

## EDITORIAL VIEWS

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### *Anesthetic Complications in Muscle Disorders*

The past several years have brought an explosion in knowledge concerning the molecular basis of muscular disorders.<sup>1</sup> Not only has information about the specific genetic defects been bountiful, but new insights into the pathomechanisms have been gained. Such information is important for the anesthesiologist because anesthetic complications commonly are associated with patients known to be suffering from active muscle disorders and those in the preclinical stages.<sup>2-8</sup>

Muscle disorders linked to anesthetic complications include malignant hyperthermia (MH), central core disease, muscular dystrophy, periodic paralysis (hyper- and hypokalemic), myotonia fluctuans, myotonic dystrophy, myotonia congenita, paramyotonia congenita, and Schwartz-Jampel syndrome. A muscle specialist looking at such a list would find it fairly easy to recall specific phenotypic features associated with most disorders and even some specific genetic mutations. This is not true for MH, because the key phenotypic features do not present themselves until a susceptible individual is administered a so-called triggering anesthetic agent and because the clinical presentation can be quite variable.<sup>9</sup> The molecular basis for susceptibility to MH is heterogenetic, *i.e.*, linkage to the skeletal muscle calcium release channel (ryanodine receptor) in some families but exclusion of this locus in others with linkage to another gene.<sup>10,11</sup> This difference should not be interpreted to mean that it is not imperative to obtain phenotypic information concerning MH. The opposite is true, and unless a significant effort is made to obtain such information, the details concerning the molecular basis of this disorder will remain obscure.

What phenotypic information can one obtain concerning the asymptomatic patient who may be susceptible to MH? In part the answer is easy, since the *in vitro* contracture test (IVCT) provides important information regarding a person's susceptibility to an anesthetic complication that may be characterized as MH. In addition, the family's anesthetic history, the details of the anesthetic complications, and knowledge of the patient's basal levels of serum creatine kinase may provide useful insights. Such information needs to be an-

alyzed critically, not only for patients suspected to have MH but also for those with other known myopathies, as described in the report by Vita *et al.* in this issue of ANESTHESIOLOGY.<sup>8</sup>

The IVCT remains the most reliable and accepted diagnostic procedure to identify susceptibility to MH.<sup>12</sup> This test has several inherent limitations: (1) a sizable muscle biopsy is required; (2) the viability and type of muscle used influences the test result; (3) it is not absolutely specific, *i.e.*, false-positive results have been obtained for patients with other known myopathies; and (4) the test is technically detailed, can be expensive to perform, and is performed at only a limited number of centers. Moreover, recent reports describing the potential for false-negative results<sup>13-15</sup> may have contributed to a feeling of uncertainty among anesthesiologists regarding the utility of the IVCT. This may explain in part why the number of tests being performed in the United States has decreased considerably. Testing has increased in Europe and other parts of the world. Thus, it has been easier for molecular biologists in Europe to obtain phenotypic information and genetic material to further knowledge about susceptibility to MH.<sup>10,11</sup>

How does one interpret true- and false-positive IVCT results? In principle, the Vita *et al.* paper is on the right track. We need to obtain more information about potential associations between the phenotypic expression and the genotype in muscle disorders that may cause anesthetic complications. The authors attempt to correlate masseter spasm and results of IVCT to specific genetic information. Unfortunately, the reader is provided little information about the characteristics of the reported masseter muscle rigidity. In a recent study using the swine model for MH, it was shown that the peak amplitude of intraoral force after a 2.0-mg/kg bolus dose of succinylcholine was not significantly different between normal animals and those susceptible to MH, whereas the duration was ten times longer in the susceptible group.<sup>16</sup> Although it would be clinically valuable to have such precise measurements of masseter muscle rigidity, we recognize that this is not practical. Yet, if an observed masseter spasm is suspected to be abnormally long, an estimate of its duration may be helpful.

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The significance of the occurrence of masseter spasm after the administration of succinylcholine is still debated.<sup>17-19</sup> Masseter spasm reportedly occurs in approximately 1% of all children receiving succinylcholine (much higher than the prevalence of all neuromuscular diseases combined), whereas in patients with myotonia or other neuromuscular complications, masseter spasm associated with generalized muscle rigidity is a common observation after the administration of a depolarizing agent. Less frequently, masseter spasm is associated with typical MH. Nevertheless, masseter spasm is taken to be an indicator of potential MH, resulting in cancellation of the surgery before hypermetabolism develops. Subsequently, without further information, such a patient and consanguineous family members would be declared MH-susceptible. Although such assumption of MH risk is the safest procedure, it has considerable medical and economic (insurability) implications for the patient. We need to do better. It is most important to perform a careful clinical assessment of a patient who has experienced masseter spasm to determine its cause. The follow-up should include a neurologic examination and the necessary routine laboratory tests to rule out or identify a primary muscle disorder, a muscle biopsy, an IVCT, and finally, if indicated, genetic screening.

