Ketones Step to the Plate

A Game Changer for Metabolic Remodeling in Heart Failure?

Stephen C. Kolwicz, Jr, PhD; Sophia Airhart, MD; Rong Tian, MD, PhD

It is increasingly recognized that metabolic remodeling is integral to heart failure (HF) development and progression.[1,2] In particular, impairments in the ability of cardiac mitochondria to oxidize fatty acids have been noted, along with an increase in glycolysis that is uncoupled from glucose oxidation.[3,4] This overall reduction in the myocardial oxidative capacity is purported to be the root cause of energy deficiency in the failing heart. Although past research has focused primarily on myocardial use of glucose and fatty acids, the heart is an omnivore and capable of oxidizing other substrates such as lactate, ketone bodies, and amino acids. The current understanding of the contribution of lactate, ketone bodies, and amino acids to cardiac metabolism is limited, particularly in the setting of HF. In this issue of *Circulation*, 2 independent studies provide new insights into the reliance of the failing heart on ketone bodies for energy supply. Proteomics analysis in mouse models of HF by Aubert et al[5] and metabolomics analysis of end-stage human failing hearts by Bedi et al[6] demonstrate strong and concordant evidence of increased ketone oxidation in the failing heart.

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Ketone bodies, that is, acetoacetate, β-hydroxybutyrate (βOHB), and acetone (in low abundance), are produced in the liver and used in peripheral tissues as an energy source when glucose is not readily available because of either a limited exogenous supply or impaired insulin signaling or when fatty acids are in surplus, which occurs in marked activation of lipolysis. On entering the cell, they rapidly form acetyl CoA via a series of reactions catalyzed by βOHB dehydrogenase (BDH1), succinyl-CoA:3-oxoacid-CoA transferase (SCOT), and mitochondrial acetyl-CoA acetyltransferase 1 (also known as thiolase), as shown in the Figure. All enzymes are present in the heart, and the reactions are driven primarily by substrate availability, except for the SCOT reaction, which is a succinyl CoA–dependent process.

In their work, Aubert et al[5] examined longitudinal changes in cardiac energy metabolism during the development of HF in murine models of compensated hypertrophy, induced by transverse aortic constriction, and HF, generated by superimposing an apical infarction on the transverse aortic constriction model. Using a proteomic approach, the group identified significant downregulation of proteins involved in fatty acid utilization in both compensated hypertrophy and HF hearts with a concurrent 2- to 3-fold increase in BDH1, the enzyme that catalyzes the initial step in the ketone oxidation pathway. The notable finding of increased BDH1 protein prodded an additional search to identify metabolic signatures of cardiac ketone body utilization. In particular, the authors found increases in hydroxybutyrylcarnitine (C4OH-carnitine) and acetylcarnitine (C2-carnitine) in the HF group (Figure). In addition, a significant increase in succinate was noted, consistent with the succinyl CoA–dependent SCOT reaction (Figure). Increased levels of C4OH-carnitine and C2-carnitine were also observed in the heart of young, healthy mice fed a 4-week ketogenic diet, supporting their utility as the metabolic signature of ketone metabolism.

Also in this issue of *Circulation,* the observations in mice are complemented by an independent study of end-stage human HF by Bedi et al[6] in which metabolomics analysis showed increased ketogenic βOHB-CoA and evidence for enhanced myocardial utilization of βOHB, for example, decreases in βOHB and succinyl-CoA levels in the cardiac tissue (Figure). These changes were accompanied by an upregulation of BDH1, BHD2 (cytosolic isoform), and SCOT (also called OXCT1), key enzymes in the ketone oxidation pathway. Furthermore, a negative correlation of OXCT1 expression and succinyl-CoA level lent further support to the increased SCOT reaction in the failing heart. These studies collectively provide direct evidence of increased reliance on ketone body metabolism in the failing hearts of both mice and humans and successfully introduce a novel player to the game of metabolic remodeling in HF.

