# Anesthesia and myopathy

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**Purpose of review**

This report reviews the derangements of neuromuscular transmission in the different types of myopathy.

**Recent findings**

The article covers recent literature on myopathy, whether prejunctional, junctional or postjunctional, as well as intensive care unit myopathy, and outlines the influence of myopathy on the action of both depolarizing and non-depolarizing muscle relaxants.

**Summary**

The review classifies myopathy according to its cause, and sheds light on the upregulation and downregulation of endplate acetylcholine receptors. These findings are important for both clinical practice, and for research into neuromuscular transmission.

**Keywords**

ICU myopathy, muscle relaxants, myopathy, neuromuscular disorders.

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**Abbreviations**

| | |
|---|---|
| **AChR** | acetylcholine receptor |
| **CIP** | critical illness polyneuropathy |
| **ICU** | intensive-care unit |
| **MG** | myasthenia gravis |
| **MH** | malignant hyperthermia |
| **MS** | multiple sclerosis |
| **NDBA** | non-depolarizing blocking agent |
| **RyR1** | ryanodine receptor |


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## Introduction

The different types of primary myopathy described include dystrophies such as Duchenne and myotonic dystrophies, infectious (viral, bacterial, protozoal), toxic (alcoholic, steroid), idiopathic (polymyositis, dermatomyositis) and metabolic (glycogenoses, mitochondrial, lipidic) [1].

The present report classifies myopathy according to its prejunctional, junctional, and postjunctional causes: (1) prejunctional functional or organic denervation; (2) junctional, for example myasthenia gravis; and (3) postjunctional (primary) myopathy, for example muscle dystrophy, myotonic dystrophy, malignant hyperthermia (MH).

The report also reviews the recent literature on the two most common disorders of critical care (intensive-care unit; ICU) myopathy; acute myopathy predominantly associated with the use of intravenous corticosteroids and neuromuscular blocking drugs; and axonal sensorimotor polyneuropathy [2••,3].

## Prejunctional denervation

Denervation, whether functional secondary to immobility or organic secondary to different factors such as spinal cord injury, upper and lower motor neuron injuries, as well as peripheral nerve injury [4], can result in the upregulation of the endplate nicotinic acetylcholine receptors (AChRs) [5,6••,7••].

A classic principle of pharmacology suggests that decreased release of or exposure to a chemical transmitter results in post-synaptic receptor upregulation, whereas increased transmitter release results in receptor downregulation [8]. Upregulation of the endplate receptors not only results in an increase in the number of receptors and their spread beyond the endplate along the muscle membrane, but also in a change in the composition of the receptor from the adult structure into the fetal structure. Fetal-type receptors are more resistant to neuromuscular non-depolarizing blocking agents (NDBAs) and more sensitive to succinylcholine. The administration of succinylcholine to patients with functional or organic denervation can result in excessive potassium release [5], with a consequent development of cardiac arrhythmias or even cardiac arrest [7••,9,10], which carries a mortality rate of 40–55% [7••]. The channel-related agonist-triggered potassium release is magnified by the number of muscles involved [7••].

Hyperkalemia can result not only from receptor upregulation, but also from rhabdomyolysis or the breakdown of muscle surface membrane. Rapid rhabdomyolysis can occur after succinylcholine [11], as well as potent inhalation anesthesia in the absence of the use of succinylcholine, especially in a patient with a known or suspected myopathy [7••]. If acute rhabdomyolysis occurs rapidly, plasma potassium increases quickly and may exceed the capacity for redistribution. The combined release of potassium from the upregulation of membrane receptors and from the breakdown of muscle membrane results in sustained and marked hyperkalemia and difficult resuscitation [7••,10].

The onset of vulnerability after denervation as well as its degree and duration will vary according to the type and degree of denervation [6••]. Prolonged immobility in which individuals are confined to wheelchairs or bed is associated with muscle disuse atrophy. Despite the presence of intact motor neurons, functional denervation occurs with a consequent upregulation of the cholinergic receptors [9]. The concomittant chronic use of NMBAs in immobilized patients results in an enhanced upregulation of the AChRs [9]. Vulnerability to succinylcholine-induced hyperkalemia may occur when immobilization exceeds 24 h. After remobilization, changes at the neuromuscular junction revert to normal within 20–50 days.

