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## ACUTE EFFECTS OF HIV PROTEASE INHIBITORS IN THE FAILING HEART

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While there is growing concern that the metabolic changes associated with the clinical use of HIV protease inhibitors (PIs) will increase long term risk of cardiovascular morbidity and mortality, the potential for PIs to produce acute changes in myocardial energy metabolism has not been previously explored. PIs are known to directly inhibit GLUT4, which is the predominant glucose transporter in the heart. The normal metabolic flexibility of myocardium is reduced under periods of acute stress and injury, with an increased reliance upon glucose. The acute effects of ritonavir on glucose tolerance, myocardial GLUT expression, glucose uptake, morbidity and mortality were therefore investigated in a novel mouse model of dilated cardiomyopathy. TG9 mice, which express high levels of the cre recombinase under the  $\alpha$ -MHC promoter, predictably die of cardiac failure between 11 and 12 weeks of life. Together with the development of cardiomyopathy, TG9 mice develop insulin resistance, with overt diabetes by 8 weeks of age. At 10 weeks of age, GLUT4 expression was unchanged whereas GLUT1 expression was increased 2.5 fold compared to age and weight matched nontransgenic littermate control mice. Treatment of TG9 mice with ritonavir (10 mg/kg) at 10 weeks of life produced an acute 30% reduction in basal cardiac 2-deoxyglucose uptake compared to vehicle treated TG9 controls. Daily dosing of ritonavir beginning on day of life #75 resulted in a significant acceleration in the time to cardiac failure and death compared to vehicle treated controls ( $78.9 \pm 1.9$  and  $83 \pm 3.7$  days, respectively;  $P < 0.02$ ). All of the PI-treated mice died within two hours of ritonavir administration whereas death in vehicle treated mice was observed irrespective of time of day. Indinavir (10 mg/kg/d) had a similar though less pronounced effect on survival ( $80.5 \pm 1.2$  days). The PI atazanavir, which does not block GLUT4 activity, had no effect on myocardial glucose uptake or survival. These data suggest that acute PI-mediated GLUT4 blockade may adversely

affect cardiac function in patients with pre-existing heart disease and/or those who develop cardiomyopathy.

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15

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