REVIEW ARTICLE

HISTORY OF NEUROMUSCULAR JUNCTION MONITORING IN ANAESTHESIOLOGY

Historia monitorowania przewodnictwa nerwowo-mięśniowego w anestezjologii

Paweł Radkowski[1,2], Kamil Sobolewski[3], Hubert Oniszczuk[4], Justyna Opolska[5], Marcin Nosek[2], Filip Ogończyk-Mąkowski[2], Katarzyna Podhorodecka[2]

1. *Department of Anaesthesiology and Intensive Care, Faculty of Medicine, School of Medicine University of Warmia and Mazury in Olsztyn, Poland*
2. *Clinical Department of Anaesthesiology and Intensive Therapy, Provincial Specialist Hospital in Olsztyn, Poland*
3. *Department of Anaesthesiology and Intensive Care, Municipal Polyclinical Hospital in Olsztyn, Poland*
4. *Faculty of Medicine, Medical University of Białystok, Poland*
5. *Student Scientific Club at the Department of Anaesthesiology and Intensive Care, School of Medicine University of Warmia and Mazury in Olsztyn, Poland*

Paweł Radkowski – 0000-0002-9437-9458
Kamil Sobolewski – 0000-0002-3404-2108
Hubert Oniszczuk – 0009-0004-4503-1174
Justyna Opolska – 0000-0001-5086-4542
Marcin Nosek – 0009-0003-0463-6727
Filip Ogończyk-Mąkowski – 0009-0003-6899-7150
Katarzyna Podhorodecka – 0000-0003-0749-3437

Abstract

The history of monitoring neuromuscular conduction dates back to the 16th century when studies were conducted on curare, a plant-derived toxin used by Native Americans to poison arrows. Later studies made it possible to describe the concept of the neuromuscular junction, but it was not until the 20th century that the mediator acetylcholine was isolated. Measurement of neuromuscular transmission gained clinical importance when it became apparent that almost half of the patients who received a long-acting muscle relaxant were admitted to the post-operative room with incomplete resolution of neuromuscular block. Today, neuromuscular junction measurement devices using acceleromiography are becoming standard equipment in the operating theatre.

Streszczenie

Historia monitorowania przewodnictwa nerwowo-mięśniowego sięga XVI wieku, kiedy prowadzono badania nad kurarą, używaną przez Indian do zatruwania strzał. Późniejsze analizy umożliwiły opisanie zjawiska złącza nerwowo-mięśniowego, jednak dopiero w XX wieku udało się sprecyzować rolę mediatora, jakim jest acetylocholina. Pomiar przewodnictwa nabierał coraz większego znaczenia klinicznego, gdy okazało się, że prawie połowa pacjentów, którzy otrzymali długodziałający środek zwiotczający mięśnie, trafiała na salę pooperacyjną z niepełnym ustąpieniem blokady nerwowo-mięśniowej. Obecnie urządzenia do pomiaru przewodnictwa nerwowo-mięśniowego wykorzystujące akceleromiografię stają się standardowym wyposażeniem bloku operacyjnego.

Keywords: history of neuromuscular junction measurement; curare; acceleromiography; train of four (TOF); post tetanic count (PTC)

Słowa kluczowe: historia pomiaru złącza nerwowo-mięśniowego; kurara; akceleromiografia; train of four (TOF); liczba potężcowa (PTC)

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Corresponding author:
Justyna Opolska
Student Scientific Club at the Department of Anesthesiology and Intensive Care, School of Medicine University of Warmia and Mazury in Olsztyn
e-mail: jopolska065@gmail.com

What is neuromuscular transmission and why is it assessed?

Neuromuscular transmission is the process of converting an electrical impulse conducted by a nerve into muscle contraction [1]. Skeletal muscles are primarily innervated by motor neurons (α-motoneurons) located in the anterior horns of the spinal cord. As they approach muscle fibres, motor neuron axons branch into fine nerve endings, become covered by Schwann cells, lose their myelin sheath, and form the neuromuscular junction [2]. The neuromuscular junction (NMJ) is a specialized connection that enables the conversion of a nerve impulse into muscle contraction through the action of the neurotransmitter acetylcholine (ACh). NMJ is composed of three primary components: the presynaptic terminal, the postsynaptic membrane, and the synaptic cleft, which is the space between the axon terminal and the muscle cell membrane [3].

