Myocardial Lipid Accumulation in the Diabetic Heart

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The prevalence of type 2 diabetes mellitus is rising in the United States, with a recent estimate suggesting that 7% of the US population (or 21 million persons) have the disease.\(^1\) In addition to well-recognized contributions to coronary artery disease risk, the metabolic derangement of diabetes also can result in abnormalities of cardiac function (diabetic cardiomyopathy) that are likely independent of effects on the vasculature. Indeed, \(>3\) decades ago, data from the Framingham Heart Study suggested that patients with type 2 diabetes mellitus have an increased risk of congestive heart failure that persists when adjusted for atherosclerotic disease.\(^2\) Although clinical appreciation of diabetic cardiomyopathy has since increased significantly, the mechanisms by which diabetes mellitus causes diastolic and systolic dysfunction in patients without epicardial coronary artery disease remain unclear.

Animal models of diabetic cardiomyopathy suggest that this phenotype may result in part from intrinsic abnormalities of cardiomyocyte energy use and lipid metabolism.\(^3\) The energy demands of the cardiac myocyte typically are met by ATP production from \(\beta\)-oxidation of fatty acids (FAs). FAs enter the cell via transport mechanisms (eg, FA transport protein-1 and CD-36), or through direct passive membrane diffusion. Fatty acids are then conjugated with acyl-CoA by the enzyme acyl-CoA synthase and transported to the mitochondria to undergo \(\beta\)-oxidation and thereby generate ATP for cellular energy needs. Fatty-acyl CoA not used for energy production can be esterified to tri-acyl glycerol (triglyceride) to provide an intracellular pool for FA storage. The deleterious effects of the accumulation of lipid and other toxic products of FA metabolism are called cardiac lipotoxicity and are presumed to be involved in the development of diabetic cardiomyopathy. Perhaps through increased signaling of the peroxisome proliferator–activated receptor-\(\alpha\) system/PGC-1, which regulates mitochondrial substrate use, nonesterified acyl-CoA can accumulate and be detrimental to the cell through a host of cytotoxic mechanisms, including the generation of ceramide (which can promote cellular apoptosis), and reactive oxygen species.\(^4\) Interestingly, it has been hypothesized that triglyceride accumulation itself may simply be a nonpathological neutral storage destination for fatty acyl-CoA sequestration (ie, a marker of metabolic derangement rather than a contributor).\(^5\)

Therefore, it is conceivable that increased cardiac myocellular FA content that overwhelms the capacity of the cell to expediently metabolize substrate can lead to acyl-CoA accumulation and the increased production of both triglyceride and toxic mediators. Insight drawn from animal models that perturb lipid homeostasis by interfering with transport of FA or with its metabolism supports this hypothesis. For example, FA transport protein-1 overexpression in a murine model produced diastolic dysfunction consistent with an early diabetic cardiomyopathic phenotype.\(^6\) Furthermore, in another mouse model, overexpression of acyl-CoA synthase\(^7\) or peroxisome proliferator–activated receptor-\(\alpha\) also resulted in cardiomyopathy and myocardial triglyceride accumulation. Other animal models that recapitulate type 2 diabetes mellitus, including the Zucker diabetic fatty rat, have likewise shown cardiac dysfunction and myocardial lipid accumulation.\(^8\) Human studies demonstrating cardiac lipid accumulation in diabetes mellitus are limited mostly by the technical challenge of performing sensitive lipid measurements in vivo. One of the few published studies that demonstrated lipid accumulation by histology used explanted hearts from patients undergoing cardiac transplantation.\(^9\)

It is in this context that McGavock et al\(^{10}\) present their important observation in this issue of Circulation that myocardial triglyceride accumulation does indeed occur in humans with diabetes mellitus and insulin resistance even before symptoms of heart failure ensue. Using the technique of proton magnetic resonance spectroscopy (MRS), the authors were able to precisely quantify the triglyceride content in human hearts noninvasively and in vivo. MRS uses the same principles as magnetic resonance imaging in that the magnetic properties of protons contained in fat and water permit spectral separation on the basis of their chemical environment. Spectral peaks corresponding to protons in lipid species (specifically the methyl CH\(_3\) and methylene CH\(_2\) groups) are distinct from those of water (the largest peak), thus permitting quantification by peak integration. Proton MRS is essentially identical to phosphorus MRS, a technique applied more widely in cardiac studies, which depends on excitation of a different nucleus (\(^{31}\)P), allowing measurement of phosphocreatine and ATP.\(^{11}\) In noncardiac studies, proton MRS has been used to measure intrahepatic triglyceride\(^{12}\) and intramyocellular or intermyocellular (skeletal) triglyceride\(^{13}\) and to quantify lipid content in atherosclerotic plaque.\(^{14}\) Unlike the liver, which is essentially stationary, cardiac motion resulting from contraction and respiration poses more of a technical challenge to obtaining good spectral fidelity. In the present study, the authors acknowledge that cardiac

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spectral data from $\approx 25\%$ of subjects were not of sufficient quality to perform measurements. Understandably, published studies of cardiac proton MRS are few, with the authors of the present study contributing the bulk of the literature to date.\textsuperscript{15, 16} Essentially, their previous work has demonstrated the feasibility and reproducibility of the MRS technique. One recently published small study from a different group of investigators suggested that myocardial triglyceride was increased in obese subjects and correlated to serum FA levels.\textsuperscript{17} The present study represents by far the largest published study of cardiac spectroscopy (using any nucleus) in human subjects.

