Advanced Drug Delivery Reviews 60 (2008) 1553–1560

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Clinical implications of mitochondrial disease ☆

Stanley Muravchick *

Department of Anesthesiology and Critical Care, Hospital of the University of Pennsylvania, Dulles Suite 680, 3400 Spruce Street, Philadelphia PA 19104-4283, USA

ARTICLE INFO

Article history:
Received 19 March 2008
Accepted 28 March 2008
Available online 4 July 2008

Keywords:
Mitochondrial myopathy
Mitochondrial cytopathy
Inherited encephalomyopathy
Oxidative stress
Aging
Ischemic preconditioning
Anesthetic toxicity
Bioenergetics
Apoptosis

ABSTRACT

The terms mitochondrial myopathy, mitochondrial cytopathy and inherited mitochondrial encephalomyopathy encompass a large grouping of syndromes produced either by genetically transmitted or acquired disruption of mitochondrial energy production or biosensor function. Many of these disorders are clinically apparent during infancy, but for some the metabolic signs of oxidative stress may not appear until the young or middle adult years. Initially thought to be a rare disorder, it now appears that mitochondrial dysfunction is relatively common but often unrecognized because symptoms are extremely variable and usually insidious in onset. It has also become apparent that mitochondrial dysfunction is a component of many common cardiovascular and neurological disease states and of physiologic aging. Recent advances in our understanding of the mechanisms of mitochondrial dysfunction may explain and link a wide variety of clinical phenomena. This review summarizes the current knowledge regarding the clinical implications of inherited and acquired mitochondrial disease, the effects of anesthetics on mitochondrial function, and the extent to which mitochondrial bioenergetic state determines anesthetic requirement and potential anesthetic toxicity.

Contents

1. Introduction

The scope of human disease attributable to inherited, acutely acquired, or insidious impairment of mitochondrial function appears to be far more extensive than previously believed. The terms "mitochondrial myopathy" or "inherited mitochondrial encephalomyopathy" originally referred to pediatric neurological syndromes produced by maternally-inherited mitochondrial genetic defects. However, it is now clear that respiratory chain deficiencies may generate almost any symptom, in any organ system, at any stage of life. In fact, mitochondrial dysfunction is emerging as a pivotal factor in the etiology of sepsis, neurodegenerative disorders, diabetes, atherosclerotic disease, and even normal human aging.[1,2] This overview will discuss the clinical implications of uncommon syndromes due to errors in mitochondrial DNA as well as those of more familiar disease states that are now thought to reflect, at least in part, disrupted mitochondrial function.

2. Background

Hundreds of mitochondrial DNA (mtDNA) mutations have been identified [3] and the clinical syndromes associated with mtDNA

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Mitochondrial Medicine and Mitochondrion-Based Therapeutics".

* Tel.: +1 215 662 3737; fax: +1 215 349 5341.
E-mail address: muravchst@uphs.upenn.edu.

0169-409X/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.addr.2008.03.019

abnormalities are commonly described as mitochondrial cytopathies [4]. Both normal ("wild type") and mutant mtDNA coexist within mitochondria. "Heteroplasmy" refers to the random differences in the ratio of mutant to normal mtDNA present in the target tissues during embryogenesis. It produces marked variability in the clinical manifestations of these conditions. The most severe inherited mitochondrial disorders, many of them lethal, become clinically apparent during infancy, but mitochondrial syndromes in which symptoms do not appear until early adulthood have also been described. Mitochondrial disorders with adult onset are characterized by great variability in severity and symptom patterns, reflecting both heteroplasmy and the markedly different metabolic demands of different tissues during adulthood. The original descriptions of mitochondrial diseases of childhood also assumed maternal inheritance patterns for transmission of mtDNA, but a recent report of a patient with mutated mtDNA of paternal origin suggests that some may survive in the zygote and contribute to the overall mtDNA pool of the embryo.[5]

As the interaction between nuclear and mitochondrial genomes has become better understood [6] the role of defects in nuclear DNA (nDNA) in disorders with impaired mitochondrial bioenergetics is becoming clearer. Many subunits of the electron transport chain are encoded not within mtDNA but arise from nDNA. In addition, the nuclear genome provides mtDNA stability, and a primary nuclear gene defect can cause secondary mtDNA information loss. Therefore, there are some clinical syndromes in which genetically determined defects in oxidative phosphorylation follow classic Mendelian patterns of dominant–recessive transmission rather than the maternal pattern usually associated with this group of disorders [7].

Table 1
Symptoms and signs of mitochondrial disorder

Disease	Mutation	Inheritance	Symptoms and signs
KSS	Large-scale mtDNA deletion	Sporadic	Ataxia, peripheral neuropathy, muscle weakness, ophthalmoplegia, ptosis, pigmentary retinopathy, sideroblastic anemia, diabetes mellitus, short stature, hypoparathyroidism, cardiomyopathy, conduction defects, sensorineural hearing loss, Fanconi syndrome, lactic acidosis, ragged-red fibers on muscle biopsy
PEO	Large-scale mtDNA deletion	Sporadic	Muscle weakness, ophthalmoplegia, ptosis, lactic acidosis, ragged-red fibers on muscle biopsy
PS	Large-scale mtDNA deletion	Sporadic	Ophthalmoplegia, sideroblastic anemia, pancreatic dysfunction, Fanconi syndrome, lactic acidosis, ragged-red fibers on muscle biopsy
MERRF	mtDNA point mutation, tRNA abnormality	Maternal	Seizures, ataxia, myoclonus, psychomotor regression, peripheral neuropathy, muscle weakness, short stature, sensorineural hearing loss, lactic acidosis, ragged-red fibers on muscle biopsy
MELAS	mtDNA point mutation, tRNA abnormality	Maternal	Seizures, ataxia, myoclonus, psychomotor regression, hemiparesis, cortical blindness, migraine, dystonia, peripheral neuropathy, muscle weakness, diabetes mellitus, short stature, cardiomyopathy, conduction defects, intestinal pseudo-obstruction, sensorineural hearing loss, Fanconi syndrome, lactic acidosis, ragged-red fibers on muscle biopsy
NARP	mtDNA point mutations, mRNA abnormality	Maternal	ataxia, peripheral neuropathy, muscle weakness, pigmentary retinopathy, optic atrophy, sensorineural hearing loss
MILS	mtDNA point mutation, mRNA abnormality	Maternal	Seizures, ataxia, psychomotor regression, dystonia, muscle weakness, pigmentary retinopathy, optic atrophy, cardiomyopathy, lactic acidosis
LHON	Multiple mtDNA point mutations, mRNA abnormality	Maternal	Dystonia, optic atrophy, cardiac conduction defects

KSS (Kearns-Sayre syndrome); PEO (progressive external ophthalmoplegia); PS (Pearson's syndrome); MERRF (myoclonic epilepsy with ragged-red fibers); MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes); NARP (neuropathy, ataxia, and retinitis pigmentosa); MILS (maternally inherited Leigh's syndrome); LHON (Leber's hereditary optic neuropathy).