When a nerve impulse (action potential) reaches the axon terminal of a motor neuron, the presynaptic membrane depolarizes, opening voltage-gated calcium channels and causing a rapid influx of calcium ions (Ca^{2+}) into the nerve terminal. The rise in calcium ion levels in the axoplasm triggers fusion of synaptic vesicles with the presynaptic membrane, mediated by the SNARE protein complex (synaptobrevin, SNAP-25, and syntaxin), which results in the release of ACh into the synaptic cleft. ACh molecules diffuse across the synaptic cleft and bind to nicotinic acetylcholine receptors (nAChRs) found on the postsynaptic membrane of the muscle fibre. These receptors are ligand-gated ion channels that open upon binding two ACh molecules, allowing sodium ions (Na^+) to enter and potassium ions (K^+) to exit the muscle cell. This generates a local depolarization of the postsynaptic membrane. If the depolarization reaches the threshold, voltage-gated sodium channels open, initiating an action potential in the muscle cell membrane. The action potential propagates along the muscle fibre and into the transverse tubules (T-tubules), where it activates dihydropyridine receptors (DHPRs). These receptors are mechanically coupled to ryanodine receptors (RyR1) in the sarcoplasmic reticulum. Activation of RyR1 leads to the release of Ca^{2+} into the cytoplasm. The increased cytoplasmic Ca^{2+} allows its binding to troponin C, causing tropomyosin to move away from the actin binding sites and enabling actin-myosin interactions. Muscle contraction is directly mediated by cross-bridge cycling. For the process to occur, acetylcholine must first be removed from the synapse. This task is carried out by acetylcholinesterase (AChE), which breaks down ACh into choline and acetic acid. The choline is then reabsorbed by the nerve ending and used to resynthesize ACh, enabling continuous transmission of nerve impulses [1–3]. Figure 1 illustrates the motor end plate function.

Neuromuscular blockers (NMBs) inhibit the mechanism described above, producing muscle relaxation. They are widely used in anaesthesiology, particularly to facilitate intubation and to maintain muscle relaxation during surgical interventions [4].

Depolarizing neuromuscular blockers, such as succinylcholine, activate nicotinic cholinergic receptors in the postsynaptic membrane of the motor end plate. Due to their structural similarity to acetylcholine, they bind to these receptors and trigger depolarization of the postsynaptic membrane. This causes transient muscle fasciculations. Succinylcholine has a short duration of action as

