THE SOURCE AND FATE OF PROTONS IN THE REPERFUSED ISCHEMIC HEART

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Summary. Metabolic modulation (i.e., optimizing the energy substrate preference by the heart during and following ischemia) is an exciting new approach to treating ischemic heart disease. However, the relationship between glucose metabolism and alterations in proton production and clearance during and following ischemia remains poorly understood. It is clear, however, that the recovery of mechanical function and cardiac efficiency in the reperfused postischemic heart is influenced by both the source and fate of protons. Inhibition of the source of protons during ischemia and/or reperfusion by improving the coupling between glycolysis and glucose oxidation will increase the rate of recovery of pH, and improve recovery of mechanical function and efficiency. Modulation of the fate of protons will also affect pH, but the consequences on function and efficiency will depend on the specific pathway by which the protons are cleared.

INTRODUCTION

Myocardial ischemia impairs contractility and, if prolonged, leads to myocardial infarction. Early restoration of blood flow, termed reperfusion, is the most effective strategy to minimize the adverse consequences of ischemia. Reperfusion is a common clinical event occurring during cardiac surgery, angioplasty, and thrombolytic therapy. Unfortunately, reperfusion, even in the absence of irreversible cell injury, does not always result in immediate and complete recovery of contractile function. An understanding of the mechanisms underlying the injury associated with ischemia–reperfusion is essential if new therapies are to be developed.

A critical component of ischemia–reperfusion injury is the accumulation of protons intracellularly that leads to a decrease in intracellular pH (pHi). Numerous
Figure 1. Overview of glucose metabolism in the heart, and how protons are produced and cleared by the heart.