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Clinical Implications of Mitochondrial Dysfunction

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Mitochondria produce metabolic energy, serve as biosensors for oxidative stress, and eventually become effector organelles for cell death through apoptosis. The extent to which these manifold mitochondrial functions are altered by previously unrecognized actions of anesthetic agents seems to explain and link a wide variety of perioperative phenomena that are currently of interest to anesthesiologists from both a clinical and a scientific perspective. In addition, many surgical patients may be at increased perioperative risk because of inherited or acquired mitochondrial dysfunction leading to increased oxidative stress. This review summarizes the essential aspects of the bioenergetic process, presents current knowledge regarding the effects of anesthetics on mitochondrial function and the extent to which mitochondrial state determines anesthetic requirement and potential anesthetic toxicity, and considers some of the many implications that our knowledge of mitochondrial dysfunction poses for anesthetic management and perioperative medicine.

MITOCHONDRIA not only generate and modulate bioenergy but also serve as the final effectors for the termination of cell viability as organisms approach the end of their lifespan. Therefore, the implications of these processes with regard to understanding evolution, disease, aging, and death are profound. Particularly relevant to anesthesiologists is the role of mitochondria in determining the response of the nervous system to anesthetic agents, in initiating mechanisms of cell injury or protection after ischemic, hypoxic, or toxic injuries, and their ability to precipitate critical illness in individuals with inherited or acquired mitochondrial disorders. These aspects of mitochondrial biology and pathophysiology will be briefly summarized in this clinically oriented review.

The Bioenergetic Process

Mitochondria produce the energy needed for normal cellular function and metabolic homeostasis by oxidative phosphorylation,[1] a process conducted by a series of five enzyme complexes located on the inner mitochondrial membrane (fig. 1). Four of these complexes comprise the mitochondrial electron transport chain (ETC) and function as a biochemical "conveyor belt" for electrons. Oxidative phosphorylation couples the oxidation of reduced nicotinamide adenine dinucleotide and flavin adenine dinucleotide, generated by the Krebs cycle and by the β-oxidation of fatty acids, to the phosphorylation of adenosine diphosphate (ADP) to adenosine triphosphate (ATP). Electron donation to complex I (reduced nicotinamide adenine dinucleotide–ubiquinone oxidoreductase) initiates this process. Alternatively, electrons originating from succinate and from reduced flavin adenine dinucleotide can be channeled into the ETC through complex II (succinate–ubiquinone oxidoreductase). Electrons are transported from complex I or II to complex III (ubiquinone–cytochrome *c* oxidoreductase) *via* a mobile electron carrier, coenzyme Q (ubiquinone), and subsequently on to complex IV (cytochrome *c* oxidase) *via* cytochrome *c*. Complex IV uses electrons from cytochrome *c* to reduce molecular oxygen, the final acceptor of electrons, to water at that site.

Intrinsically linked to this process of electron transport is the generation and maintenance of a hydrogen ion gradient across the inner mitochondrial membrane. The inner membrane separates the intermembrane space from the mitochondrial matrix. The gradient is established by proton pumps in ETC complexes I, III, and IV. The F1F0–ATPase (ATP synthase) complex within the inner membrane uses this proton motive force to phosphorylate ADP. This last step in the overall process of oxidative phosphorylation produces the ATP that serves as the fundamental "currency" needed for most energy-requiring biologic transactions. Another membrane-integrated protein, adenine nucleotide translocase, regulates an "antiport" process that moves ADP and ATP in opposite directions across the inner mitochondrial membrane. Adenine nucleotide translocase delivers ATP to energy-requiring sites, mostly in the cytosol, and simultaneously resupplies the ATP synthase complex with new substrate.

The hydrogen ion gradient established by the process of oxidative phosphorylation can also be dissipated by proton leakage back into the matrix through the inner membrane that bypasses the ATP synthase complex. Uncoupling proteins (UCPs) within the inner membrane

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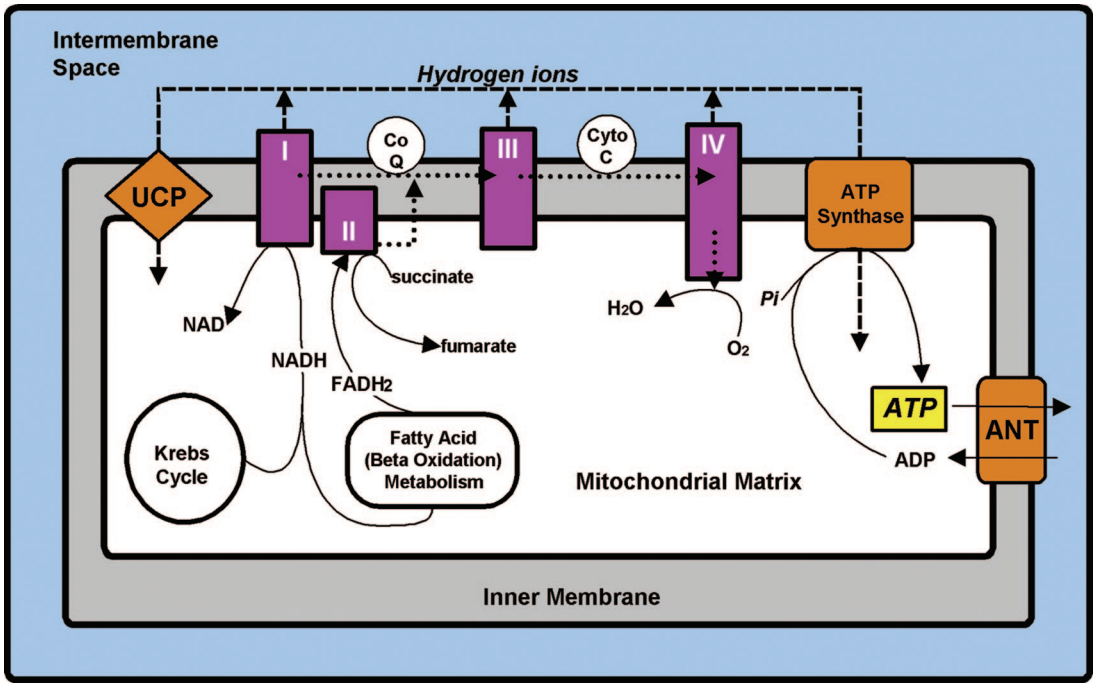

Fig. 1. Schematic representation of the mitochondrial components needed for oxidative phosphorylation. Complexes I–IV, located within the inner mitochondrial membrane, are oxidase complexes that, along with coenzyme Q (Co Q) and cytochrome *c* (Cyto C), comprise the electron transport chain. *Dotted lines* indicate pathway for electron flow. Complexes I, III, and IV also pump hydrogen ions (*dashed lines*) into the intermembrane space and generate the electrochemical gradient that ultimately powers the phosphorylation of adenosine diphosphate (ADP) to adenosine triphosphate (ATP) by ATP synthase. Inner membrane–bound uncoupling protein (UCP) is an alternate return path for hydrogen ions. Adenine nucleotide translocase (ANT) regulates the balance of ATP and ADP within the mitochondrial matrix. $FADH_2$ = flavin adenine dinucleotide; H_2O = water; NAD = nicotinamide adenine dinucleotide; NADH = reduced nicotinamide adenine dinucleotide; O_2 = oxygen; Pi = inorganic phosphate. Copyright © 2000 American Diabetes Association. Modified with permission from The American Diabetes Association, from Boss *et al.*[4]

provide this alternate pathway for proton influx. In effect, UCPs convert some of the electrochemical energy generated by the ETC into heat rather than into ATP. The rate of proton leakage through a UCP seems to be influenced by a variety of conditions, including changes in the magnitude of the hydrogen ion gradient itself, increased catecholamines levels, and variations in fatty acid concentrations.[2] UCP-1, also called thermogenin, was originally characterized in the mitochondria of brown fat cells[3] and is now known to play a role in nonshivering thermogenesis in human neonates. Subsequently, additional UCP isoforms were identified in a variety of tissues.[4] Although their precise metabolic functions have yet to be determined, UCPs may play an important role in adult obesity, diabetes mellitus,[5] and perhaps other conditions where the regulation of oxidative metabolism seems to be disrupted.

