JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 7, 2022

STATE-OF-THE-ART REVIEW

Short-Chain Carbon Sources

Exploiting Pleiotropic Effects for Heart Failure Therapy

Azariyas A. Challa, MD, PhD,[a] E. Douglas Lewandowski, PhD[a,b]

HIGHLIGHTS

- **Novel therapies of treatment of HF are urgently needed.**
- **Preclinical and clinical studies show cardioprotective effects of KBs and SCFAs.**
- **KBs and SCFAs are alternative fuels to failing hearts and have pleotropic effects.**
- **Clinical studies of the therapeutic potential of both KBs and SCFAs are warranted.**

SUMMARY

Heart failure (HF) remains the leading cause of morbidity and mortality in the developed world, highlighting the urgent need for novel, effective therapeutics. Recent studies support the proposition that improved myocardial energetics as a result of ketone body (KB) oxidation may account for the intriguing beneficial effects of sodium-glucose cotransporter-2 inhibitors in patients with HF. Similar small molecules, short-chain fatty acids (SCFAs) are now realized to be preferentially oxidized over KBs in failing hearts, contradicting the notion of KBs as a rescue "superfuel." In addition to KBs and SCFAs being alternative fuels, both exert a wide array of nonmetabolic functions, including molecular signaling and epigenetics and as effectors of inflammation and immunity, blood pressure regulation, and oxidative stress. In this review, the authors present a perspective supported by new evidence that the metabolic and unique nonmetabolic activities of KBs and SCFAs hold promise for treatment of patients with HF with reduced ejection fraction and those with HF with preserved ejection fraction. (J Am Coll Cardiol Basic Trans Science 2022;7:730–742) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Despite advances in understanding of the pathological mechanisms underlying the progression of heart failure (HF), it remains the leading cause of morbidity and mortality in the developed world.[1] Of particular concern is the lack of effectiveness of current therapies in improving outcomes for patients with HF with preserved ejection fraction (HFpEF), who account for half of all patients presenting with HF.[2] Therefore, the urgent need for novel and effective therapeutic strategies to treat patients with HF cannot be overstated.

Over the past decade, a ketogenic diet and exogenous ketone bodies (KBs) have garnered a great deal of public attention. Several preclinical studies have demonstrated the cardioprotective effects of

From the [a]Division of Cardiovascular Medicine, The Ohio State University College of Medicine, Columbus, Ohio, USA; and the [b]Division of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, The Ohio State University College of Medicine, Columbus, Ohio, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received October 27, 2021; revised manuscript received December 27, 2021, accepted December 28, 2021.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2021.12.010

elevating levels of circulating KBs.[3-8] Recently, sodium-glucose cotransporter-2 (SGLT2) inhibitors have shown remarkable effects in improving cardiovascular outcomes in patients with HF, irrespective of diabetic status.[9,10] Adding to the intrigue was the observation that SGLT2 inhibitors were associated with increased circulating KBs.[11] Thus, interest in exploring KB metabolism as a therapeutic target for treatment of HF has since amplified.

Short-chain fatty acids (SCFAs) are carboxylic acids containing up to 5 carbons, including acetate (2 carbons), propionate (3 carbons), and butyrate (4 carbons), generated primarily as products of fermentation of dietary fibers by the intestinal microbiota. Following the publication of the findings of large randomized clinical trials with associations of high-fiber diets with favorable cardiovascular outcomes,[12] increasing attention has been given to exploring cardioprotective effects of SCFAs. In particular, the protective properties of high-fiber diets against systemic hypertension and HF have been explored in preclinical studies and found to be closely associated with the salutary effects of SCFAs[13-24] (see Table 1). Consistent with these studies, findings from large cohorts have revealed decreased levels of SCFAs in the gut,[25-28] as well as in the circulation[29,30] of patients with HF and/or hypertension.

In addition to the potential of KBs and SCFAs as alternative fuels for the heart, accumulating experimental evidence suggests that both KBs and SCFAs exert a wide array of nonmetabolic functions, as signaling molecules and epigenetic modifiers and in affecting the regulation of inflammation and immunity, blood pressure (BP), the autonomic nervous system, and prevention of oxidative stress. In this review, we present the perspective that the key nonmetabolic activities of KBs and SCFAs, along with their potential role in cardiac energy metabolism, make them promising targets for the treatment of patients with HF.

SOURCES AND METABOLISM OF KBs AND SCFAs

KBs are produced in the liver, mainly from fatty acids and in small part from ketogenic amino acids, leucine, and lysine. Fatty acids enter hepatocytes and undergo β-oxidation to form acetyl coenzyme A (CoA), which is further catalyzed to acetoacetate. Reduction of acetoacetate (AcAc) for systemic transport produces β-hydroxybutyrate (β-HB) and acetone. Circulating KBs are transported into cells by monocarboxylate transporters. KBs diffuse into mitochondria entering oxidative metabolism via β-HB dehydrogenase 1 to ultimately produce acetyl-CoA and entry into the tricarboxylic acid cycle (see Figure 1). There is little direct evidence for de novo extrahepatic ketogenesis. Indeed, labeling artifact occurs because of reverse flux through the reversible key enzymes involved in the ketone utilization pathway, including succinyl-CoA:3-ketoacid CoA transferase, β-HB dehydrogenase 1, and acetoacetyl-CoA thiolase 1, a process called "pseudoketogenesis," as reviewed previously.[31]

Endogenous SCFAs are generated primarily as products of fermentation of dietary fibers and resistant starches by the intestinal microbiota. SCFAs can also be administered exogenously. SCFAs enter cells via monocarboxylate transporter and are oxidized after entry into mitochondria to enter the tricarboxylic acid cycle (see Figure 1). SCFAs can influence energy metabolism, inflammation and immunity, regulation of BP, and the autonomic nervous system.

