Malignant Hyperthermia and Muscular Dystrophies

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BACKGROUND: Patients with muscular dystrophy have been reported to experience a variety of life-threatening complications during and after general anesthesia. We performed a systematic analysis to define the spectrum of anesthetic-related complications in patients with muscular dystrophy, with an emphasis on malignant hyperthermia susceptibility.

METHODS: A literature search was undertaken using multiple search engines and the appropriate articles were reviewed by the authors to determine anesthetic-associated complications in patients with muscular dystrophy. Of all the types of muscular dystrophy, Duchenne muscular dystrophy (DMD) and Becker dystrophy (BD) represent nearly all the anesthesia-related reports.

RESULTS: Anesthetic complications in patients with DMD and BD include intraoperative heart failure, inhaled anesthetic-related rhabdomyolysis (absence of succinylcholine), and succinylcholine-induced rhabdomyolysis and hyperkalemia.

CONCLUSION: We did not find an increased risk of malignant hyperthermia susceptibility in patients with DMD or BD compared with the general population. However, dystrophic patients who are exposed to inhaled anesthetics may develop disease-related cardiac complications, or rarely, a malignant hyperthermia-like syndrome characterized by rhabdomyolysis. This latter complication may also occur postoperatively. Succinylcholine administration is associated with life-threatening hyperkalemia and should be avoided in patients with DMD and BD.

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Malignant hyperthermia (MH) is an uncommon pharmacogenetic condition that results in a hypermetabolic cascade initiated at the skeletal muscle cell on exposure to volatile anesthetics and depolarizing muscle relaxants.[1] A life-threatening clinical picture can rapidly evolve, characterized by rhabdomyolysis, lactic acidosis, hyperthermia, disseminated intravascular coagulopathy, and lethal cardiac arrhythmias.[2,3] MH susceptibility (MHS) is conferred by specific inherited mutations, most commonly related to the ryanodine receptor involved in the excitation-contraction process of the muscle cell.[3–5] When a MHS patient is exposed to a triggering agent, there is destabilization of intracellular calcium regulation resulting in acute MH syndrome.[1]

The muscular dystrophies encompass a diverse group of disorders with varying modes of inheritance and pathophysiological characteristics. The most prevalent are the X-linked recessive types, Duchenne muscular dystrophy (DMD) and Becker dystrophy (BD). Numerous publications in the anesthesia literature have suggested an association between DMD and BD and an increased risk of a MH episode.[6–11]

DMD, which occurs in approximately 30 per 100,000 liveborn males, is caused by a recessive mutation on the X-chromosome that prevents normal formation of dystrophin, a muscle-stabilizing protein. Dystrophin is an important part of the dystrophin-glycoprotein complex. The dystrophin-glycoprotein complex is part of a larger complex of proteins associated with dystrophin, which plays a role in sarcolemmal integrity (Figure 1). Loss of dystrophin (partial in BD or complete in DMD) disrupts sarcolemmal integrity and leads to muscular dystrophy.[12,13]

DMD usually presents in early childhood as weakness and motor delay. Delayed walking beyond 15-mo-old is a common initial sign. During development, clinical manifestations include progressive lower extremity weakness, pseudohypertrophy of the calves, and markedly elevated creatine kinase levels. Almost all patients with DMD are symptomatic by the age of 5 yr, with difficulty running, jumping, climbing steps, and a waddling gait. Proximal weakness causes patients to use their arms in rising from the floor (Gower's sign). Progressive and severe muscle atrophy and weakness cause loss of the ability to ambulate by the age of 14 yr. Cardiac disease in both DMD and BD manifests as a dilated cardiomyopathy and/or cardiac arrhythmias. Approximately, one third of the patients with DMD develop cardiomyopathy by the age of 14 yr and almost all patients have

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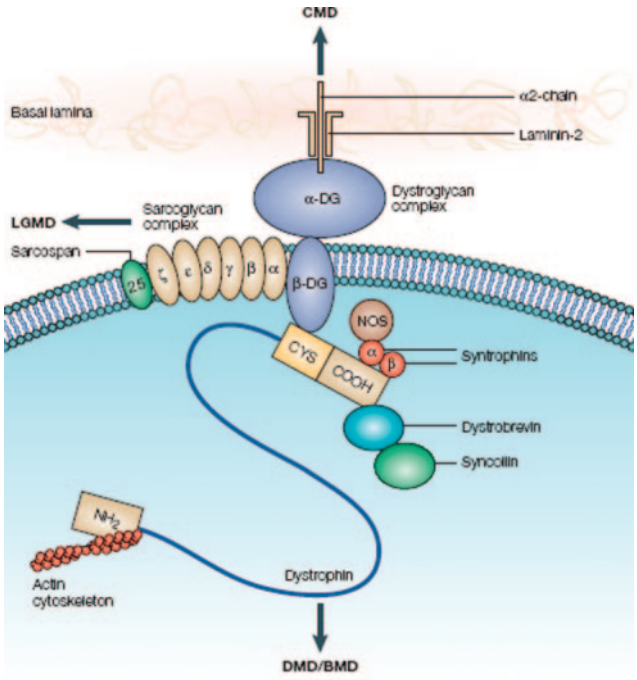

Figure 1. Schematic representation of the organization of the dystrophin-glycoprotein complex (DGC). Various muscular dystrophies (MD) result from defects in the muscle DGC. DMD results from a complete deficiency of dystrophin, whereas a partial deficiency leads to BD. Deficiency in laminin leads to congenital muscular dystrophy and defective glycosylation of the α-dystroglycan leads to limb-girdle muscular dystrophy. BMD = Becker muscular dystrophy; CMD = congenital muscular dystrophy; CYS = cysteine; DG = dystroglycan; DMD = Duchenne muscular dystrophy; LGMD = limb-girdle muscular dystrophy; NOS = nitric oxide synthase. (Adapted with permission from Khurana TS, Davies KE, Nat Rev Drug Discov, 2003, 2, 379–90.)[12]

cardiomyopathy by the age of 18 yr. Patients with DMD ultimately die in early to midadulthood secondary to a progressive cardiomyopathy and/or ventilatory pump insufficiency.

BD, which occurs in approximately 3–6 per 100,000 male births, is an X-linked recessive inherited disorder that is similar to DMD (progressive muscle weakness of the legs and pelvis), but progresses at a slower rate because of a partial loss of dystrophin. Symptoms usually appear in early adolescence, but may begin later. BD patients can present with cardiomyopathy, which is not consistent with their skeletal muscle weakness. Most patients will have cardiomyopathy by 30 yr of age. Mortality in BD patients typically occurs between 30 and 60 yr from respiratory failure or cardiomyopathy. DMD and BD carrier females may either be asymptomatic or have mild musculoskeletal symptoms, but are at risk of dilated cardiomyopathy. The accuracy of genetic testing in diagnosing DMD and BD is rapidly improving.

The risks related to anesthesia and sedation for patients with DMD include potentially fatal reactions to certain anesthetics, upper airway obstruction, hypoventilation, atelectasis, congestive heart failure, cardiac dysrhythmias, respiratory failure, and difficulty weaning from mechanical ventilation. Preoperative evaluation in patients with DMD and BD should include a detailed work-up of their pulmonary function, which includes measurement of forced vital capacity, maximum inspiratory pressure, maximum expiratory pressure, and peak cough flow.[13] Preoperative training with assist devices should be considered based on their pulmonary function.[13] Complete cardiac evaluation should be undertaken before any surgical procedure and a dobutamine stress test should be considered if any abnormalities of cardiac function are present. Medical therapy of any cardiac dysfunction should be optimized before any surgery.[14]

Myotonic dystrophy, an autosomal dominant disorder, characterized by myotonia, weakness of facial and anterior neck muscles, a progressive distal to proximal weakness of the limbs, and involvement of other systems, will be discussed in a separate article in this series of reviews.

We undertook this systematic analysis of the pertinent literature with the purpose of defining the association between DMD and BD, and MHS, and to describe additional anesthesia-related complications.

METHODS

We performed a literature search using PubMed, Medline, OVID, and ISI using the search terms "malignant hyperthermia," "muscular dystrophy," "Duchenne," "Becker," "myopathy," "rhabdomyolysis," and "cardiac arrest," and crossreferenced all with the term "anesthesia." All languages were included but only reviews of abstracts of non-English language studies were possible. References of identified literature were explored, and identified authors were used as additional search terms.

RESULTS

One hundred seventy-three references were identified and reviewed by the authors. Nearly all involved DMD or BD, and thus, the subsequent discussion will be focused on these specific disease entities.

After an initial review of these published cases and studies, and by consensus of the authors, we broadly identified four categories of anesthetic complications in patients with DMD and BD: disease-related (DMD) intraoperative heart failure, rhabdomyolysis and hyperkalemic cardiac arrest in the absence of succinylcholine administration, acute hyperkalemia after administration of succinylcholine, and MH. Postoperative respiratory failure is also a known contributor to perioperative morbidity and mortality in patients with DMD, but has been recently addressed elsewhere.[13]

Intraoperative Heart Failure

Most retrospective reports on the anesthetic management of patients with DMD attest to the safe use of

inhaled volatile anesthetics without succinylcholine.[15–18] Nevertheless, there are several reports of intraoperative heart failure attributable to ventricular insufficiency in patients with known DMD during correction of spinal scoliosis.[16,19–22] Characteristic of each was the sudden onset of a nonviable tachyarrhythmia and/or hypotension. The eventual contribution of the general anesthetic agents to the cause of the event cannot be ascertained because events occurred during IV and inhaled anesthetic exposures, without succinylcholine. Gross perturbations of serum electrolytes were not found; however, continuing intravascular volume resuscitation was an aspect of each procedure. In most cases, markers of adequate volume status just before the onset of the event were identified, but the case reports fail to identify whether the volume administered was transiently insufficient considering continuing losses or if the volume loss overstressed an already compromised left ventricle.

Hemodynamic alterations are imposed by prone positioning, positive pressure ventilation, anesthetic exposure, and blood loss.[13,23] Preoperative echocardiographic assessment of cardiac function and use of invasive monitoring would appear critical to the successful management of these patients.[7]

Rhabdomyolysis in the Absence of Succinylcholine

Intraoperative and postoperative cardiac arrests as a result of rhabdomyolysis and hyperkalemia have occurred in patients with DMD and BD in the absence of succinylcholine administration.[7,24–27]

We identified seven cases of rhabdomyolysis and intraoperative cardiac arrest secondary to hyperkalemia during the use of inhaled anesthetics in patients with DMD.[8,28–32] Halothane was the anesthetic in all cases. The muscular dystrophy status of the patients was not known in three of these cases.[8,29,31] Bradycardia and tachycardia were both observed to precede complete cardiovascular collapse. The time of onset of the clinically significant cardiac arrhythmia after anesthetic induction was variable. Cardiac arrest occurred in some cases with minimal anesthetic exposure, either shortly after induction or during the early portion of the procedure. Initial serum potassium levels exceeded 8 mEq/dL in four patients with no documentation in the other three. Resuscitations persisted in excess of 60 min, with full recoveries obtained in six patients. Dantrolene was often used empirically after documented concomitant metabolic and respiratory acidosis, with or without modest temperature increases. These cases would suggest a predisposition to rhabdomyolysis on exposure to volatile anesthetics regardless of surgical stress. The components of an effective resuscitation are difficult to discern but reduction of the serum potassium is crucial.

