Modulation of cardiac energetics as a target in ischemic heart disease

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Abstract
Substantial advances in mechanical and adjunctive pharmacological therapies have reduced the consequences of ischemic heart disease. Despite these advances, cardiovascular disease and its major contributor coronary artery disease continue to accrue substantial morbidity and mortality. Metabolic therapies (ranging from insulin to fatty acid oxidation inhibitors and late sodium channel current inhibitors) represent a novel and immediately clinical relevant class of therapies that can contribute to improving patient outcomes. In the current article, I will discuss the basic biology of cardiac metabolism and the clinical efficacy of agents, some of which have direct clinical applicability. As well as outlining the considerations that may culminate in the effective deployment of these agents in the care of patients, I also consider the likely future directions for metabolic therapy in cardiovascular disease.

Keywords: cardiac energetics; ischemic heart disease; metabolic therapies; cardiac metabolism

Introduction
Cardiovascular disease remains the leading cause of mortality in the developed world and has emerged as a major cause of morbidity and mortality in the developing world [1]. Ischemic heart disease resulting from coronary artery disease, along with hypertensive heart disease, represents the engine of cardiovascular mortality and is consequent upon the lifestyle changes occurring with increasing “development” (e.g., smoking, obesity, psychosocial factors and sedentary lifestyle) [2]. Advances in mechanical interventions (e.g., percutaneous coronary intervention and coronary artery bypass surgery) that augment the oxygen supply to the myocardium coupled with therapies that reduce cardiac oxygen demand (e.g., β-blockers and ivabradine, which reduces heart rate exclusively by acting on the sinus node-I_f current) are the mainstay of current therapy. However, despite the use of these therapies, many patients remain symptomatic, expanding the reservoir of aging patients who, having undergone the demographic transition, ail with angina and chronic heart failure. To combat the morbidity and mortality associated with these conditions, novel therapies are urgently required—therapies that modify cardiac metabolism represent a hitherto practically unexplored group of treatments that are increasingly recognized to have promise in addressing the chronic consequences of cardiac disease [3].
Metabolic changes in the ischemic myocardium

It is frequently stated that the heart is capable of metabolizing a range of substrates, including free fatty acids (FFA), glucose and other carbohydrates (e.g., pyruvate and lactate) and even amino acids. The consequence of changing this substrate is less frequently considered.

A striking exemplification of the influence of metabolism on myocardial structure, albeit in the reptile hearts, can be adduced from the influence of metabolism on Burmese python hearts. These reptile hearts hypertrophy by >40% after the snakes’ monthly meal [4]. This entirely physiological—and likely reversible—structural change derives from the metabolism of a combination of three fatty acids: myristic, palmitic, and palmitoleic acids. Importantly, mice hearts also undergo cardiac hypertrophy (~10%) when exposed to the same cocktail of FFA. Thus while the mammalian heart is therefore a metabolic omnivore [5], the choice of substrate has profound consequences on cardiac structure, energetics and function. For example, theoretically a complete switch from FFA metabolism as an energy source to glucose can save 11–13% of myocardial oxygen use based on stoichiometric considerations (and by ~50% as measured experimentally in pig and canine hearts).

The healthy adult myocardium, especially during fasting, preferentially metabolizes FFA and their derivatives (60–100%) [3]. In hypertrophy and heart failure, it is believed (though not unanimously accepted) that a downregulation of fatty acid metabolism is compensated for by increased carbohydrate metabolism in an attempt to spare oxygen. Although far from experimentally confirmed, during myocardial ischemia a rapid activation of AMP-activated protein kinase (AMPK) occurs, resulting in an activation of both glucose uptake and an increase in fatty acid oxidation [6]. It is therefore presumed that the ischemic myocardium continues to rely on FFA metabolism with the attendant inefficiency of this substrate. Not only do FFA confer an oxygen utilization penalty on the heart at a time of blood/oxygen deficiency, but inappropriately high FFA metabolism may, as Randle proposed, compromise coupled glucose metabolism and have especially adverse sequelae on ischemic hearts (e.g., due to the influence of excess FFA on calcium transients in ischemia).