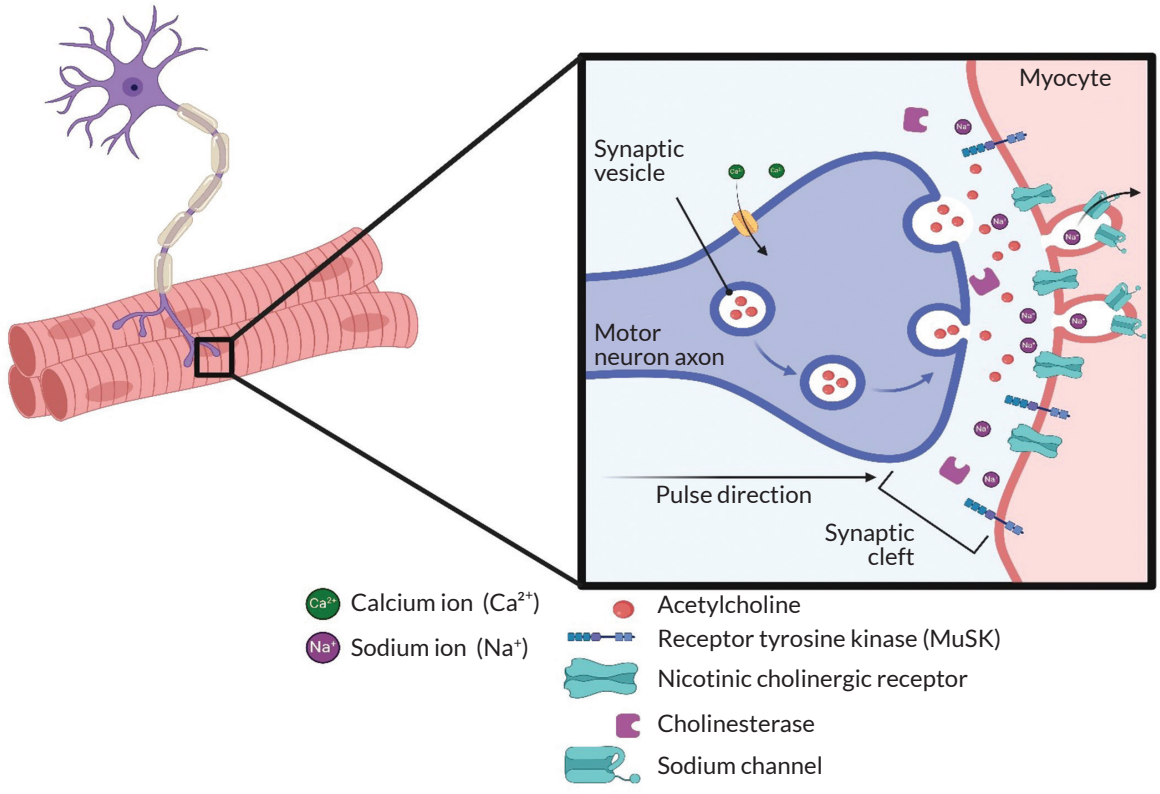

Figure 1. The mechanism of action of neuromuscular junction

it is rapidly hydrolysed by plasma cholinesterase, allowing neuromuscular function to be quickly restored once the drug is discontinued [5].

Non-depolarizing muscle relaxants, such as aminosteroids (vecuronium, rocuronium) and benzylisoquinoline derivatives (atracurium, cisatracurium), act as competitive antagonists of nicotinic cholinergic receptors, producing relaxation without depolarization [5].

Monitoring muscle relaxation helps assess the depth of neuromuscular block, enhancing anaesthetic safety. It also allows precise adjustment of muscle relaxant doses and prevents patients from leaving the operating room with residual paralysis. The importance of complete recovery from neuromuscular block was already highlighted in 1979 by Viby-Mogensen et al., who showed that about 40% of patients receiving intraoperative long-acting, non-depolarizing muscle relaxants entered the postoperative recovery room without full blockade resolution [6]. Monitoring the effects of these drugs enhances patient safety while also reducing treatment costs [7].

The history of the discovery and use of curare

First references to a muscle relaxant date back to 1516, when the Italian scholar Peter Martyr d'Anghera (1457–1526), living in Spain, documented the use of curare, a substance used by South American peoples to coat their hunting implements such as arrowheads. According to his accounts, curare was so potent that even its vapours could kill those preparing it [5, 8–10]. One of the first Europeans to encounter curare directly was likely the Spanish conquistador and explorer Francisco de Orellana, who during his Amazon River expedition (1541–1542) observed indigenous peoples using arrows soaked in the substance [11]. Alonso Pérez de Tolosa, who in 1548 explored the Lake Maracaibo region in present-day Venezuela, was another European to encounter the poison [12]. In 1745, Charles Marie de La Condamine described in his Mémoires de l'Académie des Sciences curare and its production from *Strychnos* and *Chondrodendron* species, and also brought some samples to Europe [12].

