

Dynamic Metabolomic Profiling Reveals Evidence for Metabolic Inflexibility in the Failing Heart

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Study Description

Background:

Metabolic signatures of heart failure (HF) phenotypes generally portray static, single time point differences between disease and control groups. Dynamic changes in metabolites in response to cues such as glucose loading are rarely determined in human HF studies. We aimed to characterize dynamic changes in circulating acyl-carnitines that occur with glucose challenge among heart failure patients, in comparison to controls.

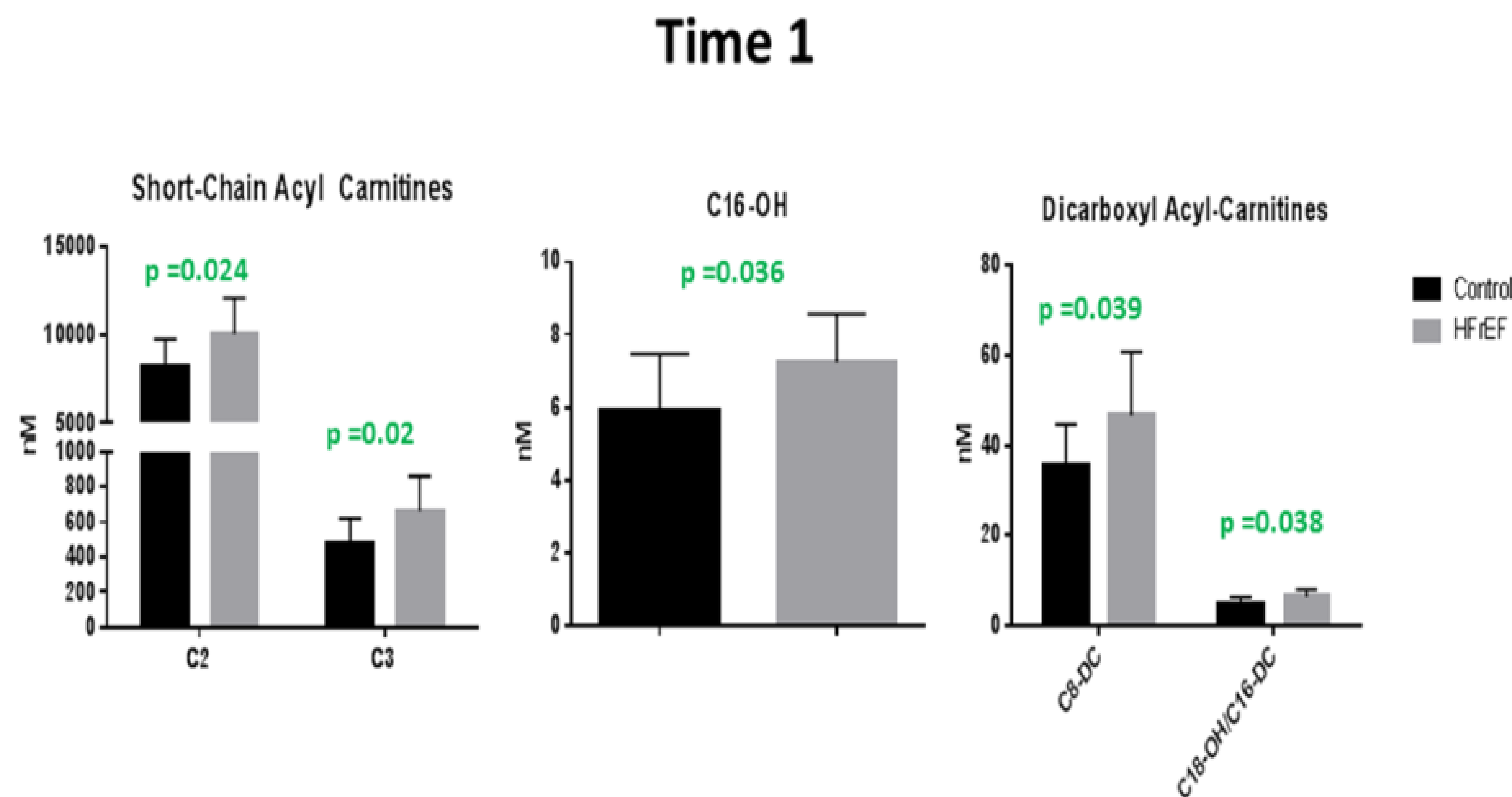
Methods:

This was a multi-centre study that involved HF patients with reduced ejection fraction (EF) and controls. All patients underwent a protocol that involved fasting overnight, followed by an early morning oral glucose drink. Blood sampling at (Time 1) baseline (prior to glucose drink), (ii) (Time 2) two hours after the glucose drink, and at (iii) (Time 3) three hours after baseline were performed. Targeted high performance liquid and gas chromatography mass spectrometry were used to measure 65 circulating acyl-carnitines in serum. Metabolite levels at each blood sampling time point were compared between HF patients and controls.

Results:

This analysis consisted of 19 subjects (mean age 53±10 years; 8 females (42%) (HF n=9 (all left ventricular EF <50%); controls n=10). All of the subjects were non-diabetic, as confirmed by fasting glucose and glycated haemoglobin levels. At Time 1, there were significant differences in short chain [(C2: 10050±2056 vs 8165±1572, p=0.024); (C3: 662±199 vs 478±143, p=0.02)], long chain (C16-OH: 7±1.3 vs 6±1.4, p=0.036) and medium-and long chain di-carboxylates [(C8-DC: 47±14 vs 36±9, p=0.039; (C18-OH/C16-DC: 6±1.5 vs 5±1.2, p=0.038)] between HF and controls, demonstrating higher accumulation of these metabolites among HF patients compared to controls. (Figure 1).

