# When Propofol is Problematic.

During the past decade the intravenous anesthetic propofol has become increasingly popular as a maintenance anesthetic. However, while propofol is viewed as a very short acting drug (due to redistribution), its ultimate excretion is metabolism dependent and thus dependent on cellular energy production. Of similar concern are the observations that propofol is well known to inhibit mitochondrial function at the level of complex I function as well as uncoupling oxidative phosphorylation (1-3). In addition, the propofol infusion syndrome is thought to result from mitochondrial dysfunction by inhibition of transport of long-chain acylcarnitine esters (4) with an indirect effect on complex II. Thus, at present propofol has been shown to affect mitochondrial function by at least four different mechanisms (**Figure 1**). It therefore seems likely that patients with mitochondrial defects may be at increased risk from this drug.

Several reports document that patients with mitochondrial defects may face an increased risk in the operating room with such perioperative complications as respiratory depression, cardiac depression and arrhythmias, metabolic disturbances and occasionally severe neurological deficits (5-11). 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 (5-8). Unfortunately, it is not clear that any particular anesthetic regimen is safer than another for these patients with mitochondrial defects.

To discuss the possible problems associated with propofol use, it is first necessary to quickly review the basics of mitochondrial function. Mitochondria are the principal source of cellular metabolism. The cellular machinery necessary for the Krebs cycle, metabolism of amino acids, fatty acid oxidation and, most importantly, oxidative phosphorylation, reside within mitochondria. The respiratory chain of the inner mitochondrial membrane synthesizes ATP by transporting electrons through multimeric protein complexes to molecular oxygen. At the same time, protons are pumped out of the mitochondrial matrix. The influx of protons back into

Figure 1. Representation of the electron transport chain showing the relationship of complexes I-V. Note that I and II both feed into III via the intermediate ubiquinone. Cytochrome c then receives electrons from III and passes them to complex IV. Electron flow is linked to protons pumped out of the matrix (dotted arrows). Proton gradient drives ATP formation by F0F1 ATPase (complex V). Propofol inhibits mitochondrial function at multiple sites.
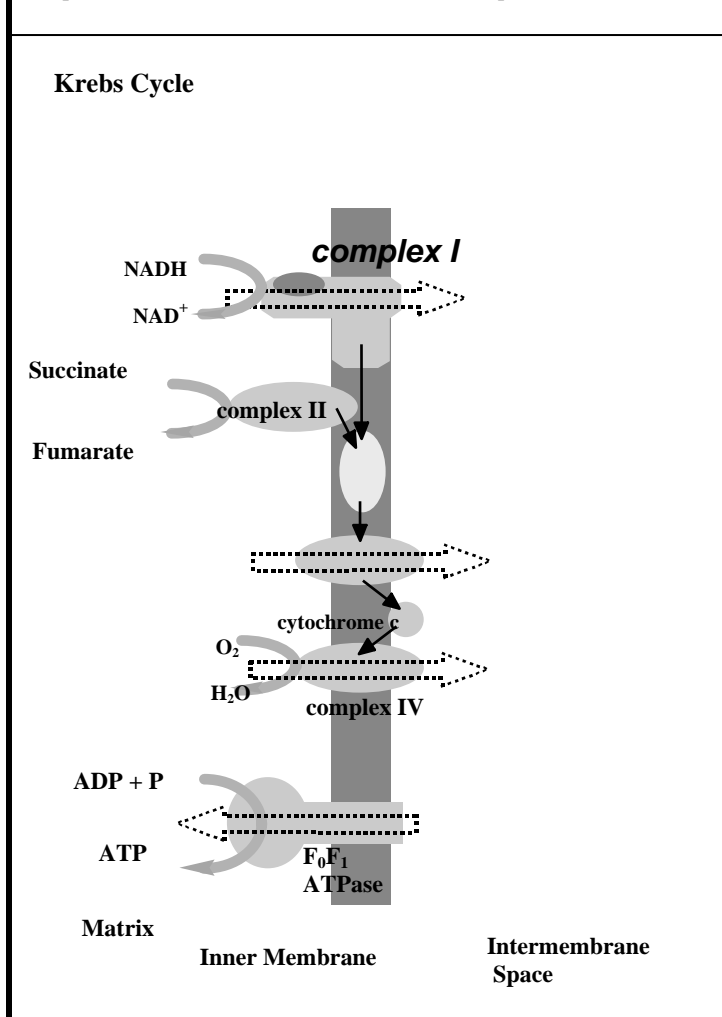
the mitochondrion drives the synthesis of ATP. Muscle and nerve cells are uniquely dependent on the energy delivered by mitochondria, and therefore have the lowest threshold for displaying symptoms of mitochondrial disease. Thus, mitochondrial dysfunction most commonly affects function of the nervous system and of the muscular system (12). Mutations in mitochondrial proteins cause striking clinical features in those two tissues types, including myopathies, cardiomyopathies, encephalopathies, seizures, and cerebellar ataxias (13,14). Once thought to be a rare clinical entity, mitochondrial disease is now recognized as an important cause of a wide range of neurological, neuromuscular, cardiac, and endocrine disorders. The incidence of disorders of the respiratory chain alone is estimated to be about 1 to 1.5 per 10,000 (15).