Circulating levels of SCFAs can vary considerably, likely depending on the timing of serum collection (fasting vs. postprandial), dietary content, species type, method of quantification, and whether exogenous supplementation is used to bolster the levels. In general, acetate has the highest circulating level, with serum concentrations ranging from 100 to 1,000 μM,[32-34] whereas the concentrations of propionate and butyrate are typically <20 μM but can be elevated up to >200 μM via exogenous supplementations.[35-37] Intravenous infusion of sodium butyrate can raise the level even further to >500 μM without significant toxicities.[38] Although in the absence of such supplementation, baseline endogenous circulating SCFAs are less likely to provide significant fuel for the myocardium, the high affinity of SCFAs for the respective G protein-coupled receptors (GPRs) can induce pleotropic nonmetabolic effects at even these low concentrations.[39]

ROLE OF KBs AND SCFAs IN CARDIAC ENERGY METABOLISM

Energy-rich long-chain fatty acids (LCFAs) have long been recognized as the primary fuel source for oxidative adenosine triphosphate production in the cardiomyocyte, contributing up to 70% of all carbon entering the tricarboxylic acid cycle.[40] A well-documented metabolic derangement in decompensated HF of various etiologies, perhaps with the exception of obesity- or diabetes-related

ABBREVIATIONS AND ACRONYMS

β-HB = β-hydroxybutyrate
BP = blood pressure
CoA = coenzyme A
CPT1 = carnitine palmitoyltransferase I
FFAR = free fatty acid receptor
GPR = G protein–coupled receptor
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
KB = ketone body
LCFA = long-chain fatty acid
SCFA = short-chain fatty acid
SGLT2 = sodium-glucose cotransporter-2

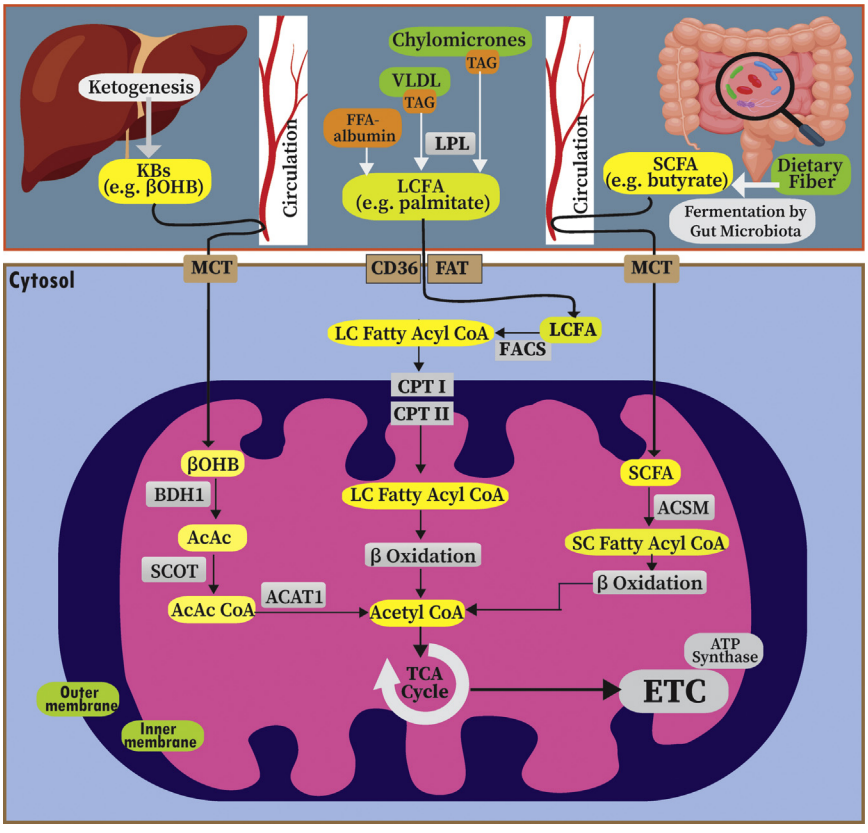
TABLE 1 Preclinical Evidence for the Cardioprotective Effects of SCFAs

Strategy for Altering the Level of SCFAs	Experimental Model	Proposed Mechanism	Results	
Supplementation with high-fiber diet or SCFAs as a mixture of acetate, butyrate, and propionate (100 mmol/L each) in drinking water	Angiotensin II infusion in mice fed a diet devoid of fiber	SCFAs activated the cognate receptor GPR43/GPR109A, decreased L-DOPA levels (effect on SNS), and increased abundance of T-regs.	SCFAs reduced blood pressure and prevented cardiac fibrosis and hypertrophy.	Kaye et al[13]
Supplementation with high-fiber diet or acetate (supplied in drinking water at 200 mmol/L)	Mineralocorticoid excess-induced HTN and HF (mouse)	Acetate down-regulated cardiac and renal Egr1, a master regulator of cardiac hypertrophy, cardiorenal fibrosis, and inflammation. It also down-regulated the renin-angiotensin system in the kidney and MAPK signaling in the heart.	Both acetate and a high-fiber diet significantly reduced systolic and diastolic BPs, cardiac fibrosis, and LV hypertrophy. Acetate also reduced renal fibrosis.	Marques et al[14]
Propionate given in drinking water at 200 mmol/L	ApoE$^{-/-}$ and wild type mice infused with angiotensin II for 28 d	Propionate reduced splenic effector memory T cells and T helper 17 cells, mitigating systemic inflammation. It also decreased local cardiac immune cell infiltration.	Propionate attenuated cardiac hypertrophy and fibrosis, aortic atherosclerosis, and HTN. It also reduced susceptibility to ventricular arrythmia.	Bartolomaeus et al[15]
Sodium butyrate orally administered (1 g/kg/day)	Rat model of angiotensin II-induced HTN and cardiac injury	Butyrate inhibited up-regulation of the proinflammatory genes *IL-1b*, *NLRP3*, and *MCP-1* in cardiac tissue by a mechanism involving inhibition of HDAC and possibly inhibiting the COX2/PGE2 pathway.	Butyrate attenuated angiotensin-II induced HTN, cardiac hypertrophy, inflammation and fibrosis.	Zhang et al[16]
Butyrate administrated intraperitoneally (1 mol/L)	Rat model of MI via ligation of the LAD	Butyrate suppressed inflammatory response in the infarct border zone by promoting M2 macrophage polarization. It also inhibited sympathetic neural remodeling.	Butyrate administration prevented cardiac dysfunction and ventricular arrythmia after MI.	Jiang et al[17]
Dietary supplementation with SCFAs (acetate, propionate, and butyrate)	Antibiotic treatment of mice for 7 d followed by ligation of the distal LAD	SCFAs enhanced cardiac repair by modulating myeloid cell populations and promoting the infiltration of CX3CR1^{+} monocytes into the peri-infarct zone.	Antibiotic treatment reduced the serum levels of SCFAs and increased mortality from MI. Supplementation with SCFAs improved survival by 50%.	Tang et al[18]
Sodium butyrate (1%) provided in drinking water for 12 wk	Mice were fed a high-fat diet for 24 wk to induce cardiac dysfunction	Butyrate attenuated myocyte apoptosis and production of ROS by inhibiting HDAC. The specific signaling pathway likely involves activation of MKK3/P38/PRAK.	Butyrate attenuated high-fat diet–induced cardiac hypertrophy, fibrosis, and dysfunction. It also prevented high-fat diet–induced obesity, insulin resistance, and hyperglycemia.	Zhang et al[19]
Treatment with sodium butyrate (5 mg/kg) daily for 8 wk	PAAC-induced cardiac hypertrophy	Butyrate reduced oxidative stress and mitochondrial DNA concentration, likely via down-regulation of class I HDACs, specifically HDAC2.	Butyrate ameliorated cardiac hypertrophy and fibrosis and preserved diastolic and systolic function.	Patel[20]
FBA, a synthetic derivative of butyrate	Mouse model of doxorubicin-induced cardiotoxicity	FBA attenuated oxidative stress and mitochondrial dysfunction via the HDAC inhibitory activity of butyrate.	FBA protected mice from doxorubicin induced cardiac dysfunction.	Russo et al[21]
Chronic cecal infusion of acetate, use of probiotic *C. butyricum*, or prebiotic Hylon VII	Rat model of OSA using a tracheal balloon that inflates during sleep	Acetate prevented OSA-induced elevated blood pressure by unclear mechanism.	Cecal acetate concentration decreased by 48% in rats with OSA. Cecal acetate infusion and supplementation with a prebiotic or a probiotic abolished OSA-induced HTN.	Ganesh et al[22]
Supplementation with butyrate (1%) for 10 wk	ApoE$^{-/-}$ mice fed regular chow diet	Butyrate attenuated vascular inflammation by inhibiting the NF-κB pathway.	Butyrate reduced atherosclerosis by 50%.	Aguilar et al[24]