Mitochondrial Biogenesis

The mitochondrion, unique among mammalian organelles, contains multiple copies of a small circular genome of approximately 16,000 nucleotide base pairs. This mitochondrial DNA (mtDNA) has been completely characterized in humans.[6] mtDNA encodes for some key subunits needed for electron transport and oxidative phosphorylation, although the majority of mitochondrial proteins needed for normal bioenergetic function are encoded by nuclear DNA (nDNA)[7] and therefore must be imported into the mitochondrial matrix from the cell cytosol.[8] Complex IV of the ETC, for example, contains 13 subunits, 10 of which are encoded in nDNA. The expression of the mitochondrial genome itself requires a single mitochondrial transcription factor that arises from the nuclear genome.[9]

Overall, the human mitochondrial genome encodes for 13 peptides (subunits of complexes I, III, and IV and the ATP synthase complex), 2 ribosomal ribonucleic acids (RNAs), and 22 transfer RNAs. Nuclear DNA encodes for at least 1,000 proteins that are needed for mitochondrial bioenergetic and metabolic functions and for mtDNA expression and replication.[10] Although there may be as many as 1,000 copies of mtDNA in most cells, acquired mtDNA point mutations and base pair deletions are extremely rare and are normally found in only a minute proportion of total mtDNA[11] despite the fact that mtDNA, unlike nDNA, lacks histone protection and is surrounded by potentially damaging oxidative influences.[12] This observation supports the hypothesis that there must be effective molecular repair and disposal mechanisms for damaged mtDNA within mitochondria.[13,14]

Oxidative Stress

Oxidative phosphorylation is the major intracellular source of reactive oxygen species (ROS). ROS or "free radicals" such as superoxide, peroxide, or hydroxyl radicals (O_2^-, H_2O_2, and OH^-) are routinely generated as byproducts of the interaction between free electrons and oxygen. ROS are an unavoidable consequence of aerobic metabolism and can be produced anywhere there is leakage of electrons from the ETC. Although only a tiny percentage of metabolically consumed oxygen is converted into ROS, these ephemeral but highly reactive molecules can degrade or destroy mitochondrial enzyme complexes, membranes, and other structural components of cell microarchitecture, either by direct contact or through lipid peroxidation.[15] ROS such as hydroxyl and reactive nitrogen species such as peroxynitrite (ONO_2^- formed from the interaction of superoxide and nitric oxide) react almost instantly with proteins to generate protein carbonyls[16,17] and with polyunsaturated fatty acids in membranes to generate a variety of lipid peroxidation products including 4-hydroxynonenal and malondialdehyde.[18] These reaction products drastically reduce the membrane fluidity needed for normal cell function. With half-lives of minutes to hours,[19] peroxidation products may impact multiple membrane-bound systems and precipitate a series of damaging "chain reaction" peroxidation sequences in adjacent cells.[20]

All obligate aerobes have intrinsic defensive systems to protect against damage by ROS.[21] This includes several forms of superoxide dismutase, catalase, and glutathione peroxidase. Copper, zinc superoxide dismutase (present in the cytosol),[22] and manganese superoxide dismutase (found within the mitochondrion)[23,24] convert superoxide into oxygen and hydrogen peroxide. The bulk of hydrogen peroxide is quickly broken down by catalases into water and oxygen,[25] although some peroxide in human cells, particularly neurons, is inactivated either by glutathione peroxidase[26] or by the more recently described peroxiredoxins,[27] a group of thioredoxin-dependent antioxidant peroxidases that reduce peroxynitrite and also modulate the role of peroxide as a second messenger molecule.[28]

Overall, endogenous antioxidant defense systems provide effective homeostasis with regard to suppressing ROS levels within the cell as well as within mitochondria, and there are endogenous "backup" systems to repair ROS-mediated damage if it occurs.[29] In many disease states, however, and perhaps in normal aging, mechanisms that prevent or limit ROS-mediated damage may become inadequate.[30] Elevation of ROS beyond normal levels, regardless of etiology, inevitably produces oxidative stress. The insidious onset or sustained low level of oxidative stress can be cytoprotective if it induces or enhances the expression of additional antioxidant or molecular repair systems. In contrast, however, rapid or overwhelming increases in ROS are fundamentally cytotoxic, primarily through disruption of intracellular calcium regulation or by initiating the destructive sequence of events known as apoptosis.

Apoptosis

Apoptosis, or programmed cell death, is a genetically controlled event that has biologic value because it permits prompt and orderly disposal of damaged, infected, or aging cells, especially in the nervous system,[31] and has survival value for the species because it facilitates complex organogenesis and tissue development.[32] It may also limit the spread of "rogue" or neoplastic cells.[33,34] It is a biochemical cascade usually mediated by caspases, a large family of proteolytic enzymes that activate the nucleases that digest DNA (fig. 2). Each cell within a multicellular organism seems to possess multiple overlapping mechanisms to accomplish what is, in effect, "cellular suicide." Because nDNA fragmentation is prominent in this process, apoptosis was originally thought to be solely a function of cell nuclei. Now, however, the central role of mitochondria in cellular apoptosis is universally acknowledged.[35]

The rate-limiting fundamental step in the mitochondrial apoptotic pathway is induction of a mitochondrial permeability transition (MPT),[36] an electrochemical event characterized by transient influx of solutes through large pores or "megachannels" in the otherwise essentially impermeable mitochondrial inner membrane. During MPT-induced permeabilization, collapse of the transmembrane electrochemical gradient for hydrogen ions stops the process of oxidative phosphorylation. In addition, there is efflux of cytochrome *c* from the intermembrane space into the cytosol. There, cytochrome *c* combines with apoptotic protease activation factor 1 and dATP to form a complex that oligomerizes, recruits, and activates procaspase 9. Subsequent procaspase-3 recruitment forms an "apoptosome "and activates caspase 3. This leads to the activation of nucleases that completes the "intrinsic" or mitochondrial-dependent pathway. Destruction of nDNA and mtDNA by nucleases is irreversible and complete within a few hours.

There is also an "extrinsic" pathway that can initiate caspase activation and apoptosis without mitochondrial involvement. Apoptosis can be triggered by the binding of a signaling messenger such as tumor necrosis factor or similar extrinsic cytokine[37] to a cell surface "death receptor." It seems that a variety of signal transducers and activators of transcription may play a role in the suppression or activation of apoptosis, especially with neoplastic cells.[38] In addition, there is at least one apoptotic cascade that uses apoptosis-inducing factor (AIF), a flavoprotein sequestered in the intermembrane region of

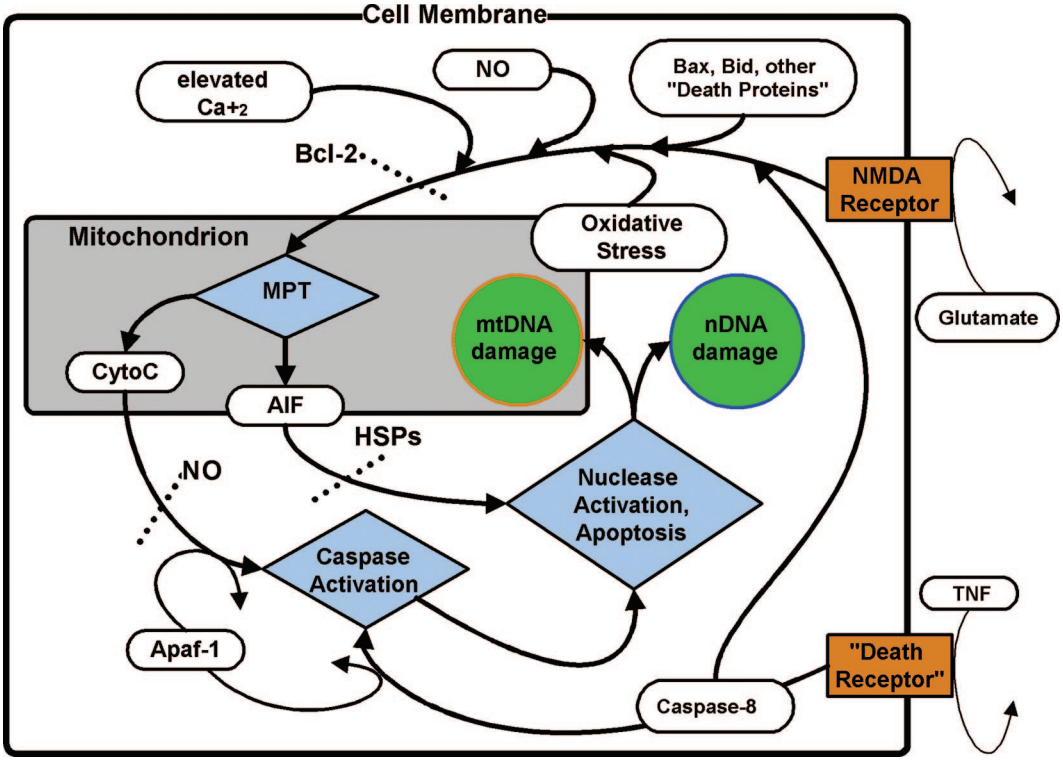

Fig. 2. Simplified schematic of major pathways for apoptosis. The intrinsic or mitochondrial pathway requires a cascade of events beginning with a mitochondrial permeability transition (MPT) that can be triggered by a variety of stimuli, including oxidative stress, high levels of nitric oxide (NO), acute hypercalcemia, or release of proapoptotic "death proteins." The intrinsic cascade releases cytochrome *c* (Cyto C) from the mitochondrial inner membrane into the cytosol, which triggers caspase activation facilitated by apoptotic protease activation factor 1 (Apaf-1). Activation of nucleases may also occur without caspase activation when an MPT releases apoptosis-inducing factor (AIF) from the mitochondrion. Extrinsic pathways for apoptosis have been described that require activation of cell surface *N*-methyl-D-aspartate (NMDA) receptors by neurotransmitters such as glutamate or by "death receptors" triggered by tumor necrosis factor (TNF) or other cytokines. *Dotted lines* indicate evidence of protective or antiapoptotic properties for low levels of NO, some Bcl proteins (Bcl-2), and heat shock proteins (HSPs). mtDNA = mitochondrial DNA; nDNA = nuclear DNA.

the mitochondrion, to initiate apoptosis without caspase activation. AIF normally stabilizes mitochondrial membrane permeability and supports oxidative phosphorylation.[39] However, if released through the outer membrane into the cytosol, AIF can produce terminal damage to nDNA.