We identified eight patients with DMD who developed cardiac arrest secondary to rhabdomyolysis and hyperkalemia in the immediate postoperative period after an uneventful intraoperative course.[10,33–38] The diagnosis of DMD was not known in three patients.[34,36,38] One patient was a female DMD carrier.[37] Nondepolarizing muscle relaxants were used in three patients and reversal drugs administered in two. Inhaled anesthetics included isoflurane, halothane, and sevoflurane. In each case, the patients arrived to the recovery unit awake and hemodynamically stable, only to abruptly develop cardiac arrest shortly thereafter. Four patients survived; two achieved return to baseline function. Four events were fatal. Marked hyperkalemia and metabolic acidosis was consistently identified during the resuscitation, with serum potassium levels in excess of 8 mmol/L in six patients with no documentation in the other two. One patient rapidly responded to defibrillation, but most resuscitation exceeded 45 min to a maximum of 3 h. In these patients, a clear precipitant rhythm or event was difficult to discern.

We identified three patients with BD from 2.5 to 18 yr, who developed anesthesia-related cardiac arrest.[28,34,35] One cardiac arrest occurred intraoperatively and two occurred in the recovery room. One arrest was fatal and the other two resulted in prolonged morbidity. All patients received dantrolene sodium to treat hyperkalemia from presumed MH. However, a diagnosis of MH is unlikely because of the absence of a hypermetabolic state preceding the rhabdomyolysis and hyperkalemic event.

In the two patients who survived, the diagnosis of BD had been established before exposure to the inhaled anesthetic. The patient who had a fatal outcome had a family history of BD that was elicited after the crisis occurred and was confirmed in a postmortem muscle biopsy. Because of the delayed appearance of signs and symptoms of patients with BD, it is possible that undiagnosed patients have undergone anesthesia without untoward complications.

Rhabdomyolysis and Life-Threatening Hyperkalemia After Succinylcholine Administration

We identified 37 patients with previously unrecognized DMD who developed succinylcholine-induced hyperkalemic cardiac arrest.[17,39–61] The majority of these patients did not manifest clinical signs or symptoms of a myopathy at the time of the succinylcholine administration, and therefore, the adverse event led to the eventual diagnosis of a myopathy. The mortality rate in this group of patients was 30%.

Do Muscular Dystrophy Patients have an Increased Risk of MHS?

Clinical suspicion of MH has been reported in patients with DMD and BD.[6,35,45,62] Nine patients with DMD developed unexplained hyperthermia and tachycardia related to the use of halothane,[15,56] and six patients had significant rhabdomyolysis without hyperkalemia.[24,26,27,49,50,63] A majority of these patients had a diagnosis of muscular dystrophy at the time of the anesthetic. In two patients, the symptoms abated after

the volatile anesthetic was withdrawn. Dantrolene was used in some patients because of suspicion of MH.[26,31,34,35,42,49] However, the rhabdomyolysis and other clinical characteristics that result from administration of succinylcholine and volatile anesthetics to patients with DMD share signs similar to those arising from a true MH episode; thus, the two entities are difficult to distinguish. The clinical presentation of an episode of MH can be variable and some patients may not demonstrate significant rhabdomyolysis or even lactic acidosis. It seems unlikely that there is a true genetic association between DMD and MH because the genetic mutation associated with DMD is located on the X chromosome, and the mutations associated with MHS are usually found on chromosome 19. Nevertheless, some patients with DMD have demonstrated a positive caffeine-halothane contracture test indicating MHS.[6,35,55,62,64] The validity of a caffeine-halothane contracture test in patients who have muscular dystrophy has been debatable as the muscles in these patients may be prone to a positive test on exposure to triggering agents.[65–67] However, in all these "clinical MH" cases, the patients suffered acute rhabdomyolysis with hyperkalemia without other classic signs and symptoms of MH, and did not have any evidence of hypermetabolism, which is a hallmark of MH.[1,2]

Although muscular dystrophy patients are unlikely to have an increased risk of MHS, exposure to volatile anesthetics may be associated with life-threatening rhabdomyolysis and therefore should be used cautiously and when the benefits of their use outweigh the possible risks. Undiagnosed motor delay or loss of motor milestones should prompt neurological evaluation before administration of general anesthetics.

Possible Mechanism of Anesthetic-Induced Hyperkalemia in DMD/BD

The pathophysiology underlying the development of inhaled anesthetic-induced rhabdomyolysis in patients with DMD and BD is not precisely known. It is possible that, in dystrophic patients, inhaled anesthetics exacerbate breakdown of already frail and vulnerable muscle membranes that are further disrupted by patient movement or administration of reversal drugs.[68] It was speculated that calcium regulation might be deranged in the dystrophic muscle.[69–71] There are signs of altered membrane permeability, such as elevated levels of muscle-specific cytoplasmic proteins (e.g., creatine kinase), in the serum of patients with DMD and BD.[69]

There are two general mechanisms underlying succinylcholine-induced hyperkalemia: excess potassium release as a result of up-regulation of abnormal extrajunctional acetylcholine receptors (e.g., burns, denervation, atrophy, etc.) and development of hyperkalemia as a result of rhabdomyolysis that occurs in patients with clinically evident, as well as subclinical, myopathic disease states, such as DMD.[72–74] Muscular dystrophy patients may not demonstrate up-regulation of abnormal extrajunctional acetylcholine receptors.[74] All these patients required prolonged resuscitation. One speculation is that the prolonged resuscitation was in response to continuous and prolonged leakage of potassium from the muscle cells secondary to rhabdomyolysis.[72]

Succinylcholine should not be administered to patients with known DMD or BD unless required as a last resort for a life-threatening airway emergency, when IV access has not been established. All children presenting for administration of general anesthesia or sedation should be screened for motor milestones. Inability to walk past 18-mo-old or other signs of motor loss or delay should prompt suspicion of a subclinical myopathy and should warrant neurological evaluation and genetic testing before elective surgery.[75] Most cases of DMD and BD will be detected by genetic testing.

CONCLUSION

We did not find an increased risk of MHS in patients with DMD or BD. Exposure to volatile anesthetics in patients with muscular dystrophy may be associated with life-threatening rhabdomyolysis and therefore should be used cautiously, and when the benefits of their use outweigh the possible risks. Succinylcholine administration is associated with life-threatening hyperkalemia and should be avoided in patients with DMD and BD.

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CME The Myotonias and Susceptibility to Malignant Hyperthermia

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Malignant hyperthermia (MH) is a pharmacogenetic disorder of skeletal muscle in which volatile anesthetics trigger a sustained increase in intramyoplasmic Ca^{2+} via release from sarcoplasmic reticulum and, possibly, entry from the extracellular milieu that leads to hypermetabolism, muscle rigidity, rhabdomyolysis, and death. Myotonias are a class of myopathies that result from gene mutations in various channels involved in skeletal muscle excitation-contraction coupling and sarcolemmal excitability, and unusual DNA sequence repeats that result in the inability of many proteins, including skeletal muscle channels that affect excitability, to undergo proper splicing. The suggestion has often been made that myotonic patients have an increased risk of developing MH. In this article, we review the physiology of muscle excitability and excitation-contraction coupling, the pathophysiology of MH and the myotonias, and review the clinical literature upon which the claims of MH susceptibility are based. We conclude that patients with these myopathies have a risk of developing MH that is equivalent to that of the general population with one potential exception, hypokalemic periodic paralysis. Despite the fact that there are no clinical reports of MH developing in patients with hypokalemic periodic paralysis, for theoretical reasons we cannot be as certain in estimating their risk of developing MH, even though we believe it is low.

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Malignant hyperthermia (MH) is a pharmacogenetic disorder in which volatile anesthetics trigger a sustained increase in intramyoplasmic Ca^{2+} via release from sarcoplasmic reticulum (SR) and, possibly, entry from the extracellular milieu that leads to hypermetabolism, muscle rigidity, rhabdomyolysis, and death.[1,2] Treatment is both supportive and specific, the latter consisting of rapid IV therapy with the drug, dantrolene, an intracellularly acting skeletal muscle relaxant that suppresses the pathologic increase in intramyoplasmic Ca^{2+} during an MH episode. Late recognition of a MH episode and delay in treatment can result in severe morbidity or death. Although easy and rapid preoperative recognition of potential MH susceptibility is the desired goal, it is not easily achieved. Preoperative diagnosis of MH susceptibility can sometimes be achieved by history, especially if the patient had a definitive previous episode. The potential for susceptibility to MH is not lessened because a patient had previous noneventful anesthetics, since MH, although transmitted by autosomal dominant inheritance, is characterized by incomplete penetrance and variable expressivity. Incomplete penetrance indicates that while one may have the requisite genetic mutation for MH susceptibility, it does not mean that MH will express itself during the first or even subsequent exposure to a volatile anesthetic. Variable expressivity signifies that the expression of clinical symptoms varies from indolent to fulminant likely depending on a number of physiological and pharmacological variables (i.e., genetic background, the degree of body hypothermia, and the use of depolarizing muscle relaxants, such as succinylcholine).

MH susceptibility may be suspected if a first degree family member had an episode. Definitive scientific diagnosis is achieved with a genetic test for known mutations in the gene Type 1 ryanodine receptor (RYR1) for the skeletal muscle intracellular Ca^{2+} release channel, the RYR1, the most common site of mutations conferring MH susceptibility, or by a positive live muscle biopsy caffeine-halothane contracture test (CHCT) in North America, or the *in vitro* contracture test (IVCT) in Europe. It is not yet feasible to screen the entire population for *RYR1* mutations because more than 170 variants,[3] of which 29 are

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known causative mutations,* have been described. Furthermore, there are at least three other described genetic loci that are associated with MH susceptibility and for which no genetic test is available. The CHCT/IVCT is expensive, painful and requires a specialized testing center of which there are only six in North America,† three in Australia, one in New Zealand, and a fairly comprehensive coverage of Europe.‡ It would be informative to the preoperative evaluation of patients if we knew there were positive associations between other disease states and likelihood of developing MH. Patients with a variety of neuromuscular disorders are sporadically reported to have developed one or more of the clinical features of MH (fever, tachycardia, hypercapnia, and/or hyperkalemia) in the perioperative period. It is important to determine whether these signs and symptoms represent true MH or whether any one or combination of these develop for other reasons, relating either to the particular myopathy in question or peculiar pathophysiological states that have nothing to do with MH. For example, a septic patient with underlying chronic obstructive pulmonary disease, along with early acute renal failure, having an emergent appendectomy under general anesthesia with a volatile anesthetic may exhibit fever, tachycardia, hypercapnia, and hyperkalemia. MH may not be the most likely diagnosis in such a patient, yet the diagnosis of MH is not excluded by the presence of a set of potentially confounding conditions. The importance of making the correct diagnosis is imperative because different underlying pathophysiological mechanisms require different treatments and have different implications for the management of future anesthetics for the patient and family.

