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The Response of Patients with Neuromuscular Disorders to Muscle Relaxants: A Review

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CONTENTS

Regional Curare Test
Intracranial Lesions
  Hemiplegia
  Parkinson's Disease
  Multiple Sclerosis
  Diffuse Intracranial Lesions
  Tetanus
Spinal Cord Lesions
  Paraplegia and Quadriplegia
  Amyotrophic Lateral Sclerosis
  Poliomyelitis and Acute Anterior Horn Cell Disease
Peripheral Nerve Lesions
  Peripheral Neuropathies
  Muscular Denervation
Neuromuscular Junction Lesions
  Myasthenia Gravis
  Myasthenic Syndrome
Muscular Lesions
  Myotonias
  Muscular Dystrophies
  The Differential Diagnosis of Rigidity Following Succinylcholine Administration

SEVERE COMPLICATIONS and occasionally death may occur in patients with neuromuscular disorders following administration of muscle relaxants.[1–20] The more common complications are prolonged paralysis, hyperkalemia, rigidity, and malignant hyperthermia (table 1). This article reviews the literature concerning the response of these patients to muscle relaxants, possible mechanisms of the abnormal responses, and recommended management of relaxation during surgery. The myopathic syndromes associated with malignant hyperthermia have been reviewed recently[21] and will not be discussed here.

For the purpose of this review I classified the neuromuscular disorders according to the site of the primary lesion, as follows: 1) Intracranial lesions: hemiplegia, Parkinson's disease, multiple sclerosis, diffuse intracranial disorders, tetanus; 2) Spinal cord lesions: paraplegia and quadriplegia, amyotrophic lateral sclerosis, poliomyelitis; 3) Peripheral nerve lesions: peripheral neuropathies, muscular denervation; 4) Neuromuscular junction lesions: myasthenia gravis, myasthenic syndrome; 5) Muscular lesions: myotonias, muscular dystrophies.

There are several methods to assess response of patients with neuromuscular disorders to muscle relaxants, but most have serious drawbacks: Systemic administration of a small dose of curare[22] may result in general paralysis; electromyographic (EMG) studies using tetanic nerve stimulation are painful and often give false results; challenge with an anticholinesterase is not reliable and often is accompanied by muscarinic side effects.

The regional curare test is considered the method of choice.[22–24] Because this test is useful in the assessment of patients with neuromuscular disorders, the following is a general description of the regional curare test administration and interpretation.

Regional Curare Test

The regional curare test has been used for many years in the diagnosis of myasthenia gravis.[23,25] Although there are several different ways to perform the test, they are all fundamentally similar. The following is the method used by Brown and Charlton.[26] The patient's forearm is isolated from the general circulation by a tourniquet and d-tubocurarine, 0.5 mg in 20 ml of saline, is administered into one of the forearm veins. After 4.5 min, the tourniquet is released. At 1, 11, and 21 min after release of the tourniquet, a train-of-nine (nine supramaximal electrical stimuli at a frequency of 3 Hz for a 3-s period) is administered to the ulnar nerve, and muscle action potentials of the abductor digitii minimi on the same side are recorded and analyzed.

If the fade of the train-of-nine is greater and its recovery slower than normal, it is concluded that the tested subject has an increased response to nondepolarizing muscle relaxants. Conversely, if the fade is smaller and recovery faster than normal, it is concluded that the tested subject is resistant to nondepolarizing muscle relaxants (figs. 1–3).

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TABLE 1. Summary of Reported Responses of Patients with Neuromuscular Disorders to Muscle Relaxants

Neuromuscular Disorder	Response to Nondepolarizing Muscle Relaxants	Response to Succinylcholine	Period of Vulnerability to Hyperkalemia
Hemiplegia	Decreased[10,11,24]	Hyperkalemia[1,3,27]	7 days[27] to 6 months[1]
Parkinsonism	Normal[24]	Normal[38]	
		Hyperkalemia[4]	Not reported
Multiple sclerosis	Normal[43,45,46]	Hyperkalemia[38]	Not reported
Diffuse head injury	Not reported	Hyperkalemia[1,12]	Not reported
Encephalitis	Not reported	Hyperkalemia[2]	Not reported
Ruptured cerebral aneurysm	Not reported	Hyperkalemia[13,27]	Not reported
Tetanus	Normal[53]	Hyperkalemia[53]	Not reported
Paraplegia	Increased[24]	Hyperkalemia[14,15,54-56]	3 weeks[54] to 85 days[56]
Amyotrophic lateral sclerosis	Increased[5,24]	Contracture[61]	
Poliomyelitis	Increased[62-64]	Not reported	
Acute anterior Horn disease	Not reported	Hyperkalemia[65]	Not reported
Neurofibromatosis	Increased[6,68,69]	Resistance[6]	
Peripheral neuropathies	Decreased[70]	Not reported	
Muscular denervation	Normal[24]	Contracture[16,39,75-78]	22 to 92 days[41]
		Hyperkalemia[39-41,57]	
Myasthenia gravis			
Active	Increased[93,94]	Resistance[95,97]	
In remission	Increased[93,104]	Not reported	
	Normal[106]		
Myasthenic syndrome	Increased[8,94]	Increased[8]	
Myotonia	Normal[24,123,127]	Contracture[7,17,133]	
	Increased[127,128]	Normal[126,130-132]	
		Increased[135]	
		Malignant hyperthermia?[18,138]	
Muscular dystrophy	Normal[135,154]	Normal[135,154]	
	Increased[24]	Cardiac arrest[20,154,157]	
		Myoglobinuria[20]	
		Malignant hyperthermia?[159-165]	
Ocular muscular dystrophy	Increased[19,155,156]	Not reported	

The fade of the train-of-nine can be expressed mathematically as the ratio between the first (T1) and the last (T9) muscle action potentials in the train. The greater the fade ratio the greater the "sensitivity" of the patient to nondepolarizing muscle relaxants. The mean fade ratios in 22 normal subjects were 1.76, 1.29, and 1.09, at 1, 11, and 21 min after the release of the tourniquet, respectively.[26]

Intracranial Lesions

HEMIPLEGIA

Hemiplegia is a common sequalae of cerebrovascular accidents and is caused by an upper motor neurone lesion in the cerebral motor cortex. It has been associated with resistance to nondepolarizing muscle relaxants[10,11,24] and hyperkalemia following succinylcholine administration.[1,3,27]

Brown and Charlton[24] studied the regional curare test in 12 hemiplegic patients and observed larger muscle action potentials and smaller fade ratios in the afflicted side when compared with the normal side (fig. 1). This suggests resistance to nondepolarizing muscle relaxants in the afflicted side. The age and severity of the stroke did not correlate with the degree of resistance. One patient with bilateral hemiplegia showed resistance to *d*-tubocurarine on both sides. In another report[28] two myasthenic patients who had become hemiplegic following cerebrovascular accidents had no clinical or EMG signs of myasthenia gravis on the hemiplegic side.

