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Anesthetic Considerations in Patients with Mitochondrial Defects

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Abstract

Mitochondrial disease, once thought to be a rare clinical entity, is now recognized as an important cause of a wide range of neurological, cardiac, muscle and endocrine disorders [1–3]. The incidence of disorders of the respiratory chain alone is estimated to be about 1 per 4–5,000 live births, similar to that of more well-known neurological diseases [4, 5]. High-energy requiring tissues are uniquely dependent on the energy delivered by mitochondria, and therefore have the lowest threshold for displaying symptoms of mitochondrial disease. Thus, mitochondrial dysfunction most commonly affects function of the central nervous system, the heart and the muscular system [1, 3, 4]. Mutations in mitochondrial proteins cause striking clinical features in those tissues types, including encephalopathies, seizures, cerebellar ataxias, cardiomyopathies, myopathies, as well as gastrointestinal and hepatic disease. Our knowledge of the contribution of mitochondria in causing disease or influencing aging is expanding rapidly [4, 5]. As diagnosis and treatment improves for children with mitochondrial diseases, it has become increasingly common for them to undergo surgeries for their long-term care. In addition, often a muscle biopsy or other tests needing anesthesia are required for diagnosis. Mitochondrial disease represents probably hundreds of different defects, both genetic and environmental in origin, and is thus difficult to characterize. The specter of possible delayed complications in patients caused by inhibition of metabolism by anesthetics, by remaining in a biochemically stressed state such as fasting/catabolism, or by prolonged exposure to pain is a constant worry to physicians caring for these patients. Here, we review the considerations when caring for a patient with mitochondrial disease.

Keywords

Mitochondrial disorders; muscle disorders; neurological disease; anesthetics; inhaled agents; anesthetics; intravenous agents; general anesthesia

Introduction

The diagnosis of mitochondrial disease remains difficult. When children present to the operating room with a diagnosis of myopathy, it is often unclear whether or not the underlying cause is mitochondrial in origin, making it challenging for the clinician when formulating an anesthetic plan. This conundrum was well discussed by Kinder Ross in an editorial in *Pediatric Anesthesia* [6]. The author, commenting on two articles in the same issue, points out that patients with myopathies and mitochondrial disease *usually* do well

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regardless of the specific anesthetic approach that is chosen [7, 8]. Despite the low incidence of perioperative complications in these two studies, the impression remains that mitochondrial patients represent a special risk [9–14]. Kinder Ross also points out that previous reports have discussed the relative merits of volatile agents and intravenous agents in the treatment of patients with mitochondrial myopathies [15, 16]. In particular, the potential risk of propofol given to such patients has been discussed [17, 18]. The problem remains to decide which myopathic patient has a mitochondrial defect and which is malignant hyperthermia susceptible [6]. This issue will be addressed at the end of this review.

Mitochondrial Overview

Mitochondria are the principal source of cellular metabolism in mammals. The cellular machinery necessary for the Krebs cycle, metabolism of amino acids, fatty acid oxidation and, most importantly, oxidative phosphorylation all reside within mitochondria, either in the mitochondrial matrix or mitochondrial membrane. Electrons usually enter the electron transport chain via complex I or complex II and are then sequentially transferred to Coenzyme Q, complex III, cytochrome c, complex IV and finally to oxygen to form water [19, 20]. The energy recovered during this transfer is used to pump protons into the inter-membrane space of the mitochondria, generating a gradient across the inner mitochondrial membrane. The proton gradient is then used as an energy source to drive phosphorylation of ADP to ATP by complex V. This entire process is termed oxidative phosphorylation and the complete system is termed the mitochondrial respiratory chain (MRC) (complexes I–V) (Figure 1).

NADH donates electrons to complex I while succinate donates electrons to complex II. Complex I is capable of using several carbon sources as fuel, among them pyruvate, malate and glutamate, each generating NADH *via* specific dehydrogenases. [19, 20]. These carbon sources are used as complex I-specific substrates for mitochondrial functional studies (oxidative phosphorylation) with *intact* mitochondria because they are transportable from the outer mitochondrial membrane into the mitochondrial matrix. NADH can not cross the outer mitochondrial membrane and therefore can only be used to drive complex I in enzymatic activity studies of individual mitochondrial complexes and partial complexes where the inner mitochondrial membrane is made porous or is removed [21]. Succinate can be used as a complex II-specific substrate for both intact mitochondria and submitochondrial particles. Complex III can be examined using dihydroquinone as a substrate and complex IV can be examined using TMPD/ascorbate as an electron donor [22, 23].

