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EDITORIAL COMMENT

The Farm to Table HFpEF Kitchen

Selecting the Right Ingredients for the Discerning Palate*

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Farm-to-table cooking is based on the concept that using fresh, in-season, and locally available ingredients results in healthy and delicious meals. The best farm-to-table restaurants leverage a network of local food sources to have a ready supply of ingredients to meet the demands of discerning diners. Analogously, the heart must also have a ready supply of ingredients to meet the immense metabolic demands of maintaining continuous systemic perfusion. In a normal farm-to-table cardiac kitchen, fatty acids (FAs) are plentiful and the heart uses adenosine triphosphate derived from FAs as its main ingredient, accounting for 85% of its fuel source. When the cardiac kitchen heats up during times of stress or exercise, the heart is capable of using additional locally available ingredients such as glucose, ketones, lactate, and amino acids to meet the increased metabolic demands.[1] However, in the setting of a dysfunctional cardiac kitchen as seen in heart failure with reduced ejection fraction (HFrEF), the heart shifts away from FA metabolism (which declines to 70% as a fuel source), and the cooks dramatically increase their use of amino acids, lactate, and ketones (a 2- to 3-fold increase in ketone body oxidation).[2]

Until recently, it was unknown which ingredients would predominate in the heart failure with preserved ejection fraction (HFpEF) kitchen. Given the increased prevalence of HFpEF in patients with obesity and diabetes, conditions associated with increased circulating FAs, an initial hypothesis was that the HFpEF kitchen would increase FA oxidation. However, in a recent cross-sectional study that analyzed endomyocardial biopsies and plasma from patients with HFrEF, patients with HFpEF, and control patients, the investigators concluded: 1) that similar to patients with HFrEF, those with HFpEF were less likely to use FA oxidation; 2) that patients with HFpEF and those with HFrEF were metabolically distinct groups; and 3) that peripheral blood samples did not consistently represent the metabolic flux of a patient with HFpEF.[3] Furthermore, after countless unsuccessful attempts to repurpose HFrEF neurohormonal antagonist treatments for HFpEF, recent clinical trials showing a beneficial effect of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 (GLP1) receptor agonists openly call out HFpEF as a metabolic kitchen in disarray. To evaluate what is going on in the HFpEF kitchen, it is essential to not only look at the food on the table but to also identify what ingredients are available and how these ingredients change when the HFpEF kitchen heats up during periods of stress and exercise.

It is with this background that O'Sullivan et al[4] present their study in this issue of *JACC: Basic to Translational Science*, analyzing "transmyocardial" blood to examine myocardial metabolic and lipidomic use at rest and with exercise in patients with HFpEF compared with healthy control subjects.[4] The investigators enrolled 20 consecutive patients with HFpEF (pulmonary capillary wedge pressure ≥15 mm Hg at rest or ≥25 mm Hg with symptom-limited exertion and an H2FPEF score ≥6) and 13 healthy control subjects with no known cardiac histories. Exclusion criteria were significant coronary artery disease; moderate or greater mitral or aortic

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stenosis; infiltrative, restrictive, or hypertrophic myocardial disease; pericardial constriction; significant right ventricular (RV) disease; and significant pulmonary disease.

While in a nonfasting state, patients had blood drawn prior to myocardial consumption (influx) from either the radial or brachial artery and immediately after myocardial consumption (efflux) from the coronary sinus. Coronary sinus blood (CSB) was compared with arterial blood at rest and during exercise using a supine cycle ergometer. CSB and arterial blood was sent for metabolomic and lipidomic analyses. Comparing metabolic and lipid substrate efflux (CSB) with influx (arterial blood), fold change was used to determine whether metabolites were extracted by the heart (<1) or released from the heart (>1) and served as a surrogate for cardiac metabolism. The investigators found that there were: 1) significant differences in cardiac metabolic preferences of patients with HFpEF compared with healthy control subjects; 2) biological sex-specific metabolic and lipidomic use preferences between male and female patients with HFpEF; and 3) distinct cardiac metabolic profiles with varying hemodynamic loading conditions.

