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The Crucial Role of Cellular Energy in Heart Rhythm Disorders

Analysis by Dr. Joseph Mercola | July 08, 2024

STORY AT-A-GLANCE

- Atrial fibrillation (AF) is a growing global health concern, affecting millions and increasing dramatically with age. It significantly impacts quality of life and poses a substantial economic burden on healthcare systems
- Mitochondrial dysfunction plays a crucial role in AF development, affecting energy production, cellular ion balance, and oxidative stress levels. This dysfunction contributes to both electrical and structural remodeling of the heart
- Several existing medications, particularly those used for diabetes management like DPP-4 inhibitors and SGLT2 inhibitors, show promise in improving mitochondrial function and potentially reducing AF risk
- Emerging therapies targeting mitochondrial function, including novel drugs and gene therapies, are being developed and may offer new approaches to AF prevention and treatment in the future
- Maintaining mitochondrial health through lifestyle choices and discussing mitochondrial-targeted therapies with healthcare providers may help reduce AF risk, especially as you age

Atrial fibrillation (AF) is a silent epidemic that's quietly taking hold across the globe. As the most common type of abnormal heart rhythm, it affects millions of people worldwide, with prevalence estimates ranging from 1% to 2% of the general population in the U.S.[1]

When you have AFib, your heart's electrical system goes haywire, causing irregular and sometimes rapid rhythms. This puts you at a much higher risk of stroke — three to five times higher, to be exact. The reason? Your irregular heartbeat can cause blood to pool and clot in your heart, and these clots can travel to your brain.[2]

What's particularly alarming is how the risk of developing AF increases dramatically with age. While it's relatively rare in younger adults, affecting only about 0.1% of those under 55,[3] the prevalence is estimated at 6.4% for those aged 65 to 69, and 28.5% for those over 85.[4]

But AF isn't just a problem of the elderly. In some cases, it can strike at a much younger age due to genetic factors or congenital heart defects. For these younger patients, the culprit is often found in the pulmonary veins, where abnormal electrical activity can trigger episodes of AF. While this type of AF, known as paroxysmal AF, can often be successfully treated with pulmonary vein ablation, the story is quite different for older patients.

As you age, your heart tissue naturally degenerates, and various health conditions can affect your heart's structure and metabolism. These factors combine to create an environment ripe for persistent or permanent AF, which is much harder to treat effectively.

The impact of AF extends far beyond just an irregular heartbeat. It significantly diminishes your quality of life, increases your risk of other health problems, and even shortens your lifespan.

The economic burden is substantial as well. In the United States alone, the cost of AF treatment was a staggering $6.65 billion in 2005, including $2.93 billion (44%) for hospitalizations.[5] In a privately insured population in the U.S., the direct annual cost of AF was estimated at $15,553 per patient, which was $12,349 more than enrollees without AF.[6]

These costs have only increased with the introduction of newer anticoagulant medications. As the population in developed countries continues to age, the number of

people affected by AF is set to rise dramatically. This looming health crisis underscores the urgent need for better understanding of how AF develops and improved strategies for prevention and treatment.

The Role of Mitochondria in AF

At the heart of this complex condition lies a fascinating and often overlooked player: your mitochondria. These tiny powerhouses within your cells have been implicated in the development of AF since the 1970s. Mitochondria are abundant in metabolically active cells like cardiomyocytes, the specialized muscle cells of your heart.

Their primary job is to produce adenosine 5'-triphosphate (ATP), the energy currency that powers almost all cellular processes, including the mechanical work of your heartbeat and the intricate dance of ions that keeps your heart's electrical system in rhythm.

When AF sets in, it puts enormous stress on your heart cells. In the early stages of paroxysmal or short-lasting persistent AF, your mitochondria try to keep up by increasing ATP production. But over time, this production starts to falter, signaling mitochondrial dysfunction. The consequences of this energy deficit are far-reaching.

With less ATP available, all energy-dependent processes in your heart cells begin to suffer. The delicate balance of ions inside and outside your cells is disrupted, enzymatic reactions slow down, and the very contraction and relaxation of your heart muscle is compromised.

Your cells, desperate for energy, begin to rely more heavily on glycolysis, a less efficient form of energy production that occurs in the cell's cytoplasm rather than in the mitochondria. This shift towards glycolysis and increased lactate production is reminiscent of the Warburg effect seen in rapidly growing tumors. It's a sign that your heart cells are under severe metabolic stress.

This stress activates a cellular energy sensor called adenosine monophosphate protein kinase (AMPK). When ATP levels drop and AMP levels rise, AMPK kicks into action,

shifting metabolic pathways towards glycolysis and putting the brakes on energy-consuming anabolic processes.

