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Editorial

Anaesthesia and the sex-linked dystrophies: between a rock and a hard place

In this issue of the *British Journal of Anaesthesia*, Poole and colleagues¹ report on a case with a successful outcome after prolonged resuscitation after a cardiac arrest affecting an apparently healthy 12-yr-old boy within 10 min of completion of an elective circumcision. The cardiac arrest was caused by hyperkalaemia secondary to rhabdomyolysis. Subsequent genetic investigation revealed the underlying disorder to be Becker's muscular dystrophy, the less aggressive form (compared with Duchenne's dystrophy) of the sex-linked disorders that result in a deficiency of dystrophin in the glycoprotein matrix that maintains the integrity of the plasma membranes of striated muscle.

This is not the first case of its type to be reported,² but it is of note as it emphasizes the value of continuing resuscitation after perioperative hyperkalaemic cardiac arrest in children until the plasma potassium concentration has been normalized. Indeed, the team involved in this case are to be congratulated as the patient's complete neurological recovery could have been achieved only with prompt recognition of cardiac arrest and successful implementation and maintenance of cardiopulmonary resuscitation. Early institution of effective cardiopulmonary resuscitation is important in hyperkalaemic cardiac arrest as it helps to redistribute the potassium load from the central compartment (and therefore away from the heart) and limits acidosis.³ Of course, appropriate treatment of hyperkalaemia presumes that the diagnosis can be made: a further lesson from this case is that no general anaesthetic is too minor to obviate the potentially critical value of 'point of care' availability of blood gas and electrolyte analysis.

It is also timely, however, to consider the cause of perioperative rhabdomyolysis in children with muscular dystrophy and whether our understanding of the pathophysiological process can help prevent similar cases

in future. The authors of this case report¹ apply the label 'anaesthesia-induced rhabdomyolysis' to imply that iso-flurane was the cause of rhabdomyolysis in their patient. Anaesthesia-induced rhabdomyolysis was a term first coined in 1978 in the context of a dystrophic patient who developed rhabdomyolysis after the administration of halothane and succinylcholine.⁴ The implication of extending the term to cases not involving succinylcholine is that perioperative rhabdomyolysis in dystrophic patients can be prevented by avoiding the potent inhalation anaesthetics: I am doubtful that this is true.

Rhabdomyolysis implies a major loss of integrity of the sarcolemma, or plasma membrane of skeletal muscle, allowing large molecular weight proteins, such as myoglobin and creatine kinase, to be lost from the cell. In health, this can occur through natural cell turnover or as a result of the mechanical stresses imposed on the sarcolemma by contractile activity. Mechanical stress associated with active change in muscle length causes microscopic tears in the sarcolemma,^{5,6} but under normal circumstances, these are repaired within 1 min.⁷ Interestingly, muscle damage is greater when contracting muscle lengthens (eccentric contraction) than when contraction is associated with muscle shortening (concentric contraction).⁸ The sarcolemmal repair mechanisms depend crucially upon the availability of an adequate energy supply.⁹ This has become evident through study of a variety of metabolic myopathies associated with rhabdomyolysis. Rhabdomyolysis occurs in these patients when there is increased demand for muscle repair, for example, with exercise, or key energy substrates are lacking such as with fasting.⁹

The primary defect in the sex-linked dystrophies, deficient or defective dystrophin, directly impairs the strength of the sarcolemma and increases its susceptibility to mechanically induced damage.¹⁰ However, the abnormal link between the cytoskeletal architecture and the

extracellular matrix also appears to alter the function of other membrane-associated protein complexes. One membrane protein that has received recent attention is the TRPC1 (transient receptor protein canonical 1) channel that is thought to be a (the) stretch-activated Ca^{2+} entry channel of skeletal muscle.^{11 12} Co-precipitation of TRPC1 with $\alpha 1$ -syntrophin and dystrophin has been demonstrated in normal muscle,¹³ while binding of TRPC1 to caveolin-3 and increased levels of both proteins have been shown in a mouse model of muscular dystrophy.¹⁴ There now appears to be a developing consensus that chronically increased intracellular Ca^{2+} concentration in the dystrophies is, at least in part, attributed to increased stretch-induced Ca^{2+} entry. Another mechanism for increased intracellular Ca^{2+} concentration is provided by the finding that the ryanodine receptor (RyR1), which is the sarcoplasmic reticulum Ca^{2+} release channel, is sensitized to Ca^{2+} release in dystrophic mouse muscle because of a high degree of nitrosylation.¹⁵ In turn, the nitrosylation was shown to be associated with the inducible form of nitric oxide synthase, presumably a consequence of the marked inflammatory response that is a feature of the dystrophies.