Table 2
Possible concurrent therapy for patients with mitochondrial disorders

Coenzyme Q
L-carnitine
Riboflavin (vitamin B_2)
Acetyl-L-carnitine
Thiamine (vitamin B_1)
Nicotinamide (vitamin B_3)
Vitamin E
Vitamin C
Lipoic acid
Selenium
Beta-carotene
Biotin
Folic acid
Calcium, magnesium, phosphorous
Vitamin K
Succinate
Creatine
Citrates
Prednisone

3. Inherited disorders with childhood onset

Many inherited mitochondrial diseases alter metabolic homeostasis shortly after birth but they produce non-specific clinical signs such as lethargy, irritability, hyperactivity, or poor feeding that may not initially suggest mitochondrial dysfunction. Symptom severity is also extremely variable, and the metabolic disruption produced by a mitochondrial disorder may initially be subtle or acute and life-threatening, producing loss of body temperature regulation, cyanosis, seizures, emesis, diarrhea, or jaundice. For pediatric patients, initial investigation involves a differential diagnosis that includes the organic acidemias such as Maple syrup urine disease, endocrinopathies such as congenital adrenal hyperplasia or diabetes, aminoacidopathies such as homocysteinuria, tyrosinemia, and nonketotic hyperglycemia, carbohydrate disorders such as galactosemia, or fructose intolerance, or urea cycle defects such as ornithine transcarbamylase deficiency.

For individuals with mitochondrial cytopathies, lactic acidosis and inability to utilize glucose is almost universal. Therefore, an initial diagnostic step is blood and urine testing for evidence of increased lactate/pyruvate and ketone body ratios as well as measurement of serum and CSF lactate concentrations, although normal lactate and glucose levels at any one time do not necessarily rule out mitochondrial disease. With equivocal blood and urine test results or a high index of suspicion for mitochondrial cytopathy, skeletal muscle biopsy may confirm the presence of pathognomonic "ragged red fibers" produced by accumulations of defective mitochondria, excess glycogen granules, and cells that are deficient in cytochrome c oxidase [4]. The biopsy material can also be used for genetic analysis and subsequent genetic counseling.

A single organ or several systems may be affected by an inherited mitochondrial disorder. Primary "target" organs are the central nervous system and the liver. Impaired renal bioenergetics produce tubular acidosis, and skeletal muscle abnormalities present largely as dystonia or weakness. Dysphagia, pseudo-obstruction, and constipation suggest gastrointestinal involvement. Vision and hearing may be compromised by ophthalmoplegia, ptosis, cataracts, optic atrophy, pigmentary retinopathy, and sensorineural deafness. Endocrine organ involvement

manifests as diabetes mellitus, hypoparathyroidism, hypothyroidism, and gonadal failure. The individual's physical deterioration and the severity of stigmata related to mitochondrial cytopathy may be exacerbated by acute or sustained stress. Some of the most common signs and symptoms of inherited mitochondrial disease are listed in Table 1. Many neurologists recommend a diet rich in anti-oxidants as well as intensive nutritional supplementation with vitamins and various cofactors such as Coenzyme Q (Table 2), although there is little data to support this recommendation.

Seizures and ataxia are associated with MERRF (myoclonic epilepsy with ragged-red fibers) syndrome [8] and encephalopathy is a cardinal feature of Leigh syndrome [9]. Dementia and stroke-like symptoms are a major feature of MELAS [10] (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes). However, mitochondrial defects can generate a confusing combination or blending of syndrome characteristics [11]. When the peripheral nervous system is involved there may be axonal sensory neuropathies. Cardiac involvement with pediatric mitochondrial disease may produce hypertrophic cardiomyopathy, seen with MELAS, or dilated cardiomyopathy, heart block, and pre-excitation syndrome, all of which are typically associated with LHON [12] (Leber hereditary optic neuropathy).

Like many mitochondrial syndromes of infancy, NARP (Neuropathy, ataxia, and retinitis pigmentosa) is caused by a point mutation in the mitochondrial genome that, in this disorder, produces defective adenosine triphosphatase [10]. Reduced enzymatic activity and lower rates of ATP production are, in fact, characteristic of mitochondrial isolates of lymphoblastoid cell lines obtained from NARP patients. Increased brain levels of phosphocreatine and inorganic phosphate compared to age- and sex-matched control subjects suggest generalized impairment of the efficiency of oxidative metabolic pathways [13]. The specific genetic defects that produce NARP and several other mitochondrial disorders have been identified (Fig. 1).

MtDNA depletion syndrome (MDS) is a severe mitochondrial disease characterized by liver failure and neurological abnormalities produced by tissue-specific loss of mtDNA [7]. MDS is thought to be caused by a defective nuclear gene that disrupts mtDNA replication or stability [14]. Similarly, children with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) may have multiple mtDNA deletions and/or mtDNA depletion also produced by nDNA mutations [7] Non-specific gastrointestinal and hepatic symptoms are the cardinal manifestations of MDS and MNGIE although they are also common to many mitochondrial disorders (Table 1).

4. Inherited disorders with adult onset

Inherited neurological and metabolic syndromes produced by mtDNA abnormalities can also appear during the early-to-middle adult years in the form of insidious neurological dysfunction. Initial symptoms, typically progressive postural muscle weakness, failing color or night vision, and worsening ataxia, are predictably referable to brain and retina, tissues with very high rates of oxidative metabolism. Mitochondrial cytopathy should be included in the differential diagnosis whenever clinical signs and symptoms include persistent muscle pain associated with weakness or fatigue [15], or if the patient presents with progressive multisystem involvement that does not clearly fit an established pattern of disease [16]. Hepatic insufficiency is common but often subclinical and renal involvement may include proximal tubular dysfunction, usually presenting as de Toni Debre Fanconi Syndrome, or, less often, renal tubular acidosis, chronic tubulointerstitial nephritis, or nephrotic syndrome [17]. As in children, confirmatory diagnostic studies include skin or muscle biopsies for microscopic evaluation and mtDNA analysis [18].

Progressive decreases in cardiac, muscle, and nervous system functional reserve due to adult-onset mitochondrial cytopathy probably begin long before the appearance of overt signs or symptoms but can usually be discovered by careful and detailed analysis of the patient's ability to accomplish the normal activities of daily life. Nevertheless, the diagnosis of a mitochondrial-based respiratory chain deficiency in