Resistance to nondepolarizing muscle relaxants in hemiplegic patients also has been observed during anesthesia.[10] In one patient, following 9 mg of pancuronium, the normal side showed complete neuromuscular blockade, while the afflicted side showed no decrease in twitch response, no fade of tetanic response, and no posttetanic potentiation. Surgical relaxation was adequate. In another patient, following 7 mg of pancuronium, the train-of-four ratio on the normal side was 0, while that on the afflicted side was 0.8. Relaxation for tracheal intubation was adequate. In yet another case, a quadriplegic patient weighing only 40 kg received 4 mg of pancuronium. Tetanic stimulation of the ulnar, median, and tibialis posterior

nerves on either side produced sustained contractions without posttetanic potentiation, suggesting resistance to nondepolarizing muscle relaxants in all four extremities. The jaw and vocal cords were relaxed adequately for tracheal intubation, suggesting normal response of the unafflicted cranial muscles to nondepolarizing muscle relaxants.

The cause for the resistance to nondepolarizing muscle relaxants in hemiplegia is not clear. EMG studies of the afflicted muscles show fibrillation potentials,[29,30] slowing of nerve conduction,[31,32] and loss of motor units.[33] Electronmicroscopic examination reveals a reduction in the number of motor units and sprouting of the remaining axons.[34] The new axonal branches produce new junctions with the muscle membrane and extend the area that responds to acetylcholine beyond the neuromuscular junction until it eventually envelops the entire muscle fiber. This phenomenon is common to all denervated muscles and is called extrajunctional chemosensitivity.

Moorthy and Hilgenberg[11] speculate that extrajunctional chemosensitivity increases the muscle's response to acetylcholine and thus produces resistance to nondepolarizing muscle relaxants. This explanation is difficult to accept, since extrajunctional chemosensitivity also occurs in patients with lower motor neurone lesions,[35] yet increased response, rather than resistance to nondepolarizing muscle relaxants, is seen in the latter.[5,6,36,37] Furthermore, resistance to nondepolarizing muscle relaxants in hemiplegia is apparent as early as two days following a stroke, while the EMG and histologic changes do not appear until 2 months later.[33]

The early appearance of resistance to nondepolarizing muscle relaxants in hemiplegia suggests a possible facilitative central nervous system (CNS) effect at the neuromuscular junction. Brown and Charlton[24] speculate that normally there is an interplay between inhibitory and facilitative CNS effects at the neuromuscular junction and that in patients with CNS lesions the interplay is unbalanced. Depending on the anatomic site of the lesion, either facilitation or inhibition prevails. This would explain the opposite effects of cerebral *versus* spinal lesions.

Of clinical importance, monitoring neuromuscular transmission in the afflicted side of hemiplegic patients may lead to underestimation of the neuromuscular blockade and possibly to the administration of excessive doses of nondepolarizing muscle relaxants. It also may lead to a premature discontinuation of mechanical ventilation postoperatively.

There are several reports of hyperkalemia and ventricular fibrillation following succinylcholine administration in hemiplegic patients.[1,3,27] Thomas[27] reported two episodes of cardiovascular collapse in a quadriplegic patient 1 week after a stroke. Serum potassium level during

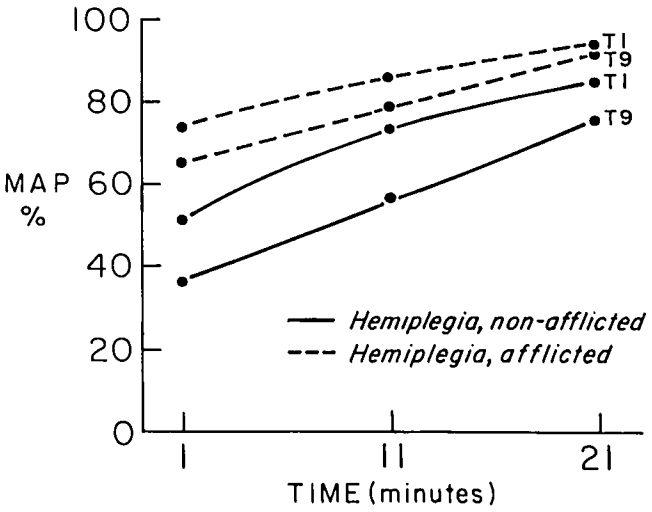

FIG. 1. Mean train-of-nine values in 12 hemiplegic patients during recovery from the regional curare test. MAP%—muscle action potential in per cent of precurare values. T1, T9—the 1st and 9th responses, respectively. Data obtained from Brown and Charlton.[24] For more details see text.

one of the episodes was 7.2 mEq/l. Cooperman *et al.*[3] reported hyperkalemia in two hemiparetic patients. In one, 3 weeks following a stroke, the serum potassium rose from 3.88 to 8.93 mEq/l.

The period of vulnerability to hyperkalemia in hemiplegic patients has not been defined. Hyperkalemia occurred as early as 1 week[27] and as late as 6 months[1] following a stroke. Although there are no reports of hyperkalemia in patients with a stroke older than 6 months,

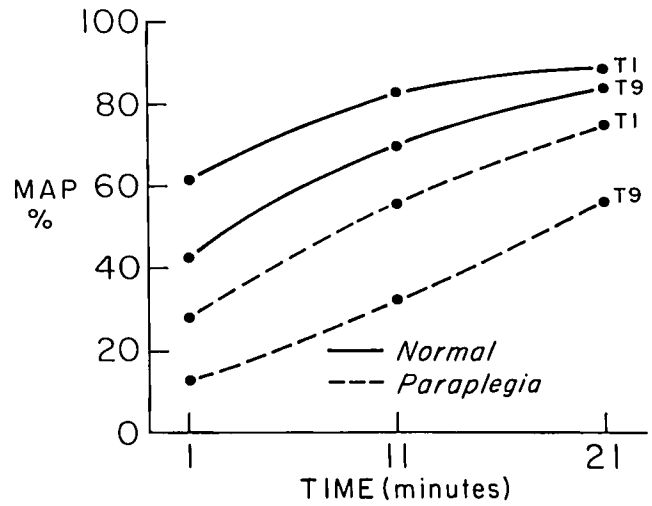

FIG. 2. Mean train-of-nine values in 22 normal subjects and 8 paraplegic patients during recovery from the regional curare test. MAP%—muscle action potential in per cent of precurare values. T1, T9—the 1st and 9th responses, respectively. Data obtained from Brown and Charlton.[24] For more details see text.

