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REVIEW ARTICLE

Cardiac considerations in the operative management of the patient with Duchenne or Becker muscular dystrophy

Linda H. Cripe[1] & Joseph D. Tobias[2]

1 The Department of Pediatrics, Nationwide Children's Hospital, Columbus, OH, USA
2 The Department of Anesthesia and Pain Medicine, Nationwide Children's Hospital, Columbus, OH, USA

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Correspondence
Linda H. Cripe, The Department of Pediatrics, The Heart Center, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205-2664, USA
Email: Linda.Cripe@nationwidechildrens.org

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Summary

Duchenne muscular dystrophy/Becker muscular dystrophy (DMD/BMD) is a progressive multisystem neuromuscular disorder. In addition to the skeletal muscle, the myocardium in the DMD/BMD patient is dystrophin deficient which results in a progressive cardiomyopathy. The myopathic myocardium poses significant risk of increased morbidity and mortality at the time of major surgical procedures. Careful attention must be given to the DMD/BMD patient during the intraoperative and postoperative period. Anesthesia selection is critical and anesthetics should be avoided which have been shown to be harmful in this patient population. Preanesthesia assessment should include cardiac consultation and detailed preoperative evaluation. Intraoperative management needs to insure that the weakened myocardium is not compromised by physiologic changes such as hypotension or major fluid shifts. Finally, attention to the cardiac status of the patient must continue into the postoperative period. The surgical care of the DMD/BMD patient requires a multispecialty approach to insure operative success.

Introduction

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are X-linked recessive diseases that result from mutations in the dystrophin gene, a 2.5-Mb gene located on chromosome Xp21.1 (1,2). Newborn screening studies indicate a birth prevalence of about 1 : 5000 (3). DMD is a progressive neuromuscular disease typically diagnosed when the child fails to meet gross motor milestones in early childhood. BMD is a milder form of the disease and results from mutations that fail to produce a functional dystrophin molecule. In addition to the skeletal muscle disease, the DMD/BMD patient develops a cardiomyopathy characterized by a progressive decline in ejection fraction (4). The cardiomyopathy becomes clinically evident during the early teen years although changes are noted in the myocardium by noninvasive imaging much earlier. The cardiomyopathy is currently the leading cause of death as improvements have occurred in the respiratory management of the disease. At autopsy, the myocardium displays areas of myocyte hypertrophy, atrophy and fibrosis (5). No effective treatment exists but corticosteroids have been shown to alter the natural history of both the skeletal and cardiac muscle manifestations (6–8).

As a result of the underlying cardiomyopathy, patients with DMD/BMD are at increased risk when they undergo sedation or general anesthesia. Unfortunately, surgery is required secondary to the multisystem nature of the disease. Orthopedic surgery, particularly scoliosis surgery, is common secondary to the progressive musculoskeletal weakness (4,7). Patients with DMD/BMD should receive a detailed preoperative assessment, thoughtful disease specific intraoperative management and aggressive postoperative monitoring if they are to avoid anesthesia and surgical-related morbidity and mortality. In addition, timing disease related major surgical procedures such as scoliosis surgery early in the child's life prior to the onset of significant myocardial dysfunction is recommended to minimize cardiovascular risk (9). Finally, surgery in the DMD/BMD patient should be undertaken in a hospital equipped to deal with the unique issues posed by patients with neuromuscular disorders.

The potential impact of DMD on perioperative morbidity and even mortality cannot be ignored as the literature has suggested a significantly increased risk during anesthetic care in these patients (10–12). Earlier reports outlined the potential for perioperative mortality with Sethna *et al*. (10) describing intraoperative cardiac arrest and death in 2 of 25 patients requiring anesthetic care. However, more recent reports demonstrate that with a better understanding of the pathophysiology of the disease, its end-organ involvement and improvements in perioperative care favorable outcomes are possible even in this challenging patient population. In a review of 91 DMD patients undergoing 232 orthopedic surgical procedures, Muenster *et al*. (13) noted no severe anesthesia-related complication and no case of unexplained fever or rhabdomyolysis.

