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Review article

Duchenne muscular dystrophy: an old anesthesia problem revisited

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Summary

Patients with Duchenne and Becker muscular dystrophy suffer from a progressive deterioration in muscle secondary to a defect in the dystrophin gene. As such, they are susceptible to perioperative respiratory, cardiac and other complications, such as rhabdomyolysis. Inhalational anesthetic agents have been implicated as a cause of acute rhabdomyolysis that can resemble malignant hyperthermia (MH). This article reviews perioperative 'MH-like' reactions reported in muscular dystrophy patients and groups them into three categories according to clinical presentation. The etiology and underlying pathophysiological process responsible for these reactions is discussed and recommendations are proposed for the safe anesthetic management of these patients.

Keywords: anesthesia; Duchenne muscular dystrophy; pediatrics; rhabdomyolysis

Introduction

Duchenne muscular dystrophy (DMD) is the most common childhood muscular dystrophy, with an incidence of approximately one in 3500 live male births (1). Patients with DMD suffer from progressive degeneration of skeletal, cardiac and smooth muscle beginning at 3–5 years of age. The progression of muscle weakness is rapid, resulting in a failure to walk by adolescence and eventual death from respiratory failure before the end of the third decade (1). Dilated cardiomyopathy occurs in over 50% of patients by 15 years of age (2). Although many of these patients undergo anesthesia and surgery without complication, perioperative adverse events are not uncommon (3–8). Acute rhabdomyolysis is one such event, and is believed to be triggered primarily by the administration of succinylcholine, a depolarizing muscle relaxant. Potent inhalational anesthetic agents have also been implicated as a cause of rhabdomyolysis and other perioperative metabolic reactions that resemble malignant hyperthermia (MH) (9–12). Controversy exists as to whether inhalational agents can be safely administered to these patients. A hypothetical clinical scenario is described below:

> A 6 year old male diagnosed with DMD undergoes an adenotonsillectomy. Baseline creatine kinase (CK) levels are 900 $IU \cdot l^{-1}$ (13) (normal range 75–230 $IU \cdot l^{-1}$). The general anesthetic includes nitrous oxide in oxygen, sevoflurane,

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and intravenous fentanyl. Postoperatively, the patient voids dark, cola-colored urine and complains of calf and heel pain. The urine is positive for myoglobin (>60 $\mu g \cdot l^{-1}$), and plasma creatine kinase levels are >10 000 $IU \cdot l^{-1}$.

The underlying cause for these 'MH-like' metabolic reactions remains unexplained, and for many years the incidence of MH was assumed to be increased in patients with DMD, presumably due to the underlying myopathy. However, evidence against this association is now available, and alternative pathophysiological mechanisms have been proposed.

This article reviews perioperative metabolic reactions that resembled MH in DMD patients reported over the past 40 years. Only patients administered inhalational anesthetic agents, not succinylcholine, were considered. These reactions are grouped into three categories according to clinical presentation, and the etiology and underlying pathophysiological process responsible for these reactions are discussed. Lastly, based on the data available, recommendations are proposed for the safe anesthetic management of DMD patients.

Clinical presentation

Acute onset of hyperkalemic cardiac arrest

A review of the literature found a total of 13 patients who had a sudden hyperkalemic cardiac arrest with no obvious preceding signs of hypermetabolism (9,10,14–22). Ages ranged from 2 to 18 years; however, 12 were 8 years of age or younger. Eight patients had, or were suspected of having, DMD. The remainder were diagnosed with Becker muscular dystrophy (BMD), a similar pathology to DMD, in which dystrophin is present but dysfunctional. For seven of the DMD and one of the BMD patients, hyperkalemic cardiac arrest was the initial 'presentation' of the underlying myopathy. Halothane was administered to over half of the patients (7/13) in this group. The others received isoflurane (two patients), sevoflurane (one patient), or a combination of the two (three patients). The timing of the cardiac arrest was unpredictable as it varied from 10 min after induction to 20 min following arrival in the recovery room. Plasma potassium (K^+) levels, when measured, ranged from 6.9 $mmol \cdot l^{-1}$ to greater than 12 $mmol \cdot l^{-1}$. All patients developed massive rhabdomyolysis with myoglobinuria and, when measured, plasma CK levels were significantly elevated (50 000–613 120 $IU \cdot l^{-1}$). An elevated body temperature and/or arterial pCO_2 level were recorded in six patients.

Gradual rise in temperature and heart rate

Two articles described a total of nine patients with DMD who developed unexplained hyperthermia (maximum 38.2°C) and tachycardia during or after anesthesia with halothane (7,23). In seven patients (ages unknown) the onset occurred within a few hours of anesthesia and resolved spontaneously (23). The other two patients (ages 6 and 8 years) developed intraoperative hyperthermia and tachycardia that resolved once halothane was discontinued (7). The arterial blood gases were normal in one patient and were not measured in the others. There was no mention of rhabdomyolysis in any of the patients, although plasma CK and K^+ levels were not reported.