The studies also sought to determine whether the upregulation of the ketone oxidation pathway was a driver of metabolic remodeling by comparing the stages of compensated hypertrophy and HF. Bedi et al[6] found that the metabolite profile characteristic of ketone oxidation was present only in failing hearts and not observed in tissues with left ventricular hypertrophy and apparently normal function (Figures IV–VI in the online-only Data Supplement by Bedi et al[6]). Moreover, gene expression of enzymes for ketone oxidation was unaltered in patients with cardiac hypertrophy (Figure VII in the online-only Data Supplement by Bedi et al[6]), suggesting that increased ketone utilization is a late event in HF. Elevations in serum levels of both fatty acids and ketone bodies implied that the upregulation of ketone oxidation is a consequence of enhanced hepatic ketogenesis and hence increased substrate delivery to the

From Mitochondria and Metabolism Center, Department of Anesthesiology and Pain Medicine (S.C.K., R.T.) and Cardiology Division, Department of Medicine (S.A.), University of Washington, Seattle.

Correspondence to Rong Tian, MD, PhD, Mitochondria and Metabolism Center, University of Washington School of Medicine, 850 Republican St, Seattle, WA 98109. E-mail rongtian@u.washington.edu

(*Circulation*. 2016;133:689-691.
DOI: 10.1161/CIRCULATIONAHA.116.021230.)

***Circulation* is available at http://circ.ahajournals.org**
DOI: 10.1161/CIRCULATIONAHA.116.021230

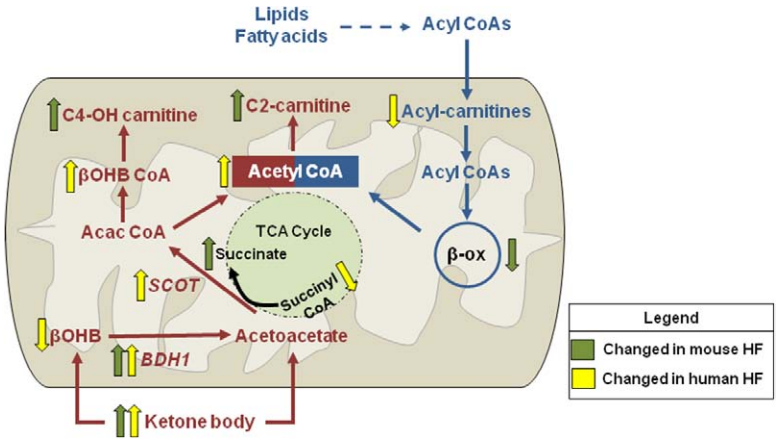

Figure. Ketone metabolism is increased in failing hearts of mice and humans. The major findings of altered ketone body (red) and fatty acid (blue) metabolism from the present studies in failing mice and humans are summarized. Decreased fatty acid oxidation was evidenced by a reduction in long-chain acylcarnitines and reduced protein abundance of several enzymes in β-oxidation (β-ox). Elevations in serum ketone body concentration were matched by alterations in metabolites and enzymes that are consistent with the upregulation of the ketone oxidation pathway. Green arrows show findings in mouse heart failure (HF); yellow arrow, findings in human HF. Acac CoA indicates acetoacetyl CoA; BDH1, mitochondrial β-hydroxybutyrate dehydrogenase; βOHB, β-hydroxybutyrate; βOHB CoA, β-hydroxybutyryl CoA; C2-carnitine, acetylcarnitine; C4-OH carnitine, hydroxybutyrylcarnitine; and SCOT, succinyl-CoA:3-oxoacid-CoA transferase.

failing heart. Because ketone availability is a primary determinant of ketone utilization, these observations suggest that impaired systemic metabolism is an important contributor to remodeling of cardiac metabolism in advanced HF.