But AMPK's influence extends beyond metabolism. It can also affect ion channels in your heart cells, including the ATP-sensitive potassium channel and the slow inward calcium channel. These changes alter the electrical properties of your heart cells, potentially exacerbating the arrhythmia. Interestingly, AMPK activation is seen in intermittent AF but not in long-lasting AF, suggesting it may be a compensatory response to the initial metabolic stress induced by the arrhythmia.

Mitochondrial Dysfunction Is a Major Source of ROS

But the problems don't stop there. Dysfunctional mitochondria become a major source of reactive oxygen species (ROS), particularly superoxide anions. These highly reactive molecules wreak havoc in your cells, oxidizing critical proteins like the ryanodine receptor (RyR2) in the sarcoplasmic reticulum and the inward sodium channel in the cell membrane.

These oxidative changes directly alter your heart cells' excitability and how they communicate with each other, creating a fertile ground for maintaining the chaotic electrical circuits of AF.

The damage caused by mitochondrial dysfunction extends beyond individual heart cells. It triggers the release of inflammatory cytokines, activates fibroblasts, and promotes the deposition of connective tissue in your heart. This structural remodeling of your heart tissue further enhances the likelihood of AF developing and persisting.

The link between altered mitochondrial function and increased risk of AF is supported by both experimental and clinical data. But to truly understand how mitochondrial dysfunction contributes to AF, you need to look at several key aspects: mitochondrial structure, biogenesis, and oxidative stress.

Mitochondrial Structure Changes in AF

When it comes to structure, mitochondria in AF-affected heart tissue show significant changes. In animal models of persistent AF, researchers have observed initial degradation of myofibrils (the contractile units of heart muscle) and accumulation of glycogen.

This is followed by elongation of mitochondria and changes in the orientation of their internal folded membranes called cristae. In mice with AF and heart failure, the mitochondria in atrial heart cells show even more severe damage, including swelling of the mitochondrial matrix and disruption of both inner and outer mitochondrial membranes. These structural changes are directly linked to decreased ATP production.

Human studies have also revealed mitochondrial abnormalities in AF.[7,8,9] Atrial tissue samples from patients with AF show an increased number of mitochondria, often with altered shapes.[10] Some studies have found swollen mitochondria with partial or complete disruption of their internal structure. These changes appear to be related to calcium overload in the cells, as they can be prevented by calcium channel blockers.

Mitochondrial Biogenesis Is Disrupted in AF

The process of mitochondrial biogenesis — the creation of new mitochondria — is a complex biological process that controls organelle self-renewal and the maintenance of mitochondrial DNA, ensuring cellular homeostasis.[11] This process involves the coordinated action of numerous regulatory proteins, most of which are encoded by nuclear DNA, with a few key players encoded by mitochondrial DNA.[12]

The master regulator of mitochondrial biogenesis is a protein called PGC-1α (peroxisome proliferator-activated receptor-γ coactivator 1-α).[13] Under normal conditions, high energy demand increases the expression of PGC-1α, stimulating the production of new mitochondria.

As mentioned, in atrial fibrillation (AF), there is evidence of mitochondrial dysfunction, characterized by both functional and morphological changes. Studies have revealed mitochondrial ultrastructural abnormalities in human AF patients, including

modifications in shape, volume, and remodeling of the cristae ultrastructure in atrial cardiomyocytes.[14]

Research has also shown that mitochondrial DNA damage occurs in human AF.[15] Initial calcium overload and chronic high oxidative stress levels in fibrillating atria may explain the rapid damage to mitochondrial DNA in human AF. Not surprisingly, improving mitochondrial function has also shown promise in reducing AF susceptibility.

Another Factor: Oxidative Stress

Oxidative stress is another crucial factor in the mitochondrial dysfunction seen in AF. While your mitochondria always produce some reactive oxygen species as a byproduct of energy production, this production spirals out of control in AF. Studies of atrial muscle from AF patients have found reduced activity of electron transport chain complexes I and II, increased activity of complex V, and a corresponding increase in superoxide production.[16]

This oxidative stress has wide-ranging effects, altering gene transcription, damaging mitochondrial DNA, increasing the activity of pro-oxidant enzymes like NADPH oxidase and xanthine oxidase, and triggering local inflammation.

The oxidative damage extends to key proteins involved in calcium handling, like the ryanodine receptors, causing them to leak calcium from the sarcoplasmic reticulum. This disruption in calcium homeostasis can, in turn, lead to even more ROS production by the mitochondria, creating a vicious cycle.