Myotonias are a class of inherited skeletal muscle diseases characterized by impaired relaxation after sudden, voluntary muscle contraction, and result from skeletal muscle membrane hyperexcitability, inappropriate firing, delay in muscle relaxation, and resultant contracture states of varying severity and duration. Other myopathies, such as the periodic paralyses, central core disease, nemaline rod myopathy, and multiminicore disease have very different pathologies, but all have muscle weakness as a primary phenomenon. All these entities have a variety of causes and modes of inheritance, and to understand them we must first review the basics of the known physiology of skeletal muscle excitability and excitation-contraction coupling (ECC) (for more extensive treatment of this subject see the following reviews.[4,5]

*Maintained as an up-to-date list by the European Malignant Hyperthermia Group at http://www.emhg.org/index.php?option=com_ryr1&Itemid=66.

†See the list at the Malignant Hyperthermia Association of the United States website http://medical.mhaus.org/index.cfm/fuseaction/Content.Display/PagePK/BiopsyTestCenters.cfm.

‡See: http://www.emhg.org/index.php?option=com_content&task=section&id=6&Itemid=54.

Skeletal Muscle ECC

Skeletal muscle excitation is initiated by motor neuron stimulation of skeletal muscle at the neuromuscular junction. This generates an action potential, detected as membrane depolarization, which travels down the length of the skeletal muscle membrane and into the interior of the muscle cell by invaginations of the muscle membrane known as transverse tubules (TT) (Fig. 1). The TT are found at regular intervals at right angles to the long axis of the muscle fiber, thereby insuring simultaneous distribution of the action potential along the long and short axes of the muscle membrane and resulting in coordinated skeletal muscle contraction. The upstroke of the depolarizing action potential results from influx of Na^+ into the muscle cell and is mediated by rapid activation of the skeletal muscle voltage-gated sodium channel ($Na_v1.4$) encoded by the *SCNA4* gene and its accessory β-subunit by the *SCNA1B* gene. Repolarization of the skeletal muscle membrane is mediated by fast inactivation of this sodium channel, and the opening of potassium channels, encoded by the *KCNC4* and the accessory subunit *KCNE3* genes, generating an outwardly rectifying K^+ current. Potentially dysfunctional after-potentials are buffered by high conductance, homodimeric Cl^- channels encoded by the *CLCN1* gene.

ECC is mediated by specialized TT groupings of skeletal muscle-specific, L-type voltage-dependent Ca^{2+} channels, also known as the skeletal muscle type dihydropyridine receptors (DHPR), and encoded by the *CACNA1S* gene, along with accessory proteins encoded by the *CACNA2D1*, *CACNG1*, and *CACNB1* genes (Fig. 1). The DHPRs overlie corresponding groupings of the homotetrameric, SR Ca^{2+} release channels known as the RyR1 encoded by the *RYR1* gene. Depolarization of the TT membrane is sensed by the DHPR, which undergoes a conformational change while experiencing intra-TT membrane charge movement, causing the intracellular loop between transmembrane segments II and III of its α-1s subunit to contact the apposed RyR1. This contact causes RyR1 to open and release Ca^{2+}, which, in turn, stimulates the contractile apparatus and results in skeletal muscle shortening. Skeletal muscle relaxation normally occurs with the timely reuptake of Ca^{2+} into the SR via the energy requiring Ca^{2+}-ATPase found in the SR membrane.

Two other processes that may also contribute to the Ca^{2+} transient in skeletal muscle underlie Ca^{2+} entry into the cell, rather than Ca^{2+} release from SR. These are Store-Operated Ca^{2+} Entry (SOCE) and Excitation-Coupled Ca^{2+} Entry (ECCE).[6,7] SOCE is classically characterized by slow Ca^{2+} entry into the cell after depletion of the SR or endoplasmic reticulum Ca^{2+} store that is sensed by an SR/endoplasmic reticulum resident transmembrane protein, STIM1, containing the EF-hand Ca^{2+} binding motif, which then binds

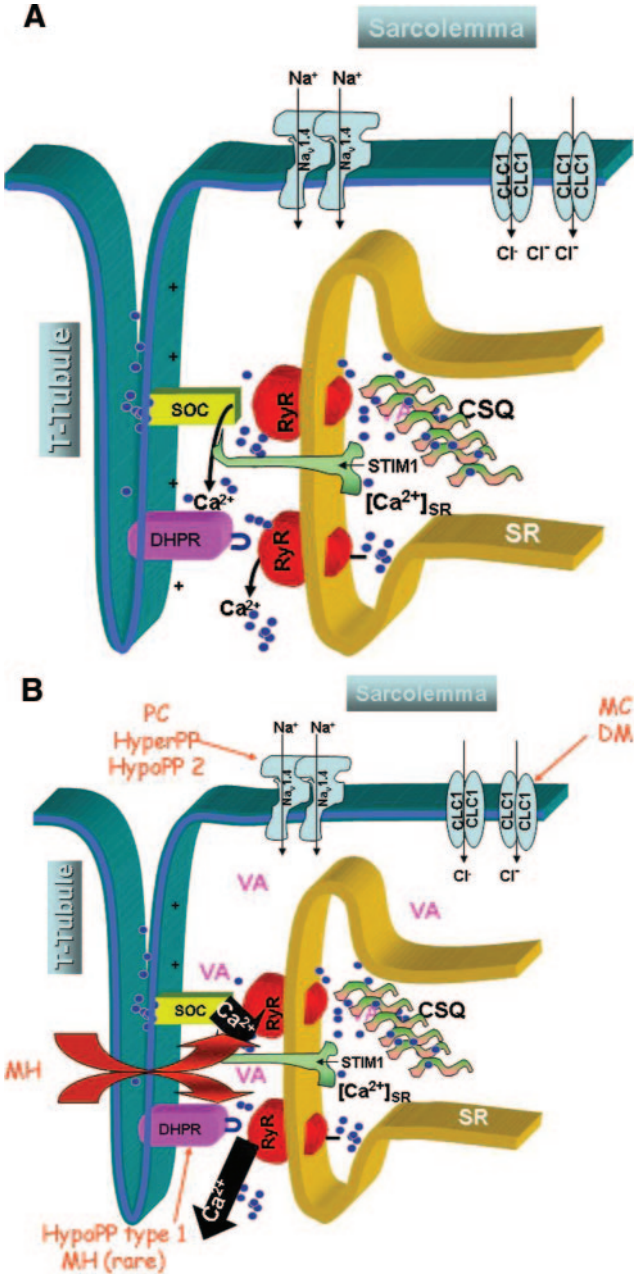

Figure 1. A, Schematic of the elements of skeletal muscle excitation-Ca^{2+} release coupling that functions in normal excitation-contraction coupling. After stimulation of the neuromuscular junction by release of acetylcholine from the motor nerve terminal (not shown), the skeletal muscle sodium channel, $Na_v1.4$, opens to allow Na^+ into the cell, thereby depolarizing the sarcolemma. The change in voltage is sensed by a voltage-dependent calcium channel in the T-tubule membrane, the dihydropyridine receptor (DHPR), which undergoes a conformational change and directly contacts the Type 1 ryanodine receptor (RyR) in the sarcoplasmic reticulum membrane (SR). RyR1 then opens to release the Ca^{2+} stored in the SR (small blue circles), primarily bound to the calcium binding protein, calsequestrin (CSQ), and now becomes available for stimulation of the contractile apparatus (not depicted). If the requirements for myoplasmic Ca^{2+} increase above that which can be provided via RyR1, this is somehow signaled to the Store-Operated Ca^{2+} (SOC) entry channels in the T-tubule via the SR membrane protein, STIM1, to allow more Ca^{2+} into the cell. See text and reviews referenced therein for more detail. B, Sites of mutation in the excitation-contraction coupling schema that result in malignant hyperthermia (MH), the myotonias, and hypokalemic periodic paralysis. Channels are as depicted in (A). In MH, the presence of volatile anesthetics (VA) ± pharmacological depolarization by succinylcholine will result in a massive release of Ca^{2+} either from the sarcoplasmic (SR) via mutated type 1 ryanodine receptor (RyR1), or as the presumed result of enhanced activation of RyR1 by a mutated DHPRα1 subunit, or as a result of mutations in unknown genes in at least three other unidentified genetic loci, all augmented by enhanced Ca^{2+} entry via SOC entry channels (SOC) and/or ECCE channels (not depicted). The site of dantrolene activity is on RyR1, and its coupling to the SOCE/ECCE channels to suppress Ca^{2+} entry and possibly release. MH = malignant hyperthermia; PC = paramyotonia congenita; MC = myotonia congenita; DM = myotonic dystrophy; HypoPP = hypokalemic periodic paralysis; HyperPP = hyperkalemic periodic paralysis; SR = sarcoplasmic reticulum; CSQ = calsequestrin. Detailed descriptions of the myopathies and references are denoted in the text.

to the plasma membrane proteins, Orai1 and TRPC1, that presumably make up the Ca^{2+} entry channel.[8,9] ECCE, however, does not require store depletion, but is activated after trains of tetanic stimuli to the muscle cell surface membrane[10] and does not involve the molecular machinery of SOCE, making these physiological properties of skeletal muscle mechanistically distinct.[11] The roles of SOCE and ECCE in the normal functioning of skeletal muscle are unknown at present, but it must be noted that dantrolene and azumolene have been shown to inhibit both these processes.[2,6,12] Indeed, it has been directly demonstrated that the dantrolene analog, azumolene, had no effect on Ca^{2+} release from SR, but dramatically reduced RyR1-coupled SOCE.[6] Furthermore, there is enhanced ECCE in mouse myotubes taken from MH-susceptible muscle.[2] Taken together, and contrary to common wisdom, these results suggest that MH may result as much from aberrant RyR1-coupled Ca^{2+} entry as from exaggerated Ca^{2+} release.

Molecular diseases are theoretically possible with mutations in any of the channels described above, in any of their regulatory proteins, or in channels and regulatory components not yet described. As we will see with the myotonic dystrophies, channelopathies are also possible without any mutations in the channel genes that underlie the disease state. No myopathies have yet been described with disruption of function of SOCE or ECCE, but it is clear that STIM1-controlled SOCE is required for the development and contractile function of skeletal muscle.[13] Description of myopathies with mutations in the molecular machinery of SOCE and ECCE is probably only a matter of time.

THE MYOTONIAS

The myotonias are generally classed into two large subgroups: the dystrophic and nondystrophic (dystrophic: defective nutrition[14]), and the descriptions cited below are taken largely from the following critical reviews: Jurkat-Rott et al.,[4] Heatwole et al.,[15] and Ryan et al.[16]

Table 1. Tabular List of Myotonias, Genes Encoding Associated Channels and Estimated Risk of Malignant Hyperthermia (MH) (in the Absence of a Family History of MH)

Disease	Gene	MH risk
Chloride channelopathies		
Myotonia congenita, Becker, or Thomsen myotonia levior fluctuating *Myotonia congenita*	*CLCN1*	Low
Sodium channelopathies		
HyperPP (adynamia episodica hereditaria) Paramyotonia congenita (Eulenberg's disease), PAM, HypoPP-2	*SCN4A*	Low
Calcium channelopathies		
HypoPP-1	*CACNA1S*	Unclear
Expanded nucleotide repeats		
Myotonic dystrophy, type 1 (DM1, Steinert's disease)	Expanded trinucleotide repeat, CTG, 3′ untranslated region of *DMPK* gene	Low
Myotonic dystrophy, type 2 (DM2, proximal myotonic dystrophy [PDM], proximal myotonic myopathy [PROMM])	Tetranucleotide repeat, CCTG, of 1st intron, *ZNF9* gene	Low

The table summarizes the known molecular genetics of the different myotonias and our estimation of associated risk of MH. Estimation of risk of MH emphasizes the underlying molecular pathology rather than phenotypic presentation. We have left the risk of MH for HypoPP-1 as "unclear," since the genetic change for this entity is in the same gene as one of the loci for MH, though the mutations for the two diseases are in different parts of the same gene. Even in the absence of clinical reports of true MH in patients with HypoPP-1, we cannot exclude this possibility at our present state of knowledge.