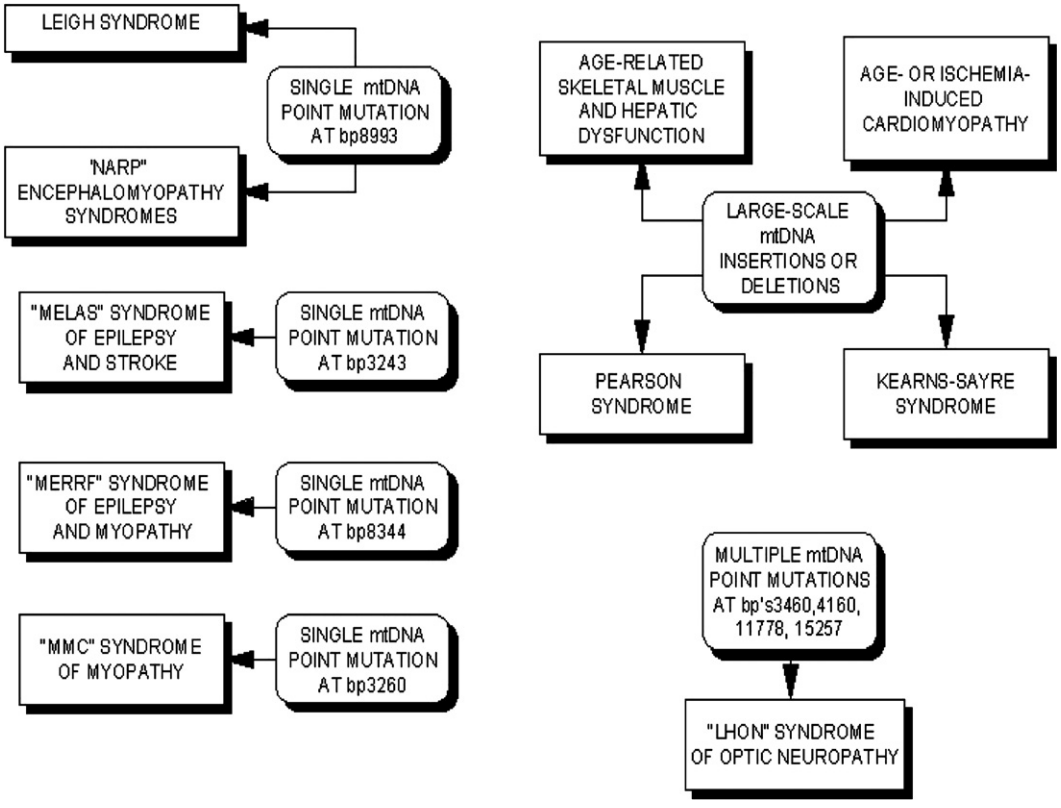

Fig. 1. Inherited mitochondrial syndromes and disorders can reflect single-point, multiple point, or large-scale errors in mitochondrial DNA (mtDNA).

adults may be overlooked unless there is obvious skeletal muscle weakness or encephalopathy. Unique concerns for patients with mitochondrial cytopathy who must undergo surgical procedures include decreased anesthetic requirement because of impaired neuronal bioenergetics, even when overt encephalopathy has not yet developed. Also of concern are intrinsic skeletal muscle hypotonia and postural imbalance, endocrinopathy, and cardiomyopathy with increased risk of sudden death from cardiac conduction abnormalities [19]. Skeletal muscle weakness may compromise postoperative ventilation following upper abdominal or thoracic surgery [20]. Finally, subclinical erosion of hepatorenal reserve may further predispose these patients to prolonged drug effects and delayed recovery from anesthesia, muscle relaxants, and opioids.

Some of the pathognomonic features of adult-onset mitochondrial disorders may not occur until long after the first symptoms are apparent. For example, stroke-like episodes may not appear until a decade or more after initial clinical onset of MELAS [21]. There are several adult-onset clinical syndromes associated with multiple mtDNA deletions, the most frequently described being autosomal dominant progressive external ophthalmoplegia (adPEO) [7]. "Late-onset mitochondrial myopathy" may be age-related and yet still reflect primary mitochondrial dysfunction due to the clonal expansion of different mtDNA deletions in individual fiber segments. While the origin of these mtDNA mutations is not clear, the phenotype seems to represent an exaggerated form of what is observed in the normal aging process [22]. Alpers syndrome, Pearson marrow-pancreas syndrome [23], and Navajo neuropathy are other proven or putative primary hepatopathies produced by a mitochondrial defect. Even carcinogenesis may reflect an unbalancing of the dynamic equilibrium between pro- and anti-apoptotic forces that normally maintain mitochondrial integrity. In fact, mitochondrial dysfunction has now been associated with two types of inherited neoplasia syndromes [24].

Mutations of mtDNA may also play an etiological role in a wide range of adult-onset neurodegenerative disorders [25] including Parkinson's disease [26] Alzheimer's dementia [27], Huntington's disease [28] and amyotrophic lateral sclerosis (ALS) [29]. Mitochondrial dysfunction may even predispose certain personality types to depressive psychopathology [30]. In Friedreich's ataxia, damage to the mitochondrial machinery by ROS may occur because of a mutation in the nuclear encoding for frataxin, a protein needed for mitochondrial iron homeostasis [3] More recently, the spinal cord atrophy characteristic of multiple sclerosis has been attributed to inflammation similar to that of other neurodegenerative disorders that may be caused by genetically-influenced mitochondrial disease [31].

However, although mitochondria provide an obvious connection between oxidative stress and neuronal death there are clearly several complex processes that contribute to the etiology of neurodegenerative disorders, in particular, excitotoxicity [32]. The degradation of lipids and proteins within neurons by reactive oxygen and nitrogen species (ROS and RNOS) [33] have also been implicated in neurodegenerative disorders, although RNOS, like ROS, may initiate either neuroprotection or neurotoxicity and appears to work synergistically with other effectors. These disorders may also reflect, at least in part, impairment of the process by which dysfunctional proteins are targeted for selective destruction by the proteasomal system [34].

5. Acquired mitochondrial disorders

There is growing evidence that acquired mitochondrial dysfunction and impaired bioenergetics play an important, if not necessarily etiologic, role in many common chronic diseases. Mitochondrial respiratory activity in the skeletal muscle of patients with occlusive peripheral arterial disease is abnormal [35] and increased oxidative stress appears to contribute to the pathology of vascular disease in diabetic patients with stroke and hypertension [36]. Insulin resistance in the children of individuals with adult-onset or Type 2 diabetes appears to reflect an inherited defect of fatty acid metabolism [37]. A reduction in oxidative phosphorylation, as assessed in vivo by NMR spectroscopy, is associated with a decline in mitochondrial function and contributes to insulin resistance in the elderly [38].

Healthy cardiac mitochondrial function is essential not only for the energy production needed for contractility but also for electrical and ionic homeostasis and myocardial cell viability. Accumulating evidence suggests that ROS play an important role in the development and progression of cardiomyopathy and heart failure, regardless of the underlying etiology [39]. Oxidative stress produces contractile dysfunction following myocardial infarction [40]. However, increasing levels of ROS within myocytes can have positive consequences as well, acting as a second messenger to initiate agonist-induced cardiac hypertrophy and permitting controlled cardiac myocyte apoptosis and subsequent remodeling of the failing myocardium. Therefore, whether the effects of increasing myocardial ROS are beneficial or harmful will depend upon site, source, timing, and amount of ROS produced, as well as the overall metabolic status of the myocyte. Many of the drugs used to treat myocardial ischemia probably exert their cardioprotective effects via their effect upon mitochondrial function [41].

Overwhelming infection can produce a diffuse and lethal acquired mitochondrial disorder. Despite recent improvements in diagnosis and therapy, the systemic inflammatory response and multiple organ dysfunction syndromes (MODS and SIRS) have mortality rates of 40% to 60% in critically ill surgical patients [42]. In these syndromes, the abrupt onset of cardiovascular, hepatic, and renal dysfunction and acute respiratory distress syndrome (ARDS) are associated with multiple diffuse metabolic abnormalities. Decreased intracellular ATP during prolonged sepsis would suggest simple impairment of mitochondrial bioenergetics, but it is now clear that mitochondria hibernate or "down regulate" their metabolic activity under a variety of conditions and therefore ATP availability is not a sensitive measure of the energy state of an intact cell nor of its capacity for oxidative phosphorylation. In fact, ATP levels may remain normal during sepsis [43]. These observations are reconciled by the concept of "cytopathic hypoxia," in which sepsis impairs the ability of cells to utilize molecular oxygen to produce ATP, but the reduced bioenergetic capacity is masked by decreased ATP demand because of down-regulation of cell metabolism [44].