Data obtained from mouse hearts provided a different perspective to this question, however. Aubert et al[5] observed a consistent upregulation of BDH1 in mouse hearts with pathological hypertrophy and failure despite similar circulating ketone levels, suggesting that an increased BDH1 level could accelerate ketone metabolism during the development of HF. Using stable isotope labeling techniques in isolated perfused hearts, the group showed a significant increase in the relative oxidation of βOHB in hypertrophied mouse hearts that coincided with the upregulation of BDH1. Because the concentration of βOHB (1 mmol/L) used in perfusion experiments was several-fold higher than serum levels in mice or humans with HF, future studies are warranted to determine whether the upregulation of BDH1 increases the use of ketone supplied at an in vivo concentration. Nevertheless, the efforts of Aubert et al[5] and Bedi et al[6] have identified a novel aspect of cardiac metabolism in the failing heart that has high clinical relevance and opens up new opportunities for translational research in metabolic therapy for HF.

Despite unambiguous observations, the mechanism for increased myocardial ketone oxidation remains unclear. Both studies showed evidence of impaired fatty acid oxidation (FAO) in the failing heart, suggesting that increased ketone use could be a part of the metabolic remodeling that shifts the substrate utilization toward non–fatty acid sources. The mouse study found marked downregulation of proteins involved in FAO, implying a decrease in the capacity of FAO in the failing heart. This is consistent with prior studies demonstrating accumulation of intermediate metabolites of fatty acid metabolism in the heart of animal models of HF and patients with HF.[7,8] The human study, however, found a depletion rather than an accumulation of myocardial lipid intermediates, particularly long-chain acylcarnitines. In contrast to the proteomics data from mice, gene expression for proteins involved in fatty acid β-oxidation or peroxisome proliferator-activated receptor-α was unchanged, whereas transporters for carnitine were downregulated in cardiac tissue of patients with advanced HF. Thus, FAO is decreased in the failing mouse heart because the system is "jammed," whereas in the human failing heart, the system is "deprived." Although increased ketone utilization is coupled with decreased FAO, the underlying mechanisms for impaired FAO in the failing hearts of mice and human could be distinct. This does not, however, rule out the possibility that observations made in the cardiac tissue obtained from patients with advanced HF are unique to the end-stage disease, which is not comparable to the stable HF stage represented by the mouse model. Future studies are necessary to clarify this point and, more important, to determine whether impaired FAO is the cause of increased reliance on ketone as an energy source in HF. Furthermore, the present studies focused on nondiabetic, nonobese HF models/patients, which allows demonstration of a diabetes mellitus–independent increase in cardiac ketone utilization in HF. Because diabetes mellitus is present in ≈40% of patients hospitalized with HF,[9] it will be important to consider the influence of comorbidities on ketone metabolism in future experimental models.

An important question raised by the studies is whether the increased reliance on ketone body metabolism is adaptive or maladaptive for the failing heart. Deletion of SCOT in mouse hearts promotes pathological remodeling and cardiac dysfunction after transverse aortic constriction,[10] suggesting that the ability to oxidize ketone bodies is important for the failing heart. An elevation in serum ketone levels has now been observed by several studies in patients with HF.[6,11,12] Therefore, the present data suggest that the increase in myocardial ketone body utilization is a consequence of increased systemic availability. In end-stage HF, insulin resistance and cardiac cachexia are common, which increases the likelihood of ketone production by the liver and renders cardiac ketone utilization unavoidable. Because the metabolite profile associated with increased ketone oxidation is indicative of impaired TCA cycle fluxes in the failing hearts,[6] measures to reduce the reliance on ketone bodies are likely desirable. In this regard, preventing the decrease in myocardial FAO during the development of pathological hypertrophy is worth consideration.[13] In turn, measures to tailor nutritional interventions or to optimize systemic metabolism to attenuate hepatic ketone body production may also be a potential therapeutic approach.

Sources of Funding

This work was supported in part by grants from the National Institutes of Health (HL088634, HL110349, HL118989, and HL129510 to

Dr Tian) and the American Heart Association (14SDG18590020 to Dr Kolwicz and 15POST22560002 to Dr Airhart).

Disclosures

None.

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KEY WORDS: Editorials ■ heart failure ■ hypertrophy ■ metabolism