In 1780, the Italian researcher Gasparo Ferdinando Felice Fontana (1730–1805) commented on the reports describing curare's extreme toxicity in a presentation to the Royal Society, noting that although its fumes had an unpleasant odour, they did not cause death in those who inhaled them [8, 9]. Charles Waterton (1782–1865), an English naturalist and explorer who, in the early 19th century, travelled to Demerara (now Guyana) to oversee his family's sugarcane plantation, was the first person to experiment with curare. He conducted his first experiment on an injured dog, which did not survive the injection. Subsequent trials on poultry and oxen showed that its effects depended on the dose administered. After returning to England in 1814, he continued his research with a series of experiments on donkeys. One donkey given curare was kept alive through tracheotomy-assisted ventilation for four hours and went on to survive for another 25 years. Waterton also appreciated curare's medicinal potential, suggesting that it might be useful in treating rabies [13, 14]. Dr. William Sewell (1781–1853), an English veterinarian, tested this theory by administering curare with simultaneous ventilation to horses afflicted with rabies. In 1811, Benjamin Brodie (1783–1862), an English philosopher and surgeon, presented to the Royal Society a study suggesting that an animal could survive curare administration if resuscitated long enough. A year later, he supported this claim by administering curare to a cat and ventilating it for 160 minutes. After ventilation ended, the animal initially remained paralyzed, but soon regained mobility and stood up on its own. Although unaware of the substance's exact mechanism, Brodie concluded that the poison likely acted centrally [10, 13, 14]. Research into curare's mechanism of action began in the 1850s with the French physiologist Claude Bernard (1813–1878), who conducted a series of experiments on frogs. He administered the substance subcutaneously and dissected the animal immediately after death. He discovered that the muscles retained normal contractility under direct stimulation but failed to respond to motor nerve stimulation [13, 14]. He performed the same experiment on birds and mammals, with identical findings. Based on this, he concluded that curare disrupts the connection between motor nerves and muscles while sparing the sensory nerves [15]. These experiments laid the foundation for the later description of the motor end plate by Claude Bernard's colleagues Wilhelm Kühne and Wilhelm Krause (1833–1910) [16]. The definitive explanation of curare's mechanism of action emerged only in the first half of the 20th century. In his paper published in the Journal of Pharmacology and Experimental Therapeutics (1914), British physiologist and pharmacologist Professor Henry Dale (1875–1968) demonstrated that acetylcholine functions as a neurotransmitter in neuromuscular junctions [9]. In 1921, Otto Loewi described the function of acetylcholine as a neurotransmitter in his work "Über humorale Übertragbarkeit der Herznervenwirkung". In 1936, both scientists were awarded the Nobel Prize in Physiology or Medicine for their discoveries concerning the "chemical transmission of nerve impulses" [13, 14].

L. A. Sayers was first to use curare in human medicine. In 1858, he administered the substance locally to a wound on the thumb, which unfortunately resulted in the patient's death. In 1932, West used curare to treat spastic states such as Parkinson's disease, tetany, and hemiplegia. However, treatment outcomes were inconsistent as the preparation he used was not standardized [8]. Curare entered clinical practice in 1940, when Abram Elting Bennett (1898–1985) used it to treat metrazol-induced convulsive seizures. Curare was introduced into the operating room in 1942 by Canadian anaesthesiologists Harold Griffith (1894–1985) and Enid Johnson (1909–2001), who employed its muscle relaxant properties during surgeries.

Measurement of neuromuscular block

Efforts to assess the degree of neuromuscular block did not begin until 1949 [17], when English anaesthesiologist Geoffrey Organe (1908–1989) and colleagues explored human sensitivity to muscle relaxants and investigated whether their effects paralleled those observed in animals. Three volunteers participated in the study. The drug's efficacy was assessed based on clinical measurements. They assessed leg lifting, standing ability,

grip strength, as well as abdominal and eyelid muscle tone. Graphs were presented showing hand strength as a percentage relative to the time elapsed after drug administration [18]. That same year, Professor William W. Mushin (1910–1993) and colleagues explored the effects of Flaxedil, a gallamine-based nondepolarizing muscle relaxant widely used in the mid-20th century. They used several tests to monitor its effects on the body. They measured finger flexion strength with a dynamometer and assessed abdominal muscle contraction strength. The latter was measured in a volunteer laying supine with their legs attached to a couch. A device with a pointer and spring was placed over the centre of the rectus abdominis, which was pushed out by the muscle during an attempt to raise legs on the doctor's command. Breathing was recorded with a spirometer, along with blood pressure and the plantar reflex [19].

