The Relationship Between Cardiac Energy Metabolism and Cardiac Function in Obesity and Type 2 Diabetes: Revisiting a 2003 *Diabetes* Classic by Aasum et al.

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The development of the isolated Langendorff heart preparation in the late 19th century could be viewed as the birth of the cardiac metabolism field, as this led to the first studies interrogating cardiac energy metabolism in animals (1). The next major evolution in this field would arise from the advent of the coronary sinus catheter in the late 1940s, following which Bing and colleagues first measured cardiac substrate extraction in humans (2,3). Several other advancements, including the isolated working heart preparation developed by Morgan et al. (4) as well as noninvasive imaging techniques such as positron emission tomography and hyperpolarized magnetic resonance spectroscopy (5), have proven to be instrumental to our overall understanding of cardiac energy metabolism. Indeed, several landmark discoveries in cardiac metabolism can be directly attributed to the foundations of these techniques. This includes fatty acids being the primary fuel source of the heart, while fatty acids and carbohydrates compete for oxidative metabolism through a substrate cycle, often referred to as the Randle Cycle due to findings from Randle et al. in the 1960s (6). However, it should be noted that these observations were actually first reported by Shipp et al. a few years prior (7).

Importantly, given that it is the organ with the highest metabolic demand per gram, the heart must have a robust intermediary metabolism to adapt to its continuously varying workload (5). Hence, the progression of cardiovascular disease is often associated with alterations in cardiac energy metabolism, and the first studies making these connections were primarily in the context of ischemic heart disease or heart failure (5). These observations naturally led to a "chicken or egg" scenario regarding whether changes in cardiac energy metabolism are a driver of cardiovascular disease pathology or are merely a passenger resulting from the cardiovascular disease itself. While this question remains an ongoing topic of debate, a plethora of studies support that alterations in cardiac energy metabolism can directly precipitate cardiovascular disease. For example, cardiac-specific deletion of pyruvate dehydrogenase (PDH), the rate-limiting enzyme of glucose oxidation, results in a near-complete abolishment of cardiac glucose oxidation and causes diastolic dysfunction (8). As the 21st century has witnessed an explosion in the prevalence of obesity, there has been a surge in studying cardiac energy metabolism in response to obesity and/or type 2 diabetes (T2D) and whether optimizing cardiac energy metabolism might be a viable target to alleviate obesity- and T2D-related cardiovascular disease.

THE CLASSIC

In this Classics in *Diabetes* article, we revisit a seminal article by Aasum et al. titled "Age-Dependent Changes in Metabolism, Contractile Function, and Ischemic Sensitivity in Hearts From *db/db* Mice" (9). Published in the February 2003 issue of *Diabetes*, this article helped lay the foundation for many scientists with interest in how obesity and T2D affect cardiac energy metabolism. The principles for assessing energy metabolism in the working rat heart were first adapted for the mouse heart in 1999 (10), which paved the way for widespread study of genetically modified mouse models to improve our understanding of cardiac energy metabolism. In the study by Aasum et al. (9), isolated working hearts from female *db/db* mice (a genetic model of obesity and T2D due to leptin receptor deficiency) and their heterozygous littermates were aerobically perfused

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with 11.0 mmol/L glucose and 0.7 mmol/L fatty acids (0.4 mmol/L palmitate added to 0.3 mmol/L endogenous fatty acids) bound to 3% BSA. The inclusion of [U-^{14}C]glucose and [9,10-^{3}H]palmitate in the perfusate allowed for the determination of both glucose and palmitate oxidation via measurement of the released $^{14}CO_2$ and $^{3}H_2O$, respectively. Of interest, it was observed that substrate oxidation was changed toward a higher reliance on fatty acids at the expense of glucose in the hearts of *db/db* mice. Furthermore, these experiments were repeated in isolated working hearts from mice at three separate ages (6 weeks, 10–12 weeks, and 16–18 weeks), whereby it was demonstrated that these alterations in cardiac energy metabolism in *db/db* mice were present before a decline in cardiac function. Such findings thus lend further support to the notion that alterations in cardiac energy metabolism can directly precipitate cardiac dysfunction.

The authors also demonstrated that the increases and decreases in palmitate and glucose oxidation were also present in 12-week-old male *db/db* mice. These alterations in myocardial energy metabolism were associated with a worsened recovery of contractile function (peak systolic pressure × cardiac output) following a 13-min global no-flow and 10-min reperfusion protocol. Lastly, the authors demonstrated that via treatment with a selective peroxisome proliferator–activated receptor-α ligand, BM 17.0744 (0.24 mg/mL in the drinking water for 3 weeks), they could reverse the metabolic profile in reperfused hearts of male *db/db* mice. However, this normalization of cardiac energy metabolism did not lead to improvement in any ex vivo parameter of contractile function.

THE IMPACT

Over two decades later, it cannot be overstated how influential this finding of a decrease in myocardial glucose oxidation and an increase in myocardial fatty acid oxidation has been on our understanding of cardiac energy metabolism in obesity and/or T2D (11,12). In particular, these findings directly challenged a conclusion from another study published nearly half a year prior in the August 2002 issue of *Diabetes*, where it was reported that myocardial fatty acid oxidation was decreased in isolated working hearts from male obese Zucker rats (13). Reasons for the discrepancies between these two studies are unclear but could stem from differences in species (mice versus rats) or perfusate conditions (e.g., presence of insulin and lactate during perfusion of obese Zucker rat hearts). Furthermore, fatty acid levels in the perfusate (0.4 mmol/L) were lower during the perfusion of working obese Zucker rat hearts, and at lower fatty acid levels it has been shown that the heart will increase its reliance on its endogenous triacylglycerol stores as a source of oxidative ATP production (14). Therefore, it also remains possible that myocardial fatty acid oxidation rates were underestimated in the male obese Zucker rat hearts.

