In vivo Creatine Kinase Kinetics in Diabetic Heart: Relationship to Cardiac Work.

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INTRODUCTION: The creatine kinase (CK) system is central to mammalian energy production and reversibly converts adenosine diphosphate (ADP) and phosphocreatine (PCr) to adenosine triphosphate (ATP) and creatine (Cr). It serves as an energy reserve and transport mechanism ensuring that there is an abundant and immediate ATP supply for contractile work (1). Magnetization transfer 31P magnetic resonance spectroscopy (MRS) is the only non-invasive tool to study CK flux in the heart (2). The role of CK system in diabetic heart has been investigated in small number of studies using isolated perfused heart preparation and has led to contradictory results (3, 4). This may be because of the impaired metabolic stability of ex vivo diabetic heart, reduced oxygen carrying capacity of buffer, substrate composition in the buffer, and reduced levels of workload achieved in perfused heart. In this work we demonstrate for the first time in vivo CK flux measurement at 4.7T in closed chest rat hearts. We also investigated the role of energy metabolism in diabetic heart and its relationship with cardiac work.

METHODS: Sprague Dawley (SD) (n = 6), and Zucker Diabetic Fatty (ZDF) rats (lean = 6 and obese = 3), as a model for non-insulin-dependent diabetes mellitus, were used in this study. The rats were anesthetized with 1.5% isoflurane and placed prone on 2 cm diameter 31P surface coil and the body temperature was maintained via warm water bag under the animal stomach. The CK flux was measured using 31P saturation transfer technique at rest and at high cardiac work (stress) during 20 µg/Kg/min dobutamine infusion via tail vein catheter.

Experiments were done on Varian 4.7T magnet. Spatial localization was performed in one dimension using 1D image-selected in vivo spectroscopy (1D-ISIS) sequence with an adiabatic inversion pulse of 3 ms duration (3300 Hz bandwidth). An adiabatic half passage pulse optimized to provide a 90° flip angle at a distance of 1 cm from the coil was used for excitation. Other acquisition parameters were: 64 signal averages, 6 sec repetition delay, 3000Hz spectral width, and acquisition time of 170 ms. Magnetization transfer data was obtained by progressively saturating γ-ATP resonance frequency with saturation times ranging between 0.1 to 9 sec with a total data collection time of ~ 90 minutes. An external phantom consisting of 0.15 mM phosphate solution was used to quantify the in vivo metabolite concentrations. Spectra were analyzed using jMRUI software package and saturation transfer data were fit to a two-site chemical exchange model to determine the CK rate constant (Kf) and flux (Kf • [PCr]) using MATLAB software.

RESULTS: The average heart rate at baseline was 308.6 ± 15.4 and increased to 421.7 ± 34.7 during dobutamine infusion. Figure 1 shows the results of CK flux at rest and high work.

CONCLUSIONS: We have demonstrated that using optimal saturation transfer method we can quantify the CK flux in closed chest in vivo rat hearts within reasonable time. We found that CK flux was closely coupled to cardiac performance in normal SD and ZDF lean rats. PCr concentration was lower in diabetic animals and energy production for cardiac work was maintained at rest by higher CK rate constant. When cardiac work was increased the CK flux in diabetic animals did not increase in proportion to the work indicating impaired energy production. Recent studies have shown that contractile dysfunction becomes apparent at higher work load in diabetic animals and CK flux is coupled to oxygen consumption, i.e., the rate of ATP synthesis. This taken together indicates that reduced energy production in diabetes may be a cause of contractile dysfunction at high workload.