The precise regulation of calcium ion flux across mitochondrial membranes is essential both to normal mitochondrial bioenergetic function and to the apoptotic process.[40] Calcium is of special importance because it is a signaling cation for many preprogrammed cell functions. Calcium concentrations within the cytosol are normally orders of magnitude less than extracellular calcium concentrations. With their capacity for calcium uptake, mitochondria may therefore function as a reservoir or buffer to stabilize calcium concentrations within the cytosol at very low levels. It is also possible that tiny fluctuations in cytosol calcium concentrations are "sensed" within the mitochondrion, providing a control system that links changes in cellular energy demand to the rate of energy production by oxidative phosphorylation.[41]

Pathways for apoptosis involve counterbalancing concentrations of antiapoptotic and proapoptotic proteins, many of which are encoded by the Bcl-2 B-cell leukemia gene.[33,42] Although the precise role and interactions between the members of this large family of proteins are still under intense investigation,[37] they modulate the likelihood of an MPT initiating permeabilization and triggering apoptosis, probably through their effects on inner membrane stability.[43] In addition, Bcl-2 family proteins such as Bid may act as a "bridge" between different apoptotic pathways, allowing them to share some, but not all, mediators.[44] Oxidative stress or high levels of ionized calcium within the mitochondrial matrix can also induce an MPT. During a state of oxidative stress, there is a synergistic relation between MPT and ROS formation that produces an upward spiral of mitochondrial damage and continuing release of ROS and calcium into the cytosol.[45]

It has been difficult to distinguish clearly between proapoptotic and antiapoptotic factors. For example, at low intracellular concentrations, nitric oxide is a potent but reversible inhibitor of cellular respiration and oxygen consumption[46] and inhibits mitochondrial-dependent apoptosis. At higher levels, however, or in the presence of increased intracellular or intramitochondrial calcium, nitric oxide enhances the apoptogenic effects

of ROS or may even become a "death messenger" capable of initiating apoptosis.[47] It has also recently been emphasized that caspases, as do cytochrome *c* and AIF, play a prominent role in programmed cell death but are also essential to many vital nonapoptotic cell processes.[48] Therefore, therapeutic strategies that suppress or block the effects of putative proapoptotic agents may produce unintended interruptions of other cell functions and actually compromise cell viability. Clearly, more investigation is necessary to define the importance and role of apoptosis in the maintenance of normal cellular function and in the pathogenesis of disease.

Effect of Anesthetics on Mitochondrial Function

Although the extent to which they alter mitochondrial function *in vivo* is not yet understood, it has long been known that intravenous drugs with anesthetic properties can depress carbohydrate metabolism, oxygen consumption, and energy production in the nervous system.[49] Early studies of narcotics demonstrated that they inhibit oxidation of glucose, lactate, and pyruvate in neural tissues at clinically relevant concentrations,[50] and seven decades later, it has been proposed that morphine may actually have a mitochondrial-based mechanism of clinical action.[51] It has also been recently shown that propofol markedly decreases oxygen consumption and ATP production in brain synaptosomes[52] and reduces electron flow in cardiac mitochondria.[53,54] Propofol inhibits complex I of the ETC but may also effect ATPase and UCPs, uncoupling electron transport from ATP production.[55,56] The primary effect of barbiturates on oxidative phosphorylation in mitochondria obtained from brain, heart, and liver also seems to be inhibition of complex I, and, like propofol, they seem to "uncouple " metabolic activity from ATP production, further reducing bioenergetic capacity.[57]

Inhalational anesthetic agents have similar depressant effects on mitochondrial respiration, at least *in vitro*.[58–62] Studies of cardiac mitochondria exposed to halothane, isoflurane, and sevoflurane suggest that the most common site of action is, again, inhibition of complex I.[63] At concentrations equal to twice minimum alveolar concentration, complex I activity is reduced by 20% after exposure to halothane and isoflurane and by 10% after exposure to sevoflurane. Oxidative phosphorylation in isolated liver mitochondria is also measurably depressed after exposure to halothane.[64] Concentrations of 0.5–2% halothane lead to reversible inhibition of complex I that is further exacerbated by the addition of nitrous oxide,[65] although nitrous oxide itself seems to have little effect on ATP production.[66]

Local anesthetics also depress bioenergetic capacity and disrupt oxidative phosphorylation[67–70] in a manner similar to that of the intravenous agents. Given these observations, it is tempting to speculate that reversible inhibition of mitochondrial electron transfer and decreased energy availability within neural tissues provide a unitary and simple hypothesis for the mechanism of anesthesia. However, the effect of any of these drugs on mitochondrial function or apparent bioenergetics may be incidental and does not necessarily explain their anesthetic actions. In addition, given the demonstrated ability of cells to "down-regulate" their metabolic activity under a variety of conditions,[71] ATP levels do not provide a sensitive measure of the energy state of an intact cell or of its capacity for oxidative phosphorylation. In fact, much of the available data regarding *in vivo* ATP levels in various tissues at clinically relevant concentrations of inhalational agents[72–74] suggests that there is no consistent change. Consequently, the most recent concepts regarding the underlying mechanism of general anesthesia emphasize the complexity, rather than the simplicity, of anesthetic effects and the high probability that there are multiple effect sites for anesthetics, probably involving transmembrane receptor protein structures.[75]

Similarly, propofol-induced depression of myocardial bioenergetics at low clinical concentrations is not sufficient to account for observed alterations of contractile function.[76] Although earlier work proposed that impaired bioenergetics might be a primary factor in anesthetic-induced depression of myocardial function,[77] the depression seen with inhalational agents seems to be due to the consequences of impaired calcium utilization on excitation–contraction coupling rather than to inadequate myocardial energy availability.[78] Although anesthetics therefore probably do not exert their obvious clinical effects through limitation of ATP availability, they may interfere with ATP utilization, produce oxidative stress, or impair mitochondrial function in some other manner.

In isolated individual neurons, 5 min of exposure to lidocaine at clinically relevant concentrations initiates an MPT and complete loss of mitochondrial membrane electrochemical potential.[79] Subsequently, there is release of mitochondrial cytochrome *c* into the cytoplasm and activation of caspases. This suggests that even simple exposure of nerve cells to local anesthetics may be sufficient to trigger apoptotic pathways. The myocardial toxicity of bupivacaine seems to be similarly mediated by a mechanism involving mitochondrial bioenergetics.[80] It has been proposed that anesthetics impair the ability of the mitochondrion to function as a "biosensor" for oxidative stress, disrupting the normal balance between ROS and endogenous antioxidants or antiapoptotic molecules.[81]

Whatever their relative importance to the production of the anesthetic state, the effects of anesthetics on mitochondria described above largely occur on the inner

membrane of mitochondria. Therefore, they seem to reflect the physicochemical actions of anesthetics[82,83] on the lipid or protein components of mitochondrial membranes.[84,85] In general, it seems a reasonable working hypothesis that drugs with anesthetic properties influence bioenergetic activity through disruption of mitochondrial membrane structure,[86] either by diffuse, or perhaps by highly specific, effects at lipid or protein sites.[87] A strong correlation between their anesthetic potency and affinity for cytochrome *c* oxidase (ETC complex IV) suggests that it may be a discrete target site for local anesthetics.[88] The consistent relation between inhibition of complex IV and the octanol–water partition coefficient of local anesthetics[89] also suggests that lipophilic interactions may produce reversible, short-term distortion or perturbation of essential ETC components. Reversible depression of oxidative phosphorylation in mammals has recently been shown to be initiated by molecules as simple as hydrogen sulfide.[90]

Mitochondria and the Response to Anesthetics

Manipulation of the nuclear genome of nematodes has shown a direct link between the composition of mitochondrial proteins and anesthetic requirement.[91,92] A defect in a subunit of complex I of the ETC is associated with depressed mitochondrial bioenergetics and hypersensitivity to volatile anesthetics.[93,94] In addition, there seems to be a clear, albeit empirical, correlation between increasing age and declining anesthetic requirement in humans from mid-adulthood through senescence,[95] a time period during which bioenergetics also seem to be progressively depressed.[96] Finally, and most recently documented, is the increased sensitivity to inhalational anesthesia seen in children who have depressed mitochondrial bioenergetics due to inherited mitochondrial cytopathies.[97] These observations hint at a fundamental but still undefined relation between anesthetic requirement and mitochondrial function within the nervous system.