Chronically elevated intracellular Ca^{2+} concentration is likely to be important in the dystrophies because it impairs maximum force generation during tetanic (physiological) contraction¹⁶ to cause muscle weakness, and because it will lead to increased activity of calcium-dependent proteolytic enzymes, such as the calpains,¹⁷ promoting muscle necrosis. The latter will undoubtedly contribute to the chronically elevated serum concentrations of muscle enzymes in patients with muscular dystrophy, but is it also related to the acute profound rhabdomyolysis described in the case report¹ and other similar cases?

Although the sex-linked dystrophies are now recognized as separate entities to malignant hyperthermia, it is in considering a role for calcium ions in acute rhabdomyolysis that parallels with malignant hyperthermia are often drawn. Malignant hyperthermia is caused by an acute elevation of myoplasmic Ca^{2+} concentration and is associated with rhabdomyolysis. The triggering anaesthetics are understood to act on a sensitized RyR1 to cause uncontrolled Ca^{2+} release from the sarcoplasmic reticulum.¹⁸ The discovery of sensitized nitrosylated RyR1 in models of muscular dystrophy¹⁵ might suggest that this is the cause of anaesthetic-induced rhabdomyolysis. However, after exposure of a malignant hyperthermia patient to potent inhalation anaesthetics, the increasing intracellular Ca^{2+} concentration always causes a profound life-threatening hypermetabolic response with sympathetic nervous system activation before rhabdomyolysis becomes apparent. It would appear implausible, therefore, in the case described¹ where the authors stress the lack of evidence for either sympathetic stimulation or hypermetabolism that the rhabdomyolysis can be attributed to an acute increase in global intracellular Ca^{2+} concentration, as occurs in malignant hyperthermia. Nitrosylated RyR1 may, however, explain

reports of tachycardia, increased CO_2 production, and increased body temperature in dystrophic patients administered potent inhalation anaesthetics.²

This is not to say that the potent inhalation anaesthetics are not implicated in cases of acute rhabdomyolysis in patients with muscular dystrophy. It is possible, for example, that they affect the fluidity of the weakened sarcolemma, thereby further increasing its fragility. Another possibility is that they enhance the opening of TRPC1 channels leading to localized sub-membrane accumulation of Ca^{2+} which activates proteases and phospholipases. Limited evidence to date suggests, however, that potent inhalation anaesthetics inhibit TRPC activity,¹⁹ and that the increased membrane permeability associated with Ca^{2+} entry takes a matter of hours to develop²⁰ rather than the minutes associated with cases of hyperkalaemic cardiac arrest.^{1 2} Furthermore, if the potent inhalation anaesthetics are a major factor, it is surprising that so few cases have been reported. This is especially so if one considers that muscle biopsies under inhalation anaesthesia were routinely carried out in young boys suspected of having Duchenne's or Becker's dystrophy from the late nineteenth century²¹ until the advent of genetic diagnosis in the 1990s. Case series^{22–24} support this contention.

What then are the other factors that might contribute to acute rhabdomyolysis in dystrophic patients? In the knowledge that episodes of spontaneous acute rhabdomyolysis occur in dystrophic patients,²⁵ it is reasonable to suppose that these patients are prone to exaggerated responses to any cause of rhabdomyolysis, and these are legion.⁹ However, many of these are not relevant to the well-managed child in the perioperative period. The remaining possibilities are excessive muscle activity (agitated or physically struggling child, drug-induced rigidity), impaired metabolic repair (hypoxia, ischaemia, acidosis, reduced oxidative phosphorylation capacity), or direct membrane toxicity (drugs, reactive oxygen species).