Preoperative assessment

The cardiac status needs to be carefully considered in the preoperative evaluation of the DMD/BMD patient. Preanesthesia consultation with a cardiologist is highly recommended for patients undergoing general anesthesia for major surgical procedures such as scoliosis surgery. Timing the cardiac evaluation in close proximity to the procedure insures that accurate hemodynamic information is available to the surgical team. The preoperative evaluation should focus on the end-organ involvement of DMD, its evaluation, and the development of an anesthetic plan based on these findings.

In addition to cardiac involvement as noted above, respiratory involvement is universally present in patients with DMD. Given the synergistic relationship that the respiratory system has on cardiac function, it is recommended that consultation with a pulmonologist is included in the preoperative assessment. For a full discussion regarding the respiratory concerns of patients with DMD, the reader is referred to the review manuscript in this journal written by the pulmonologists who participated in the development of the consensus statement from the American College of Chest Physicians document (14).

History and physical examination

The preoperative evaluation should begin with a detailed history and physical exam. The New York Heart Association (NYHA) classification of heart failure is difficult to apply to this patient population secondary to the presence of the underlying musculoskeletal disease. The signs and symptoms of heart failure are frequently subtle and include but are not limited to weight loss, vomiting, abdominal pain, sleep disturbance, decreased urinary output, fatigue and inability to tolerate daily activities. Chest pain is a common complaint and although most likely musculoskeletal in origin should not be discounted especially when severe or persistent.

The preoperative physical exam should start with the measurement of vital signs including weight, blood pressure and heart rate. Establishment of the baseline heart rate is also critical as many patients with DMD manifest a resting sinus tachycardia even in the absence of ventricular dysfunction. The etiology of the sinus tachycardia is unclear. Some investigators have postulated that it represents dysregulation of the autonomic nervous system but this is likely an incomplete explanation (15). Blood pressure should also be accurately noted as hypotension is often present in the older nonambulatory patient. The hypotensive patient is at increased risk of clinically significant blood pressure drops with dramatic changes in fluid status during procedures associated with significant blood loss. Medical management by the cardiologist should be maximized prior to the procedure.

The preoperative physical examination should include a detailed cardiac exam. Attention should be paid to documentation of a regular rhythm and the presence or absence of a murmur or gallop rhythm. Signs of heart familiar should be noted such as peripheral edema and hepatosplenomegaly. Dependent edema is frequently present in the nonambulatory patient and should not be misinterpreted as being related to cardiac dysfunction.

Of primary importance to the anesthesia provider is the potential for airway involvement which may lead to difficulties with airway management. In their review, Muenster *et al*. noted that difficult laryngoscopy was reported in eight patients or 3.4% of the cases which is significantly higher than that routinely encountered in the pediatric population. Although the literature has not specifically addressed this issue in great detail, anecdotal reports exist regarding the potential for difficulties with endotracheal intubation in patients with various muscular dystrophies. In most cases, these issues relate to progressive fibrosis or skeletal muscle with involvement of the masseter muscles thereby limiting mouth opening and involvement of the neck muscles thereby limiting flexion and extension. These should be addressed during the preoperative airway evaluation.

Preprocedure cardiac testing

Preprocedure testing should include an electrocardiogram (ECG) as well as a noninvasive evaluation of cardiac function such as an echocardiogram or a cardiac MRI (9). In rare instances, a dobutamine stress echocardiogram may also be indicated preoperatively. Unfortunately, a resting preoperative echocardiogram may not

reflect the ability of the cardiomyopathic heart to respond to the intraoperative stress associated with major surgical procedures. A dobutamine stress echocardiogram may provide additional information needed for intraoperative management. This should be discussed with the cardiologist during the preprocedure evaluation. Finally, a Holter or event monitor may also be indicated particularly in patients where a known rhythm abnormality has previously been documented. Frequent ventricular ectopy can be present, particularly in the older DMD patient.

