Thus, the usage of mechanomyography is limited to research and has nearly no application in clinical practice.

Meanwhile, different techniques for neuromuscular monitoring are commercially available; partly as stand-alone devices (e.g. TOF-Guard, TOF-Watch, ParaGraph) or as module integrated in the narcosis machine (e.g. AS/5 M-NMT, Datex Ohmeda, Helsinki, Finland). The clinical results of this solution could never be accurately correlated to mechanomyography. It was often proved that measurements of different methods could not be used interchangeably. (Loan, Paxton *et al.* 1995; Dahaba, Von Klobucar *et al.* 1999; Dahaba, von Klobucar *et al.* 2002; Capron, Alla *et al.* 2004; Fuchs-Buder, Claudius *et al.* 2007) The Copenhagen GCRP Conference lately acknowledged that these devices are highly prone to errors resulting from movements (Fuchs-Buder, Claudius *et al.* 2007), including those caused inadvertently by the surgeon or other operating room personnel. (Dubois, Gourdin *et al.* 2005; Fuchs-Buder, Claudius *et al.* 2007) Though, today's technique is nonsatisfying in finding a compromise between reliability and usability.

In our clinic, we developed a new device for and method of determining a muscle activity called Pneumatomyograph (PMG, patent number:

WO2008028572), for pneumatically determining the muscle activity. (Dahaba and Bornemann 2008)

After constructing a prototype and developing the software for electronical processing of the assessed data, we conducted a study for testing the PMG and comparing it to the MMG. The aim was to compare the neuromuscular block of rocuronium 0.6 $mg \cdot kg^{-1}$ (twice the 95% effective dose, ED_{95}) monitored by the PMG to that monitored by the Relaxometer® mechanomyograph (Groningen University, Groningen, The Netherlands), (Rowaan, Vandenbrom *et al.* 1993) and to evaluate the new system for its diagnostic accuracy. (Bossuyt, Reitsma *et al.* 2003)

2 Fundamentals of neuromuscular monitoring

The neuromuscular junction (NMJ) is the place of conversion of electrical to chemical signal and *vice versa* in order to transmit an impulse from the nerve to the muscle. It is one of the most intensely studied synapses, both in animals and humans and serves as an archetype for understanding synapses. Scientific exploration of this field has a long tradition starting from Claude Bernard in 1846, including Nobel Prize Laureates like Sir Henry Dale and Sir Bernard Katz. Even nowadays, after more than 150 years of research, many details of the NMJ are still unclear.

The NMJ is the site of action of neuromuscular blocking agents, as they are competitive inhibitors of the ACh-receptors. Hence, basic knowledge of the physiological procedures in this area is pivotal for understanding neuromuscular monitoring.

2.1 Historical background

The development of neuromuscular monitoring was an inevitable result of the proceeding research on the neuromuscular junction and muscle relaxants.

Already in the year 1846 Claude Bernard used electrical impulses on nerves in his experiment with curarized frogs. He was the first to establish the technique of nerve stimulation and measuring the muscle activity, as it is in principle still used today. He showed that curare injected into a limb of a frog prevented the muscle contraction in response to nerve stimulation; even so, the muscle continued to respond when stimulated directly. Though, when applied directly to the nerve, curare failed to abolish muscle contraction in response to both, either nerve stimulation or direct muscle stimulation. Bernard concluded that curare acted at the nerve–muscle junction. (Diefenbach 1999)

It took until 1905 that Langley could prove the initiation of contraction by chemical transmitters. (Langley 1905)

In the year 1936, Dale *et al.* first described the fundamental structure of the motoric endplate with acetylcholine as the transmitter. (Dale, Feldberg *et al.* 1936) He was awarded with the Noble Price, which he received together with the Austrian scientist Otto Loewi "for their discoveries relating to chemical transmission of nerve impulses". (Nobel Web AB 2010)

On the 23rd January 1942, Harold Randall Griffith was the first to use curare – labeled with the trade name *Intocostin* – in patients undergoing general anesthesia at the *Homeopathic Hospital of Montreal*. In July 1942 he published his promising results in the newly founded journal *Anesthesiology*. (Griffith and Johnson 1942)

In 1941, Harvey and Masland applied the technique of supramaximal nerve stimulation in humans. (Harvey and Masland 1941) They stimulated the ulnar nerve in the cubital tunnel, and sensed the response at the hypothenar.

In 1955, S.Y. Botelho wrote the first article applying electro- and mechanomygraphic recordings in curarized subjects. (Botelho 1955)

In 1958 the first device for intraoperative neuromuscular monitoring was presented by Christie called *St. Thomas's Hospital nerve stimulator*. Based on this method it was possible to titrate the dosage of muscle relaxants and furthermore to monitor neuromuscular recovery. (Christie and Churchill-Davidson 1958)

Some years later, Ronald L. Katz established the usage of the adductor pollicis muscle as the standard method, as this muscle is the only adductor of the thumb innervated by the ulnar nerve. (Katz 1965)

In the early 1970th Hassan Ali *et al.* introduced the *train-of-four* (TOF) as a new stimulation pattern. (Ali, Utting *et al.* 1970; Ali, Utting *et al.* 1971; Ali, Utting *et al.* 1971) (Figure 3) This was a milestone in the evolution of neuromuscular monitoring, as it allowed quantitative assessment of muscle relaxation. Even today, 40 years after the development, it is the most widely used stimulation pattern in clinical practice.

Over the years, other stimulation patterns were developed witch the purpose to increase the quality of neuromuscular monitoring. Tetanic stimulation was described in 1975, post-tetanic count in 1981. (Tassonyi 1975; Viby-Mogensen, Howardy-Hansen *et al.* 1981) In 1988 double-burst-stimulation was described by Engbaek *et al.* (Engbaek, Ostergaard *et al.* 1989)

In 1988, acceleromyography was described by the group of Viby-Mogensen. (Viby-Mogensen, Jensen *et al.* 1988) With this easy to use

technique, neuromuscular monitoring started to spread from pure research to every day practice.

Today, the TOF ratio measured *via* acceleromyography at the adductor pollicis muscle is the established standard.

2.2 Neuromuscular transmission

A motor unit consists of a single motor neuron and all muscle fibers innervated by this neuron. The number of corresponding fibers varies between 1.000 in the gross gluteal muscle und 5 to 10 in the fine motoric muscles of orbit. The interface for neuromuscular impulse transduction between the motoric nerve and the muscle fiber takes place in the motoric end plate (*Synapsis neuromuscularis*, *neuromuscular junction*, NMJ), a chemical synapsis with acetylcholine (ACh) as transmitter. The basic principle was first described by Nobel-prize winner Sir Henry Dale in 1936. (Dale, Feldberg *et al.* 1936)

Most muscle cells contain just a single motoric end plate; some facial and laryngeal muscles and the muscle fibers in the upper esophagus however contain several synapses. (Diefenbach 1999)

2.2.1 The neuromuscular junction

The neuromuscular junction is divided into a presynaptic part, the synaptic cleft and the postsynaptic part. It is responsibly of converting the electrical signal to a chemical, and *vice versa* on the postsynaptic side.

The axon of the motoric nerve carries electrical potentials without discontinuance from the anterior horn of the spinal cord (*cornu anterius*) in close proximity to the muscle fiber. There, the axon strips the myelin sheet and split into branches. This single nerve fiber ends in relative plane and oval presynaptic terminal boutons (*bulbulus terminalis)*.

The nerve terminal is responsible for the release of neurotransmitter over the synaptic cleft. In the neuromuscular junction, ACh is the primary neurotransmitter. It is synthesized from acetate and choline in the Golgi apparatus and then stored and released as 40-60 nm vesicles (*vesiculae synapticae*) by the nerve terminal. (Figure 1) Each vesicle contains 6000-8000 molecules ACh. (Dudziak 2001) It seems that different

sort of vesicles exists, distinguished by their availability for release, depending on the level of demand. (Campbell and Liu 2009) Nevertheless, the actual mechanisms by which ACh is packed and stored in nerve terminal vesicles are still not fully understood. (Fagerlund and Eriksson

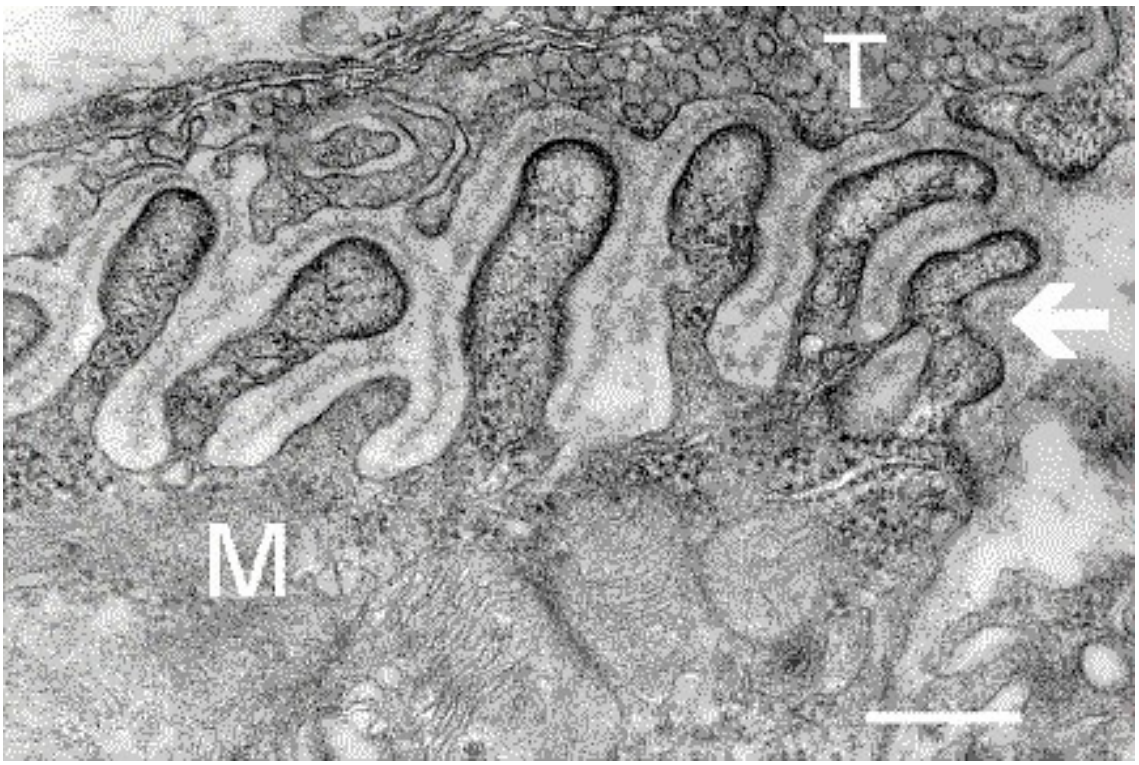

Figure 1: Neuromuscular junction

Electron micrograph of a neuromuscular junction. Scale is 0.3 µm. T = axon terminal, M = muscle fiber, the arrow marks a postsynaptic fold. (Wikimedia Commons contributors 2008)

Source: Synapse Web at National Institutes of Mental Health, NIH

2009)

In random pattern, vesicles fuse with the preynaptic membrane and set their amount of ACh free into the synaptic cleft. This process of exocystosis is responsible for transient changes in electric potential (~0.5mV), known as miniature endplate potential (MEPP). (Campbell and Liu 2009)

This MEPP are insufficient to reach threshold and to cause an action potential in the endplate. (Sellin, Molgo *et al.* 1996)

Separated by the 20 to 50 nm wide synaptic cleft (*fissura synaptica*), the postsynaptic membrane, and located in the bottom of this postsynaptic folds, tissue bound acetylcholine esterases are found.

2.2.2 Acetylcholine receptors

An average postjunctional endplate contains about 50 million ACh-receptors. The receptors are situated at the crest of the junctional folds, a folded area of the sacrolemma. These folds are sub-classified in primary (shallower) and secondary (deeper) folds. Located in the bottom of this postsynaptic folds, tissue bound acetylcholine esterases are found. (Campbell and Liu 2009)

Nicotinic ACh-receptors are proteins with a molecular weight of about 290.000 Daltons. (Unwin 2005) They consist of 5 polypeptide subunits: two identical alpha-1, one beta-1, one delta plus either one gamma in adults or one epsilon subunit in the embryonic form. The five subunits are arranged symmetrically around a central funnel-shaped pore. This pore corresponds with the ion channel. (Itier and Bertrand 2001) (Figure 2)

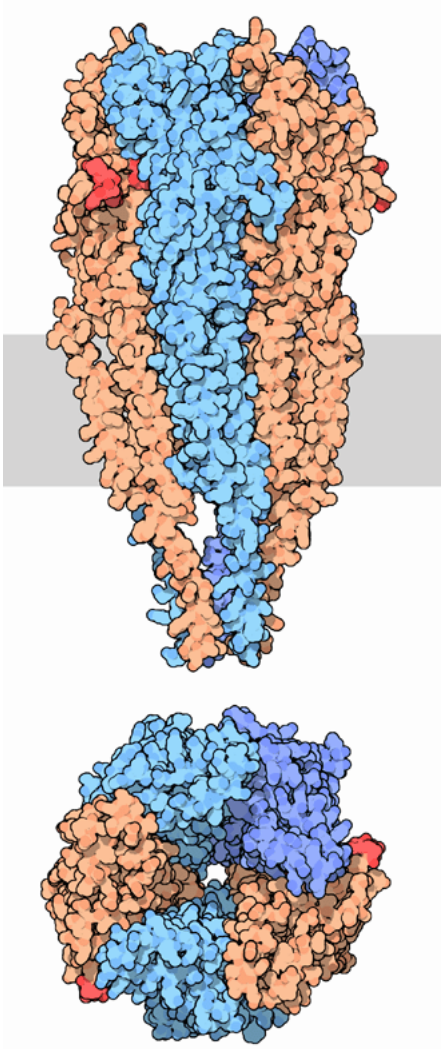

Figure 2: ACh-receptor

Acetylcholine receptor (nicotinic) from electric torpedo rays (very similar to human receptor) is made of 5 subunit, 2 of which (shown in orange) binds to ACh (red)

(Goodsell 2005)

The specific binding site of the ACh-molecule is situated on the alpha subunit. The interaction between the molecule and the receptor results in a change of the configuration of the protein. The central pore opens, allowing Na^+ ions to pass in the direction of the concentration and electrical gradient. (Campbell and Liu 2009)

2.2.3 Action potential generation

A nerve impulse leads to a change in conformity of presynaptic Na^+ channels, which lasts for 2-4ms. Voltage gated Ca^{2+} channels are activated, causing an influx from extracellular. The increase of intracellular Ca^{2+} triggers an increase in exocytosis and releases ACh vesicles. The total amount of ACh released is influenced by two factors: the extracellular concentration of Ca^{2+} and the duration of the Ca^{2+} influx. (Dudziak 2001) In average, 60 ACh-vesicles are released. This correlates to the 10fold amount of ACh-receptors needed to reach the threshold value. In the use of neuromuscular blocking agents, this reflects to the "safety margin". The nerve terminal has cholinergic autoreceptors, which - when activated by ACh - stimulate the release of more ACh from the presynaptic terminal.