N-methyl-D-aspartate antagonism or γ-aminobutyric acid receptor stimulation can initiate neuronal apoptosis, at least in immature brain tissue.[98] This seems to provide a physiologic mechanism to facilitate brain development or to cull redundant or failing neurons and provide neuroplasticity. The process may become pathologic when immature or minimally stressed neurons are exposed to drugs such as anesthetic agents, which generally have *N*-methyl-D-aspartate antagonist or γ-aminobutyric acid mimetic properties. In fact, widespread nonphysiologic apoptosis and neurodegeneration have been observed in laboratory rodent fetal brains after short-term anesthetic exposure[99] as well as in adult brain after prolonged exposure to nitrous oxide.[100] Even in mature brain, the transition of immature cells into more highly differentiated neurons with the complex synaptic structure needed for learning could be compromised by routine anesthetic exposure. This hypothesis is supported by recent investigations demonstrating that cognitive deficits persist in aged, but not in young adult, laboratory rodents after routine inhalational anesthesia.[101,102] Exposure to anesthetic agents also measurably depresses mitochondrial bioenergetics in peripheral T lymphocytes, possibly contributing to impairment of perioperative immune competence.[103]

Some preliminary clinical data could also be interpreted to support the hypothesis that anesthetics have intrinsic potential neurotoxicity. In elderly surgical patients, for example, deeper levels of inhalational anesthesia are associated with more severe early postoperative cognitive impairment as well as with a significantly decreased probability of postoperative survival.[104,105] This suggests that in individuals with limited nervous system reserve or impaired tolerance for oxidative stress, prolonged exposure, or higher anesthetic concentrations could be, in effect, neurotoxic.[106] Anesthetic exposure may increase mitochondrial ROS sufficiently in some individuals to damage cells through a lipid peroxidation pathway.[107] Therefore, it is possible that both the desired clinical effects of anesthetics as well as their potential to injure neurons may reflect their interaction with mitochondria, although there is obviously need for caution before extrapolating from laboratory observations to clinical practice.[108]

Implications for Perioperative Medicine

The scope of human disease attributable to inherited, acutely acquired, or insidious impairment of mitochondrial function is clearly far greater than had been previously believed.[109,110] Given the universal role of mitochondrial bioenergetics in sustaining the normal function of cells in every tissue and organ, mitochondrial cytopathy or short-term mitochondrial dysfunction can potentially produce virtually any symptom, in any organ system, at any stage of life. Many presumably unique "diseases" may actually be expressions of progressive organ system dysfunction due to disordered oxidative metabolism or disruption of other aspects of mitochondrial function. In fact, with more than a hundred mtDNA mutations implicated in human disease,[111] mitochondrial dysfunction is emerging as a primary focus for investigations into the etiology of sepsis, neurodegenerative disorders, diabetes, cardiovascular disease, and various forms of hepatic and metabolic derangement.[112] Anesthesiologists are therefore in a unique position to observe and to explore the relevance of congenital and acquired cytopathies to perioperative patient care.

Patients with Mitochondrial Cytopathy

The terms mitochondrial myopathy, inherited mitochondrial encephalomyopathy, and mitochondrial cytopathy are generally equivalent. Clinically, they encompass a wide variety of neurologic syndromes, most described only within the past three decades, that are due to errors in the synthesis of mitochondrial proteins caused by defects in nDNA, mtDNA, or mitochondrial transfer RNA (appendix 1). Symptoms generally reflect inadequate oxidative phosphorylation, usually first apparent in skeletal muscle or in the retina or other parts of the nervous system with high energy requirements.[113,114] In addition, inherited or acquired respiratory chain enzymatic deficiencies degrade the efficiency of oxidative phosphorylation and can result in excessive levels of ROS.[115] Subclinical hepatic and renal involvement is common, but the diagnosis of a mitochondrial-based respiratory chain deficiency is often not considered unless associated with evidence of skeletal muscle weakness or encephalopathy.

The phenotypic variability of inherited mitochondrial cytopathies reflects the uneven distribution of mutant mtDNA to different tissues during the early phases of embryogenesis.[116] Consequently, even when a defined mtDNA mutation is involved, patients with mitochondrial disorders may present with a wide variety of symptoms, many of them extremely vague or subtle. Mitochondrial cytopathy should be included in the differential diagnosis whenever persistent clinical signs and symptoms include muscle pain in conjunction with weakness or fatigue[117] or if there is diffuse involvement of several organ systems that does not conform to an established pattern of conventional disease.[114]

Because mitochondrial cytopathies involve enzymatic defects that lead to organ dysfunction through impaired oxidative phosphorylation, lactic acidosis and abnormalities in glucose metabolism are common sequelae. The diagnostic algorithm for suspected mitochondrial cytopathy investigations therefore should include screening for measurement of serum and spinal fluid lactate and increased lactate/pyruvate as well as ketone body molar ratios. For pediatric patients, the diagnostic process includes both blood and urine testing, although normal lactate and glucose values do not necessarily rule out the diagnosis of mitochondrial disease. When the index of suspicion for mitochondrial cytopathy is very high in children or in adults, skeletal muscle biopsy can confirm the diagnosis if it reveals the characteristic ragged-red fibers on trichrome stain, which are caused by accumulations of defective mitochondria beneath the sarcolemmal membrane, excess glycogen granules, and cytochrome *c* oxidase (complex IV) deficient cells.[118]

Biopsy of muscle or skin can also provide material for mtDNA analysis and facilitate genetic counseling. Syndromes caused by inherited mtDNA point deletions or insertions such as Leber hereditary optic neuropathy or NARP (neuropathy, ataxia, retinitis pigmentosa) can be detected by a polymerase chain reaction blood test and are generally maternally inherited.[119] Similarly, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, myoclonus epilepsy and ragged-red fibers, and maternally inherited disorder with adult-onset myopathy and cardiomyopathy, each of which is the consequence of a single transfer RNA missense mutation, also follow maternal inheritance patterns.[120] However, Pearson[121] and Kearns-Sayre[122] syndromes, both produced by a single mtDNA base pair deletion or insertion, have sporadic inheritance patterns.[123] Large-scale mtDNA deletions are usually acquired, not inherited, defects.[124]

Mutations of nDNA that produce unstable mtDNA can produce mitochondrial cytopathy syndromes that are clinically indistinguishable from those associated with classic mtDNA mutations.[125,126] One example is an inherited defect in the nuclear gene that encodes for the mitochondrial transcription factor, producing an inevitably fatal mtDNA deficiency syndrome of infancy.[127] mtDNA depletion syndrome is a severe disease of childhood characterized by liver failure and neurologic abnormalities due to tissue-specific loss of functional mtDNA. This syndrome is thought to be caused by a putative nuclear gene that controls mtDNA replication or stability.[128] Similarly, children with mitochondrial neurogastrointestinal encephalomyopathy may have multiple mtDNA deletions and/or mtDNA depletion that results from an nDNA mutation.[129] Regardless of etiology, however, mitochondrial cytopathies of infancy invariably compromise the developing nervous system and are therefore diagnosed early because symptoms are severe and progress rapidly. Nonspecific neurologic signs include lethargy, irritability, hyperactivity, and poor feeding.

