Laboratory investigations into preserving viability of the ischemic myocardium or to promote recovery during reperfusion have often focused on the intermediary pathways of energy metabolism. However, in the clinical treatment of angina, the application of metabolic therapies has generally lagged behind or has been incidental to other approaches, such as a vasodilators, calcium antagonists, and negative inotropes. A study published in this issue of Circulation Research has demonstrated that the antianginal agent trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride [TMZ]) inhibits the activity of one of the enzymes of the β-oxidation pathway in cardiac mitochondria with direct increases in glucose oxidation. These findings confirm in an intact, functioning heart model the well-documented, anti-ischemic properties of TMZ and the inhibitory effects of TMZ on long-chain fatty acid oxidation with reciprocal enhancement of glucose uptake. The study localizes the inhibition of β-oxidation to a specific enzyme, the mitochondrial long-chain 3-ketoacyl coenzyme A (CoA) thiolase. The suggestion by the authors is that the effectiveness of TMZ as an antianginal agent is directly linked to this inhibitory effect on long-chain fatty acid oxidation.

Although studies on the isolated heart preparation can neither specifically nor conclusively identify an antianginal mechanism, the findings of the University of Alberta group1 are consistent with the known effectiveness of TMZ as an antianginal agent that reduces long-chain fatty acid oxidation, while lacking both vasodilator activity and negative inotropic effects.9 The inhibitory effects of TMZ on long-chain fatty acid transport into rat heart mitochondria, via inhibition of carnitine palmitoyltransferase 1 (CPT 1) enzyme, have already been demonstrated, but TMZ was also found to be much less potent than two other proven antianginal drugs, perhexiline and amiodarone.5,10 However, TMZ does not induce the confounding vasoactive, inotropic and chronotropic responses of these other agents. Thus, the data suggesting that TMZ inhibits the long-chain 3-ketoacyl CoA thiolase, downstream from CPT 1, add to the argument for a purely metabolic mechanism of antianginal therapy. The implied effectiveness of pharmacological changes in the oxidative pathways of mitochondria in treating stable angina warrants a heightened awareness of metabolic enzyme activity and mitochondrial function as targets for clinical therapeutics.

### Shifting the Balance of Fuels for Energy Production

The ischemic and reperfused myocardium benefits from a shift away from fatty acid oxidation to that of carbohydrates.11–13 The ability of anaerobic glycolysis to support the ischemic myocardium is well established,14 but the benefits of glucose oxidation over that of fatty acid oxidation in the flow-limited myocardium are only now being realized. A shift toward glucose oxidation, which is a more efficient mode of ATP production per mole of oxygen used, is likely to benefit hypoperfused myocardium.

An agent that promotes carbohydrate oxidation via activation of pyruvate dehydrogenase (PDH), dichloroacetate, has improved left ventricular function in patients with coronary artery disease.15 Other agents, such as oxfenecine, etomoxir, and methylplamoxirate inhibit the oxidation of fatty acids. Among the inhibitors of long-chain fatty acid oxidation, TMZ and ranolazine, both have antianginal effects. Despite a growing body of evidence that enhancing carbohydrate oxidation, but not necessarily glycolysis, and reducing fatty acid oxidation are beneficial to the ischemic and reperfused heart, clinical studies of such metabolic protocols remain limited.

Noting the paucity of clinical data on metabolic support strategies is not to imply that the notion has not been a longstanding consideration. The use of glucose-insulin-potassium (GIK) solution as an adjunctive therapy for acute myocardial infarction is one of the first examples of an approach to intervene on cardiac substrate utilization.16 The bottom line to this approach is to maintain high-energy phosphate stores in ischemic myocardium. However, even on revascularization and the restoration of cellular energy charge, the postischemic heart remains abnormal and benefits from additional metabolic interventions that are shown experimentally to counter myocardial stunning. Thus, the observed changes in fatty acid and carbohydrate oxidation induced by TMZ, and related antianginal compounds, aid recovery during myocardial reperfusion.