O'Sullivan et al[4] should be commended for this novel study, as it identifies unique insights about HFpEF metabolism and provides a framework for further investigation into the mechanisms of metabolic interventions as HFpEF treatments. A key finding of this study is that HFpEF hearts were less likely to use FAs and favored a more complex lipid extraction and protein catabolism. In some cases, both control and HFpEF hearts extracted the same metabolites, but in HFpEF, metabolites such as taurine and lactate were extracted more significantly, suggesting increased use of a shared fuel source. However, in other cases, new fuel sources were used, such as glycerol-3-phosphate, hydroxyglutarate, alpha-ketoglutarate, and oxoglutarate, which were extracted in HFpEF but not control hearts. Similarly for lipids, HFpEF hearts but not control hearts extracted triacylglycerol (16:0_14:0_22:6), ceramide (d16:0_24:1), phosphatidylcholine (18:0_16:0), and lysophosphatidylcholine (18:0). Importantly, the use of these fuel sources was independent of circulating concentrations. Of note, the investigators did not identify changes to ketone or amino acid use. These data suggest that HFpEF hearts not only increase their use of metabolites already being used in the heart but also find new metabolites and lipids to fuel the heart.

A second key finding the investigators identified is noted biological sex differences in cardiac metabolism, specifically as it pertains to lipid consumption. Female HFpEF heart lipid consumption became restrained and limited to nontraditional lipids such as campesterol ester, wax esters, and monoglycerides, whereas male HFpEF hearts became more flexible and extracted a broader range of lipid classes, including sphingolipids, glycerolipids, and glycerophospholipids. It is possible that alterations in lipid metabolism could be an explanation for the previously identified biological sex-specific differences in HFpEF.

Finally, a unique strength of this study was the investigators' ability to link cardiac metabolism to cardiac loading conditions. For example, uridine, an important mitochondrial metabolite, was more highly extracted in HFpEF hearts as mean arterial pressure increased. One hypothesis generated in this study is that in HFpEF hearts, cardiac metabolism is more correlated to RV dynamics (ie, mean pulmonary artery pressure and pulmonary systolic pressure) than left ventricular loading (limited correlations with pulmonary capillary wedge pressure). Increased sample size with hemodynamic monitoring may further clarify if indeed RV metabolism and hemodynamic status are more sensitive to metabolic shifts. Ultimately, comparison of RV and left ventricular tissue samples could answer this question. Disproportionate ventricular metabolism may be of significant interest in cardiac diseases other than HFpEF that have a prominent RV phenotype, such as arrhythmogenic cardiomyopathy.

This study did have several limitations. First, the patients were in a nonfasting state. Although a nonfasting state is more biologically relevant, it is possible that nonstandardized diets and differences in metabolite influx could have confounded some of the results. A standardized or recorded diet could shed light on the dietary contribution to the results.

Second, patients were able to continue all their medications throughout the study period. Although this study predates the introduction of sodium-glucose cotransporter 2 inhibitors and GLP1 receptor agonists, other medications such as insulin could have confounding effects.

Third, this study was not designed to directly analyze the metabolism of myocardial tissue through tissue biopsy or to differentiate cell-specific metabolism. It is increasingly accepted that cells within the heart (myocytes, stromal cells, and immune cells) have unique functions that are spatially and

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temporally controlled by the metabolic environment and disease state of the heart.[5]

Last, given the invasive nature of this study, its sample population was limited in recruitment size and restricted to a single center.

Despite these limitations, this study does advance our understanding of the cardiometabolic perturbations in HFpEF. There are significant differences in the metabolic fuel sources used in HFpEF, highlighted by a reduction in FA use and increased use of nontraditional metabolites and complex lipids. These differences are even more pronounced among female patients with HFpEF and dependent on RV hemodynamic loading conditions. In addition, the study provides a mechanistic rationale for why therapies that increase FA availability could improve outcomes in HFpEF. As the investigators postulate, does the weight loss associated with GLP1 receptor agonists result in increased lipolysis, a subsequent increase in FA oxidation, and resultant improvement in HFpEF outcomes? If such shifts in cardiac fuel sources result in better HFpEF outcomes, trials of metabolic therapies in HFpEF such as gastric bypass procedures and intermittent fasting could be considered. Indeed, akin to a great farm-to-table restaurant, perhaps the key to fixing the cardiometabolic disarray in the HFpEF kitchen is ensuring that a ready supply of the best ingredients is available to create the most delicious meal for even the most discerning of palates.

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