Postoperative rhabdomyolysis without cardiac arrest

Significant muscle cell breakdown has been reported in six patients following exposure to halothane, sevoflurane, and enflurane (24–29). Interestingly, although an inhalational agent was not used during the maintenance of anesthesia in one of the six patients, it was observed that the anesthesia machine had not been properly flushed prior to the administration of anesthesia (29). Five of the six patients, aged 15 months to 11 years, had a diagnosis of DMD (24–27,29), and one patient, aged 22 years, had BMD (28). Rhabdomyolysis resulted in plasma CK levels that were elevated (12 900–105 000 $IU \cdot l^{-1}$) from baseline in five patients (24–28). The patient who received a 'trigger-free' anesthetic had myoglobinemia but did not have an elevated CK level compared with baseline (29). One patient had an inappropriate sinus tachycardia and perioperative elevation in body temperature (40.3°C) despite the use of dantrolene (29); otherwise there were no other signs of hypermetabolism.

Etiology

Malignant hyperthermia

A longstanding view is that MH is the underlying mechanism responsible for these reactions (6,12). This is not surprising for two reasons: first, the combination of clinical signs such as tachycardia, elevated body temperature, raised arterial pCO_2 levels, and rhabdomyolysis are suggestive of MH; second, many DMD and BMD patients have tested positive for MH using skeletal muscle *in vitro* contracture tests. However, neither of these arguments is convincing. With respect to the clinical signs of MH, the reactions described above are atypical. The Malignant Hyperthermia Clinical Grading Scale is a method for estimating the qualitative likelihood of an MH reaction in a given patient using a standardized point system based on diagnostic criteria grouped into six 'processes': muscle rigidity, muscle breakdown, respiratory acidosis, temperature increase, cardiac involvement and a family history of MH (30). The diagnostic criteria within each process are assigned points based on their relative severity. For example, within the muscle breakdown category, 'elevated CK >10 000 $IU \cdot l^{-1}$ after anesthetic without succinylcholine' is worth 15 points, whereas 'myoglobin in serum >170 $\mu g \cdot l^{-1}$, is worth three points. The points for each criteria are then added together to produce a raw score that is converted to an MH rank (1–6) and 'description of likelihood' of MH, from 'almost never' (rank 1) to 'almost certain' (rank 6). If multiple criteria represent a single process, only the indicator with the highest score is counted.

Using this scale, patients in the first group would achieve an 'MH likelihood' of 'somewhat less than likely' (10–19 points) or 'somewhat greater than likely' (20–34 points): all had excessively elevated CK levels (15 points); six had elevated arterial pCO_2 levels (15 points); two patients had an 'inappropriately increased body temperature >38.8°C' (10 points). It is important to note that elevated arterial pCO_2 levels always occurred in the context of a low cardiac output state and no patients had evidence of excessive CO_2 production or hypermetabolism prior to the event. Additionally, the acuity of the cardiac arrest with no preceding signs of hypermetabolism is very unusual. This point was emphasized by the Malignant Hyperthermia Association of the United States (MHAUS) in an Anesthesia Patient Safety Foundation (APSF) newsletter (22):

> Cardiac arrest related to MH is usually preceded by rapidly rising endtidal carbon dioxide, muscle rigidity, acidosis and hyperthermia, and most often occurs during anesthetic administration rather than in the postoperative period. In such cases, the cause…is significant metabolic and/or respiratory acidosis rather than hyperkalemia.

Patients in the second group would be assigned an MH score of 'somewhat less than likely' because of an 'inappropriately rapid increase in body temperature' (15 points) and unexplained tachycardia (3 points). This is not surprising for two reasons: first, hyperthermia is considered a late sign of MH, and would be unlikely to precede or occur in the absence of other signs of hypermetabolism; second, tachycardia is a nonspecific sign of hypermetabolism. Of note, arterial blood gases were normal when measured. This contradicts the diagnosis of MH as increased CO_2 production and metabolic acidosis, due to accelerated aerobic or anaerobic metabolism, are hallmarks of MH (31).

For patients in the third group, the MH rank would also be 'somewhat less than likely': five of the six developed isolated rhabdomyolysis (15 points), and one had an inappropriate tachycardia (3 points), elevated temperature (10 points), and myoglobinemia (5 points). Again, the absence of any other clinical and metabolic signs of hypermetabolism is unusual for an MH reaction.