Accordingly, substantial emphasis has been placed on physiological or therapeutic strategies designed to suppress FFA uptake and/or oxidation in order to stimulate coupled myocardial glucose utilization. Although this substrate switch continues to be the primary focus for metabolic therapies, it is increasingly recognized that redox and aldehyde-induced stress responses can effect a shift in glucose metabolism from glycolysis to the pentose phosphate pathway [7]. Such studies provide a rationale for investigating other such signaling pathways with a broader view to elaborating resistance against acute oxidative stress induced by ischemia/reperfusion through metabolism.

Metabolic therapies

Glucose-insulin

In an attempt to recapitulate and exaggerate “physiological” glucose uptake into myocardium, Sodi-Pallares et al., in 1962, successfully applied “polarizing solution”, i.e., glucose-insulin-potassium infusion (GIK), for treatment of acute myocardial infarction. GIK infusion was initially thought to confer benefit primarily by increasing glycolysis and by reducing in FFA uptake and metabolism. More recently, we have demonstrated that GIK treatment also engenders a number of signaling changes (e.g., increased signaling protein phosphorylation and O-GlcNAcylation) likely to contribute to myocardial protection [8].

A number of early studies supported this early promise, for example the ECLA (Estudios Cardiológicos Latinoamérica) Collaborative Group were able to show a dramatic reduction of death rate of acute myocardial infarction from 11.5% in the control group to 6.7% in patients treated with GIK. However the negative results of large trials such as the CREATE-ECLA trial, which studied 20,201 patients with ST-elevation acute myocardial infarction, mostly in India and China, have questioned the role of GIK in the context of modern reperfusion therapy [9]. The conclusions of the latter study are moderated by the observation that GIK may have been given too late to be effective [10], its efficacy may have depend on the dose, its efficacy may have been limited by pharmacokinetics and pharmacodynamics and may depend on the exact population studied (including the nature of the adjunct pharmacology/coronary revascularisation).

Nevertheless, the current evidence suggests that GIK provision as performed in existing trials does not reduce mortality in patients with AMI but that tight
glycemic control is beneficial [11]. One way in which these limitations of insulin have been overcome is by the use of the incretin glucagon-like peptide-1 (GLP-1), which has demonstrable cardioprotective properties in experimental models and patients with cardiac ischemia [12]. Indeed, there is accumulating evidence suggests that albiglutide, a novel longer lasting GLP-1, rather akin to the early GIK studies, may protect the heart against from ischemic injury by altering substrate use and ameliorating cardiac energetics [13].

Partial fatty oxidation (pFOX) inhibitors
In order to achieve a more enduring and practicable switch between FFA and carbohydrate metabolism, a number of inhibitors of fatty acid oxidation have been sought and executed. CPT-1 is the rate-limiting enzyme that transports FFA into the mitochondria. Pharmacological inhibition of CPT-1 by etomoxir, oxfenecine and perhexeline and experimental malonyl CoA decarboxylase inhibitors (which augments the native CPT-1 inhibitor - malonyl CoA) have been investigated in pre-clinical models and human studies of cardiac ischemia. Similarly, the β-oxidation enzymes downstream of CPT-1, such as mitochondrial 3-ketoacyl-CoA thiolase inhibited by trimetazidine, are recognized to be therapeutic targets in the treatment of ischemic heart disease. Notably, despite the challenges of dose monitoring and intellectual property issues, both perhexiline and trimetazidine continue to be used successfully in the clinical setting [14].