Abbreviations: ApoE = apolipoprotein E; BP = blood pressure; COX2 = cyclo-oxygenase 2; CX3CR1 = CX3C chemokine receptor 1; FBA = phenylalanine-butyramide; L-DOPA = l-3,4-dihydroxyphenylalanine; GPR = G protein-coupled receptor; HDAC = histone deacetylase; HF = heart failure; HTN = hypertension; LAD = left anterior descending coronary artery; LV = left ventricular; MAPK = mitogen-activated protein kinase; MI = myocardial infarction; MKK3 = mitogen-activated protein kinase kinase 3; NF-κB = nuclear factor κB; OSA = obstructive sleep apnea; PAAC = partial abdominal aortic constriction; PGE2 = prostaglandin E_2; PRAK = p38-regulated/activated protein kinase; ROS = reactive oxygen species; SCFA = short-chain fatty acid; SNS = sympathetic nervous system; T-regs = regulatory T cells.

cardiomyopathy,[41-43] is the downward shift in the oxidation of LCFAs, which can drop as much as 30%.[44-47] This reduced LCFA oxidation is, in large part, the consequence of reduced activity of the rate limiting enzyme for LCFA oxidation in mitochondria, carnitine palmitoyltransferase I (CPT1) on the outer mitochondrial membrane.[44,48-50] Neither KBs nor SCFAs require transport into the mitochondria via CPT1 and bypass this step required for LCFAs.[51,52] Thus, these small-molecule oxidative fuels are more

FIGURE 1 Source and Metabolism of KBs, LCFAs, and SCFAs in Cardiomyocytes



The **top panel** shows sources of ketone bodies (KBs), long-chain fatty acids (LCFAs), and short-chain fatty acids (SCFAs). KBs are generated primarily in the liver. LCFAs can be found in the circulation as free fatty acid (FFA) bound to albumin or could also be derived from the release of fatty acids from triacylglycerol (TAG)-containing very low-density lipoprotein (VLDL) or chylomicrons via the action of lipoprotein lipase (LPL). SCFAs are by-products of fermentation of dietary fibers by gut microbiota. The **bottom panel** shows the entry of KBs, LCFAs, and SCFAs into the cytosol and mitochondria and their subsequent metabolism. KBs and SCFAs enter the cytosol via monocarboxylic acid transporter (MCT), while LCFAs enter the cytosol through protein-mediated transport involving a cluster of differentiation 36 (CD36) and fatty acid transport protein (FAT). Uptake of KBs and SCFAs into the mitochondria occurs by diffusion, whereas uptake of LCFAs into the mitochondria requires activation into long-chain (LC) fatty acyl coenzyme A (CoA) by fatty acyl CoA synthetase (FACS) and enzymatic activity of carnitine palmitoyltransferase (CPT) I and II. The Figure further depicts the intermediary metabolism of LCFAs (eg, palmitate), KBs (eg, β-hydroxybutyrate [βOHB]) and SCFAs (eg, butyrate) in the mitochondria and their subsequent metabolism into acetyl-CoA. Acetyl-CoA is subsequently metabolized further in the tricarboxylic acid (TCA) cycle, the products of which donate electrons to the electron transport chain (ETC) driving the oxidative phosphorylation and the adenosine triphosphate (ATP) generation needed for sustaining contractile function. AcAc = acetoacetate; ACAT = acetoacetyl-coenzyme A thiolase; ACSM = acyl-coenzyme A synthetase medium chain; BDH = β-hydroxybutyrate dehydrogenase; FA = fatty acid; SC = short-chain; SCOT = succinyl-CoA:3-ketoacid CoA transferase.

readily oxidized than LCFAs, leading to the observed increases in the oxidation of the 4-carbon chain KB β-HB in failing hearts.[6,53]

Importantly, a recent study showed that SCFAs, which afford similar adenosine triphosphate production per mole as ketones, are preferentially utilized over KBs,[54] casting doubt on the concept of KBs as unique "superfuels." A crucial limitation for the proposition that the failing heart adapts or remodels its metabolic machinery to use KBs as a rescue fuel is the discrepancy in the findings from animals compared with humans. Increased expression of genes involved in KB oxidation is reported in mouse modes of HF.[6,53,55] But although myocardial samples from patients with HF show increased messenger RNA levels for the ketolytic enzyme β-HB dehydrogenase 1, unlike the rodent model of HF, β-HB dehydrogenase 1 enzyme protein content was not elevated in human failing hearts[54,55] and may be species specific, not translating to humans. As

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 7, 2022
JULY 2022:730–742

mentioned earlier, SCFAs are more readily oxidized than even KBs in the failing heart when provided at equimolar concentrations, and this may be attributed to an increase in the content of the enzyme acyl-CoA synthetase medium chain family member 3 (ACSM3), which despite the nomenclature shows broad substrate specificity (C4-C11) and esterifies butyrate to butyryl-CoA for mitochondrial oxidation. Importantly, acyl-CoA synthetase medium chain family member 3 is elevated in the failing hearts of both rodents and humans.[54] Of the putative short chain acetyl-CoA synthetase, acetyl-CoA synthetase short chain family member 1 (ACSS1), also referred to as acetyl-CoA synthetase 2, is activated by Sirt3[56] and facilitates the entry of acetate into the tricarboxylic acid cycle. However, acetyl-CoA synthetase short chain family member 1 does not activate butyrate[57] and is therefore not involved in the preference for SCFAs over KBs that was recently elucidated.[54] In addition unlike acyl-CoA synthetase medium chain family member 3, acetyl-CoA synthetase short chain family member 1 has not been shown to be elevated in the failing heart, so its significance in HF is unknown.