After spinal cord injury or stroke, because upregulation occurs within 48 h after denervation, succinylcholine appears to be safe within the first 24 h after the insult. The upregulation of the endplate receptors may last for more than one year after injury [6••]. In Guillain–Barré syndrome, an acute inflammatory demyelinating polyradiculopathy, the risk of hyperkalemic cardiac arrest after succinylcholine may persist over a long period after recovering from the symptomatic neurological defect. These patients also have a high incidence of autonomic instability.

Chronic inflammatory demyelinating polyradiculoneuropathy is a rare disease occurring in less than one in 100 000 individuals. It is a symmetric sensorimotor neuropathy manifesting as paresthesia and weakness of the proximal and distal muscles, including the respiratory muscles, with depressed deep tendon reflexes and mild muscle atrophy [12]. It is thought to be mediated by the immune system but is different from Guillain–Barré syndrome, which is an acute inflammatory demyelinating polyradiculopathy [12]. The effect of non-depolarizing muscle blockade may be prolonged in these patients and accordingly should be used cautiously [12].

Multiple sclerosis (MS) is the most frequent demyelinating disease. MS may be exacerbated postoperatively after regional anesthesia because of the increased sensitivity of demyelinating axons to local anesthetic toxicity [13]. The response to muscle relaxants whether depolarizing or non-depolarizing is usually normal in patients with MS [13].

In contrast to the upregulation of AChRs after functional or organic denervation, a downregulation of the receptors may result from autonomous peripheral nerve hyperactivity, with a consequent sensitivity to non-depolarizing relaxants and the absence of succinylcholine-induced fasciculations [14]. Conditioning exercise can also result in the repeated release of acetylcholine; whether exercise elicits the downregulation of AChRs is unknown, but the leftwards shift in the dose–response curve of NDBAs is suggestive of such a change [15].

## Junctional

In addition to the prejunctional neuronal lesions that result in the downregulation or upregulation of the endplate receptors, myopathy can result from junctional receptor dysfunction secondary to myasthenia gravis (MG).

### Myasthenia gravis

MG is an autoimmune disease, resulting from the production of antibodies against the AChRs of the neuromuscular synapse [16••,17]. The muscular weakness and fatigability that are the hallmarks of MG are known to be the result of this antibody-mediated autoimmune attack directed against the AChRs at the neuromuscular junction [18]. The thymus could represent a unique site of autosensitization against AChR antigenic determinants, because myoid cells bearing AChRs are present in the normal thymus. The disease is frequently associated with morphological abnormalities of the thymus gland.

### Neuromuscular junction

Under normal conditions, only 25–30% of the endplate receptors are required to maintain neuromuscular transmission. The remaining 70–75% of the receptor pool constitutes a 'safety margin' [19]. In MG, there is a decrease in the number of functional AChRs available [20], with a subsequent decrease in the 'safety margin'. A reduction in the number of active receptors at the endplate is brought about either by functional block, by an increased rate of receptor degradation, or by complement-mediated lysis of the postsynaptic membrane [21].

### Clinical presentation of myasthenia gravis

Table 1 is a summary of the different clinical presentations of MG [16••]. The clinical course of MG is marked by periods of exacerbations and remissions. The extraocular muscles are involved at some time in the

**Table 1. Summary of the different clinical presentations of myasthenia gravis (Baraka)**

| | Aetiology | Onset | Sex | Thymus | Course |
|---|---|---|---|---|---|
| Neonatal myasthenia | Passage of antibodies from myasthenic mothers across the placenta | Neonatal | Both sexes | Normal | Transient |
| Congenital myasthenia | Congenital endplate pathology genetic, autosomal recessive pattern of inheritance | 0–2 years | Male > female | Normal | Non-fluctuating, compatible with long survival |
| Juvenile myasthenia | Autoimmune disorder | 2–20 years | Female > male (4 : 1) | Hyperplasia | Slowly progressive, tendency to relapse and remission |
| Adult myasthenia | Autoimmune disorder | 20–40 years | Female > male | Hyperplasia > thymoma | Maximum severity within 3–5 years |
| Elderly myasthenia | Autoimmune disorder | > 40 years | Male > female | Thymoma (benign or locally invasive) | Rapid progress, higher mortality |

course of the disease in almost every patient during the first year. However, in three-quarters of patients whose initial symptom is ptosis or diplopia, the disease becomes clinically generalized within the first 1–3 years.