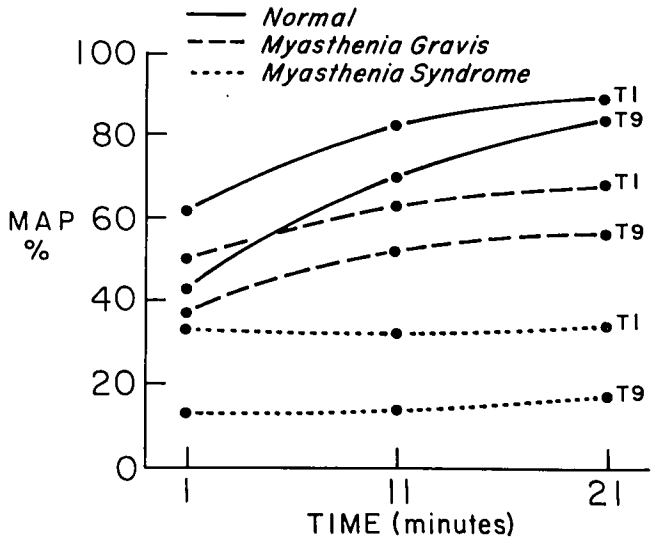

FIG. 3. Mean train-of-nine values in 22 normal subjects, 21 myasthenia gravis patients, and 2 myasthenic syndrome patients during recovery from the regional curare test. MAP%—muscle action potentials in per cent of precurare values. T1, T9—the 1st and 9th responses, respectively. Data obtained from Brown and Charlton.[93] For more details see text.

succinylcholine administration should be avoided when possible in all hemiplegic patients.

PARKINSON'S DISEASE

Parkinson's disease is an extrapyramidal disorder characterized by muscular weakness, rigidity, and tremor. There are no reports of abnormal response to nondepolarizing muscle relaxants in patients with this disorder. Brown and Charlton[24] performed the regional curare test in eight patients and found a wide range of responses, but all were within normal limits.

There are conflicting reports on the response of Parkinson patients to succinylcholine. Cooperman,[38] in an unspecified number of patients, observed insignificant changes in serum potassium. In contrast, Gravlee[4] reported in one patient a rise in serum potassium from 4.2 to 7.6 mEq/l and hyperkalemic electrocardiographic (EKG) changes during succinylcholine infusion. Serum potassium level, determined 10 and 45 min after the succinylcholine infusion had been discontinued, was 6.0 and 3.9 mEq/l, respectively.

The lack of other reports of hyperkalemia in a common disorder such as Parkinson's disease casts doubt on the cause of hyperkalemia in Gravlee's patient. The patient had had two lumbar laminectomies for low back pain and possibly had sustained muscular denervation. The hyperkalemia observed by Gravlee therefore could be due to potassium released from denervated muscles[39-41] rather than "Parkinsonian" muscles.

MULTIPLE SCLEROSIS

Multiple sclerosis, a demyelinating disorder of the CNS, causes muscular weakness, visual disturbances, numbness, and parasthesias. Some patients exhibit a myotonia-like contracture without the typical myotonic EMG.[42] (The characteristics and possible mechanisms of muscular contracture are discussed under Muscular Denervation in this review). Occasionally the symptoms of multiple sclerosis get worse following anesthesia and surgery,[43] probably due to a rise in body temperature.[44,45]

There are no reports of abnormal response to nondepolarizing muscle relaxants in multiple sclerosis. "Usual" doses of alcuronium,[43] *d*-tubocurarine,[45,46] and gallamine[46] were tolerated well. There is one report of hyperkalemia following succinylcholine.[38] The lack of other reports suggests low vulnerability and incidence of succinylcholine-induced hyperkalemia in this disorder.

DIFFUSE INTRACRANIAL LESIONS

There have been several reports of hyperkalemia and cardiac arrest following succinylcholine administration in patients with diffuse intracranial lesions.[1,2,12,13,27] These patients had neither focal neurologic deficits nor muscular denervation and paralysis. Smith and Grenvik[1] reported two episodes of cardiac arrest in one patient 26 and 35 days after a head injury. The patient was resuscitated, and surgery was postponed on both occasions. A third attempt to anesthetize the patient, this time avoiding succinylcholine, was uneventful. Stevenson and Birch[12] also reported two episodes of hyperkalemia and ventricular tachycardia in one patient 52 and 60 days after a head injury.

The cause for cardiac arrest in Smith and Grenvik's patient[1] is not clear. In addition to the head injury, the patient had injuries to the chest and extremities. Massive trauma has been associated with succinylcholine-induced hyperkalemia,[47-50] and this, rather than the head injury, possibly could be the cause of the hyperkalemia in their patient.

Cowgill *et al.*[2] reported serum potassium level over 10 mEq/l following succinylcholine administration in a patient with terminal encephalitis. The patient had been bed ridden for 5 months and had hyperactive deep tendon reflexes but no other neurologic abnormalities. Although it has been suggested that debilitated patients with disuse atrophy possibly may sustain hyperkalemia following succinylcholine administration,[51] this has never been reported in humans.

Hyperkalemia following succinylcholine administration also has been reported in patients with ruptured cerebral aneurysm.[13,27] In a series of 22 patients, 10–50 days after the rupture, succinylcholine administration caused 1–6 mEq/l rise in serum potassium in eight patients.[13] Al-

though some of the patients had motor paralysis, the degree of hyperkalemia did not correlate with the extent of paralysis. Surprisingly, although substantial rises in serum potassium occurred (in one patient up to 10 mEq/l), there were no incidents of cardiovascular collapse or hyperkalemic EKG changes in this series. The authors did not describe their method of serum potassium determination.

Tetanus

Tetanus is an acute infectious disease of the CNS caused by *Clostridium tetani.* The bacteria release an endotoxin that enters the CNS, probably via peripheral motor fibers, and blocks the normal inhibitory effect of the CNS on peripheral synapses. This is believed to be the cause of spasticity and tonic convulsions in this disease.[52]

No complications were observed in tetanus patients who were given nondepolarizing muscle relaxants for passive muscular exercise.[53] In contrast, succinylcholine-induced hyperkalemia, up to 7.4 mEq/l, and cardiac arrest were reported in two patients.[53] Although tetanus patients are bed-ridden and often sustain disuse atrophy, this is probably not the cause for the hyperkalemia, since muscular wasting *per se* never has been associated with succinylcholine-induced hyperkalemia in humans.

Spinal Cord Lesions

Paraplegia and Quadriplegia

Paraplegia and quadriplegia usually are caused by a traumatic or pathologic transection of the spinal cord and interruption of pyramidal tracts. Increased response to nondepolarizing muscle relaxants[24] and hyperkalemia following succinylcholine administration[14,15,54–56] have been reported in these patients.