PAM = potassium aggravated myotonias; HyperPP = hyperkalemic periodic paralysis; HypoPP = hypokalemic periodic paralysis; CLCN1 = skeletal muscle chloride channel; SCN4A = sodium channel α-subunit; CACNA1S = α1-subunit of L-type, voltage-dependent calcium channel; MH = malignant hyperthermia.

Nondystrophic Myotonias

Chloride Channelopathies

Myotonia Congenita. This myotonia falls into two subtypes of inheritance, autosomal dominant (Thomsen's Disease) and autosomal recessive (Becker's Disease), and both are linked to mutations in *CLCN1*, the skeletal muscle chloride channel that suppress muscle membrane after potentials (Table 1 and Fig. 1B). Under normal conditions, influx of chloride stabilizes the membrane potential after a depolarization of the muscle fiber membrane. In Thomsen's and Becker's myotonia, however, the reduced chloride conductance of the mutated chloride channels leads to hyperexcitability of the muscle fiber membrane leading to bursts of aberrant action potentials. The clinical picture is characterized by slowed relaxation after forceful voluntary contractions (myotonic stiffness). As of 2007, more than 80 mutations in the *CLCN1* gene have been reported, though it is not clear how many of them are actually causative. Moreover, the same disease-associated mutation has been reported to be inherited in a dominant fashion in one family, yet be recessive in another. No real explanation for this disease-related inheritance anomaly has yet emerged. Moreover, even with the same mutation within a family, there can be marked phenotypic variation in presentation and progression of disease, implying multigenic and/or epigenetic modulation of these myotonic phenotypes. Significantly, both forms of myotonia tend to improve with exercise, the so-called "warm-up" phenomenon.

In Thomsen's disease, symptoms tend to present in early childhood, and although the myotonia is generalized, it tends to be more severe in the upper limbs, often with marked muscular hypertrophy. Symptoms are predominantly painless, transient muscle stiffness in the upper extremities and facial muscles and are characteristically initiated by muscle use after rest. The prognosis is good, with no reduction in life expectancy. Because of their muscle hypertrophy, children with Thomsen's disease often appear stronger than their counterparts and tend to be more involved in sports than others of their age.

Becker's disease, however, tends to present sometime during the second decade of life, progressing slowly into the third and fourth decades. Symptoms earlier in life are often insidious, only diagnosed with electrical testing. The symptoms of this form of myotonia are more severe than in Thomsen's and tend to involve the lower limbs first. It is sometimes accompanied by a slowly progressive weakness, hypertrophy of lower limb muscles, and by peculiar transient episodes of proximal weakness, especially involving the hands and arm muscles. Some Becker myotonia patients show permanent weakness in some muscle groups, distal muscle atrophy, and unusually high serum creatine kinase levels making the differentiation from myotonic dystrophies difficult.[17]

Two other rarer forms of myotonia congenita are described with mutations that are also in the *CLCN1* gene: *myotonia levior* and *fluctuating myotonia congenita*. There is disagreement whether these are distinct entities or variants of Thomsen's, autosomal dominant, myotonia. The constellation of symptoms in myotonia levior consists of stiffness, particularly of the grip, that is provoked by prolonged rest. In contradistinction to Thomsen's disease, myotonia levior is later in onset, has milder symptoms, and is not associated with muscle hypertrophy. Fluctuating myotonia congenita, also an autosomal dominant entity, is characterized by stiffness, primarily of the lower extremities that is initiated by movement after rest, pregnancy, fasting, cold exposure, or emotional stress and is associated

with lower extremity pain. It can affect the upper extremities as well and has varying effects on ocular and masticatory muscles. This form of myotonia temporally fluctuates in severity (hence, its name), and there can be long periods with no symptoms at all. Muscle hypertrophy is not a characteristic of this entity.

Anesthetic Implications and Susceptibility to MH. These chloride channel myotonias are sensitive to succinylcholine, administration of which can result in sustained total body rigidity and difficulty in intubation or mask ventilation.[18] Indeed, depolarizing muscle relaxants induce prolonged contractures in myotonic human skeletal muscle.[19] There is one report of a family with myotonia congenita referred for live muscle biopsy and halothane contracture testing after two sisters both developed rigidity under anesthesia.[20] Another report of a nondystrophic myotonic family and an identified mutation in the SCN4A gene of the α subunit of the skeletal muscle sodium channel correlated the presence of masseter muscle rigidity and an IVCT positive for MH susceptibility.[21] The validity of assigning MH susceptibility on the basis of contracture testing in patients with skeletal muscle channelopathies has yet to be validated and is likely fraught with confounding physiological variables that can result in contracture tests that are factitiously assigned to MH. Two reports of fatal hyperthermia and acidosis (not definitive MH) during a general anesthetic in patients with myotonia have been found: one in a girl anesthetized with halothane/ether,[22] and one in a boy with Thomsen's disease pretreated with oral dantrolene and anesthetized with a nontriggering anesthetic (thiopental/dextroramide§/nitrous oxide).[23] Although these case reports are widely quoted, the assignment of MH susceptibility in this disease on one case report in which a triggering anesthetic was used and one in which a nontriggering anesthetic was used is suspect. Indeed, in the latter case, one could just as easily assign the cause to side effects of the little-studied dextroramide. Furthermore, one study in a goat model of myotonia congenita failed to induce MH with 1% halothane and a single injection of succinylcholine,[24] and the results of IVCT in control and myotonic (arrested development of righting response) mice did not differ (W. Klingler, Ulm, Germany, unpublished data). Indeed, the rarity of clinical reports of MH-like responses to volatile anesthetics in myotonic patients allows for the suggestion that a myotonic patient who experiences a true MH crisis could easily have the misfortune of having mutations at two distinct genetic loci, one for myotonia and one for MH susceptibility. We conclude that it is highly unlikely that patients with any of the chloride channel myotonias have a risk of developing MH above that of the general population.

Despite the generalized myotonia induced by succinylcholine, nondepolarizing muscle relaxants seem to behave normally in myotonic patients, but will not counteract a myotonic response caused by succinylcholine. Nevertheless, in the myotonic conditions in which muscle wasting can develop (i.e., Becker's disease), an exaggerated response may occur.[25] Ideally, a short-acting nondepolarizing muscle relaxant should be used, as anticholinesterase drugs to antagonize the effects of the nondepolarizing neuromuscular blocking drugs have been reported to precipitate myotonia.[26] The use of propofol, in conjunction with epidural anesthesia, was reported to be safe in a patient with myotonia congenita (Becker type).[27]

Sodium Channelopathies

Paramyotonia Congenita. This entity, eponymously known as Eulenberg's disease, is the result of autosomally dominant transmitted mutations in the SCN4A gene of the skeletal muscle sodium channel, $Na_v1.4$, and has high penetrance (Table 1 and Fig. 1B). The exact physiological mechanism of the induction of symptoms is unknown, but this subunit is also the site of mutations that produce hyperkalemic periodic paralysis with myotonia. Symptoms, often beginning in the first decade of life, are characterized by cold- or exercise-induced stiffness of the facial, lingual, neck, and hand muscles. These symptoms can last from minutes to hours. Frozen or slow tongue is often reported by affected individuals after eating ice cream or ices, and a frozen smile-like appearance is noted after facial exposure to cold temperatures. Interepisode periods may be characterized by residual stiffness of the facial, eyelid, and pharyngeal muscles. Unlike most other myotonias, symptoms of paramyotonia congenita paradoxically worsen with repeated movement of affected muscles, hence, paramyotonia, the opposite of the warm-up phenomenon. Symptoms are most common in the ocular and hand muscles. Indeed, the classical physical finding in paramyotonia congenita is the inability to open the eyelids after a bout of repeated, sustained eyelid closures. Later in life, episodes of myotonia may be followed by periods of flaccid paralysis of the affected muscle. At this point in time, weakness is sometimes precipitated when rest is followed by exercise, after the ingestion of potassium-containing compounds and prolonged fasting.

Several variants of paramyotonia congenita are known; among them is hyperkalemic periodic paralysis (HyperPP) with myotonia (see below), which is characterized less by cold-induced symptoms than by potassium ingestion or exercise. Similar to HyperPP, weakness is more common in the early hours of the day and is often accompanied by elevated serum

§Electronic search of the literature does not show a listing for dextroramide, but it does for dextromoramide, an analgesic structurally related to methadone and in limited use in Europe to treat severe pain. It has been recommended not to give this drug to patients taking MAO inhibitors, though no reports of hyperthermic crises or serious drug interactions have been found in electronic search of the literature.

potassium levels. Significant to anesthetic practice is that respiratory muscles are usually spared.[28] Dysrhythmias due to ictal hyperkalemia have been reported, but are rare.[29,30]

Anesthetic Implications and Susceptibility to MH. There are no case reports of MH index cases with general anesthesia in patients with paramyotonia congenita, and there is one in which an infant was anesthetized with sevoflurane without untoward incidents.[31] One patient had an IVCT performed after masseter spasm during anesthesia induction. The IVCT was negative, and the patient was later diagnosed as having paramyotonia congenita (T. Girard, unpublished data). Risk of MH in this entity is considered to be that of the general population (Table 1).

Potassium-Aggravated Myotonias (PAM). This rubric describes three similar entities of somewhat overlapping phenotypes all caused by mutations in the skeletal muscle sodium channel: *myotonia fluctuans, myotonia permanens, and acetazolamide-sensitive myotonia*. Symptoms in all of these are aggravated by potassium ingestion. In contrast to paramyotonia congenita, they do not worsen after cold exposure, and, unlike hyperkalemic periodic paralysis, they do not present with significant weakness.

Myotonia Fluctuans. This entity is transmitted by autosomal dominant inheritance, and symptoms, which include extraocular, bulbar, and limb stiffness exacerbated by potassium ingestion or exercise, begin in the first or second decade. There are five classic symptoms of this myotonia: fluctuating myotonia of variable severity, the presence of the warm-up phenomenon, the absence of periodic weakness or cold-induced myotonia, and the exacerbation of myotonia after potassium ingestion or exercise. Curiously, the exercise-induced stiffness is particularly severe, even resulting in immobilization, when the exercise is performed after a narrow window of rest, typically 20–40 min after a previous period of exercise. The variability of clinical myotonia is the result of episodic periods of myotonia lasting from 30 to 120 min and separated from each other by prolonged periods of normal muscle function. With this entity creatine phosphokinase (CPK) levels can be 2–3 times normal. Rigidity and rhabdomyolysis may occur during surgery, but an association with MH is not a feature of myotonia fluctuans.

