Mitochondrial Cardiomyopathy and Related Arrhythmias

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KEYWORDS

• Mitochondrial cardiomyopathy • Mitochondrial syndrome • Mitochondrial DNA mutation
• Diabetic cardiomyopathy • Arrhythmia mechanisms • Arrhythmia management

KEY POINTS

- Inherited mitochondrial cardiomyopathy results from a mutation of the mitochondrial DNA, most often on a maternal inheritance pattern, and commonly shows multisystemic dysfunction, that is, mitochondrial syndromes.
- Mitochondrial cardiomyopathy commonly presents as nonobstructive symmetric left ventricular (LV) hypertrophy and more rarely as dilated cardiomyopathy with systolic dysfunction, the latter most often being a complication of the former phenotype called the burn-out form.
- Atrioventricular (AV) block and supraventricular arrhythmias associated with pre-excitation syndrome are the most common rhythmic issues in mitochondrial disease, irrespective of the phenotype.
- Progressive and unpredictable hallmarks of AV block prompt prophylactic cardiac pacing device implantation even on early occurrence of conduction disorders in asymptomatic patients.
- Incidence of ventricular arrhythmia depends on the cardiomyopathy phenotype rather than on its mitochondrial origin.

INTRODUCTION

Mitochondria have emerged as a key actor in arrhythmogenesis, apart from their core role in cardiomyocyte energetic homeostasis and life/death pathways. Basic laboratory studies pointed out mitochondria-related modulations of electrophysiological and calcium cycling properties of cardiomyocyte in both physiologic and pathologic situations.

After being first reported 30 years ago in encephalomyopathy,[1,2] mutations in mitochondrial DNA responsible for mitochondrial respiratory chain disorders have been proved a rare but classic cause of inherited cardiomyopathy, presenting with associated multisystem disorders in mitochondrial syndrome and a specific mode of inheritance. Mitochondrial dysfunction has been involved in acquired cardiomyopathy, such as ischemic or diabetic cardiomyopathies, and their related arrhythmias, opening a new area for promising mitochondria-targeted drugs.

This article briefly discusses the basics of mitochondrial physiology and details the mechanisms underlying mitochondrial function and arrhythmia. The clinical spectrum of inherited and acquired cardiomyopathies associated with mitochondrial dysfunction is discussed, followed by the general

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aspects of the management of mitochondrial cardiomyopathy and related arrhythmia.

MITOCHONDRIAL PHYSIOLOGY

Mitochondria are subcellular organelles that play an important role in most cellular biological processes. The following are the most critical functions (Fig. 1):

- Providing the cell with a constant and adaptive amount of energy in synthesizing ATP through oxidative phosphorylation by the respiratory chain complexes
- Dealing with cellular reactive oxygen species (ROS), which are mainly by-products of mitochondrial respiration that can lead to cell death signaling activation
- Participating in calcium homeostasis through sarcoplasmic reticulum-mitochondria calcium cross talk, energized mitochondria being able to accumulate calcium

The heart is a tissue with one of the highest rates of energy conversion in the body, critically depending on mitochondrial oxidative phosphorylation as a major source of ATP.[3] Thus, cardiac mitochondria represent a key actor of the biological systems addressed to prevent any mismatch between ATP production and utilization. Therefore, mitochondrial respiratory chain disorders often present with cardiac features.

MECHANISMS BY WHICH MITOCHONDRIAL DYSFUNCTION CAUSES ARRHYTHMIA

As detailed further, mitochondrial disorders are responsible for contractile cardiac dysfunction and can thus indirectly lead to arrhythmias,

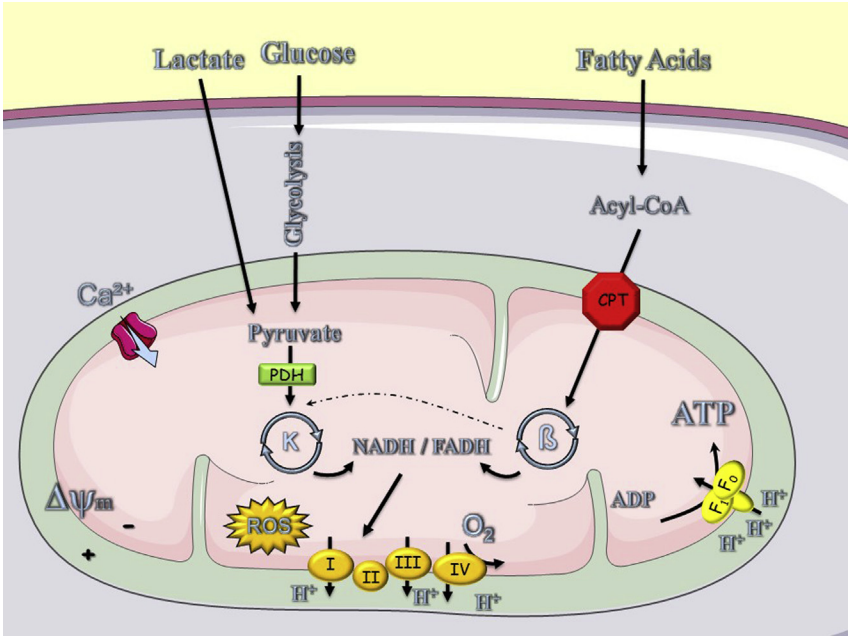

Fig. 1. Mitochondrial phosphorylative oxidation. Mitochondrial phosphorylative oxidation takes place along the mitochondrial inner membrane and corresponds to the oxidation of reduced form of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH) by oxygen, allowing the synthesis of adenosine triphosphate (ATP). The oxidative process is catalyzed by the 4 respiratory chain complexes (complex I, II, III, and IV), with oxygen as the final electron acceptor at complex IV. Along the oxidoreduction reactions, part of the high redox energy of the electrons from NADH and FADH is turned into an electrochemical gradient of proton across the mitochondrial inner membrane, protons being pumped from the matrix to the intermembrane space by complexes I, III, and IV. Mitochondrial respiration creates a mitochondrial membrane potential ($\Delta\Psi m$), which is the driving force allowing mitochondria to participate to cardiomyocyte calcium homeostasis. The proton gradient is used by the ATP synthase (F1-F0 ATPase) to synthesize the energy-enriched ATP from ADP, a process called phosphorylation. In physiology, oxidation and phosphorylation are coupled. Reactive oxygen species (ROS) are highly reactive compounds harmful when produced in large amounts. Minute amounts of ROS are by-products of normal mitochondrial respiration and are involved in physiologic signaling of cardiomyocyte. Yet, produced in large amounts during mitochondrial dysfunction, ROS activate cardiomyocyte cell death signaling. ß, fatty acid β-oxidation; CPT, carnitine palmitoyltransferase complex; κ, Krebs cycle; PDH, pyruvate dehydrogenase.