Brown and Charlton[24] performed the regional curare test in eight paraplegic patients and found increased response to *d*-tubocurarine (fig. 2). This is in contrast to the findings in hemiplegia, which is also an upper motor neurone disorder, where resistance to nondepolarizing muscle relaxants, rather than increased response, was observed.[10,11,24] A possible explanation for this difference is discussed under "Hemiplegia" in this review.

The clinical implications of increased response to nondepolarizing muscle relaxants in paraplegia and quadriplegia depend on whether or not the respiratory muscles are involved. If the paralysis is limited to the lower extremities, the increased response is of little concern. However, if the respiratory muscles are involved, the administration of nondepolarizing muscle relaxants during surgery may cause respiratory failure postoperatively. Continuous monitoring of the neuromuscular junction and reduced doses of muscle relaxants are recommended in these patients.

There are numerous reports of hyperkalemia and cardiac arrest following succinylcholine administration in paraplegic patients.[14,15,54–56] Brooke *et al.*[55] described the sequence of events: Immediately following succinylcholine administration the patient developed bradycardia of 50–60 beats/min and then tachycardia of 100–120 beats/min, followed by ventricular fibrillation. Cardiopulmonary resuscitation restored regular sinus rhythm within 3–4 min. Serum potassium levels, determined 5 min and then 3 h later, were 7.4 mEq/l and 3.4 mEq/l, respectively.

Tobey[56] observed cardiac arrest following succinylcholine in four paraplegic patients 44 to 85 days following a spinal cord injury. He then studied another four paraplegic patients and determined the serum potassium level during succinylcholine infusion. Four minutes after the infusion was started, hyperkalemic EKG changes were seen and the serum potassium level rose significantly in all patients. Although the succinylcholine infusion was discontinued immediately, one patient developed ventricular fibrillation. Five minutes after succinylcholine was discontinued, serum potassium level returned to normal in all patients. Serum potassium level in blood drawn from the inferior vena cava was significantly higher than in that drawn from the superior vena cava, suggesting that the hyperkalemia is due to potassium released from the paralyzed muscles of the lower extremities.

The period of vulnerability to hyperkalemia in paraplegic patients has not been defined. There are no reports of succinylcholine-induced hyperkalemia immediately following spinal cord injury, however, as early as 3 weeks[54] and as late as 85 days[56] after spinal cord injury, significant hyperkalemia was reported. In paraplegic dogs, succinylcholine caused no rise in serum potassium during the first week after spinal cord injury, incremental rises between the second and the fourth weeks, and decremental rises between the fourth and the eighth weeks.[57] Succinylcholine should be avoided in paraplegic patients except during the immediate postinjury period. If tracheal intubation is indicated, it can be facilitated by a nondepolarizing muscle relaxant or a potent inhalation anesthetic agent. In cases of full stomach and potential danger of pulmonary aspiration, awake tracheal intubation is the method of choice for securing the airway.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis is a degenerative disease of motor ganglia in the anterior horn of the spinal cord and of spinal pyramidal tracts. The presenting symptoms are weakness and atrophy of the hands and arms and weakness and spasticity of the legs. EMG studies of the

afflicted muscles indicate reduction in the number of motor units and increase in the size of the individual muscle action potentials.[36] Histologically, sprouting of the remaining axons occurs.[58]

Patients with amytrophic lateral sclerosis exhibit signs of myasthenia gravis, such as progressive muscular weakness during exercise, fade of tetanic contraction,[36,59] increased response to *d*-tubocurarine,[24] and favorable response to anticholinesterases.[36,59] In one case, following 20 mg of gallamine, muscular paralysis lasted for 2 h.[5]

The cause of neuromuscular transmission failure in amyotrophic lateral sclerosis is not clear. Mulder *et al.*[37] suggest that the new motor end-plates produced by the sprouting axons in the afflicted muscles are defective and "sensitive" to nondepolarizing muscle relaxants. Another more plausible explanation is that acetylcholine synthesis declines at the motor nerve terminals. The enzymes choline acetyltransferase and acetylcholinesterase, which are essential for the synthesis of acetylcholine, normally are manufactured in the anterior horn of the spinal cord and then delivered to the motor nerve endings along motor nerve axons.[58,60] Mulder *et al.*[37] speculate that degeneration of the anterior horns in amytrophic lateral sclerosis results in a reduction in the level of these enzymes at the motor nerve endings. This, in turn, reduces acetylcholine synthesis and causes neuromuscular junction transmission failure and increased response to nondepolarizing muscle relaxants.

The clinical implications of the increased response to nondepolarizing muscle relaxants in amyotrophic lateral sclerosis are the same as in paraplegia: If the paralysis is limited to the lower extremities, the increased response is of little concern. However, if the respiratory muscles are involved, the administration of nondepolarizing muscle relaxants during surgery may cause respiratory failure postoperatively.

A myotonialike contracture may occur following succinylcholine administration in amyotrophic lateral sclerosis patients.[61] The characteristics and possible mechanisms of muscular contracture in this and other neuromuscular disorders are discussed under "Muscular Denervation" in this review.

There are no reports of hyperkalemia following succinylcholine in amyotrophic lateral sclerosis. However, the muscular denervation and atrophy that often occurs in these patients is likely to be associated with potassium release and hyperkalemia following succinylcholine administration. Succinylcholine therefore should be avoided in patients with significant muscular denervation.

Poliomyelitis and Acute Anterior Horn Cell Disease

Poliomyelitis is an infectious viral disease of motor ganglia in the anterior horns of the spinal cord and in the medulla. It causes flaccid paralysis of the extremities and may involve the respiratory muscles. EMG studies of the afflicted muscles suggest neuromuscular junction transmission failure: The single muscle action potentials are small and tetanic trains fade.[62–64] The cause of neuromuscular junction dysfunction in poliomyelitis is not known but possibly could be the same as that suggested for amyotrophic lateral sclerosis, namely a decrease in acetylcholine synthesis.[37]

The clinical implications in poliomyelitis are the same as in paraplegia and amyotrophic lateral sclerosis: If the paralysis is limited to the lower extremities increased response to nondepolarized muscle relaxants is of little concern. However, if the respiratory muscles are involved the administration of nondepolarizing muscle relaxants during surgery may cause respiratory failure postoperatively.

Succinylcholine-induced hyperkalemia and circulatory collapse were reported in a patient with acute idiopathic anterior horn cell disease.[65] The patient, an 8-year-old boy, had developed acute generalized motor weakness and respiratory failure and required mechanical ventilation. On the 61st day of his illness, during direct laryngoscopy under general anesthesia, cardiac arrest occurred 3 min after succinylcholine administration. Cardiopulmonary resuscitation was successful, and normal sinus rhythm was restored within 30 s. The serum potassium level during the cardiac arrest was 7.9 mEq/l.