### Classification of myasthenia gravis

The various stages of MG have been classified by Ossermann and Genkins [22] as I, IIA, IIB, III and IV, and were modified by Baraka [16••] as: I. ocular signs and symptoms only; II. generalized mild muscle weakness; III. generalized moderate weakness, or bulbar dysfunction, or both; IV. acute fulminating presentation, or respiratory dysfunction, or both; V. late, severe, generalized MG.

### Medical treatment

Current medical treatment of MG is aimed at: (1) enhancing neuromuscular transmission by anticholinesterases; (2) suppressing the immune system by corticosteroids and other immunosuppressive drugs; and (3) decreasing the circulating antibody level by plasmapheresis [23].

### Thymectomy

Thymectomy is the preferred form of treatment of MG with generalized weakness, particularly for patients younger than 55 years. Removal of as much thymic tissue as possible (anterior mediastinal exenteration) via the trans-sternal approach is the logical goal of thymectomy in the treatment of MG [24].

### Anesthetic management

Optimization of the condition of myasthenic patients can markedly decrease the risk of surgery and improve the outcome. Recently, plasmapheresis has been used to optimize the medical status of the myasthenic patient before surgery. Anticholinesterase agents are discontinued, unless the patient is physically or psychologically dependent on them. Corticosteroid medications are maintained to be tapered and discontinued postoperatively. Those patients receiving chronic steroid therapy require additional parenteral coverage during the perioperative period.

### Anesthetic techniques

Because of the unpredictable response to succinylcholine [25,26] and the marked sensitivity to non-depolarizing muscle relaxants, some anesthesiologists avoid muscle relaxants and depend on deep inhalational anesthesia [27]. However, others utilize a balanced technique of anesthesia that includes the use of carefully titrated muscle relaxants [16••]. The combination of balanced and regional anesthesia has also been recommended [28].

### Response to muscle relaxants

In MG, there is a decrease in the number of functional AChRs available, with a subsequent decrease in the safety margin. The decrease in functional endplate receptors can decrease the response to the chemical transmitter acetylcholine, and to other depolarizing agents such as succinylcholine. In contrast, the decreased safety margin results in a marked sensitivity to non-depolarizing relaxants. The abnormal response of myasthenic patients to muscle relaxants is encountered even in patients with localized ocular myasthenia and during remission.

### Postoperative respiratory failure

The most important preoperative factor predicting the need for postoperative mechanical ventilation is the severity of bulbar involvement, associated with a previous history of respiratory failure and concurrent steroid therapy [29].

### Outcome

Thymectomy benefits nearly 96% of patients regardless of preoperative characteristics: 46% develop complete remission, 50% are asymptomatic or improve on therapy, and 4% remain the same [18,24].

## Post-junctional: primary muscle diseases

Post-junctional myopathy includes different types of 'primary' myopathies such as Duchenne muscular dystrophy, myotonic dystrophy, MH, as well as ICU myopathy.

### Muscular dystrophies

Duchenne muscular dystrophy is a common genetic disease in humans, with an incidence of one per 3500 male births, and is caused by an X-linked recessive mutation resulting in abnormal or absent dystrophin [30]. Progressive cardiomyopathy develops in the mid-teens, and patients succumb to cardiac or pulmonary complications in their late teens or 20s. Patients with myopathy should thus have cardiological evaluation as soon as the diagnosis is established [31]. It is also associated with a non-progressive cognitive deficit [30].

Innervation is relatively normal in dystrophic muscle. However, as a result of chronic muscle regeneration in patients with Duchenne dystrophy, there is the co-expression of both fetal and adult AChRs, characteristic of upregulation after chronic denervation [30,32]. Patients are usually sensitive to non-depolarizing relaxants. They are more susceptible to MH, rhabdomyolysis after the administration of succinylcholine or the administration of inhalation anesthetics. They are also liable to develop succinylcholine-induced hyperkalemia.

