

Six hours of hyperglycemia and hyperinsulinemia affects cardiac function and increase myocardial lipid accumulation.

M. Krssak^{1,2}, Y. Winhofer³, D. Jankovic³, C. Anderwald³, G. Reiter⁴, S. Trattnig^{2,5}, A. Luger³, and M. Krebs³

¹Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Wien, Austria, ²Center of Excellence, HF MR, Medical University of Vienna, Wien, Austria, ³Internal Medicine III, Medical University of Vienna, Wien, Austria, ⁴Siemens AG Healthcare, Wien, Austria, ⁵Radiology, Medical University of Vienna, Wien, Austria

Background and Aims:

Diabetic cardiomyopathy is a disease specific entity which is present in patients with diabetes even in the absence of coronary artery disease and arterial hypertension. The pathophysiology of this disease is still unknown. However, recent evidence suggests that increased myocardial lipid accumulation (lipotoxicity) likely contributes to its development. Although recent investigations confirmed increased myocardial lipid content in patients with type 2 diabetes and impaired glucose tolerance [1,2,3], no evidence for cardiac steatosis in normoglycemic prediabetic-insulin resistant subjects was found [4]. Hence, we hypothesized that myocardial lipid accumulation might be linked to overt hyperglycemia/hyperinsulinemia typical for early type 2 diabetes. Therefore the aim of this study was to investigate the impact of hyperglycemia and associated hyperinsulinemia during a 6-h hyperglycemic-clamp on cardiac function and myocardial lipid content.

Material and Methods:

Hyperglycemic (HG; ~200 mg/dl, 6h) clamps were performed in 13 young, healthy, lean subjects (6 males, 7 females, BMI= 22.9±2.3 kg·m⁻², age= 28.9±6.0 y.). Plasma samples for determination of insulin, C-peptide and free fatty acid(FFA) -concentrations were obtained every hour. ¹H magnetic resonance imaging and ECG triggered localized ¹H single voxel MR spectroscopy were employed to measure left ventricular dynamic parameters and myocardial lipid accumulation in cardiac septum on a 3T Tim Trio MR System (Siemens Healthcare, Erlangen, Germany) at baseline and after 6 hours of hyperglycemia. In detail, visualization of cardiac function was performed using prospective ECG-gated cine TrueFISP sequences in 2-chamber, 4-chamber and short axes orientation. Short axes images were used to quantify left ventricular (LV) global (end-diastolic and end-systolic volume, stroke volume, ejection fraction and myocardial mass) via ARGUS software (Siemens Medical, Erlangen, Germany). Additionally FLASH-based prospective ECG-gated cine phase velocity encoding sequence was used to determine E/A ratio of mitral inflow as a measure of left ventricular diastolic function. ECG triggered localized ¹H single voxel MR spectroscopy (PRESS; TE= 30ms, NS= 8-12) was applied during a single breath hold and used to measure myocardial lipid accumulation in ventricular septum of study participants. Repetition time of the sequence was given by the heart beat of individual volunteer and ranged from 750 to 1250 ms. An additional spectrum without water suppression (NS= 4) obtained during a separate breath hold was used as the internal concentration reference. The spectra were processed by the Spectroscopy Processing tool within Syngo VB17 user interface provided by system manufacturer. The myocardial lipid content was calculated as a ratio of the sum of intensities of (CH₂)_n (1.25 ppm) and CH₃ (0.8-0.9 ppm) group resonances to the intensity of the water resonance from non-water suppressed spectra of the same VOI. Intensities of lipid and water resonance lines were corrected for T₁- and T₂- relaxation using individual repetition time and already published relaxation times of skeletal muscle at 3T[2]. Data are given as mean±SEM and were analyzed by paired t-Test.

Results: Plasma glucose levels were raised during the first hour of clamp to 200 mg/dl and stayed so till the end of the study. Plasma insulin concentration increase gradually to ~ 140 μU/ml and c-peptide concentrations to ~11 ng/ml. It is of note, that plasma free fatty acids were completely suppressed during hyperinsulinemia. ¹H MRS spectra of ventricular septum obtained before and after 6 hours of hyperglycemia are shown in the Figure. Detailed results of the study regarding the myocardial function and lipid accumulation are shown in table. Hyperglycemia and associated hyperinsulinemia for 6 hours was followed with a significant increase in myocardial lipid content (+25.7 %, p<0,01, Table & Fig), an increase in left ventricular ejection fraction (+4%, p=0.004) and a decrease in end-systolic-volume (-11%, p=0.02) (Table).

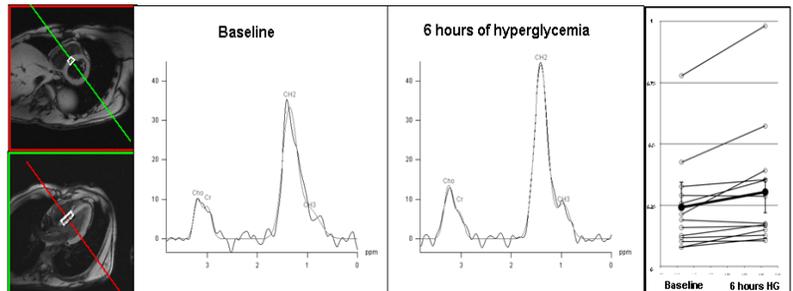


Figure: Position of VOI within intraventricular septum (left), typical ¹H MR spectra (middle) and individual myocardial lipid content value before and after 6h of hyperglycemia expressed in T₁ and T₂ relaxation corrected % of water signal.

Conclusion:

Combined hyperglycemia and hyperinsulinemia induce a short term increase in myocardial lipid content in healthy subjects indicating that these metabolic alterations might be directly responsible for myocardial steatosis in type 2 diabetes.

Grant support: Austrian National Bank to M.K. (Jubiläumsfond # 13249)

References: [1] McGavock et al. Circulation 2007; 116(10):1170-5. [2] Rijzewijk et al. J Am Coll Cardiol 2008; 52(22):1793-9. [3] Iozzo et al. J Clin Endocrinol Metab, 2009, 94(11) 4472-82 [4] Krssak et al. Proc ISMRM 18 (2010) 174

	Baseline	6 h HG	p-values
Left ventricular			
Ejection fraction [%]	66.5 ± 4.4	70.4 ± 6.6	0.004
End-diastolic-volume [ml]	137 ± 35	135 ± 41	ns
End-systolic-volume [ml]	47 ± 17	42 ± 20	0.02
Stroke volume [ml]	90 ± 20	93 ± 23	ns
Cardiac output [l/min]	5.7 ± 1.2	6.1 ± 1.4	ns
Myocardial mass [g]	122 ± 36	124 ± 35	ns
Myocardial Lipid Acc. [%]	0.24 ± 0.05	0.30 ± 0.07	0.009
Myocardial function and lipid accumulation before and after 6 hours of hyperglycemia (HG)			