Peripheral Nerve Lesions

Peripheral Neuropathies

Peripheral neuropathies often are a result of systemic disorders such as diabetes mellitus, peripheral vascular insufficiency, metastatic neoplasms, alcoholism, vitamin deficiencies, and heavy metal poisoning.[66] The clinical signs of peripheral neuropathy are sensory loss, parasthesias, and occasionally muscular weakness and atrophy. In some patients the EMG may resemble that of myasthenia gravis, but unlike myasthenia gravis patients, these patients do not respond to anticholinesterases.[67]

The regional curare test in patients with peripheral neuropathies is normal.[24] However, resistance to succinylcholine[6] and increased response to nondepolarizing muscle relaxants[6,68,69] were observed in patients with neurofibromatosis. Baraka[6] administered succinylcholine 100 mg to a patient with neurofibromatosis and observed no decrease in twitch response and no clinical relaxation. He then administered 30 mg of *d*-tubocurarine and observed complete paralysis for 2.5 h and partial paralysis for another 5 h. Prolonged apnea also was reported following pancuronium.[69] The response of patients with neurofibromatosis to muscle relaxants resembles that of

myasthenia gravis patients and suggests similar pathophysiology at the neuromuscular junction.

An unusual response to *d*-tubocurarine was reported in a patient with severe peripheral neuropathy associated with metastatic carcinoma of the uterus[70]: following 21 mg of *d*-tubocurarine, the twitch response decreased in a normal fashion, but the tetanic response remained sustained and posttetanic potentiation did not occur. The authors speculate that in severe peripheral neuropathies the afflicted nerves fail to conduct the complete frequency of tetanic trains and that only a fraction of the original train reaches the neuromuscular junction. The decimated train is possibly too weak to cause tetanic fade and posttetanic potentiation.

Muscular Denervation

Muscular denervation is usually a result of a traumatic peripheral nerve damage. The afflicted muscles undergo atrophy and the EMG shows fibrillation potentials.[71] One to two weeks following the denervation, extrajunctional chemosensitivity develops and eventually the entire muscle membrane responds to acetylcholine.[34] Also, denervation apparently induces the appearance of abnormal sodium channels,[72] which apparently cause significant sodium current at resting potential. The resting potential therefore is relatively reduced when compared with normally innervated muscles.[73] This possibly may be the explanation for the spontaneous oscillations in membrane potential and fibrillation potentials seen in denervated muscles.[74]

The regional curare test of denervated muscles is normal, suggesting normal response to nondepolarizing muscle relaxants.[24] The response to succinylcholine, however, is abnormal and characterized by muscular contracture[16,39,75–78] and hyperkalemia.[39–41,57]

Muscular contracture is defined as an abnormal state of tension in a muscle, usually caused by an agonist such as acetylcholine or succinylcholine and accompanied by total electrical silence. In contrast, muscular contraction is defined as a normal state of tension in a muscle caused by an electrical stimulation of a peripheral nerve and accompanied by muscle action potential.[79] Muscular contracture may occur spontaneously or following succinylcholine in denervated muscles,[16,39,75–78] multiple sclerosis,[42] amyotrophic lateral sclerosis,[61] or myotonia.[80]

There are several theories on the cause of muscular contracture. Brim[76] suggests the following possibilities: a prolonged and intense action of acetylcholine at the end-plate; an increase in the number of acetylcholine receptors at the end-plate; a decrease in cholinesterase activity at the end-plate. Others suggest extrajunctional chemosensitivity as the cause of contracture.[16,35,39,75,77,81]

These theories are all based on the well-documented increased response of denervated muscles to acetylcholine.[35] Smaller amounts of acetylcholine are required to produce action potential and muscular contraction when compared with normally innervated muscles. These theories, however, are difficult to accept because the normal response of the end-plate to acetylcholine is "all-or-none." Once the postjunctional membrane is depolarized, further potentiation of acetylcholine or succinylcholine would prolong depolarization and cause paralysis rather than muscular contracture. Also, the electrical silence observed during muscular contracture[35] does not support theories that are based on either increased acetylcholine receptor binding by agonists or repetitive membrane depolarization and firing.

Jenkinson and Nicholls[82] studied the effect of acetylcholine on ion movements and contractility in chronically denervated diaphragms of rats. They showed that acetylcholine caused an increase in ion movements across the membrane of denervated and depolarized muscles and produced a state of contracture that was not accompanied by electrical activity. They also showed that the presence of calcium in the experimental bath was essential for the development of a state of contracture. They concluded that in denervated muscles acetylcholine promotes the entry of calcium ions into the cell, which in turn interact directly with the contractile elements inside the cell and cause contracture. This occurs independent of acetylcholine receptors binding and membrane depolarization.

A major concern in patients with denervated muscles is the hyperkalemia that often occurs following succinylcholine administration. This has been well documented[39–41,57] and its mechanism reviewed.[83] In humans, 22 to 192 days after muscular denervation, an average increase of 4 mEq/l was observed in blood samples drawn from the afflicted extremities.[41] In dogs succinylcholine-induced hyperkalemia became significant at 14 days after denervation and it peaked at 28 days.[57] In baboons significant succinylcholine-induced hyperkalemia occurred at 4 days after denervation and it peaked at 14 days.[84] That the hyperkalemia is due to potassium released from denervated muscles is supported by the observation that blood drawn from afflicted extremities had significantly higher levels of potassium than that drawn from normal extremities.[40]

A small dose of a nondepolarizing muscle relaxant, given prior to the administration of succinylcholine, attenuates the state of contracture and the release of potassium in patients with denervated muscles.[41] However, complete prevention of succinylcholine-induced hyperkalemia required up to 0.5 mg/kg of *d*-tubocurarine.[77] Pretreatment with a nondepolarizing muscle relaxant, therefore, does not afford protection against succinylcholine-induced hyperkalemia. Succinylcholine should be

avoided in patients with significant muscular denervation, except during the first postinjury week.

Neuromuscular Junction Lesions

Myasthenia Gravis

Myasthenia gravis is a disorder of the neuromuscular junction manifested by weakness and fatigability of voluntary muscles. Characteristics of the neuromuscular junction dysfunction are a decremental response of the evoked muscle action potentials to a train of electrical stimuli, increased jitter and neuromuscular blockade on single fiber EMG study, small miniature end-plate potentials, and reduced junctional acetylcholine sensitivity.[85] Electronmicroscopic examination of the neuromuscular junction shows pathologic changes in the postsynaptic area.[86] Using bungarotoxins[87] and measuring miniature end-plate currents,[88] the presence of a postsynaptic acetylcholine receptor lesion has been confirmed.

