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Reviews

Ischemic Heart Disease: Metabolic Approaches to Management

DANIEL F. PAULY, M.D., PH.D., AND CARL J. PEPINE, M.D.

University of Florida College of Medicine, Division of Cardiovascular Medicine, Gainesville, Florida, USA

Summary: The number of patients with coronary artery disease and its risk factors is increasing in Western nations. New treatments for these patients may soon include a class of agents known as the metabolic modulators. This group of agents consists of the partial fatty acid oxidation inhibitors trimetazidine and ranolazine, as well as dichloroacetate, which promotes carbohydrate utilization. Metabolic modulators also include the nutriceuticals L-carnitine and D-ribose. The available evidence regarding the benefits of each of these five agents is reviewed.

Key words: trimetazidine, ranolazine, dichloroacetate, carnitine, ribose, angina, ischemia, coronary artery disease

Introduction

Various coronary artery disease risk factors continue to increase among Western populations. These include advancing age of the population as well as ever-increasing prevalences of obesity, diabetes, and hyperlipidemia. As a result, the prevalence of coronary artery disease continues to increase. Therapeutic options for patients with coronary disease include percutaneous coronary interventions, coronary bypass surgery, and newer therapies including enhanced external counterpulsation and investigational gene therapy approaches. As the number of patients living with coronary artery disease continues to increase, however, the number of patients with coronary disease that is refractory to these therapies also continues to increase. It therefore remains important to continue to develop new medical treatments for ischemic heart disease.

Current medical therapies for treating angina include agents that increase coronary arterial blood flow (such as nitrates) and agents that decrease myocardial work (such as beta-adrenergic blockers and calcium-channel antagonists). Myocardial work can be decreased by a variety of mechanisms including reductions in heart rate, preload, afterload, or myocardial contractility. Current management paradigms focus on medications directed toward optimizing these hemodynamic effects. In addition to hemodynamic treatments, a novel group of agents that work via other mechanisms are available for the treatment of myocardial ischemia. These agents are designed to improve cardiac metabolism and cardiac energy availability and are termed metabolic modulators. They include trimetazidine, ranolazine, dichloroacetate, L-carnitine, and D-ribose.

In cardiac muscle, free fatty acids comprise the primary fuel for aerobic metabolism. During ischemic episodes, oxygen supply to the tissue becomes limited. Agents that decrease fatty acid utilization and increase glucose utilization are believed to be beneficial, since glucose use results in more adenosine triphosphate (ATP) per unit atom of oxygen consumed than do fatty acids. By switching from fatty acids to glucose, various models of ischemia result in an 11% greater yield of ATP for each unit atom of oxygen consumed.[1] Animal studies have shown that during periods of moderate to severe cardiac ischemia the fatty acid oxidation produces reducing equivalents and conversion of pyruvate to lactate is increased. Drugs that decrease fatty acid oxidation, therefore, also result in less lactate accumulation and less lactic acidosis.

Trimetazidine

Trimetazidine is one such fatty acid oxidation inhibitor. It is available for clinical use worldwide and acts via selective inhibition of 3-ketoacyl CoA thiolase. Trimetazidine has been shown to be efficacious in the treatment of ischemic heart disease in various studies. The Trimetazidine European Multicenter Study (TEMS) included 149 men with stable angina and documented coronary artery disease. Patients were randomly assigned to treatment with trimetazidine or propanolol

Address for reprints:

Daniel F. Pauly, M.D., Ph.D.
Associate Professor of Medicine
Division of Cardiovascular Medicine
University of Florida College of Medicine
1600 S.W. Archer Road
Gainesville, FL 32610, USA
e-mail: paulydf@medicine.ufl.edu

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orally for 3 months. The time to ST-segment depression on exercise testing and the time to onset of symptomatic angina were comparable in both groups.[2] In another study, trimetazidine was added to standard antianginal therapy (with long-acting nitrates, calcium-channel antagonists, and beta blockers). After 4 weeks of therapy, there were significant reductions in the number of symptomatic episodes of angina and significant improvements in the time to ischemia-related electrocardiographic (ECG) changes on exercise testing.[3]

In a large, recently published meta-analysis, 12 clinical studies of trimetazidine performed between 1985 and 2001 were evaluated. Trimetazidine emerged as efficacious in the treatment of angina pectoris both as monotherapy and in combination with other antianginal agents. Trimetazidine significantly reduced the number of symptomatic anginal episodes and improved the time to objective, exercise-induced ECG changes.[4]

Ranolazine

Ranolazine is a partial fatty acid oxidation inhibitor.[5, 6] It acts in a similar way as trimetazidine. In addition to decreasing fatty acid oxidation, ranolazine has been found to inhibit the electron transport chain in damaged, uncoupled mitochondria.[7] It has, therefore, been postulated that ranolazine may prevent mitochondria that are damaged by an ischemic insult from wasting energy via futile cycling of the electron transport chain.

Two phase III studies of ranolazine in patients with angina have recently been performed. These are Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) and Combination Assessment of Ranolazine in Stable Angina (CARISA). In MARISA, 175 patients were assigned to monotherapy with sustained-release ranolazine at one of three dosing schedules or were assigned to placebo.[8] Time of exercise, time to onset of ST-segment depression on ECG, and time to onset of symptomatic angina were all improved with ranolazine treatment.