The proposition that KBs are the rescue "superfuel" for the failing heart have also been challenged by conflicting evidence from several studies. Yurista et al[8] reported that ketonemia induced by long-term supplementation with ketone ester attenuated the development of left ventricular dysfunction and remodeling and increased myocardial adenosine triphosphate production in 2 rodent models of HF, transverse aortic constriction or myocardial infarction in mice, and post-myocardial infarction remodeling in rats. In contrast, Ho et al[58] reported that the marked increase in ketone oxidation at high concentrations of β-HB in isolated mouse heart was not accompanied by an increase in cardiac work or efficiency. Similarly, short-term intravenous infusion of β-HB in patients with HF with reduced ejection fraction improved cardiac output without increasing myocardial efficiency as measured by stroke work per myocardial oxygen consumption.[59]

In healthy adults, SCFAs provide about 5% to 10% of energy for the human host.[60] Because of their low serum concentrations in physiological conditions (with the possible exception of acetate), it is not clear to what degree, if at all, the heart accesses and oxidizes circulating SCFAs as a source of energy. In a porcine model of coronary artery stenosis, the hypoperfused myocardium preferentially oxidized SCFAs over LCFAs, which is likely a consequence of bypassing the inhibition of CPT1 caused by moderate tissue hypoxia.[52] The ability of SCFAs and KBs to bypass CPT1, and thus LCFA oxidation, is particularly relevant in the failing heart, which is characterized by decreased activity of CPT1.[44,48]

In summary, accumulating evidence from experimental studies suggests the potential beneficial roles of SCFAs in patients with HF. Recent research has elucidated that metabolic remodeling in the failing heart, leading to a reduced ability to oxidize LCFAs, could favor the utilization of SCFAs over other substrates, including KBs. It is currently unclear if the observed salutary effects of SCFAs in patients with HF are caused by increased utilization by the failing heart as a fuel source. Given their superior efficiency and the observation that the enzymatic machinery for oxidation of SCFAs is up-regulated in the failing hearts of both rodents and humans, targeting this unexplored source of energy for therapy for patients with HF could be a promising area of future clinical studies.

MULTIDIMENSIONAL ROLES OF KBs AND SCFAs PERTINENT TO HF THERAPY

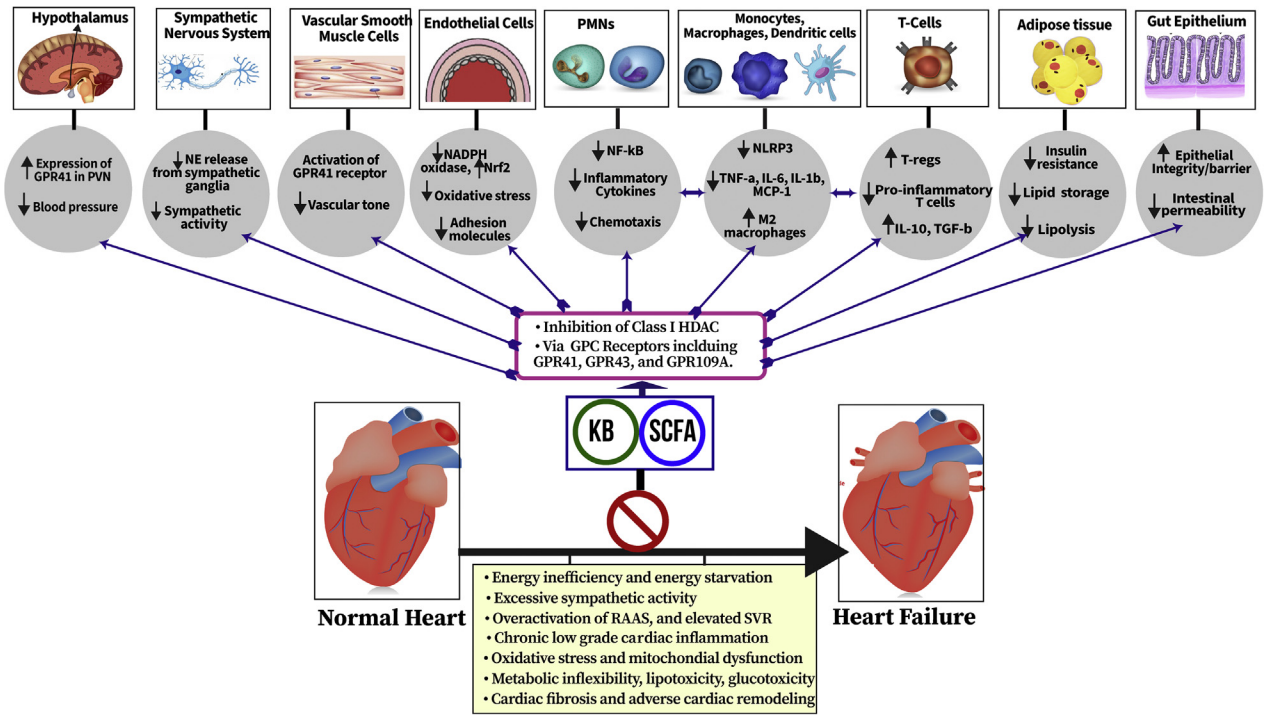
Growing body of evidence shows that KBs and SCFAs act not only as energy substrates but also as epigenetic modifiers and signaling molecules with diverse functions (see **Figure 2**). KBs (eg, β-HB) as well as SCFAs (eg, butyrate) can act as epigenetic modifiers by inhibiting class I histone deacetylases.[61] In addition, both KBs and SCFAs also act as signaling mediators through GPRs expressed in a variety of cells and tissues, including intestinal epithelial cells, adipocytes, immune cells, and vascular smooth cells. β-HB has been shown to have an inhibitory effect on GPR41 (free fatty acid receptor [FFAR] 3)[62] and an activating effect on GPR109A (hydroxycarboxylic acid receptor 2).[63] Recently, acetoacetate was shown to be an agonist of GPR43 (FFAR2) and was proposed to play a role in the regulation of lipid metabolism and energy homeostasis.[64] SCFAs exert their pleotropic physiological actions partly through their effects on GPR41 (FFAR3), GPR43 (FFAR2), olfactory receptor 78 (olfactory receptor 51E2), and GPR109A (hydroxycarboxylic acid receptor 2).[65,66]

In the following sections, we review some of the beneficial roles of KBs and SCFAs, with an emphasis on those potentially relevant for HF therapy.

