Evidence for A Direct Effect of Myocardial Steatosis on LV Hypertrophy and Diastolic Dysfunction in Adult and Adolescent Obesity

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Previous studies have shown that myocardial steatosis occurs with age, diabetes and the metabolic syndrome, and that myocardial triglyceride content (MTGC) is related to concentric left ventricular hypertrophy (LVH) (1) and diastolic dysfunction (2), suggesting a direct and negative effect on the heart. Despite this, whether a relationship between MTGC, concentric LVH and diastolic function exists in obesity *per se* is unclear and in childhood obesity remains unknown.

^{1}H -magnetic resonance spectroscopy (^{1}H-MRS) is a technique that can measure MTGC non-invasively. (3) We used ^{1}H-MRS and cardiovascular magnetic resonance imaging to explore; a) the relationship between increasing body fat and MTGC b) the relationship between MTGC, LVH and diastolic dysfunction, and c) whether any changes were present in an adolescent population.

128 adult subjects (71 female BMI, 18.5-53.0 kg/m^{2}) and 22 male adolescents (aged 10-15 years, BMI percentile 8-100) underwent ^{1}H-MRS and LV studies as previously described. (4,5). Total Body fat content (DXA, GE Lunar system) and abdominal visceral fat mass, (4^{th}/5^{th} lumbar water-suppressed turbo-spin-echo) were also assessed. Age, BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were similar between men and women. All subjects were normotensive (adult 121±11/74±8, children 113±13/67±10mmHg), normoglycaemic (adult 5.0±0.5, children 4.8±0.6mmol/l) and normocholesterolaemic (adult 5.1±0.8, children 3.9±0.5mmol/l). Mean HOMA-IR was 2.7±1.3 (adult population). All subjects had normal LVEF (>58%).

In adults, although MTGC was positively correlated with all measures of obesity (BMI r 0.59, visceral fat r 0.46, total fat r 0.60, females; BMI r 0.53, Figure 1), only total fat mass (+0.013%/kg fat, $p<0.001$) was an independent predictor of MTGC. No sex difference in the regression coefficient for the associations of obesity with MTGC was seen. In adolescents MTGC was also positively correlated with BMI percentile (r 0.45, $p=0.035$).

Increasing BMI was associated with LV cavity dilatation in both males (r 0.32, $p=0.014$) and females (LVEDV r 0.39, $p<0.001$). In contrast, with increasing BMI concentric LV remodeling was only seen in males (LV mass: volume ratio r 0.44, $p=0.01$) and was positively correlated with MTGC (r 0.39, $p=0.003$), a relationship that remained after adjustment for SBP and HOMA-IR (r 0.40, $p<0.005$). In adolescent males, increasing BMI percentile was not related to cavity dilatation (r 0.32, $p=0.14$), but again was positively correlated with indexed-LV mass ($g/m^{2.7}$, r 0.54, $p=0.01$) again suggesting concentric remodeling. Importantly, in the adolescent group, LV mass-index was also positively correlated with MTGC (r 0.45, $p=0.037$), again remaining significant after controlling for SBP (r 0.45, $p=0.04$). Overall, these findings suggest a role for cardiac steatosis, independent of the effects of blood pressure, in the development of concentric LV remodeling in male obesity.

There was no correlation between MTGC and global systolic function in the form of LVEF in either adults (males, r -0.15, females, r 0.12, both $p>0.29$), or adolescent males (r-0.2, $p=0.36$). In contrast, even after controlling for LV mass, SBP and HOMA-IR increasing MTGC remained correlated with impaired diastolic filling rate (r-0.34 $p<0.01$). This would suggest that the accumulation of myocardial TG *per se* is related to diastolic dysfunction in

obesity. As obstructive sleep apnea (OSA) was only excluded on an interview basis, it is possible that undiagnosed OSA is related to some of the diastolic dysfunction in this study.

This study has shown that, even in the absence of co-morbidities, both adult and childhood obesity are related to cardiac steatosis, and that elevated MTGC is related to diastolic dysfunction. In addition, we have shown that significant gender differences exist in the effects of MTGC with increased levels correlating with concentric LVH in adult and adolescent males, but not females (adults, Sex BMI interaction $p = 0.039$) . Overall, this suggests not only that myocardial steatosis is related to LV structural and functional changes that occur in obesity, but also that cardiac steatosis occurs early in obesity and has significant effects in childhood.