Once the membrane potential exceeds the threshold value, an action potential occurs in the postsynaptic membrane. (Campbell and Liu 2009)

The binding of ACh to the postsynaptic receptor has a maximum duration of 0.5ms. Once the action potential is repolarized ACh is hydrolyzed by acetylcholine esterase (AChEase) in acetyl and choline. By reabsorbance in the terminal end, these substances are "recycled". The short exposure time prevents a permanent depolarization of the postsynaptic membrane and ensures a quick recovery. (Dudziak 2001)

The model of voltages and currents of the action potential was first described by Alan Lloyd Hodgkin and Andrew Huxley in 1952. (Hodgkin

and Huxley 1952) In 1963, their research was awarded with the Nobel Prize "for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane". (Nobel Web AB 2010)

The action potential is divided into five phases: threshold, depolarization, peak, repolarization, and hyperpolarization. The threshold value describes the potential at which the opening of the voltage gated ion channels is inducted with duration of approximately 1msec. The rapid influx of Na^+ results in a positive membrane potential, the so called depolarization of the endplate currents (EPC). The K^+ channels are slower acting; thus outflux of K^+ ions counteracting the Na^+ influx is delayed. In the peak, the influx and outflux are equally, and do not affect membrane polarity. When Na^+ channels begin to inactivate, the repolarization starts. As the K^+ channels are slow acting, they overshoot the resting potential, causing hyperpolarization. During this phase, the membrane is unresponsive to any stimulation, known as the refractory period. The normal balance of ions is restored by Na/K-ATPase.

When a critical amount of receptors is activated, voltage-gated Na/K-channels are activated and to a conduction of the signal in the muscle according to the "all-or-none" principle, triggering a cascade of intracellular mechanisms resulting in a muscle contraction. (Martyn, White *et al.* 1992)

2.3 Features of neurostimulation

2.3.1 Basic principle

Stimulation of a single muscle fiber follows the "all-or-none" principle. The reaction of the whole muscle depends on the number of muscle fibers stimulated. If the nerve is stimulated with sufficient intensity, i.e. supramaximal current, all muscle fibers will contract, resulting in the maximum force of the muscle. Administrating NMBAs decreases the number of fibers reacting to a stimulus, and subsequently decreases the force of the muscle contraction. The decrease of force is correlated to extend of neuromuscular blockade. (Viby-Mogensen 2004)

2.3.2 Wave form

The impulse should be monophasic and rectangular, described as a square wave. This ensures, that the current is constantly maintained for the entire duration of the impulse.

A biphasic impulse could cause repetitive firing by releasing a burst of action potential in the nerve. Thereby, it could increase the response to the stimulus.

2.3.3 Pulse duration

Pulse duration describes the duration of the single impulse. It should be >0.1 and <0.5 msec to ensure the depolarization of the nerve. Pulse width of <0.5 msec result in repetitive firing, as it excesses the refractory period, or may could stimulate the muscle directly. (Viby-Mogensen 2004)

2.3.4 Current

The current required to induce depolarization in some fibers and to cause a detectable muscle response is called threshold current. The current required to depolarize all fibers in a nerve bundle is the maximal current. It is influenced by skin resistance. Thus, to increase the required current, skin should prepared by removing hair, decornifying and degreasing the skin and cleaning it with alcohol. (Murphy and Szokol 2004)

The maximal current is determined in a patient not receiving NMBAs by increasing the current of a single twitch stepwisely, until a further increase does not lead to a consecutive increase of the force of the muscle contraction. Intraoperatively, the skin resistance is variable. To adept for these changes, e.g. to compensate an increase of resistance caused by a decrease of body temperature, and to ensure accurate measurements the current for the maximum response is increased by 15-20 percent as a reserve. Correspondingly, this value is called supramaximal current. (Gerber 1995)

As this procedure is time-consuming and to laborious for daily practice, in routine most often a current of convenience is applied. However, for scientific purposes the supramaximal current needs to be determined.

Applying a stimulus of 50-60 mA may be painfully for a wake patient or during recovery. To overcome this problem some authors suggested decreasing the current to submaximal to assess neuromuscular recovery. (Brull, Ehrenwerth *et al.* 1990; Brull, Ehrenwerth *et al.* 1991; Silverman and Brull 1993) This method however was shown to result in an unacceptable low accuracy of prediction. (Helbo-Hansen, Bang *et al.* 1992)

2.4 Stimulation pattern

The methods to measure neuromuscular blockade objectively are based on evoked response of a stimulated motoric nerve. The first device used for intraoperative neuromuscular monitoring, the *St. Thomas's Hospital nerve stimulator* used single electrical impulses to stimulate the nerve. (Christie and Churchill-Davidson 1958) Since then, different patterns were described. (Table 1) In today's clinical routine, the most often used patterns are single-twitch, TOF and post-tetanic count. (Hemmerling and Le 2007)

	During induction		**During operation**			**Recovery**
	Supramax. stimulation	tracheal intubation	intense blockade	moderate blockade	Reversal	**Room**
Single Twitch	1.0Hz	0.1Hz				
TOF-R						?
PTC						
DBS						

Table 1: The application of different stimulation patterns in different clinical situations. "?" indicating, that TOF is less useful in recovery room unless measured using mechano-, electro-, or acceleromyography. (Modified from (Viby-Mogensen 2004))

2.4.1 Single twitch

Single twitch is the oldest and simplest method of neuromuscular stimulation. In fact, it was the only available stimulation pattern for years. Today, the clinical use is limited to detect the supramaximal current. (Pino and Ali 1995)

Generally, the frequency of the single stimuli is set to 0.1 Hz, depending on the stimulator. Above 0.15 Hz the fade-phenomenon may occur, a temporal decrease of the neuromuscular response leading to false re-

sults. (Ali and Savarese 1980) However, a frequency of 1.0 Hz is sometimes used for shortening the time to detect supramaximal current.

Interpretation of the single twitch was very rough, especial with no recording available. Later, after the development of mechano- and electromyography offering the possibility to compare intraoperative measurements with control-values measured before induction, every contraction of the muscle could be assessed objectively.

The twitch height remains stabile until 75% of the ACh-receptors are inhibited, and will completely vanish when 90-95% of the receptors are occupied.

2.4.2 Train-of-four stimulation

The train-of-four (TOF) stimulation was first described by Ali *et al.* in the early 1970th, and is since then the most commonly used stimulation pattern in perioperative routine. (Ali, Utting *et al.* 1970; Ali, Utting *et al.* 1971; Ali, Utting *et al.* 1971) (Figure 3: Train of FourFigure 3) Until then, single twitch was the only method available, restricting neuromuscular monitoring to research, as it implied complex and time-consuming equipment, and delivered accident-sensitive data. Though, the development objectives were to establish a stimulation pattern able to detect neuromuscular blockade at any time of an operation without relying on a preoperative reference value and without the need for complex equipment.

The stimulation pattern consists of 4 square waves with supramaximal current and a length of 0.2 msec. The frequency of repetition is 2 Hz. To avoid interferences, the gap between one train and the next has to be minimally 10 seconds. The response is observed as TOF count or TOR ratio.

In the absence of NMBA all of the 4 stimuli causing muscle contractions of equal strength. If nondepolarizing neuromuscular blocking agents are applied, fading can be observed; first, the forth response (T4) is weaker; then, with increasing muscle relaxation, fading is progredient until no response can be detected, correlating to 90-98% of the ACh-receptors occupied.

Clinically, this pattern can be interpreted tacitly or visually. The absence of the forth contraction correlates strongly with a T1% of 25 and indicates in most cases the end of sufficient surgical relaxation, e.g. in abdominal surgery.

A more reliable method for quantifying the level of relaxation is the TOF-ratio (TOF-R). For this, the strength of the fourth contraction is compared to the first (T4/T1). The biggest advantage of this indicator is that it is independent from a preoperative baseline value. Monitoring can be started at any time. With a neuromuscular blockade of 70% of the nicotinic acetylcholine receptors, the forth response (T4) is decreased. With increasing block, T1 and T4 are decreasing parallel, with T4 vanishing first. In accordance to the single twitch, at rate of 90-98% of the receptors being

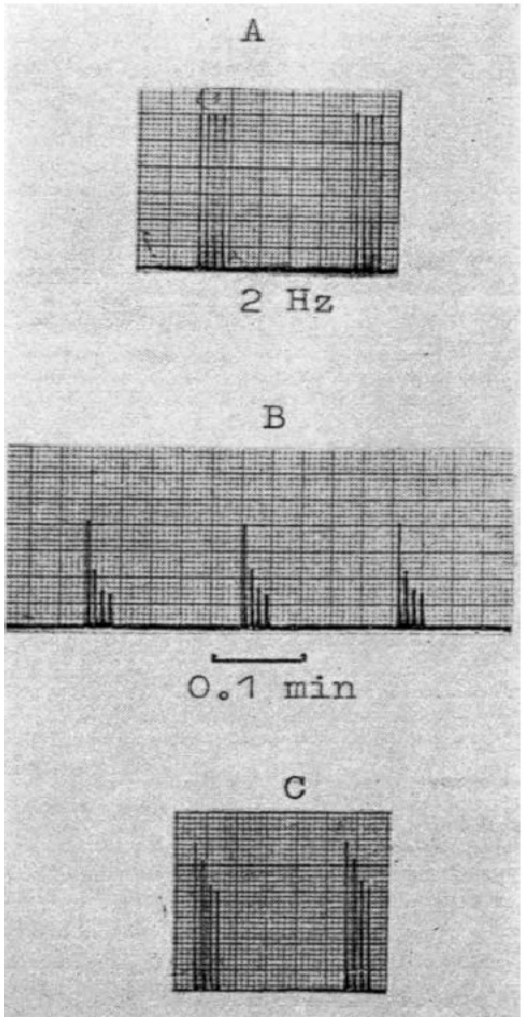

Figure 3: Train of Four

Figure from the original publication of Ali et al.

A=control tracing
B=after tubocurarin
C= substantial recovery

(Ali, Utting *et al.* 1970)

blocked, also T1 is gone. (Figure 4)

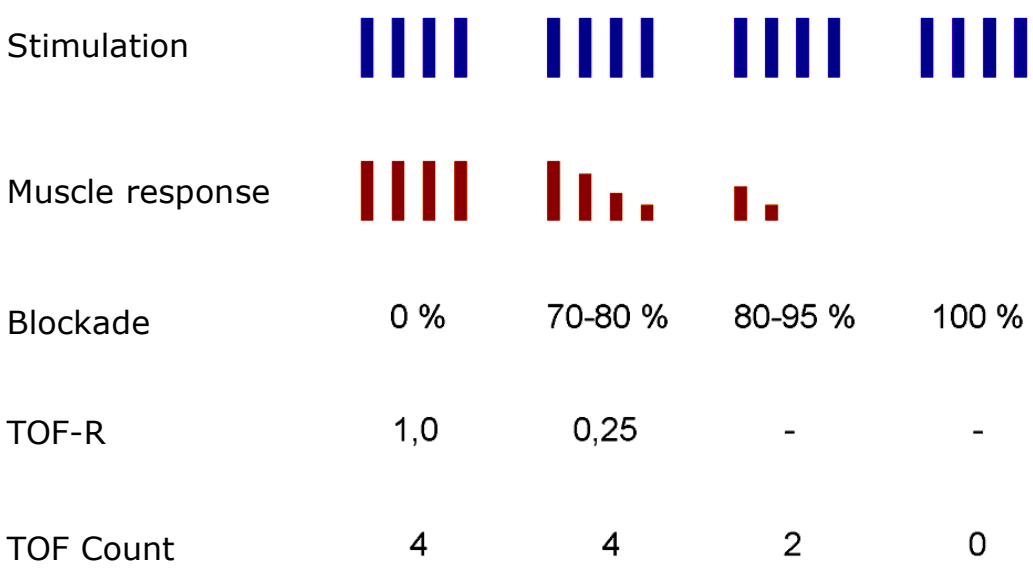

Figure 4: Schematic overview of the train-of-four

Different stages of neuromuscular blockade are displayed with the correlating TOF-responses. Modified from (Wikimedia Commons contributors 2009)