Myotonia Permanens. This myotonia is also dominantly inherited, extremely rare, and a very severe form of nondystrophic myotonia whose symptoms include persistent myotonia predominantly of facial, limb, and respiratory muscles and often begins within the first decade of life. Myotonia may worsen with exercise or potassium ingestion, but the effects of cold exposure are variable. Hypertrophy of the neck and shoulder muscles is common, and severe stiffness of the intercostal muscles can result in respiratory compromise. CPK levels are elevated in this entity as well.

Acetazolamide-Responsive Myotonia. This is another autosomal dominant, sodium channelopathy that is characterized by generalized myotonia after potassium ingestion, cold exposure, or fasting. Symptoms progress during childhood, involve the extraocular muscles, muscles of mastication, and those of the proximal limbs, and do not involve episodes of weakness or paralysis. Episodes are often painful, mildly affected by exercise and, in contrast to other myopathies, unusually responsive to the therapeutic effects of acetazolamide. CPK levels are normal to mildly elevated. Close monitoring during surgery is recommended for the development of rigidity and rhabdomyolysis.

Anesthetic Implications and Susceptibility to MH. No reports of MH susceptibility were found for any of the PAMs, and the risk is estimated to be that of the general population (Table 1).

HyperPP With (or Without) Myotonia. This is an autosomal dominant sodium channelopathy with nearly complete penetrance, also known as *adynamia episodica hereditaria*, which results in episodic attacks of weakness, the result of hyperkalemia-induced electrical inexcitability (Table 1 and Fig. 1B). In some individuals, this entity is accompanied by clinical and electrical myotonia. Symptoms begin in early childhood with attacks of weakness brought about by resting after exercise, cold exposure, fasting, emotional stress, or potassium ingestion. The clinical myotonia, when it occurs, can be reduced with repeated exercise, i.e., the warm-up phenomenon. Curiously, the attacks of weakness can be generalized or localized to a single limb, but usually spare the facial and respiratory muscles. The ingestion of glucose is therapeutic.

Almost all mutated sodium channels have an impaired fast-inactivation leading to increased sensitivity to elevated potassium or reduced temperature.[30] In HyperPP, there is a gain of function leading to excessive depolarization followed by inactivation. A milder depolarization maintains the channel in a noninactivated state and sustained inward sodium current leads to repetitive firing.[32,33] As a result, small differences in the extent of depolarization are responsible for symptoms of weakness or myotonia.[34] During an attack, potassium is shifted from the intracellular to the extracellular space, causing serum potassium to increase. This relative hyperkalemia depolarizes the muscle membrane sufficiently to prevent activation of the normal sodium channels (50% of the population in patients) and, thereafter, the propagation of the action potential.

Anesthetic Implications and Susceptibility to MH. Despite the above, the administration of potassium-releasing drugs, such as succinylcholine, should be avoided.[35] Indeed, a prolonged episode of muscle weakness for 4 days after a general anesthetic that included succinylcholine has been described.[36] Furthermore, succinylcholine may induce severe muscle spasms

in these patients.[37,38] Several reports document the safe use of nondepolarizing muscle relaxants.[35,39] A number of case reports have shown an uneventful course of anesthesia when volatile anesthetics were administered to patients with HyperPP[35,39] and have suggested using inhaled induction of anesthesia in these patients.[40] IVCT of muscle biopsies from patients with HyperPP did not reveal MH susceptibility.[41] In contrast, a genetic linkage was suggested between mutations in *SCN4A* for HyperPP and MH, but in this pedigree the only person tested by IVCT had an abnormal response to caffeine only, making him MH-equivocal by European Malignant Hyperthermia Group criteria and MH-normal by North American criteria.[42] Depolarizing drugs, such as succinylcholine or anticholinesterases, worsen myotonia and should therefore be avoided.[43] Propofol, as a voltage gated sodium channel inhibitor, seems theoretically advantageous in these patients, and there are reports of its safe use.[44–46] The perioperative management of these patients should include preoperative potassium depletion by diuretics,[35] continuous electrocardiogram monitoring, administration of glucose to avoid carbohydrate depletion during the fasting period, and temperature monitoring with emphasis on maintaining normothermia.[25]

Of the various types of PAM, the incidence of adverse anesthetic events seems to be most frequent in families with myotonia fluctuans.[43] This most likely relates to the frequent absence of clinical signs before surgery, and, thus, the anesthesiologist is unaware of the condition. With other types of myotonia, patients often report that they have myotonic episodes or attacks of weakness. Depolarizing drugs should be avoided, thereby decreasing the risk of an adverse event. Paramyotonia congenita patients may be paralyzed for several hours upon awakening from general anesthesia. Both preventive therapy before surgery and maintaining a normal body temperature will help to prevent such attacks.

In contrast to the muscle contractures in MH that respond well to dantrolene,[47] myotonic contractions are generally relieved by lidocaine (a sodium channel blocker) rather than by dantrolene because they result from bursts of action potentials. Dantrolene would reduce the contractile force and thus the complication-inducing stiffness of the myotonia, but not the primary hyperexcitability of the membrane.[43]

Given the above, and because no reports of MH susceptibility have been found, we do not consider this population of patients with sodium channelopathies to be at increased risk for MH (Table 1).

Dystrophic Myotonias

In contrast to the nondystrophic myotonias, the two major myotonic dystrophies are primary, autosomally dominant inherited, multisystem disorders that have significant neuromuscular findings that prominently involve the presence of myotonia and weakness, but do not involve mutations in ion channels. Rather startlingly, they result from expanded repeats in the 3′ untranslated regions of specific genes and join a growing number of unrelated diseases (>20) whose common pathophysiological base is that of heritable, unstable nucleotide repeats[48] (Table 1 and Fig. 2). In Type 1 myotonic dystrophy (DM1), the more common entity, the expanded trinucleotide repeat, CTG, is expanded from 50 to 200 times in the 3′ untranslated region of the myotonic dystrophy protein kinase gene. In DM2, the less common form, there is an expansion (80–11,000 times) of a tetranucleotide repeat of CCTG in the first intron of the zinc finger protein 9 (ZNF9) gene. As it turns out, the disease mechanisms have nothing to do with either the dystrophy protein kinase or the ZNF9 proteins or their expression. Rather, the long RNA repeats that result from the translation of these expanded repeats fold into an unusual pathological hairpin structure that results in their accumulation in the nucleus and disruption of normal alternative splicing of messenger RNA. As a result, many normal proteins are dysregulated and, in our cases, result in wasting myotonias with multisystem involvement. The severity of clinical symptoms in both DM1 and DM2 are roughly correlated with the length of triplet or tetranucleotide repeats. The descriptions of DM1 and DM2 below are taken from the following critical reviews.[49–54]

Clinical features common to both DM1 and DM2 include: myotonia, muscle weakness, and atrophy (face, neck, fingers, and limbs), cardiac conduction defects, cognitive dysfunction, cataracts, hypersomnia, insulin resistance, testicular atrophy, frontal balding in males, hypogammaglobulinemia, and muscle pain. The myotonia, muscle weakness and atrophy, cardiac conduction defects, and hypersomnia are clinically more significant and can present at an earlier age in DM1. In both DM1 and DM2, and like myotonia congenita, there is a defect in the skeletal muscle chloride channel, but this is due to loss of appropriate splicing and resultant retention of the embryonic form of the channel, thereby inhibiting its replacement by the adult form appropriate to postnatal function. This gives rise to the myotonic symptoms, and, in contradistinction to the nondystrophic myotonias, there is early and progressive muscle weakness. Similarly, there is inappropriate splicing of the insulin receptor, giving rise to insulin resistance.

DM1. DM1, also known as Steinert's Disease, is the most common form of myotonic dystrophy and is a dominantly inherited multisystem disorder that usually results in death from skeletal muscle wasting and cardiac conduction defects. Clinical symptoms specific for DM1 include distal muscle weakness with muscle atrophy at onset, learning and speech disabilities, hypotonia, facial diplegia, and sometimes gastrointestinal problems. DM1 is associated with the phenomenon of generational anticipation, by which the disease has an