Fatty acids also serve as a major substrate for mitochondria and enter the matrix via an enzyme (actually a group of transporters) known as acylcarnitine transferase. Once inside the mitochondria, the carnitine moiety is removed and the fatty acid is metabolized using beta-oxidation. Fatty acid metabolism generates acetyl-coA which also donates electrons to complex I via the citric acid cycle. However, the beta-oxidation of fatty acids by specific dehydrogenases also donates electrons to electron-transferring flavoprotein (also known as ETF). ETF transfers electrons to ETF ubiquinone oxidoreductase which then transfers them to Coenzyme Q. From Coenzyme Q electrons are transferred to complexes III and IV as described previously. Defects in this pathway (including transport and beta-oxidation) often lead to elevations of acylcarnitines in the serum of patients. Since the pathways also rely on the citric acid cycle and normal electron transport chain complexes, defects in these components can also lead to elevated acylcarnitines. Diagnosing the specific steps that are defective requires biochemical study of the mitochondria, both in intact mitochondria (oxidative phosphorylation) and mitochondrial particles (specific electron transport chain

assays). It is these studies that usually require a muscle biopsy for isolation of the mitochondria.

Genetics

Mitochondria are the only organelles that have their own DNA (mitochondrial DNA or mtDNA), and their own cellular machinery for making RNA and protein. Since essentially all mitochondria are maternally inherited, mutations in mtDNA are passed on to all offspring of an affected mother, but only transmitted further through her daughters. Mitochondrial DNA encodes only 37 genes (13 proteins, 22 transfer RNAs, 2 ribosomal RNAs); the other 1100 or so gene products within the organelle are encoded by genes within the nuclear genome of the cell [19, 20] and thus follow classical Mendelian inheritance patterns. Therefore, mitochondria are under dual genetic control (Mendelian as well as mitochondrial). As a result of this dual genetic control, mitochondrial deficiencies may stem from literally hundreds of different genetic causes, with different physiologic presentations and modes of inheritance. Obviously, this can make diagnosis difficult.

Cells may contain thousands of mitochondria; if all the mitochondria are identical, the mitochondrial genotype is known as homoplasmic. However, pathogenic mutations of mtDNA are generally present in some but not all genomes of the mitochondria. During development the random segregation of organelles in mitosis can lead to varying amounts of mutant mitochondria received by daughter cells. Cells and tissues can harbor both normal and mutant mtDNA, a situation known as heteroplasmy. Thus, if only a fraction of the inherited mitochondria contain mutant mtDNA, defects may be unevenly distributed into tissues, and various tissues will have different thresholds for displaying a physiologic defect. As a result, different offspring from a single mother may demonstrate strong variation in phenotype despite being genetically quite similar. Therefore it would be inappropriate to conclude that a drug or anesthetic approach used safely with one patient having a mitochondrial defect would be equally safe in all other patients with mitochondrial disease even in siblings with genetic changes resulting in identical mutations.

Recognizing the Mitochondrial Patient

Ideally, to design the best anesthetic for myopathic patients one would know the underlying defect causing the myopathy. Often this is not possible and the anesthesiologist must contact genetic or biochemical specialists for additional input. With or without such consulting input, the anesthesiologist will need to evaluate the patient and history to make the best possible interpretation of the available data as to whether the patient has a mitochondrial defect. However, as noted above, the genetics of mitochondrial disease can be difficult to easily decipher.

As is well known to physicians, mitochondria are the main producers of energy (as ATP) in the cell. Disruption of this energy production leads to defects in those tissues that have the highest requirement for energy use. Patients presenting with myopathies associated with diseases in other tissues (*e.g.* CNS, intestinal, kidney) should raise the suspicion for mitochondrial causes. However, it is important to remember that an isolated myopathy does not rule out the potential for a mitochondrial defect.