2.4.3 Double-burst stimulation (DBS)

Double-burst stimulation was introduced in the year 1989 by Engbaek *et al.* The aim was to develop a stimulation pattern with a higher prognostic value for residual blockade. (Engbaek, Ostergaard *et al.* 1989)

DBS consists of two short bursts of 50 Hz, which are separated by a 750ms interval. The first burst series consists of 3 impulses, whereas the second may consist of 2 (DBS 3,2) or 3 (DBS 3,3) impulses. The impulses impress as a single contraction. The response is observed as the ratio between second and first burst (D2/D1). It correlates well to TOF-R. (Brull, Connelly *et al.* 1990) (Figure 5)

DBS allows more subtle tactile detection of the neuromuscular block as the TOF. With TOF, manual evaluation is only reliable when TOF-R < 0.4; DBS allows detection of fade up to TOF-R of 0.6. (Drenck, Ueda *et al.* 1989)

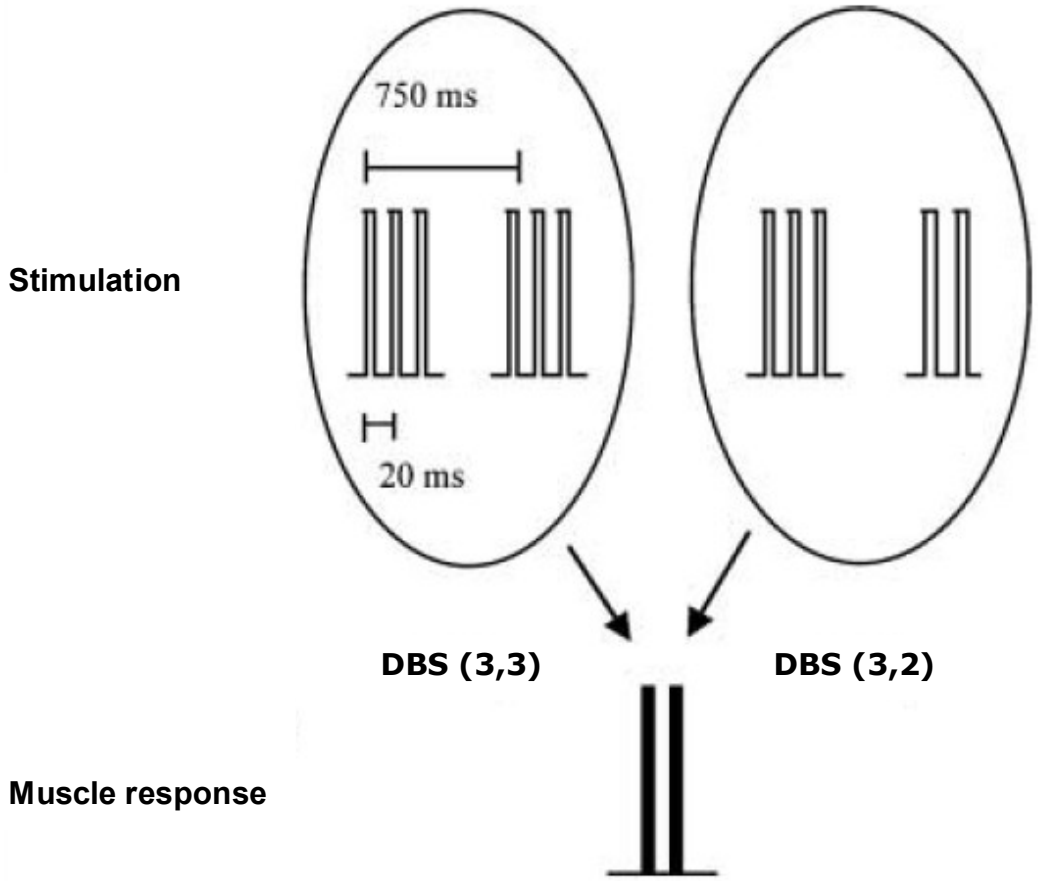

Figure 5: Double-Burst-Stimulation (DBS)

Schematic diagram of the DBS pattern. Both DBS 3,3 and DBS 3,2 result in two muscle twitches.

Modified from (Fuchs-Buder and Mencke 2001)

2.4.4 Tetanic stimulation

Tetanic stimulation was first described by Tassonyi in the year 1975 for measuring the neuromuscular safety margin for recovery. (Tassonyi 1975) Regarding the limitations in validity of DBS and TOF for recognizing residual blockade, tetanic stimulation was suggested to be used increasingly. (Fuchs-Buder 2008)

Tetanic stimulation describes a high frequency of electrical stimulations (30-200Hz); the most commonly used pattern is 5 seconds interval stimulation with 50Hz. The single depolarization cannot be separated by the investigator and fuse to one contraction of the muscle. In patients not fully recovered from nondepolarizing muscle relaxants or with phase-II-block a so called fade-phenomenon is detected. Initially, the muscle contractions are stronger with a subsequent reduction. The reduction is correlating to the frequency of stimulation. (Viby-Mogensen 2004)

Tetanic stimulation allows the most reliable detection of residual blockades. Its use is limited for monitoring induction and intraoperative blockade. The application of high frequency tetanic stimulation is painfully, and should therefore be restricted to anesthetized patients.

A problem in clinical application is the low specificity. This method only showed no fading in half of the patients, even after full neuromuscular recovery. (Samet, Capron *et al.* 2005)

Another limitation is the posttetanic fascilation, caused by transient augmented liberation of acetylcholine in the end plate and provoking an overestimation of neuromuscular recovery in repeated measurements. To avoid this, tetanic stimulation should not be used for continuous monitoring. (Fuchs-Buder 2008)

Furthermore, it is very painful for a wake patient. Thus, in every day clinical practice its application is very limited.

2.4.5 Post-Tetanic-Count (PTC)

Post tetanic count was developed by Viby-Mogensen *et al.* in 1981. (Viby-Mogensen, Howardy-Hansen *et al.* 1981) They used the fade-phenomenon described for tetanic stimulation for measuring profound blockade not detectable with TOF-stimulation. For the post-tetanic-count, a tetanic stimulus with 50 Hz is applied for 5 sec, followed by 10-20 single twitches. The number of detectable contractions is counted. Two cycles of PTC have to be separated by a 3 minute break to assure validity and not to overestimate neuromuscular recovery.

The theory behind this method is that high frequency stimulation of motor nerves mobilizes ACh from reserve pools to the immediate stores and enhances ACh synthesis. (Viby-Mogensen 2004)

PTC is superior to other stimulation patterns in situations when profound blockade e.g. of the diaphragm is necessary, both for intubation or intraoperative monitoring. (Ueda, Muteki *et al.* 1993) In this case, a PTC of 0 is to aim for. A PTC of 12-15 contractions correlates to the first response in TOF. (Werba, Klezl *et al.* 1993)

2.5 Muscles used for neuromuscular monitoring

Various muscle groups differ significantly regarding the intensity and the time-course of action of muscle relaxants. (Diefenbach 1999) Introducing curare to anesthesia in 1942, Griffith could dose the effect to paralyze abdominal and extremity muscles, while still enable the patients to breathe. (Griffith and Johnson 1942)

Different models for explaining the varying sensibility of muscles to relaxants were formulated, including differences in muscle perfusion, liberation of ACh and types of muscle fibers (fast twitch vs. slow twitch fibers). Also, the shorter distance for diffusion of the agent in smaller muscles was discussed to contribute. (Diefenbach 1999)

While neuromuscular monitoring, this fact attains clinically relevance, as it implies that measurements of one muscle cannot be directly interchanged to others.

2.5.1 M. adductor pollicis

In 1965, Ronald L. Katz established the usage of the adductor pollicis muscle as the standard method, as this muscle is the only adductor of the thumb innervated by the ulnar nerve. (Katz 1965) (Figure 8) Nowadays, the adductor pollicis muscle is still by far the most frequently used muscle in neuromuscular monitoring. The biggest advantage is the easy accessibility in the operation rooms setting.

Because of decades of research and experience, as well as the high sensibility in detecting residual blockade, the adductor pollicis muscle is still regarded as the first choice in the clinical routine of neuromuscular monitoring. (Diefenbach 1999)

2.5.2 Laryngeal muscles

In 1996, Plaud *et al.* compared the influence of mivacurium on the laryngeal muscles and the adductor pollicis muscle. In their study, the transcutaniously stimulated the recurrent laryngeal nerve. They positioned a cuff in the rima glottis and measured the pressure change caused by contraction of the vocal cord muscles. They found a prolonged time to response, a higher dose needed for full relaxation and an earlier recovery of the laryngeal muscles compared to the peripheral. (Plaud, Debaene *et al.* 1996)

2.5.3 M. geniohyoideus

The geniohyoid muscle is important for the inspiratory integrity of the upper airways. A study comparing it with the adductor pollicis muscle showed that its sensibility to muscle relaxants is nearly the same. (D'Honneur, Guignard *et al.* 1995) Compared with laryngeal muscles and the diaphragm, time to full recovery is prolonged for 15 minutes. Correspondingly, a TOF-R of 0.9 or less measured in peripheral muscles is associated with an impaired pharyngeal function and airway protection and thus a four- to fivefold increase in the incidence of aspiration. (Eriksson, Sundman *et al.* 1997)

The mechanism behind is a delayed initiation of the swallowing process and an impaired coordination of the pharyngeal muscular activity during partial neuromuscular block. Moreover, pharyngeal function and airway protection may be impaired, even if the adductor pollicis muscle has recovered to a TOF ratio of more than 0.90. (Sundman, Witt *et al.* 2000)

2.5.4 Diaphragm

For many operations, the influence of muscle relaxants on the diaphragm is of special interest, e.g. craniotomy or abdominal surgery. Un-

fortunately, today there is no routinely applicable method for monitoring this muscle. Hence, knowledge about the correlation of the diaphragm with muscles that are easier accessible to clinical evaluation is important.

In a study, Cantineau *et al.* could demonstrate that the dose-response-relationship of rocuronium is shifted to the right in the diaphragm compared to the adductor pollicis muscle. Both the ED_{50} as well as the ED_{95} were nearly twice for the diaphragm. The response time was shorter for 30-50 seconds; time to recovery was also relevantly shorter. Below twice the ED_{95}, response time was prolonged and neuromuscular blockade was decreased due to the high dosage demand of the diaphragm. (Cantineau, Porte *et al.* 1994)

2.5.5 M. flexor hallucis brevis

The idea of using the flexor hallucis brevis muscle for neuromuscular monitoring dates back to the early 1990s. The main advantages of this muscle are good accessibility and uncomplicated stimulation via the posterior tibial nerve. Response time is delayed for 1.2 minutes compared to the adductor pollicis muscle, recovery is proponed for approximated 3 minutes. Thus, clinically these muscles are comparable. (Kern, Johnson *et al.* 1997)

2.5.6 Vastus medialis muscle

The usage of the vastus medialis muscle was proposed in patients undergoing procedures in prone position, e.g. spinal surgery. It was shown to work with acceleromyography and phonomyography. (Saitoh, Nakajima *et al.* 2003; Michaud, Trager *et al.* 2005) The onset of neuromuscular blockade was faster, the maximum effect less pronounced and recovery more rapidly at the vastus medialis muscle compared to the adductor pollicis muscle.

2.5.7 M. orbicularis oculi

The M. orbicularis oculi is more resistant to neuromuscular blocking agents then the adductor pollicis muscle. The dose-response-curve is comparable to that of the diaphragm. (Donati, Meistelman *et al.* 1990) Response time is 40-70 sec. shorter than in the adductor pollicis muscle, while recovery occurs 10-15min earlier. Referring to this fact, some authors recommend to use the orbicualris oculi muscle for determine the ideal moment for intubation. Thus, intubation could be proponed up to one minute. However, monitoring this muscle for recovery could contrariwise increase the risk of residual neuromuscular block.

2.6 Phases of clinical muscle relaxation

2.6.1 Before induction

Before administration of NMBAs, the supramaximal current has to be determined. As this is sometimes described as painful, it should be done when the patient has already received analgesics and hypnotics, but no NMBA.

As discussed above, this time consuming procedure is only necessary in scientific environment. For daily practice, most often a current of convenience is chosen.

2.6.2 Induction

For induction of anesthesia a weight depending dose of a muscle relaxant is applied, commonly 1.5-2.5 times the ED_{95}. Adapting the dose individually would theoretically be possible, but in clinical practice the time to intubation would be unnecessarily prolonged and though the approach potentially dangerous.

On the other hand, neuromuscular monitoring offers the possibility to detect the first moment of full relaxation and therefore could be used to decide on the ideal moment for intubation. Particularly the orbicularis oculi muscle correlates well to the relaxation of the laryngeal muscles. (Plaud, Laffon *et al.* 1997; Sparr 2000)

Some studies however could not demonstrate a reduction of the time to intubation by neuromuscular monitoring. Accordingly, only a minority of clinical anesthetists uses neuromuscular monitoring in the phase if induction. (Fuchs-Buder, Hofmockel *et al.* 2003)

In some special situation, neuromuscular monitoring should be utilized anyway during induction. This includes neurosurgical patients with in-

creased intracranial compliance and patients with open eye injuries. In these cases, full relaxation of the diaphragm is necessary to avoid coughing and pressing while intubation. (Sparr 2000; Fuchs-Buder and Mencke 2001) In this context, Werba *et al*. demonstrated that a post tetanic count less than two correlates good to a full suppression of coughing while tracheal suction in sedated patients. (Werba, Klezl *et al.* 1993)

2.6.3 Maintenance of neuromuscular block

Neuromuscular monitoring during anesthesia allows maintenance of stable relaxation and is therefore enhancing surgical conditions. Sufficient relaxation for general surgery is normally defined as a T1% of 5-10%. (Katz 1971) This roughly correlates to the appearance of the 1st response in the TOF. The appearance of the 4th twitch is correlated with 25% T1, and is generally considered as insufficient neuromuscular block e.g. in abdominal surgery.

