

Mitochondrial Disease and Anaesthesia

Varun Desai^{1†}, Jon Salicath²

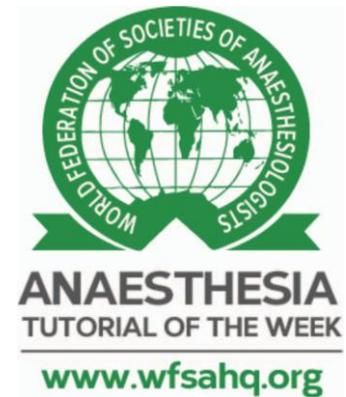
¹Provisional Anaesthetic Fellow, The Children's Hospital at Westmead, Australia

²Anaesthetic Consultant, The Children's Hospital at Westmead, Australia

Edited by: Dr. Michael Cooper, Anaesthetic Consultant, The Children's Hospital at Westmead, Australia

[†]Corresponding author e-mail: varun.desai@health.nsw.gov.au

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KEY POINTS

- Mitochondrial diseases are diverse and can affect a wide range of organs and present with a multitude of symptoms.
- Perioperative management involves minimising the metabolic stress of surgery and the risk of a 'metabolic encephalopathy', which is often contributed by fasting or an intercurrent illness.
- Intraoperative goals include maintenance of core temperature, blood glucose, organ perfusion and oxygenation.
- Inhalational agents are safe to use in patients with mitochondrial diseases, although some patients might have increased sensitivity.
- Propofol infusions should probably be avoided in patients with mitochondrial diseases; however, single bolus doses for induction of anaesthesia are generally well tolerated.

INTRODUCTION

Mitochondrial diseases comprise a diverse group of disorders that adversely affect the function of the mitochondria. The first mitochondrial disease was identified 30 years ago, and today there are nearly 300 known genetic mutations.¹ This article will review basic mitochondrial biology, mitochondrial diseases and their anaesthetic implications.

Mitochondrial Biology

Mitochondria are organelles of eukaryotic cells that may have been ancient independent life forms that symbiotically fused with bacteria nearly 2 billion years ago.¹ They possess their own DNA and are ubiquitously present in all cells except erythrocytes. They have multiple membranes and folds that carry out specialised functions. Mitochondrial proteins are coded by both nuclear DNA (Mendelian inheritance) and mitochondrial DNA (maternal inheritance); thus, mitochondrial diseases can occur as a result of nuclear and/or mitochondrial DNA mutations.²

Mitochondria are known as the 'ATP powerhouse of the cell'. Their primary function is the production of adenosine triphosphate (ATP) via oxidative phosphorylation, whereby electrons are passed between the different complexes of the electron transport chain (Figure 1).^{2,4} Mitochondria are also important in other metabolic pathways including the Krebs cycle, urea cycle and beta-fatty acid oxidation.^{3,4}

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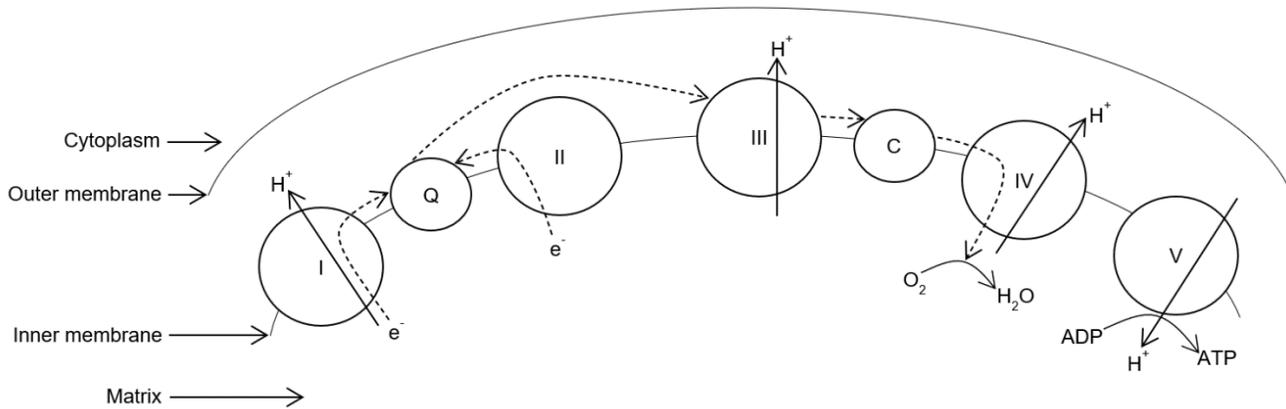


Figure 1. Electron transport chain. The circled figures labeled I-V represent complexes. Q, coenzyme Q; C, cytochrome C; H⁺, proton; e⁻, electron; ADP, adenosine diphosphate; ATP, adenosine triphosphate; O₂, oxygen; H₂O, water.