The mechanism of cytopathic hypoxia may involve disruption of genetic transcription or translation of electron transport chain components or direct depression of their enzymatic functions. Both cytochrome oxidase subunit I protein levels and mRNA are decreased in heart and macrophage mitochondria during sepsis [45] and electron transport chain enzyme activity is depressed [46]. Myocardial cytochrome oxidase is reversibly inhibited early in sepsis but eventually becomes irreversibly inhibited during the later phases [47]. Sepsis-related abnormalities in pH, temperature, or the presence of inhibitors all could alter enzyme kinetics within the metabolic machinery [48]. Potential mitochondrial enzyme inhibitors include nitric oxide (NO) [49], peroxynitrite [50], and carbon monoxide (CO), produced when heme is broken down by heme oxygenase [51]. Oxidative stress also causes lipid peroxidation, damaging membranes and mtDNA and irreversibly inhibiting complex IV [52]. All of these agents are produced in various tissues during sepsis and may contribute to sepsis-associated mitochondrial dysfunction.

6. Aging

An evolving concept portrays cellular aging as a self-sustaining cycle [53] of bioenergetic failure and rising levels of ROS within the mitochondria (Fig. 2). As ROS scavenging and mtDNA repair mechanisms become less effective during senescence due to random degradation of genetic messaging, mtDNA becomes increasingly vulnerable to further oxidative damage and mutation [54]. In fact, more than two-dozen mutations of mtDNA have been observed in the somatic tissues of aged human individuals. Although these mutations

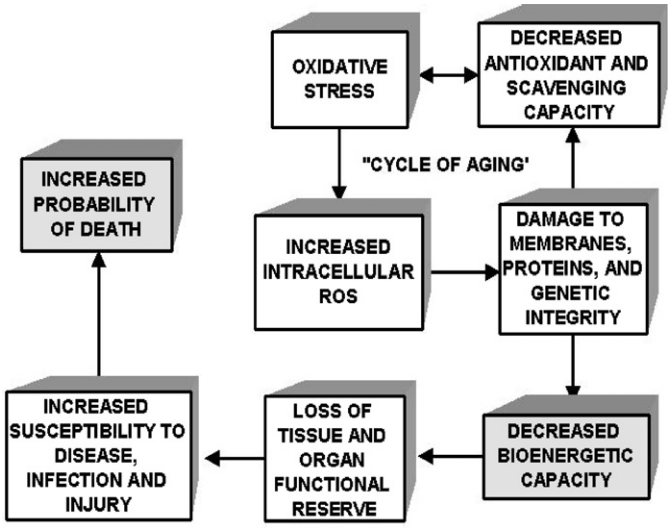

Fig. 2. Schematic representation of the mitochondrial "cycle of aging" and the link between bioenergetics and the increased risk of perioperative morbidity and mortality in a geriatric population.

are present at relatively low levels they accumulate exponentially with increasing age in skeletal muscle, cardiac muscle and other human tissues [55]. This may lead to both a decline in bioenergetic capacity as well as impaired synthesis of protective enzymes such as superoxide dismutase that scavenge ROS from the cytosol.

Nevertheless, because the decreased functional reserve and declining bioenergetics seen in normal individuals during the middle to late adult years are both universal and progressive, they must be regarded as part of a physiological process rather than an age-related or acquired mitochondrial disorder. In addition, it has long been known that, from a clinical perspective, aging inevitably produces a progressively smaller "aerobic machine" [56]. The modest decrease in resting cardiac index, reduced skeletal muscle mass and reduced maximal breathing capacity seen in normal human aging may therefore reflect a constellation of distinct anatomic and physiological changes, and those changes may reflect decreased functional demand and withdrawal of somatotrophism, perhaps hormonally driven, rather than simple bioenergetic failure [57]. In fact, many clinical changes appear to be part of a well-integrated response to the reduced requirements for perfusion and metabolism that occur with aging because of the loss of tissue mass in major organs with high intrinsic metabolic rates. Altered mitochondrial function could be a coincident, rather than a causal, agent in human aging.

Nevertheless, in order to explain age-related changes in mammalian tissues, biogerontologists continue to actively investigate oxidative metabolism as the etiology of increasing damage to mtDNA [58] and intracellular protein [59]. Mice with a defective mtDNA repair system develop premature physical stigmata of aging and have a reduced life span [60] Accelerated aging syndromes such as Down's, Werner's and the Hutchinson–Gilford syndromes are also characterized not only by shortened life span but also by symptoms and disorders associated with increased oxidative stress [61]. In contrast, avian species have disproportionately long life spans despite high metabolic rates [62], but they reportedly have additional mechanisms at the mitochondrial level that minimize the deleterious effects of ROS [63]. When viewed from this metabolic perspective, therefore, aging may eventually turn out to be a form of chronic oxygen toxicity, i.e., acquired mitochondrial dysfunction related to being an obligate aerobe [64,65].

7. Implications for perioperative management

Although patients with inherited mitochondrial cytopathies have received a variety of different general anesthetic regimens without apparent adverse consequences [66,67] it remains unclear whether there is a "safe" or "best" anesthetic for these patients. Clinical reports also suggest that patients with mitochondrial disorders "do well" with regional anesthetics [68]. There are very few reports that describe the anesthetic treatment of adult-onset or acquired mitochondrial encephalomyopathy [69] and only one, for example, dealing with NARP syndrome [70]. Whatever anesthetic regimen is selected, patients with known mitochondrial syndromes must be considered at significant increased risk of adverse surgical outcome compared to the general population, in particular for perioperative stroke, coma, seizures, respiratory failure, and cardiac arrhythmias. Informing patients with cytopathies and their families of these risks is an essential part of their preoperative evaluation.

Patients with mitochondrial cytopathy are usually instructed not to fast for long durations and to eat small frequent meals, a regimen that can be problematic in the setting of perioperative guidelines regarding limitation of oral intake. In children an intravenous infusion of glucose should be initiated during the period of preoperative fasting to avoid metabolic crisis. Choice of intravenous fluids may also be important intraoperatively, with most anesthesiologists choosing to avoid Ringer's solution because of the lactate load. Arterial cannulation facilitates frequent sampling for blood glucose, arterial blood gases, and serum lactate levels. Regardless of the drugs used, key principles of perioperative management always include generous hydration, loading with intravenous glucose, and careful control of body temperature and pH both intraoperatively and post-operatively.

Susceptibility to malignant hyperthermia (MH) or myasthenia-like sensitivity to neuromuscular blockade are issues routinely considered by anesthesiologists for patients with classic muscular dystrophies and neurogenic myopathies. Clinical reviews of anesthesia for mitochondrial disease commonly recommend MH precautions [71], but, in fact, only the very rare mitochondrial myopathies with "multicore" or "minicore" histology may actually predispose to MH [72–74]. There is one clinical report suggesting increased sensitivity to nondepolarizing blockade [75], creating controversy with regard to the wisdom of using neuromuscular blockade, especially in children. However, prolonged drug effects and intrinsic muscle weakness will always increase the risk of post-operative ventilatory failure in patients with mitochondrial disease and therefore the anesthesiologist must consider carefully if the patient can be extubated immediately after surgery or remain electively intubated for ventilatory support in an intensive care unit.

