Interplay of Mitochondrial Biogenesis and Oxidative Stress in Heart Failure

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The dawn of mitochondrially powered cells began 1 to 2 billion years ago when an amitochondriate host subsumed α-proteobacterium, a hydrogen-producing symbiont.1 Equipped to oxidize nutrients, eukaryotic cells acquired a boost to cellular energy, enabling the emergence of multicellular mammals, sustained by a nearly inexhaustible muscular pump: the heart.

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In this issue of Circulation, Ahuja et al2 examine the interplay of mitochondrial biogenesis and oxidative stress in human cardiomyopathy. They reveal that disparate changes in mitochondrial biogenesis and mitochondrial oxidative stress distinguish between ICM and DCM.

Using a complement of ultrastructural, biochemical, and genetic analyses, Ahuja et al convincingly show that mitochondrial content is increased in dilated cardiomyopathic (DCM) hearts (n=8) but not ischemic cardiomyopathic (ICM) hearts (n=8). Regardless of the type of heart failure, oxidative phosphorylation (OXPHOS) was severely impaired, a finding universally reported by others. Given that mitochondrial content was increased ≈2-fold in DCM hearts, these data may imply better maintenance of total cellular OXPHOS in DCM hearts compared with ICM hearts. Because mitochondrial mass is influenced by proliferation (mitochondrial biogenesis) and clearance (mitophagy), the authors investigated the mechanistic basis for increased mitochondrial content in DCM hearts. Notably, PGC-1α (PPARGC1α), a potent regulator of mitochondrial biogenesis,3 and several target genes of PGC-1α were induced at the level of mRNA and protein in DCM hearts but not in ICM hearts. These genetic data replicate a previously reported study.4 Even so, this topic is not immune to controversy or the Proteus phenomenon; findings by others oppugn the conclusions of Ahuja et al. Using a mixed cohort, 1 study showed that PGC-1α, which promotes mitochondrial biogenesis, was reduced in both ICM and DCM hearts.5 Induction of adenine nucleotide translocator (SLC25A4), a gene with an induction that signifies mitochondrial biogenesis, was reported by Corral-Debrinski et al6 in ICM hearts (but not DCM hearts), implying that mitochondrial biogenesis is specific to ICM. Similar disparities are found throughout the literature, some of which are mentioned in the work by Ahuja et al. What then accounts for these differences? The obvious answer is that differences in patient demographics, classification, heart failure staging, or medical treatment could have influenced conclusions. Alternatively, the effect of cardiomyopathy on mitochondrial proliferation might depend on a variable that is independent of heart failure classification. To this end, Ahuja et al evaluated additional mitochondrial variables in cardiomyopathic hearts. Most notably, in DCM hearts, mutation of mitochondrial DNA, a sensor of oxidative stress within mitochondria, was increased ≈4-fold compared with nonfailing control hearts, whereas no significant difference was found between nonfailing hearts and ICM hearts.

Nearly a half-century ago, DNA was identified inside mitochondria.7,8 Using electron microscopy, fine fibrous (rod-like) structures were initially observed in the matrix of mitochondria from several organisms,7 including ameba9 and mouse oocyte mitochondria.10 Using an assortment of fixatives, fibers within mitochondria exhibited staining patterns consistent with DNA, and further studies using metabolic labeling confirmed the initial observations. Two decades after the discovery of mitochondrial DNA, Anderson et al11 sequenced the entire human mitochondrial DNA, revealing a circular genome of 16,569 bp that encodes 37 genes: 2 rRNA, 22 tRNAs, and 13 polypeptides. Unlike mitochondrial DNA of yeast or most prokaryotes, the genome of mammalian mitochondria proved highly compact with very little noncoding sequence, and its genetic code and tRNAs differed from the nucleus. Considering that there are 50 to several hundred mitochondria per cell and that each mitochondrion contains 5 to 10 genomes, a single cell contains several hundred to a few thousand mitochondrial genomes.12 In cooperation with nuclear encoded subunits, proteins encoded by mitochondrial DNA comprise the respiratory chain and ATP synthase, a multienzyme system critical for OXPHOS. A byproduct of respiration, reactive oxygen species are liberated by mitochondria, exposing mitochondrial DNA to constant oxidative stress. Because of its location within the mitochondrial matrix and lack of histones, mitochondrial DNA is highly susceptible to oxidative damage.13 To maintain genomic integrity, mitochondria use an armamentarium of detoxifying enzymes and rely on a machinery of base excision repair enzymes that mend oxidative damage.14 When oxidative stress exceeds defense mechanisms, de novo mutations (and deletions) accrue in the mitochondrial genome, giving rise to a variegated population of mitochondrial DNA genomes, a mixed population of mitochondrial genomes referred to as heteroplasmy. The extent of heteroplasmy varies across tissues and is particularly increased in heart and skeletal muscle.14–16

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Assuming a low fixed error rate for the mitochondrial DNA polymerase, mitochondrial DNA is an incidental sensor of oxidative stress that reflects the equilibrium between DNA damage and repair.

