

Failing Heart and Starving Brain

Ketone Bodies to the Rescue

One of my favorite quotes in literature comes from the biochemist-turned-writer Isaac Asimov (1920–1992), who wrote, “The saddest aspect of life right now is that science gathers knowledge faster than society gathers wisdom.”¹ Two recent articles^{2,3} published back to back in *Circulation* seem to challenge this notion by exposing results of strategic value. Both studies analyzed and sorted vast amounts of metabolites, proteins, and gene transcripts in failing human heart muscle,^{2,3} and both came independently to the same conclusions: Of all of the energy-providing substrates for the heart, the enzymes regulating ketone body metabolism are upregulated while those regulating glucose and fatty acid metabolism are downregulated. In other words, a strong signal emerged from a mountain of data. What does this mean? Here are my thoughts.

When I am in congenial company, and especially over a glass of wine, I like to reflect on the story of metabolism, which is actually the story of people. It has been said that I am the only practicing cardiologist with a living connection to the Krebs cycle. Krebs often referred to metabolism as “biochemistry with a purpose”. More specifically, contraction and metabolism in the heart are inextricably linked and obey the First Law of Thermodynamics (energy in=energy out). Notable exceptions are futile cycles and the uncoupling of oxidative phosphorylation of ADP. As one of Krebs’ last graduate students, I used the isolated working rat heart as a model for probing cardiac metabolism and function under simulated physiologic conditions. We speculated that ketone bodies would be an excellent fuel for respiration because of their direct access to the enzymes of the Krebs cycle. To our surprise, when provided as the only fuel for respiration, ketone bodies induced an acute contractile dysfunction reversed by the addition of glucose as a second fuel.⁴ Biochemically, ketone bodies inhibited the Krebs cycle by sequestering coenzyme A and by robbing the cycle of its intermediates downstream of one of its dehydrogenases. Subsequently, my graduate student Raymond Russell and I were able to show that replenishing the Krebs cycle intermediates through a group of reactions, collectively called anaplerosis, also restored contractile function of the heart. How do these observations fit into the present reports? Let me explain why they may fit and may offer a new strategy for the treatment of the failing heart.

First, one needs to recognize that in vivo the heart, a metabolic omnivore, is always exposed to >1 substrate. Second, we need to consider the role of the liver as a major regulator of substrate supply for the heart and for the body as a whole. This story begins with a group of brave students in the 1960s recruited by George Cahill⁵ for a study probing substrate metabolism of the brain during starvation. The students were divinity students because they were considered trustworthy for a study like this. What happens with a 36-hour fast? The brain, as we know, prefers glucose to all other substrates. Does the brain continue to rely on glucose, produced by the liver as an emergency fuel, or does the brain switch to an alternate energy-providing substrate?

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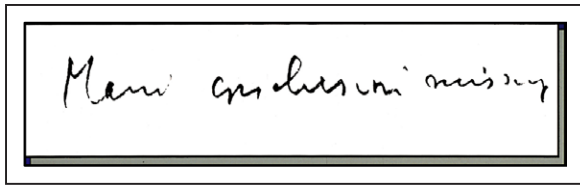


Figure. The handwriting of Hans A. Krebs (“Main conclusion missing”) on the first draft of my DPhil thesis titled, “Metabolic Activities of the Isolated Rat Heart” (Oxford, 1981).⁷

The answer was fascinating because it revealed that organs talk to each other not only through hormones but also through metabolites. This much we know about the wisdom of the body. When its main fuel, glucose, is in short supply, a vital organ such as the brain switches to ketone bodies made in the liver by incomplete oxidation of fatty acids.⁵ For the brain, there is a distinct evolutionary advantage from this switch as our distant ancestors adapted to cycles of feast and famine. Now we find that the failing heart also relies on ketone body metabolism when the other pathways of energy substrate metabolism begin to shut down. The question is: Are there any parallels between the starving brain and the failing heart? One parallel is that the liver sends ketone bodies to both, and both organs begin to derive ATP from them.

Are there any practical implications of this line of reasoning? More specifically, would it be possible to introduce a metabolic substrate to support the nonischemic failing heart, a heart that fails in the midst of plenty and has been likened to an engine out of fuel, at least at the cellular level? First, we do not know whether the footprints of enhanced ketone body metabolism are causes or consequences of heart failure. Second, we do not know whether boosting ketone body metabolism in the heart would also boost ATP production. Because of their association with diabetes mellitus and starvation, ketone bodies (or ketones) have earned a somewhat morbid connotation. However, Cahill and Veech⁶ have proposed that D- β -hydroxybutyrate, the principal ketone body, may actually be a “superfuel,” producing ATP more efficiently than glucose or fatty acids. Indeed, the early success of a ketogenic diet in epilepsy treatment holds great promise. Admittedly, however, the reasons for this success are complex.

The footprints of ketone body metabolism are clearly present in the failing heart, although the rates of ketone body oxidation and their effect of contractile function in the failing heart are still to be determined. Additionally, it may be risky to place patients with heart failure on a ketogenic diet. A concomitant rise in fatty acids in the circulation may suppress the metabolism of glucose as anaplerotic substrate for the Krebs cycle. Although there may be an alternative, in the form of

ketone esters, giving ketone bodies to patients with heart failure seems almost paradoxical. Krebs would have probably used the same 3 words he wrote across the cover page for the first draft of my thesis: “Main conclusion missing” (Figure), and he would have quoted John Hunter⁸ (1728–1793): “Why argue and not do the experiment?” That is what is on my mind right now.

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FOOTNOTE

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