Detection of Myocardial Microvascular Disease in Latino Type-I Diabetes Mellitus Patients using P-31 MRS

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Introduction. Type-1 diabetes mellitus (DM) patients are known to have microvascular disease involving the kidneys, the peripheral nerves and the retina [1]. Such patients have a substantial increase in the incidence of coronary artery disease. Yet, the presence and impact of diabetic microvascular disease on the myocardium has not been established. Stress testing in association with electrocardiography, echocardiography or radionuclide myocardial perfusion imaging has not established the presence of microvascular dysfunction associated with DM. Decrease in phosphocreatine (PCr) using stress myocardial ^{31}P MRS suggestive of ischemia has been observed in patients with coronary artery stenosis [2]. It has been previously reported that a significant decrease in PCr/ATP during stress in women with chest pain but normal coronary arteries was observed that suggests myocardial ischemia associated with microvascular dysfunction or disease [3]. The present study aims at determining if there are metabolic changes in the myocardium in diabetics that could suggest microvascular dysfunction. We used ^{31}P MR spectroscopy during rest and stress in young Latino patients with Type-1 DM to determine if there are changes in myocardial high energy phosphates (HEP) suggestive of myocardial ischemia.

Methods.

Patient population: Latino patients with Type-1 DM of greater than 10 years in duration were selected from a registry of more than 2,000 Type-1 DM patients at University of Southern California. They are younger and have a lower incidence of large vessel coronary artery disease compared to patients with Type-2 DM. Patients with signs or symptoms of epicardial coronary artery disease (CAD) or of overt renal disease were excluded. A comprehensive history and physical examination were obtained for all study subjects. All subjects underwent a metabolic panel, urinalysis and an ophthalmologic fundoscopic examination. Of 71 patients enrolled in the study, 45 had technically adequate stress ^{31}P MRS. Mean age was 28±7 years. The mean duration of diabetes was 16±4 years, body mass index was 29.7± 6.1, hemoglobin A1C was 9.6±2.2, total cholesterol was 183±40 gm/dl, and triglyceride levels were 123±10.6 gm/dl. Microalbuminuria or diabetic retinopathy was present in 12.5%, and in 31% of patients, respectively. Seven age-matched Latino normal controls also underwent stress MR examinations as well as metabolic panel.

MRI & ^{31}P MRS: MR examinations were performed at 3T (General Electric HD, Milwaukee). Both ejection fraction and high energy phosphates (HEP) were evaluated using cine MRI and ^{31}P MRS during rest and stress. During stress, mild level stress was applied using home built digital handgrip stressor using a McMaster Cu-Be strain gauge in which the stress was measured in pressure [kg-g/m2]. The Beekley MR-spots (Bristol, CT) were placed on the surface coil to correctly place the coil during scout imaging. The cine MR imaging was performed using a 2D-FIESTA sequence to evaluate ventricular function during rest and stress. After B_o shimming with PRESS voxel, ^{31}P signal was obtained from the 15mm-thick double-oblique DRESS [4] slice which mainly covers anterior left ventricle and septum (3 R-R TR, 128 avg, 5kHz). Three sets of ^{31}P spectra were obtained at rest, stress and recovery. During the stress acquisition, the subject was asked to squeeze the handgrip by 30% of maximum voluntary contraction.

Coil: Either a laterally elongated quadrature surface coil (transceiver mode), or single-turn linear coil was used as we previously reported [5]. The ^{31}P acquisition with quadrature coil pair yielded better signal-to-noise ratio with minimized contamination from the liver. The circular coil (10 cm in dia.) was primarily used as it showed higher signal-to-noise ratio for deeper slices (>6 cm), yet with the contamination signal from the liver within controllable amount. The coil was placed as the homogeneous B_1 field was overlaid on the anterior left ventricle and septum.

Analysis: HEP levels were evaluated by processing ^{31}P spectra in the time domain using AMARES (MRUI 3.0, European Union), and T_1 and blood correction were made.

Results and Discussion. Thirteen of 45 subjects showed a significant decrease (> 20%, 2 SD [3, 6]) in PCr/ATP (mean change in DM=-12.2%±0.19) during handgrip stress whereas seven normal controls showed no significant decrease (-1.1%±0.07) (Figure 1). No significant change in ejection fraction during stress was observed (5.1%±0.05). Retinopathy was present in 43% of the diabetics and none of the controls. The significant drop was observed more frequently in the patients with retinopathy than without (67% vs. 18% (female) 40% vs. 11% (male) p=0.01) (Figure 2), Albuminuria was present in 30% of diabetics and none of the controls. This stress-induced reduction in PCr/ATP suggests myocardial microvascular abnormality. This abnormal response probably occurs earlier than retinal or renal involvement. Our findings may indicate that in a subgroup of Type-1 DM patients, stress ^{31}P MRS can identify abnormal cardiac metabolism that is likely microvascular in origin. Non-invasive stress myocardial ^{31}P MRS identifies abnormal HEP metabolism that predicts an ischemic response in DM patients unlikely to have epicardial CAD, but suggestive of microvascular dysfunction/disease and ultimately possible cardiomyopathy.

References
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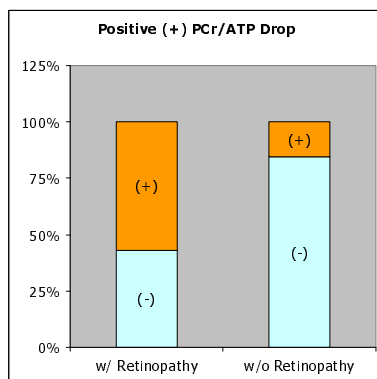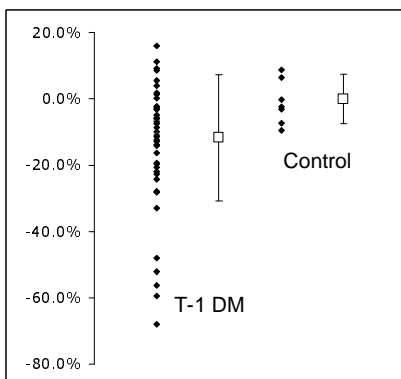6. Johnson BD, et al. Circulation 109:2993-2999 (2004)

Figure 1(left). PCr/ATP drop during stress in T-1 DM patients (mean -12.2%) vs. normal controls (mean -1.1%).

Figure 2 (right). PCr/ATP drop more than 2 SD in controls during stress are regarded as significant. 57% of the patient with retinopathy showed significant drop in PCr/ATP during the stress whereas only 15% without retinopathy.