Cardiac-Specific GLUT1 Overexpression Preserves Contractile Reserve in Diabetic Mouse Hearts: a Multi-Phase DENSE MRI Study under Dobutamine-Induced Cardiac Stress

J. Zhong[1,2], F. Bian[1,2], W. Li[1,2], P. Chaudhuri[1], R. Tian[3], and X. Yu[1,2]

[1]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, United States, [2]Case Center for Imaging Research, Case Western Reserve University, Cleveland, OH, United States, [3]NMR Laboratory for Physiological Chemistry, Brigham and Women's Hospital, Boston, Massachusetts

Introduction

Diabetes mellitus is associated with increased cardiac morbidity and mortality. Cardiomyopathy occurs commonly in diabetics independent of known risk factors such as coronary artery disease or hypertension. Although the underlying mechanism is multifactorial, evidences are emerging towards metabolic disturbance that may play a causal role in modulating myocardial contractile performance and the pathogenesis of diabetic cardiomyopathy (1,2). In our previous study, we found normalized basal cardiac function in diabetic mice with cardiac-specific overexpression of a basal cardiac glucose transporter, GLUT1. In the current study, we aimed to test the hypothesis that contractile reserve in Type I diabetic mouse hearts is preserved by metabolic modulation through GLUT1 overexpression. Such preservation will lead to normalized β-adrenergic response. To test this hypothesis, we investigated cardiac functions in diabetic mouse hearts using multi-phase MR Displacement Encoding with Stimulated Echoes (DENSE) under dobutamine-induced cardiac stress.

Methods

Animal Models Type I diabetes was induced by streptozotocin (STZ, 50 mg/kg body wt) injection in 2-month-old GLUT1-overexpressed (GLUT1-TG) mice (n=5). Saline-injected, age-matched GLUT1-TG (n=5) mice were used as the controls. Blood glucose level was measured two weeks after STZ injection. Mice with a blood glucose level above 250 mg/dl were considered diabetic.

MR Imaging and Image Analysis Animals (n=10) were scanned 16 weeks after STZ injection using Bruker (Bruker Biospec, Germany) 9.4T scanner with a 3.5 cm quadrature volume coil (Rapid Biomedical GmbH, Germany). The body temperature was maintained at 35.5±0.6°C during imaging through a feedback control system that blew hot air into the magnet (SA Instruments, NY). Multi-phase DENSE images before and during dobutamine infusion were acquired at apex and base (1 mm below and above mid-ventricle). Following the acquisition of the baseline DENSE images, the mouse was continuously infused with dobutamine at a dose of 40 μg/min/kg body wt/min through tail vein catheterization. After about 10 minutes of stabilization, DENSE images were acquired at the same short-axis positions.

Multi-phase DENSE sequence was developed using SPAMM11 tagging and cine-FLASH (3). With other parameters unaltered, displacement encoding and unencoding gradients with same magnitude but opposite polarities were used in 2 separate acquisitions. The subtraction of these two acquisitions eliminated baseline phase errors and increased displacement sensitivity. Imaging parameters were: flip angle, 20°; TE, 2.3 ms; FOV, 3 cm × 3 cm; matrix size, 128×128; slice thickness, 1 mm; NA, 6. Displacement encoding frequency (*k*) was 0.91 cycles/mm. 14 frames were acquired in one cardiac cycle which yielded a temporal resolution of 7-11ms.

Images were analyzed using a MATLAB-based MR Image Analysis Tool. A k-space filter was used to eliminate T1-relaxation echo and residual complex conjugate echo. After 2D-IFT, phase images from opposite gradient polarities were subtracted. Afterwards, the deformation gradient tensor, *F*, was calculated using the spatial gradient of the phase images. 2D Lagrangian strain tensor (*E*) was calculated directly as $E=1/2(F^TF-I)$ without the need for phase-unwrapping.