The report by Vita *et al.* describes a family with myotonia fluctuans, succinylcholine-induced masseter spasm in two affected family members, and IVCT results that are positive according to the protocol supported by the North American Malignant Hyperthermia Registry (NAMHR).<sup>12</sup> In contrast, Ricker *et al.* recently published negative IVCT results according to the protocol supported by the European Malignant Hyperthermia Group (EMHG) for three families with myotonia fluctuans and five anesthesia-related events. All events included masseter spasm, which became generalized in other muscles and, in one patient, led to severe hypoxia.<sup>7</sup> Could myotonia in the North American families differ from that in the European families, particularly in consideration of the fact that myotonia has been associated with chloride and sodium channel defects? To date, eight chloride channel mutations have been reported for myotonia congenita, and three sodium channel point mutations have been identified for myotonia fluctuans. Two additional sodium channel mutations cause other unique forms of myotonia, and another 11 mutations have been identified within the same gene to cause hyperkalemic periodic paralysis or

paramyotonia congenita, diseases also associated with myotonia.<sup>20</sup>

Surprisingly, the family with myotonia fluctuans described by Vita *et al.* and those characterized by Ricker *et al.* all had not only anesthetic-related events but the same point mutation in the sodium channel gene. Apparently, this rare mutation predisposes patients to a high risk for anesthesia-related events and raises the question of whether the risk in myotonia fluctuans is greater than in other forms of myotonia. Probably not, with the high incidence of masseter spasm as compared to the low prevalence of myotonia fluctuans (less than 1:25,000),<sup>20</sup> reflecting the fact that a significant number of patients, and thus their anesthesiologists, are unaware of their defect. As the term fluctuans suggests, myotonia is not always present in this disorder, although latent myotonia can be recorded by the use of electromyography. Clinical myotonia will be induced, however, even in the most latent cases in which potassium or succinylcholine is administered. In contrast to patients with myotonia fluctuans, those with other inherited myotonic disorders frequently have more apparent abnormal muscle function. Consequently, they are more likely to be aware of their muscle disorder and can inform their anesthesiologists, who should avoid depolarizing relaxants.

Although most experts would agree that the initial responses to succinylcholine in such patients are induced or aggravated by myotonic reactions, some may contend that these individuals also are predisposed to MH-susceptibility. Interestingly, anesthesia was not discontinued in any of the patients discussed by Ricker *et al.* In the one severe event, life-threatening hypoventilation occurred (26% hemoglobin oxygen saturation, end-tidal carbon dioxide of 95 mmHg, and maximum temperature of 39.6°C, although MH was diagnosed and dantrolene given). In the other patients, metabolism did not increase, and in no case did muscle damage occur (maximum creatine kinase of 743 U/l). It is an acceptable conclusion that these anesthetic complications were not MH. This is corroborated by the additional studies with one of these families, which included forearm exercise test, forearm cooling test, oral potassium loading, bicycle exercise testing, and clinical trials with mexiletine hydrochloride.<sup>20</sup>

Why were the IVCT results for families with myotonia fluctuans carrying the same mutation different between these two reports? Was it related to different test protocols? The NAMHR suggests that a single concentration of halothane (3%) be administered to muscle bundles,

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whereas the EMHG uses a graded administration. Until recently, the suggested classification schemes for diagnosis (used in the two reports under discussion) also differed across the ocean. Specifically, if any bundle responded abnormally using the suggested NAMHR protocol, the test was interpreted to indicate susceptibility to MH. Using the EMHG protocol, if a muscle specimen has an abnormal response to either halothane or caffeine administration, but not both, the test is considered equivocal. At the NAMHR 5th MH Biopsy Standards Conference (September 1994), it was suggested that an equivocal category for IVCT results be supported. This is a step in the right direction, with the hope that someday there will be one international protocol for IVCT.

The extensive evaluation of myotonia fluctuans patients as used by Ricker *et al.* may not be appropriate for all patients who experience an anesthetic complication. On the other hand, these additional evaluations, even if they provide negative results, supply further phenotypic assessment. For most muscle disorders, several specific evaluation protocols have been established, whereas for MH, only the IVCT is employed. This may be considered shortsightedness on the part of individuals working in this field, because other evaluations have been identified that may provide useful insights, although they do not provide diagnostic information as definitive as the IVCT does. We would like to suggest that muscle function evaluation, blood cell studies, and plasma enzyme measurements be used in a complimentary fashion.<sup>5,21</sup>

The molecular basis of myotonia fluctuans has been described only recently,<sup>7</sup> but it represents a relatively asymptomatic disease, which in the presence of succinylcholine, assumes characteristics easily confused with early MH. Additional inherited muscle disorders probably remain to be described. There is a need to phenotypically and genetically characterize all patients who may have had a muscle-related anesthetic complication and to accurately identify the etiology. It is the responsibility of the anesthesiologist to follow up with a careful clinical evaluation and to refer the patient to a biopsy center for the IVCT and possibly for genetic testing. It is the responsibility of the testing center to diagnose the cause as accurately as possible.

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## Masse Glycin Sodium

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