In this issue of Circulation, Ahuja et al exploited high-throughput sequencing to quantify mitochondrial DNA mutations (0.04% in DCM versus 0.01% in nonfailing hearts) and deletions (0.05% in DCM versus 0.003% in nonfailing hearts). They identify a higher frequency of mitochondrial DNA mutations and deletions in patients with DCM but not in those with ICM. Given that heteroplasmic mutations approaching 60% were required to observe biochemical defects in OXPHOS,17 a mutation frequency of 1 in 1000 to 2500 mitochondrial genomes was unlikely to directly influence OXPHOS. Nonetheless, the increase in mutations and deletions is indicative of increased oxidative stress in DCM hearts. Interestingly, regardless of the type of heart failure, manganese superoxide dismutase activity in whole-cell lysate was similar, despite DCM hearts having twice as many mitochondria. The fact that manganese superoxide dismutase is localized to mitochondria implies reduced detoxification activity per mitochondrion in DCM hearts and may explain the increased frequency of mitochondrial DNA mutations and deletions. Similar to Ahuja et al, others have reported an association between oxidative stress and mitochondrial biogenesis in cardiomyopathic hearts. Corral-Debrinski et al6 found increased oxidative stress and likely induction of mitochondrial content in ICM hearts. This group also reported a 7- to 220-fold increase in mitochondrial DNA deletions in ICM heart, which showed the greatest oxidative stress.6 In maternally inherited cardiomyopathy, one group found an association between oxidative stress and mitochondrial biogenesis, including an induction of PGC-1α.5 The central theme of all these reports, including the study by Ahuja et al, is that cardiomyopathy, coupled with marked increases in oxidative stress, is associated with the induction of PGC-1α and mitochondrial biogenesis, whereas cardiomyopathy with a lesser degree of oxidative stress is associated with reduced (or normal) levels of PGC-1α. Ahuja et al also show a decline in one mitochondrial-base excision repair protein for ICM and DCM hearts. These data, however, require caution interpretation because repair activity was not measured and ICM hearts do not have increased mitochondrial DNA mutations.

In terms of cardiomyopathy and mitochondrial biogenesis, several interesting questions remain. Is mitochondrial biogenesis adaptive or maladaptive? Although the salutary effect of increasing OXPHOS via PGC-1α-mediated mitochondrial biogenesis is intuitive, heart muscle has a limited capacity for mitochondrial biogenesis because of its dense myofibrillar network. In mice, Lehman et al18 showed that unchecked mitochondrial biogenesis crowds the contractile apparatus, impairing myocardial performance and culminating in DCM. In conditional transgenic mice, controlled induction of PGC-1α still promoted DCM,19 accompanied by dysmorphic mitochondria and myofibrillar degeneration. Analogous to mitochondrial biogenesis reported by Ahuja et al in DCM hearts, mitochondrial content was increased ≈2-fold in the inducible mouse model.19 Shutting off the transgene in these mice reversed cardiomyopathy and aberrant changes in mitochondria.19 Interestingly, in the study by Ahuja et al, implantation of a left ventricular assist device reduced mitochondrial DNA mutations in DCM hearts. On the basis of the accumulated data and recent data by Ahuja et al, a simple (but unifying) model can be hypothesized...
Regardless of the type of heart failure, a disproportional increase in oxidative stress triggers the induction of PGC-1α, culminating in mitochondrial proliferation. This in turn would have implications for fuel utilization because induction of PGC-1α was associated with cardiac induction of genes involved in fatty acid oxidation, a process that further exacerbates oxidative stress. Under this scenario, oxidative stress, which is injurious to contractile function, and mitochondrial proliferation, which crowds the contractile apparatus, would collectively impair myocardial performance. Although increased PGC-1α and mitochondrial biogenesis might initially preserve OXPHOS, over time, increased mitochondrial content (and possible repression of mitochondrial biogenesis) would lead to myofibrillar disarray and contractile dysfunction, as reported by Russell and colleagues. Presumably, differences in loading of the heart and host factors determine the degree of oxidative stress because unloading of DCM hearts with left ventricular assist devices reduced the frequency of mitochondrial DNA mutations, indicating reduced oxidative stress. In contrast, if oxidative stress is not sufficiently elevated in the cardiomyopathic heart, there is a decline in PGC-1α, mitochondrial content, and OXPHOS, culminating in impaired contractile function. A decline in PGC-1α and mitochondrial content would likely necessitate a reliance on glycolysis, a reversal of the so-called fetal switch. Further work is necessary to determine which signals downregulate mitochondrial biogenesis in certain heart failure patients. On the basis of the discussed model, induction of mitochondrial biogenesis initially is adaptive but over time proves maladaptive as a result of ill effects on metabolism and the contractile apparatus, whereas insufficient mitochondrial content limits myocardial performance owing to reduced OXPHOS. In heart failure, this implies that there is a delicate balance between myocardial content and myocardial performance (Figure).

Although controversy continues to bedevil this topic, the work by Ahuja et al in this issue of Circulation moves us closer to a consensus. Cardiomyopathies differ not only in their clinical type but also at the level of mitochondrial biogenesis and oxidative stress. Apart from advancing our basic understanding of mitochondrial biogenesis in human heart failure, their work may inform the search for diagnostic and therapeutic interventions. Classifying cardiomyopathies as glycolytic heart failure or oxidative heart failure may lead us closer to more tailored therapies.

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References


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