Figure 1 represents the mitochondrial electron transport chain (ETC). The oxidative phosphorylation pathway consists of five protein complexes (I-V). Complexes I and II independently transfer electrons to coenzyme Q which then are sequentially passed to complexes III, and IV (13,14). Complex V uses the energy gained in this transfer to synthesize ATP. Electrons enter the ETC by one of two complexes, *i.e.* complex I or II. 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 glutamate and pyruvate. For mitochondrial functional studies, glutamate or malate may be used as complex I-specific substrates as they generate NADH via the Krebs cycle. NADH can not pass the mitochondrial membrane, so studies of complex I using intact mitochondria must use glutamate or malate while studies of mitochondrial particles (where the inner mitochondrial membrane is made porous or is removed) use NADH to drive complex I. Complex II is restricted to the use of succinate as an energy source. Succinate is used as a complex II specific substrate for both intact mitochondria and submitochondrial particles.

Unfortunately, essentially every general anesthetic studied has been shown to depress mitochondrial function (16,17). The most notable of these are the volatile anesthetics and propofol. It is often said that these agents only depress mitochondria at doses higher than their clinical concentrations. However, a recent study has shown that even at dose commonly used in the operating room, anesthetics cause a significant depression of mitochondria from normal patients (18). Studies in model organisms have shown that when complex I is abnormal, sensitivity to volatile anesthetics is markedly increased (19). Case reports have also indicated that some children exhibit an increased sensitivity to sevoflurane (20). In contrast, a retrospective study from Smeitink and colleagues found no complications in 122 patients presenting for mitochondrial workup (21). However, there remains a strong clinical impression that children with mitochondrial myopathies have an increased risk during surgery (17,22). Since metabolism is altered in patients with mitochondrial disease, the abilities of the cell to generate ATP and to effectively use oxygen are diminished and exposure to anesthetics probably represents an increased risk compared to other patients (22).   The use of regional anesthetics should be considered if appropriate for the case. However, it has also been noted that mitochondria are the probable target for the cardiac complications of bupivicaine (23-25); thus, patients with mitochondrial myopathies may be at increased risk with this drug as well.

From an anesthesiologist's point of view, the primary complications of mitochondrial myopathies include respiratory failure, cardiac depression, conduction defects and dysphagia. Each of the volatile anesthetics depresses respiration, though to different degrees. Isoflurane and desflurane depress the ventilatory response to CO_2 more than does halothane or sevoflurane. In addition, isoflurane and desflurane cause more direct muscle relaxation complicated respiratory depression and dysphagia. Thus, from this standpoint, halothane and sevoflurane would seem to be advantageous for use in patients with mitochondrial defects. However, halothane is capable of sensitizing the heart to dysrrythmias and is best avoided if patients have cardiac conduction defects. Isoflurane and desflurane are noted for their ability to maintain cardiac output to a greater degree than the other two anesthetics. 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 breathed off. 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 (20,21)

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, its ultimate excretion is metabolism dependent. Both propofol and thiopental have been used as induction agents successfully and seem to have little negative effect in this setting.

Of more concern are the observations that propofol is well known to inhibit mitochondrial function at the level of complex I function as well as uncoupling oxidative phosphorylation (1-3). In addition, the propofol infusion syndrome is thought to result from mitochondrial dysfunction by inhibition of transport of long-chain acylcarnitine esters (4) with a resulting indirect effect on complex II. It therefore seems likely that patients with mitochondrial defects may be at seriously increased risk from this drug.

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 which has led to the above noted affects on complexes I and II and other mitochondrial components. 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 (26). There exists concern that patients with mitochondrial myopathy may have an increased risk of developing propofol infusion syndrome during prolonged exposure. These same authors suggested that patients with unexplained responses to propofol should be tested for mitochondrial abnormalities.

A recent editorial highlighted the dilemma facing anesthesiologists at present (27). If a patient with an unknown myopathy presents for surgical care, what is the best course of action? Two related and discussed articles appear in the same issue of *Pediatric Anesthesia*. The first presents the low risk of general anesthesia (primarily using sevoflurane) to mitochondrial patients (21) while the second article demonstrated a low risk of MH in patients with unknown myopathies exposed to volatile anesthetics (28). If the patient has an increased susceptibility to MH, 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. During this presentation, we will discuss this conundrum and ways to try to decide the safest approach.

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 (8,29,30) including the volatile anesthetics, propofol and bupivicaine (11). However, in each case reported, 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 likely more prone to untoward effects. There is no theoretically perfect way to anesthetize children with mitochondrial disease. However, each of the GAs has been used successfully to anesthetize specific patients with mitochondrial disease.

In conclusion, all of the general anesthetic agents are known to directly inhibit mitochondrial function and may add to preoperative 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. In addition, great care must be exercised to document that the effects of the anesthetics are largely gone before assuming that the patient can ventilate adequately and that cellular homeostasis is returned to normal after anesthetic exposure.

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