The methods described above were the first attempts to objectify the effects of muscle relaxants. While simple, they had a major limitation: they could not be applied to anaesthetized patients, who were unable to follow commands. Thus, assessing neuromuscular block in unconscious patients requires alternative approaches, such as direct stimulation of muscle contractions [7].

The first reported use of nerve stimulation in anaesthetized patients to assess muscle relaxant–induced relaxation likely dates to 1952 [17]. Finnish pharmacology professor Stephen Thesleff (1924–2020) described the effects of succinylcholine in his publication. To measure the degree of muscle relaxation, the patient's right hand was mounted on a Brown-Schuster myograph. An electrode connected to a stimulator delivering discharges at 0.1 Hz was fixed to the right elbow, above the ulnar nerve. Stimulation caused contraction of the fourth and fifth fingers, and their movements were recorded by the myograph. The responses were then traced with a kymograph (a pen on a paper cylinder rotating at a constant speed). In his study, Thesleff also monitored patients' respiratory muscle activity using two pneumographs and a Marey's tambour. The pneumographs were placed in the middle of the sternum and halfway between the umbilicus and the xiphoid process. Volume changes detected by the pneumographs were transmitted to the Marey's tambour and recorded on a kymograph [20]. Electromyography was introduced into clinical practice by Fritz Buchthal, and later adopted in anaesthesiology by Thomas Hildred Christie (1927–2017) and Harry Cunningham Churchill-Davidson (1922–1995). In 1958, a description of a user-friendly neuromuscular conduction stimulator designed for anaesthesiologists for use in the operating room was published in the Lancet. The authors highlighted its potential for diagnosing the causes of incomplete postoperative recovery of muscle strength. This device allowed for determining whether incomplete recovery was caused by muscle relaxants, analgesics, or anxiolytics. It generated a stimulating current at 3 Hz or 50 Hz, with adjustable intensity. The study recommended using maximum intensity in unconscious patients to ensure a distinct contraction of all muscle fibres supplied by a given nerve [21]. Figure 2 schematically illustrates the device described above.

Churchill-Davidson gradually improved the device he had developed, presenting the first small, battery-powered stimulator in Anesthesiology in 1965. The device allowed voltage regulation from 0 to 250 V, generated pulses of fixed 0.3 ms duration, and could deliver them individu-