Other variants of inherited cytopathy present later in childhood or even in the young and middle adult years. In these syndromes, subclinical decreases in cardiac, skeletal muscle, and nervous system functional reserve probably begin long before the appearance of overt signs or symptoms. Therefore, preoperative assessment of organ system functional reserve such as maximal oxygen uptake is more useful than routine preoperative "screening" tests in defining the extent to which declining mitochondrial energy production has produced clinical compromise. Patients may ultimately be diagnosed during the evaluation of unexplained muscle weakness, ventilatory failure,[130] or even upper airway obstruction.[131] Deterioration is gradual but progressive and inevitably leads to incapacitation. Some mtDNA mutations accumulate over time in a single tissue type (*e.g.*, skeletal muscle) where clinical deterioration during adulthood correlates with an increasing fraction of mutant mtDNA.[132] In fact, in patients with skeletal muscle

mtDNA mutations, the "mutation load" determines the extent of metabolic impairment and therefore the degree of exercise intolerance as indicated clinically by a reduced rate of muscle oxygen extraction in the face of exaggerated cardiopulmonary responses.[133] Measurement of venous oxygen partial pressure during forearm exercise may therefore be of value, at least in adults, to assess the severity of aerobic compromise due to mitochondrial dysfunction.[134] Nevertheless, the true incidence of these later-onset syndromes is unclear because of their insidious onset and the diversity of organ systems involved.[135,136]

Perioperative Management

For both childhood- and adult-onset cytopathies, the general principles of perioperative medical management are comprehensive interdisciplinary consultation and the expectation of a need for supportive care to avoid metabolic acidosis or ventilatory and circulatory insufficiency. Informing these patients and their families that they are at increased risk of adverse outcome is an important part of the preoperative evaluation. Many neurologists recommend nutritional supplementation with vitamins or other purported antioxidants as well as treatment with various cofactors needed for oxidative metabolism (appendix 2), although, except for coenzyme Q,[137] there is a paucity of data supporting their therapeutic value. Patients with mitochondrial cytopathy are usually conditioned not to fast for long durations and to eat small, frequent meals, a routine that conflicts with typical perioperative fasting guidelines. To avoid metabolic crisis, therefore, especially in children, an intravenous infusion of glucose should be initiated preoperatively. Choice of fluids may also be important intraoperatively, most anesthesiologists choosing to avoid the lactate load intrinsic to Ringer's solution. Monitoring and controlling blood glucose, body temperature, and acid–base values within normal limits is crucial perioperatively, and as with any anesthetic, electrocardiogram, blood pressure, pulse oximetry, temperature, and exhaled gas concentrations should be continuously monitored. In addition, arterial catheterization should be considered to facilitate frequent sampling for blood glucose, arterial blood gases, and serum lactate levels.

Other unique concerns regarding the design of an anesthetic plan for these patients include the pharmacodynamic implications of mitochondrial cytopathy such as decreased anesthetic requirement[97] and susceptibility to prolonged drug-induced nervous system depression because of impaired neuronal bioenergetics, as well as intrinsic skeletal muscle hypotonia and cardiomyopathy[138] with increased risk of sudden death from conduction abnormalities.[139] Bulbar muscle weakness may predispose to aspiration of gastric contents, suggesting the need for "full stomach" precautions. Skeletal muscle weakness may compromise postoperative ventilation, especially after upper abdominal or thoracic surgery.[140] Subclinical erosion of hepatorenal reserve may alter clinical pharmacokinetics for intravenous drugs and predispose to delayed recovery from anesthetic agents, muscle relaxants, and opioids.[141]

Susceptibility to malignant hyperthermia or myasthenia-like sensitivity to neuromuscular blockade are issues typically considered for patients with the more familiar muscular dystrophies and neurogenic myopathies. There is a case report that describes increased sensitivity to nondepolarizing blockade in a patient with mitochondrial myopathy,[142] but this observation has not been confirmed for most forms of inherited mitochondrial cytopathy.[143,144] Although there is understandable caution, especially in children, regarding the use of halogenated inhalational anesthetics,[145] only the very rare mitochondrial myopathies with "multicore" or "minicore" histology seem to warrant concerns of an increased risk of malignant hyperthermia.[146] Therefore, at least at the present time, there is inadequate data to support the recommendation of some authors that the anesthetic plan for patients with mitochondrial disease should routinely include malignant hyperthermia precautions.[147,148]

The residual effects of nondepolarizing agents in these patients, who commonly have compromised hepatic and renal function, may further exacerbate their intrinsic muscle weakness and increase the risk of ventilatory failure postoperatively. In addition, anesthetic techniques requiring spontaneous ventilation may predispose to intraoperative metabolic exhaustion and airway obstruction and therefore should probably be avoided. Tracheal intubation with positive-pressure ventilation will prevent intraoperative ventilatory failure, but the anesthesiologist must decide whether the patient should be extubated immediately after surgery or remain intubated and receive prolonged recovery in an intensive care unit.[149]

Although individual patients with inherited mitochondrial encephalomyopathies have been exposed to many different general anesthetic regimens without apparent adverse consequences,[150–153] it remains unclear whether there is a "safe" or "best" anesthetic plan for these patients. There are few reports that describe the anesthetic treatment of adult-onset or acquired mitochondrial encephalomyopathy[154] and only one, for example, dealing with NARP syndrome.[155] Clinical reports often suggest only that patients with mitochondrial disorders "do well" with regional anesthetics despite the facts that these agents, like those used for general anesthesia, are known to disrupt mitochondrial function and bioenergetics. Specialized textbooks offer some further detail regarding preoperative assessment and anesthetic management of patients with mitochondrial cytopathies.[156]

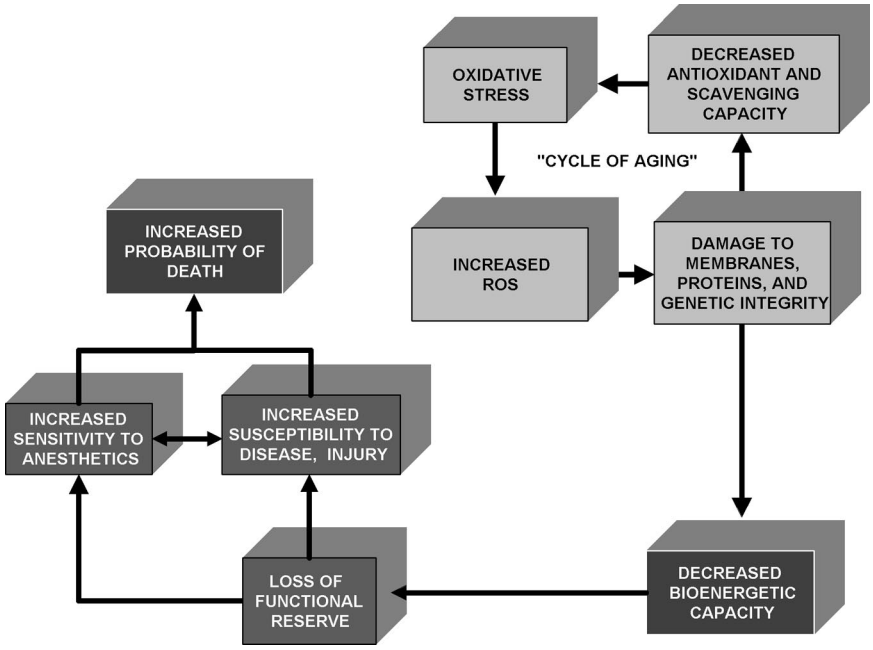

Fig. 3. Reactive oxygen species (ROS) are continually generated as byproducts of oxidative metabolism. A self-perpetuating, physiologic "cycle of aging" has been proposed[96,180] in which oxidative stress within mitochondria slowly degrades the components needed for energy production and self-repair of damage done by ROS. The resulting decrease in bioenergetic capacity could eventually compromise organ system functional reserve and predispose to increased probability of adverse perioperative outcome.

Elderly Surgical Patients

Age-related decline in organ system functional reserve is subtle but progressive during the middle adult years. It eventually becomes clearly apparent, even in the most fit older subjects, during the later years of geriatric senescence. Because functional reserve provides the "safety margin" needed to meet the additional cellular and bioenergetic demands imposed by trauma or disease and by surgery, healing, and convalescence, inadequate reserve contributes substantially to perioperative morbidity and mortality in older surgical patients.[95] Significant limitations in the availability of energy derived from oxidative phosphorylation would impact normal physiologic function and the capacity for physical activity and also compromise the energy supply needed for maintenance of normal tissue structure and cell microarchitecture.[157] It is now generally appreciated that disruption of oxidative phosphorylation is intrinsically involved in the age-related decline of organ function and functional reserve,[158,159] although the precise mechanism remains elusive.[160]

Many observations are consistent with the hypothesis that failing bioenergetic capacity is central to, if not the cause of, human aging. Acquired mtDNA mutations accumulate at a rate that is a thousandfold greater than that of acquired nDNA mutations.[161] This may reflect greater exposure of mtDNA to mutagenic factors, more effective endogenous nDNA repair mechanisms, or the diploid nature of nDNA itself. Whatever the cause, the prevalence of mutagenic mtDNA lesions increases exponentially during late adulthood and senescence,[162,163] primarily in brain,[164] skeletal muscle,[165,166] and heart,[167,168] where defects accumulate more extensively than in rapidly dividing tissues.[169] It is less clear whether increased ROS levels in the cytosol of a cell can damage nDNA and disrupt synthesis of bioenergetic proteins encoded in the nuclear genome.[170] The age-related increase in mtDNA defects is also coincident with decrements of cytochrome *c* oxidase activity,[171] although the overall decline in skeletal muscle bioenergetic capacity seen in older adults is largely due to reduced general physical activity and not simply to loss of functional mtDNA.[172,173]