The ECG is important in the preoperative assessment of the patient with DMD/BMD. A baseline ECG should be obtained as close to the procedure as possible given the ECG evolves as the disease progresses. It is important to recognize that ECG abnormalities are present in the infant and young child as well as the older boy and precede the development of functional evidence of systolic dysfunction or left ventricular enlargement (16). Left ventricular hypertrophy is the most common finding in the young DMD patient manifested by the presence of a Q wave >98th percentile in lead III or V6. Right ventricular hypertrophy is the second most common abnormality. Hallmark findings in the older patient include sinus tachycardia, tall right precordial R-waves with an increased R-wave/S-wave (R/S) ratio, a short PR interval, right ventricular hypertrophy (RVH and deep Q waves in leads I, aVL, V5 and V6) (15,17).

Improved cardiac imaging has demonstrated that the cardiomyopathy associated with DMD is present at an early age, long before the onset of symptoms. Diastolic abnormalities are also present and have been shown to precede systolic abnormalities (18). It is recommended that cardiac function be assessed at diagnosis or by the age of 6 years and at least biannually until the age of 10 years. Annual evaluation should be undertaken starting at age 10 or sooner if symptoms are present (9,17).

Echocardiography historically has been the preferred mode of cardiac imaging, however, cardiac MRI (CMR) is emerging as the imaging modality of choice. Echocardiography is frequently limited by poor acoustic windows making images difficult to accurately interpret particularly in the older DMD patient. CMR provides significant advantages in this patient population allowing for accurate information to be obtained regarding right and left ventricular function. In addition, CMR permits the identification of myocardial fibrosis through the use of late gadolinium enhancement. Fibrosis has been demonstrated to be present in patients prior to the onset of left ventricular dysfunction (19,20). CMR allows for the identification of myocardial strain abnormalities shown to be present in the young DMD patient in the presence of a normal left ventricular ejection fraction (20).

Transfusion management

Potential strategies to limit the need for allogeneic transfusions can also be addressed during the preoperative evaluation (21). These may be particularly relevant for major orthopedic surgeries as patients with DMD and other neuromuscular causes of scoliosis have been shown to have a significantly greater blood loss during spinal fusion losing an average of 78% of their estimated blood volume compared with 20% in idiopathic scoliosis patients (22). This is of particular importance in the older patient with DMD who may have impaired myocardial reserve. Additionally, cardiovascular causes of cardiac arrest are the most common (41% of all arrests in the study of Bhananker *et al.*), with hypovolemia from blood loss and hyperkalemia from transfusion of stored blood the most common identifiable causes (23). Given these concerns, attention to blood avoidance may begin during the preoperative evaluation with an evaluation of the baseline hemoglobin and treatment for anemia as needed. Other preoperative options include the use of erythropoietin and autologous blood donation.

Issues with erythropoietin include not only variation in its efficacy as reported in the literature with some studies showing no benefit, but also its cost and the inconvenience to the patient including the need for weekly visits with laboratory measurement of hemoglobin and subcutaneous injections (24–26). Similar cost and time constraints have also decreased the enthusiasm for preoperative autologous donation. An additional concern with erythropoietin is the potential increase in thrombotic events. In the adult, population, Stowell *et al.* (27) reported a higher incidence of deep vein thrombosis of 4.7% vs 2.1% in a cohort of 680 adults. Patients with chronic diseases may have associated medical or nutritional conditions that affect coagulation function. Nutritional issues and poor intake of vitamin K may result in low levels of vitamin K-dependent coagulation factors resulting in preoperative coagulation dysfunction. Preoperative screening of coagulation function and simple measures such as the administration of vitamin K (oral or intramuscular) may alleviate such problems. Coagulation function may be further affected by the chronic use of nonsteroidal anti-inflammatory agents (NSAID's). Discontinuation of most NSAIDs for 2–5 days prior to surgery will result in return of normal platelet function. Attention to the use of herbal medications or homeopathic remedies, which are frequently utilized in the DMD population, should also be investigated as several of these including garlic, ginkgo biloba and ginseng may impact coagulation function.