The oxidative stress and inflammation also upregulate expression of transforming growth factor β1 (TGF-β1), promoting fibrosis of the atrial myocardium — a key component of the structural remodeling that perpetuates AF.

Encouragingly, animal studies have shown that treatments targeting oxidative stress can prevent the development of AF and the associated atrial remodeling.[17] For example, the antioxidant probucol has been shown to attenuate oxidative stress, inhibit inflammatory signaling, and prevent AF development and atrial remodeling.

Similarly, genetically enhancing the antioxidant capacity of mitochondria in mice was sufficient to prevent mitochondrial structural abnormalities, calcium leak from the sarcoplasmic reticulum, and susceptibility to AF.

Common Drug Treatments and Helpful Supplements

Given the crucial role of mitochondrial dysfunction in AF, there's growing interest in pharmacological interventions that can improve mitochondrial function and potentially prevent or treat AF. Several classes of drugs, some already in use for other conditions like diabetes, show promise in this area.

Dipeptidyl peptidase-4 (DPP-4) inhibitors, a class of drugs used to treat Type 2 diabetes, have shown potential in reducing AF risk. These drugs work by increasing levels of incretin hormones, which in turn stimulate insulin release and inhibit glucagon. But their benefits extend beyond blood sugar control. In heart cells, DPP-4 inhibitors can attenuate oxidative stress and improve mitochondrial function.

Ubiquinone, also known as Coenzyme Q10, is another compound that's gained attention for its potential role in AF prevention. This naturally occurring substance is an important cofactor in the mitochondrial electron transport chain and a potent antioxidant. Levels of CoQ10 in the heart can decrease with age, statin use, or due to genetic factors.

Some studies have shown that CoQ10 supplementation can improve mitochondrial respiratory function and reduce oxidative stress,[18,19] and in patients with heart failure, CoQ10 treatment has been shown to significantly reduce major adverse cardiovascular events[20] and lower the death rate.[21]

While there is no direct evidence that CoQ10 improves AF, it seems reasonable to assume that it might, and its good safety profile makes it an interesting candidate for further research as an adjuvant therapy in certain AF risk situations.

Fibrates, which are used to treat high triglyceride levels, may also have a role in AF prevention through their effects on mitochondrial function. These drugs activate PPARα, which can influence mitochondrial function through the PPARα/PGC-1α pathway. Animal

studies have shown that fibrates can reverse some of the metabolic and electrical remodeling associated with AF.[22]

While there's some evidence that lipid-lowering medications, including fibrates, may be associated with a lower prevalence of AF in certain patient populations, the clinical benefits for AF outcomes have not been thoroughly evaluated.

While these existing medications show promise, researchers are also developing new drugs specifically targeting mitochondrial function. One such approach is a synthetic combination of four amino acids (a tetrapeptide) and is called elamipretide, which is designed to improve mitochondrial energetics and reduce ROS generation by stabilizing the mitochondrial membrane.[23]

Initial results in heart failure were promising, showing improvements in mitochondrial function and left ventricular volumes.[24]

Anticoagulants are also frequently prescribed for AF. One of the most recommended is Eliquis, a type of drug known as a direct oral anticoagulant. However, Eliquis can be expensive, potentially costing you up to $594 per month depending on your insurance.[25] New legislation is now aiming to lower drug costs for Medicare beneficiaries though.

Mitochondrial Function Impacts Many Aspects of Atrial Remodeling

As you can see, the relationship between mitochondrial dysfunction and AF is complex and multifaceted. Your mitochondria play a crucial role in maintaining the energy balance and electrical stability of your heart cells. When they falter, it sets off a cascade of events that can lead to the development and perpetuation of AF.

From structural changes in the mitochondria themselves to impaired biogenesis and increased oxidative stress, mitochondrial dysfunction touches on many aspects of atrial remodeling.

The good news is that this understanding opens up new avenues for prevention and treatment. Many strategies to improve mitochondrial function show promise in reducing AF risk. This is why as you age, maintaining mitochondrial health becomes increasingly important for preserving your heart's rhythm. While you can't control all the factors that influence your risk of AF, there are steps you can take to support your mitochondrial function and potentially reduce your risk.

Regular exercise, particularly aerobic activities, can stimulate mitochondrial biogenesis and improve mitochondrial function. Walking in the sun at solar noon with minimal clothes is a terrific strategy along with **lowering your intake of seed oils**.

My new book, "Cellular Health: The Unifying Theory of Health for Ultimate Longevity and Joy" will be out shortly and it is loaded with details on how to improve your mitochondrial function. I can't wait to share it with you.

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