No Low-Fat Diet for the Failing Heart?

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Chances are that everyone knows about the heart’s oxygen requirement, but few would consider the heart’s metabolism of energy-providing substrates a big issue. Since the celebrated work of C. Lovatt Evans and Ernest Starling at the beginning of the last century, physiologists have recognized the heart as an efficient transducer of energy. Like an engine, the heart turns chemical energy into mechanical energy, efficiently and at a high rate. Metabolism of energy-providing substrates and contractions of the heart are tightly coupled. Because the heart’s energy for contraction is derived from oxidative phosphorylation of adenosine diphosphate to adenosine triphosphate, myocardial oxygen consumption is also commonly used to measure cardiac efficiency. Another feature of the heart is also worth mentioning. The heart is a metabolic omnivore, and for any given environment it uses the most economic fuel available (Figure). In the fasted state, when the fatty acid levels are high, the heart oxidizes predominantly fatty acids. Metabolic adaptability comes into play when the heart is stressed and veers toward carbohydrate oxidation. With a short-term increase in workload, the working heart ex vivo covers its increased need for energy through the oxidation of glycogen, lactate, and glucose, in that order. For a given amount of oxygen used, the heart in vivo performs up to 40% more efficiently with glucose than with fatty acids as the main energy-providing substrate. In a simulated state of exercise, the heart spares glycogen and oxidizes lactate almost exclusively. With long-term changes in workload, extensive metabolic remodeling accompanies the structural and functional changes of the heart in the course of hypertrophy, atrophy, and heart failure, and this remodeling includes a reactivation of the fetal metabolic gene program. A hallmark of energy substrate metabolism of the fetal heart is its reliance on carbohydrates (especially lactate) for energy conversion. In contrast to the fetal heart, however, with its abundant glycogen reserves, the failing heart has a depleted metabolic energy reserve. The failing heart relies on exogenous substrate for energy provision because of the lack of endogenous energy reserves.

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Fuel spectrum of the heart. Major energy-providing substrates for the heart are fats (triglycerides and fatty acids, represented as dark shades) and carbohydrates (glycogen, glucose, and lactate, represented as light shades). Depending on its environment, the heart selects the most efficient fuel for respiration (normal), and it does so even when stressed (adaptation). The absence or the overabundance of one fuel (extreme parts of the spectrum) may result in metabolic toxicity and contractile dysfunction.

A single study by Tuunanen et al.\textsuperscript{12} is that the patients developed insulin resistance. The homeostasis model assessment index value for patients, calculated from Table 2 in the Tuunanen et al.\textsuperscript{12} article, is 3.0, which puts patients into the fourth of 5 quintiles, with 5 indicating most serious.\textsuperscript{19} Therefore, these patients are likely to have defects of their insulin receptors and are less likely able to adapt to the need for a sudden increase of glucose uptake as FFA levels fall. Whatever the mechanism might be, the present study\textsuperscript{12} is the first to show decreased FFA uptake and inferred reduced oxidation rates with the use of a supposed FFA inhibitor.

After reading the article by Tuunanen et al.,\textsuperscript{12} the practicing cardiologist will ask the obvious question: No low-fat diet for the failing heart? Although it is reasonable to assume that the heart functions best when it oxidizes a variety of substrates, including fats, simultaneously\textsuperscript{20} (Figure), the complexities of intermediary metabolism continue to challenge the cardiac physiologist. After measuring the homeostasis model assessment index, clinicians need to consider how to treat the probable insulin resistance, for instance, by a low-fat Mediterranean-type diet, by exercise, and, if still needed, by metformin. All of these measures would bring the heart back from the extreme forms of either glucotoxicity or lipotoxicity to a normal or adaptive metabolic state (Figure).

The ancient Greeks knew that the truth has many faces. Remember Diogenes and his lamp? The reason for decreased cardiac efficiency with acipimox may be found both inside and outside the heart. Despite some imperfections in the execution of the study by Tuunanen et al.,\textsuperscript{12} however, one point seems especially important: When it comes to energy substrate metabolism of the heart, extremes are never good.

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References

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