A TOF count of 0 measured on the adductor pollicis muscle is by no means the same as a complete paralysis, as different muscles, e.g. the diaphragm are differently affected by NMBA. In the case, that it is required that the patient is fully paralyzed, e.g. neurosurgical procedures or manipulation on the diaphragm, the PTC is indicated to monitor profound neuromuscular blockade. (Werba, Klezl *et al.* 1993)

2.6.4 Recovery

Monitoring und documenting full recovery plays a pivotal role in neuromuscular monitoring. For many years, a TOF-ratio of 0.6 was regarded as adequate recovery; both forced vital capacity (FVC) as well as forced expiratory volume in the 1st second (FEV_1) is in normal range in these patients.

In 1997 a multicenter study was conducted, demonstrating a correlation of a TOF ratio below 0.7 measured at the adductor pollicis muscle and a higher incidence of pulmonary complication including atelectasis and pneumonia. (Berg, Roed *et al.* 1997) In the year 1996 a TOF ratio of 0.8 was defined as adequate recovery by a consensus conference. (Viby-Mogensen, Engbaek *et al.* 1996)

In the following years studies demonstrated the influence of minimal residual blockade - defined as a TOF-R of 0.7-0.9 - on the upper airways, the hypoxic respiratory response, and the pharyngeal muscles. As a result of these studies, in the year 2007 the revised edition of the consensus paper recommended a TOF-ratio of 0.9 as save recovery. (Fuchs-Buder, Claudius *et al.* 2007) However, in a radiological study analyzing the movement of several pharyngeal anatomic structures Sundman *et al*. reported that even a TOF-R of 0.90 measured at the thumb may be associated with impaired pharyngeal function and airway protection. They could clearly demonstrate a significantly prolonged initiation of the pharyngeal stage of swallowing and a decreased tension of the upper esophageal sphincter. (Sundman, Witt *et al.* 2000) Therefore the "safety" of a TOF-R of 0.9 must not be overestimated.

Independent from the definition of residual blockade, studies showed that only a minority of patients are fully recovered at the time of extubation. Especially clinical evaluation is prone to misinterpretation and potential harmful false decision. Also, it was shown that the common practice of antagonizing residual blockade with neostigmine at a TOF response level of 2 twitches does not avoid residual block. (Murphy, Szokol *et al.* 2005).

In the year 2008 sugammadex, a selective relaxant binding agent (SRBA) for steroidal NMBAs, i.e. rocuronium, vecuronium and pancuronium, was approved by the European Medicine Agency (EMEA). (EMEA 2008) Thus, there is a target-orientet pharamacological approach to re-

duce the incidence of PORC. Generally, the usage of this substance is considered as safe and causes only minimally side effects. (Naguib 2007) However, establishing neuromuscular monitoring in daily routine clearly is a safer approach than reversal of muscle relaxantion.

2.6.5 Postoperative monitoring

Already in the year 1979 Viby-Mogensen *et al*. demonstrated, that approximately 40% of patients receiving neuromuscular blocking agents intraoperatively suffered from a postoperative residual paralysis (PORC) in the postoperative care unit (PACU). (Viby-Mogensen, Jorgensen *et al.* 1979) Data about this topic is rarely comparable due to different pharmacokinetics and –dynamics of substances used, resulting in different half-times; furthermore differences in length of operation, usage of antagonists, renal and hepatic function, and preexisting disease, i.e. myasthenia gravis influence the results and makes it more difficult to draw conclusions.

	TOF-Ratio		
	0.5	**0.8**	**1.0**
tidal volume	normal	normal	normal
forced vital capacity	frequently reduced	frequently normal	normal
pharyngeal function	definitely reduced	mostly reduced	mostly normal
integrity of the upper airway	definitely reduced	mostly reduced	mostly normal
Hypoxic response	frequently reduced	frequently normal	normal

Table 2: Quantification of clinical relevant effects of residual neuromuscular blockade defined by the TOF ratio at the adductor pollicis muscle.

Summary of study results of two working groups of Eikermann and Eriksson. (Eikermann, Groeben *et al.* 2003; Eikermann, Groeben *et al.* 2005; Eikermann, Blobner *et al.* 2006) (Eriksson 1996) (Eriksson, Sundman *et al.* 1997) Studies were carried out with healthy, awake patients during partial residual neuromuscular block. Modified from (Fuchs-Buder and Eikermann 2006)

However, even with modern NMBAs like rocuronium and atracurium, PORC is still an underestimated problem. In a prospective study, De-

baene *et al*. demonstrated that nearly half of the 526 patients receiving a single dose of a midlong-acting NMBA (rocuronium, vecuronium, or atracurium) had a residual paralysis on arriving in the PACU. 16% had a TOF-R below 0.6, corresponding to restricted ventilation. Even 2 hours after admission, 37% had a TOF-R below 0.9%. (Debaene, Plaud *et al.* 2003)

Clinical evaluation
Acceptable minute ventilation
Five-second hand grip
Maximum inspiratory force >30 cm H_20
Head lift >5 seconds
Head lift >10 seconds
Peripheral nerve stimulation
Visual/tactile assessment fade-single twitch
Visual/tactile assessment fade-tetanus (5 sec.)
Visual/tactile assessment fade-DBS
Quantitative monitoring-acceleromyography
Quantitative monitoring-electromyography
Quantitative monitoring-mechanomyography

Table 3: Different methods of measuring neuromuscular recovery

Ordered by increasing sensitivity. Cited to (Murphy 2006)

As clearly proven by these discouraging results, muscle relaxants are not that predictable as supposed. Clinical evaluation allows no conclusion on the neuromuscular recovery of a patient. If neuromuscular monitoring is not possible, the authors recommend routinely antagonizing the NMBA. (Debaene, Plaud *et al.* 2003)

3 Pneumatomyography

A monitor for assessing neuromuscular function should fulfill miscellaneous needs. It should be easy to use, light in order to minimize the required space in an often overcrowded operating room, versatile to allow movement of the patient even with the sensors attached, and most of all it should be reliable as it is the basis of potentially perilous decisions.

Even today, more than 50 years after the introduction of the first neuromuscular monitor, these needs are not satisfyingly fulfilled in a single device. Therefore, in our institution we developed a new method of monitoring the neuromuscular function called Pneumatomyography. (Dahaba and Bornemann 2008) It was designed to provide a solution for solving these problems.

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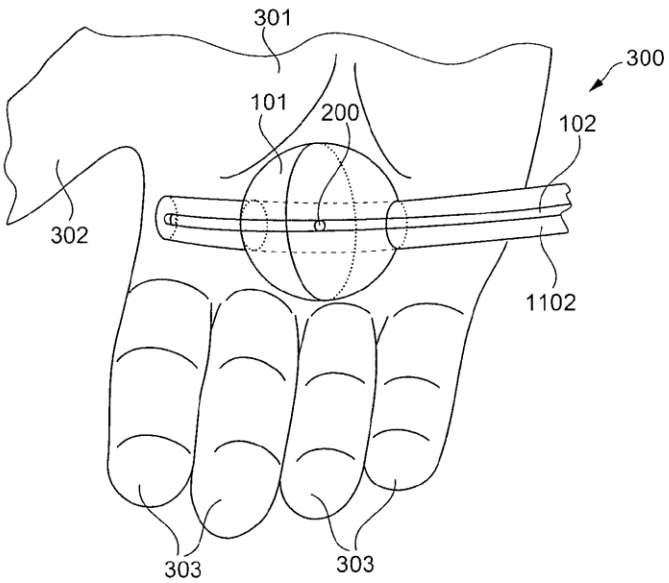
(54) **Title:** DEVICE FOR AND METHOD OF DETERMINING A MUSCLE ACTIVITY



(57) **Abstract:** A device (100) for determining a muscle activity of a physiological object, the device (100) comprising a pneumatic mechanism (101 to 105) adapted for pneumatically determining the muscle activity of the physiological object.

WO 2008/028572 A1

Figure 6: Frontpage of the application file

from (Dahaba and Bornemann 2008)

3.1 Assessing neuromuscular blockade

Depending on how neuromuscular function is detected, neuromuscular monitors are differentiated in two main groups: (Fuchs-Buder and Mencke 2001)

- Simple nerve stimulators are devices which are not able to quantify neuromuscular blockade, but allow "semi quantitative" estimation.
- Quantitative measurement delivers objective data.

Modern neuromuscular monitors are measuring the response objectively and display it. Today most of the available products have an internal memory allowing the use of patterns demanding a baseline value.

3.1.1 Clinical assessment

Clinical assessment of neuromuscular residual blockades is limited to the usage in awake and cooperative patients, and is therefore not an appropriate instrument for neuromuscular monitoring. Since Ali 1975 a head lift of 3 seconds is regarded as not to be accomplished by patients with a TOF-R less than 0.4, meeting the criteria of residual blockades at that time. (Ali, Wilson *et al.* 1975) As the definition of clinical important residual blockade was repeatedly increased, other studies found out, that a head lift of 5 seconds could be performed by all patients with a TOF-R > 0.8 (Engbaek, Ostergaard *et al.* 1989).

With increasing understanding of the crucial effect of even minimal paralysis on the pharyngeal and other small muscles, the clinical assessment of the strength of major muscle groups as an indicator of neuromuscular recovery cannot be recommended. (Sundman, Witt et al. 2000) (Table 2)

Clinical assessment was divided in reliable and unreliable signs for neuromuscular recovery. In a recent study Debaene *et al.* concluded that even reliable signs come into question despite their high specificity, since they have a low sensitivity. The authors recommend interpreting this signs only in combination with TOF-R. (Debaene, Plaud *et al.* 2003)

3.1.2 Visual and tactile assessment

Visual or tactile assessment is still a common way of monitoring evoked potentials. Unfortunately, this qualitative test is not appropriate for diagnosing neuromuscular recovery. Using TOF, it is possible to discriminate the strength of the forth *versus* the first twitch up to a ratio of 0.4. With DBS, the quality of assessment is slightly better, but with a TOF-R of 0.6 still not accurate enough. (Drenck, Ueda *et al.* 1989)

Qualitative test can be applied for assessing sufficiency of neuromuscular block intraoperatively. Furthermore, the time point for a reasonable administration of antagonists (e.g. neostigmine) can be detected. By no means, visual or tactile assessment can be used to exclude residual paralysis. (Fuchs-Buder and Eikermann 2006) Accordingly there is a broad consent to recommend the usage of objective neuromuscular monitoring whenever NMBA are administrated in a patient. (Viby-Mogensen 2000; Eriksson 2003; Viby-Mogensen 2004) (Table 3)

3.1.3 Mechanomyography

Mechanomyography is the longest established method for objective neuromuscular monitoring. Since many years it is regarded as the gold standard. (Viby-Mogensen, Engbaek *et al.* 1996) It is a direct measurement of isometric force, most often of the adductor pollicis muscle. The preload, which is necessary for the isometric contraction, should be set to 2-3 Newton. (Donlon, Savarese *et al.* 1979) *In praxi*, stabilizing the preload plays a pivotal role for the reliability of the measurement.

Though, the patients arm is fixed to a board, allowing the adduction of the thumb with a minimum of contraction. Every variation of the hands position resulting in a change of the preload alters the reliability of the results. The force of the muscle is quantified by a force transducer and digitally processed.

The main advantage of this method for neuromuscular monitoring is the direct measurement of force as the parameter of interest. The limitations in clinical use are the complex setup and the need of the rigid stabilization of the arm in order to ensure stable preload.

3.1.4 Electromyography

Electromyography was the first method described for neuromuscular monitoring. (Churchill-Davidson and Christie 1959) It records the compound action potential produced by skeletal muscles foregoing the muscle contraction. Two electrodes are placed over the muscle body and tendinous insertion, a third on a remote site. Most often this method is applied at the adductor pollicis muscle or the interosseus dorsalis I muscle. The main advantage however of this technique is that it facilitates monitoring of muscle not accessible to mechanical recording, e.g. muscles of respiration. Additionally, the versatility is an advantage as no preload has to be applied and no rigid fixation is necessary. Though, changes if the position might influence the field of projection of the compound potential and therefore could cause false data. (Viby-Mogensen 2004) Other sources of disturbance are high electric frequencies, which are common in some operating rooms. Even with modern filter techniques these signals are sometimes misinterpreted. (Diefenbach 1999)

The EMG was shown to correlate with the mechanomyograph. However, the results cannot be used interchangeably. (Engbaek, Ostergaard *et al.* 1989)

3.1.5 Acceleromyography

Acceleromyography was introduced in clinical use in anesthesia in 1988 by Viby-Mogensen. (Viby-Mogensen, Jensen *et al.* 1988) It was primarily developed as an easy-to-use method for detecting PORC.

Acceleromyography is based on the principle of Newtons second axiom (force=mass x acceleration). As the mass is constant, muscle force is proportional to acceleration, which can be quantified using a piezoelectric transducer. The piezo sensor is attached to the thumb, and the depolarization caused by the thumbs movement is proportional to the isotonic acceleration. Over the time, the system was optimized, e.g. the artifact detection was steadily improved by providing more sophisticated filter software. Today, many different versions of this technology are commercially available. Though, because of differences in the software, the results are not interchangeably.