Cells are able to use glucose to generate ATP by use of glycolysis without involvement of the mitochondria. Of course, restriction of energy production to glycolysis is anaerobic and often leads to a lactic acidosis. All other energy-producing substrates (further oxidation of the glucose product pyruvate, fatty acids, amino acids) require the mitochondrion for their effective use. Inhibition of any of these metabolic pathways will lead to chemical derangements, often with profound effects. It is these changes that frequently lead to the

diagnosis of probable mitochondrial defects prior to a muscle biopsy. Defects in the electron transport chain usually lead to the inability to remove some metabolic intermediate. Since NADH is the common electron transport chain substrate generated by the citric acid cycle, inability of the electron transport chain to remove NADH causes the citric acid cycle to stop or run poorly. Other pathways intersect with the citric acid cycle and are far beyond the scope of this review. However, in general, mitochondrial defects can be recognized by increases in lactate or pyruvate, increases in systemic acylcarnitines, or altered amounts of amino acids. Generally, a metabolic abnormality in a patient with a myopathy or encephalopathy, should raise the possibility of a mitochondrial defect. Great care must be taken to account for these defects when caring for these patients in the operative or perioperative period since the abnormal metabolite may be partially causative for the disease symptoms (*e.g.* acidosis). As discussed later, the anesthesiologist faced with an undiagnosed myopathy should determine whether such metabolic derangements are, or have been, present to help in his/her decision for the most likely diagnosis.

Perioperative Period

Surgical procedures usually involve a general anesthetic for mitochondrial patients, which are typically young children. While many different anesthetic techniques have been used successfully for patients with mitochondrial disease, there are reports of serious, unexpected complications occurring during and following anesthetic exposure. As a result, there exists a general opinion among anesthesiologists that these patients are at increased risk from the stress of surgery and anesthesia [2, 6]. The general considerations for anesthetizing patients with mitochondrial disease have been well reviewed [9, 10, 14, 24] and will not be presented in depth here. From an anesthesiologist's point of view, the primary complications of mitochondrial myopathies include respiratory failure, cardiac depression, conduction defects and dysphagia. Thus, muscle relaxants and cardiac depressants must be used with great caution. It is also extremely important to avoid circumstances that place a metabolic burden on these patients. These circumstances include prolonged fasting, hypoglycemia, postoperative nausea and vomiting, hypothermia (with resulting shivering), prolonged tourniquets, acidosis and hypovolemia.

The precise fluids these patients should receive are also somewhat variable. In general, it is wise to avoid hypoglycemia in mitochondrial patients as they may not be able to easily mobilize other substrates for metabolism. However, there are patients who are kept on ketogenic diets to avoid seizures; obviously these patients should *not* have added glucose in their IV fluids. It has also been noticed that many of these patients can not handle large amounts of glucose and may become hyperglycemic when glucose administration is higher than usual maintenance. A prudent approach would be to discuss glucose status with the primary physician. If that is not possible, one must avoid glucose in those patients on ketogenic diet while supplying glucose at maintenance rates with perioperative serum glucose monitoring in the remainder of the patients. Finally, some of these patients are unable to metabolize lactate; thus, it is best to avoid the addition of lactate to their fluids [25].

Several reports document that mitochondrial patients may face an increased risk in the operating room [10, 16, 26]. Respiratory depression can occur simply from the combination of anesthetics and muscle weakness seen in any myopathic state. More disturbing, however, are reports of late, profound respiratory depression and/or CNS white matter degeneration in patients seemingly only mildly affected preoperatively, and who have had relatively uneventful anesthetic courses during surgery [11–13]. Unfortunately, it is not clear that any particular anesthetic regimen is safer than another for these patients. What is disturbing is the presence in the literature of reports from small numbers of mitochondrial patients or limited outcome measurements concluding that the use of anesthetics is uniformly safe [7,

27–29]. It is worth reminding the reader that mitochondrial disease represents probably hundreds of different defects, both genetic and environmental in origin, and is thus difficult to characterize from any limited case series. The specter of possible delayed complications in patients caused by inhibition of metabolism by anesthetics, by remaining in a biochemically stressed state such as fasting/catabolism, or by prolonged exposure to pain is not easily recognized and remains troubling.