For patients with acquired rather than inherited mitochondrial dysfunction, the anesthetic implications are more subtle but equally important. Anesthetic agents impair the ability of the mitochondrion to function as a "biosensor" for oxidative stress, disrupting the normal balance between ROS and endogenous antioxidants or anti-apoptotic molecules [76]. Anesthetic agents may also increase mitochondrial ROS sufficiently in some individuals to damage cells through a lipid peroxidation pathway. Exposure of nerve cells to local anesthetics has clearly been shown to trigger apoptotic pathways [77], and the myocardial toxicity of bupivacaine appears to be similarly mediated by a mechanism involving mitochondrial bioenergetics [78]. Therefore it is possible that in neonates [79], the elderly [80], or other individuals with limited nervous system functional reserve or impaired tolerance for oxidative stress due to acquired mitochondrial damage, anesthetics can be neurotoxic [81,82]. In elderly surgical patients, in fact, deeper levels of inhalational anesthesia are associated with an increased probability of postoperative cognitive dysfunction [83]. Postoperative cognitive dysfunction, increasing age, and deeper levels of anesthesia are also predictive of increased mortality within 1 year of surgery [84–86].

Nevertheless, extrapolation from laboratory to clinical realms must always be made with great caution [87]. Anesthetic exposure may also have salutary effects with regard to limiting tissue injury during surgery. Volatile anesthetics enhance the ability of the mitochondrion to respond to rising levels of ROS and can offer some protection from

apoptosis caused by hypoxia or ischemia [88]. The mechanism of "anesthetic preconditioning" remains speculative [89], but anesthetic agents appear to disrupt mitochondrial bioenergetics sufficiently to produce the low levels of oxidative stress that induce genetic expression of heat shock protein (HSP), a protective cytokine induced during sepsis [90]. HSP and perhaps other protective substances can also be induced in cardiac and neural tissues by ischemic or hypoxic preconditioning [91], a basic cellular adaptation that may have great species survival value [92]. Therefore, the prophylactic administration of HSP or similar interventions is an intriguing potential therapeutic approach for cardiac- and neuroprotection during surgery [93] in which tissue perfusion or oxygenation will be disrupted [94]. In addition, there is some early evidence to support "post-conditioning," the application of brief periods of ischemia prior to reperfusion of cardiac tissues that have already been subjected to a major ischemic insult [95]. The postconditioning mechanism appears to involve modulation of mitochondrial permeability by opiate receptors [96].

8. Mitochondrial effects of anesthetic agents

Virtually all anesthetics have significant depressant effects upon mitochondrial bioenergetics, at least *in vitro* [97], primarily within the electron transport chain on the inner membrane of mitochondria [98–100]. In cardiac mitochondria, nitrous oxide and the potent inhalational agents halothane, isoflurane, and sevoflurane all inhibit complex I of the electron transport chain [101]. Similarly the primary effect of barbiturates on oxidative phosphorylation in mitochondria obtained from brain, heart, and liver is inhibition of complex I. Like propofol, barbiturates also appear to "uncouple" metabolic activity from ATP production, further reducing bioenergetic capacity [97]. Local anesthetics have also been shown to disrupt oxidative phosphorylation [102–104] and significantly degrade bioenergetic capacity in mitochondrial isolates.

It has been tempting to speculate that the reversible inhibition of mitochondrial electron transfer and decreased energy availability within neural tissues provides a unitary and simple hypothesis for the mechanism of anesthesia [105]. However, it appears that the effect of these drugs on mitochondrial bioenergetics is incidental and may produce some anesthetic side-effects [106] but does not explain their primary anesthetic properties [107]. Similarly, propofol-induced depression of myocardial bioenergetics at low clinical concentrations is not sufficient to account for observed alterations of contractile function [108]. Therefore, although anesthetics probably do not work by reducing ATP availability within the nervous system, they may interfere with ATP utilization, produce oxidative stress, or impair mitochondrial function in some other manner. In fact, the most recent concepts regarding mechanisms of general anesthesia emphasize the complexity, rather than the simplicity, of the anesthetic state and the high probability that there are multiple effect sites for anesthetics.

9. Other clinical considerations

The nervous system plays a particularly prominent role in our understanding of the consequences of altered mitochondrial function, whether inherited or acquired. Consciousness is the most complex manifestation of nervous system function. Because cortical neurons and deeper nervous system tissues with high rates of neurotransmitter synthesis have very high rates of oxygen utilization, depression of mitochondrial bioenergetics or organelle injury due to oxidative stress usually compromises nervous system function before other tissues appear to be affected. Therefore, resistance to loss of consciousness, one possible definition of anesthetic requirement, could provide the clinician with a metric for assessing remaining nervous system functional reserve. Basic genetic manipulation in subprimates has demonstrated a direct link between mitochondrial genetics and anesthetic requirement [109]. Children with inherited mitochondrial disorders also have significantly increased sensitivity to volatile anesthetics [110]. In addition, a general relationship between declining anesthetic requirement and increasing age has been unequivocally established for adults in the general population [111]. All of these observations suggest that understanding mitochondrial bioenergetics at all phases of life may play a central, perhaps life-critical, role both in caring for patients with mitochondrial disorders and in anticipating the responses of children and adults to anesthetics.