Advanced directives

Many DMD patients undergoing surgical intervention will have complex medical problems as a result of their multisystem disease. Patients may be receiving continuous chronic ventilatory support or may only require support at night. Advanced directives should include resuscitation parameters and investigate attitudes toward prolonged dependence on mechanical ventilation should it be necessary. These issues should be addressed by the patient and family prior to any surgical intervention.

Intraoperative care

Depending on the type of surgical procedure and the neurocognitive level of the patient, options include general anesthesia, regional anesthesia or monitored anesthesia care. Although there is no evidence-based medicine to demonstrate the advantage of one technique over another, one may postulate that the avoidance of general anesthesia and endotracheal intubation would be beneficial in decreasing the incidence of perioperative events especially respiratory complications (28–30). However, for major surgical procedures, general anesthesia and endotracheal intubation are necessary. Given the potential difficulties with airway management, the appropriate equipment for dealing with the difficult airway should be readily available including the tools for indirect laryngoscopy (31).

The technique and medications used for the induction of anesthesia are guided by the patient's comorbid conditions, the assessment of the ease of tracheal intubation, as well as the patient's preference and/or demographics (age and cognitive function). Although controversial, the use of volatile anesthetic agents may result in rhabdomyolysis and hyperkalemia unrelated to malignant hyperthermia. Although the exact mechanisms remain poorly defined, there is evidence to suggest that the prolonged use of these agents should be avoided in patients with DMD (11,32,33). It is likely that there is limited risk of such problems during the brief inhalation induction of anesthesia prior to placement of an intravenous cannula. However, given that an intravenous cannula may be placed easily after oral midazolam as a premedicant, 50–70% nitrous oxide via mask, and a topical anesthetic cream, there appears to be limited need for the volatile agents.

The agents used for anesthetic induction should be based on the patient's comorbid cardiac condition. Although its effect on adrenal function has led to a re-evaluation of its use during endotracheal intubation in the critically ill ICU patient, etomidate may still be an appropriate choice for anesthetic induction in patients with diminished myocardial function (34). Once adequate bag-mask ventilation has been demonstrated, a nondepolarizing neuromuscular blocking (NMBA) can be administered. The depolarizing agent, succinylcholine, is absolutely contraindicated, and should not even be drawn up into a syringe. When motor-evoked potentials are being used to monitor spinal cord function, a single dose of a nondepolarizing NMBA can be used to facilitate endotracheal intubation. However, in patients with myopathic conditions such as DMD, it can be expected that the duration of blockade will be prolonged. Using 0.3 $mg \cdot kg^{-1}$ of rocuronium, Muenster *et al*. (35) demonstrated that the onset time to maximum blockade was significantly prolonged in DMD patients (median: 315; range: 120–465) compared with controls (median or 315 vs 195 s) although the peak effect was not. As expected, recovery was significantly prolonged in DMD patients compared with controls at all recorded time points. The median clinical duration was 40.3 min (range, 22–89 min) in the DMD group. Although not yet available in the United States, there is anecdotal evidence to demonstrate the efficacy of sugammadex for reversal of prolonged blockade in this setting (36). Although no longer available for clinical use, mivacurium and rapacuronium offered the possibility of providing neuromuscular blockade without concerns regarding a clinically significant prolongation of its duration (37,38). There are limited data regarding other nondepolarizing neuromuscular blocking agents including atracurium and cisatracurium in this population. Although the use of atracurium has been reported, data are lacking as to whether there is an appreciable effect on recovery time (39). Given its pharmacodynamics profile and data from other myopathic conditions, the rate of recovery following cisatracuruium may be more predictable in patients with DMD (40). Alternatively, endotracheal intubation can be accomplished with a combination of propofol and remifentanil to avoid the need for a neuromuscular blocking agent, although the potential hemodynamic impact must be considered (41).