Mitochondrial Disease

Mitochondrial diseases have an estimated prevalence of 1 in 4000, and most cases manifest by the age of 20 years.⁵ Mitochondrial diseases resulting from mitochondrial DNA mutations demonstrate heteroplasmy and threshold level. Heteroplasmy is the phenomenon whereby each cell may harbour a mixture of mutant and normal mitochondrion, and threshold level is the phenomenon whereby a certain amount of mutant mitochondrion needs to be present before the cell begins to display dysfunction (Figure 2). This means that identical mutations amongst family members may have variable clinical phenotypes.^{2,6}

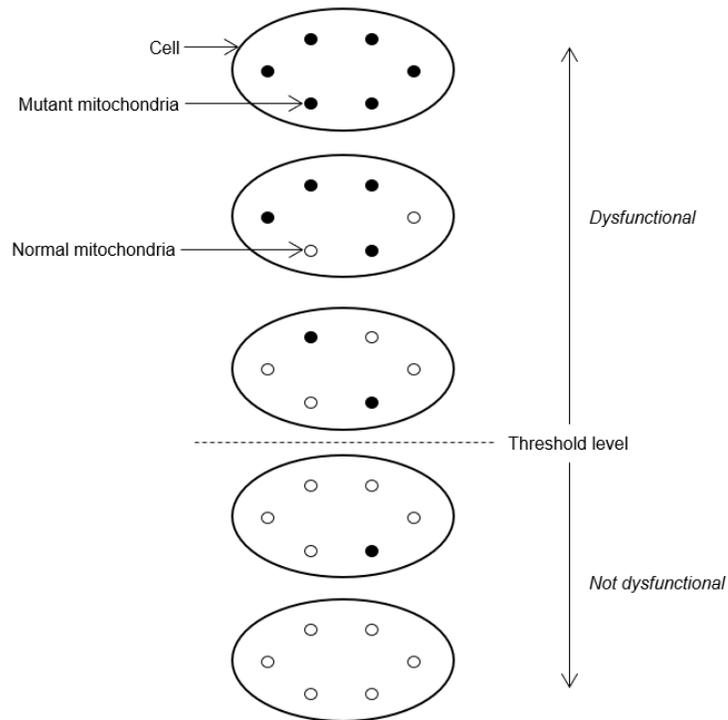


Figure 2. Threshold level. With increasing amounts of mutant mitochondria (dark circles), cells will cross a given threshold and become dysfunctional.

System	Features
Neurological/myopathic	Developmental delay Regression Weakness Fatigability Hypotonia Spasticity Ataxia Seizure disorders
Cardiovascular	Cardiomyopathy Conduction abnormalities
Respiratory	Central hypoventilation/apnoea Respiratory muscle weakness
Ophthalmic	Ophthalmoplegia Retinal depigmentation Optic atrophy
Renal	Renal insufficiency
Hepatic	Hepatic insufficiency
Metabolic	Intermittent/persistent lactic acidaemia
Endocrine	Diabetes mellitus Hypoparathyroidism
Haematological	Macrocytic anaemia Neutropenia Thrombocytopenia

Table. Clinical Features of Mitochondrial Disease. From Wallace et al² by permission of Wiley on behalf of *Paediatric Anaesthesia*. This image/content is not covered by the terms of the Creative Commons licence of this publication. For permission to reuse, please contact the rights holder.

Mitochondrial diseases are frequently referred to as disorders that can 'affect any system, with any symptom, and by any mode of inheritance'.¹ Organs and tissues that have a high turnover of ATP are proportionately affected. In general, a patient with a myopathy or encephalopathy with an elevated lactate level should raise the consideration of the possibility of a mitochondrial defect.⁶ In addition, multiple other organ systems may be affected (Table).² The classification of mitochondrial diseases is varied and based on either specific electron transport chain complex abnormalities, mitochondrial DNA and/or nuclear DNA mutations or on clinical phenotypes. Clinical classification includes syndromes such as MELAS (mitochondrial encephalopathy, lactic acidosis and strokelike episodes), MNGIE (mitochondrial neurogastrointestinal encephalopathy), MERRF (myoclonic epilepsy with ragged red fibres), Kearns-Sayre syndrome and Leigh syndrome. There is, however, a large overlap and no clear correlation between clinical findings and the site of the biochemical defect.⁷ The best diagnostic test is a muscle biopsy; however, this is carried out only if genetic testing is equivocal. Muscle biopsies are preferentially done on the vastus lateralis, and the characteristic findings of ragged-red fibres or cytochrome c-oxidase negative fibres are often sought on histochemical staining. Other supportive biochemical features include elevated blood, urine or cerebrospinal fluid lactate levels. Supportive neuroimaging features include strokelike lesions in nonvascular distributions; diffuse white matter disease; bilateral involvement of deep grey matter nuclei in the basal ganglia, mid-brain and/or brainstem; and lactate doublet on brain magnetic resonance spectroscopy.⁸

