Cardiac structure and function are altered in adults with non-alcoholic fatty liver disease with no known cardiac involvement

Kieren Grant Hollingsworth[1], Kate Hallsworth[2], Christian Thoma[2], Djordje G Jakovljevic[2], Guy A MacGowan[3], Quentin Anstee[1], Andrew M Blamire[1], Roy Taylor[1], Chris P Day[1], and Michael I Trenell[2]

[1]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, Tyne and Wear, United Kingdom, [2]MOVElab, Newcastle University, Newcastle upon Tyne, Tyne and Wear, United Kingdom, [3]Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, Tyne and Wear, United Kingdom

Target Audience MR cardiac physicists and clinicians interested in early quantification of cardiac disease, particularly in metabolic disease.

Purpose Non-alcoholic fatty liver disease (NAFLD) is associated with a twofold greater risk of developing cardiovascular disease than those without [1]. Despite this, little is known about the specific effect of NAFLD upon cardiac function or cardiac energetics despite studies showing impairments in obesity [2], ageing [3] and type 2 diabetes (T2D) [4], with only one study in young men [5], limiting our ability to identify therapeutic strategies. This study aimed to address this by defining the effect of NAFLD without T2D on cardiac function, structure and metabolism in a clinically representative population.

Methods *Subjects:* Nineteen adult patients with MRS-confirmed NAFLD (11 males, age 54 ± 15 y, BMI 29 ± 3 kg/m^2 with >5% intrahepatic lipid on T_2-corrected PRESS), but no known cardiac involvement or T2D, were recruited. All 19 patients were matched with healthy controls (<5% intrahepatic lipid) for gender, age and BMI (56 ± 14 y, BMI 28 ± 4 kg/m^2). All 38 subjects had a normal 12-lead ECG and echocardiogram and no history of cardiovascular disease. Ethical approval and informed consent were obtained. *MRI protocol.* Scans were performed using a 3T Philips Achieva with a 6 channel cardiac coil. *Cardiac morphology:* High resolution, short axis cine-MRI was analyzed using methods reported previously [6] to provide measurements of LV mass, LV mass index (normalized to body surface area), and blood pool volumes, using a Philips Viewforum. The ratio of LV mass to end diastolic volume was calculated as a measure of concentric remodelling. *Cardiac tagging:* Tagged images of the myocardium in the short axis were obtained throughout the cardiac cycle. A multishot turbo-field echo sequence with turbo factor 9 was used (TR/TE/FA/NEX = 4.9/3.1/10°/1, SENSE factor 2, FOV 350x350mm, voxel size 1.37x 1.37 mm with an orthogonal grid with tag spacing of 7 mm). Circumferential strain and the rotation of the planes were calculated throughout the cardiac cycle using the Cardiac Image Modelling package (University of Auckland). Torsion between two mid-ventricular planes (taken as the circumferential-longitudinal shear angle) was calculated [7]. Longitudinal shortening was measured as the percentage change in distance from the mitral plane to the apex between end-diastole and end-systole. *Cardiac spectroscopy:* A 10cm diameter ^{31}P surface coil (Pulseteq, UK) and a 7 cm slice-selective, cardiac gated 1D-CSI sequence was used with spatial pre-saturation of skeletal muscle. 16 coronal phase-encoding steps were used, each 10mm thick (TR = heart rate, 96 averages, 20 mins). The first spectral line without skeletal muscle contamination was selected. Quantification was performed using AMARES (jMRUI), and the PCr/ATP ratios were calculated and corrected for blood contamination, saturation and coil excitation profile as detailed in [6]. *Clinical measures:* Fasting plasma glucose and triglycerides were measured. Statistics were performed with SPSS 17.0.

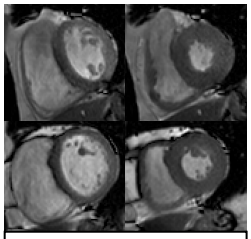

Fig 1 : Cine-image of NAFLD subject (*top)* and control (*bottom*) showing wall thicknesses and blood pool volumes at end-diastole (*left*) and end-systole (*right)*

Results Table 1 summarizes the results and significant differences for patient blood tests, cardiac morphology, tagging and energetics. There were no significant differences in cardiac output, ejection fraction or stroke volume.