Specific Diseases

There seem to be two major groups of mitochondrial or related diseases that deserve particular consideration in the perioperative period. These are defects of the respiratory chain, and in fatty acid transfer and metabolism. When discussing the effects of anesthetics, we will concentrate on these two aspects of mitochondrial function.

Respiratory Chain Defects—As shown in Figure 1, the respiratory chain consists of five complexes each containing multiple protein subunits. The number of subunits ranges from 4 for complex II to at least 46 for complex I. It is clear that mutations in over 100 genes can directly affect the function of the respiratory chain and perhaps over 1000 genes that can indirectly affect the respiratory chain or other aspects of metabolism. These changes may be restricted to specific complexes each of which has different sensitivities to anesthetics.

Of the five respiratory chain components, complex I is uniquely sensitive to many anesthetic agents [30–32]. All tested volatile anesthetics (though notably not nitrous oxide [33]) and many parenteral agents are potent inhibitors of complex I with significant effects within the clinical range even on normal mitochondria. It is difficult to predict how this sensitivity varies in the presence of mutations affecting complex I. In children, several patients with complex I defects were noted to be hypersensitive to sevoflurane using a BIS reading of 60 as the endpoint [34]. Of course, it is not known whether these changes in sensitivity result in an increased risk to those patients.

Fatty Acid Metabolism Defects—Fatty acids are an important contributor to the substrates for both complex I and complex II. Fatty acids are converted by the addition of a coenzyme A (CoA) group to acyl-CoA followed by exchange of carnitine for the CoA group, resulting in acylcarnitine. Acylcarnitines are then transported across the mitochondrial membrane by acylcarnitine transferase. Acyl-coA is regenerated and enters the beta-oxidation pathway generating the molecules which serve to drive oxidative phosphorylation. Defects in this process or in ETC function often result in elevated acylcarnitines in the serum and urine of patients.

Defects in fatty acid metabolism do not directly affect respiratory complexes, though it seems logical that combinations of complex I inhibition and fatty acid defects might be additive. We are aware of no reports of defects in fatty acid metabolism affecting responses to volatile anesthetics. However, defects in acylcarnitine transferase have been reported to alter the responses to bupivacaine [35] and may affect responses to propofol [36, 37]. These possibilities are discussed in the following sections.

Anesthetics

Anesthetics have their primary effect in tissues that have high-energy requirements. In some cases (propofol, etomidate, barbiturates) it is clear that the anesthesia-inducing effects of the anesthetic (enhancement of the $GABA_A$ receptor) are likely separate from any effect on the mitochondria [38, 39]. The same can be said for ketamine though the active target is different than in the former drugs (NMDA receptor). In the case of volatile anesthetics, the separation of anesthetic targets and mitochondria is less clear, since the mechanism of action

of these drugs remains elusive [38–40]. However, it is clear that the crucial tissue affected is the central nervous system for all these drugs, a tissue also profoundly dependent of mitochondrial function.

Unfortunately, essentially every general anesthetic studied has been shown to depress mitochondrial function [30, 31, 41–45]. The most notable of these are the volatile anesthetics [30, 42, 43] and propofol [46, 47]. It is often said that these agents only depress mitochondria at doses higher than their clinical concentrations. However, Miro *et al.* showed that even at doses commonly used in the operating room, anesthetics cause a significant depression of mitochondria from normal patients [41] although they felt that depression of individual complexes was not involved. Studies in model organisms have shown that when complex I is abnormal, sensitivity to volatile anesthetics is markedly increased [48–50]. Multiple defects of complex I in *C. elegans* were shown to increase sensitivity to halothane [49]. In the mouse, a defect in the NDUFS4 subunit of complex I decreased MAC to about 1/3 that of normal for halothane and isoflurane [43].