With respect to positive *in vitro* contracture tests in DMD patients, there are two problems: first, those related to *in vitro* contracture tests in general, and second, difficulties with *in vitro* contracture tests in patients with myopathies. The current 'gold standard' for *in vitro* contracture tests is the measurement of the force of contraction of viable, nonskinned muscle strips exposed to increasing levels of halothane or caffeine (caffeine–halothane contracture test). Two caffeine–halothane contracture test protocols, a North American and a European, exist (32). The European protocol uses more increments in the caffeine and halothane concentrations than the North American protocol, resulting in lower diagnostic thresholds (32,33). Sensitivity thresholds are intentionally kept high at the sacrifice of specificity to avoid false-negative results (32). The sensitivity is

97–99% for both protocols, whereas the specificity is 80–85% for the North American protocol and 90% for the European (32). Therefore, a positive caffeine–halothane contracture test is not a guarantee that a patient is truly MH susceptible.

With respect to muscular dystrophy patients, some have been deemed MH susceptible using invalidated *in vitro* contracture tests methods, such as Ca^{2+} uptake and ATPase activity (9,29), and skinned muscle fibers (the sarcolemma is removed chemically or mechanically before exposure to the agent) (11,34). The results of caffeine–halothane contracture tests in muscular dystrophy patients are conflicting. A few case reports have described patients as MH susceptible on the basis of positive contracture tests with halothane alone (12,35,36). This would be considered an MH-equivocal result by others (37). Abnormal contractures to both halothane and caffeine have been documented in both BMD (10,37) and DMD patients (38), although the latter reference did not use an established caffeine–halothane contracture test protocol. Numerous reports have demonstrated negative contracture tests in both DMD and BMD patients (37,39–41) using both the North American (39) and European protocols (40). Moreover, contracture tests of dystrophic muscle may be unreliable for two reasons: first, the underlying defect of raised intracellular Ca^{2+} levels may produce abnormal contractures (32,39) and thus a greater incidence of false-positive results; second, the muscle specimens are often of poor quality because of progressive fibrosis (42).

A dystrophin-deficient mouse model (*mdx)* has been used to provide additional insight into this issue (43). The *mdx* mouse myocytes, like human DMD myocytes, lack dystrophin and have abnormal intracellular Ca^{2+} homeostasis. However, the cells are much less dystrophic and the mice exhibit only a mild myopathy. MH testing of *mdx* muscle using the European protocol produced normal responses, suggesting that dystrophin deficiency and abnormal Ca^{2+} homeostasis *per se*, do not predispose to MH (43).

Anesthesia-induced rhabdomyolysis

The lack of evidence to support an association between DMD or BMD and MH has led to the proposal of an alternative mechanism termed 'anesthesia-induced rhabdomyolysis' (AIR) (27,44,45). The concept of AIR has been discussed in the literature since 1985, recognizing that rhabdomyolysis not associated with MH can occur in DMD patients after exposure to potent inhalational agents and/or the administration of succinylcholine (10,20,27,36,39,45,46). The supporting evidence for AIR is the same as that against MH: the reactions are atypical for MH despite some similar characteristics, and most caffeine–halothane contracture test results are negative, and probably unreliable, in muscular dystrophy patients. There is also indirect evidence that supports the notion that the lack of dystrophin is the root cause of rhabdomyolysis after exposure to inhalational anesthetic agents. Patients with muscle disorders, such as myotonic dystrophy, have normal dystrophin and thus stable sarcolemma. Despite the presence of massive contractures following the administration of succinylcholine, there is no significant rhabdomyolysis observed in these patients.

Why a small minority of muscular dystrophy patients suffer AIR after exposure to inhalational anesthetic agents remains unknown. Susceptibility may be, in part, related to the relative amount of muscle 'at risk'. In DMD patients under 8 years of age, muscle fibers are attempting to regenerate, and are more prone to rhabdomyolysis (47–49). As the patient ages, greater proportions of muscle fibers stop regenerating and become fibrotic (47,49,50). This observation may explain why the majority of AIR reactions occur in preadolescent patients, or older patients with BMD, which progresses more slowly than DMD.

Pathophysiology of rhabdomyolysis

Duchenne muscular dystrophy is an X-linked recessive disease characterized by a lack of dystrophin because of an abnormal dystrophin gene located on the short arm of the X chromosome (Xp21 position) (45). The majority (65%) of mutations of the dystrophin gene are large-scale deletions and approximately 5% are because of duplications (51). Dystrophin, a large intracellular protein, and dystrophin-related glycoproteins form a complex that connects the subsarcolemmal cytoskeleton to the extracellular matrix. The absence of dystrophin prevents either the assembly or integration of the components of the glycoprotein complex into the muscle cell membrane (sarcolemma) or accelerates

degradation (51). The absence of the dystrophin–glycoprotein complex results in instability and increased permeability of the sarcolemma and increased intracellular calcium levels (45). Additionally, chronically elevated intracellular Ca^{2+} levels may result in the activation of enzymes that proteolyze the cytoskeletal components and further degrade the structural stability of the sarcolemma (52). Exposure of the sarcolemma to a potent inhalational agent (or succinylcholine) stresses the muscle cell membrane and further increases the instability and permeability. Consequently, intracellular Ca^{2+} levels increase further and cell contents, such as K^+ and CK, leak out. A compensatory hypermetabolic response occurs in an attempt to reestablish membrane stability and prevent Ca^{2+} fluxes (39). This proposed mechanism may explain the hyperkalemia, hyperthermia, tachycardia and rhabdomyolysis observed in these patients.