Wrong measurements may also result from the thumbs movement being hindered, or the sensor not positioned correctly. It is recommended to fixate the hand in suppination to allow free movement of the thumb. (Viby-Mogensen, Jensen *et al.* 1988) The application of a preload, to be analogous to the MMG, was tested in different studies; however, there is insufficient evidence to recommend this. (Claudius and Viby-Mogensen 2008)

Acceleromyography is increasingly used in scientific environment; also it was never actually intended for research purposes and a recent systematic review clearly concludes that it cannot be interchangeably used with EMG or MMG. There is not enough evidence to support scientific use. (Claudius and Viby-Mogensen 2008) Values of the acceleromyograph simultaneously measured to 25% TOF-R in the MMG differ between 3 and 69%. (Loan, Paxton *et al.* 1995; Dahaba, Rehak *et al.* 1997) Furhtermore, acceleromyographic devices are highly prone to errors resulting from movements (Fuchs-Buder, Claudius *et al.* 2007), in-

cluding those caused inadvertently by the surgeon or other operating room personnel. (Dubois, Gourdin *et al.* 2005; Fuchs-Buder, Claudius *et al.* 2007)

However, for daily use in clinical practice it is a sufficiently reliable and easy to use method for assessing neuromuscular blockade. (Claudius and Viby-Mogensen 2008)

3.1.6 Kinemyography

Kinemyography is based on the principle of piezo electricity. By bending a piezo strip between thumb and index finger, an electric potential is generated. As this is proportional to the force applied, it can be used as a measurand. Its popularity increased within the last years, as a commercial version of this technology is available as build-in module for the Datex-Ohmed anesthesia monitors.

It is mainly characterized by its easy usability; though, the hand needs to be properly positioned. Studies about the accuracy of data comparing it with mechanomyograhy lead to different conclusions. (Dahaba, von Klobucar *et al.* 2002; Motamed, Kirov *et al.* 2003)

3.1.7 Phonomyography

In 1999, Dascalu *et al*. reported on a novel method for neuromuscular monitoring called MIC. They applied a microphone on the tenar muscles while stimulating the ulnar nerve. They detected low frequencies emitted by the contraction of the muscle, i.e. the movement of tissue layers. In their study, MIC correlated to mechano-, accelero-, and electromyography. (Dascalu, Geller *et al.* 1999)

Hemmerling *et al*. developed the idea further. In 2003 they published a method for monitoring acoustic responses of the vocal cords after superficial stimulation of the recurrent laryngeal nerve. They positioned

the microphone both in the larynx and on the skin, with diverging results. (Hemmerling, Michaud *et al.* 2004; Hemmerling, Michaud *et al.* 2005)

3.2 Description of Pneumatomyography

The new PMG neuromuscular transmission monitor consists of a nerve stimulator unit, a pressure transducer connected to a balloon, a pressure-monitoring unit, and a data processing unit. (Dahaba and Bornemann 2008) The balloon (placed between two anatomically shaped plastic strips in the patient's hand and held by a fastener strap) is inflated with air using a syringe, giving an overpressure of 20 mbar monitored via a manometer attached to the 3-way connector valve.

The patient's fingers do not directly touch the balloon, but rather touch the 2 plastic strips that are, in turn, uniformly in contact with the balloon. (Figure 7) This ensures a uniform deformation of the spherical balloon with each hand contraction. In our *in-vivo* studies removing the balloon after measurement and placing it again in the patient's hand for repeated measurement yielded near identical responses. The stability in these results may imply robustness for changes in the hands position.

The PMG measures pressure changes generated from the hand contraction in response to electric stimulation of the ulnar nerve at the wrist, mainly resulting from the adductor pollicis muscle's powerful adduction of the thumb as it opposes the rest of the digits in gripping movement. The flexor digiti minimi brevis and opponens digiti minimi hypothener muscles flex the little finger and oppose it to the thumb. The medial two lumbricals flex the metacarpo-phalangeal joints of the little and ring fingers. In addition, the palmaris brevis muscle contraction tightens the handgrip as a whole. (Figure 8)

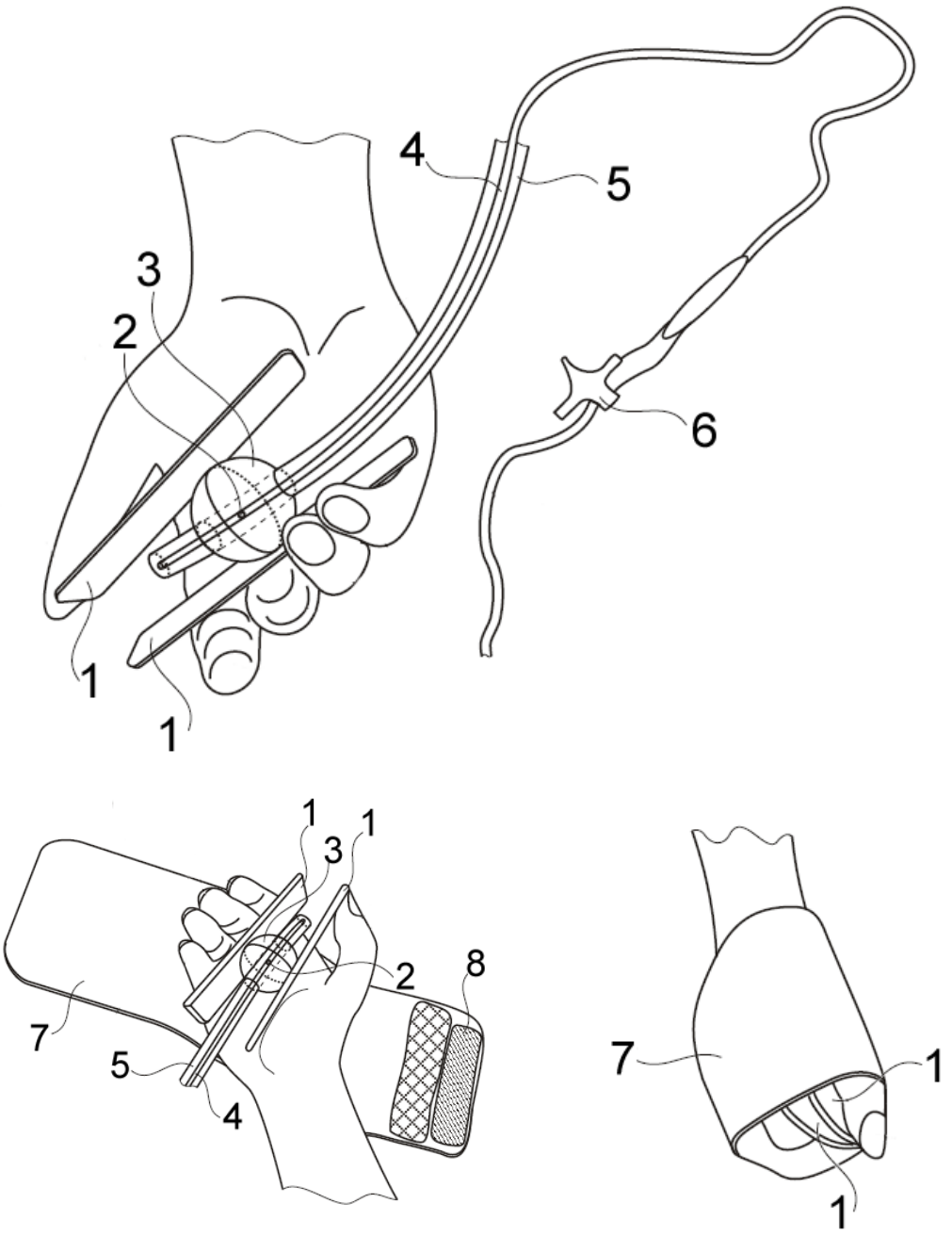


Figure 7: Schematic illustration of the PMG system

The PMG quantifies the pressure changes in a hand-held balloon as a measure of the force created by the hand contraction.

The PMG system (top), the hand strap (left) and the closed fastener strap (right).

1: two plastic strips; 2: aperture for air delivery to the balloon; 3: balloon; 4: inner tubing for air delivery to the balloon; 5: outer rigid tubing to hold the balloon in place; 6: three-way valve connector for air delivery to the balloon 7: hand strap; 8: hook and loop fastener strap.

Modified from (Dahaba and Bornemann 2008)

The PMG measures pressure changes generated from the hand contraction in response to electric stimulation of the ulnar nerve at the wrist, mainly resulting from the adductor pollicis muscle's powerful adduction of the thumb as it opposes the rest of the digits in gripping movement. The flexor digiti minimi brevis and opponens digiti minimi hypothener muscles flex the little finger and oppose it to the thumb. The medial two lumbricals flex the metacarpophalangeal joints of the forth and the fifth fingers. In addition, the palmaris brevis muscle contraction tightens the handgrip as a whole. (Figure 8)

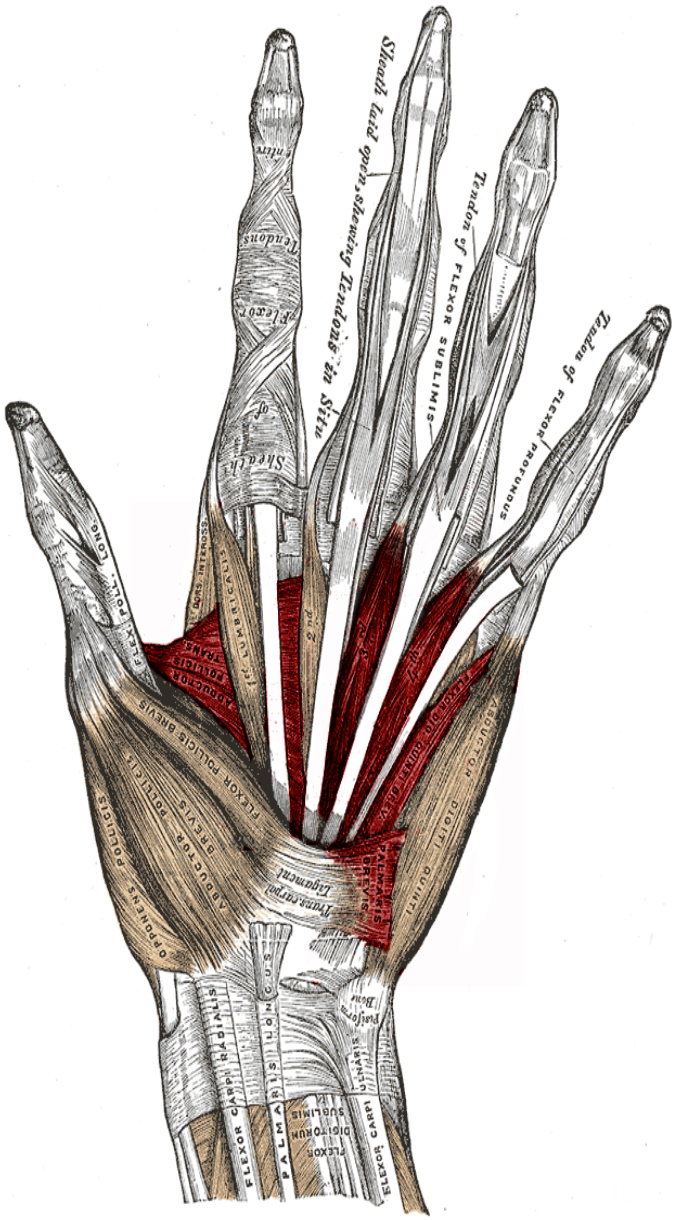


Figure 8: The muscles of the hand

Muscles innervated by the ulnar nerve are colorized in dark red

Modified from Gray's Anatomy (Gray and Lewis 1918)

The pressure change in the balloon is detected by a standard strain-gauge pressure transducer (KPY63 AK sensor, sensor signal: 25-250

mV, pressure range 0-1.6 bar, R≈5kΩ, 50-150 μV·mbar^{-1} at U=5V). The pressure change deforms a small membrane in the pressure transducer causing a change in the membrane resistance, as a result of its deformation, which is measured by using a Wheatstone bridge configuration (four resistors integrated using lithography) (Figure 9). The transducer output is a voltage signal proportional to the pressure change, which is then amplified to a signal in the voltage range. This signal is filtered through a low pass filter with a cut off frequency of 20 Hz.