Case reports have also indicated that some children exhibit an increased sensitivity to sevoflurane [34]. A retrospective study from Smeitink and colleagues found no complications in 122 patients presenting for mitochondrial workup [7]. However, others have voiced the opinion that children with mitochondrial myopathies have an increased risk during surgery [10, 16, 51]. Since metabolism is altered in patients with mitochondrial disease, the abilities of the cell to generate ATP and to effectively use oxygen are diminished; thus exposure to anesthetics probably represents an increased risk compared to other patients [10]. The use of regional anesthetics should be considered if appropriate for the case. However, it has also been noted that mitochondria are a probable target for the cardiac complications of bupivacaine [35, 52]. Weinberg showed that bupivacaine inhibited acylcarnitine transferase and extended this discussion to explain why different mitochondrial patients may respond differently [18, 35, 53]. Thus, patients with mitochondrial myopathies may be at increased risk with this drug as well. Each class of anesthetic will be discussed below.

Volatile Anesthetics and Mitochondrial Function—Volatile anesthetics (VAs) have been shown to depress oxidative phosphorylation in cell free studies of isolated mitochondria. The enzyme complex most sensitive to inhibition by VAs has consistently been complex I (also known as NADH dehydrogenase; NADH:ubiquinone reductase; EC 1.6.5.3) [30, 32, 42, 54]. Complex I is a multi-subunit complex within the mitochondrial electron transport chain that initiates the transport of electrons from NADH to oxygen, and which is linked to the generation of ATP via oxidative phosphorylation. Kayser et al. showed that, in *C. elegans*, isoflurane inhibited transfer of electrons from complex I to coenzyme Q [32], while complexes II, III and IV were strikingly resistant to inhibition by volatile anesthetics. Complex V is only minimally affected [55, 56].

Concentrations of VA that range from 1–2 times the EC_{50} of an organism inhibit complex I function, while complex II (succinate dehydrogenase) is unaffected. With increasing concentrations of VAs, other components of the electron transport chain are affected. As noted previously, studies in model organisms have shown that mutations in multiple mitochondria! proteins lead to increased sensitivities of animals [43, 48–50] and humans [34] to VAs. Since VAs exert much of their effects in high-energy tissues, it is possible that patients with mitochondrial disease may have an abnormal sensitivity to VAs.

Each of the volatile anesthetics depresses respiration, though to different degrees. Isoflurane and desflurane depress the ventilatory response to CO_2 response more than does sevoflurane [57]. In addition, sevoflurane and desflurane cause more direct muscle relaxation than does

isoflurane, though the differences are small [58, 59]. Thus, from the standpoint of ventilation, sevoflurane would seem to be mildly advantageous in patients with mitochondrial defects. Isoflurane and desflurane are noted for their ability to maintain cardiac output to a greater degree than sevoflurane. In short, each of the volatile anesthetics presently in use is capable of interacting negatively with a mitochondrial myopathy. Fortunately, patients may be supported during the perioperative period to avoid the side effects of these drugs. The currently used volatile anesthetics do not require metabolism for excretion, rather they are exhaled. This represents an advantage over intravenous anesthetics, which are dependent on energy requiring metabolism. In addition, at present it appears that the risk from exposure of these patients to sevoflurane is low [7, 34].

Parenteral Anesthetics and Mitochondrial Function—Each of the parenteral sedatives have their primary effects on ligand gated ion channels or G-protein coupled receptors. However, etomidate, ketamine and barbiturates are also complex I inhibitors [44, 45, 60]. Each of these drugs has been shown to inhibit complex I function at concentrations within the clinical range. Effects of these drugs on other aspects of components of the respiratory chain have also been reported but the judicious use of these medications has not been reported to cause problems in mitochondrial patients. Sensitivity of mitochondrial mutants to the parenteral anesthetics has only been examined in the mouse mutant, *Ndufs4,* containing a complex I defect [43]. Interestingly, *Ndufs4* mice have an increased sensitivity to propofol but a decreased sensitivity to ketamine. It is not known what underlies this difference nor whether such a difference in sensitivities is seen in humans.

So where does propofol fit in? Propofol has many of the same side effects as volatile anesthetics. One notable exception is that it is not known to cause much muscle relaxation. However it is quite capable of decreasing ventilatory drive as well as cardiac output and contractility. While it is viewed as a very short acting drug, the ultimate excretion of propofol is metabolism dependent. Both propofol and thiopental have been used as induction agents successfully and seem to have little negative effect when used in a limited fashion as a bolus.