Although most investigators agree that the principle cause of myasthenia gravis is a postsynaptic reduction in the number of acetylcholine receptors caused by autoimmune disease,[89] some still believe that a presynaptic lesion that interferes with acetylcholine production and release also exists.[90] A recent report, however, suggests that presynaptic acetylcholine pool is normal and acetylcholine release is two to five times greater than normal in myasthenia gravis.[91]

An additional possible mechanism of neuromuscular junction dysfunction in myasthenia gravis has been recognized recently.[92] Studies with autoimmune myasthenia gravis sheep sera suggest that the antibodies inhibit postsynaptic receptor function by occupying the receptor's ion channel molecule, rather than its acetylcholine recognition site. The binding of ion channel molecules by antibodies interferes with confirmational changes that normally occur in these molecules subsequent to acetylcholine binding of the acetylcholine recognition sites and thus inhibits ion exchange and function of the neuromuscular junction.

The regional curare test in myasthenia gravis patients usually shows increased response to *d*-tubocurarine and prolongation of its effect[93] (fig. 3). This suggests increased response and affinity between acetylcholine receptors and nondepolarizing muscle relaxants.[94]

The response of myasthenia gravis patients to succinylcholine is also abnormal. Resistance and early appearance of phase II block have been reported.[95–97] Many anesthesiologists, therefore, refrain from using muscle relaxants in patients with myasthenia gravis, and when surgical relaxation is needed they resort to volatile inhalation anesthesia.[98–101]

The use of volatile inhalation anesthetics, however, also has drawbacks. Ether type agents such as diethylether[98] methoxyflurane,[102] and possibly enflurane and isoflurane have potent neuromuscular blocking effect, particularly in myasthenia gravis. Low concentrations of diethyl ether and methoxyflurane cause muscular paralysis in myasthenia gravis patients and, because of high fat solubility and slow elimination, the agents possibly may cause postoperative respiratory failure. Also, myasthenia gravis patients with cardiac disorders may not tolerate volatile inhalation anesthesia. In such patients the use of muscle relaxants should be considered.

There are several reports of uneventful administration of muscle relaxants in myasthenia gravis patients. Baraka *et al.*[97] observed 90% twitch depression following 20 mg succinylcholine. I observed, following succinylcholine 1 mg/kg, 90% twitch depression, adequate relaxation for tracheal intubation, and normal recovery time, despite early appearance of phase II block.† Although recovery from phase II block following one dose of succinylcholine was uneventful, the effect of larger and repeated doses is unknown.

Pancuronium[103] and *d*-tubocurarine† in small doses have been used in myasthenia gravis patients without complications. As little as 0.005 mg/kg of pancuronium or 1.5 mg of *d*-tubocurarine were sufficient to produce over 90% twitch depression. The recovery from these small doses was uneventful, and no respiratory support was required postoperatively.

There are conflicting reports on the response of myasthenia gravis patients in remission to nondepolarizing muscle relaxants. Brown and Charlton[93] reported no improvement in the regional curare test of one patient, but they gave no clinical details. Lake[104] reported 90% twitch depression following 3 mg *d*-tubocurarine in a patient who allegedly had been in remission. Six weeks later, while being treated with prednisone, further surgery was necessary, and this time 6 mg of *d*-tubocurarine produced 90% twitch depression during enflurane (1.5%) anesthesia. Based on these observations, Lake concluded that myasthenia gravis patients in remission remain "hypersensitive" to nondepolarizing muscle relaxants.

Lake's conclusion is questionable for the following reasons: On admission the patient had divergent strabismus, bilateral ptosis, and weakness of the triceps and was not in remission, contrary to the author's statement. It is not surprising, therefore, that during the first surgical procedure the patient exhibited increased response to *d*-tubocurarine. Six weeks later, while taking prednisone under supervision, the patient's response to 6 mg of *d*-tubocurarine under enflurane anesthesia was within

† Azar I: Unpublished data.

normal limits, the author's conclusion notwithstanding. Enflurane normally potentiates the neuromuscular blocking effect of nondepolarizing muscle relaxants and significantly reduces the dose required to produce surgical relaxation.[105]

Fillmore *et al.*[106] reported normal response to *d*-tubocurarine in one myasthenia gravis patient in remission. The patient was given 24 mg of *d*-tubocurarine during enflurane anesthesia, and 24 h later he responded promptly to neostigmine. A year later, while still in remission, the patient had another surgical procedure under general anesthesia. This time 30 mg of *d*-tubocurarine were given and the patient recovered uneventfully at the conclusion of a 3-h procedure.

Despite the conflicting reports it seems that myasthenia gravis patients in remission respond normally to nondepolarizing muscle relaxants. However, since remission is often incomplete, muscle relaxants should be used in small intermittent doses and neuromuscular transmission should be monitored continuously during surgery.

If a myasthenia gravis patient is given muscle relaxants, precautions should be taken when other drugs that possess neuromuscular blocking effect are being administered simultaneously. Profound paralysis occurred in one patient who had recovered uneventfully from 1 mg pancuronium and was then given thiophosphoramide (Thiotepa®; Lederle, Wayne, New Jersey) and gentamycin.[107] The latter two drugs are known potentiators of muscle relaxants, and in myasthenia gravis patients they may cause complete paralysis. Similarly, antiarrhythmic drugs such as quinidine[108,109] and procainamide[109,110] should be used cautiously because of their ability to aggravate the symptoms of myasthenia gravis and possibly potentiate muscle relaxants.

When possible, anticholinesterase therapy should be discontinued the night before surgery, since this therapy may complicate the anesthetic management of the myasthenic patient. Anticholinesterases have a dual effect at the neuromuscular junction and occasionally may aggravate, rather than ameliorate, the symptoms of myasthenia gravis.[111] Their presence may complicate the differential diagnosis and treatment of postoperative respiratory failure. Also, if the use of muscle relaxants becomes necessary during surgery, excess anticholinesterase would prolong the effect of succinylcholine and antagonize the effect of nondepolarizing muscle relaxants. Some recommend to discontinue anticholinesterase therapy 24 h prior to surgery[112] and others 1–4 days earlier.[100]

Myasthenic Syndrome

Myasthenic syndrome differs clinically and electromyographically from myasthenia gravis. It occurs mostly in male patients 50–70 years old and is associated with small cell carcinoma of the lung[113,114] and other malignancies.[115] The symptoms are fatigability and aches in the proximal muscles of the extremities. Unlike myasthenia gravis patients, myasthenic syndrome patients experience an increase in muscle strength with exercise, respond poorly to anticholinesterase, and have an exaggerated response to both depolarizing and nondepolarizing muscle relaxants.[8]

The pathology in myasthenic syndrome is believed to be a presynaptic lesion at the neuromuscular junction.[28,91] Although the number of acetylcholine vesicles and their quantal contents are normal, the total amount of acetylcholine released by nerve stimulation is smaller than normal.[91,116]

The response to *d*-tubocurarine in myasthenic syndrome is significantly greater than in myasthenia gravis. Brown and Charlton[93] studied the regional curare test in two patients with myasthenic syndrome and found smaller muscle action potentials and greater fade ratios when compared with patients with myasthenia gravis (fig. 3). Wise[8] reported a 24-h period of paralysis following 5 mg *d*-tubocurarine in one patient.