However, any loss of functional mtDNA may itself increase oxidative stress[174,175] and further predispose to oxidative damage of the polypeptides of the respiratory complex.[176] Coincident age-related decline in the effectiveness of ROS scavenging[177,178] or age-related compromise of endogenous mtDNA repair systems such as the base excision repair pathway may further accelerate the adverse consequences of accumulated oxidative stress.[179,180] Data supporting the possibility of a self-perpetuating cycle of impaired or inefficient mitochondrial bioenergetics and a coincident increase in ROS has recently been presented in insect studies.[181] Dysfunction of ETC complex I, which is a rate-limiting component of aerobic respiration, affects the entire process of oxidative phosphorylation, further decreasing the efficiency of electron transfer and increasing levels of ROS, especially superoxide. A similar process could occur in the aging mammalian cell (fig. 3). Given the high energy requirements of neural tissue, it is likely that neuronal bioenergetics, in particular, decline significantly with increasing age and may eventually provide biomarkers for physiologic aging.[182]

Study of the genetic factors determining human longevity suggest that inheritable factors determine approximately one quarter of the observed variability in life expectancy,[183] and the importance of mtDNA in this relation is becoming clearer.[184] At least in subprimates,

there are recent data that seem to support the concept that genetic alterations that increase susceptibility to damage by oxidative stress are primarily responsible for increased frailty[185] and reduced lifespan.[186] For example, genetically altered mice that express a proof-reading deficient version of mtDNA polymerase develop into a young adult mouse phenotype with a threefold to fivefold increase in mtDNA point mutations and increased mtDNA deletions.[187] In these mice, the increased number of somatic mtDNA mutations is also associated with phenotypic stigmata of aging such as reduced subcutaneous fat, hair loss, and osteoporosis during young adulthood. It is not yet clear whether this mutant phenotype simply mimics aging rather than prematurely expressing genuine manifestations of physiologic aging, but these mice also have a significantly reduced lifespan.

The extent to which aging and perhaps age-related pathophysiology may reflect impaired mitochondrial bioenergetics and accumulated oxidative stress is only now becoming fully apparent.[188] Tangential support for this concept comes from observations that reduced calorie intake increases lifespan in some laboratory animals, presumably by reducing accumulated oxidative damage[18] or by decreasing the rate, or increasing the efficiency, of oxidative phosphorylation,[189] although life extension through caloric restriction is not a consistent observation.[190] An effective antiaging therapy based on antioxidant effects has yet to be demonstrated,[191,192] and genetically manipulated overexpression of superoxide dismutase and catalase actually reduces, rather than prolongs, lifespan in transgenic *Drosophila*.[193] It has also not yet been shown that genetic manipulation of intrinsic mtDNA repair and replication mechanisms will produce animals with decreased mtDNA mutation rates and increased longevity, although there is evidence of less mitochondrial oxidative stress in long-lived than in short-lived mammalian species.[194] Some investigators simply remain unconvinced that there is compelling proof of a significant decline in electron transport or oxidative phosphorylation during normal aging.[195]

Patients with Neurodegenerative Disorders

Because the nervous system has adequate functional redundancy and structural plasticity, aging does not seem to degrade day-to-day neurologic or cognitive function. In addition, the degenerative effects of prolonged oxidative stress in neurons may be ameliorated by effective scavenging of ROS,[196] accelerated mtDNA repair, increased production of Bcl-2 protein or other apoptosis-inhibiting substances, generation of neurotrophic factors, and mobilization of neural stem cells to replace damaged neurons.[197] Nevertheless, inadequate mitochondrial energy production and cumulative oxidative stress leading to apoptosis may also explain many of the stigmata of age-related neurodegeneration and some neurologic diseases.[198–201]

Presbyacusis, the hearing loss that inevitably occurs in old age, has been shown to be a consequence of the progressive deterioration of cochlear mtDNA.[202] Interestingly, a specific mtDNA point mutation has been shown definitively to predispose patients to sensorineural hearing loss after aminoglycoside antibiotic exposure.[203] In general, mtDNA mutations are thought to contribute to or predispose patients to the development of many common neurodegenerative disorders, although they rarely display the same inheritance characteristics as classic inherited mitochondrial cytopathies described previously. Parkinsonism, caused by selective inhibition of complex I of the ETC, critically compromises energy availability and leads to apoptosis and death of the dopaminergic cells in the substantia nigra.[204] Although a greater fraction of mtDNA is defective in parkinsonian patients than in age-matched controls, there does not seem to be a consistent mtDNA mutation. This suggests that defects in nDNA that lead to dysfunctional complex I bioenergetics, rather than mtDNA mutations, may hold the key to explaining this disorder. Similarly, patients with Alzheimer dementia exhibit higher-than-normal rates of mtDNA mutation, but mtDNA defects are neither consistent nor invariable findings.[205] Friedrich ataxia is a consequence of ROS-mediated damage to the respiratory chain initiated by an nDNA mutation that eventually compromises mitochondrial iron homeostasis.[111] Therapy with antioxidants and coenzyme Q may improve mitochondrial function in patients with Friedrich ataxia and slow the progression of symptoms.[137]

Neuronal excitotoxicity is a major cause of neuronal death. Excitotoxicity represents a state of greatly increased neuronal electrical and metabolic activity that produces oxidative stress. Even when many neurons are initially destroyed by primary necrosis after traumatic brain injury, excitotoxicity contributes to the additional neuronal damage that follows such an event.[206] During an excitotoxic event, the intrinsic neuronal mechanisms that scavenge ROS and repair ROS-induced damage are quickly overwhelmed.[207] High levels of excitatory neurotransmitters such as glutamate also interact with cell-surface *N*-methyl-D-aspartate receptors (fig. 2) to generate excess calcium within mitochondria. Loss of calcium homeostasis induces an MPT, collapsing the hydrogen ion gradient and releasing of cytochrome *c* and other proapoptotic proteins from mitochondria into the cytosol. The culmination of this sequence is apoptosis and neuronal death.

Recent work suggests that genetic mutations predisposing patients to Alzheimer dementia also make neurons susceptible to excitotoxic apoptosis after exposure to certain inhalational anesthetics. Isoflurane, for example, has been shown to induce cytotoxicity in primary cortical neurons under these circumstances.[208] The pro-

posed mechanism, again, is an influx of ionized calcium from the endoplasmic reticulum into the cytosol, but another potential trigger of neuronal apoptosis is zinc. Elemental zinc is highly concentrated in neurons. Zinc release from damaged cells, even in nanomolar quantities, during traumatic or ischemic brain injury or in Alzheimer dementia or parkinsonism, can cause apoptosis in neighboring neurons and increase the extent of neurologic damage.[209]

Similarly, the high levels of ROS that define oxidative stress may also produce secondary neuronal damage beyond the area of initial injury after traumatic brain injury. Endogenous nitric oxide can combine with superoxide to form lipid-destructive peroxynitrite. Lipid peroxidation by peroxynitrite can damage mitochondria and the cellular microarchitecture directly, leading to apoptosis and cell death.[210] In addition, oxidized lipoproteins can be taken up by neighboring neurons, generating a penumbra, or expanded zone, of neuronal injury.[20] Limiting oxidative stress by maintaining normoxia during cardiopulmonary resuscitation, as opposed to imposing hyperoxia, has, in fact, been shown to cause less brain lipid peroxidation and improve neurologic outcome, at least in the laboratory.[211] Increased nitric oxide and peroxynitrite with glutamate-mediated activation of nitric oxide synthase has been proposed as a mechanism for neurodegenerative disorders as well.[212] Older individuals have been shown to be at increased risk of damage from membrane peroxidation under conditions of oxidative or nitrosative stress,[213] perhaps explaining, at least in part, the relation between acquired neurodegenerative disorders and age.[214]

Caspase-mediated apoptosis is a complex biochemical cascade that requires ATP. Fatally compromised cells, especially those that have undergone a bioenergetic catastrophe, may not be able to produce ATP in amounts adequate to support apoptosis. These neurons may instead undergo passive, or primary, necrosis.[215] Unlike apoptosis, where cell loss is contained and tissue injury relatively controlled, necrosis of neurons leads to mitochondrial swelling, cell lysis, and fragmentation and the diffuse release of proinflammatory substances that invoke a vigorous immune response.[216] The interaction between the aging immune system and necrotic neurons may explain the amyloid deposits seen in Alzheimer dementia.[217] The progressive age-related decline in the specificity of the immune system[218] and failure to clearly distinguish between "self" and "nonself" may therefore play an important role not only in infection, neoplasm, and autoimmune disorders but also in age-related neurodegenerative disease. Complex interactions between neuronal mitochondrial dysfunction and the mechanisms that control necrosis and apoptosis are now also suspected in playing a key role in amyotrophic lateral sclerosis, hepatolenticular degeneration, and perhaps many other neurodegenerative phenomena.[219]