THE HEMODYNAMIC EFFECTS OF KBs AND SCFAs.

Effects of KBs on BP, heart rate, and myocardial contractility. In healthy volunteers, high-dose intravenous infusion of β-HB resulted in increased heart rate, decreased diastolic BP, and increased in myocardial blood flow.[67] The increased heart rate was thought to be compensatory for the decreased diastolic BP, likely from peripheral vasodilation. In

FIGURE 2 Pleotropic Effects of KBs and SCFAs



This Figure shows the salutary effects of KBs and SCFAs in various tissues that are relevant in the context of their potential as heart failure therapy. GPC = G protein–coupled; GPR = G protein–coupled receptor; HDAC= histone deacetylase; IL = interleukin; MCP-1 = monocyte chemoattractant protein 1; NADPH = nicotinamide adenine dinucleotide phosphate; NE = norepinephrine; NF-kB = nuclear factor κB; NLRP3 = nucleotide-binding oligomerization domain–like receptor protein 3; Nrf2 = nuclear factor–erythroid factor 2–related factor 2; PMN = polymorphonuclear cell; PVN = paraventral nucleus of the hypothalamus; RAAS = renin-angiotensin-aldosterone system; SVR = systemic vascular resistance; TGF-b = transforming growth factor-beta; TNF-a = tumor necrosis factor-alpha; T-regs regulatory T cells; other abbreviations as in Figure 1.

another study involving patients with HF with reduced ejection fraction, intravenous infusion of β-HB at 0.18 kg/h for 3 hours achieved a serum level of 3.3 mmol/L and resulted in a 40% increase in cardiac output, a mild increase in heart rate, a decease in peripheral vascular resistance, and a mild reduction in filling pressures.[59] Whether KBs decreased vascular resistance by acting as direct vasodilators or via their effect on the sympathetic nervous system was not clear. Recently, β-HB was shown to have a direct vasodilatory effect, potentially via potassium channels independently of the receptors GPR41 and GPR109A.[68]

Effects of SCFAs on BP, heart rate, and myocardial contractility. SCFAs can act directly on the heart, affecting cardiac contractility. Indeed, butyrate has been shown to ameliorate myocardial stunning, promoting contractility in the postischemic myocardium.[69] SCFAs have been shown to exhibit antihypertensive properties in several experimental animal models[13-15,22,28,62,70,71] (see Table 1). Human studies have also demonstrated a strong association between elevated levels of SCFAs and decreased BP.[72,73] The mechanisms by which SCFAs reduce BP include their activity on GPR41 (FFAR3) receptors located on smooth muscles of low-resistance blood vessels[74] and endothelial cells.[65] SCFAs also influence the autonomic nervous system[75]; for instance, it was reported that increased delivery of butyrate in the colon resulted in hypotension and decreased heart rate through a mechanism involving the afferent colonic vagus nerve and the cognate GPR41/43 receptor.[76] Interestingly, intravenous butyric acid resulted only in reduced BP, without affecting heart rate or contractility, supporting the oral route's negative chronotropic effect via its activity on the colonic vagus nerve.[76]

ROLE OF KBs AND SCFAs IN REGULATION OF INFLAMMATION AND IMMUNOMODULATION.

Role of KBs in regulation of inflammation and immunomodulation. Although whether KBs can categorically be deemed anti-inflammatory is

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 7, 2022
JULY 2022:730–742

controversial, β-HB has been shown to exert anti-inflammatory effects in various experimental models.[77-80] One mechanism for the anti-inflammatory effects of β-HB includes activation of the GPR109 receptor, which is abundantly expressed in neutrophils, monocytes, and macrophages, with downstream inhibition of the nuclear factor κB signaling pathway.[77,78] The other proposed mechanism includes inhibition of the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome independent of GPR109 via inhibition of K^+ efflux from inflammatory cells[79] and activation of the adenosine monophosphate-activated protein kinase-Foxo3 (AMPK-Foxo3) pathway.[80] Mice with elevated circulating β-HB caused by deletion of succinyl-CoA:3-ketoacid CoA transferase in skeletal muscles were protected from TCA-induced HF, likely because of reduced activation of cardiac nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome.[5] Similarly, increasing β-HB level ameliorated cardiac fibrosis and diastolic dysfunction in a mouse model by inhibiting formation of the nucleotide-binding oligomerization domain-like receptor protein 3 inflammasome and attenuating inflammatory cytokine formation.[81]

Role of SCFAs in regulation of inflammation and immunomodulation. Strong evidence from preclinical and clinical studies supports a pivotal role for SCFAs in the regulation of local inflammation in the gut,[82,83] and preclinical studies have shown that SCFAs are capable of regulating inflammation and immune modulation at peripheral sites, including the cardiovascular system.[18,23,84,85] The anti-inflammatory and immunomodulatory roles of SCFAs have also been reported as beneficial in the context of cardiac remodeling and HF.[13-16] In a rat model of angiotensin II-induced hypertension and cardiac injury, oral administration of sodium butyrate inhibited up-regulation of the proinflammatory genes *IL-1b*, *NLRP3*, and *MCP-1* in cardiac tissue via inhibition of histone deacetylase and attenuated angiotensin II-mediated pathological remodeling.[16] In a mouse model of hypertension, administration of SCFAs prevented adverse cardiac remodeling by promoting regulatory T cells.[13] In a mouse model of angiotensin II infusion-induced cardiac injury, oral propionate significantly attenuated cardiac hypertrophy, fibrosis, vascular dysfunction, hypertension, and systemic inflammation, associated with regulatory T cell activity.[18]

From the foregoing evidence, it can be deduced that KBs (β-HB in particular) and SCFAs play vital roles in the regulation of inflammation and immunity and have the capacity to exert potent anti-inflammatory and immunomodulatory activities relevant in the context of prevention and treatment of patients with HF. Associated cardioprotective benefits may also derive from potential antioxidant properties, especially of SCFAs, as evidenced by several animal studies,[61,86-91] summarized in **Table 2**.