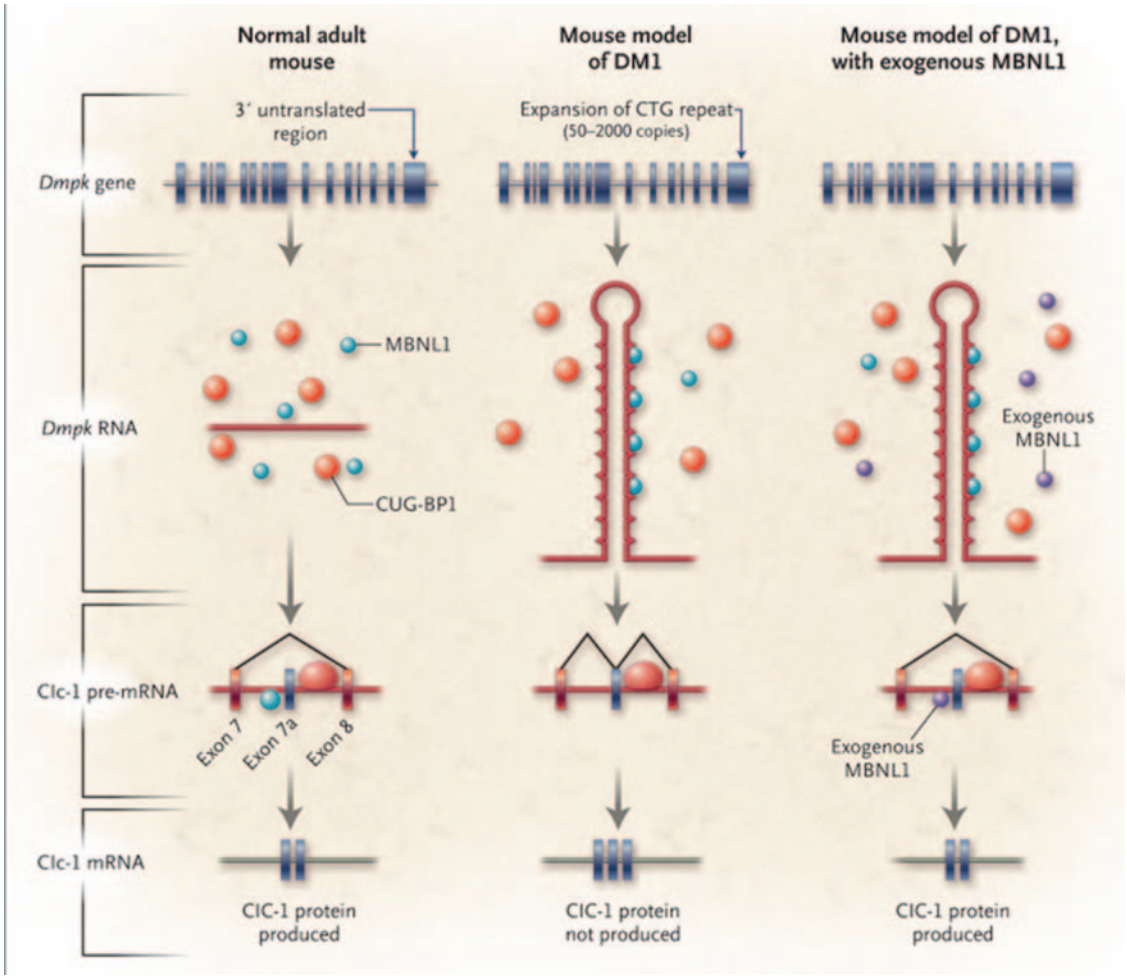

Figure 2. Schematic depicting the splicing abnormalities caused by CTG expansion repeats and their reversal in a mouse model of myotonic dystrophy. Myotonic dystrophy (DM) is caused by CTG repeats within a noncoding region of the *Dmpk* gene. It is also caused by the expansion of a four-base motif CCTG in a noncoding region of the *Znf9* gene (not shown). Transcribed RNA repeats fold into a long, misshapen hairpin, and the RNA is retained in the nucleus, where it alters the ratio of CUG RNA-binding proteins, such as CUG-BP1 and MBNL1. These proteins are mutually antagonistic mediators of a subgroup of alternative splicing events that are disrupted in myotonic dystrophy, in which "embryonic" forms of some proteins, that is, isoforms typically expressed in the developing embryo and fetus, predominate. A primary result of this dysregulation in both forms of DM is dysfunctional splicing of the embryonic form of ClC1 into the adult form, resulting in lack of buffering of sarcolemmal after-potentials and the induction of sustained contractures, i.e., myotonia. A recent study showed that increasing the expression of MBNL1 in a mouse model of DM restored the adult splicing pattern of the ClC-1 protein and reversed the myotonia associated with ClC-1 dysregulated splicing. Figure and modified legend reprinted with permission from ref. 54 (Cooper TA. A reversal of misfortune for myotonic dystrophy? N Engl J Med 2006;355:1825–7).

earlier onset and more severe course in subsequent generations. There are four subsets of DM1 related to the age of onset: congenital, childhood onset, adult-onset, and late onset/asymptomatic. This is roughly correlated with the size of CTG expansion repeats.

DM2. DM2, previously known as proximal myotonic dystrophy or proximal myotonic myopathy, before this entity was identified as a member of the expansion nucleotide repeat family of myotonias, is also a dominantly inherited disorder. Though there is some evidence of generational anticipation in this disease, there is no congenital form yet identified, and the earliest age of onset is approximately 13 yr. Symptoms specific to this entity are proximal muscle weakness and atrophy at onset and hypertrophy of calf muscles.

Anesthetic Implications and Susceptibility to MH. There are no case reports in the literature directly linking the myotonic dystrophies to MH. The IVCT of 44 patients with myotonias, including the myotonic dystrophies, resulted in four positive results, 10 equivocal results, and 30 negative results.[41] The four positive results all came from DM patients, but 12 of these patients were negative. There is one report of a patient with DM2 who developed muscle stiffness, oculogyric cramps, and elevated creatine kinase levels after treatment with neuroleptics and had a positive IVCT with halothane.[55] Undoubtedly, the IVCT cannot be used to diagnose MH susceptibility in a patient population with membrane channelopathies without worrying about false positives.[56] Succinylcholine will

induce generalized skeletal muscle rigidity in these patients, raising the specter of MH susceptibility, but the latter seems unlikely to occur in the absence of a second genetic change specifically causative for MH.

Our assessment of the triplet expansion myopathies is that susceptibility to MH is that of the background population. IVCT/CHCT results in these patients are likely misleading even if contractures reach the threshold we have set for MH susceptibility. One should avoid the use of succinylcholine in these patients. Given the intrinsic weakness of these patients, we recommend the judicious use of nondepolarizing drugs, along with careful attention to respiratory status.

Calcium Channelopathies

Hypokalemic Periodic Paralysis (HypoPP)

HypoPP is a rare, autosomal dominant, skeletal muscle disorder with episodes of muscle weakness.[57] Affected patients first exhibit episodes of asymmetrical muscle paralysis associated with low potassium levels in the second decade of life. The muscle weakness affects mainly the proximal muscles, sparing the diaphragm, and muscles supplied by the cranial nerves.[58] In most patients the disorder is caused by mutations in the skeletal muscle voltage-gated calcium channel encoded by *CACNA1S* (HypoPP Type 1), although it is less frequently associated with mutations in the *SCN4A* gene (HypoPP Type 2)[43] (Fig. 1B). All HypoPP mutations are situated in the so-called voltage sensors of the channels.[43] These mutations result in pore currents with reduced amplitude and shifted voltage-dependence, i.e., findings that cannot explain the disease pathogenesis.[59] The exact mechanisms leading to hypokalemic paralysis are unclear.[28,43]

Anesthetic Implications and Susceptibility to MH. Several authors have described the uneventful use of inhaled anesthetics and succinylcholine in patients with HypoPP.[60,61] However, there are case reports of intraoperative hypermetabolic crises after administration of MH trigger drugs to patients with HypoPP,[57,62,63] and one group also described contracture-like responses to succinylcholine.[64] In one of these case reports, a positive IVCT was obtained in one of the two patients with clinically suspected MH.[63] Genetic investigations in this same patient excluded known mutations in *CACNA1S* and *SCN4A*, whereas a novel mutation (Asn2342Ser, subsequently found in other MH susceptible families) was identified in the *RYR1* gene, which was likely the source of that patient's MH susceptibility. Myotonia in this patient must have arisen from a mutation in *CACNA1S* or *SCN4A* that was not tested for, or from a new, unidentified locus. This illustrates the possibility that "lightning does strike twice," i.e., it is possible to have two separate genetic mutations that predispose to two separate conditions in the same patient, and may underlie the rare confluence of myotonia and MH susceptibility.

As noted above, mutations in specific regions of *CACNA1S* confer susceptibility to HypoPP. A few mutations in another region of this gene have been associated with MH.[65] There is a similar situation for central core disease and MH in which both conditions are linked to mutations in *RYR1*, and the incomplete clinical overlap between the two seems to correlate with the region of the protein in which the mutations are found (for more complete treatment of this, see the reviews by Refs. 66, 67). Because there are a few MH patients known to have mutations in another region of *CACNA1S*, a theoretical association between MH and HypoPP in this small subset of patients has been made, but never been confirmed. Moreover, there is a lack of evidence for MH susceptibility that is generalizable to all HypoPP patients, and it is unclear that all of the few reports of anesthetic-associated reactions suspected of being MH were really MH. Indeed, the patient with the highest MH clinical grading score (33, "somewhat > than likely" vs 18, "somewhat < likely"[68]) reported above,[63] and retrospectively determined by the authors of this manuscript, had a normal IVCT. It would seem, therefore, that not all "hypermetabolic" responses of anesthetized patients with neuromuscular disease are MH. However, anesthesiologists must have a heightened suspicion for hypermetabolic reactions when caring for these patients because, should volatile anesthetics be used, the reaction might be MH. As noted above, one can have the misfortune of having mutations in two separate genes resulting in both an unrelated channelopathy and susceptibility to MH.

Depolarizing neuromuscular blocking drugs should not be administered to patients with HypoPP, and their anesthetic management should focus on the prevention of perioperative episodes of muscle weakness. This includes avoiding large glucose and salt loads, maintaining normothermia, keeping serum potassium levels in the upper part of the normal range, and reducing the patients' anxiety, because all these factors are associated with increased occurrence of postoperative paralytic episodes.[40] If nondepolarizing muscle relaxants are required, drugs with a relatively short duration of action are best[69,70]; neuromuscular function must be monitored if neuromuscular blocking drugs are given. Because there are no definitive reports of MH in patients with HypoPP, we conclude that the likelihood of HypoPP patients being susceptible to MH is that of the general population. However, the mutational locus linked to HypoPP is the DHPR α1s gene, the same gene that is also a locus of a few MH mutations. There is the theoretical likelihood, therefore, that susceptibility to MH may overlap with that of HypoPP, despite the fact that the mutations for the two entities segregate to separate parts of the gene. Our present state of knowledge does not allow definitive recommendations. We leave it to the discretion of the clinician as to whether to use volatile

anesthetics in these patients but, if they do, they should be extra vigilant.

SUMMARY

The care of myopathic patients is often difficult enough without having to worry about their often-touted, potential susceptibility to MH. We hope the above review and recommendations clarifies that, for the channelopathies reviewed above, the risk of MH is that of the general population. Only for HypoPP can we not yet definitively say that risk of MH is that of the general population for the reasons explained above, despite the fact that there are no reports of MH occurring in patients with this entity. Readers are cautioned, however, that it is not impossible for patients to have the genetic disposition toward two separate entities, MH and another of the myopathies that has no genetic relation to MH, no matter how unlikely. Clinicians should act on the side of caution if perioperative signs and symptoms of MH present themselves in someone with one of the above myopathies and treat the event as a potential MH episode. There is no significant downside to treatment with dantrolene in suspected but not true MH. Potential disaster awaits if true MH is undiagnosed and left untreated.

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Core Myopathies and Risk of Malignant Hyperthermia

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In this article, we analyze myopathies with cores, for which an association to malignant hyperthermia (MH) has been suggested. We discuss the clinical features, the underlying genetic defects, subsequent effects on cellular calcium metabolism, and *in vitro* muscle responses to MH triggers. We describe in detail central core disease, multiminicore disease, and nemaline rod myopathy. We categorize the diseases according to the affected proteins and discuss the risk for MH, which is high or theoretically possible when the calcium-conducting proteins are affected.
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Malignant hyperthermia (MH) is a pharmacogenetic disorder in which volatile anesthetics trigger a sustained release of Ca^{2+} from the sarcoplasmic reticulum that leads to hypermetabolism, muscle rigidity, rhabdomyolysis, and death. Although the mechanism of MH triggering is specific, the resulting clinical features are not. Thus, patients with a variety of neuromuscular disorders are sporadically reported to have developed one or more of the clinical features of MH (such as pyrexia, tachycardia, hypercapnia, and hyperkalemia) in the perioperative period. It is important to distinguish such nonspecific problems from MH, because the different underlying pathophysiological mechanism is likely to require different treatment and have different implications for future anesthetic management of the patient and their family. Therefore, except in conditions where sarcoplasmic reticulum Ca^{2+} release is specifically sensitized to volatile anesthetics, as in MH, these drugs should not be absolutely contraindicated. It will be apparent, therefore, that a fully informed decision concerning the use of volatile anesthetics in a patient with a myopathy requires an understanding of the underlying molecular defect. There are, however, other important factors that should be considered when planning anesthetic management in general, and choice of anesthetic drugs in particular, in patients with congenital myopathies and these will be briefly discussed before detailing specific myopathies.