After anesthetic induction and endotracheal intubation, adequate intravenous access and invasive cardiovascular monitoring as indicated are obtained. Close attention to myocardial function, cardiac output, and blood pressure is warranted during this time as the change from spontaneous to positive pressure ventilation may have significant hemodynamic consequences. Clinical experience also suggests that changes in position such as turning to the prone position may compromise cardiac output in patients with comorbid cardiac disease. When considering the perioperative implications of the associated myocardial disease, issues may arise

related to the anesthetic agents used, the patient's comorbid condition or the surgical procedure itself. An example of the latter which may significantly impact cardiac output related to changes in afterload and preload is laparoscopy (42). Although generally well tolerated in patients with normal myocardial function, there may be a precipitous and clinically significant decrease in cardiac output during abdominal insufflation. Although these procedures have been performed successfully in patients with compromised myocardial function, the intra-abdominal pressure should be less (less than 8–10 mmHg) and surrogate markers of cardiac output should be followed (see below). While technically more challenging during prone positioning, transesophageal echocardiography (TEE) should be considered in patients with an ejection fraction <55%, especially during major surgical procedures (43).

When there is a risk of significant blood loss such as posterior spinal fusion, our practice is the placement of two large bore peripheral cannulas for the administration of blood and blood products as needed. The use of ultrasound and the Seldinger technique for cannulation of deep peripheral veins may be especially useful in patients with difficult venous access (44). Poor peripheral venous access is commonly encountered in patients with DMD. Additional invasive hemodynamic monitoring with an arterial cannula and central venous access may be obtained depending on the patient's condition and the surgical expertise. Difficulties with arterial cannulation may arise related to skeletal muscular contractures and positioning problems. It is not uncommon for patients to be unable to extend and supinate their arms for radial artery cannulation. The use of ultrasound is definitely recommended for central venous access and may be invaluable for placement of peripheral intravenous and arterial cannula. Although the definitive accuracy of central venous pressure monitoring in the prone position has been questioned, central access provides a route for the rapid administration of vasoactive medications as well as the potential for monitoring central venous oxygen saturation as a surrogate marker of cardiac output (45).

Given the problems with assessment of cardiac output, surrogate markers (venous PaO_2, lactate or near-infrared spectroscopy) may be followed to guide therapy. Depending on the site of placement, central venous access may be used to obtain venous blood gases (46). Although co-oximetry is not routinely performed in the operating room using point-of-care testing, the venous PaO_2 may reflect changes in cardiac output. Optimization of myocardial function may need to be addressed in patients who develop a venous saturation less than 50% (PaO_2 <26 mmHg). This may include the administration of fluids to increase preload or the use of vasoactive infusions such as milrinone to augment inotropy, improve lusitropy, and decrease afterload. Given its availability using point-of-care testing, periodic measurement of serum lactate may be useful in guiding intraoperative therapeutic decisions. During prolonged procedures with the administration of large volumes of isotonic fluids, a dilution acidosis may develop. Intermittent measurements of lactate during the intraoperative and postoperative period provide another monitor of the adequacy of end-organ perfusion. Although used most commonly during cardiac surgical procedures, monitoring cerebral oxygenation using near-infrared spectroscopy can be applied to other major surgical procedures even in the prone position thereby serving as another surrogate marker of cardiac output.

Maintenance anesthesia during surgery for scoliosis generally includes total intravenous anesthesia (TIVA) not only given the above-mentioned concerns of rhabdomyolysis related to the volatile anesthetic agents, but also to facilitate neurophysiological monitoring using motor and somatosensory evoked potentials. Dexmedetomidine may be added to decrease the propofol dose (47,48). Despite the popularity and clinical experience with the use of propofol for TIVA in these patients, recent concern has been expressed regarding the effect of propofol on mitochondrial oxidative function (12). These concerns haven raised due to the fact that rhabdomyolysis thought to be secondary to disruption of mitochondrial fatty acid oxidation can occur with prolonged propofol infusion in the pediatric ICU setting and there is a known defect in mitochondrial oxidative capacity in the muscular dystrophies (49,50). Despite such concerns, TIVA with propofol and a synthetic opioid remains the most commonly chosen anesthetic regimen. The hemodynamic effects of such combinations must be considered especially in patients with compromised myocardial function.