There is no known cure for mitochondrial diseases, and treatment is largely supportive. This includes focusing on optimisation of energy production, reduction of energy losses, avoidance of toxins, alleviating symptoms and monitoring for complications. Exercise has been shown to improve symptoms and strength and to increase mitochondrial content and oxygen uptake. Nutritional supplementation is commonly prescribed to replace deficiencies that may occur when mitochondrial function fails. It consists of multiple vitamins and cofactors including coenzyme Q10, alpha-lipoic acid, L-carnitine, creatine and certain B-vitamins. Evidence supporting the use of most of these supplements is limited.⁸

Anaesthetic Implications

Preoperative

Patients with mitochondrial diseases often have procedures in the operating room for diagnostic and therapeutic purposes such as muscle biopsies, magnetic resonance imaging/computed tomography scans, endoscopy, gastrostomy creation and strabismus surgery. During the preoperative assessment, the anaesthetist should ascertain the degree of neurological and muscular compromise with evidence of cardiorespiratory involvement. Features to seek on history and examination are the

severity of fatigability, dysphagia, hypoventilation, apnoea, cardiomyopathy, and/or heart block. Preoperative investigations largely depend on the severity of the disease, organ systems affected and surgery required. Useful baseline blood tests include a full blood count, electrolytes, creatinine, urea, liver function tests, blood glucose, lactate, pyruvate and CK. Other useful investigations may include spirometry, chest x-ray, blood gas, electrocardiogram and echocardiogram. It is paramount that these patients are not fasted for a prolonged period of time.^{2,6,8} At our institution, we use maltodextrin either mixed with water or pulp-free apple juice up to 2 hours prior to induction to prevent hypoglycemia. Maltodextrin is an easily digestible polysaccharide that can be considered a clear fluid. Lastly, multidisciplinary consultations may be required as patients are often treated by a variety of medical specialists.⁷

Intraoperative

The overarching goal in patients with mitochondrial diseases is to minimise the metabolic stress of surgery and the risk of a 'metabolic encephalopathy', which is often triggered by an intercurrent illness and/or fasting. It is important to avoid intraoperative hypotension, hypoxia, hypoglycaemia and hypothermia.^{6,9} To maintain glucose homeostasis, glucose-containing solutions should be administered with regular blood glucose measurements. The exception to this rule is in patients with disorders of pyruvate metabolism or ketogenic diets for seizure control; such patients should have glucose administered with caution and be monitored to ensure they do not develop hyperglycaemia and/or lactic acidosis.^{6,8} Lactate-containing solutions such as compound sodium lactate/Ringer's solution are best avoided, and intraoperative measurement of lactate may be a useful marker of metabolic stress.^{10,11}

Postoperative

Good postoperative analgesia is important for these patients as the pain response to surgery may worsen lactic acidosis. As a result, a multimodal analgesic approach should be used. Regional techniques should be used if possible and practical to do so.²

Drug Safety Profile

Concerns have been raised regarding the safety of different drugs used in anaesthesia. Almost all drugs demonstrate biochemical evidence of direct mitochondrial inhibition, but the clinical implications of these are less clear. The following section will briefly review the safety profiles of each major class of anaesthetic drugs.

Volatile Anaesthesia

Volatile anaesthetic agents have been shown to inhibit complex I of the electron transport chain (Figure 1) in in vitro studies. Studies correlating this biochemical effect to a clinical one have been sparse. A study looking at 16 children with biopsy-proven mitochondrial disease found that 1 patient with a complex I mutation and another with Leigh's disease may have an increased sensitivity to volatile anaesthesia.³ Although there have not been further studies to elucidate this question, a retrospective review has demonstrated the use of 'normal' clinical ranges of inspiratory sevoflurane concentrations without harm.⁴

Concerns regarding the association of mitochondrial diseases and malignant hyperthermia probably started in 1985. A single case report from Japan described a 2-year-old child with mitochondrial disease who developed muscle rigidity, hyperkalaemia and hyperthermia after a general anaesthetic that included halothane and suxamethonium.¹² Despite the widespread use of volatile agents, there have been no further case reports of malignant hyperthermia in patients with mitochondrial diseases. Furthermore, the Malignant Hyperthermia Association of the United States (MHAUS) recommends that volatile agents should not be avoided out of concern for possible malignant hyperthermia susceptibility.¹³