References

[1] A.W. Linnane, S. Marzuki, T. Ozawa, M. Tanaka, Mitochondrial DNA mutations as an important contributor to ageing and degenerative diseases, Lancet 1 (1989) 642–651.
[2] Y.H. Wei, Mitochondrial DNA mutations and oxidative damage in aging and diseases, an emerging paradigm of gerontology and medicine, Proc. Natl. Sci. Council (China)-Part B 22 (1998) 55–67.
[3] A.H. Schapira, Primary and secondary defects of the mitochondrial respiratory chain, J. Inherit. Metab. Dis. 25 (2002) 207–214.
[4] J. Schmiedel, S. Jackson, J. Schafer, H. Reichmann, Mitochondrial cytopathies, J. Neurol. 250 (2003) 267–277.
[5] M. Schwartz, J. Vissing, New patterns of inheritance in mitochondrial disease, Biochem. Biophys. Res. Commun. 310 (2003) 247–251.
[6] Y. Kagawa, T. Hamamoto, H. Endo, M. Ichida, H. Shibui, M. Hayakawa, Genes of human ATP synthase, their roles in physiology and aging, Biosci. Rep. 17 (1997) 115–146.
[7] A. Suomalainen, J. Kaukonen, Diseases caused by nuclear genes affecting mtDNA stability, Am. J. Med. Genet. A 106 (2001) 53–61.
[8] D.C. Wallace, X.X. Zheng, M.T. Lott, J.M. Shoffner, J.A. Hodge, R.I. Kelley, C.M. Epstein, L.C. Hopkins, Familial mitochondrial encephalomyopathy (MERRF), genetic, pathophysiological, and biochemical characterization of a mitochondrial DNA disease, Cell 55 (1988) 601–610.
[9] M. Zeviani, B. Bertagnolio, G. Uziel, Neurological presentations of mitochondrial diseases, J. Inherit. Metab. Dis. 19 (1996) 504–520.
[10] M.B. Graeber, U. Muller, Recent developments in the molecular genetics of mitochondrial disorders, Neurol. Sci. 153 (1998) 251–263.
[11] M.L. Zupanc, C.T. Moraes, S. Shanske, C.B. Langman, E. Ciafaloni, S. DiMauro, Deletion of mitochondrial DNA in patients with combined features of Kearns–Sayre and MELAS syndromes, Ann. Neurol. 29 (1991) 680–683.
[12] K. Mroczek-Tonska, B. Kisiel, J. Piechota, E. Bartnik, Leber hereditary optic neuropathy — a disease with a known molecular basis but a mysterious mechanism of pathology, J. Appl. Genet. 44 (2003) 529–538.
[13] Y. Tatuch, B.H. Robinson, The mitochondrial DNA mutation at 8993 associated with NARP slows the rate of ATP synthesis in isolated lymphoblast mitochondria, Biochem. Biophys. Res. Commun. 192 (1993) 124–128.
[14] W.R. Treem, R.J. Sokol, Disorders of the mitochondria, Semin. Liver Dis. 18 (1998) 237–253.
[15] R.C. Griggs, G. Karpati, Muscle pain, fatigue, and mitochondriopathies, N. Engl. J. Med. 341 (1999) 1077–1078.
[16] U.A. Walker, S. Collins, E. Byrne, Respiratory chain encephalomyopathies, a diagnostic classification, Eur. Neurol. 36 (1996) 260–267.
[17] A. Rotig, Renal disease and mitochondrial genetics, J. Nephrol. 16 (2003) 286–292.
[18] B.H. Cohen, Mitochondrial cytopathies, A primer. in: Mitochondrial cytopathies June 2000, online publication, http,//www.umdf.org/pdf/MITOCYTO.PDF.
[19] M.R. Lauwers, C. Van Lersberghe, F. Camu, Inhalation anaesthesia and the Kearns–Sayre syndrome, Anaesthesia 49 (1994) 876–878.
[20] P.J. Grattan-Smith, L.K. Shield, I.J. Hopkins, K.J. Collins, Acute respiratory failure precipitated by general anesthesia in Leigh's syndrome, J. Child Neurol. 5 (1990) 137–141.
[21] H. Minamoto, K. Kawabata, B. Okuda, N. Shibuya, H. Tachibana, M. Sugita, Y. Goto, I. Nishino, I. Nonaka, Mitochondrial encephalomyopathy with elderly onset of stroke-like episodes, Intern. Med. (Tokyo) 35 (1996) 991–995.
[22] W. Johnston, G. Karpati, S. Carpenter, D. Arnold, E.A. Shoubridge, Late-onset mitochondrial myopathy, Ann. Neurol. 37 (1995) 16–23.
[23] L.A. Gillis, R.J. Sokol, Gastrointestinal manifestations of mitochondrial disease, Gastroenterol. Clin. North Am. 32 (2003) 789–817.
[24] C. Eng, M. Kiuru, M.J. Fernandez, L.A. Aaltonen, A role for mitochondrial enzymes in inherited neoplasia and beyond, Nat. Rev.Cancer 3 (2003) 193–202.
[25] D.C. Wallace, M.T. Lott, J.M. Shoffner, M.D. Brown, Diseases resulting from mitochondrial DNA point mutations, J. Inherit. Metab. Dis. 15 (1992) 472–479.
[26] M.F. Beal, Mitochondria, oxidative damage, and inflammation in Parkinson's disease, Ann. N.Y. Acad. Sci. 991 (2003) 120–131.
[27] V. Calabrese, G. Scapagnini, A.M. Giuffrida Stella, T.E. Bates, J.B. Clark, Mitochondrial involvement in brain function and dysfunction, relevance to aging, neurodegenerative disorders and longevity, Neurochem. Res. 26 (2001) 739–764.
[28] M. Orth, A.H. Schapira, Mitochondria and degenerative disorders, Am. J. Med. Genet. A 106 (2001) 27–36.
[29] J. Jordan, V. Cena, J.H. Prehn, Mitochondrial control of neuron death and its role in neurodegenerative disorders, J. Physiol. Biochem. 59 (2003) 129–141.
[30] A. Gardner, A. Johansson, R. Wibom, I. Nennesmo, U. von Dobeln, L. Hagenfeldt, T. Hallstrom, Alterations of mitochondrial function and correlations with personality traits in selected major depressive disorder patients, J. Affect. Disord. 76 (2003) 55–68.

