Molecular mechanisms of cardiac metabolic stress pathology

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Energy stress in the myocardium occurs in a variety of acute and chronic pathophysiologic contexts including ischemia, nutrient deprivation, and diabetic disease settings of substrate disturbance. Although the heart is highly adaptive and flexible in relation to fuel utilization and routes of ATP generation, maladaptations in energy stress situations confer functional deficit. An understanding of the mechanisms which link metabolic stress to impaired myocardial performance is currently lacking. Emerging evidence suggests that, in parallel with regulated enzymatic pathways which control intracellular substrate supply, other processes of 'bulk' autophagic macromolecular breakdown may be important in energy stress conditions. Recent findings indicate that cargo-specific autophagic activity may be important in different stress states. In particular, induction of glycophagy, a glycogen specific autophagy, has been described in acute and chronic energy stress situations. The impact of altered cardiomyocyte glucose flux relating to glycophagy dysregulation on contractile function is unknown. A cardiomyocyte cytosolic environment involving oxidative stress and altered hexose sugar flux, predisposing to protein glycation processes, is indicated. Both the occurrence of *O*-GlcNAcylation events and the formation of advanced glycation end-products as myofilament post-translational modifications may be implicated in contractile dysfunction in metabolic stress pathology.