KBs AND SCFAs AS POTENTIAL THERAPIES FOR HFPEF AND DIABETIC (METABOLIC) CARDIOMYOPATHY

Numerous clinical and epidemiologic studies over the past 2 decades have demonstrated the strong associations between incident HF (particularly HFpEF) and obesity,[92-95] insulin resistance,[96,97] and diabetes.[98,99] Of the mechanisms involved in HFpEF, altered substrate metabolism accompanying obesity, insulin resistance, and diabetes could be the earliest and most critical for the development of cardiac dysfunction, including a mismatch between excess availability of free fatty acid and glucose and the rate of mitochondrial oxidation, leading to decreased energy efficiency, glucotoxicity, and lipotoxicity.[43,100]

KBs and SCFAs may have great potential in preventing or managing HFpEF and metabolic cardiomyopathy. First, both exogenous ketones[63,101,102] and SCFAs[103,104] have been shown to decrease circulating LCFA and glucose levels, potentially counteracting the development of cardiac steatosis and glucotoxicity, thought to be the inciting events for the development of obesity related HFpEF. Second, both KBs and SCFAs can be oxidized by the failing heart as alternative fuels, potentially bolstering cardiac adenosine triphosphate production. Third, KBs as well as SCFAs possess anti-inflammatory[23,79,84,85] and antioxidative[24,61,86,90] properties, potentially severing the key links between metabolic syndrome and HFpEF. Last, both KBs and SCFAs have BP-lowering effects; given that hypertension is a common comorbid condition associated with HFpEF, their BP-lowering effects could be advantageous.[67,76] Thus, KBs and SCFAs hold promise as potential therapeutics because of their effects on factors that contribute to the pathogenesis of HFpEF and metabolic cardiomyopathy.

SGLT2 INHIBITORS, KBs, AND HF

Recently, several large randomized clinical trials have demonstrated that SGLT2 inhibitors markedly reduced the risk for cardiovascular mortality and hospitalizations in patients with HF.[10,105] On the basis of these impressive findings, SGLT2 inhibitors are

TABLE 2 Preclinical Evidence for the Antioxidative Stress Effects of KBs and SCFAs

Method of Increasing or Delivering KBs or SCFAs	Experimental Model	Results	Proposed Mechanism	
Administration of β-HB via intraperitoneal osmotic pump	Mice model of oxidative stress using IV injection of paraquat, a toxic herbicide that induces oxidative stress and generates ROS in several tissues	Administration of β-HB protected against paraquat-induced oxidative stress and ROS production.	Inhibition of class I HDACs with resultant up-regulation of genes involved in protection from oxidative stress, including *FOXO3A* and *MT2*	Shimazu et al[61]
Treatment of incubated cardiomyocytes with β-HB	Stimulation of cardiomyocytes using H_2O_2 to induce oxidative stress and generation of ROS	β-HB decreased production of ROS and prevented oxidative stress–induced apoptosis of H_2O_2-treated cardiomyocytes.	Up-regulation of *FOXO3A* rescued the decreased levels of the antioxidant enzymes SOD2 and catalase in H_2O_2-treated cardiomyocytes.	Nagao et al[86]
IV administration of sodium butyrate (500 mg/kg) to rats 6 h prior to exposure to contrast	Rat model of contrast-induced acute kidney injury using IV administration of metaglumine diatrizoate sodium (6 mL/kg)	Butyrate decreased levels of lipid peroxidation, IL-6, and renal tubular damage.	Butyrate prevented nuclear translocation of NF-κB and thereby decreased subsequent oxidative damage.	Machado et al[87]
Diet supplemented with 1% sodium butyrate for 10 wk	ApoE$^{-/-}$ mouse model of atherosclerosis and analysis of atherosclerotic lesions in the aorta.	Butyrate decreased area of atherosclerotic lesions in the aorta and decreased oxidative stress in atherosclerotic lesions.	Butyrate resulted in down-regulation of NADPH oxidase in endothelial cells and decreased release of ROS and iNOS from ox-LDL-stimulated macrophages.	Aguilar et al[89]
Diet containing sodium butyrate at 5 g/kg/d for 20 wk	Streptozotocin-induced diabetes in WT and Nrf2$^{-/-}$ mice	Butyrate attenuated aortic endothelial oxidative stress in WT but not Nrf2$^{-/-}$ mice.	Inhibition of HDAC by butyrate up-regulated the expression of the transcription factor Nrf2, which in turn promoted expression of antioxidant enzymes.	Wu et al[90]
Acetate or butyrate administered in drinking water at 100 mmol/L and 0.5 mg/kg/d, respectively	SHRs as a genetic model of hypertension	Acetate or butyrate reduced blood pressure and decreased NADPH oxidase–driven production of ROS in the endothelium.	Acetate or butyrate inhibited the lipopolysaccharide/Toll-like receptor 4 pathway and increased T-regs in the vasculature and local lymph nodes.	Robles-Vera et al[91]

