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EDITORIAL COMMENT

Fueling the Failing Heart

The Key May Be Ketones*

Adam J. Chicco, PhD

A primary goal of cardiovascular medicine is ultimately to ensure that myocardial perfusion meets the oxygen demands of the heart. This is because oxygen facilitates production of nearly all the adenosine triphosphate (ATP) required to sustain cardiac function through mitochondrial oxidative phosphorylation, without which contractile failure would ensue in seconds. Advances in atherosclerotic disease prevention and interventional cardiology have substantially reduced mortality from acute coronary syndromes in recent decades, but this has inevitably increased the burden of heart failure in our aging population. The pathogenesis of heart failure is complex and multifactorial, but is increasingly recognized to involve metabolic perturbations that may limit myocardial performance even with adequate myocardial perfusion.

The human heart is a metabolic omnivore, capable of using a variety of fuels for oxidative metabolism to meet its constant energy demands.[1] A defining feature of the healthy myocardium is its "metabolic flexibility," that is, being able to shift its reliance on substrates for energy metabolism based on their availability in the circulation under resting and stressed conditions. At rest, circulating fatty acids provide 60% to 90% of the fuel for oxidative phosphorylation, with the remainder coming largely from carbohydrates as pyruvate oxidation and, to a lesser extent, glycolysis. During strenuous exercise, the heart becomes a major consumer of lactate, increasing its oxidation linearly as circulating levels rise >10-fold above resting conditions. Contributions of glucose oxidation also increase with greater cardiac work or when fatty acid availability is low, perhaps facilitating increased contractile performance under acute stress.

In their recent study in this issue of *JACC: Basic to Translational Science*, Vite et al[2] demonstrate for the first time that cardiomyocytes from failing human hearts lose this metabolic flexibility, exhibiting reduced functional capacity when only carbohydrate-derived substrates are available (glucose, pyruvate, and lactate [G/L/P]). Their results parallel decades of evidence supporting impaired energy production in the hypertrophied and failing heart in humans and animal models, as well as an "uncoupling" of glucose use from mitochondrial ATP production that has been implicated in disease pathogenesis.[3] Importantly, markers of cardiac oxidative capacity were similar in failing compared to healthy cardiomyocytes, emphasizing that the bioenergetic deficiencies lie in the upstream substrate use pathways. When fatty acids were provided to failing cardiomyocytes in tandem with G/L/P, contractile function improved, but remained lower than in healthy cardiomyocytes. However, when 3-hydroxybutyrate (a ketone body) was provided along with G/L/P and fatty acids, contractile function of diseased cardiomyocytes was similar to that of healthy cells. In contrast, 3-hydroxybutyrate did not augment contractile function in healthy cardiomyocytes, consistent with accumulating evidence that the hypertrophied and failing heart specifically upregulates its reliance on ketone oxidation as a supplemental energy source.[4] Cardiomyocyte contractile function correlated with the left ventricular ejection fraction of corresponding donors regardless of substrates used in the non-failing group, but only when a mix of substrates

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From the Department of Biomedical Sciences, Colorado State University, Fort Collins, Colorado, USA; and the Division of Cardiology, University of Colorado School of Medicine, Aurora, Colorado, USA.

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were used in the failing group. This emphasizes the reliance of the failing heart on multiple fuel sources to support its function in vivo and highlights the importance of considering cardiac substrate use when designing and interpreting studies that investigate the links between myocardial metabolism and contractile function.

Ketone bodies are produced mainly by the liver from circulating fatty acids when glucose availability is low (eg, during prolonged fasting) and are exported to the circulation for uptake and oxidation as a glucose-sparing fuel by ketolytic organs such as the heart. Although circulating ketones are normally low and contribute minimally to cardiac ATP production, myocardial ketone oxidation can increase 2- to 3-fold in heart failure, potentially outstripping endogenous supply.[5] This has led to the hypothesis that therapeutic elevation of circulating ketones may improve myocardial energy metabolism and contractile function in the failing heart. Several dietary approaches have been explored to increase circulating ketone levels in humans and animal models, each with their own logistical and biological advantages and disadvantages. These studies are beginning to reveal diverse impacts of therapeutic ketosis on cardiovascular function by mechanisms beyond effects on myocardial energy production, including vascular endothelial function, anti-inflammatory and antioxidant effects, and epigenetic regulation.[4] Many existing pharmacotherapies also have the potential to directly or indirectly impact myocardial metabolism and substrate use.[6] Most notable in the present context are sodium-glucose co-transporter 2 inhibitors, which induce systemic ketosis and elicit favorable affects cardiac function and remodeling, along with improvements in blood pressure, weight loss, and glucose control. Whether these benefits are ketone-dependent or may be augmented by adjuvant dietary interventions merits further investigation.

Metabolic modulation as a therapeutic approach in heart failure is an exciting concept derived from basic and translation science that has the potential to advance current treatment strategies by optimizing myocardial energy supply rather than reducing energy demand. The study by Vite et al[2] highlights the value of developing creative experimental model systems from opportunistic clinical sampling to complement findings from animal models and cell lines, particularly when data can be correlated with patient outcomes. Integrating these approaches with traditional gain- and loss-of-function techniques, metabolic tracer technologies, and the growing power of multiomics and single-cell analyses hold promise for elucidating the mechanisms by which shifts in cardiac metabolism impact cardiovascular function in health and disease.

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ADDRESS FOR CORRESPONDENCE: Dr Adam J. Chicco, Department of Biomedical Sciences, Colorado State University, 200 West Lake Street, Mailstop 1617, Fort Collins, Colorado 80523-1617 USA. E-mail: Adam.Chicco@colostate.edu.

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