Because of the high energetic demands required to maintain contractile function, the heart can utilize a variety of substrates, including fatty acids, glucose, lactate, ketone bodies and amino acids. Under normal flow conditions, the well-oxygenated heart oxidizes fatty acid as its primary source of ATP. However, during ischemia, when oxygen becomes rate limiting, the heart relies to a much greater extent on glycolysis for ATP production. The cellular changes responsible for this switch in substrate metabolism in the ischemic heart form the basis of current PET methods used to identify ischemic myocardium based on exercise-induced increases in fluorodeoxyglucose uptake (1).

The increase in glycolysis in the setting of myocardial ischemia is due to two factors. First, the inhibition of β-oxidation of fatty acids by the lack of adequate oxygen results in increased glycolysis through the activity of the Randle cycle. Second, glycolysis is increased in ischemic myocardium by translocation of the facilitative glucose transporters (GLUT) 1 and 4 (2, 3), which mediate the first (and rate-limiting) step of myocardial glucose utilization, glucose transport across the plasma membrane. This translocation occurs independent of the insulin signaling pathway that also causes translocation of GLUT1 and GLUT4 in the heart. Our group has demonstrated that the translocation of GLUT1 and GLUT4 in response to ischemia is mediated by AMP-activated protein kinase (AMPK), which is a metabolic “fuel gage” for the cell (4). AMPK is activated through both noncovalent and covalent mechanisms by decreases in the cellular ATP concentration and increases in the AMP concentration during ischemia. The activation of AMPK stimulates energy providing pathways, such as glycolysis, and inhibits energy consuming pathways, such as protein synthesis.

During reperfusion, when sufficient oxygen is once again present, fatty acid oxidation can become the predominant source of ATP synthesis. Interestingly, this is due in part to activation of fatty acid oxidation by AMPK (5). However, there is evidence that glucose uptake may remain elevated for up to 24 hours in previously ischemic areas (6). These findings suggest that the translocation of glucose transporters to the cell surface may persist for up to 24 hours following ischemic insult. Further studies are necessary to determine if either the activation of AMPK by ischemia or the translocation of glucose transporters may represent novel targets for molecular imaging of early and/or late ischemia.

Selected References