In contemplating what might set the background to sporadic perioperative rhabdomyolysis, it is interesting to note that dystrophic muscle has a markedly reduced mitochondrial metabolic capacity, consistent with mitochondrial Ca^{2+} overload secondary to chronically elevated myoplasmic Ca^{2+} concentration.²⁶ Thus, dystrophic patients, in the same way as patients with metabolic myopathies, may well be at increased risk of developing rhabdomyolysis if they are fasted. There is therefore a theoretical basis for establishing a dextrose infusion in dystrophic patients who are being fasted before surgery.

Advice regarding choice of anaesthetic drugs is more difficult. Of course, for appropriate procedures in the older child, regional anaesthesia is a preferred option. When general anaesthesia is required, there is no risk-free choice, as propofol, ketamine, benzodiazepines, barbiturates, and opioids have all been associated with rhabdomyolysis,⁹ although with the latter three groups of drugs rhabdomyolysis is most likely associated with muscle ischaemia and

hypothermia after overdose-related immobility rather than a toxic effect of the drug on muscle tissue. Etomidate, propofol, and ketamine can be associated with an increase in muscle tone, while propofol infusions in children have caused profound rhabdomyolysis thought to be secondary to disruption of mitochondrial fatty acid oxidation.²⁷ With the known defect in mitochondrial oxidative capacity in muscular dystrophies,²⁶ the use of propofol infusions in these children requires at least caution. I would also advise caution in using non-steroidal anti-inflammatory drugs (NSAIDs) in dystrophic patients. NSAIDs have been reported to cause rhabdomyolysis in healthy patients,²⁸ and the case reported here¹ is the second case of rhabdomyolysis in Becker's dystrophy that I am aware of where an NSAID has been given before the operation.

Of course, rhabdomyolysis is not the only concern when planning general anaesthesia for a patient with muscle disease.²⁹ The danger in trying to eliminate the risk of a relatively rare complication, such as rhabdomyolysis, is that the interventions may disproportionately increase the risk of more common complications. Dystrophinopathy also affects cardiac muscle leading to cardiomyopathy, while respiratory muscle weakness can be confounded by restrictive lung defects secondary to kyphoscoliosis. It is the presence of such common complications of the disease and the reduction of prevalent generic risks of anaesthetizing children, such as airway problems, that should be the major considerations when choosing an anaesthetic technique for an individual dystrophic child. If potent inhalation agents and other drugs that might contribute to the development of acute rhabdomyolysis cannot be avoided without compromising other aspects of the safety of anaesthesia, then the small risk of rhabdomyolysis should be accepted and the patient monitored appropriately.

The preceding discussion assumes that the muscular dystrophy has been identified before the operation. The boy described here,¹ was, however, apparently healthy, and there were no features in his developmental or family history to suggest the presence of a dystrophy. Many parents of children diagnosed with muscular dystrophy do, however, subsequently report their child to have had delayed motor milestones. This applies to both Duchenne and Becker dystrophies, even though the average age of diagnosis of the latter is 11 yr. In 1995, in the context of avoiding the administration of succinylcholine to children with an undiagnosed myopathy, I suggested that systematic enquiry concerning evidence of a personal or family history of muscle disease become a routine part of pre-anaesthetic assessment of children.³⁰ Now that it is clear that risk management of anaesthesia for children with muscular dystrophy is much more complex than simply avoiding succinylcholine, I can only emphasize the potential value in routinely enquiring about symptoms of poor muscle function, delayed motor milestones, and a family history of muscle disease or childhood disability.

In conclusion, acute rhabdomyolysis is an uncommon but potentially fatal complication of surgery under general anaesthesia in patients with muscular dystrophy. Fasting may be an aetiological factor and provision of metabolic substrate in the form of a dextrose infusion may be beneficial. Avoidance of certain groups of drugs, such as potent inhalation anaesthetics, NSAIDs, and possibly propofol, may reduce the risk of rhabdomyolysis but is unlikely to remove it, although the use of alternative agents may unacceptably increase the likelihood of other complications. If hyperkalaemic cardiac arrest secondary to rhabdomyolysis does occur, cardiopulmonary resuscitation should be continued until hyperkalaemia is corrected.

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