Intravenous Anaesthesia

Propofol has been shown to inhibit multiple complexes of the electron transport chain and transport of free fatty acids (FFA) across the mitochondrial membranes.¹⁴ Propofol was probably used more commonly as part of a nontriggering anaesthetic in the early 1990s, when it was thought that these patients were susceptible to malignant hyperthermia. However concerns started to be raised approximately 20 years ago, with case reports suggesting that patients with propofol infusion syndrome (PRIS)¹⁵ had biochemical abnormalities similar to that of mitochondrial diseases.¹⁶ Further case reports have described the development of PRIS in a patient with an acquired carnitine deficiency¹⁷ and others with mitochondrial disease^{18,19} who were given propofol infusions. The pathophysiology of PRIS remains unclear; however, evidence suggests mitochondrial defects in ATP production as the most likely cause.²⁰ Some authors have suggested that patients who develop PRIS may have subclinical forms of mitochondrial diseases,¹¹ and others have recommended that patients who develop PRIS be screened for these diseases.¹⁸ Evidence regarding propofol is conflicting: a recent review suggests that although propofol boluses are probably safe in mitochondrial diseases, infusions may not be.¹⁴ Our opinion, from assessment of published literature, is that propofol is not the anaesthetic agent of choice; careful titration of propofol boluses in patients without severe forms of mitochondrial diseases and without critical illness is probably safe. However, propofol infusions should probably be avoided.

The use of ketamine, dexmedetomidine and benzodiazepines in patients with mitochondrial diseases has not been associated with harm in the literature.¹⁴

Neuromuscular Blockers

Concerns surrounding neuromuscular blockers relate mainly to their pharmacodynamics profile. Depolarising neuromuscular blockers such as suxamethonium should be avoided given the risk of an exaggerated hyperkalaemic response.¹⁴ There are conflicting reports whether patients with mitochondrial diseases have an increased sensitivity to nondepolarising neuromuscular blocking drugs; although some studies report an increased sensitivity compared with the general population, others have shown no difference.² It has been recommended that 'any child with hypotonia should be considered at risk of variable response to muscle relaxation and doses adjusted accordingly'.²¹ Almost all recommendations include the use of a nerve stimulator.^{2,5,10} Reversal of neuromuscular blockade with neostigmine⁵ or sugammadex²²⁻²⁴ has not been associated with harm.

Local Anaesthetics

In vitro animal studies have demonstrated that bupivacaine inhibits the transport of FFA similar to propofol²⁵; however, evidence of harm in humans is scant. There is a single case report of an intraoperative bradyarrhythmia following the subcutaneous infiltration of ~0.3 mg/kg of bupivacaine in a patient with carnitine deficiency.²⁶ Subsequent to this, there have been no further adverse events reported in humans to the authors' knowledge. Furthermore, multiple institutions report using bupivacaine for muscle biopsies in patients with mitochondrial diseases without harm.^{4,27} A recent review article suggests that there are advantages to the use of local anaesthesia, as it provides analgesia without the respiratory depressant effects of opioids; however, it does not recommend any one agent over another.¹⁴

Opioids

Opioids have not been implicated in having significant biochemical effects on mitochondria.¹⁴ There are no case reports of harm associated with its use; however, caution is generally advised with regard to their respiratory depressive effects.² Remifentanyl is particularly advantageous in this regard, given its favourable pharmacokinetic profile.¹⁴

SUMMARY

Mitochondrial disease is a relatively common and complex multisystem disease. It may present with a variety of symptoms, and establishing a diagnosis remains challenging and potentially invasive. The anaesthetist may be involved in the care of such patients with procedures that are diagnostic and/or therapeutic. It is important to preoperatively identify the end-organ effects of the disease, minimise the stress of surgery and be aware of the potential issues with each class of anaesthetic drug.