[31] B. Kalman, T.P. Leist, A mitochondrial component of neurodegeneration in multiple sclerosis, Neuromolecul. Med. 3 (2003) 147–158.
[32] J. Emerit, M. Edeas, F. Bricaire, Neurodegenerative diseases and oxidative stress, Biomed. Pharmacother. 58 (2004) 39–46.
[33] K.M. Boje, Nitric oxide neurotoxicity in neurodegenerative diseases, Front. Biosci. 9 (2004) 763–776.
[34] A. Stolzing, T. Grune, The proteasome and its function in the ageing process, Clin. Exp. Dermatol. 26 (2001) 566–572.
[35] I.I. Pipinos, V.G. Sharov, A.D. Shepard, P.V. Anagnostopoulos, A. Katsamouris, A. Todor, K.A. Filis, H.N. Sabbah, Abnormal mitochondrial respiration in skeletal muscle in patients with peripheral arterial disease, J. Vasc. Surg. 38 (2003) 827–832.
[36] M.A. Yorek, The role of oxidative stress in diabetic vascular and neural disease, Free Radic. Res. 37 (2003) 471–480.
[37] K.F. Petersen, S. Dufour, D. Befroy, R. Garcia, G.I. Shulman, Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes, N. Engl. J. Med. 350 (2004) 664–671.
[38] K.F. Petersen, D. Befroy, S. Dufour, J. Dziura, C. Ariyan, D.L. Rothman, L. DiPietro, G.W. Cline, G.I. Shulman, Mitochondrial dysfunction in the elderly, possible role in insulin resistance, Science 300 (2003) 1140–1142.
[39] M. Corral-Debrinski, G. Stepien, M. Shoffner, M.T. Lott, K. Kanter, D.C. Wallace, Hypoxemia is associated with mitochondrial DNA damage and gene induction; implications for cardiac disease, J. Am. Med. Assoc. 266 (1991) 1812–1816.
[40] J.A. Byrne, D.J. Grieve, A.C. Cave, A.M. Shah, Oxidative stress and heart failure, Arch. Mal. Coeur Vaiss. 96 (2003) 214–221.
[41] P. Monteiro, P.J. Oliveira, L. Concalves, L.A. Providencia, Pharmacological modulation of mitochondrial function during ischemia and reperfusion, Rev. Port. Cardiol. 22 (2003) 407–429.
[42] M.G. Davies, P.O. Hagen, Systemic inflammatory response syndrome, Br. J. Surg. 84 (1997) 920–935.
[43] G.R. Budinger, J. Duranteau, N.S. Chandel, P.T. Schumacker, Hibernation during hypoxia in cardiomyocytes; role of mitochondria as the O2 sensor, J. Biol. Chem. 273 (1998) 3320–3326.
[44] M.P. Fink, Bench-to-bedside review, cytopathic hypoxia, Crit. Care 6 (2002) 491–499.
[45] J.A. Watts, J.A. Kline, L.R. Thornton, R.M. Grattan, S.S. Brar, Metabolic dysfunction and depletion of mitochondria in hearts of septic rats, J. Mol. Cell. Cardiol. 36 (2004) 141–150.
[46] F.N. Gellerich, S. Trumbeckaite, K. Hertel, S. Zierz, U. Muller-Werdan, K. Werdan, H. Redl, G. Schlag, Impaired energy metabolism in hearts of septic baboons, diminished activities of complex I and complex II of the mitochondrial respiratory chain, Shock 11 (1999) 336–341.
[47] R.J. Levy, C. Vijayasarathy, N.R. Raj, N.G. Avadhani, C.S. Deutschman, Competitive and noncompetitive inhibition of myocardial cytochrome *c* oxidase in sepsis, Shock 21 (2004) 110–114.
[48] S. Bruemmer-Smith, F. Stuber, S. Schroeder, Protective functions of intracellular heat-shock protein (HSP) 70-expression in patients with severe sepsis, Intensive Care Med. 27 (2001) 1835–1841.
[49] M. Brunori, A. Giuffre, P. Sarti, G. Stubauer, M.T. Wilson, Nitric oxide and cellular respiration, Cell Mol. Life Sci. 56 (1999) 549–557.
[50] M.A. Sharpe, C.E. Cooper, Interaction of peroxynitrite with mitochondrial cytochrome oxidase; catalytic production of nitric oxide and irreversible inhibition of enzyme activity, J. Biol. Chem. 273 (1998) 30961–30972.
[51] C. Taille, J. El-Benna, S. Lanone, J. Boczkowski, R. Motterlini, Mitochondrial respiratory chain and NAD(P)H oxidase are targets for the antiproliferative effect of carbon monoxide in human airway smooth muscle, J. Biol. Chem. 280 (2005) 25350–25360.
[52] R. Luft, The development of mitochondrial medicine, Proc. Natl. Acad. Sci. 91 (1994) 8731–8738.
[53] T. Ozawa, Genetic and functional changes in mitochondria associated with aging, Physiol. Rev. 77 (1997) 425–464.
[54] R.S. Sohal, R. Weindruch, Oxidative stress, caloric restriction, and aging, Science 273 (1996) 59–63.
[55] K. Hattori, M. Tanaka, S. Sugiyama, T. Obayashi, T. Ito, T. Satake, Y. Hanaki, J. Asai, M. Nagano, T. Ozawa, Age-dependent decrease in mitochondrial DNA in the human heart; possible contributory factor to presbycardia, Am. Heart J. 121 (1991) 1735–1742.
[56] M.L. Pollock, L.J. Mengelkoch, J.E. Graves, D.T. Lowenthal, M.C. Limacher, C. Foster, J.H. Wilmor, Twenty-year follow-up of aerobic power and body composition of older track athletes, J. Appl. Physiol. 82 (1997) 1508–1516.
[57] A.P. Wickens, Aging and the free radical theory, Res. Physiol. 128 (2001) 379–391.
[58] B.S. Mandavilli, J.H. Santos, B. Van Houten, Mitochondrial DNA repair and aging, Mutat. Res. 509 (2002) 127–151.
[59] E.R. Stadtman, Protein oxidation in aging and age-related diseases, Ann. N.Y. Acad. Sci. 928 (2001) 22–38.
[60] A. Trifunovic, A. Wredenberg, M. Falkenberg, J.N. Spelbrink, A.T. Rovio, C.E. Bruder, Y.M. Bohlooly, S. Gidlof, A. Oldfors, R. Wibom, J. Tornell, H.T. Jacobs, N.-G. Larsson, Premature ageing in mice expressing defective mitochondrial DNA polymerase, Nature 429 (2004) 417–423.
[61] J.A. Knight, The biochemistry of aging, Adv. Clin. Chem. 35 (2000) 1–62.
[62] D.J. Holmes, R. Fluckiger, S.N. Austad, Comparative biology of aging in birds, an update, Exp. Gerontol. 36 (2001) 869–883.
[63] A. Herrero, G. Barja, H_2O_2 production of heart mitochondria and aging rate are slower in canaries and parakeets than in mice, sites of free radical generation and mechanisms involved, Mech. Ageing Dev. 103 (1998) 133–146.
[64] G. Barja, A. Herrero, Oxidative damage to mitochondrial DNA is inversely related to maximum life span in the heart and brain of mammals, FASEB J. 14 (2000) 312–318.
[65] M.L. Genova, M.M. Pich, A. Bernacchia, C. Bianchi, A. Biondi, C. Bovina, A.I. Falasca, G. Formiggini, G.P. Castelli, G. Lenaz, The mitochondrial production of reactive oxygen species in relation to aging and pathology, Ann. N.Y. Acad. Sci. 1011 (2004) 86–100.
[66] A. Maslow, A. Lisbon, Anesthetic considerations in patients with mitochondrial dysfunction, Anesth. Analg. 76 (1993) 884–886.
[67] S. Matsuno, H. Hashimoto, A. Matsuki, Neuroleptanesthesia for a patient with mitochondrial encephalomyopathy, Masui 43 (1994) 1038–1040.
[68] O.P. Rosaeg, S. Morrison, J.P. MacLeod, Anaesthetic management of labour and delivery in the parturient with mitochondrial myopathy, Can. J. Anaesth. 43 (1996) 403–407.
[69] S. Sabate, M. Ferrandiz, P. Paniagua, J.M. Villamor, F. Vilanova, J.M. Villar-Landeira, Anesthesia in Kearns–Sayre syndrome mitochondrial myopathy, Rev. Esp. Anestesiol. Reanim. 43 (1996) 255–257.
[70] K.K. Ciccotelli, E.L. Prak, S. Muravchick, An adult with inherited mitochondrial encephalomyopathy; report of a case, Anesthesiology 87 (1997) 1240–1242.
[71] K. Itaya, O. Takahata, K. Mamiya, T. Saito, S. Tamakawa, Y. Akama, M. Kubota, H. Ogawa, Anesthetic management of two patients with mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), Masui 44 (1995) 710–712.
[72] D. Figarella-Branger, G. Kozak-Ribbens, L. Rodet, M. Aubert, J. Borsarelli, P.J. Cozzone, J.F. Pellissier, Pathological findings in 165 patients explored for malignant hyperthermia susceptibility, Neuromuscul. Disord. 3 (1993) 553–556.
[73] S. Wiesel, J.C. Bevan, J. Samuel, F. Donati, Vecuronium neuromuscular blockade in a child with mitochondrial myopathy, Anesth. Analg. 72 (1991) 696–699.
[74] M.N. D'Ambra, D. Dedrick, J.J. Savarese, Kearns–Sayre syndrome and pancuronium-succiny1choline induced neuromuscular blockade, Anesthesiology 51 (1979) 343–345.
[75] M. Naguib, A.A. el Dawlatly, M. Ashour, M. al-Bunyan, Sensitivity to mivacurium in a patient with mitochondrial myopathy, Anesthesiology 84 (1996) 1506–1509.
[76] Y.H. Wei, H.C. Lee, Oxidative stress, mitochondrial DNA mutation, and impairment of antioxidant enzymes in aging, Exp. Biol. Med. 227 (2002) 671–682.
[77] M.E. Johnson, C.B. Uhl, K.H. Spittler, H. Wang, G.J. Gores, Mitochondrial injury and caspase activation by the local anesthetic lidocaine, Anesthesiology 101 (2004) 1184–1194.
[78] Irwin, E. Fontaine, L. Agnolucci, D. Penzo, R. Betto, S. Bortolotto, C. Reggiani, G. Salviati, P. Bernardi, Bupivacaine myotoxicity is mediated by mitochondria, J. Biol. Chem. 277 (2002) 12221–12227.
[79] A. Fredriksson, E. Ponten, T. Gordh, P. Eriksson, Neonatal exposure to a combination of *N*-methyl-D-aspartate and [gamma]-aminobutyric acid type A receptor anesthetic agents potentiates apoptotic neurodegeneration and persistent behavioral deficits, Anesthesiology 107 (2007) 427–443.
[80] V. Jevtovic-Todorovic, L.B. Carter, The anesthetics nitrous oxide and ketamine are more neurotoxic to old than to young rat brain, Neurobiol. Aging 26 (2005) 947–956.
[81] R.D. Mellon, A.F. Simone, B.A. Rappaport, Use of anesthetic agents in neonates and young children, Anesth. Analg. 104 (2007) 509–520.
[82] J.W. Olney, C. Young, D.F. Wozniak, C. Ikonomidou, V. Jevtovic-Todorovic, Anesthesia-induced developmental neuroapoptosis; does it happen in humans? Anesthesiology 101 (2004) 273–275.
[83] A. Schubert, E. Farag, J. Dilger, G. Chelune, J. Beercheck, Depth of anesthesia and recovery from postoperative cognitive dysfunction, Anesthesiology 95 Suppl. (2001) A52.
[84] B.C. Weldon, M.E. Mahla, M.T. van der Aa, T.G. Monk, Advancing age and deeper intraoperative anesthetic levels are associated with higher first year death rates, Anesthesiology 96 Suppl. (2002) A1097.
[85] C. Lennmarken, M.-L. Lindholm, S. Greenwald, R. Sandin, Confirmation that low intraoperative BIS™ levels predict increased risk of post-operative mortality, Anesthesiology 99 Suppl. (2003) A303.
[86] T.G. Monk, B.C. Weldon, C.W. Garvan, D. Dede, M.T. van der Aa, K.M. Heilman, J.S. Gravenstein, Predictors of cognitive dysfunction after major noncardiac surgery, Anesthesiology 108 (2008) 18–30.
[87] K.J.S. Anand, Anesthetic neurotoxicity in newborns, should we change clinical practice? Anesthesiology 107 (2007) 2–4.
[88] H. Kitano, J.R. Kirsch, P.D. Hurn, S.J. Murphy, Inhalational anesthetics as neuroprotectants or chemical preconditioning agents in ischemic brain, J. Cereb. Blood Flow Metab. 27 (2007) 1108–1128.
[89] K. Tanaka, L.M. Ludwig, J.R. Kersten, P.S. Pagel, D.C. Warltier, Mechanisms of cardioprotection by volatile anesthetics, Anesthesiology 100 (2004) 707–721.
[90] H.W. Chen, C. Hsu, T.S. Lu, S.J. Wang, R.C. Yang, Heat shock pretreatment prevents cardiac mitochondrial dysfunction during sepsis, Shock 20 (2003) 274–279.
[91] J.M. Gidday, Cerebral preconditioning and ischaemic tolerance, Nat. Rev. Neurosci. 7 (2006) 437–448.
[92] B. Jia, M. Crowder, Volatile anesthetic preconditioning present in the invertebrate *Caenorhabditis elegans*, Anesthesiology 108 (2008) 426–433.
[93] K. Sheth, A. De, B. Nolan, J. Friel, A. Duffy, R. Ricciardi, C. Miller-Graziano, P. Bankey, Heat shock protein 27 inhibits apoptosis in human neutrophils, J. Surg. Res. 99 (2001) 129–133.
[94] C.D. Raeburn, J.C. Cleveland Jr., M.A. Zimmerman, A.H. Harken, Organ preconditioning, Arch. Surg. 136 (2001) 1263–1266.
[95] H.H. Patel, Y.M. Tsutsumi, D.M. Roth, Mito-controversies. mitochondrial permeability transition pore and myocardial reperfusion injury, Anesthesiology 108 (2008) 182–184.
[96] Y. Jang, J. Xi, H. Wang, Postconditioning prevents reperfusion injury by activating delta-opioid receptors, Anesthesiology 108 (2008) 243–250.
[97] P.J. Cohen, Effect of anesthetics on mitochondrial function, Anesthesiology 39 (1973) 153–164.