Propofol infusion syndrome is well described as a serious reaction in patients receiving long-term infusions. The syndrome is characterized by a severe lactic acidosis, followed by rhabdomyolysis and lipidemia, which can lead to cardiovascular collapse and death. The appearance of the lactic acidosis resulted in the study of mitochondrial function in the presence of propofol. Propofol has also been shown to be associated with an increase in serum acylcarnitines during prolonged infusions. This increase is part of the propofol infusion syndrome and is seen with profound metabolic acidosis, cardiac failure and rhabdomyolysis [36]. Withington also showed that propofol infusion syndrome is associated with abnormal acylcarnitine metabolism [61]. These studies are most consistent with a model that propofol inhibits acylcarnitine transfer into mitochondria.

Propofol is somewhat more promiscuous than the other parenteral anesthetics in its mitochondrial effects as it inhibits both multiple electron transport chain complexes as well as fatty acid transport into the mitochondrion [46, 56]. Of concern are the observations that propofol is well known to inhibit mitochondrial function at the level of complex I and complex IV as well as uncoupling oxidative phosphorylation [46, 47, 62, 63]. In addition, propofol infusion syndrome is thought to result from mitochondrial dysfunction by inhibition of transport of long-chain acylcarnitine esters coupled with an indirect effect on complexes I and II [36, 61]. Thus, at present propofol has been shown to affect mitochondrial function by at least four different mechanisms. It therefore seems likely that at least some patients with mitochondrial defects may be susceptible to adverse reactions from propofol [51].

There exists concern that patients with mitochondrial myopathy may have an increased risk of developing propofol infusion syndrome during prolonged exposure. However, it is not really known if patients with mitochondrial disease are more prone to this syndrome, though such susceptibility has been suggested by Niezgoda and colleagues [51]. These same authors suggested that patients with unexplained responses to propofol should be tested for mitochondrial abnormalities. A recent report also indicates that patients with mitochondrial dysfunction may be at increased risk for propofol infusion syndrome [64].

Other commonly used medications in the operating room include narcotics and muscle relaxants. These drugs have generally not been shown to alter mitochondrial function (with the possible exception of morphine [65, 66]). However, their noted side effects (respiratory depression) must be considered carefully in patients who may already have respiratory compromise.

Local Anesthetics and Mitochondrial Function—Weinberg reported ventricular dysrhythmias after a small dose of bupivacaine in a patient later shown to have a carnitine deficiency [18, 35]. Weinberg went on to show that bupivacaine inhibited carnitine-acylcarnitine translocase [35]. Weinberg's report shows that patients with defects in fatty acid metabolism may have an increased sensitivity to toxicity from bupivacaine. It seems likely that they may also have an increased sensitivity to adverse effects from propofol, though such evidence is not in the literature. It is also worth considering that patients fasted for prolonged periods of time will increase their use of fatty acids as a mitochondrial substrate. As a result, these patients may be relatively intolerant to the use of propofol.

Conclusion

Clearly, one must consider direct inhibition of the respiratory chain separately from the indirect effects of anesthetics on physiologic functions also affected by mitochondrial function (*e.g.* respiratory drive, cardiac contractility, muscle strength). Anesthetics may depress certain systems by mitochondrial-independent mechanisms (*e.g.* $GABA_A$ enhancement) but still lead to additive inhibition of organ systems affected by mitochondrial defects. These general mitochondrial considerations have been previously discussed by others [2, 9, 24] but their importance warrants repetition here. These include 1) minimizing preoperative fasting to avoid hypovolemia, decreased blood glucose levels and increased use of fatty acids; 2) increasingly cautious use of muscle relaxants in those patients with a pre-existing myopathy or decreased respiratory drive; 3) avoiding the use of lactate as some patients have difficulty metabolizing lactate and may become acidotic; 4) avoiding tourniquets and pressure points to minimize regions of poor perfusion and oxygen delivery; 5) avoiding swings in body temperature as mitochondrial patients are unable to adapt well to either hypothermia or hyperthermia; 6) slow titration of volatile and parenteral anesthetics to minimize hemodynamic changes; 7) using measures to decrease PONV (hydration, opioid-sparing techniques, including the use of other analgesics such as nonsteroidal anti-inflammatory drugs and regional blocks, *etc.*).