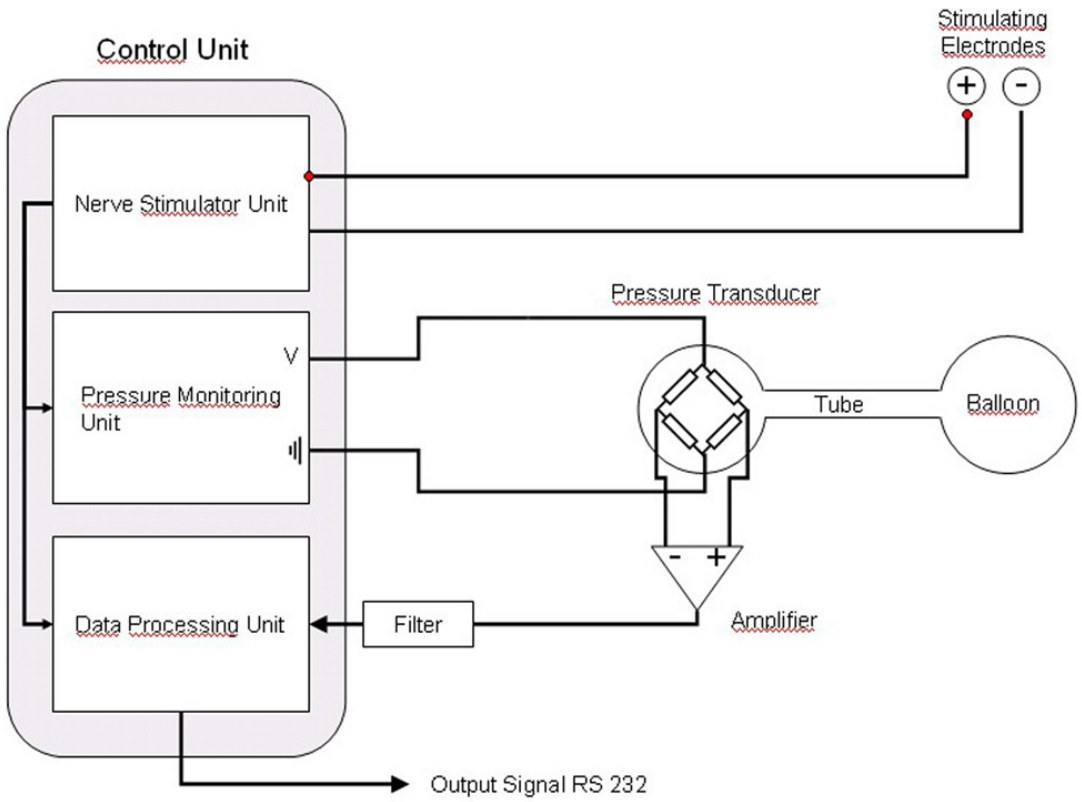


Figure 9: PMG architecture and hardware connections

Modified from (Dahaba and Bornemann 2008)

For calibration, the pressure response to the supramaximal current is set to 100% as a benchmark for all following stimulations. This approach is similar to the procedure used in the MMG where the corres-

ponding force is set to 100%. The final signal is displayed and recorded using a RS 232 interface connecting the monitoring unit to a lap top computer (Figure 12).

The maximum pressure change in the balloon is 0.5 mbar. Because the balloon is made of thin flexible latex, quite similar to the texture of the cuff of a tracheal tube, it gave a linear response to an ascending sequence of externally applied pressures in our preliminary testing of the balloon. Our *in vivo* studies showed a similar linear response to ascending forces created by the hand contraction (Figure 10).

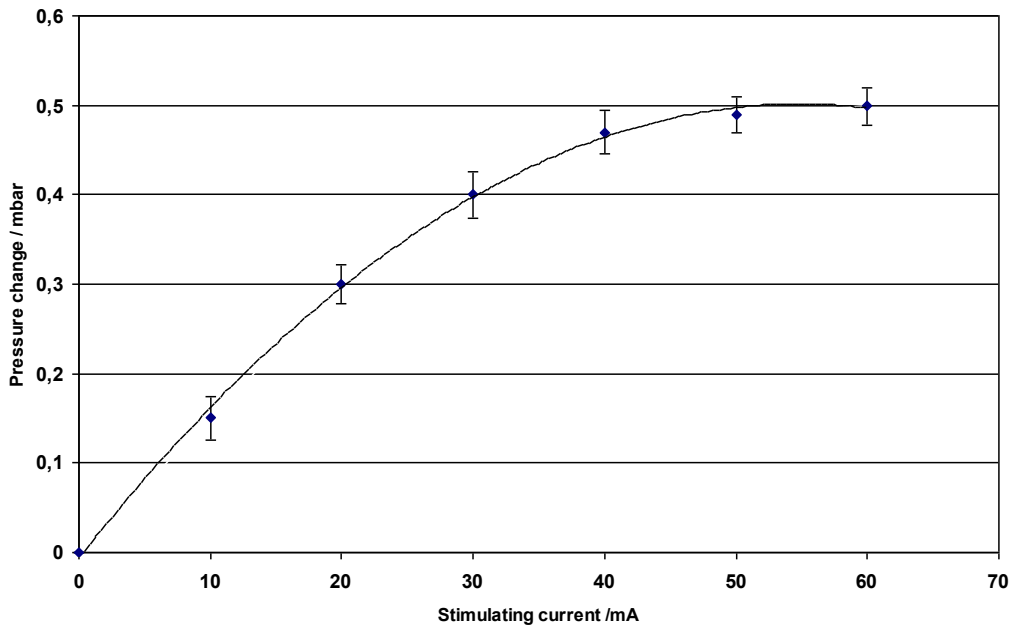


Figure 10: In-vivo calibration of the PMG.

The change of the pressure applied by awake, unmedicated subjects was measured as a function of the stimulation current. The results showed a sigmoid progress.

Since pressure is defined as force per area ($p=F \cdot A^{-1}$), thus as long as the area over which the force of the contracting hand is applied remains constant (balloon's contact area with the 2 plastic strips), pressure change in the balloon will be directly proportional to the force. Simple

geometrical calculations showed that this condition is fulfilled for small pressure changes where the deformation of the balloon is small relative to its total volume. MMG measurements provided the clinically relevant muscle force range. In our present design the relative volume change of the balloon is less than 3% for the clinically relevant range of nerve stimulations up to 60 mA.

3.3 Comparing the PMG with the MMG

The MMG is regarded as the gold standard in the field of neuromuscular monitoring. Thus, after building a prototype of the PMG, we conducted a study comparing the PMG with the MMG.

3.3.1 Patients and methods

A prospective, consecutive, randomized, cross-over-study was conducted in accordance with the 2005 Stockholm revision of the guidelines of the "Good Clinical Research Practice (GCRP) in Pharmacodynamic Studies of Neuromuscular Blocking Agents II" (Fuchs-Buder, Claudius *et al.* 2007) and "Standards for Reporting of Diagnostic Accuracy" (STARD) criteria. (Bossuyt, Reitsma *et al.* 2003)

After ethics committee approval (study registration number at Medical University of Graz: 17-190 ex 05/06), all patients who agreed to participate in the study gave written informed consent. (Figure 11) Inclusion and exclusion criteria were formulated according to the revised version of "Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents". (Fuchs-Buder, Claudius *et al.* 2007) (Table 4)

Inclusion Criteria	**Exclusion Criteria**
ASA I-II	history of neuromuscular disease
18-60 years	small joint arthritis
elective operation	treatment with drugs interfering with neuromuscular transmission
supine position	
duration of surgical procedure approximately 1 h	

Table 4: Inclusion and exclusion criteria

For premedication, 7.5 mg midazolam p. o. was administered one hour preoperatively. Anesthesia was induced with propofol 2-3 $mg \cdot kg^{-1}$ and fentanyl 1.5 $\mu g \cdot kg^{-1}$ until the eyelash reflex was obtunded. A ProSeal

Laryngeal Mask Airway was inserted and after capnographic confirmation of correct positioning, the lungs were ventilated mechanically with 40% oxygen in air. Ventilation was adjusted to maintain 30-40 mm Hg end-tidal carbon dioxide.

Anesthesia was maintained with propofol 100-150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and remifentanil 0.1-0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusions. Patients were warmed using a forced-hot-air-blanket to maintain core temperature above 35°C and skin temperature above 32°C. (Fuchs-Buder, Claudius *et al.* 2007)

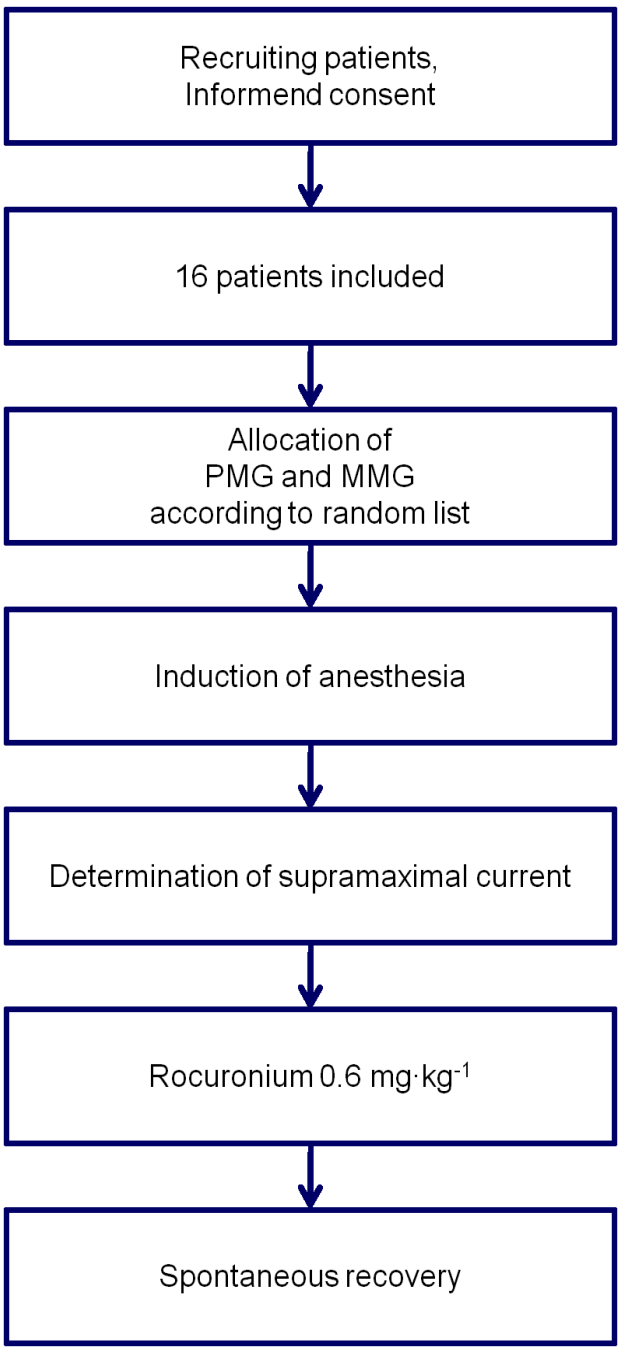


Figure 11: Study flow

Schematic diagram of the study flow

Both arms were comfortably positioned on arm boards. To level out the effect of dominance of one hand, the two monitors were randomly allocated to the left or right hands according to a computer-generated scheme. The force transducer of the Relaxometer was attached to one hand, and the preload on the thumb was maintained within 200-400 g throughout the whole procedure according to the manufacturer's instructions. (Rowaan,

Vandenbrom *et al.* 1993) The PMG balloon was placed between the 2 small plastic strips in the other hand and held by the specially designed "hook and pile Velcro®" fastener strap for simultaneous monitoring. The balloon was then inflated with 20 ml air. The stimulating electrodes were silver/silver chloride surface electrodes placed 4 cm apart on the ulnar nerve at the wrist. (Fuchs-Buder, Claudius *et al.* 2007)

In response to evoked stimulation of the ulnar nerve, the pressure changes in the air-filled balloon generated a voltage potential across the pressure transducer that is directly proportional to the force created by the hand contraction. In an ascending sequence of electric stimulations starting from 10 mA, supramaximal currents were determined as the stimulation intensity +20% higher than the current that produced maximal response in the MMG (force) and PMG (pressure). (Fuchs-Buder, Claudius *et al.* 2007)

After supramaximal current determination by both monitors, the ulnar nerves were stimulated by train-of-four (TOF) stimuli (2-Hz, pulse width 200 μs, square wave for 2 s) at 12-s intervals. T_1, first twitch of the TOF expressed as percentage of control response and the TOF ratio (T_4: T_1) were used for evaluating the neuromuscular block.

The MMG and PMG data were simultaneously collected and stored on a lap top computer using the "AZG-Relaxometer 5.0 program" and the "PMG data collection software". (Figure 12) After stable control responses (variation ≤5% T_1 for the last 2 min), (Fuchs-Buder, Claudius *et al.* 2007) rocuronium 0.6 mg·kg^{-1} (twice the 95% effective dose, ED_{95}) was administered and patients were allowed to recover spontaneously from the neuromuscular block until a stable recovery signal occurred, defined as TOF ratio of ≥0.9 with response variation ≤5% for 2 min.

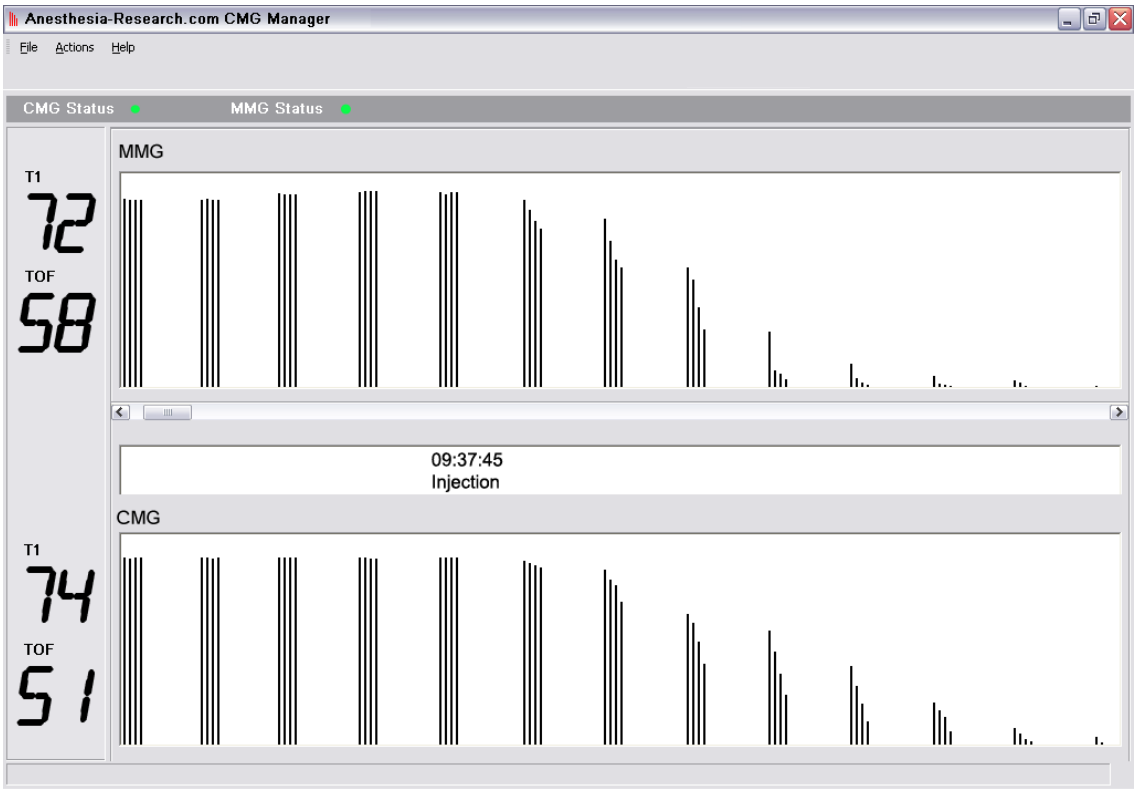


Figure 12: PMG Manager

The newly developed software allows parallel recording of MMG (top) and PMG data (bottom).

