**PATHOGENESIS AND THERAPY OF DIABETIC CARDIOMYOPATHY**

**N.S. Dhalla**

St. Boniface Hospital Albrechtsen Research Centre, University of Manitoba, Winnipeg, MB, Canada

Chronic diabetes is known to be associated with the development of cardiomyopathy, metabolic derangement and cardiac dysfunction. Extensive studies in our laboratory have revealed that cardiac dysfunction due to chronic diabetes is associated with marked alterations in subcellular organelles such as myofibrils (MF), sarcoplasmic reticulum (SR) and sarcolemma (SL). These diabetes-induced changes in the heart appear to be due to the development of oxidative stress as a consequence of elevated levels of plasma glucose as well as prolonged activation of different hormonal systems and platelets. This view is based on our observations that treatment of streptozotocin-diabetic rats for 8 weeks with different antioxidants attenuated alterations in cardiac function as well as MF Ca2+-stimulated ATPase, SR Ca2+-release and Ca2+-uptake, and SL Na+-K+ ATPase activities. Furthermore, treatment of diabetic animals with sarpogrelate, an antiplatelet agent, for 8 weeks was observed to attenuate changes in the protein content of glucose transporters (GLUT 1 and GLUT 4), oxidative stress and abnormalities in cardiac function as well as alterations in various activities of MF, SR and SL. Several metabolic interventions, which prevented the occurrence of intracellular Ca2+-overload, were also observed to produce beneficial effects on the diabetes-induced abnormalities. These results suggest that elevated levels of plasma 5-HT due to platelet aggregation, in addition to metabolic derangement and oxidative stress, may play an important role in inducing defects in glucose utilization and cardiac dysfunction in chronic diabetes.