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GENERAL CONSIDERATIONS WHEN ANESTHETIZING PATIENTS WITH CONGENITAL MYOPATHIES

Anesthetic management of patients with muscle diseases is challenging. In addition to unpredictable sporadic responses, such as rhabdomyolysis and metabolic stimulation, more predictable risks are associated with respiratory and bulbar muscle weakness, myocardial involvement, and difficult airway anatomy. To identify and minimize risk, a thorough preoperative workup is indispensable. Initially, a review of the diagnosis should be made in conjunction with the patient's neurologist. In the preoperative workup of a patient with a myopathy, the anesthesiologist should not be content with a diagnosis of a specific myopathy made purely on clinical features, but should try to establish the underlying molecular mechanism, i.e., the underlying mutated channel, for reasons that will become apparent later. Myopathies share common clinical features, and the underlying molecular mechanism is frequently not identified through clinical evaluation: histopathological examination of muscle biopsy specimens may be misleading, and optimal interpretation is a highly specialized field.

Confirmation of the diagnosis of the type of myopathy will determine further preoperative evaluation. Unlike the muscular dystrophies, the congenital myopathies are not usually associated with primary myocardial involvement, although scoliosis may be associated with a restrictive lung deficit, which in turn can lead to right ventricular strain and ultimately failure. Furthermore, skeletal muscle weakness can make it difficult to assess cardiovascular reserve from the history of daily activities.

The presence of skeletal muscle weakness itself, however, is a major concern for the anesthesiologist, especially if it involves the respiratory and/or bulbar

muscles. A formal clinical evaluation of respiratory and bulbar muscle function, appropriate to the age of the patient, is a mandatory aspect of the preoperative evaluation of patients with congenital myopathies. In older children and adults, this should be complemented by respiratory function tests. Sensitivity to respiratory-depressant drugs should be anticipated and, where possible, doses titrated to the desired effect. Even with the most careful anesthetic management, postoperative ventilatory support may be required and, therefore, postoperative intensive care unit availability should be planned. Furthermore, we consider it prudent to admit for overnight postoperative observation, rather than treat as a day case, any patient diagnosed preoperatively to have bulbar or respiratory muscle involvement even if they do not require immediate postoperative ventilatory support.

Our final recommended addition to routine preoperative management for patients with muscle diseases is baseline serum potassium and creatine kinase (CK) concentrations to assess muscle membrane integrity. It is possible that high baseline values may be associated with increased risk of profound perioperative rhabdomyolysis, whereas the baseline value *per se* is required to differentiate perioperative rhabdomyolysis from preexisting muscle damage.

All anesthetic techniques and drugs are associated with increased risk in patients with myopathies. Invariably, reducing the risk of one type of complication by avoiding a particular drug will lead to increasing the risk of another complication from the alternative drug. In such circumstances, a recommendation for an absolute contraindication to a drug in a particular patient group requires good evidence. Thus, because of the potential advantages of volatile anesthetics and potential disadvantages of alternative techniques, we consider it unhelpful to contraindicate their use in congenital myopathies except when the associated risk of MH is high for the myopathy under consideration.

The situation is different with succinylcholine. Use of depolarizing neuromuscular blocking drugs should be generally discouraged in patients with neuromuscular diseases. Although depolarizing muscle relaxants are triggers of MH, the prolonged depolarization leads to potassium release and calcium influx. These adverse effects are exaggerated in patients with extrajunctional acetylcholine receptors, increased proportion of the fetal γ-isoform, and those susceptible to myotonic reactions.[1] As the same might be true about reversal of neuromuscular block with anticholinesterases, this group of substances is generally not recommended in patients with neuromuscular diseases. The recent introduction of cyclodextrin reversal drugs (such as sugammadex) provides an attractive alternative in these circumstances. Succinylcholine may also cause acute profound rhabdomyolysis in patients susceptible to MH and those with one of a range of myopathies. If neuromuscular blockade is required, a nondepolarizing neuromuscular blocking drug should be used, albeit in the knowledge that patients with myopathies may show increased sensitivity to these drugs.

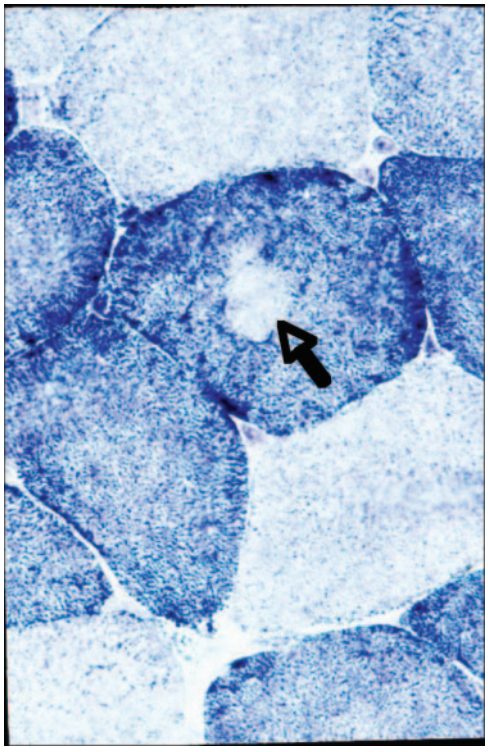

Figure 1. Histology of central core disease: muscle fibers containing unstructured cores (arrow) and no mitochondria (NADH reductase staining, ×400).

RYANODINE RECEPTOR GENE MUTATIONS AND MH

In up to 70% of MH families, variants in the skeletal muscle isoform of the ryanodine receptor (*RYR1*) gene have been identified.[2] Only 29 of the more than 200 sequence variations in *RYR1* have been investigated for their functional effect and meet the criteria to be included in the guidelines for molecular genetic detection of MH susceptibility (www.emhg.org). In the absence of a "high-throughput" method to investigate novel variants for their causativity, these functional analyses remain laborious, and they have not kept pace with the detection rate of novel variants in this large gene. Although it is likely that many of the currently uncharacterised *RYR1* variants associated with MH susceptibility will have pathological significance, until this is proven they have no diagnostic utility.[3] In these circumstances, patients with a personal or family history suggestive of MH should be considered at risk of the condition until proven otherwise by normal responses of muscle biopsy specimens to *in vitro* contracture tests (IVCT).

CENTRAL CORE DISEASE

Central core disease (CCD) is a rare hereditary myopathy, which presents clinically with muscle weakness of variable degree and histologically with central cores in the muscle fibers (Fig. 1). Common

features are floppy infant syndrome, delayed motor milestones, and generalized muscle hypotonia during adolescence. Additional features are skeletal abnormalities such as club foot, scoliosis, or hip displacement. There is no bulbar or diaphragmatic weakness and no external ophthalmoplegia. In adulthood, the syndrome usually is nonprogressive. Functional improvement can occur and approximately 40% of affected adults are considered asymptomatic. However, the evolution is unpredictable, and weakness may cause severe disability in daily life.[4,5]

Laboratory investigations reveal serum CK concentrations that are normal or slightly elevated. Histological findings are characterized by demarcated cores, which lack oxidative enzyme activity. The cores are only found in the predominant Type I fibers. The muscle involvement can also be demonstrated by various imaging techniques.[6]

Genetic Basis of CCD

The mode of inheritance of CCD is autosomal dominant. Disease-causing mutations in, or linkage to, *RYR1* have been shown in the majority of cases. Recessive transmission has been described for variant forms of CCD.[7] There is also an overlap of CCD with other myopathies (e.g., nemaline myopathy [NM] and multiminicore disease [MmD]).[8]

CCD and MH-Susceptibility

The clinical severity of CCD and the number of cores can vary with age: there is also variability between and within families. Individuals with MH susceptibility may have cores in the muscle but the diagnosis of CCD should be limited to those with a clinical myopathy. The current understanding of CCD suggests a strong link between subcellular Ca^{2+} metabolism and the pathophysiological mechanism of the disease.[2,9] This is corroborated by clinical episodes of MH and pathological contractures in the MH-diagnostic IVCT in some patients with CCD. However, in some cases of patients tested for MH susceptibility because of a diagnosis of CCD, rather than a suspected clinical MH episode, the IVCT gives negative results.[10,11] These findings are consistent with evidence that some CCD mutations in the C-terminal region of the RyR1 protein are associated with excitation-contraction uncoupling or a partially depleted sarcoplasmic reticulum through a constant Ca^{2+} leak (Fig. 2).[12] The resulting myoplasmic Ca^{2+} overload has been associated with mitochondrial damage.[13] On the other hand, both mechanisms lead to lower peak Ca^{2+} levels, which explains the muscle weakness and the lower *in vitro* sensitivity to Ca^{2+}-releasing drugs.[14,15] However, there are insufficient genotype-phenotype correlations, to make a definitive statement about the clinical risk, based on mutation type alone, and caution persuades us to recommend a non-triggering anesthetic unless the patient has had a normal IVCT.

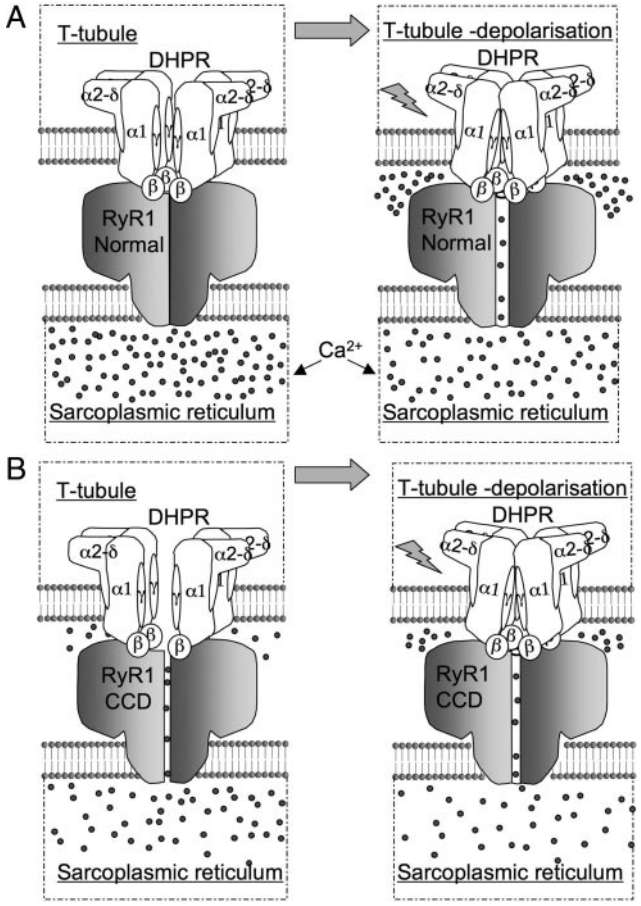

Figure 2. Cartoon of the key structures of excitation contraction coupling (EC-coupling) in the transverse tubule (T-tubule) of skeletal muscle. The dihydropyridine receptor (DHPR) is linked to the homotetrameric ryanodine receptor (RyR), which is the calcium release channel situated in the membrane of the sarcoplasmic reticulum (SR). The cytosolic part of the protein complex, the so-called foot, bridges the gap between the T-tubular system and the SR. Normally (A), the RyR channel is active only when the DHPR responds to T-tubule depolarization. In B, a leaky RyR channel and impaired EC-coupling due to C-terminal RYR1 mutations lead to central core disease (CCD).