Recent articles have highlighted the dilemma facing anesthesiologists at present when caring for patients with undiagnosed myopathies [6, 24]. If a patient with an unknown myopathy presents for surgical care, what is the best course of action [7, 8]? If the patient has an increased susceptibility to malignant hyperthermia, then one might still try to avoid volatile agents and use a nontriggering anesthetic (usually including propofol). On the other hand, if the patient has a known mitochondrial defect, then perhaps propofol is not the best choice.

In conclusion, all of the general anesthetic agents are known to directly inhibit mitochondrial function and may add to perioperative problems. However, each of the above

anesthetics has been used successfully when caring for patients with mitochondrial disease. It may be that as the different types of mitochondrial disease are better defined, preferences for an anesthetic in certain cases may become clear. What is clear is that these patients must be monitored more closely than other patients when using a general anesthetic, titrating medications slowly on induction and exercising great care to document that the effects of the anesthetics are largely gone before assuming that the patient can ventilate adequately.

Fortunately most exposures to anesthetics for mitochondrial patients are without apparent complications. There are several reports in the literature of such patients tolerating a wide variety of anesthetics including the volatile anesthetics, propofol and local anesthetics. However, in general the specific defect in the respiratory chain underlying the mitochondrial disease was not known. Mitochondrial function is dependent on hundreds of different proteins; the electron transport chain alone is predicted to require approximately 100 proteins. Thus, mitochondrial myopathies actually represent a wide variety of molecular defects and thus a wide range of different diseases with similar phenotypes. However, it is likely that some types of defects are more sensitive to inhibition by anesthetics than are others and therefore possibly more prone to untoward effects. There is no theoretically perfect way to anesthetize all children with mitochondrial disease. The astute physician will carefully review the history to guide the choice of anesthetic regime least likely to add complications to the already compromised patient.

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Abbreviations

ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
NAD^+	Nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
GABA	gamma amino-butyric acid

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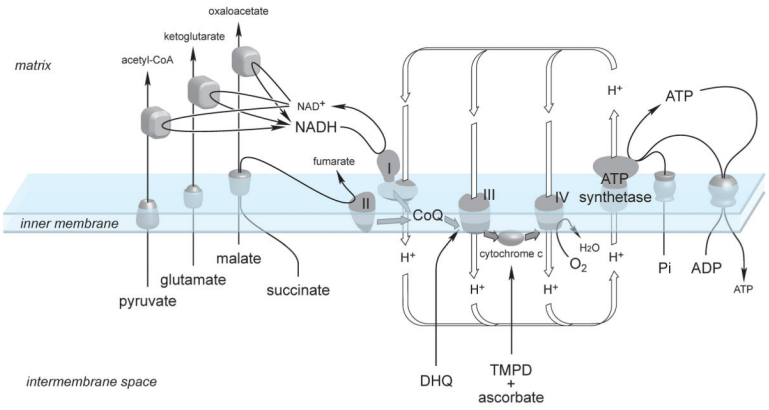

Figure 1. The Mitochondrial Respiratory Chain

Electron donor substrates (pyruvate, glutamate, malate, succinate) for the respiratory chain are transported across the mitochondrial membrane by their respective carriers. In the matrix, electrons from pyruvate, glutamate, and malate are transferred to NAD^+ by substrate-specific dehydrogenases (boxes) and enter the respiratory chain via *complex I*. Succinate donates electrons specifically to *complex II*. Electrons from *complex I* and *II* are transferred to *complex III* by the common shuttle Coenzyme Q. The electrons reach oxygen, the terminal acceptor, via cytochrome c and *complex IV*. Electron transport down the respiratory chain (flat grey arrows) is linked to proton transfer to the intermembrane space by *complexes I,-III, and –IV* (flat dotted arrows). ATP synthetase (complex V) allows protons to reenter the matrix and uses the energy released in this process to phosphorylate ADP to ATP. The Coenzyme Q analog DHQ can be used to reduce *complex III* directly while electrons from ascorbate can be shuttled to cytochrome c by the redox carrier TMPD (Tetramethylphenylenediamine).