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Editorial Review

Modulation of myocardial energetics: An important category of agents in the multimodal treatment of coronary artery disease and heart failure

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ABSTRACT

The combined and relative contribution of glucose and fatty acid oxidation generates myocardial energy, which regulates the cardiac function and efficiency. Any dysregulation in this metabolic homeostasis can adversely affect the function of heart and contribute to cardiac conditions such as angina and heart failure. Metabolic agents ameliorate this internal metabolic anomaly, by shifting the energy production pathway from free fatty acids to glucose, resulting in a better performance of the heart. Metabolic therapy is relatively a new modality, which functions through optimization of cardiac substrate metabolism. Among the metabolic therapies, trimetazidine and ranolazine are the agents presently available in India. In the present review, we would like to present the metabolic perspective of pathophysiology of coronary artery disease and heart failure, and metabolic therapy by using trimetazidine and ranolazine.
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1. Case study

A 72-year old woman presented with the complaints of chest pain and dyspnea occurring since the last 3–4 weeks, which is increased during her routine chores and resolved after rest, hampering her daily activities. Her medical history revealed that she has been a hypertensive for eight years. She had complained of chest discomfort 2 years ago and had undergone Percutaneous Coronary Intervention (PCI) with two drug eluting stents, following which her angina was relieved. Her left ventricular ejection fraction (LVEF) on 2D echo is 35%. Her blood pressure is under control at 138/82 mm Hg with amlodipine 5 mg and perindopril 8 mg. In addition, since the onset of angina, metoprolol 50 mg twice a day and nicorandil 5 mg twice a day has been added. In spite of these medications she presently needs to take nitroglycerin (0.4 mg sublingually) approximately 2–3 times a day for angina relief. This case scenario presents a challenge for the physician as the patient is already under treatment with most of the existing potential medications for stable angina. An alternate modality is the need in this case to effectively manage her troublesome angina and improve her quality of life. For personal reasons she is not willing to undergo further intervention.

As described by Opie L in 1999, "*The heart is more than just a pump. It is also an organ that needs energy from metabolism. A metabolic disease, ischemia, should ideally be treated by metabolic therapy*".[1] Hence, metabolic therapy has been evolved as a potential and effective treatment modality, which could be prescribed in this situation to overcome her ongoing complaints.

Usually stable coronary artery disease (CAD) patients would be prescribed two to three antianginal drugs such as beta-blockers, calcium channel blockers and nitrates.[2] As these agents act by altering hemodynamic system, the addition of multiple drugs may be associated with side effects. Furthermore, usage of nitrates regularly can lead to tolerance. Therefore, in such situations, the need would be to treat the patients with an alternative and effective treatment modality.[2]

Metabolic therapy can be considered for cardiovascular ailments such as CAD and heart failure (HF). Indeed, recent several studies have shown that metabolic therapy can be a potential and promising approach in dealing with CAD and HF.[3] Metabolic therapy functions by modulating metabolism, i.e. shift the energy production pathway from fatty acid to glucose in the presence of decreased oxygen supply. As these agents function without affecting the hemodynamic alterations, they would not add further to the side effects already produced by heavy multiple hemodynamically acting agents.[2] Trimetazidine and ranolazine are the two main metabolic modulators, which are available in clinical practice today. Trimetazidine has been extensively studied for patients with angina and those with reduced left ventricular (LV) function, with or without HF. Recent guidelines published by European Society of Cardiology (ESC 2016), have recommended trimetazidine in patients with HF with ongoing angina.[4] Moreover, trimetazidine has also been clinically tested for its cardioprotective role in combination with other interventions. The objective of this article is to present the role of metabolic management and the future perspectives of metabolic therapy in patients with angina and HF due to CAD.

2. Deranged myocardial metabolism in CAD and HF

During normal conditions, the heart generates most of its energy from free fatty acid (FFA) oxidation with the rest from glucose oxidation and lactate.[5] The number of moles of adenosine triphosphate (ATP) produced per mole of carbon oxidized is approximately 29% higher for FFA compared to glucose.[6] In hypoxia, glucose is preferred for energy production, since glycolysis requires less oxygen per mole of ATP generation compared to FFA oxidation.[7] The number of moles of ATP produced per mole of oxygen spent is 12% higher for glucose than for FFA oxidation.[8] Increasing the use of glucose and lactate can improve the oxygen utilization and efficiency of the myocardium by 16–26%.[9,10] Hence, generation of energy becomes more dependent on glucose metabolism.

Meanwhile, continued availability of FFAs, inhibit pyruvate dehydrogenase (PDH), which in turn allows accumulation of pyruvate. Pyruvate converts into lactate resulting in intra cellular acidosis. This in turn causes metabolic, morphological and functional alteration of the myocardium leading to arrhythmias, contractile failure and electrophysiological abnormalities.[7] In addition, FFAs reduce glucose uptake at cellular level, leading to further increased conversion to lactate, resulting in cell acidosis. Hence, FFA pathway slows down ATP production. These metabolic alterations ultimately lead to cell death. Heart failure is a late manifestation of CAD, because ischemia contributes to the advancement of LV systolic dysfunction. Therefore, altered metabolism is likely to be an indirect but important cause of HF (Fig. 1).[5]

Abnormalities in cardiac functioning may also arise at the level of energy transfer from mitochondria to myocardial muscles. The generated ATP in mitochondria can be transferred to the myofibrils by the creatine kinase (CK) energy shuttle. In this process, the high-energy phosphate bond in ATP can be transferred to creatine by mitochondrial CK to form phosphocreatine (PCr). Phosphocreatine in turn diffuse through the mitochondrial membrane into myofibrils, where myofibrillar CK catalyses the reformation of ATP from PCr.[11] The work of the heart is continuous, and this is reflected in the high rate of ATP hydrolysis ($\approx$0.5 μmol/g wet weight per second).[11] Consequently, the high-energy phosphate pool in the heart can be exhausted within a short time. Eventually, the PCr level decreases, but the free adenosine diphosphate (ADP) level rises. The amplified level of free ADP inhibits the function of many intracellular enzymes, resulting in failure of the heart's contractile mechanism. Thus, a metabolic imbalance in the cardiac cell can occur when PCr levels fall and free ADP levels rise.[11] Hence, the PCr:ATP ratio is a measure of myocardial energetics and its reduction may cause reduced efficiency of myocardial contraction (Figs. 2 and 3).

In principle, the approach of metabolic management is to switch the energy substrate preference from fatty acid oxidation to glucose oxidation.

3. Metabolic management of CAD and HF

Given the above described pathophysiological background and the difficulty of standard treatment to control the total symptomatic and prognostic burden in many patients with ischemia and HF, it seems logical to consider pharmacological manipulation of cardiac energy metabolism as an adjunctive therapeutic option. As mentioned earlier, optimization of cardiac energy metabolism is based on promoting cardiac glucose oxidation.

3.1. Trimetazidine

Trimetazidine is the most extensively studied drug among the metabolic therapies. It has multimodal action on cardiac energy metabolism. Major cardioprotective actions involve, (1) inhibitory effects on fatty acid oxidation, thus favoring glucose oxidation; (2) redirect fatty acids toward membrane phospholipids; (3) preserve PCr and ATP intracellular levels (PCr/ATP ratio).[11]

Trimetazidine inhibits the mitochondrial long chain 3-ketoacyl-CoA thiolase, the terminal enzyme, which participates in FFA β-oxidation. A decrease in FFA oxidation results in increase of

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