### Mechanisms of Substrate Utilization

The effectiveness of direct strategies to shift the balance from fatty acid oxidation toward glucose oxidation in the reperfused myocardium now appears to be linked to both the recovery of intracellular pH and the cytosolic redox state of the myocytes.11,17 These two factors, pH and redox state, are
linked to proton production due to the counterbalance between coupling of glycolysis to the oxidation rate of glycolytic end products and the production and oxidation of lactate.\(^{11,17,18}\) However, beneficial effects of a more carbohydrate-based, oxidative energy metabolism are not uniquely dependent on glycolytic flux.\(^{\text{359-363}}\) Indeed, improved contractile recovery during reperfusion is more associated with the stimulation of pyruvate oxidation, as opposed to the nonoxidative metabolism of glycolytic end products that forms alanine and lactate in the cytosol.\(^{\text{19}}\) This balance between oxidative and nonoxidative pyruvate metabolism is central to the recovery of pH and cytosolic redox state that are both associated with posts ischemic contractile function.

Regulating the balance between the oxidation of fatty acids and pyruvate is the enzyme complex PDH. During early reperfusion, PDH is primarily in the inactive, phosphorylated state.\(^{\text{20}}\) Activating PDH is effective in improving the recovery of reperfused myocardium.\(^{11,17,19,21}\) However, such protocols on animal models have not proven effective during conditions of low-flow ischemia,\(^{\text{22}}\) when PDH remains in the active form.

The activity of PDH is also influenced by fatty acid oxidation rates. Thus, reductions in fatty acid oxidation, such as those produced by TMZ, increase the fraction of active PDH to produce an increase in carbohydrate oxidation. On the reciprocal end, when PDH activity is stimulated, as with inhibitors of PDH kinase, fatty acid oxidation becomes reduced.

Other mechanisms for reducing fatty acid oxidation hold potential for therapeutic use. A strong influence on the reduction in fatty acid oxidation is the inhibitory effect of malonyl CoA on CPT 1.\(^{\text{23}}\) Malonyl CoA is produced in the cytosol from the action of the enzyme acetyl CoA carboxylase on acetyl CoA. Thus, increased production of acetyl CoA has the effect of reducing long-chain fatty acid oxidation. Different isofom distributions of CPT 1 have the potential to mediate its responsiveness to malonyl CoA, in particular during pathophysiological changes.\(^{\text{24}}\) However, at different fatty acid oxidation rates in the heart, changes in CPT 1 activity have not yet been noted in the absence of a change in malonyl CoA level. This finding suggests that the modulation of CPT 1 responsiveness to malonyl CoA is not a strong regulatory factor in the normal myocyte.\(^{\text{13}}\) Thus, beyond pharmacological strategies, it remains to be seen whether differential expression of enzyme isoforms will prove effective in inducing similar therapeutic changes in cardiac metabolism.

**Ischemic Stress and Protein Activation**

Can the activity of one single enzyme, or the flux rate through one specific metabolic pathway be responsible for angina? Such an overly simplified scenario is unlikely the case, but the necessity of minimizing confounding variables in an experimental protocol may suggest such oversimplification. On the other hand, a less direct, but intriguing, notion is to target stress-activated proteins. The increased production and activation of enzymes that respond to pathophysiology can trigger a cascade of events, including metabolic changes that influence cell function and viability (Figure).

Such an example is the activation of stress proteins during ischemia, which leads to changes in glucose uptake and fatty acid oxidation. As a specific example, the glucose transporters GLUT-4 and GLUT-1 are translocated from the intracellular membranes to the sarcolemma in response to the low-energy, state-linked activation of 5′ AMP-activated protein kinase (AMPK) in the ischemic heart.\(^{25,26}\) Interestingly, the activity of AMPK also inactivates acetyl CoA carboxylase, with the net result of decreasing malonyl CoA levels.\(^{\text{27}}\) Thus, other regulating factors upstream from the enzymes of the metabolic pathways are potential targets for therapeutic approaches to improving the energy balance of the ischemic myocardium.

The efficacy of antianginal drugs, such as TMZ, that invoke a direct metabolic effect underscores the need for further elucidation of metabolic regulatory mechanisms that influence myocyte function and viability. Many of these mechanisms can be induced by protein production responses to ischemic stress, which is, in part, the product of impaired energy metabolism. Thus, we come full circle in the intervention of cardiac metabolism in ischemic and reperfused myocardium. The challenge then is to detect these metabolic changes in the functioning organ, where the physiological consequences can be elucidated.

**References**


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