McGavock et al obtained cardiac proton spectra and magnetic resonance imaging measurements of cardiac function from an ethnically diverse population of 134 subjects recruited from the Dallas area. They also measured intrahepatic triglyceride (by a similar proton MRS technique) and quantified subcutaneous and visceral fat. Subjects were divided into 4 groups based on body mass index (BMI) and/or weight/obese subjects (BMI $< 25$ kg/m$^2$, normal glucose tolerance response), overweight/obese subjects (BMI $\geq 25$, normal glucose tolerance test), impaired glucose tolerance (defined as a 2-hour glucose between 140 and 199 mg/dL), and type 2 diabetes mellitus (2-hour glucose $\geq 200$ mg/dL). Baseline metabolic parameters demonstrated the predictable elevation in glucose, insulin, and insulin resistance estimates (homeostasis model assessment or HOMA) in the subjects with impaired glucose tolerance and diabetes mellitus. As expected, both serum-free FAs and triglycerides also were elevated in the diabetic and impaired glucose tolerance groups.

The principal finding of this article is that myocardial triglyceride content (presented as the ratio of lipid to total water content) was lowest in the lean subjects, greater but not statistically so in obese subjects, and greatest ($\approx 2$-fold higher) in subjects with diabetes mellitus and impaired glucose tolerance. Consistent with prior reports, intrahepatic triglyceride content also was increased in subjects with impaired glucose tolerance and type 2 diabetes mellitus.\textsuperscript{18} The authors report that cardiac systolic function was normal in all groups; however, a magnetic resonance imaging estimate of diastolic function (as determined by the rate of change in left ventricular volume during ventricular filling) was abnormal in each of the nonlean groups. Correlation studies did not demonstrate an association between myocardial triglyceride and serum triglyceride and demonstrated only a weak correlation to hepatic triglyceride ($r = 0.3$). Finally, multiple regression analysis demonstrated that age and BMI did not correlate to myocardial triglyceride.

These data tend to contradict previous smaller studies that suggested that myocardial triglyceride was related to age or BMI. The present report is much larger and much more rigorous in terms of endocrinologic characterization than prior studies and therefore more likely accurate. The observation of myocardial lipid accumulation with insulin resistant states makes perfect sense in the context of both animal and human studies showing ectopic lipid accumulation in other organs (liver and skeletal muscle) in diabetes mellitus. What is also quite intriguing is that subtle measures of cardiac dysfunction (specifically diastolic) were observed among the groups with elevated myocardial triglyceride. It should be noted, however, that diastolic dysfunction also was observed in the obese group, whereas myocardial triglyceride in these subjects was increased but not significantly compared with the lean group. Although observational, these data as a whole support the hypothesis that lipid accumulation and diastolic dysfunction may indeed be related in insulin-resistant states. None of these patients had known coronary artery disease or prior myocardial infarction, and presumably, no symptoms of heart failure (although it is not explicitly excluded). This study does not imply causality but does strongly suggest that accumulation of myocardial triglyceride is at least a marker of early cardiac dysfunction in patients with insulin resistance. There appears to be no difference in myocardial triglyceride or diastolic function between the impaired glucose tolerance group and those with overt type 2 diabetes mellitus, suggesting that the severity of insulin resistance (as supported by HOMA) may not be related to myocardial lipid accumulation and cardiac dysfunction. More rigorous studies of diastolic characterization (perhaps by echocardiography) in subjects with more advanced heart failure and diabetes mellitus would be interesting to test whether increased lipid content is associated with more profound dysfunction. Similarly, longitudinal studies of diabetic subjects with various amounts of myocardial triglyceride using different hypoglycemic treatment strategies would be equally as intriguing.

The authors also wisely chose to exclude subjects taking thiazolidinediones, agents known to modulate intracellular lipid content, to avoid confounding the results. In animal studies, thiazolidinediones have been shown to reduce ectopic lipid accumulation in skeletal muscle, liver, and even the heart.\textsuperscript{19} However, thiazolidinediones are well known for increasing clinical heart failure episodes, and given the recent attention paid to thiazolidinediones and their potential contribution to increased myocardial infarction risk, these agents are unlikely to be used in diabetic patients with heart failure.\textsuperscript{20} Perhaps other agents that favorably modulate myocardial FA oxidation will reduce FA accumulation and thereby slow the progression to heart failure in those at risk.

One limitation to the clinical significance of this work is that in contrast to other magnetic resonance imaging–based techniques, proton MR spectroscopy is technically challenging to perform and is unlikely to be widely applied clinically. The absolute magnitude of the ratios of myocardial fat to water reported in this study was $< 1\%$, requiring both high sensitivity and a degree of precision that may be difficult to reproduce. Nonetheless, cardiac proton MR spectroscopy remains a powerful research tool—one that will continue to provide a window into the potential mechanism(s) of cardiac dysfunction in insulin-resistant states.

The principal finding of myocardial triglyceride accumulation in humans with insulin resistance presented by McGavock et al is of significant importance because it provides strong evidence linking observations from animal models of cardiac lipotoxicity to humans with diabetes mellitus. With future simplification of spectroscopic techniques, it is foreseeable that myocardial lipid content may one day be used as a biomarker to predict the development of cardiac dysfunc-
tion in patients with insulin-resistant states and may serve as a measurable target for intervention before the development of diabetic cardiomyopathy.

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None.

References

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