On the basis of several case reports of hyperkalemic cardiac arrest after succinylcholine administration, particularly in children with undiagnosed Duchenne muscular dystrophy [10], the Food and Drug Administration and the manufacturer revived the product label stating 'Since it is difficult to identify which patients are at risk, it is recommended that the use of succinylcholine in pediatric patients be reserved for emergency intubation or in instances where immediate securing of the airway is necessary e.g. laryngospasm, difficult airway, and full stomach, or for intramuscular route when a suitable vein is inaccessible' [33].

### Myotonic dystrophy

Myotonic dystrophy is an autosomal-dominant disorder with a prevalence of one per 8000–20 000 individuals. It mostly affects patients between the second and fourth decades of life [13,34]. It is characterized by incomplete muscle relaxation, marked wasting of the muscles of mastication, neck, pharynx and distal limbs. The disease is associated with frontal balding, cataracts, and testicular atrophy. It may also be associated with cardiomyopathy and conduction abnormalities, restrictive lung disease, central and obstructive sleep apnea [13]. The myotonic muscles are hyperexcitable secondary to abnormal chloride or sodium channels, with consequent repetitive action potentials. Myotonia may be precipitated by hypothermia, shivering, and mechanical or electrical stimulation. Intraoperative and early postoperative cardiovascular and respiratory complications may result from sensitivity to sedative and anesthetic [34]. In addition, succinylcholine can induce generalized muscular contracture, and is not recommended in this group of patients [13,34]. Succinylcholine-induced myotonic contracture can be relieved by the subsequent administration of NDBAs [35]. Non-depolarizing muscle relaxants are not associated with an abnormal muscular response in the myotonic patient. However, the reversal of blockade with anticholinesterase drugs may precipitate myotonia, secondary to increased sensitivity to the stimulatory effect of acetylcholine [13,34].

### Malignant hyperthermia

MH is a dominantly inherited muscle disorder with variable penetrance that predisposes susceptible individuals to potentially fatal reaction during general anesthesia [36,37]. It has been reported to occur in one out of 50 000 anesthetics administered to adults and one out of 15 000 in children [38,39]. A predisposition to MH is found in patients with inherited myopathy central core disease, Evans myopathy and King Denborough syndrome, and MH has been reported in patients with other types of myopathies [38,39]. It is debatable whether MH susceptibility is associated with various musculoskeletal abnormalities such as scoliosis, hernias, cryptorchidism, strabismus and ptosis [39,40].

MH is a disorder of calcium regulation within skeletal muscle, and results from a rapid, sustained increase in myoplasmic calcium triggered by commonly used potent inhalational anesthetics and depolarizing muscle relaxants [39]. The concurrent use of succinylcholine with volatile anesthetic agents decreases the threshold of MH [41]. Skeletal muscles have abnormalities in the sarcoplasmic reticulum release channel (or ryanodine receptor; RyR1). RyR1 plays a major role in myoplasmic calcium control, allowing the release of calcium stored in the sarcoplasmic reticulum to be available for electromechanical coupling and thus contraction [37]. The *RyR1* gene is located on chromosome 19 and is identified as the primary locus for MH susceptibility [36]. Mutations in the amino acid sequence of this channel can lead to dysfunction in calcium regulation [37]: the release channel is activated at lower cytoplasmic calcium concentrations and inhibited at higher concentrations than normal [39]. The diagnosis of susceptibility uses the in-vitro contracture response to caffeine and halothane [37,39,40].

An MH crisis constitutes a hypermetabolic state manifesting as metabolic and respiratory acidosis, hyperthermia, which may be a late sign, tachycardia, cardiac arrythmias, skeletal muscle rigidity and rhabdomyolysis.

Clinical parameters necessary to diagnose this condition include temperature monitoring, end-tidal capnography, arterial blood gases, heart rate and the presence of muscle rigidity and masseter spasm [42]. The clinical course of MH is highly variable, ranging from mild forms to fulminant. Postoperative rhabdomyolysis may be the only symptom of MH [42]. The mortality and morbidity associated with MH has decreased with the introduction of dantrolene, a calcium-blocking agent that can stop the crisis if administered early, in addition to the treatment of the life-threatening hyperkalemia and acid-base disturbances [42].