Despite these discrepancies, the findings of Aasum et al. have since been consistently repeated, and it is now widely accepted that the heart in obesity and T2D is characterized by a decrease in glucose oxidation and an increase in fatty acid oxidation (11,12). Indeed, isolated working heart perfusions in both male *db/db* and *ob/ob* (a genetic model of obesity and T2D due to leptin deficiency) mice displayed this same metabolic phenotype (15,16). Of translational relevance, nearly 1 year later, it was demonstrated using positron emission tomography imaging that myocardial fatty acid oxidation rates are also elevated in women with insulin resistance and obesity (17). In addition, worsening insulin resistance in these women was positively associated with further elevations in myocardial fatty acid oxidation rates. Similar changes in cardiac energy metabolism have been recapitulated with dietary models of obesity, including short-term and chronic high-fat diet (HFD) feeding and HFD feeding in combination with a low-dose injection of streptozotocin (STZ) to induce experimental T2D (18–20). Although methods were not previously available to assess myocardial glucose oxidation noninvasively in humans, hyperpolarized magnetic resonance spectroscopy using ^{13}C stable isotopes has recently been used to confirm that myocardial glucose oxidation is decreased in humans with T2D (21). Intriguingly, the metabolic profile characterizing the heart in T2D is not exclusive to diabetes phenotypes associated with obesity, as a nonobese mouse model of diabetes is also characterized by decreased myocardial PDH activity and subsequent glucose oxidation (22).

As there is a multitude of evidence supporting these metabolic alterations, the reduction of myocardial glucose oxidation in obesity and T2D has presented as a key target for pharmacotherapy over the past decade. Studies in rats subjected to HFD– and low-dose STZ–mediated T2D exhibit diastolic dysfunction, and this diabetic cardiomyopathy phenotype can be reversed via treatment with dichloroacetate, which restores myocardial glucose oxidation rates via preventing inhibitory phosphorylation of PDH (23). Furthermore, studies have suggested that elevations in FoxO1 activity increase gene transcription of PDH kinase 4 (24). Accordingly, pharmacological inhibition of FoxO1 can also preserve myocardial PDH activity and glucose oxidation by preventing upregulation of PDHK4 and inhibitory phosphorylation of PDH, which alleviates diastolic dysfunction in mice subjected to HFD– and low-dose STZ–mediated T2D (25). Research with glucagon-like peptide-1 receptor (GLP-1R) agonists supports the clinical potential of this approach; GLP-1R agonists are a glucose-lowering drug class that have been demonstrated to improve cardiovascular outcomes in people with T2D (26), and these actions may relate to this specific mechanism. Recent evidence has shown that the GLP-1R agonist liraglutide can increase myocardial glucose oxidation in mice subjected to HFD– and low-dose STZ–mediated T2D, and this is also associated with an alleviation of diastolic dysfunction (18).

The increase in myocardial fatty acid oxidation has also been explored as a target for pharmacotherapy in obesity and T2D. For example, treatment with trimetazidine, which decreases myocardial fatty acid oxidation secondary to inhibition of the β-oxidation enzyme 3-ketoacyl CoA thiolase, improves both systolic and diastolic function while reducing cardiac hypertrophy in male mice subjected to HFD-induced obesity (27).

THE FUTURE

The original article by Aasum and et al. (9) highlighted here has undoubtedly played a foundational role in shaping the views of scientists interested in cardiac energy metabolism in obesity and T2D, solidifying its stature as a classic in *Diabetes*. Research in this field continues to elucidate how these alterations in cardiac energy metabolism contribute to cardiac dysfunction in obesity and T2D, and brings us closer to finding the ideal metabolic enzyme to target to treat obesity- and T2D-related cardiovascular disease. However, one major unanswered question that needs to be addressed relates to the molecular mechanisms by which correcting these metabolic alterations in the myocardium leads to an alleviation of the cardiovascular pathology. While much of the focus previously centered on improvements in contractile efficiency, with glucose being the more oxygen-efficient fuel in terms of ATP production, it is becoming increasingly recognized that obesity and T2D are often associated with diastolic rather than systolic dysfunction. Studies have demonstrated that in both *db/db* and obese (HFD-fed) mice, reduced cardiac efficiency correlates with a higher cost of processes involved in excitation contraction coupling (e.g., ATP utilization to support Ca^{2+} homeostasis), which suggests a link between cardiac inefficiency and diastolic dysfunction (20,28). In addition, improving intracellular Ca^{2+} clearance has been demonstrated to improve diastolic performance in male Sprague Dawley rats with diabetic cardiomyopathy (29). Thus, researchers may want to shift their attention to the energetic cost of ventricular relaxation and how this is affected by substrate preference in obesity and T2D. Another potential mechanism may relate to the nonenergetic aspects of fuel metabolism, as the metabolites (i.e., substrates and byproducts) of a metabolic pathway can regulate signaling processes (11). Studies have demonstrated that glucose oxidation–derived acetyl CoA has a greater preference for conversion to acetylcarnitine via carnitine acetyltransferase than fatty acid oxidation–derived acetyl CoA (30). Whether modifying acetyl CoA production from glucose versus fatty acid oxidation differentially affects protein acetylation (e.g., tubulin) or epigenetics (e.g., histone acetylation) and how that may affect diastolic function should also be considered in future studies.

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