MULTIMINICORE DISEASE

MmD is usually considered a recessively inherited congenital myopathy with a pattern of weakness that differs from CCD in that there is often severe axial involvement, while respiratory, bulbar, and extraocular muscles are commonly affected. As with CCD, the condition is stable or minimally progressive and the serum CK normal or only mildly elevated. MmD is characterized by cores lacking oxidative enzyme activity on histochemical analysis. However, in contrast to CCD, the cores in MmD are usually multiple, poorly defined (Fig. 3), and do not extend along the axis of the fiber. Four clinical subtypes of MmD have been described[16]:

1. The classical form, which is the most prevalent, consists of axial muscle weakness, commonly leading to severe scoliosis.
2. The moderate form with hand involvement, consists of generalized muscle weakness affecting

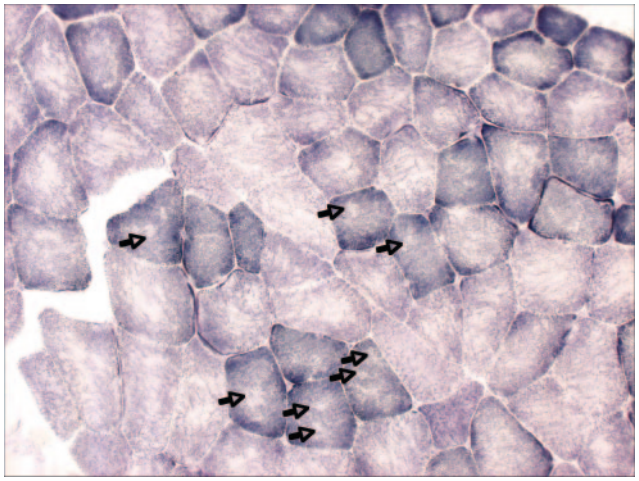

Figure 3. Histology of multiminicore disease. Oxidative enzyme staining (NADH, ×200) reveals multiple, poorly-defined cores (some cores are highlighted by arrows). Image provided by Professor Francesco Muntoni, Institute of Child Health, London, UK.

predominantly the pelvic girdle but also includes amyotrophy and hyperlaxity: in this form scoliosis is mild or absent.
3. A form that is similar to classical MmD but also includes ophthalmoplegia.
4. Antenatal onset MmD with arthrogryposis (multiple joint contractures).

Genetic Basis of MmD

MmD is genetically heterogeneous. The moderate form with hand involvement is most often associated with mutations in *RYR1*.[17] These can be homozygous, compound heterozygous, or heterozygous with monoallelic expression.[17–19] At least 10 different *RYR1* variants have been associated with cases of MmD, and these variants are spread across the *RYR1* gene.[2]

The classical predominant form of MmD is, however, most frequently associated with mutations in the selenoprotein N 1 gene.[20] This is the same gene that is responsible for congenital muscular dystrophy with rigid spine.[21] Selenoprotein has recently been shown to be required for RyR1 calcium release.[22] Mutations in patients with core myopathies have also been described in the α-actin gene (*ACTA1*).[23] Furthermore, there are myopathic patients with histological cores in whom mutations in *RYR1*, *ACTA1*, and selenoprotein N 1 gene have been excluded.

MmD and MH Susceptibility

There are no reports of patients with MmD developing clinical MH during general anesthesia: indeed, we could find no reports of potent inhaled anesthetics being used in a patient with MmD. Therefore, there are no reports of conventional MH diagnostic tests done on muscle biopsy specimens from patients with MmD, although abnormal Ca^{2+} release has been reported in a skinned fiber preparation from a Japanese patient with MmD.[24] The functional effects of MmD-associated *RYR1* mutations have been studied in HEK293 cells and in immortalized lymphocytes[25]: some of these mutations result in increased evoked Ca^{2+} release whereas others do not.

There is, however, a report of a large MH kindred in whom the majority of MH susceptible individuals have histopathological features of MmD but have no clinical myopathy.[26] There also seems to be a growing recognition that there is considerable overlap between CCD and MmD. In some patients with clinical features more consistent with CCD, histology reveals multiple cores or minicores. Indeed, a time-related change in the morphology from minicores to cores has been described.[27] So, although there is no definitive evidence to absolutely contraindicate volatile anesthetics in MmD, we would currently advise caution in patients with MmD with a *RYR1* etiology. It may indeed be a pragmatic approach, at least in respect to the association of core myopathies with MH, to consider the possibility of MH risk to be associated with an *RYR1,* rather than a core histology, etiology.

NEMALINE ROD MYOPATHY

NM is a rare congenital myopathy with an incidence of about two cases per 100,000 live births.[28] NM has considerable clinical and genetic heterogeneity.[28–30] The cardinal features of all nemaline subtypes are muscle weakness and the presence of nemaline bodies (rod-shaped structures) in the muscle fibers.[31,32]

Phenotype

The clinical spectrum of NM ranges from a severe fatal neonatal form to adult onset forms. The European Neuromuscular Centre International Consortium report on NM classifies the disease into six different subtypes: 1) severe congenital; 2) intermediate congenital; 3) typical congenital; 4) mild childhood; 5) adult onset; and 6) other forms.[33] NM is typically mild, nonprogressive, or slowly progressive with hypotonia and feeding difficulties in early life, small muscles, slender extremities, and proximal muscle weakness. The latter may also appear in the distal limb, neck flexor, trunk muscles, and in facial and masticatory muscles. Dysmorphic features include narrow, high-arched palate, micrognathia or marked prognathism, chest deformities, contractures of the fingers, and pes cavus or talipes equinovarus. A murine model of NM has been established, but the association of MH with NM has not yet been studied in this model.[34]

Histology

NM is characterized by dense sarcoplasmic inclusions in extrafusal skeletal muscle fibers[32] (Fig. 4). These rod bodies are assembled in an irregular distribution as clusters. They are derived from the Z-disk and consist of Z-disk proteins (α-actinin and actin).[35] In the vast majority of cases, the inclusions are located exclusively in the cytoplasm, about 10% of patients

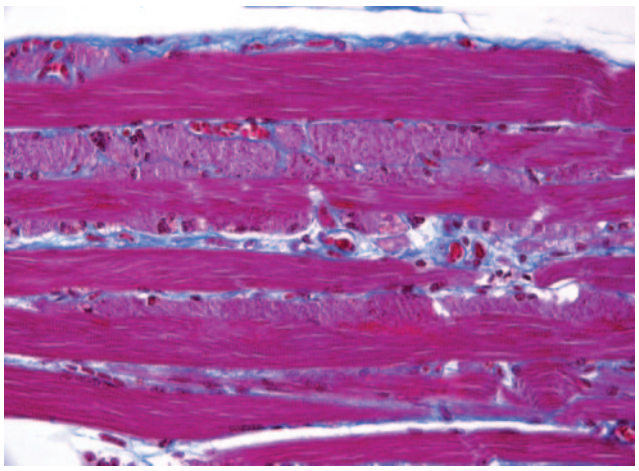

Figure 4. Skeletal muscle of an adult nemaline myopathy, autopsy case. In the longitudinal section of several muscle fibers shown here, the normal cross-striated fibrils are partially replaced by accumulations of rod-shaped nemaline bodies (Masson, ×400).

Table 1. Core Myopathies and Genes Associated with the Diseases and Estimated Risk of MH (Given There Is No Particular Malignant Hypothermia (MH) History in Family)

Disease	Gene	MH risk
Central core disease (CCD)	*RYR1*	High[a]
Multiminicore disease	*SEPN1*	Low
	ACTA1	Low
	RYR1	High[a]
Nemaline rod myopathy	*NEB, TPM3, TNNT1, TPM2, ACTA1*	Low
	RYR1	High[a]

The table summarizes molecular genetic knowledge, i.e., involved genes, of the different core myopathies. Emphasis should be on the underlying molecular pathology rather than phenotypic presentation. In patients in whom the genes associated with MH (*RYR1* and the α-1 subunit of the dihydropyridine receptor, *CACNA1S*) are involved, a nontriggering anesthesia technique is to be chosen. Websites of the North American and the European MH Group provide further information available at: www.mhaus.org and www.emhg.org.

RYR1 = ryanodine receptor Type 1; *SEPN1* = selenoprotein N1; *ACTA1* = α-actine; *NEB* = nebuline; *TPM3* = tropomyosin 3; *TNNT1* = troponin T1; *TPM2* = β-tropomyosin.

[a] Dependent on the underlying mutation; to be on the safe side, risk to be considered high until more information becomes available.

with NM also show intranuclear deposits.[36,37] Rare intranuclear inclusions appear to be associated with a more rapid progression and a worse outcome.

It has been hypothesized that the hypotonia may be caused by an altered regulation of Ca^{2+} activated force production in the muscle fibers and that rod formation is secondary to contractile dysfunction.[38,39]

Genetic Basis of NM

Most cases of NM are sporadic (approximately 63%). Familial forms are observed in about one-third of cases (24% autosomal recessive and 13% autosomal dominant).[30] Five genes have been associated with NM, all encoding known components of skeletal muscle sarcomeric thin filaments: 1) slow α-tropomyosin 3 gene[40]; 2) slow troponin T1 gene[41]; 3) β-tropomyosin gene[42]; 4) nebulin gene[43]; and 5) *ACTA1*.[44,45] In many cases, there is no strict genotype-phenotype correlation, indicating clinical and genetic heterogeneity of the disease.[46]

In the majority of cases, NM is caused by mutations in the nebulin gene,[47] in particular by dominant *de novo* mutations, followed by mutations in the *ACTA1* gene.[48] In a few cases, mutations in *RYR1* have also been associated with nemaline bodies. However, these nemaline bodies appeared together with central cores, indicating a mixed core-rod myopathy.[49–51]

NM and MH Susceptibility

There are few reports concerning the anesthetic implications of NM, but they focus on the management of patients with NM with poor respiratory function (muscle weakness and thoracic deformities) or difficulties with orotracheal intubation (in case of facial dysmorphism).[52–54] Concerns about the association of NM with MH appear to be of secondary relevance. As in other neuromuscular disorders, the use of depolarizing muscle relaxants is generally not recommended in patients with NM to avoid the potential risk of developing muscle damage or life-threatening hyperkalemia as well as other nonspecific symptoms.[55,56] A close association between typical NM (patients who exclusively present rod bodies) and MH is rather unlikely, because there are no reports in which patients with NM developed a severe MH crisis or were tested as MH susceptible by IVCT.

Some patients exhibit the histological feature of cores and rods in the same muscle biopsy. Based on reports in the literature, it may be hypothesized that in these patients' nemaline (like) bodies may be a secondary feature of CCD and that the CCD itself may represent the major risk factor for MH reactions.[49,51,57] There are insufficient data to draw a firm conclusion but for reasons of patient safety, we suggest managing these patients as we describe for patients with CCD.

CONCLUSION

There is definitive clinical and laboratory evidence that some *RYR1* mutations are associated with the coexistence of MH and CCD phenotypes: MH triggering drugs are contraindicated in patients with CCD carrying these mutations. There is less certainty about the MH risk for patients with CCD or other congenital myopathies who carry other *RYR1* mutations. In congenital myopathies caused by mutations in genes other than *RYR1*, the risk of MH appears to be low. Table 1 in this article gives a summary of the genes involved in the covered diseases and aims at estimating the associated risk of MH.

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