Myocardial energy mis-appropriation in metabolic stress

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In various cardiac energy stress conditions, abnormal energy storage processes are evident. In particular when cardiomyocyte glucose uptake is limited there is paradoxical accumulation of glycolysis substrate in the form of glycogen. In experimental settings, the cardiac glycogen content in fasted animals is increased despite reduced levels of plasma glucose induced by nutrient restriction. This cardiac glucose elevation occurs in parallel with skeletal muscle and hepatic glycogen depletion. In diabetic metabolic stress states where glucose transport is profoundly reduced, either due to insulin deficiency or insulin resistance, cardiac glycogen levels are elevated. Clinically, in severe diabetic states the extent of glycogen accumulation in cardiomyocytes is substantial and has the potential to disrupt sarcomere ultrastructure and electromechanical coupling. The mechanistic basis for this apparent energy mis-appropriation in the form of increased stores of glycolytic substrate under conditions of decreased cellular import of glycolytic fuel is not understood. Our findings indicate that impaired glycogen flux managed *via* a glycogen phago-lysosomal breakdown process termed ‘glycophagy’ is implicated. Deranged glycophagy emerges as a prospective therapeutic target in remediation of diabetic cardiomyopathy.