

## **Cardiac hypertrophy and cardiomyocyte metabolic disturbances – cause and consequence**

*L.M.D. Delbridge, Department of Physiology, University of Melbourne, Parkville, VIC, Australia*

Disturbed cellular Ca handling is a hallmark feature of the hypertrophic myocardium. In a variety of cardiomyopathic states alterations in intracellular Ca cycling and/or sarcomeric Ca-stimulated ATP utilization have been identified. It is becoming increasingly apparent that, in parallel with these Ca homeostatic defects, a variety of metabolic and substrate utilization adaptations are integral to the hypertrophic phenotype. In the compensatory response of the hypertrophic myocardium to pressure overload a metabolic shift which comprises a ‘fetal recapitulation’ to glucose-reliant energy production is frequently observed. Paradoxically, restriction of glucose availability, the situation which occurs with insulin resistant down-regulation of glut4-mediated cardiomyocyte glucose uptake, is also associated with the development of hypertrophy. An increased role for peroxisomal B-oxidation in energy generation in many hypertrophic conditions, including diabetic cardiomyopathy, is also indicated and this may be linked with an elevation in the cellular levels of reactive oxygen species (ROS). The study of experimental models in which coincident metabolic and Ca homeostatic defects are observed provide mechanistic insights into the role of ROS in the development of cardiac hypertrophy. In particular our investigations of glut4-deficient mice and rodent models of diet-induced insulin resistance have been informative, where assessment of cardiomyocyte excitation-contraction coupling performance, ex vivo heart function and response to substrate substitution can be evaluated. The use of DNA microarray expression profiling to examine global shifts in myocyte signalling and metabolic pathways in hypertrophic cardiomyopathic states provides additional information about the relationship between Ca, metabolism and ROS production in the hypertrophic response.