Muscular Lesions

Myotonias

The genetic and clinical features of the myotonias have been reviewed recently.[80] A symptom common to all myotonias is delayed relaxation of skeletal muscles following voluntary contractions. The site of the lesion is in the muscle fiber distal to the neuromuscular junction but its nature is uncertain.[117–120] Repetitive nerve stimulation causes a gradual and sustained increase in muscle tension without concomitant electrical activity in the muscle.[121] Sprouting of motor nerve axons, extrajunctional chemosensitivity,[122] and a decrease in cholinesterase level at the neuromuscular junction[120] have been observed in myotonic muscles.

There are conflicting reports on the response of myotonic patients to nondepolarizing muscle relaxants. The regional curare test in 12 patients was normal.[24] The response to "usual" clinical doses of *d*-tubocurarine[123–126] and pancuronium[127] also was normal. Mudge *et al.*,[128] however, reported in one patient paralysis that lasted for 3.5 h after 25 mg *d*-tubocurarine. Also, Mitchell *et al.*[129] reported in one patient 99% twitch depression and prolonged recovery time following 0.25 mg/kg of *d*-tubocurarine. Reversal with neostigmine was prompt.

Since myotonias often are associated with dystrophic muscular changes, it is conceivable that in advanced cases there will be an increased response to nondepolarizing

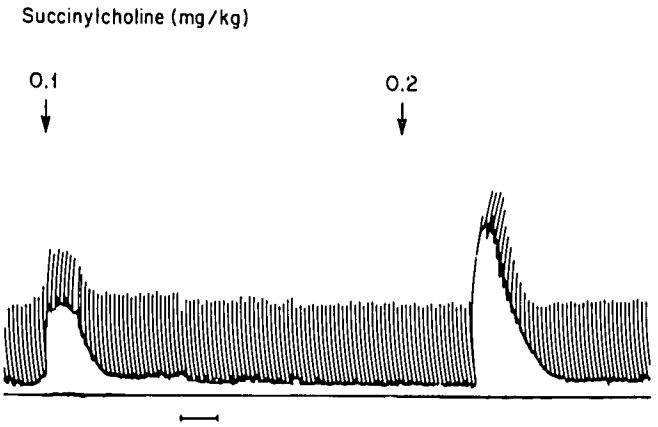

FIG. 4. The response of a myotonia patient to succinylcholine. The depression in twitch response occurred concomitantly with an increase in baseline tension of the muscle. Reprinted from Mitchell MM, et al.: Myotonia and neuromuscular blocking agents. Anesthesiology 49:44–48, 1978, with permission from the publishers.

muscle relaxants. The dose of a nondepolarizing muscle relaxant should be reduced according to the degree and extent of muscular waste, and the neuromuscular junction should be monitored continuously during surgery.

The response of myotonic patients to succinylcholine is unpredictable. Some report normal response,[126,130–132] others generalized myotonia and ventilatory embarrassment,[7,17,133] and still others relaxation of the myotonic state.[134,135] A test dose of 3 mg of succinylcholine given to two myotonic siblings had no effect in one and caused generalized contracture and respiratory distress in the other.[136]

Thiel[133] described a typical myotonic response to succinylcholine: One minute following the administration of succinylcholine generalized spasm developed, the jaw became rigid, the abdomen tight, the limbs flexed, and the cervical and lumbar spine were arched. Respiration ceased. Two minutes later the jaw relaxed, but intubation was impossible until 4 min later. The duration of the apnea was within normal limits. Spontaneous breathing and relaxation of the myotonic contracture occurred simultaneously.

A more severe response to succinylcholine, complicated by laryngospasm and cyanosis, was reported in a patient with myotonia congenita.[7] The myotonic contracture resolved spontaneously, and respiration returned to normal 3.5 minutes later.

Orndahl and Stenberg[61] conducted a prospective study on the response of myotonic patients to succinylcholine. All patients developed generalized myotonic contracture with dose-dependent intensity. Doses of succinylcholine larger than 40 mg did not increase the intensity of the contracture, and multiple repeated doses cause tachyphylaxis and a decrease in the intensity of the contracture.

The mechanical response of myotonic patients to succinylcholine suggests a dual effect of succinylcholine at the neuromuscular junction.[61,129] The twitch response decreases as usual, but tension develops in the muscle and the base line rises concurrently in a dose-dependent fashion (fig. 4). This explains the simultaneous onset of respiratory arrest and muscular contracture following succinylcholine administration.

The similarities between myotonic and denervation contractures suggest similar pathophysiology in these disorders: abnormal ion channels[72] and abnormal entry of calcium ions into the muscle during depolarization.[82] The therapeutic effectiveness in myotonia of quinidine and procainamide, two well-known ion channel blockers,[137] support this hypothesis. The characteristics and possible mechanism of muscular contracture are discussed under "Muscular Denervation" in this review.

The succinylcholine-induced rigidity in myotonia is similar to that observed in malignant hyperthermia. This suggests an association between the two disorders. There are indeed two reports of hyperthermia following succinylcholine administration in myotonia patients,[18,138] however, muscle biopsy studies in five patients, two with congenital myotonia and three with dystrophic myotonia, were not diagnostic of malignant hyperthermia.[139] It generally is believed that there is no increase in susceptibility to malignant hyperthermia in myotonia.[139–141]

Since the response of myotonia patients to succinylcholine is unpredictable, it is recommended that succinylcholine administration be avoided in these patients.

A major difficulty in the anesthetic management of myotonic patients is the myotonic contracture and lack of surgical relaxation. Since the disorder is located inside the muscle fiber, neither muscle relaxants[118,142] nor regional anesthesia and nerve blocks[117,120,143,144] affect the contracture. Only drugs with direct effect on muscle membrane such as quinine,[61,135,145] procainamide,[135,142,146] local anesthetics,[120,144,147] diphenylhydantoin,[148] volatile anesthetic agents,[127] and steroids[146] can attenuate the myotonic contracture.