In CARISA, therapy with ranolazine was added to standard, hemodynamic antianginal therapy.[9] Patients (n = 823) were randomized to 12 weeks of treatment with one of two doses of sustained-release ranolazine or placebo. Exercise time and time to onset of symptomatic angina were significantly improved in the treatment groups. In addition, the time to onset of ST-segment depression by ECG showed a trend toward improvement in the ranolazine group. The anti-ischemic benefits of trimetazidine and ranolazine occur without effects on heart rate or blood pressure, leading to these agents being called metabolic modulators.

Dichloroacetate

Dichloroacetate is a specific inhibitor of pyruvate dehydrogenase kinase. As a result, this compound stimulates pyruvate dehydrogenase activity and increases oxidation of pyruvate. This enhances carbohydrate oxidation in preference to fatty acids. In addition, the presence of dichloroacetate results in increased utilization of lactic acid, so that the lactic acid levels that rise during periods of ischemia are preferentially metabolized.

In one study, dichloroacetate was given to patients with coronary artery disease via intravenous infusion.[10] In this study, left ventricular stroke volume was improved. This occurred in the absence of effects on heart rate, left ventricular end-diastolic pressure, or myocardial oxygen consumption, suggesting that more efficient carbohydrate metabolism was responsible for the beneficial effect on stroke volume.

L-Carnitine

Supplementation of L-carnitine has also been studied as a metabolic treatment in coronary heart disease. As discussed above, fatty acid metabolism is altered during periods of cardiac ischemia, resulting in substantial increases in intracellular levels of lysolecithins, free arachidonic acid, and acylcarnitines, as well as substantial decreases in free carnitine levels.[11] In addition, brief periods of cardiac ischemia result in depressed activities of the acylcarnitine transport enzymes.[12, 13] L-carnitine is the biologically active isomer of carnitine, and supplementation of this molecule is believed to protect cardiac cells against oxidative stress, hypoxia, and ischemia. One theory is that carnitine is cardioprotective by its indirect effect of decreasing levels of toxic coenzyme A derivatives.[14] Others theorize that carnitine is beneficial due to upregulation of carbohydrate metabolism.[15]

The effect of supplemental carnitine on long-term left ventricular dilatation was studied in a multicenter trial of 472 patients with first acute myocardial infarction.[16] In a randomized design, patients received placebo or carnitine within 24 h of symptoms of myocardial infarction. Carnitine was administered as a 9 g/day intravenous dose for the first 5 days and then 6 g/day orally for 12 months. In all, 348 patients were assessed for left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and ejection fraction via echocardiography.

In the carnitine-treated patients, LVEDV and LVESV were significantly improved compared with placebo at 3, 6, and 12 months. At 12 months, LVEDV for the carnitine-treated patients averaged 99.3 ± 2.1 ml vs. 105.4 ± 2.4 ml for the placebo group ($p = 0.01$). Clinical outcomes at 12 months of follow-up also showed fewer deaths (10 vs. 13%) and less clinical heart failure (4 vs. 10%) in the carnitine-treated group.

D-Ribose

D-ribose supplementation in ischemic heart disease is believed to be beneficial via pathways different from those outlined above. During transient myocardial ischemia, the electron transport chain becomes limited. Levels of adenosine monophosphate (AMP) and adenosine diphosphate (ADP) increase, as their rephosphorylation to adenosine triphosphate (ATP) is impaired. After longer ischemic times, AMP and

ADP are degraded to adenosine, inosine, and hypoxanthine, which diffuse out of the cell and are washed away during the reperfusion period. Once lost from the heart cell, these metabolites are not available to the purine salvage pathway, and depletion of adenine nucleotides limits the ability of the cells to regenerate ATP.

One strategy for therapy is to enhance replenishment of adenine nucleotide pools by providing exogenous D-ribose. D-ribose supplementation has been tested in human cardiac ischemia. In one study, 24 patients with severe coronary artery disease and stable exertional angina were exercised to the point of anginal symptoms and 1 mm ST-segment depressions.[17] The treadmill test was repeated the next day, and those who had reproducible times to reaching angina were randomized to a 3-day course of oral D-ribose or placebo. Those in the D-ribose-treated group showed significant improvement in their time to anginal symptoms and in their time to ST-segment depression on ECG. This suggests that D-ribose supplementation improves synthesis of adenine nucleotide pools, leading to improved tolerance to ischemia.[17]

Conclusion

The treatment of myocardial ischemia continues to be an ongoing challenge. Along with traditional hemodynamic methods of decreasing oxygen consumption by reducing heart rate, blood pressure, and cardiac work, metabolic modulators that improve biochemical efficiency of the cardiac myocyte represent a promising new therapeutic approach. Trimetazidine decreases fatty acid oxidation and has a large body of evidence supporting its antianginal and anti-ischemic benefits. Ranolazine, which is still under development, also has data showing protection against the deleterious effects of myocardial ischemia. Carbohydrate promoting agents such as dichloroacetate, and nutriceuticals such as L-carnitine and D-ribose, are other potential beneficial agents. Clinical trials to confirm the magnitude of benefit of each of these agents in the treatment of ischemic heart disease continue.

While the latest trends in revascularization procedures now include drug-eluting stents to minimize vessel restenosis, not all patients have target vessels amenable to revascularization approaches. Therefore, there continues to be a place for new medical strategies for treating ischemic heart disease. It therefore seems clear that the management of ischemic heart disease will continue to include new medical approaches in addition to the ever-evolving interventional approaches.

Addendum

Since the development of this review, two pivotal publications have provided strong additional support for the concept of metabolic approaches to managing ischemic heart disease.[18, 19]

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