Patients with Cardiovascular Disease

Cardiac mitochondria are essential to myocardial energy production and myocyte homeostasis and also impact cardiac myocyte viability through their role as oxidative biosensors. Cardiac myocytes, skeletal muscle fibers, and other long-lived postmitotic cells show dramatic age-related alterations in the morphology of their mitochondria, with a generalized loss of mitochondrial volume and numbers.[220] There seems to be an increase in oxidative stress in aging cardiac myocytes, especially with coincident atherosclerotic disease,[221] and antioxidants such as coenzyme Q may provide some protection against oxidative stress in senescence.[222] In fact, many drugs used to treat myocardial ischemia seem to exert their cardioprotective effects *via* their actions on cardiac mitochondrial function.[223] Angiotensin-converting enzyme inhibitors have been shown to contribute to enhancement of antioxidant defenses. Some of the beneficial effects associated with inhibition of the renin–angiotensin system may therefore be due to the ability of enalapril and losartan to attenuate oxidative damage to mitochondria.[224] Angiotensin-converting enzyme inhibitors may also facilitate vascular remodeling.[225]

Chronic hypoxia produces a loss of mitochondrial bioenergetic capacity in the left ventricular myocardium despite increases in myocardial mass.[226] Accumulating evidence also suggests that ROS play an important role in the development and progression of other forms of heart failure[227] as well as in acute contractile dysfunction after myocardial infarction.[228] In addition to their direct detrimental effects on cellular metabolic function, ROS have been implicated in the development of agonist-induced cardiac hypertrophy, cardiac myocyte apoptosis, and the subsequent remodeling of the failing myocardium. These restorative alterations are driven by metabolically sensitive gene expression, and in this way, ROS may act as potent intracellular second messengers.[228] Therefore, the effects of increasing myocardial ROS seem to be either beneficial or harmful, depending on site, source, and amount of ROS produced, and the overall metabolic status of the myocyte.

Oxidative stress seems to contribute to the pathology of vascular disease in stroke, hypertension, and diabetes.[229] Observations that mitochondrial function is disturbed in the skeletal muscle of patients with occlusive vascular disease[230] further supports the concept that mitochondrial processes are involved in the etiology of vascular diseases. Nuclear magnetic resonance spectroscopy has shown a 40% reduction of *in vivo* muscle glucose metabolism in insulin-resistant older adults,[231] although it is not yet established that this is part of the fundamental pathophysiology of diabetic vascular pathology. This form of insulin resistance may actually reflect an inherited mitochondrial defect altering fatty acid metabolism.[232] Taken together, however, these ob-

servations regarding the etiology and treatment of cardiovascular disease suggest that the role of mitochondrial dysfunction will assume progressively greater importance as the molecular mechanisms involved in ischemic cardiovascular disease are more completely understood.

Patients with Sepsis

Sepsis, the systemic inflammatory response syndrome, and multiple organ dysfunction syndrome are the leading causes of morbidity and mortality in critically ill surgical patients. Acute-onset cardiovascular, hepatic, and renal insufficiency and failure are common features of these syndromes. Inadequate delivery of oxygen to the mitochondria of affected tissues is a possible explanation for tissue or organ dysfunction under these circumstances, but measures that increase cardiac output or tissue perfusion in septic patients have not been of value in improving outcome.[233] It is now clear that impaired bioenergetic capacity plays an important role in explaining the diffuse and persistent cellular and organ dysfunction that occurs under these circumstances. The concept of "cytopathic hypoxia" proposes that, during sepsis, many cells become unable to use readily available molecular oxygen to produce ATP,[234] explaining inconsistencies in reported data regarding cellular ATP levels during sepsis. Even with impaired bioenergetic capacity, ATP levels would remain relatively unchanged if there is a parallel reduction both in ATP supply and ATP demand in a hypoxic environment.

There is experimental support for the concept of mitochondrial-based cytopathic hypoxia as a primary factor in sepsis. Data from cardiac myocytes confirm that the mitochondria can act as a modulating biosensor for oxidative phosphorylation, which can send poorly perfused or hypoxic tissues into what is, in effect, a hibernation-like state.[235] The mechanism remains unclear, but it could include uncoupling of ATP production from aerobic metabolism or inhibition of any or all of the five protein–enzyme complexes required for oxidative phosphorylation.[236] It may also reflect changes in ETC enzyme kinetics. Abnormalities in pH, temperature, or inhibitor-induced conformational changes in enzyme structure could also disrupt oxidative metabolism and explain the appearance of cytopathic hypoxia during sepsis. Myocardial cytochrome oxidase is reversibly inhibited early in sepsis but seems to become irreversibly inactivated during the later phase of sepsis.[237] Possible mediators of mitochondrial enzyme inhibition during sepsis include ROS, nitric oxide, peroxynitrite, and carbon monoxide. High levels of nitric oxide reversibly inhibit complex IV.[238]

Impaired functioning of any of the enzymes within the ETC is itself associated with decreased cardiac cytochrome oxidase subunit IV and complex II protein levels.[239] Recent evidence suggests that sepsis induces reduced expression of both of the genes that encode for glycolytic proteins and those needed for the protein components of the ETC.[240] The synthesis of messenger RNA could be disrupted by abnormalities of either nuclear or mitochondrial transcription, because the subunits of the five respiratory chain enzymes arise from both nDNA and mtDNA. Similarly, errors in protein synthesis due to faulty messenger RNA translation would compromise the electron transport chain and disrupt ATP production. In fact, the messenger RNA that encodes for cytochrome oxidase subunit I is decreased within myocardial cells as well as in macrophages during both sepsis and sepsis-related disorders.[241] Sepsis is also associated with increased expression of endogenous protective antiapoptotic proteins known as heat shock proteins (HSPs).[242,243] HSP synthesis can be induced by hypoxia, ROS, endotoxins, or cytokines, all of which are common in sepsis. HSPs may either reconfigure or isolate electron transport chain proteins that have been damaged by the mechanisms described above.[244] Failure to adequately express HSPs during sepsis or shock may be directly related to propagation of tissue injury and poor outcome,[245] although a recent clinical study suggests that glutamine-enhanced parenteral nutrition can restore HSPs to protective levels.[246]

Preconditioning and Organ Protection

Hormesis refers to a state of low-level chronic stress that presumably induces the expression of protective genes that increase host survival during physiologic extremes. Although the general phenomenon of stress-induced expression of genes that facilitate ROS scavenging and mtDNA repair is well established,[197] hormesis may be more easily initiated in some species or tissues than in others. Cold stress has been shown to prolong lifespan in *Caenorhabditis elegans*,[247] and heat stress significantly increases longevity of the fruit fly.[248] Brief periods of sublethal ischemia generates low-level oxidative stress that induces an adaptive form of metabolic self-protection, limiting the necrosis and tissue injury that would normally follow a subsequent ischemic injury. Hormesis seems to involve modulation of intracellular ion flux[249] to minimize the probability of initiating the MPT that can trigger apoptosis (see second paragraph under "Apoptosis"). This phenomenon, ischemic preconditioning (IPC), seems to be initiated largely by the receptor-triggered activation of multiple protein kinases.[250]

It is now also established that exposure to volatile anesthetics can generate a state of hormesis in mammalian tissues that mimics IPC and shares many triggers or modulators with IPC.[251] Even at subclinical concentra-

tions, previous exposure to halothane, isoflurane, sevoflurane, or desflurane[252,253] has been shown to provide prolonged neuroprotection. Anesthetic preconditioning (APC) has also been demonstrated in the myocardium, where previous exposure to isoflurane, desflurane, and sevoflurane confers protection *in vivo* against a subsequent ischemic injury.[254–256] Although the mechanisms may very somewhat, mitochondrial bioenergetics seem to be significantly affected by all these agents.[257] After isoflurane exposure, excess ROS are generated at complex III of the ETC and seem to trigger APC.[258] Sevoflurane, on the other hand, attenuates complex I but also leads to increased ROS production.[259] Therefore, endogenous oxidative stress seems to be a trigger for APC, a concept supported by the observation that molecular species that scavenge ROS block the APC effect.[260] Nitrous oxide does not produce APC, but neither does it block nor alter the APC phenomenon associated with the potent inhalational agents.[261]

Although the full mechanism of APC is not yet fully understood, it may, like IPC, involve multiple G protein–coupled receptor triggers that activate protein kinases.[262] APC and IPC also seem to have many other common essential steps, including modulation of ATP-sensitive potassium channels. ATP-sensitive potassium channels are essential for normal endovascular function and responsiveness to vasodilators, and they have also been shown to be important biosensors for excitotoxicity.[263] They seem to limit ischemic injury both in neurons[264] and in cardiac muscle.[265] Opening of myocardial mitochondrial ATP-sensitive potassium channels may also be an intrinsic step in APC after exposure to inhalational anesthetics[266] or, as recently demonstrated, in response to δ-opioid receptor agonists.[267]

