High fat diet rewires cardiac metabolism and restores cardiac function experimental heart failure

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Introduction: Heart failure is characterized by a metabolic reprogramming changing from fatty acids to glucose as the preferential fuel of the failing myocardium. Whether metabolic reprogramming is a therapeutic target remains controversial.

Purpose: To evaluate whether a nutritional intervention rewiring cardiac metabolism towards a fatty acids has a beneficial effect on cardiac function in a large animal model of hibernated myocardium.

Methods: Heart failure with reduced ejection fraction (HF\textsubscript{REF}) was induced in pigs by generating a hibernated myocardium secondary to progressive stenosis of the proximal left anterior descending (LAD) after surgical insertion of an ameroid. Pigs underwent a serial multimodality imaging study including magnetic resonance imaging (MRI), PET/CT with 18FDG. Once hibernated myocardium with metabolic reprogramming was documented (complete occlusion of LAD on invasive angiography, LVEF <50% on MRI, animals were randomized to HFD (20% of fat) or control diet (3% of fat) for 2 months. At 2 months, a second imaging session were performed and tissue was evaluated.

Results: Both groups presented the same LV systolic dysfunction at basal (54.0\% [47.0, 62.5] vs 41.0\% [38.0, 43.3], p=0.94). Two months after diet, animals receiving HFD displayed significantly better LVEF than controls (54.0\% [47.0, 62.5] vs 41.0\% [38.0, 43.3], p=0.012). At baseline, hibernated myocardium presented a small degree of LGE (mostly endocardial) on CMR (4.58\%LV [2.03, 9.39] for both pooled groups). After nutritional intervention, the extent of LGE was significantly smaller (0.558\%LV [0.213, 1.78] vs 6.24\%LV [4.95, 9.18], p=0.0043). 18FDG PET scan showed a metabolic rewiring in the hibernated area of pigs receiving HFD (anterior region FDG uptake normalized to remote was 0.465 counts [0.214, 0.646] vs 1.80 [1.53, 2.83], p=0.016). On transmission electron microscopy, cardiomyocytes’ lipid droplets in cardiomyocytes from HFD-fed pigs were significantly less that those from controls (38.5 per 10 \textmu m\textsuperscript{3} [34.3, 50.3] vs 96.0 [78.5, 124], p=0.022). Protein expression of MMFN2, a protein involved in lipid droplet formation, was significantly downregulated in HFD pigs (0.696- fold/Vinculin [0.532, 0.916] vs 1.72 [1.48, 2.45], p=0.041). Expression of genes involved in fatty acid metabolism was significantly upregulated: ACOX1 (1.46 [1.37, 1.67] vs 1.09 [0.943, 1.19], p=0.0043), and CRAT (1.85 [1.55, 2.14] vs 1.19 [0.926, 1.50], p=0.041). Conversely, expression of genes involved in glucose mobilization were downregulated: GLUT1 (0.645 [0.611, 0.678] vs 0.993 [0.946, 1.19], p=0.041) and HK2 (0.192 [0.148, 0.400] vs 1.46 [0.680, 2.00], p=0.015).

Conclusions: In a large animal model of HF\textsubscript{REF} secondary to hibernated myocardium with a metabolic switch, a nutritional intervention based on high fat diet was associated with a cardiac metabolic rewiring (normalization of fatty acid substrate utilization) and a significant improvement of LVEF.