Cardiac steatosis, or the abnormal accumulation of myocardial lipid, has recently emerged as an identifiable feature of insulin-resistant states including obesity and type 2 diabetes mellitus. Although the presence of increased myocardial lipid has been associated with both systolic and diastolic dysfunction in human and animal studies, it remains unclear whether accumulated lipid species are intrinsically pathological (the “lipotoxicity” hypothesis) or simply a marker of a fundamental derangement in cellular metabolism. It has been hypothesized that in insulin-resistant states, cellular fatty acid uptake exceeds mitochondrial oxidative capacity, leading to the generation of cytotoxic lipid metabolites that affect cardiac function through a variety of potential mechanisms. Indeed, many of the mouse models that recapitulate the diabetic phenotype and elicit myocardial steatosis also alter cellular systems that regulate lipid metabolism and energy substrate utilization.

It is relatively simple to measure myocardial lipid in animal models because cardiac tissue is readily available ex vivo for histological processing. In vivo measurements from a beating heart and breathing animal, although much more challenging, are possible with the application of image-guided proton magnetic resonance spectroscopy (MRS). Proton MRS is similar to MRI in that protons, principally contained in water and fat in biological tissue, generate a measureable nuclear magnetic resonance (NMR) signal when placed in a strong external magnetic field and exposed to tuned radiofrequency energy. In MRI, the NMR signals from all protons irrespective of their chemical environment are summed to generate an intensity that is localized in space by the application of multiple magnetic field gradients. In MRS, the various populations of protons can be separated into a signal intensity spectrum by differences in their intrinsic resonance signatures. In this way, chemical species’ concentrations can be determined noninvasively from a volume of tissue with a high degree of accuracy and reproducibility. Specifically, intracellular lipids can be quantified by determining the total spectral peak areas corresponding to the methylene (CH2, seen at approximately 1.4 parts per million) and methyl (CH3, seen at approximately 0.8 to 1.0 parts per million) side chains expressed as a fraction of the total water signal (at 4.7 parts per million).

Although cardiac proton MRS studies offer tremendous potential for clinical and research applications, the technique remains challenging to perform and interpret. Furthermore, as opposed to MRI-based techniques such as late gadolinium enhancement, no clinical question has been identified that cardiac MRS can uniquely answer to affect patient treatment, limiting its widespread adaptation. This is in contrast to the research applications of proton MRS to assess myocardial lipid or phosphorus MRS to quantify cardiac high-energy phosphates.

A few centers have developed expertise in the use of proton MRS to measure myocardial lipid in human subjects and have thus contributed to our understanding of cardiac physiology and metabolism. One critical publication compared myocardial lipid content by MRS among lean, obese, obese with impaired glucose tolerance, and type 2 diabetic subjects and found a stepwise increase in lipid content that was associated with subclinical diastolic dysfunction. Another publication demonstrated declining diastolic performance as a function of both increasing myocardial lipid content and age, and another identified a modest improvement in systolic function that associated with a reduction in myocardial lipid after a short exercise training period. Finally, the effects of short-term dietary interventions on myocardial lipid, including increased fat intake or caloric restriction, have yielded intriguing findings that increase our understanding of myocyte fuel preference.

These studies, although most relevant to human disease, are largely correlative and do not permit a more refined methodology to explore biochemical mechanisms, as is possible in rodent studies. Various transgenic models have sought to recreate the human cardiomyopathic phenotype seen in diabetes through the deletion, suppression, or overexpression of proteins thought to be dysregulated. Rodent models also permit direct measurement of enzymes and metabolites including putative lipotoxic species such as ceramide—a sphingolipid created from the metabolism of nonesterified fatty acids that can induce cellular apoptosis through a variety of mechanisms. Although a complete review of the merits and shortcomings of these many mouse models of insulin resistance is beyond the scope of this editorial, it is important to note that myocardial steatosis is a common unifying feature.
vated receptor-alpha (PPAR-α) overexpression murine model to study the effects of a high-fat diet on both systolic function and myocardial lipid accumulation using sensitive proton MRS and tagged MRI strain techniques. The purpose of the study was to determine whether changes in myocardial lipid after a short-term, high-fat diet would be associated with changes in systolic function and thereby provide insight into the relationship between lipid accumulation and the development of dysfunction.

The study is a well-executed technological accomplishment in that ECG and respiratory-gated MRS data were acquired from a 1-mm isotropic voxel localized to the interventricular septum in anesthetized but spontaneously breathing animals with a heart rate range from 400 to 600 beats per minute. Despite the small sample volume, the authors report a variation of <10% in the total water signal by MRS. Next, tagged MRI data were acquired with a spatial resolution of approximately 0.3 × 0.3 mm in plane and with a temporal resolution of 8 ms. This degree of resolution is rather typical for murine MRI studies. These data permitted calculation of the maximal (E1) and minimal (E2) principal radial systolic strain of epicardial and endocardial layers of the interventricular septum. To achieve this degree of precision, an ultrahigh field 14.1 T (600 MHz) vertical-bore magnet was used.