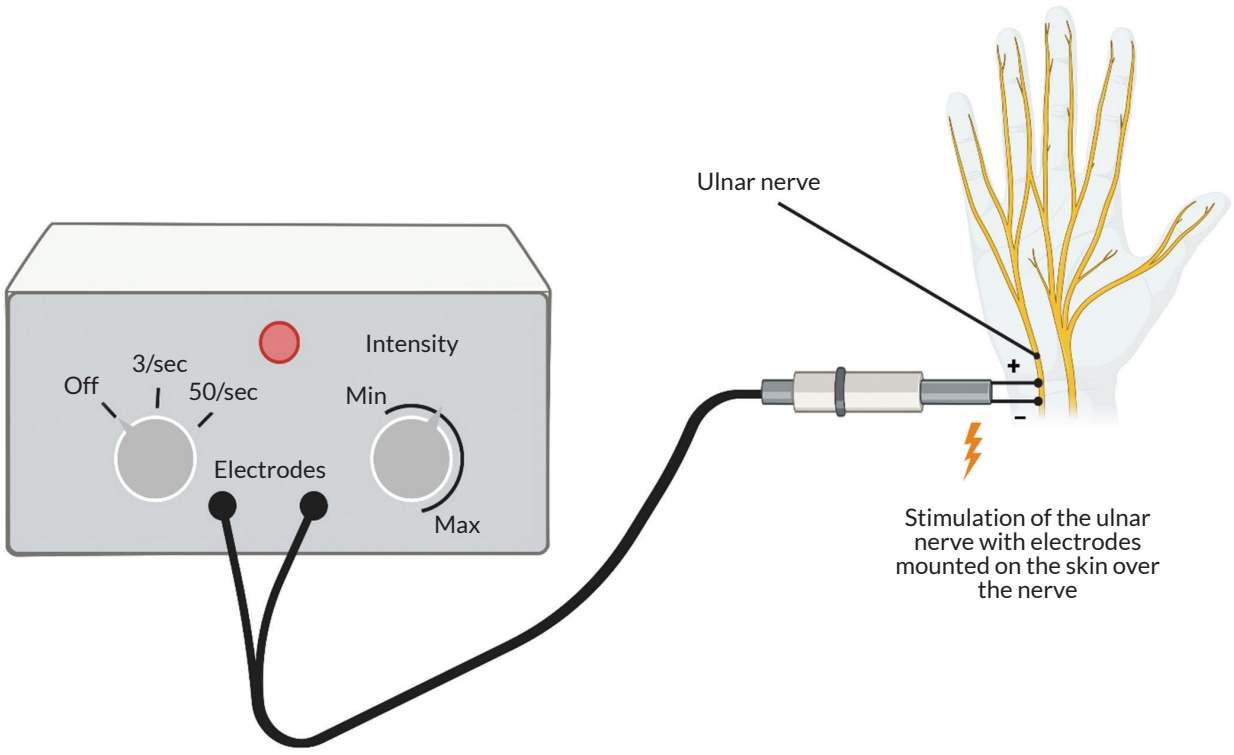

Figure 2. A representative diagram of the St. Thomas Hospital Nerve Stimulator [15]. Illustration created with BioRender.com

ally or in series at a frequency of 50–60 Hz. Interestingly, while developing this device, he discovered a method to differentiate between depolarizing and nondepolarizing block based on muscle responses to stimuli. He noted that cessation of contractions after, typically, four consecutive single pulses or following tetanic stimulation, is a hallmark of nondepolarizing blockade [22].

Similar observations were made by Roberts and Wilson, who in 1968 described a gradual decrease in muscle responses after four twitches when a 4 Hz current was applied in patients with myasthenia gravis. In 1970 and 1971, Hassan H. Ali et al. (1931–2022) published a series of articles in the British Journal of Anaesthesia describing the use of train-of-four (TOF) monitoring to assess the degree of curarization in humans. Based on their experience, they concluded that the TOF monitoring was superior to using frequency shifts between 0.1 and 10 Hz for quantitative assessment of nondepolarizing block. They also noted that this test could help evaluate individual sensitivity to muscle relaxants and determine dose requirements for specific procedures. In a 1971 publication, the same authors reported similar studies involving 26 patients given muscle relaxants preoperatively. They introduced the concept of the TOF ratio, expressing the amplitude of the fourth muscle twitch (T4) to the first muscle twitch (T1), thereby providing an indicator of the degree of neuromuscular block. According to the authors, limiting the stimuli to four at 2 Hz was intended to ensure maximum depletion of acetylcholine stores. Subsequent studies evaluated the practical utility of the TOF ratio, comparing it to clinical manifestations signalling cessation of muscle relaxant action. They found that a patient's ability to raise the head for at least three seconds (a clinical indicator of recovery) was only possible with a TOF ratio greater than 0.6 [17].

The 1979 study conducted by Viby-Mogensen et al. convinced the authors of the need to measure the degree of relaxation in operating rooms to reduce the incidence of residual curarization in postoperative recovery rooms [6]. In their 1980 paper entitled 'A New Nerve Stimulator (Myotest)', they presented a new device measuring 90 × 45 × 165 mm, weighing approximately 400 g, and powered by four 1.5 V alkaline batteries, and able to operate for about 200 hours. The device offered several functions, including single contractions at varying frequencies and a TOF programme, which delivered a series of four pulses every 10 seconds at 0.5-second intervals. The authors noted that their stimulator differed from that of Christie and Churchill-Davidson by precisely generating unipolar pulses at constant voltage, enhancing result reproducibility. They also found it more practical due to its multiple functions, as demonstrated by their year-long use of the Myotest [23].

In 1981, Viby-Mogensen et al. introduced the term 'post-tetanic count' (PTC). In one of their papers, the authors reported results of assessing neuromuscular block during the period of no response to single or TOF stimulation and first described using PTC to monitor deep neuromuscular block [24].