Anesthesia for patients with Duchenne muscular dystrophy

Although only a small proportion of DMD patients develop AIR after exposure to inhalational anesthetic agents, the question is: should we continue to use inhalational anesthetic agents when total intravenous anesthesia (TIVA) is a safe and readily available alternative? The opinion in the literature has shifted over the last decade from 'yes' (1,53) to 'no' (49,54). Not only do we agree with this, we also suggest that a 'trigger-free' anesthetic and 'clean' anesthesia machine be used, similar to that for MH-susceptible patients. This recommendation is based on the fact that the minimum triggering concentration of inhalational agent remains unknown. Many of the most severe AIR reactions occur in the recovery room when drug concentrations are low (49). For instance, rhabdomyolysis has been reported in a 3-year-old patient who received a trigger-free anesthetic but with an anesthesia machine that had not been flushed prior to this procedure (29).

In certain clinical situations, such as a DMD patient with the potential for difficult airway management, and where an intravenous technique is not believed to be an option, a short exposure to an inhalational agent until the airway has been secured can be supported. However, immediate conversion to TIVA and a clean anesthesia machine is recommended, and the child should be carefully monitored for signs of rhabdomyolysis (serum K^+ level) because, even if the risk is low, its occurrence is unpredictable.

In the event that AIR is suspected, the inhalational anesthetic agent should be discontinued immediately. Serial serum potassium levels should be measured and immediately treated if greater than 5.5 $mmol \cdot l^{-1}$. To shift potassium back into the muscle cells, intravenous sodium bicarbonate and insulin with 10% dextrose should be administered and the patient hyperventilated to produce a respiratory alkalosis. Serial plasma CK, plasma myoglobin and urine myoglobin levels should be measured to detect rhabdomyolysis. If present, the patient should be treated with intravenous hydration and mannitol to maintain the urine output greater than 1 $ml \cdot kg^{-1} \cdot h^{-1}$ and minimize the risk of renal impairment.

Perioperative hyperkalemic cardiac arrest in an asymptomatic young male patient may be the initial presentation of occult muscular dystrophy. In such an event, the American Heart Association (AHA) Guidelines recommend the immediate administration of intravenous calcium chloride to antagonize the myocardial effects of hyperkalemia and help restore a spontaneous cardiac rhythm (55). The protective effect of Ca^{2+} on myocardial cells is most likely related to the influx of Ca^{2+} into the cell, which raises intracellular Ca^{2+} levels and transiently decreases the resting potential of the cell membrane (56,57). This reduces the potassium-related hyperexcitability of the myocardium and maintains a spontaneous cardiac rhythm. Intracellular Ca^{2+} levels are elevated in skeletal muscle cells of DMD patients and in the myocardium of older, but not necessarily younger, *mdx* mice (52,58,59). Therefore, the administration of calcium chloride may not depress the myocardial membrane resting potential to the same degree, and thus may not be as effective for the treatment of hyperkalemic cardiac arrest. Nonetheless, the AHA Guidelines regarding the administration of calcium chloride for hyperkalemic cardiac arrest should be adhered to. However, initial treatment should also focus on measures to shift potassium back into muscle cells, as sinus rhythm cannot be reestablished until the serum potassium levels are lowered to a near normal level.

The role of dantrolene in the management of AIR is unknown. The mechanism of action of dantrolene for the treatment of MH is likely inhibition of excessive

release of Ca^{2+} from the sarcoplasmic reticulum (SR) by binding to the ryanodine receptor isoform 1 (RYR1) (60). Dantrolene may be of no use for AIR as the proposed mechanism involves the breakdown of muscle cell membranes and subsequent leakage of cell contents. Dantrolene was administered to many of the patients described above with no obvious clinical benefit (10,14,16,18,20,29).

Conclusions

Differentiation between AIR and MH may be difficult, especially if the patient is not known to have DMD. However, acute hyperkalemic cardiac arrest or isolated rhabdomyolysis with no signs of systemic hypermetabolism strongly suggest AIR. Conversely, the presence of rapidly rising endtidal CO_2, unexplained metabolic acidosis, inappropriate tachycardia or tachypnea in a spontaneously breathing patient, muscle rigidity and increasing body temperature >38.8°C are consistent with MH. The Malignant Hyperthermia Clinical Grading Scale is a useful resource for retrospective analysis of the event if uncertainty persists.

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