The authors chose to study 2 groups of animals—one transgenic group overexpressing PPAR-α and the other wild-type—by tagged MRI and MRS measurements at baseline and then again after a 2-week high-fat diet challenge. After the 2-week interval, the mice were euthanized and hearts were excised for triglyceride measurement, generating biochemical data to compare with MRS lipid measurements. Additional control animals, both wild-type and PPAR-α transgenic, were euthanized before diet challenge to determine baseline cardiac triglyceride content; another control group of animals receiving a normal chow diet underwent the same serial measurements as the treatment animals to control for changes that might be detected by serial measurement alone.

There are 2 principal findings from this study. The first relates to the exact species of lipid as measured by MRS. The authors found that at baseline before the high-fat diet, myocardial lipid content by both MRS and triglyceride assay was higher in the transgenic mice than the wild-type controls, as predicted by prior studies. After a high-fat diet, myocardial lipid increased as measured by MRS in both transgenic and wild-type animals but to a greater degree in the transgenic group, whereas there were no differences in myocardial lipid identified by MRS in the groups of wild-type and transgenic animals that received a normal chow diet. However, biochemically determined triglyceride content remained similar in transgenic animals before and after the high fat diet, suggesting that some component of the increased mobile lipid signal identified by MRS was not triglyceride—the first key finding. This disparity between mobile lipid as measured by MRS and biochemically measured triglyceride was not seen in the wild-type animals. Therefore, although both wild-type and transgenic animals accumulated lipid after the high-fat diet, MRS detected additional nontriglyceride lipid species in the transgenic animals.

The second key finding was that the authors identified a reduction in systolic strain (roughly 30%) after the high-fat diet in only the transgenic mice, for example, those with the highest lipid content, but not the wild-type control animals treated with high fat diet. Baseline strain measurements were similar between the wild-type and transgenic mice, despite differing lipid content at baseline, and, interestingly, strain did not significantly change in the wild-type mice fed a high fat diet despite increase in lipid as detected by MRS and triglyceride analysis. Strain did not change in either wild-type or transgenic mice after a normal chow diet. The authors concluded that a threshold level of lipid accumulation (roughly 2-fold) was necessary to affect systolic function but attainable only after high-fat challenge in susceptible animals.

As the authors acknowledge in the discussion, this study does not distinguish whether the observed reductions in principal strain are related simply to changes in tissue compliance from triglyceride droplet accumulation or the generation of cytotoxic lipid metabolites. Recent data from a different transgenic mouse model support the hypothesis that triglyceride accumulation is not in itself pathological. In addition, a human trial of pioglitazone induced changes in myocardial fatty acid metabolism that were associated with improved diastolic function but not associated with changes in myocardial triglyceride. It is reasonable to conclude that the additional nontriglyceride mobile lipid signal identified by MRS in this study may represent a lipid species that contributed to the strain abnormality. It is known that PPAR-α overexpression not only increases fatty acid transport into the cell but also affects lipid esterification and oxidation through modulation of mitochondrial function. Therefore, its is possible that lipotoxic species, such as ceramide, may have been generated by the high-fat diet and subsequently increased fatty acid substrate, resulting in the observed abnormalities of strain. In this animal study, the authors had the opportunity to but did not directly measure ceramide, cellular apoptosis, evidence of increased generation of reactive oxygen species from mitochondrial dysfunction, and/or key proteins that are regulated by PPAR-α. Such examinations, perhaps the subject of future reports, would help better define the relationship between mechanism and phenotype.

Another potential area of interest is the assessment of diastolic function, as the authors acquired strain images only during the systolic phase of the cardiac cycle. It is possible that more subtle abnormalities in diastolic function could also be identified with even lower levels of myocardial lipid, as in PPAR-α animals at baseline or in wild-type animals after a high fat diet. Such an observation would be predicted from the various human and animal studies discussed above. The finding that a higher threshold of lipid must be reached to affect systolic function would fit nicely into this continuum.

This work further substantiates proton MRS as an in vivo technique with tremendous utility in both human and mouse studies for acquisition of reproducible measurements of myocardial lipid. Hankiewicz et al are to be congratulated for having completed this ambitious and well-designed study;
but, as with any good work, many questions are raised by its findings that merit further investigation. In future studies, serial MRS-derived myocardial lipid measurements can be integrated into trials of targeted therapeutics or dietary modifications designed to modulate myocardial metabolism.

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