Figure 1:
Differences in short chain, long chain and dicarboxylates between controls and heart failure patients



Following oral glucose loading, metabolite levels decreased at Time 2-and Time 3, in both HF patients and in controls. However, metabolite levels decreased more robustly among controls compared to HF patients after oral glucose loading. *The magnitude of the change from Time 1 to Time 3 (ratio of time 3: time 1) for short chain (C2: 0.6±0.11 vs 0.7±0.08, p=0.022), long chain (C16:2: 0.5±0.1 vs 0.6±0.1, p=0.036) and medium- chain di-carboxylates (C8-DC: 0.6±0.1 vs 0.7±0.1, p=0.018) was reduced for HF compared to controls (Figure 2).*

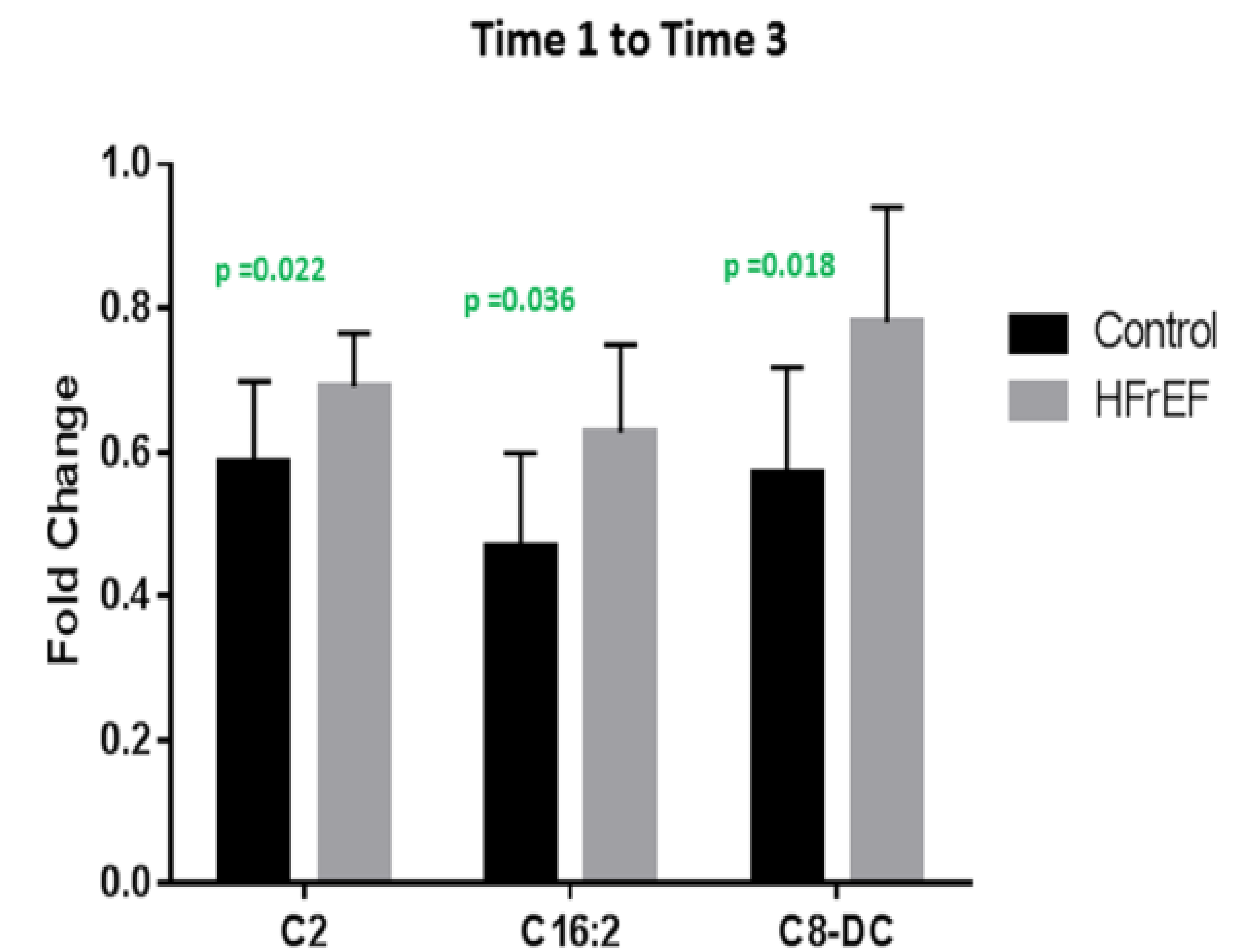


Figure 2:
Differences in magnitude of change from Time 1 to Time 3 (ratio of Time 3: Time 1) for short chain, long chain and dicarboxylates between controls and heart failure patients

Conclusions

Our novel pilot data characterizes dynamic changes in circulating acyl-carnitines following glucose loading conditions, demonstrating distinct differences in rates of metabolite clearance among in HF patients. These findings, observed in the absence of diabetes mellitus, suggest that a state of reduced metabolic-flexibility is present among HF patients. These hypothesis-generating data warrant further investigation into potential modifiable metabolic pathways in HF.