Procainamide and prednisone are equally effective in attenuating myotonic contracture.[146] Significant improvement was observed in two patients following 0.8–1.0 g of procainamide, although "percussion" myotonia, triggered by the surgeon's handling of the patients' muscles, remained unchanged.[142] Potent inhalation anesthetics usually are effective but at the cost of depressing the cardiovascular system.[127] "High" inspiratory concentration of halothane failed to relax myotonic contracture and did not facilitate tracheal intubation in one patient.[136] Althesin, an intravenous anesthetic agent commonly used in Europe but not approved in the United States, has a direct muscle relaxing effect and has been recommended in the anesthetic management of myotonia patients.[127]

When everything else fails, infiltration of the muscles around the surgical incision with a local anesthetic is recommended.[120,144,146]

Potassium,[143] neostigmine,[143,149] and hypothermia and shivering[133] provoke myotonic contracture. Potassium administration should be avoided except in cases of life-threatening hypokalemia. Neostigmine should be avoided if possible, although it has been used without complications.[120,126,129] Shivering may trigger myotonic contracture and should be avoided by placing the patient on a thermal blanket and raising the room temperature to a level that maintains normal body temperature.

Muscular Dystrophies

The genetic and clinical features of the muscular dystrophies have been reviewed recently.[80] Although considered to be primarily disorders of the muscle fiber proper, some believe that they are secondary to a neurogenic disorder.[150-153] Pathologic changes were observed in the neuromuscular junction of muscular dystrophic patients[152] and mice[151] well before the dystrophic changes appeared in the muscle fiber proper.

There are conflicting reports on the response of muscular dystrophy patients to nondepolarizing muscle relaxants. The regional curare test in 11 patients showed a normal initial blockade, but it lasted significantly longer than normal[24] (fig. 5). However, the response during surgery to gallamine[135,154] and *d*-tubocurarine[154] was reported as "normal."

One particular type of muscular dystrophy, the ocular muscular dystrophy, exhibits exquisite "sensitivity" to *d*-tubocurarine, similar to that seen in myasthenia gravis. Unlike patients with myasthenia gravis, however, patients with ocular muscular dystrophy respond poorly to anticholinesterase therapy.[19,155,156]

A variety of responses to succinylcholine have been reported in patients with muscular dystrophy. Normal response was reported in large series.[135,154] In contrast, cardiac arrest was reported in four patients.[20,154,157] The patients were resuscitated and they all recovered uneventfully, except for postoperative myoglobinuria in one and elevated CPK in another.[20] Although serum potassium levels were not determined, hyperkalemia was suspected as the cause of cardiac arrest in these patients.

Serum levels of CPK and other intracellular enzymes often are elevated in patients with muscular dystrophy.[154] Although malignant hyperthermia has been associated with elevated serum CPK levels,[158] this syndrome did not occur in a series of 43 muscular dystrophy patients that were subjected to general anesthesia. However, there are several case reports of atypical malignant hyperthermia in muscular dystrophy patients.[159-164] Muscle biopsies were studied in some of the patients and found positive

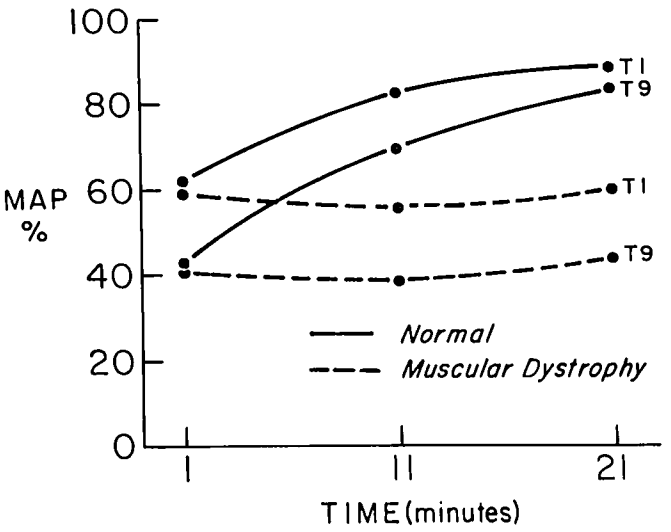

FIG. 5. Mean train-of-nine values in 22 normal subjects and 11 muscular dystrophy patients during recovery from the regional curare test. MAP%—muscle action potential in per cent of precurare values. T1, T9—the 1st and the 9th responses, respectively. Data obtained from Brown and Charlton.[24] For more details see text.

for malignant hyperthermia. Based on these reports Rosenberg and Heiman-Patterson[165] have suggested recently that "It now seems appropriate to state that patients with DMD (Duchenne Muscular Dystrophy) are at greater risk for malignant hyperthermia compared with the general population." However, they do not substantiate this statement with statistical analysis.

Since the response of patients with muscular dystrophy to succinylcholine is unpredictable, it is recommended that succinylcholine administration be avoided in these patients.

The Differential Diagnosis of Rigidity Following Succinylcholine Administration

Rigidity following succinylcholine administration, particularly that of the jaw, is not a rare phenomenon.[16,61,75-78,166-172] Although this may be a prelude to malignant hyperthermia,[172] other disorders also should be considered. Rigidity following succinylcholine has been reported in myotonia,[17,61] muscular dystrophy,[20] amyotrophic lateral sclerosis,[61] chronically denervated muscles,[16,75-78] polymyositis,[18,156] and mitochondrial myopathies.[170,171] Since the clinical symptoms of dystrophic myotonia are not apparent until the third decade of life,[167] some of the unexplained cases of succinylcholine-induced rigidity probably are due to undiagnosed myotonia. Occasionally the cause of the rigidity cannot be determined.

Rigidity after succinylcholine also has been associated with a particular syndrome described as a hypermetabolic muscular derangement.[168] This syndrome shares several

features with malignant hyperthermia. Following the administration of succinylcholine the patient becomes rigid, body temperature rises moderately (usually not higher than 38° C), and limited metabolic and respiratory acidosis develop. The patients usually recover uneventfully, except for postoperative myalgia and myoglobinuria. Studies of muscle biopsy are negative for malignant hyperthermia.[167,168]

The succinylcholine-induced rigidity in myotonia usually is self-limited and benign, while in malignant hyperthermia it may be a prelude to a catastrophe. It is important, therefore, to distinguish between the two as early as possible. One distinguishing sign is the duration of the rigidity. In myotonia the rigidity is short-lived, lasting only as long as the normal paralyzing effect of succinylcholine; in malignant hyperthermia the rigidity lingers well after the normal paralyzing effect of succinylcholine dissipates.[167,172]

When a patient becomes rigid following succinylcholine administration, postponement of surgery should be considered, particularly if it is accompanied by a rise in heart rate, temperature, or blood carbon dioxide level. Cody[17] reviewed the literature and observed that when patients had developed rigidity following succinylcholine, three out of four died when surgery was continued and three out of four survived when it was postponed.

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