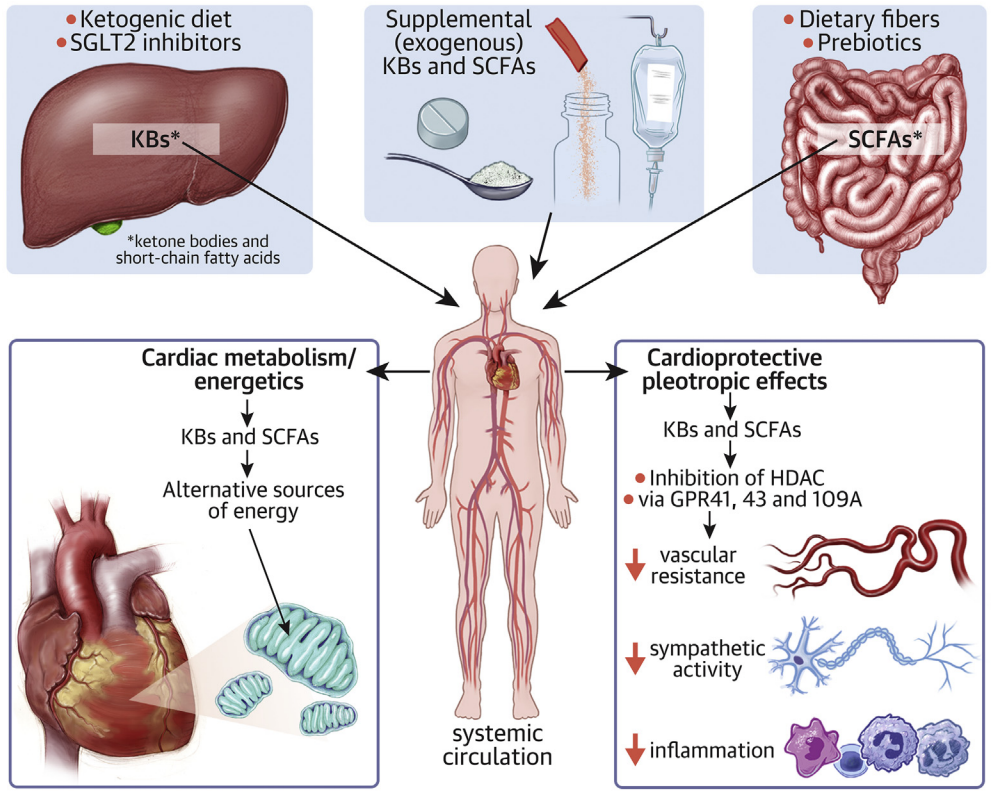
β-HB = β-hydroxybutyrate; IL = interleukin; iNOS = inducible nitric oxide species; IV = intravenous; ox-LDL = oxidized low-density lipoprotein; SHR = spontaneously hypertensive rat; SOD2 = superoxide dismutase 2, mitochondrial; WT = wild-type; other abbreviations as in Table 1.

now included as guideline-directed medical therapies for patients with HF with reduced ejection fraction irrespective of diabetic status.[106] In animal models of pathologic cardiac remodeling, including a rat model of myocardial infarction and a mouse model of diabetic cardiomyopathy, treatment with SGLT2 inhibitors ameliorated adverse cardiac remodeling and prevented diastolic dysfunction.[107,108] This was similar to the improved diastolic function and reduced left ventricular mass observed in patients with diabetes receiving short-term empagliflozin treatment.[109] Although multiple hypotheses have been proposed to explain the mechanism for the beneficial effects of SGLT2 inhibitors in patients with HF, this remains an area of debate. SGLT2 receptors are not expressed in cardiomyocytes; thus, it is likely that the beneficial cardiac effects of SGLT2 inhibitors occur via indirect mechanisms and may involve the generation of KBs.

SGLT2 inhibitors are associated with increased ketosis caused by increased adipose lipolysis that occurs as a consequence of reducing renal glucose reabsorption.[110] SGLT2 inhibitors can raise the level of β-HB to about 0.6 mmol/L in patients with diabetes and to about 0.3 mmol/L in those without diabetes.[110] Induction of KB oxidation by the failing heart has been hypothesized as a potential explanation for the observed cardiovascular benefits of SGLT2 inhibitors.[110] In support of this, Santos-Gallego et al[11] reported that empagliflozin ameliorated adverse cardiac remodeling and HF while reducing glucose extraction by the heart in favor of KBs and LCFA extraction.[11] In a rat model of cardiac arrest, empagliflozin significantly improved postarrest survival and left ventricular function. The investigators attributed the favorable post-cardiac arrest effects to the observed increased myocardial utilization of KBs.[111] However, other studies have reported conflicting results.[112-114] In a mouse model of diabetes, empagliflozin increased myocardial adenosine triphosphate production by increasing glucose oxidation, while KB utilization was unaltered.[113] Similarly, in a rat model of hypertension and diabetes, empagliflozin did not increase KB utilization, despite increased circulating levels.[114] Therefore, whether any increase in ketosis by SGLT2 inhibitors contributes to their beneficial effects on HF by improving cardiac energetics is debatable and warrants further investigation.

Although recent clinical trials have shown convincing beneficial effects of SGLT2 inhibitors in patients with HF, the primary mechanism has thus far been elusive. Perhaps SGLT2 inhibitors exert their beneficial effects through one or more of the nonmetabolic functions of KBs. However, if a primary

CENTRAL ILLUSTRATION **Sources and Cardioprotective Actions of Ketones and Short Chain Fatty Acids**



Challa AA, et al. J Am Coll Cardiol Basic Trans Science. 2022;7(7):730–742.

GPR = G protein-coupled receptor; HDAC = histone deacetylase; KB = ketone body; SCFA = short-chain fatty acid.

benefit of SGLT2 inhibition in failing hearts proves to be a shift toward KB oxidation, then strategies to enhance the availability of the more readily oxidized SCFAs may be more strongly indicated.

ELEVATING KETONES FOR TREATMENT OF PATIENTS WITH HF: CAUTIONS AND CONTRAINDICATIONS

Strategies that increase circulating levels of KBs for the treatment of patients with HF and diabetes come with the risk for severe elevations, potentially inducing diabetic ketoacidosis, a life-threatening acute complication of diabetes. Diabetic ketoacidosis is a consequence of excessive lipolysis and ketogenesis associated with absolute or relative insulin deficiency and elevated levels of counterregulatory hormones. The circulating level of β-HB at which diabetic ketoacidosis occurs is variable, but most cases are seen at >3 mmol/L, and it is more common in patients with type 1 diabetes.[115]

Similar to levels that can be reached with prolonged fasting (2-3 mmol/L), acute intravenous infusion of β-HB in patients with HF with reduced ejection fraction raised the serum level to 3 mmol/L.[59] SGLT2 inhibitors can raise the level of β-HB to an average level of 0.6 mmol/L in patients with diabetes and 0.3 mmol/L in those without diabetes. However, there are several case reports in which euglycemic diabetic ketoacidosis was associated with SGLT2 inhibition in both type 1 and type 2 diabetes.[116] Thus, even with modest increases in β-HB level by SGLT2 inhibition, potentially deleterious elevations have occurred in susceptible individuals, supporting the need to meticulously examine therapies that aim to boost KBs. Practically, consideration of therapeutic ketosis may entail routine monitoring of levels to avoid risk for serious complications such as

ketoacidosis, particularly when used in patients at high risk for diabetic ketoacidosis.