## Intensive-care unit myopathy and polyneuropathy

The development of muscle weakness and atrophy in critically ill patients is not simply the result of physical inactivity, but the consequence of newly acquired neuromuscular disorders [43]. Weakness may result from pathological changes occurring in the muscles, peripheral nerves and neuromuscular junctions of patients [2••,43].

Among the various neuromuscular conditions described, critical illness polyneuropathy (CIP) is the most prevalent [43]. CIP will manifest as difficulty weaning from the ventilator and varying degrees of limb weakness [44]. As initially described in 1984, CIP is a sensorimotor polyneuropathy, frequently a complication of sepsis and multiorgan failure, occurring in 70–80% of these patients during their stay in the ICU [43–45], but has the potential for complete recovery after 2–3 weeks should the patient survive the systemic inflammation reaction syndrome [44]. CIP is primarily a distal axonopathy with distal degeneration of motor and sensory axons without inflammation [45], while sparing the cranial nerves [46]. Most patients who developed CIP had underlying sepsis, whereas there was no correlation between the use of NDBAs and the development of polyneuropathy.

The myopathy that develops in critically ill patients has been termed acute myopathy of intensive care. It may coexist and be confused with CIP [2••]. It occurs in up to 50% of ICU patients [2••], and manifests as diffuse weakness or flaccid paralysis, with involvement of the respiratory muscles resulting in difficult weaning [2••]. ICU diffuse myopathy may result as a complication of sepsis. The underlying disorder in most patients who develop myopathy is an acute respiratory disorder such as pneumonia or severe asthma, in conjunction with the use of high-dose intravenous steroids, NDBAs and aminoglycosides [45]. Myopathy can be provoked in experimentally denervated muscles exposed to corticosteroids [3,43]. NDBAs and synthetic steroids were found to produce additive inhibition of nicotinic AChRs [47]. The underlying mechanism may be a hypersensitivity to corticosteroids, and it is postulated that denervation of the muscle by pharmacological or immunological blockade of neuromuscular transmission as well as by immobilization renders muscles susceptible to the myopathic effects of steroids [43].

Because there is no definite treatment for this condition, prolonged infusion of NDBAs should be avoided and used cautiously, especially when corticosteroids are administered concurrently. Accordingly, it has been suggested to avoid NDBA overdose and to limit the use of NDBAs to 48 h [43,48]. Also, succinylcholine administration in the critically ill patient with receptors up-regulation can result in hyperkalemic cardiac arrest [7••].

## Conclusion

Myopathy can result from prejunctional, junctional and postjunctional causes. Prejunctional causes include both functional or organic denervation, which can result in the upregulation of the endplate receptors with a consequent resistance to non-depolarizing relaxants and sensitivity to depolarizing relaxants. MG is an autoimmune process, resulting from the production of antibodies against the junctional AChRs of the neuromuscular synapse, with a consequent resistance to depolarizing relaxants and sensitivity to non-depolarizing relaxants. The report also discusses postjunctional causes of myopathy such as muscular dystrophy, myotonic dystrophy and MH, as well as ICU myopathy and polyneuropathy. Table 2 summarizes the underlying

**Table 2. The underlying pathogenesis and the response to succinylcholine versus non-depolarizing relaxants in the different types of myopathy**

| Disorder | Pathogenesis | Succinylcholine | Non-depolarizing relaxants |
|---|---|---|---|
| Denervation | Upregulation of acetylcholine receptors | Hyperkalemia | Resistance |
| Myasthenia gravis | Autoimmune disease<br>Anti-acetylcholine receptors' antibodies | Resistance | Sensitivity |
| Muscular dystrophy | X-linked recessive mutation resulting in abnormal dystrophin | Hyperkalemia, rhabdomyolysis | Sensitivity |
| Myotonic dystrophy | Autosomal dominant disorders<br>Hyperexcitable muscles secondary to abnormal chloride or sodium channels | Myotonic contracture | Normal |
| Malignant hyperthermia | Dominant inheritance of abnormal ryanodine receptors | Hypermetabolism and muscular rigidity | Normal |

pathogenesis and the response to succinylcholine versus non-depolarizing muscle relaxants in the different types of myopathy.

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