Given the above-mentioned concerns of blood loss during major orthopedic surgery, which may be exaggerated in muscular dystrophy patients, techniques to avoid blood loss are generally employed. In addition to simple, conservative measures such as the aggressive maintenance of normothermia, these may include pharmacologic manipulation of the coagulation cascade, the administration of an antifibrinolytic agent, acute normovolemic hemodilution, intraoperative and postoperative blood salvage, and controlled hypotension.

Postoperative care

The DMD patient requires attentive hemodynamic monitoring in the postoperative period until the

respiratory and the fluid status returns to normal. Treatment with inotropic agents such as milrinone or dobutamine may be necessary to support myocardial function. Postoperative echocardiography can be performed at the bedside and has the ability to provide important information regarding left ventricular systolic and diastolic function. Close monitoring of cardiac rhythm should be standard and rhythm abnormalities should be promptly treated. Electrolyte disturbances can precipitate rhythm abnormalities which can further compromise cardiac function. Careful attention should also be paid to the nutritional status of the DMD/BMD patient as it can impact cardiac function.

Although the majority of patients presenting for spinal surgery will not require postoperative mechanical ventilation, the severity of the comorbid conditions, intraoperative blood loss, and surgical duration may affect the decision as to whether provide a short period of postoperative mechanical ventilation. In addition to respiratory function, airway issues may necessitate postoperative mechanical ventilation. Prolonged procedures in the prone position may result in airway or lingual edema thereby necessitating postoperative endotracheal intubation. In a review of an 18-month experience in a cohort of 42 patients with nonidiopathic scoliosis, 23.8% of patients required postoperative mechanical ventilation (51). Patients with Duchenne muscular dystrophy and those with a preoperative FVC $\leq$ 30% were more likely to require postoperative respiratory support. The authors suggested the use of noninvasive ventilator techniques to ease the transition from mechanical to spontaneous ventilation. To achieve effective ventilation in patients with diminished respiratory function, complete reversal of neuromuscular blockade is mandatory prior to tracheal extubation. One additional area of controversy in patients with DMD is the potential deleterious effects of cholinesterase inhibitors. Altered responses to reversal of neuromuscular blockade have been reported in adult patients with neuromuscular disorders other than DMD (52). Although the pharmacological antagonism of acetylcholine breakdown has been postulated as one mechanism which may precipitate rhabdomyolysis in patients with DMD, reversal of nondepolarizing neuromuscular blockade has been reported without adverse sequelae (37,39,53).

Given the severity of the surgical procedure, several options exist for the provision of postoperative analgesia. Given their effects on central control of ventilation and cough effort, options which limit the use of opioids including adjunctive agents or regional anesthesia should be considered. Preliminary data from the adult population have demonstrated the potential role of the preoperative administration of pregabalin or gabapentin (54). Additionally, there may be a role for the postoperative administration of the α_2-adrenergic agonist, dexmedetomidine, and intravenous acetaminophen. Caution has been suggested with the use of nonsteroidal anti-inflammatory agents given their anecdotal and temporal association with rhabdomyolysis (32,55).

Carrier females

Female carriers of DMD/BMD are also at risk of developing cardiomyopathy and should also undergo cardiac evaluation as outlined above prior to major surgical procedures (56). Given the emotional aspects of the diagnosis, it is important to appreciate that many at risk individuals will not submit to genetic testing. A detailed history is likely to reveal individuals likely to have positive carrier status and be at increased risk (57). In the absence of confirmatory genetic data, these individuals need careful preoperative evaluation.

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