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REFERENCES

1. Falk MJ, Medscape. Mitochondrial diseases: current state of understanding. <https://www.medscape.com/viewarticle/896188>. Accessed December 2, 2019.
2. Wallace JJ, Perndt H, Skinner M. Anaesthesia and mitochondrial disease. *Paediatr Anaesth*. 1998;8:249-254.
3. Morgan PG, Hoppel CL, Sedensky MM. Mitochondrial defects and anesthetic sensitivity. *Anesthesiology*. 2002;96:1268-1270.
4. Driessen J, Willems, S, Dercksen, S, et al. Anesthesia-related morbidity and mortality after surgery for muscle biopsy in children with mitochondrial defects. *Paediatr Anaesth*. 2007;17:16-21.
5. Wisley NA, Cook PR. General anaesthesia in a man with mitochondrial myopathy undergoing eye surgery. *Eur J Anaesthesiol*. 2001;18:333-335.
6. Niezgoda J, Morgan PG. Anesthetic considerations in patients with mitochondrial defects. *Paediatr Anaesth*. 2013;23:785-793.
7. Shipton EA, Prosser DO. Mitochondrial myopathies and anaesthesia. *Eur J Anaesthesiol*. 2004;21:173-178.
8. Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med*. 2015;17:689-701.

9. Farag E, Arglaious M, Narouze S, et al. The anesthetic management of ventricular septal defect (VSD) repair in a child with mitochondrial cytopathy. *Can J Anaesth*. 2002;49:958-962.
10. Hoppe K, Lehmann-Horn F, Jurkat-Rott K, et al. Mitochondrial disorders. *Anasth Intensivmed*. 2017;58:S125-S133.
11. Farag E, DeBoer G, Cohen BH, et al. Metabolic acidosis due to propofol infusion. *Anesthesiology*. 2005;102:697-698.
12. Ohtani Y, Miike T, Ishitu T, et al. A case of malignant hyperthermia with mitochondrial dysfunction. *Brain Dev*. 1985;7:249.
13. Malignant Hyperthermia Association of the United States. Does mitochondrial myopathy (MM) increase an individual's susceptibility to malignant hyperthermia (MH)? <https://www.mhaus.org/healthcare-professionals/mhaus-recommendations/does-mitochondrial-myopathy-mm-increase-an-individuals-susceptibility-to-malignant-hyperthermia-mh/>. Accessed December 1, 2019.
14. Hsieh VC, Krane EJ, Morgan PG. Mitochondrial disease and anesthesia. *J Inborn Errors Metab Screen*. 2017;5:1-5.
15. Monojit, P. Propofol Infusion Syndrome. Anaesthesia Tutorial of the Week. 2020:435. <https://resources.wfsahq.org/atotw/propofol-infusion-syndrome-atotw-435/> (accessed on 3rd Nov 2020)
16. Wolf A, Weir P, Segar P, et al. Impaired fatty acid oxidation in propofol infusion syndrome. *Lancet*. 2001;357:606-607.
17. Uezono S, Hotta Y, Takakuwa Y, et al. Acquired carnitine deficiency: a clinical model for propofol infusion syndrome? *Anesthesiology*. 2005;103:909.
18. Savard M, Dupre N, Turgeon AF, Desbiens R, Langevin S, Brunet D. Propofol-related infusion syndrome heralding a mitochondrial disease: case report. *Neurology*. 2013;81:770-771.
19. Vanlander AV, Jorens PG, Smet J, et al. Inborn oxidative phosphorylation defect as risk factor for propofol infusion syndrome. *Acta Anaesthesiol Scand*. 2012;56:520-525.
20. Hemphill S, McMenamin L, Bellamy MC, et al. Propofol infusion syndrome: a structured literature review and analysis of published case reports. *Br J Anaesth*. 2019;122:448-459.
21. Ross AK. Muscular dystrophy versus mitochondrial myopathy: the dilemma of the undiagnosed hypotonic child. *Paediatr Anaesth*. 2007;17:1-6.
22. Iwata K, Tanabe K, Sugiyama Y, et al. Anesthetic management for a patient with very-long-chain acyl-coenzyme A dehydrogenase deficiency. *J Anesth*. 2012;26:957-958.
23. Syed F, Turner H, AlGhamdi F, et al. Anesthetic management of a patient with carnitine-acylcarnitine translocase deficiency. *J Med Cases*. 2018;9:127-130.
24. Kynes JM, Blakely M, Furman K, et al. Multidisciplinary perioperative care for children with neuromuscular disorders. *Children*. 2018;5:126.
25. Weinberg GL, Palmer JW, VadeBoncouer TR, et al. Bupivacaine inhibits acylcarnitine exchange in cardiac mitochondria. *Anesthesiology*. 2000;92:523-528.
26. Weinberg GL, Laurito CE, Geldner P, et al. Malignant ventricular dysrhythmias in a patient with isovaleric acidemia receiving general and local anesthesia for suction lipectomy. *J Clin Anesth*. 1997;9:668-670.
27. Schnabel RM, Marcus MA, Theunissen HM, et al. Anesthetic management for a child with mitochondrial complex II deficiency. *Paediatr Anaesth*. 2008;18:802-803.



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