Genomic analysis suggests that IPC and APC each reflect a unique pattern of induced gene expression for the synthesis of proapoptotic and antiapoptotic proteins.[268] APC, if not IPC, may involve inducible nitric oxide synthase in neurons,[252] whereas a delayed form of APC seen in the myocardium requires induction of endothelial nitric oxide synthase.[269] It remains unclear how many patterns of protective gene expression are possible, but isoflurane pretreatment may also protect cardiac myocytes against apoptosis by increasing the expression of the antiapoptotic protein Bcl-2.[270] In addition, it may be possible to use the protective effect of inhalational anesthetics even after severe oxidative stress has occurred. A recent study demonstrated a significant "postconditioning" effect for isoflurane in cardiac muscle, largely through the inhibition of MPTs during the reperfusion of injured cells.[271] Using inhalational anesthetics or G protein–coupled receptor agonists to protect organs that have been, or may subsequently be, exposed to an ischemic or hypoxic event is an attractive prophylactic and therapeutic option.[272] However, the practicality and the clinical effectiveness of APC still remain to be established.[273]

In mammals, brief, sublethal periods of ischemia and hypoxia also induce the expression of HSPs and block the AIF-mediated apoptotic pathway. Adenovirus-mediated gene therapy has been shown to increase HSP expression and reduce mortality from experimentally induced, sepsis-related pulmonary injury.[274] The prophylactic use of artificial liposomes and nonviral transfection to deliver HSP or to provide either the DNA or messenger RNA[275] needed to enhance the synthesis of HSP in neurons or cardiac myocytes is another promising concept that may provide organ protection perioperatively without the need for anesthetic exposure.[276] Transfection can quickly increase HSP in patients at risk for ischemic or traumatic brain injury, perhaps through an effect on the ATP-sensitive potassium channels in the cerebral vasculature.[277] Other approaches to minimizing cellular injury during periods of oxidative stress or postinjury reperfusion include enhancement of endogenous expression of cytoprotective antioxidants.[278] Resveratrol, found in grape skin and in red wine, demonstrably reduces the ischemic damage associated with myocardial and brain reperfusion injury.[279] At least some of the cytoprotective effect of this substance is due to increased expression of heme oxygenase (HO), the enzyme that accelerates destruction of heme, a pro-oxidant that accumulates rapidly after ischemia and oxidative stress.[280] HO-deficient diabetic mice have an increased risk of ischemic injury compared with wild-type diabetic mice, suggesting that reduced expression of HO in response to oxidative stress may play a role in the etiology of diabetes-related sequelae.[281]

Heme oxygenase pathways may be essential to several other forms of cellular adaptation to stress. Inhalational anesthetic exposure in hepatocytes induces expression of an HO isoform through a pathway that, like APC in heart and brain, involves protein kinases.[282] Increased endothelial HO activity due to up-regulation during oxidative stress is further potentiated by the interaction of thiols with nitric oxide,[283] which suggests that HO gene expression may also protect against nitric oxide–related, or nitrosative, stress.[284] Carbon monoxide, generated by HO as a heme breakdown product, may also act as a signaling mediator of hypoxic stress. It has been shown to provide protection from anoxic injury in nematodes by inducing a state of suspended animation.[285] Transitional metal carbonyls which expedite the intracellular release of carbon monoxide could therefore have therapeutic value as cardioprotective agents.[286]

Intramitochondrial glutathione, normally approximately 15% of total cellular glutathione pool, is another endogenous antioxidant that seems to protect against ROS damage, and depletion of mitochondrial glutathione has been linked to apoptosis.[287] Similarly, melatonin is a significant scavenger of ROS and an antioxidant.[288] If administration

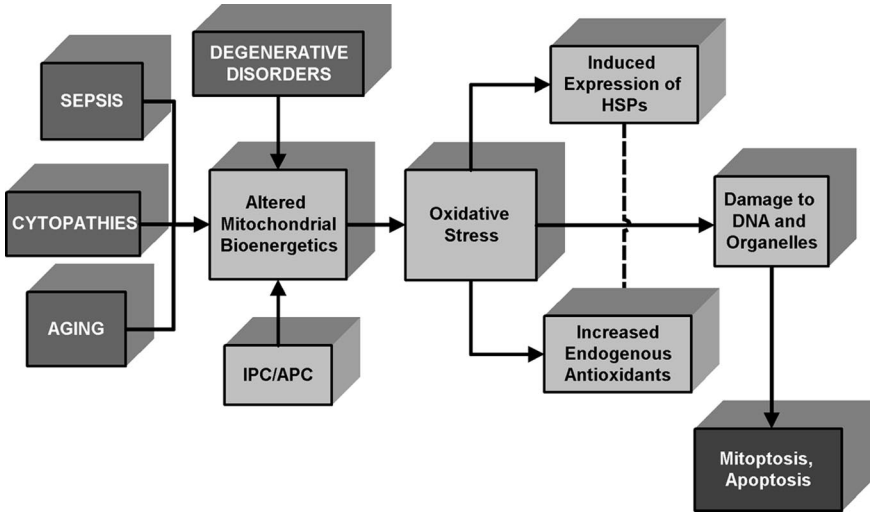

Fig. 4. Altered mitochondrial bioenergetics seems to be central to a variety of physiologic and pathophysiological states that share oxidative stress as a common characteristic. Despite the protective effects (*dashed lines*) of DNA repair mechanisms, endogenous antioxidants, and antiapoptotic substances such as heat shock proteins (HSPs), some of which may be further stimulated by ischemic or anesthetic preconditioning (IPC/APC), oxidative stress eventually disrupts the mitochondrion and triggers rapid mitochondrial and cellular self-destruction (mitoptosis and apoptosis).

of exogenous melatonin can decrease tissue damage and dysfunction related to oxidative stress,[289] it may be useful if given prophylactically for ischemic or reperfusion injury or to minimize the potential neurotoxicity of anesthetic exposure in patients with decreased neural reserve. Given recent interest and investigation into the role of anesthetic agents in causing postoperative cognitive dysfunction in older adults,[290,291] the clinical observation that melatonin reduces postoperative delirium in this surgical patient group[292] is particularly intriguing with regard to potential prevention of anesthesia-related cognitive impairment.

Summary and Future Directions

Advancements in our understanding of the role of the mitochondrion in generating and responding to oxidative stress have supplemented awareness of its pivotal function as a cell energy source. The central role of the mitochondrion as the final mediator of cell death makes it particularly important to evolving concepts of hypoxic tissue injury and protection as well as to our understanding of senescence and degenerative disease. These manifold mitochondrial functions generate many possible hypotheses that seem to link a wide range of phenomena that are of interest to anesthesiologists from both a clinical and a scientific perspective (fig. 4).

At the present time, it seems that all anesthetic agents are associated with measurable effects on some aspect of mitochondrial function, although causal relations are difficult to establish, and the primary effect of these drugs does not seem to reflect simple depression of bioenergetic activity. Much work remains to be done, but previously unrecognized effects of anesthetics on mitochondrial bioenergetics and apoptotic pathways suggest that they may have both cytoprotective and potentially neurotoxic actions, depending on clinical context. It is now also increasingly apparent that there are many subgroups of the surgical patient population that should be considered to be at increased risk perioperatively because of mitochondrial dysfunction, whether it is inherited, acquired, or a consequence of comorbid disease.

Future investigation might appropriately focus on the mitochondrion as the site of anesthetic action and mediator of anesthetic pharmacodynamics, as well as the likely source of potential anesthetic neurotoxicity. Other obvious areas in need of continuing investigation include establishing more precise guidelines for the perioperative treatment of surgical patients with inherited or acquired mitochondrial cytopathies, in all their many and varied manifestations, defining the full spectrum of mitochondrial pathways that contribute to tissue injury, and use of anesthetics to provide perioperative organ protection.

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Appendix 1: Clinical Characteristics of Inherited Mitochondrial Cytopathy

For large-scale mtDNA deletions: ataxia, peripheral neuropathy, muscle weakness, ophthalmoplegia, ptosis, pigmentary retinopathy, hypoparathyroidism, cardiomyopathy, cardiac conduction defects, sensorineural hearing loss, Fanconi syndrome, lactic acidosis, ragged-red fibers on muscle biopsy

For single mtDNA point mutation with mRNA abnormality: seizures, ataxia, psychomotor regression, dystonia, muscle weakness, pigmentary retinopathy, optic atrophy, cardiomyopathy, lactic acidosis, sensorineural hearing loss

For multiple mtDNA point mutations with mRNA abnormality: dystonia, optic atrophy, cardiac conduction defects

Appendix 2: Common Therapeutic Treatments and Supplements Used by Patients with Inherited Mitochondrial Cytopathy and Neurodegenerative Disorders

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