In 1989, Engbaek et al. sought an approach superior to TOF for assessing residual neuromuscular block after muscle relaxant administration. They suggested that TOF might fail to reliably detect residual curarization because the two middle responses complicate comparison between the first and last twitch. Their study aimed to investigate a new diagnostic system for residual NMB: double-burst stimulation (DBS). DBS consisted of two short 50-Hz tetanic stimuli separated by a 750-ms pause. This stimulation pattern produced two single muscle contractions, with the second being less pronounced than the first one during the non-depolarizing NMB. The DBS version with three impulses in each burst (DBS3i3) was found to be the most sensitive and least painful, thus most suitable for clinical use. It was also more sensitive than TOF for manual detection of residual block [25].

In 1988, Jensen et al. introduced Accelograph®, the first device for objectively measuring NMB. It used two electrodes placed on the thumb and near the ulnar nerve. Finger movement in response to nerve stimulation generated a voltage difference between the electrodes, which was then measured and recorded. The inventors of the device noted that since, according to Newton's law ($F = m \times a$), force (F) is directly proportional to acceleration (a), the latter one could be used to quantify NMB, assuming that mass (m) remains constant. Measuring acceleration is more convenient than measuring contractile force, as it requires no additional device to stabilize the hand. It also allowed an assessment of both TOF and PTC [26]. Table 1 summarizes key discoveries and milestones in neuromuscular transmission monitoring.

The newly developed TOF-Cuff® neuromuscular transmission monitor, which utilizes compressomyography, is a product of RGB Medical Devices. It integrates electrode

Table 1. Chronology of major discoveries and advances in neuromuscular monitoring

Year	Discovery	Description/Achievements
1516	First mentions of curare	Peter Martyr d'Anghiera's description of the substance used by the Indians to poison their arrows
1811	Benjamin Brodie's Research	Suggesting the possibility of survival after administration of curare with appropriate resuscitation
1932	The first use of curare for therapeutic purposes	West's Attempts to use curare in the treatment of spastic states
1942	The first use of curare in anaesthesiology	Harold Griffith and Enid Johnson use curare to achieve muscle relaxation during surgery
1970–1971	Introduction of TOF	Hassan H. Ali describes the use of train of four (TOF) for monitoring neuromuscular block

Table 2. Types of devices used to monitor neuromuscular conduction

Type of device	Description	Clinical use	Benefits	Limitations
Electromyography (EMG)	Measuring muscle electrical activity in response to nerve stimulation	Precise assessment of NMB	High accuracy	Requires precise electrode placement
Acceleromyography	Measuring the acceleration of muscle contraction following nerve stimulation	Used to assess the degree of NMB	Mobility, ease of use	Requires precise electrode installation EMG
Mechanomyography	Recording the strength of muscle contraction after nerve stimulation	Mainly research use	High precision	Not very clinically available, requires special equipment

stimulation into a blood pressure monitoring cuff. The device can be used to stimulate the brachial plexus and assess the degree of neuromuscular block based on changes in cuff pressure. Compared to conventional NMB monitors, it can offer both neuromuscular block assessment and non-invasive blood pressure measurement on the upper arm or lower leg, the latter being less affected by patient positioning and medical personnel interventions [27].

Future directions in the development of NMJ monitoring

Acceleromyography remains one of the most effective and widely used methods for monitoring neuromuscular transmission, with devices such as TOF-Scan, TOF Watch SX, and its predecessor TOF Watch known and commonly employed in hospital settings. Other approaches are also being developed, including mechanomyography, electromyography, kinematography, phonomyography, and the newest, informally known as 'compressomyography'. Table 2 summarizes the types of devices used to monitor neuromuscular transmission.

Future research is focusing on integrating these technologies with hemodynamic and respiratory monitoring systems to enable comprehensive, real-time assessment of patient status. Additionally, artificial intelligence and machine learning algorithms may predict individual responses to muscle relaxants, allowing personalized dosing and reducing the risk of complications. Implementing these advanced monitoring approaches in clinical prove the quali care and patient safety [28].

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