Table 1 : Characteristics, cardiac morphology, tagging and energetics results

Parameter	Controls	Patients
Weight (kg)	83 ± 14	78 ± 11
Fasting plasma glucose (mmol/l)	5.2 ± 0.5	5.0 ± 0.6
Triglycerides (mmol/l)	1.7 ± 0.9	1.5 ± 0.8
Intrahepatic Lipid (%)	2.5 ± 0.9	9.4 ± 4.3
Blood pressure (mmHg)	131 ± 11/82 ± 8	146 ± 16‡/90 ± 12
LV mass (g)	102 ± 26	114 ± 31
LV mass index (g/m^2)	55 ± 12	59 ± 11
Wall thickness in systole (mm)	12 ± 2	14 ± 3 ‡
Wall thickness in diastole (mm)	7 ± 1	8 ± 1 ‡
End diastolic volume (ml)	117 ± 36	102 ± 32
End systolic volume (ml)	48 ± 19	39 ± 20
Mass/End Diastolic Volume ratio	0.9 ± 0.2	1.1 ± 0.2 ‡
Peak torsion (°)	6.6 ± 1.8	6.9 ± 2.2
Peak endocardial circumferential strain (%)	22 ± 5	28 ± 4 *
Longitudinal shortening (%)	17 ± 3	14 ± 3 #
PCr/ATP ratio (-)	1.89 ± 0.30	1.79 ± 0.30

# p < 0.02, ‡ p<0.01, * p <0.0001

Discussion This is the first study to examine cardiac status in a clinical group of NAFLD patients using the combined techniques at 3.0 T of phosphorus spectroscopy, cardiac tagging and cine MRI to measure cardiac energetics, torsion and circumferential strain, and morphology. The major findings in NAFLD patients compared to age, gender and BMI-matched controls are: 1) there was no significant difference in cardiac energetics; 2) there was thickening of the cardiac wall, independent of changes in LV mass; 3) altered myocardial strains occur without a change in peak torsion. There was no significant difference in PCr/ATP ratio between the NAFLD and control groups, although the NAFLD group mean was 5% lower than that of controls. This may be due to the heterogeneous nature of our NAFLD and control groups in terms of age and BMI since substantial increases in BMI and/or age have been associated with a lower PCr/ATP [2-4]. It has been postulated that changes in cardiac metabolism occur as a result of high levels of circulating NEFA [8] and that these fatty acids are preferentially utilised by the heart as a fuel relative to glucose, decreasing cardiac efficiency as more oxygen is needed per ATP molecule generated, reducing the PCr/ATP ratio. Given that there were no variations in the levels of triglycerides (surrogate biomarkers for NEFA) between our NAFLD and control groups, the lack of difference in PCr/ATP may not be surprising. Both groups had relatively high baseline levels of triglycerides which may have resulted in a lowering of PCr/ATP in both groups when compared to the study of NAFLD in younger subjects (mean age 35), where a 50% increase in triglyceride was observed compared to controls alongside a decrease of 12% in PCr/ATP [5]; a study of obesity where a 15% decrease in PCr/ATP ratio accompanied a 100% increase in triglycerides compared to a lean group [2]; and a study among a population of Type 2 diabetic patients of similar BMI and age to our cohorts found that those with NAFLD were characterized by lower PCr/ATP and a 50% increase in mean triglyceride levels [4]. Despite the raised blood pressure in the NAFLD group, an ANCOVA analysis showed that the differences found were preserved irrespective of blood pressure difference. The unchanged torsion suggests that increased endocardial strain arises mainly from the thickening of the cardiac wall. While the small increases in wall thickness and decreases in longitudinal shortening might not be clinically significant for an individual, they may be significant in predicting future risk of cardiac impairment for the population.

Conclusions Cardiac MR detected morphological change in middle aged patients with NAFLD without T2D. Wall thickness and longitudinal shortening were affected without overt hypertrophy as in diabetic cardiomyopathy. Cardiac energetics were unaffected in contrast to studies in younger men and in T2D.

Acknowledgements KGH thanks the UK Medical Research Council (G110060) for funding, Wellcome Trust, NIHR.

References [1] Ekstedt *Atherosclerosis* 191:391 (2007), [2] Rider *Circulation* 125:1511 (2012), [3] Perseghin *Diabetes Care* 30:1520 (2007) [4] Rijzewijk *JACC* 56;255 (2010), [5] Perseghin *Hepatology* 47:51 (2008), [6] Jones *Am. J. Physiol. Gastrointest Liver Physiol* 298: G764 (2010), [7] Lumens *Am. J. Physiol. Heart. Circ. Physiol.* 291:H1573 (2006), [8] Larsen *Cardiovasc. Drug Ther.* 22:91 (2008).