It is important to recognize that the more potent pFOX inhibitors (inhibitors) tend to be limited by their side effect of cardiac lipotoxicity arising from excess cardiac lipid accumulation (etomoxir, oxfenecine). In contrast, competitive inhibitors of these enzymes such as perhexilene and trimetazidine, which allow excess endogenous FFA to break through the inhibition, do not show such effects. It is likely, therefore, that any successful cardiac metabolic therapy should be carefully moderated in order to prevent extreme inhibition of any single metabolic pathway, highly likely to be harmful to an organ.

Late sodium channel current
In the ischemic myocardium, inhibition of the energy-requiring Na+K+ ATPase and other ATP dependent currents results in excess of myocellular sodium loading through failure of sodium efflux. The late sodium current, as a result of its persistent flow throughout the action potential, may make a substantial contribution to this ischemic sodium loading [15]. Excess sodium loading increases oxidative stress, increases myocellular calcium loading perhaps through the influence of sodium on calcium countertransport through NCX and depletes mitochondria of their calcium (which reduces the mitochondrial Kreb’s cycle activity and exacerbates energy deficiency) [16]. The mechanism through which blocking late inward sodium currents, leads to a reduction in angina remains the subject of active investigation but ranolazine, a late inward sodium current blocker with pFOX activity [17] does exhibit some anti-anginal properties [18].

The Future
A number of successful metabolic therapies are therefore presently available for clinical therapy, especially for chronic ischemic heart disease. Two directions remain to be pursued.

Greater experience with existing therapies
Substantial advances have been made in developing and demonstrating the safety and efficacy of a number of metabolic agents for the treatment of ischemic heart disease. Indeed a number of these agents, e.g., ranolazine and trimetazidine, have been tested in clinical trials. The paucity of use of these agents partially reflects the requirement for further education of clinical colleagues. However, perhaps a more trenchant reason for the lack of extensive use of these agents derives from a lack of clarity about the ideal context for their use. Existing agents such as β-blockers, nitrates, calcium channel antagonists and specific rate-limiting agents, such as ivabradine, all successfully mitigate the consequences of ischemia in many patients. One of the challenges for many practitioners is, to identify the population in which these products will offer them the most adapted benefits, e.g., those with concomitant metabolic disease such as the metabolic syndrome/diabetes mellitus or those with ventricular dysfunction, whose cardiac metabolic dysfunction may respond especially well to metabolic modulation.

Novel metabolic therapies
While inhibition of FFA oxidation continues to represent a credible strategy for the treatment of chronic ischemia, there is substantial potential for identifying novel metabolic nodes for treatment. Existing interesting...
metabolic therapies such as dichloroacetate which, through liberating pyruvate dehydrogenase from its kinase inhibitors, augments carbon flux into the Kreb’s cycle have been disappointing by virtue of their pharmacokinetics and their potential side effects. However, there are a number of novel avenues to pursue. Firstly, it is increasingly recognized that as well as their roles in energy generation, metabolites can marshal a wider group of biological responses that are amenable to therapeutic modulation. For example, the Kreb’s cycle intermediate, succinate, acting through G protein-coupled receptor-91, can determine angiogenesis as a response to chronic ischemic stress. This observation supports the contention that a broader vision of metabolic manipulation is likely to elevate metabolic therapy beyond energy modulation [19]. Pursuing this theme further, established metabolic therapies such as GLK and more specifically agents such as glucosamine post-translationally modify serine and threonine residues of proteins by the O-linked attachment of the monosaccharide β-N-acetyl-glucosamine (i.e., O-GlcNAc) [20]. As well as subserving metabolic benefits, metabolic therapies also have profound influences on other aspects of cardiac biology as diverse as contractility and clock function [21].

**Conclusion**

Accordingly, the future of metabolic therapies likely lies in a redoubling of clinical efforts to apply existing therapies to patients likely to benefit most from them, and to recognize the potentially beneficial consequences of metabolic therapies on exciting novel biological pathways, a better understanding and application of which holds promise for conferring additional benefits to patients with acute or chronic cardiac ischemia.

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**References**