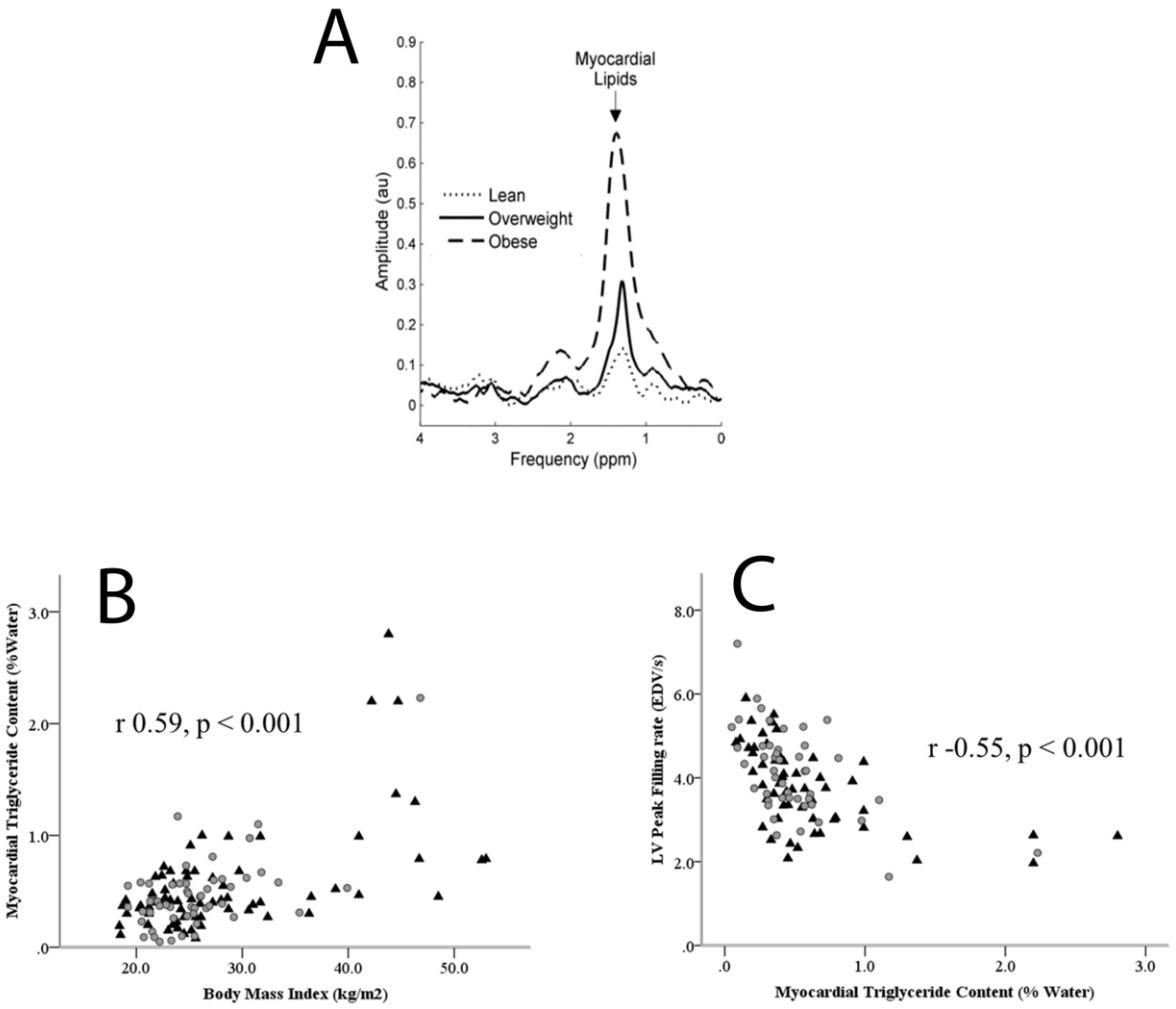
A
Myocardial Lipids
Lean
Overweight
Obese
Amplitude (au)
Frequency (ppm)
B
r 0.59, p < 0.001
Myocardial Triglyceride Content (%Water)
Body Mass Index (kg/m2)
C
r -0.55, p < 0.001
LV Peak Filling rate (EDV/s)
Myocardial Triglyceride Content (% Water)

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Figure Legend

Figure 1 Cardiac Steatosis

(A). Example ^{1}H-spectra. Relationship between MTGC and (B) Body Mass Index and (C) LV peak filling rate (Adults; males grey circles, females black triangles).