(Fuchs-Buder, Claudius *et al.* 2007) Lag and onset times (time from start of rocuronium administration until the first measurable and maximal neuromuscular blocks), Dur_{25} and $Dur_{0.9}$ (time from start of rocuronium administration until T_1 25% and 0.9 TOF ratio recoveries), Dur_{25-75} and $Dur_{25-0.9}$ (time from 25% T_1 to 75% T_1 and 0.9 TOF ratio

recoveries) time-course-of-action variables were calculated. (Fuchs-Buder, Claudius *et al.* 2007) (Figure 13)

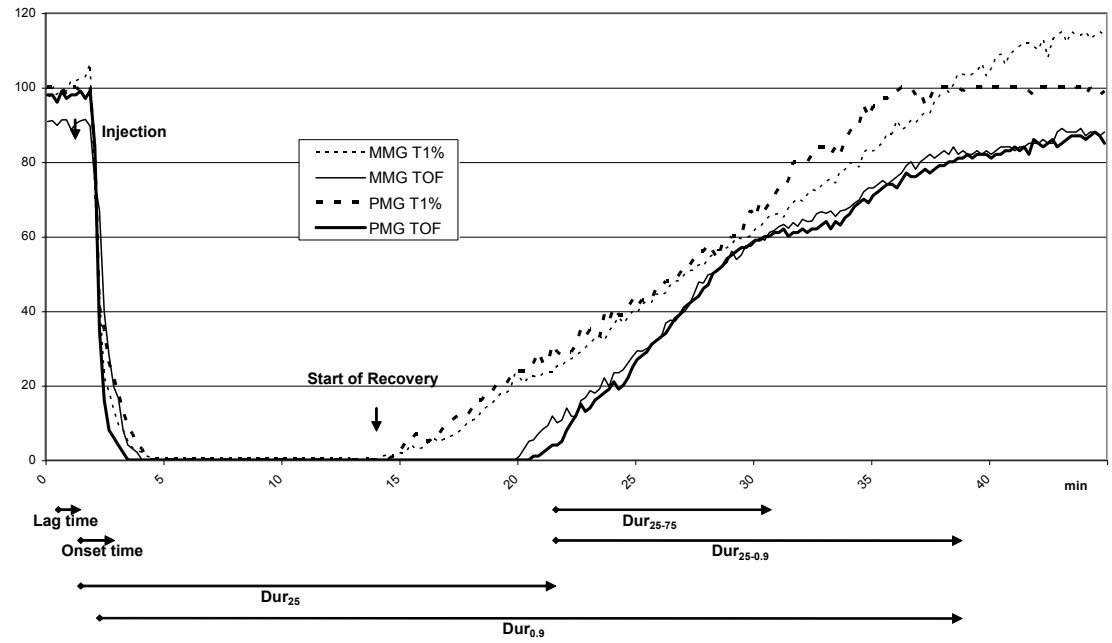


Figure 13: Time course of muscle relaxation

Mean T1% and TOF-R measured by pneumatomyography (PMG) and mechanomyography (MMG) during muscle relaxation with rocuronium in 6 patients.

3.3.2 Statistical analysis

Because the PMG monitor was newly developed in our centre, no preexisting data on PMG monitoring to enable an *a-priori* sample size calculation was available. Thus our *a priori* power analysis was based upon a previous study in which Dur_{25} using the MMG was 20.2 (6.3) min compared to 25.6 (8.0) min using the M-NMT. (Dahaba, von Klobucar *et al.* 2002) Our power analysis (α=0.05) showed that a sample size of 9 patients would be required to reveal a statistically significant difference between the two monitors with >90% power. The sample size was increased by >50% to 16 patients in a preliminary study. Student's *t*-test was used to compare the differences in the time-course-of-action variables. Data were expressed as mean ± SD. Significance level was set to 0.05.

To assess the sensitivity, specificity and positive/negative predictive values (PPV/NPV) of the PMG, we used three clinically relevant endpoints, namely MMG T_1 5% at induction for tracheal intubation, (Fuchs-Buder, Claudius *et al.* 2007) MMG T_1 25% recovery for repeat neuromuscular blocking agents administration, and MMG 0.9 TOF ratio for full recovery from neuromuscular block. (Fuchs-Buder, Claudius *et al.* 2007)

Data collected during recovery from neuromuscular block were further analyzed using the statistical method for comparing two diagnostic devices described by Bland and Altman. (Bland and Altman 1986) Although mechanomyography might be regarded as the standard method for quantification of neuromuscular block (Fuchs-Buder, Claudius *et al.* 2007) still Bland and Altman analysis considers both techniques subject to experimental error. The limits of agreement are defined as the bias $\pm$1.96 SD in which 95% of the differences between the two monitors are expected to lie. (Bland and Altman 1986)

Statistical analysis was performed using NCSS. (Hintze 2007)

3.3.3 Results

Sixteen patients were recruited for the study. No dropout has to be reported. Therefore, no differentiation for intention-to-treat and per-protocol analysis has to be made. The age ranged between 18 and 59 years with 18.5-24.9 body mass index. All patients were grade I-II in the American Society of Anesthesiologists (ASA) classification. The patients' characteristics are presented in Table 5.

Age (yr)	44.9 (30.3-58.4)
Weight (kg)	65 ± 8
Height (cm)	173 ± 13
Male/Female	11/5

Table 5: Patients' characteristics
Means ± SD, or Median (range)

MMG preload was kept constant during the whole measurement (range 244-367 g). There was no significant difference in the stimulating currents of the 2 monitors. Following the stabilization period (3.9 ± 0.5) min] before rocuronium administration, mean MMG T1 exceeded 100% (104.14 ± 1.95), whereas mean PMG T1 did not (98.5 ± 0.8). The mean pre-relaxation TOF ratios of neither the MMG nor the PMG did exceed 1.0 (0.97 ± 0.01 *vs*. 0.98 ± 0.01).

Following rocuronium administration, T1% and TOF ratios of both monitors started simultaneously to decrease. Full neuromuscular block was reached in all patients independent of the monitoring technique. All recovery T1 indices were not "normalized" 1 as they were determined in relation to T1 control baseline and not T1 at full recovery. There were no significant differences in the two monitors' time-course-of-action parameters (Table 6).

	MMG	PMG	Bias	Limits of agreement	
				Upper	Lower
Lag time	0.9 ± 0.4	1.0 ±0.4	-0.1 ± 0.2	0.25	-0.45
Onset time	2.1 ± 0.9	2.4 ±0.9	-0.3 ±0.2	0.09	-0.69
Dur_{25}	22.9 ± 3.3	22.6 ± 4.1	0.3 ± 1.9	4.02	-3.42
Dur_{25-75}	8.8 ± 3.5	8.2 ± 3.4	0.6 ± 0.9	2.36	-1.16
$Dur_{25-0.9}$	20.4 ± 8.7	20.5 ± 9.0	-0.1 ± 2.4	4.53	-4.70
$Dur_{0.9}$	43.3 ± 10.0	43.1 ± 10.3	0.2 ± 1.3	2.79	-2.45

Table 6: Rocuronium time-course-of-action variables (min)

Mean (SD), MMG = Mechanomyograph, PMG = Pneumatomyograph, Bias = difference between the two monitors, Limits of agreement = bias ± 1.96xSD, lag time = time from start of rocuronium administration until first measurable effect of neuromuscular block, onset time = time from start of rocuronium administration until maximum suppression of first response of train-of-four (T_1), Dur_{25} = time from start of rocuronium administration until 25% T_1 recovery, $Dur_{25–75}$ = time from 25% to 75% T_1 recovery, $Dur_{0.9}$ = time from start of rocuronium administration until 0.9 train-of-four ratio recovery, $Dur_{25–0.9}$ = time from 25% T_1 to 0.9 train-of-four ratio recovery. There was no significant differences ($p > 0.05$) between the 2 monitors in lag time, onset time, Dur_{25}, $Dur_{25–75}$, $Dur_{0.9}$ and $Dur_{25–0.9}$.

Our study demonstrated that the PMG showed high sensitivity and specificity in indicating time for tracheal intubation, rocuronium re-injection and full recovery from neuromuscular block (Table 7).

	Sensitivity	Specificity	PPV	NPV	PMG
MMG at 5% T_1 induction	100%	75%	67%	100%	13.9% ± 6.3
MMG at 25% T_1 recovery	88%	75%	88%	75%	26.9% ± 6.8
MMG at 0.9 TOF ratio recovery	80%	86%	80%	86%	0.92 ± 0.05

Table 7: Pneumatomyograph sensitivity, specificity, positive and negative predictive values.

Mean (SD), MMG = Mechanomyograph, PMG = Pneumatomyograph, PPV = positive predictive value, NPV = negative predictive value, T_1 = first response of train-of-four, TOF = train-of-four. MMG TOF ratio was 0.891 (0.048) at PMG 0.9 TOF ratio recovery.

According to Bland and Altman analysis, during recovery from neuro-muscular block, T1 bias was –0.3% (Figure 15), and TOF ratio bias was –0.01 (Figure 14). The T1% and TOF ratio regression plots showed a linear relationship between the two monitors (Figure 17, Figure 16).

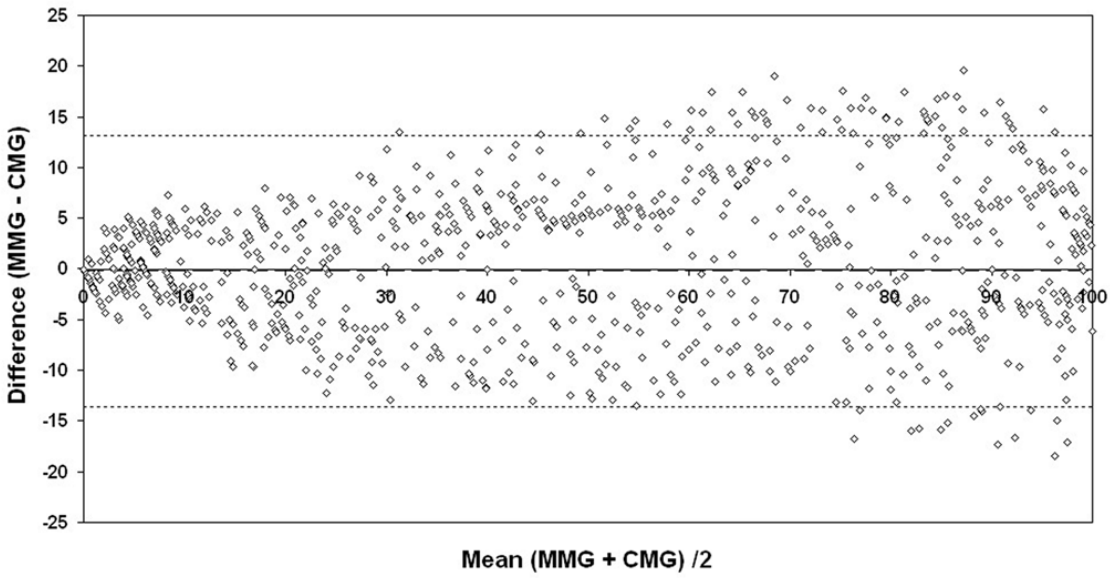


Figure 15: Bland and Altman diagram of T1%

Bland and Altman scatter plot of the difference between the first twitch (T1%) of the MMG and the pneumatomyograph PMG against the mean of the two measurements, during recovery from neuromuscular block.

The dotted lines represent the bias and the limits of agreement.

