Numerous cancer studies demonstrate that tumors exhibit both increased glucose metabolism and an increased propensity to survive in the face of stressful stimuli. These studies overwhelmingly correlate with overexpression of the rate-limiting glycolysis enzyme hexokinase-2 (HK2). However, the mechanisms linking increased glucose metabolism and survival are unknown. Therefore, the current studies were designed to determine the mechanisms by which increased HK2 expression promotes cell survival, as well as investigate whether HK2 overexpression could attenuate a mouse model of cardiac disease. We demonstrate that HK2 binding to voltage-dependent anion channel 3 (VDAC3) on the mitochondria is important for protection against cell death. We also show that cardiac HK2 overexpression limits cardiomyocyte hypertrophy and cell death in response to chronic isoproterenol administration. Results from these studies demonstrate that HK2 acts as an antioxidant during cardiac hypertrophy, and that this decrease in reactive oxygen species accumulation is mediated via the pentose-phosphate pathway. Collectively, our data establish several mechanisms by which HK2 overexpression and increased glucose utilization protect against cardiac cell death and disease. Additionally, these findings raise the possibility that activation of HK2 may be a therapeutic target in cardiac pathologies.