No Low-Fat Diet for the Failing Heart?

Heinrich Taegtmeyer, MD, DPhil; Kalpana Ballal, PhD

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\textsuperscript{1,2} 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.\textsuperscript{3} Because the heart’s energy for contraction is derived from oxidative phosphorylation of adenosine diphosphate to adenosine triphosphate, myocardial energy consumption is also commonly used to measure cardiac efficiency.\textsuperscript{4} 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\textsuperscript{5} (Figure). In the fasted state, when the fatty acid levels are high, the heart oxidizes predominantly fatty acids.\textsuperscript{6} 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.\textsuperscript{7} 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.\textsuperscript{8} In a simulated state of exercise, the heart spares glycogen and oxidizes lactate almost exclusively.\textsuperscript{9} 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.\textsuperscript{8,9,10} 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,\textsuperscript{11} 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.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the University of Texas Houston Medical School, Department of Internal Medicine, Division of Cardiology, Houston, Tex.

Correspondence to Heinrich Taegtmeyer, MD, DPhil, Department of Internal Medicine, Division of Cardiology, University of Texas Houston Medical School, 6431 Fannin, MSB 1.222, Houston, TX 77030. E-mail Heinrich.Taegtmeyer@uth.tmc.edu

© 2006 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org
DOI: 10.1161/CIRCULATIONAHA.106.659235

Article p 2130

We have provided such a detailed introduction because the new findings of an international group of investigators led by Tuunanen et al\textsuperscript{12} at the Turku PET-Centre in Finland, published in this issue of Circulation, seem to contradict a great deal of what is known about myocardial energy substrate metabolism in the failing heart.\textsuperscript{13} The investigators used acipimox, a nicotinic acid derivative with profound antilipolytic effects, to manipulate substrate supply to the heart. The drug accomplished the desired goals to lower fatty acid levels in the serum and rates of fatty acid uptake in the heart in a group of patients with idiopathic dilated cardiomyopathy and in a group of normal volunteers. It was anticipated that a shift from fatty acid oxidation to glucose oxidation might improve contractile function in the failing heart. Unexpectedly, in both groups, the stroke volume of the left ventricle decreased, and the rate $\times$ pressure product and myocardial perfusion remained unchanged.

How is it possible that changes in metabolic substrate fluxes would lead to impaired contractile function of the heart? There are several explanations for this phenomenon. First, the study by Tuunanen et al\textsuperscript{12} describes a short-term change in substrate supply. It also lends support to 2 recent reports in lipase-deficient mouse models. Energy metabolism is altered in mice lacking adipose triglyceride lipase,\textsuperscript{14} and a cardiac-specific loss of HPL\textsubscript{0} lipoprotein lipase–derived fatty acids is associated with cardiac dysfunction in the face of increased cardiac glucose metabolism.\textsuperscript{15} The data suggest a lipase-derived fatty acid requirement for normal contractile function of the heart. The exact mechanism for these phenomena has not yet been elucidated.

Second, the drug itself may have direct hemodynamic effects independent of its fatty acid–lowering actions. The conclusions of the present study would be stronger if a control group had been included and been given both acipimox and a fatty acid infusion. Furthermore, the hemodynamic data are also consistent with an increase in systemic vascular resistance. Hydraulic resistance (R) is defined by analogy to Ohm’s Law as the ratio of the mean pressure drop (P) to flow (Q) between 2 points in a liquid flowing in a tube. This hemodynamic explanation would lead to questions about the causality between decreased rates of fatty acid oxidation and a decreased stroke volume. A third explanation would be that short-term lowering of free acids by acipimox not only enhances peripheral insulin-mediated glucose uptake\textsuperscript{16} but also lowers insulin secretion by the pancreatic beta cells.\textsuperscript{17} Because insulin is a vasodilator,\textsuperscript{18} the fall in insulin levels may have resulted in an increase in systemic vascular resistance. In the present study,\textsuperscript{12} there is no information on insulin levels after administration of the drug. One likely reason for an abrupt decrease of free fatty acids (FFAs) in the
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 in the failing heart.

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 (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.

Disclosures

The work in the authors’ laboratory is supported by a grant from the US Public Health Service (ROI-HL 073162).

References


Key Words: Editorials \[ diet \[ heart failure \[ metabolism \[ fatty acids \]
No Low-Fat Diet for the Failing Heart?
Heinrich Taegtmeyer and Kalpana Ballal

Circulation. 2006;114:2092-2093
doi: 10.1161/CIRCULATIONAHA.106.659235

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/114/20/2092

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/