[98] S.L. Lee, L.E. Alto, N.S. Dhalla, Subcellular effects of some anesthetic agents on rat myocardium, Can. J. Physiol. Pharmacol. 57 (1979) 65–71.
[99] O. Einarsdottir, W.S. Caughey, Interactions of the anesthetic nitrous oxide with bovine heart cytochrome c oxidase; effects on protein structure, oxidase activity, and other properties, J. Biol. Chem. 263 (1988) 9199–9205.
[100] G.L. Becker, D.A. Pelligrino, D.J. Miletich, R.F. Albrecht, The effects of nitrous oxide on oxygen consumption by isolated cerebral cortex mitochondria, Anesth. Analg. 65 (1986) 355–359.
[101] P.J. Hanley, J. Ray, U. Brandt, J. Daut, Halothane, isoflurane and sevoflurane inhibit NADH, ubiquinone oxidoreductase (complex I) of cardiac mitochondria, J. Physiol. 544 (2002) 687–693.
[102] K.D. Garlid, R.A. Nakashima, Studies on the mechanism of uncoupling by amine local anesthetics; evidence for mitochondrial proton transport mediated by lipophilic ion pairs, J. Biol. Chem. 258 (1983) 7974–7980.
[103] F. Dabbeni-Sala, G. Schiavo, P. Palatini, Mechanism of local anesthetic effect on mitochondrial ATP synthase as deduced from photolabelling and inhibition studies with phenothiazine derivatives, Biochim. Biophys. Acta 1026 (1990) 117–125.
[104] C. Tarba, C. Cracium, A comparative study of the effects of procaine, lidocaine, tetracaine, and dibucaine on the functions and ultrastructure of isolated rat liver mitochondria, Biochim. Biophys. Acta 1019 (1990) 19–28.
[105] M.L. Nahrwold, C.R. Clark, P.J. Cohen, Is depression of mitochondrial respiration a predictor of in-vivo anesthetic activity? Anesthesiology 40 (1974) 566–570.
[106] G. Delogu, A. Antonucci, S. Moretti, M. Marandola, G. Tellan, M. Signore, G. Famularo, Oxidative stress and mitochondrial glutathione in human lymphocytes exposed to clinically relevant anesthetic drug concentrations, J. Clin. Anesth. 16 (2004) 189–194.
[107] P.J. Cohen, Effect of hydrostatic pressure on halothane-induced depression of mitochondrial respiration, Life Sci. 32 (1983) 1647–1650.
[108] D. Branca, E. Vincenti, G. Scutari, Influence of the anesthetic 2,6-diisopropylphenol (propofol) on isolated rat heart mitochondria, Comp. Biochem. Physiol. C Toxicol. Pharmacol. 110 (1995) 41–45.
[109] E.B. Kayser, P.G. Morgan, M.M. Sedensky, GAS-1, a mitochondrial protein controls sensitivity to volatile anesthetics in the nematode *Caenorhabditis elegans*, Anesthesiology 90 (1999) 545–554.
[110] P.G. Morgan, C.L. Hoppel, M.M. Sedensky, Mitochondrial defects and anesthetic sensitivity, Anesthesiology 96 (2002) 1268–1270.
[111] S. Muravchick, The effects of aging on anesthetic pharmacology, Acta Anaesthesiol. Belg. 49 (1998) 79–84.