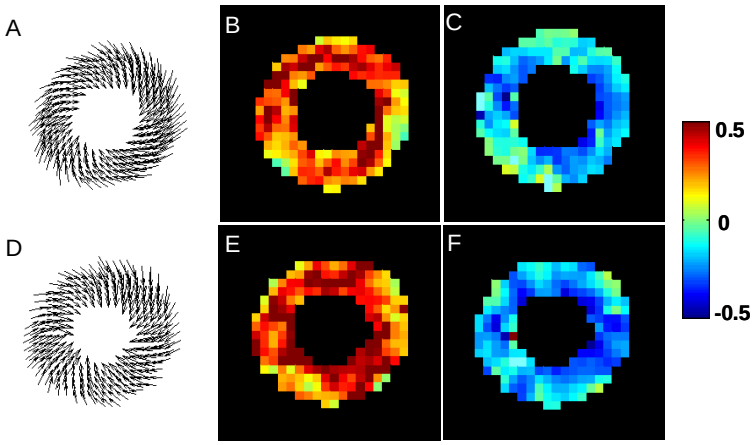

Figure 1. Representative 2D displacement fields (A&D), radial (B&E) and circumferential strains(C&F) of a GLUT1-TG diabetic mouse heart at baseline (A,B,&C) and under dobutamine-induced cardiac stress (D,E,&F) at apex.

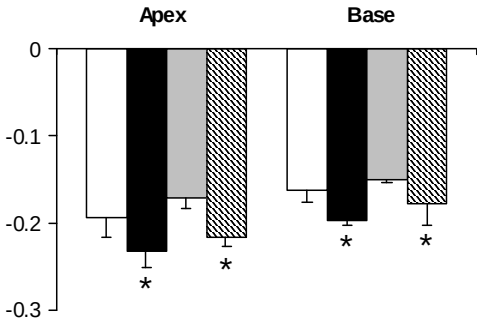

Figure 2. Peak systolic circumferential strains of GLUT1-TG diabetic mice at baseline (open bars), under dobutamine-induce cardiac stress (solid bars), and GLUT1-TG controls at baseline (grey bars) and under dobutamine stimulation (hatched bars) at apex and base. *: P<0.05 comparing with its baseline.

Results

Dobutamine-induced heart rate (HR) increase was 23% in GLUT1-TG diabetic mice and 18% in the controls (P<0.05 compared to baseline HR). There was no difference in dobutamine-stimulated HR between the diabetic and the control mice (P=NS). Under dobutamine stress, similar ejection fraction (EF) were observed in the diabetic mice comparing to its controls at apex (75.5±0.8% vs. 74.1±2.1%, P=NS) and base (76.3±2.5% vs. 76.7±2.8%, P=NS). Dobutamine induced significant increases in both groups (P<0.05 comparing with baseline EF). Representative displacement fields and myocardial strain maps of a GLUT1-TG diabetic mouse are shown in Figure 1. Significantly increased displacement, radial and circumferential strains were evident in dobutamine-stimulated hearts. Peak systolic circumferential strains of the two groups are shown in Figure 2. In response to β-adrenergic stimulation, no contractile depression was found in diabetic hearts comparing to the controls at both apex (-0.23±0.02 vs. -0.22±0.01, P=NS) and base (-0.20±0.01 vs. -0.18±0.02, P=NS). The circumferential strain in stressed diabetic mice was 19% and 21% higher than basal strains at apex and base, respectively, which was comparable to the increase in non-diabetic mice.

Conclusion

In the current study, myocardial contractile reserve was examined in STZ-treated, GLUT1-overexpressed mice using multi-phase DENSE under dobutamine-induced cardiac stress. In addition to the absence of diabetes-associated myocardial dysfunction at baseline, β-adrenergic response was also preserved in GLUT1-TG diabetic mice. Our results suggest that enhanced glucose utilization through cardiac-specific GLUT1 overexpression may have a beneficial effect in preventing contractile dysfunction in diabetic hearts. Our study also demonstrates the utility of multi-phase DENSE method in evaluating cardiac function of mouse hearts both at baseline and during β-adrenergic stimulation.

References

1. H Taegtmeyer, *et. al.,* Circulation, 2002;105:1727-33
2. S Boudina, *et. al.*, Circulation, 2007;115:3213-3223.
3. XD Zhong, *et. al.,* ISMRM, 2008