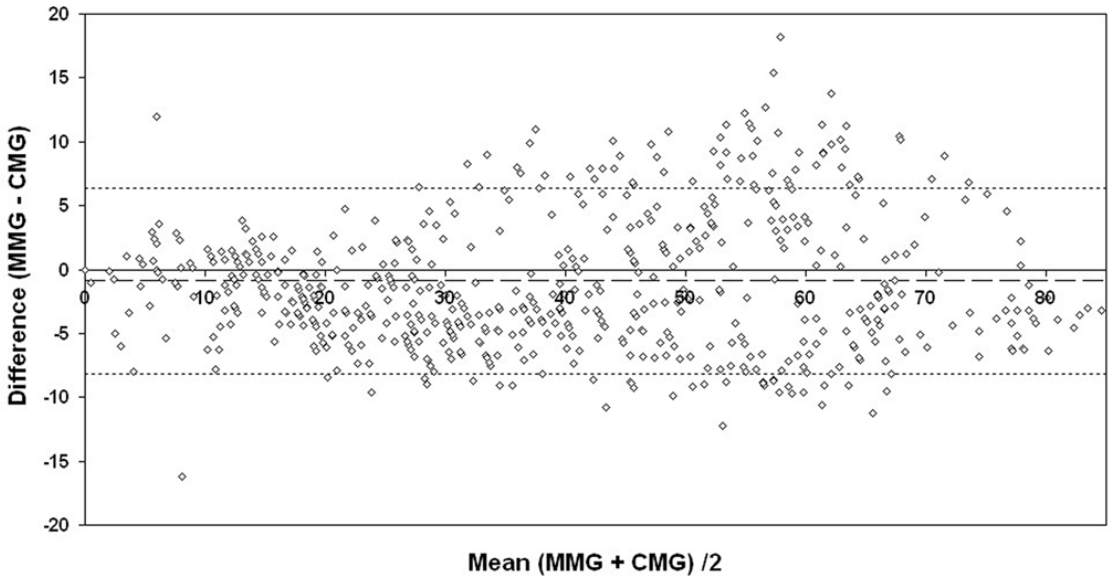


Figure 14: Bland and Altman diagram of TOF percentage

Bland and Altman scatter plot of the difference between the TOF percentage of the MMG and the PMG against the mean of the two measurements, during recovery from neuromuscular block.

The dotted lines represent the bias and the limits of agreement.

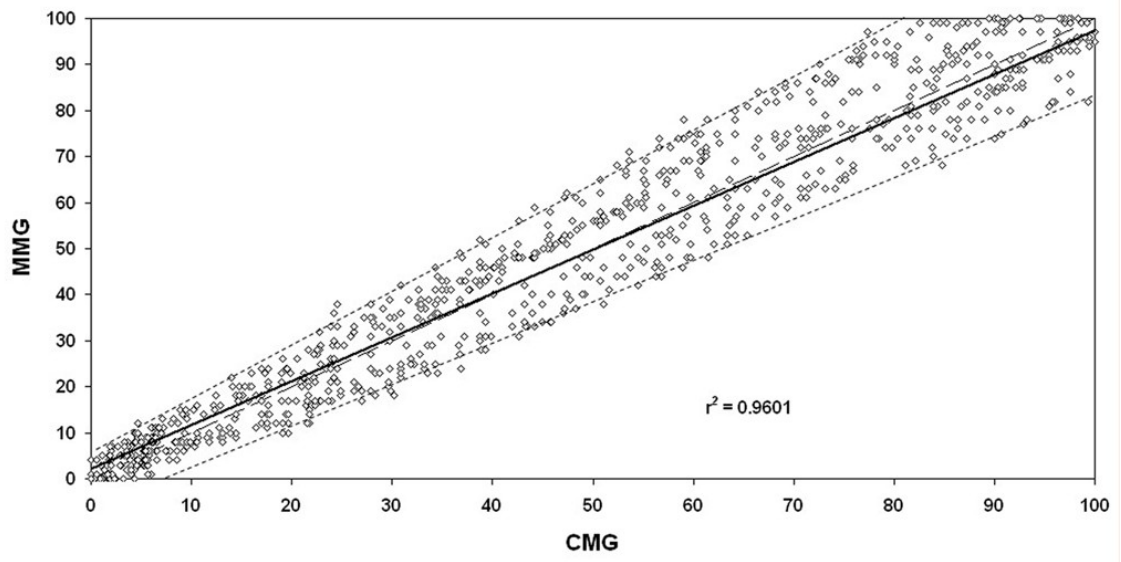


Figure 17: Regression plot of T1%

Regression plot of the first twitch (T1%) of MMG against PMG during recovery from neuromuscular block

The continuous line represents the correlation, dotted lines the 95% confidence interval.

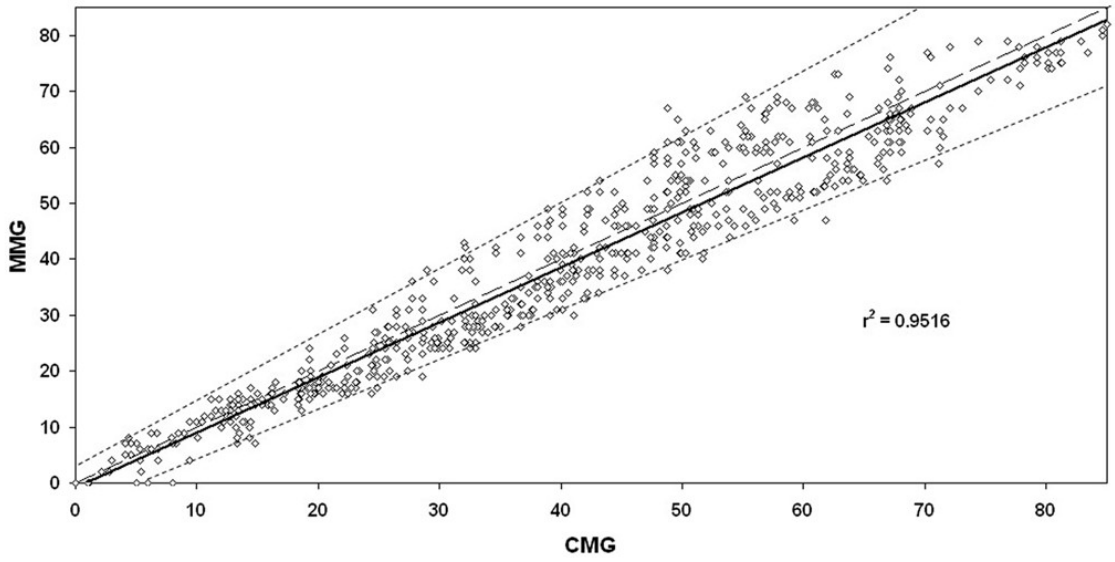


Figure 16: Regression plot of TOF percentage

Regression plot of the TOF percentage of MMG against PMG during recovery from neuromuscular block

The continuous line represents the correlation, dotted lines the 95% confidence interval.

After full recovery from neuromuscular block, mean MMG T1 exceeded 100%, whereas PMG T1 did not (112.2 ± 5.1 *vs.* 97.6 ± 1.3).

3.4 Discussion of the PMG

With our prototype there were no significant differences between the PMG and MMG regarding the time-course-of-action parameters. Compared to MMG, we demonstrated that the upper and lower limits of agreement of PMG Dur_{25} (3.9 and -3.4 min), and Dur_{25-75} (2.4 and 1.1 min) were considerably narrower than the TOF-Guard Dur_{25} (8 and 5 min) and Dur_{25-75} (11 and –7 min). (Loan, Paxton *et al.* 1995)

During the stabilization period before rocuronium administration, PMG did not exhibit the phenomenon of pre-relaxation "reverse fade" in which T4 exceeds T1, nor did the PMG T1 exceed 100%. The "reverse fade" phenomenon was previously reported with the kinemyographic ParaGraph (Dahaba, Von Klobucar *et al.* 1999), with the acceleromyographic TOF-Guard (Loan, Paxton *et al.* 1995), as well as several earlier models such as the Acceleration transducer (Viby-Mogensen, Jensen *et al.* 1988), or the Mini-Accelograph (Biometer, Copenhagen Denmark) (Harper, Martlew *et al.* 1994), as the TOF ratio was constantly >1.0 before NMBA administration.

Pre-relaxation reverse fade could be attributed to the fact that, despite the period of stabilization before NMBA administration, the non-relaxed free-moving thumb of the above-mentioned monitors (Viby-Mogensen, Jensen *et al.* 1988; Harper, Martlew *et al.* 1994; Loan, Paxton *et al.* 1995; Dahaba, Von Klobucar *et al.* 1999) might not necessarily always return to exactly the same position after each stimulus. (Loan, Paxton *et al.* 1995) Originally, unrestricted movement of the thumb was considered a prerequisite for the use of acceleromyographic monitors. The Copenhagen GCRP Conference lately acknowledged the fact that acceleromyographic devices are highly prone to errors resulting from movements (Fuchs-Buder, Claudius *et al.* 2007), including those caused inadvertently by the surgeon or other operating room personnel. (Dubois, Gourdin *et al.* 2005; Fuchs-Buder, Claudius *et al.* 2007) On the other

hand, the "contained" PMG hand movement might explain the lack of pre-relaxation "reverse fade", as the PMG fastener strap freely allows the hand contraction during evoked stimulation while at the same time restricting the hand from sliding off the original position over the time. Furthermore, this "contained" design provides greater flexibility and freedom in positioning of the patient's measuring hand without disturbing neuromuscular monitoring, which is often an operating room requirement, as for many surgical procedures the patient has to be repositioned after induction.

We demonstrated that, compared to MMG, the upper and lower limits of agreement of PMG TOF ratio (0.06 and -0.08) are considerably narrower than those of the Mini-accelerograph (0.30 and -0.30) (Harper, Martlew *et al.* 1994) or the kinemyographic M-NMT (0.22 and -0.28), (Dahaba, von Klobucar *et al.* 2002) compared to MMG in previous studies. This probably indicates that the discrepancies between the above-mentioned monitors (Harper, Martlew *et al.* 1994; Dahaba, von Klobucar *et al.* 2002) and MMG are largely due to an inherent difference in their fundamental fade characteristics, which might not be the case with PMG.

One of the main objectives of neuromuscular monitoring is the detection of residual paralysis. Our study demonstrates that, in addition to the PMG reliably indicating the time for tracheal intubation with 100% sensitivity and 75% specificity, the PMG could indicate MMG 0.9 TOF ratio full recovery with 80% sensitivity and 86% specificity (Table 7). This could be attributed to the fact that the two monitors quantify the neuromuscular function based upon two equivalent principles, namely the force transducer of the MMG detecting the force displacement of the thumb and the pressure transducer of the PMG detecting the force created by the hand contraction.

Appropriate monitoring devices for the precise detection of residual paralysis in the clinical setting are still lacking as the "drift" phenomenon, in which T1 recovery deviates above the 100% control value, was reported with the kinemyographic ParaGraph (Dahaba, Von Klobucar *et al.* 1999) and M-NMT (Dahaba, von Klobucar *et al.* 2002) monitors, as well as the acceleromyographic TOF-Watch (Capron, Alla *et al.* 2004) and Mini-Accelerograph (Harper, Martlew *et al.* 1994) monitors. This was lately acknowledged by the Copenhagen GCRP Conference (Fuchs-Buder, Claudius *et al.* 2007) for the TOF-Watch and TOF-Watch–S monitors that do not display the actual erroneous "drift" readings. (Capron, Alla *et al.* 2004; Fuchs-Buder, Claudius *et al.* 2007) Recovery T1% drift, in which T1 recovery deviates above the 100% control value was suggested to be a sequence of the reverse fade manifested in the pre-relaxation stabilization period. (Loan, Paxton *et al.* 1995)

In our study, MMG was prone to reverse fade in the pre-relaxation stabilization period and consequently manifested recovery T1% drift. On the other hand, T1% of PMG recovered to baseline value and was not prone to "drift". The design of the PMG seems to evade the phenomenon of pre-relaxation reverse fade at induction and consequently the drift phenomenon at recovery. Thus, in a clinically relevant context the PMG could reliably detect residual paralysis.

In conclusion, the PMG could be a reliable clinical monitor in the daily anesthesia practice that does not require time to set up or rigid support of the arm. The PMG could detect the time for tracheal intubation, repeated dose administration and full recovery from neuromuscular block as indicated by MMG.

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Index of Abbreviations

ACh	acetylcholine
AChEase	acetylcholine esterase
ASA	American Society of Anesthesiologists Physical Status Classification
DBS	double burst stimulation
$Dur_{0.9}$	time from NMBA until 0.9 TOF-R recovery
Dur_{25}	time from NMBA until 25 T1% recovery
$Dur_{25-0.9}$	time from 25 T1% recovery until 0.9 TOF-R recovery
Dur_{25-75}	time from 25 T1% recovery until 75 T1% recovery
ED_{50}	effective dose, 50%
ED_{95}	effective dose, 95%
EMEA	European Medicines Agency
EPC	end plate current
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCRP	good clinical research practice
MEPP	miniature endplate potential
MMG	mechanomyography
NMBA	neuromuscular blocking agent
NMJ	neuromuscular junction
NPV	negative predictive value

PACU	post anesthesia care unit
PMG	Pneumatomyography
PORC	postoperative residual curarization
PPV	Positive predictive value
PTC	post titanic count
SRBA	selective relaxant binding agent
STARD	standards of reporting of diagnostic accuracy
T1	1^{st} twitch of a train of four
T1%	Percentage of 1^{st} twitch compared to baseline values
T4	4^{th} twitch of a train of four
TOF	train of four
TOF-R	train of four ratio

Statement of previous publications

Parts of this work were previously published

(Dahaba and Bornemann 2008; Dahaba, Bornemann *et al.* 2008; Bornemann-Cimenti and Dahaba 2009)

"*Comparison of a new neuromuscular transmission monitor compressomyograph with mechanomyograph*."

Dahaba AA, Bornemann H, Holst B, Wilfinger G, Metzler H.

Br J Anaesth. 2008 Mar;100(3):344-50.

"*Device for and method of determining a muscle activity*."

Dahaba AA, Bornemann H

European Patent Office, Publication number: WO2008028572, 2008

"*Compressomyography – A New Neuromuscular Transmission Monitor.*"

Bornemann-Cimenti H, Dahaba, AA

22. Alpe Adria Symposium: 4-5 September 2009, Klagenfurt, Austria.

Conflicts of interest

The author is inventor of the "Device for and method of determining a muscle activity" called Compressomyography. (Dahaba and Bornemann 2008)

The technology of CMG and PMG is the same, both names are applicable.