The ketogenic diet is popular for its effect on lipolysis and associated weight loss.[117] Studies evaluating the effect of a short-term ketogenic diet on cardiac function have shown decreased cardiac energetics and diastolic dysfunction.[118] Studies have revealed several untoward effects of the ketogenic diet, including decreased exercise capacity caused by glycogen depletion in skeletal muscle and increased low-density lipoprotein levels.[117] Consistent with the latter, in a recent case series, patients following a ketogenic diet developed marked hypercholesteremia.[119] Furthermore, the ketone precursor 1,3-butanediol is associated with adverse effects resembling alcohol intoxication, with dizziness and gait abnormalities.[120] With these concerns, the ketogenic diet may not be a safe strategy for the prevention of HF or treatment of patients with HF.

In this review, we have compiled evidence supporting the benefits of SCFAs in the treatment of patients with HF. Several animal studies have demonstrated that SCFAs have the capacity to ameliorate adverse cardiac remodeling in the failing heart[13-24] (see **Table 1**). Like KBs, SCFAs possess histone deacetylase-inhibiting properties and act as signaling molecules with multiple pleotropic salutary effects that can be harnessed in the treatment of patients with HF.[16,19,24,62,65,76] Importantly, SCFAs are preferentially oxidized over KBs in both normal and failing hearts.[54] In situations in which raising the levels of KBs could potentially be hazardous, raising the levels of SCFAs could be an attractive alternative strategy that warrants further exploration.

CONCLUSION AND FUTURE DIRECTION

Therapeutic ketosis is a promising strategy for HF therapy. Both short- and long-term administration of KBs have been shown to have beneficial effects that can be exploited in HF therapy. The mechanisms by which KBs improve cardiac function are currently not clear and include potential roles in intracellular signaling, vasodilation and reduced vascular resistance, and as a fuel to enhance oxidation energy production. It is also important to investigate to what extent the nonmetabolic salutary effects of KBs are relevant in the treatment of patients with HF. The availability of well-tolerated oral preparations such as ketone esters makes future clinical trials feasible. Along the same line, more studies are needed to examine the intriguing proposition that increased KB contribute to the remarkable beneficial effects of SGLT2 inhibitors in HF (**Central Illustration**).

Similarly, a better understanding of the mechanisms underlying the beneficial roles of SCFAs in HF will help in the design of novel therapies for HF, in particular targeting histone deacetylase activity or a role as an alternative, efficient fuel for oxidative energy production. Given the recent finding of the superior efficiency of SCFAs with a rapid rate of utilization by the failing heart, and the observation that the enzymatic machinery for oxidation of SCFAs is up-regulated in the failing hearts of both rodents and humans, targeting this unexplored source of energy for therapy for HF could be a promising area of future clinical studies.

In summary, although short-chain carbon sources appear to be attractive therapeutic targets with potential benefit in the treatment of patients with HF, confirmation of the role of leveraging KBs and SCFAs in HF remains an unmet need that requires prudent experiments in both basic and translational laboratories. Future investigation of whether they can be used in the treatment of patients with HF will provide exciting opportunities at alleviating the enormous burden of HF in the modern world.

ACKNOWLEDGMENT The authors thank Dr Andrew N. Carley for reading the manuscript and offering helpful comments.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by National Institutes of Health grants T32HL149637, R01HL132525, and R01HL049244. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr E. Douglas Lewandowski, The Ohio State University Medical Center, Biomedical Research Tower, BRT Room 312, 460 West 12th Avenue, Columbus, Ohio 43210, USA. E-mail: doug.lewandowski@osumc.edu.

REFERENCES

1. Writing Group Members, Mozaffarian D, Benjamin EJ, et al. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation*. 2016;133:e38–e360.

2. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res*. 2019;124:1598–1617.

3. Zou Z, Sasaguri S, Rajesh KG, Suzuki R. dl-3-Hydroxybutyrate administration prevents myocardial damage after coronary occlusion in rat hearts. *Am J Physiol Heart Circ Physiol*. 2002;283:H1968–H1974.

4. Snorek M, Hodyc D, Sedivy V, et al. Short-term fasting reduces the extent of myocardial infarction

and incidence of reperfusion arrhythmias in rats. *Physiol Res*. 2012;61:567–574.

5. Byrne NJ, Soni S, Takahara S, et al. Chronically elevating circulating ketones can reduce cardiac inflammation and blunt the development of heart failure. *Circ Heart Fail*. 2020;13:e006573.

6. Horton JL, Davidson MT, Kurishima C, et al. The failing heart utilizes 3-hydroxybutyrate as a metabolic stress defense. *JCI Insight*. 2019;4:e124079.

7. Schugar RC, Moll AR, Andre d'Avignon D, Weinheimer CJ, Kovacs A, Crawford PA. Cardiomyocyte-specific deficiency of ketone body metabolism promotes accelerated pathological remodeling. *Mol Metab*. 2014;3:754–769.

8. Yurista SR, Matsuura TR, Sillje HHW, et al. Ketone ester treatment improves cardiac function and reduces pathologic remodeling in preclinical models of heart failure. *Circ Heart Fail*. 2021;14:e007684.

9. Nikolic M, Zivkovic V, Jovic JJ, et al. SGLT2 inhibitors: a focus on cardiac benefits and potential mechanisms. *Heart Fail Rev*. 2022;27(3):935-949. https://doi.org/10.1007/s10741-021-10079-9

10. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.

11. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, et al. Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. *J Am Coll Cardiol*. 2019;73:1931–1944.

12. Estruch R, Ros E, Martinez-Gonzalez MA. Mediterranean diet for primary prevention of cardiovascular disease. *N Engl J Med*. 2013;369:676–677.

13. Kaye DM, Shihata WA, Jama HA, et al. Deficiency of prebiotic fiber and insufficient signaling through gut metabolite-sensing receptors leads to cardiovascular disease. *Circulation*. 2020;141:1393–1403.

14. Marques FZ, Nelson E, Chu PY, et al. High-fiber diet and acetate supplementation change the gut microbiota and prevent the development of hypertension and heart failure in hypertensive mice. *Circulation*. 2017;135:964–977.

15. Bartolomaeus H, Balogh A, Yakoub M, et al. Short-chain fatty acid propionate protects from hypertensive cardiovascular damage. *Circulation*. 2019;139:1407–1421.

16. Zhang L, Deng M, Lu A, et al. Sodium butyrate attenuates angiotensin II-induced cardiac hypertrophy by inhibiting COX2/PGE2 pathway via a HDAC5/HDAC6-dependent mechanism. *J Cell Mol Med*. 2019;23:8139–8150.

17. Jiang X, Huang X, Tong Y, Gao H. Butyrate improves cardiac function and sympathetic neural remodeling following myocardial infarction in rats. *Can J Physiol Pharmacol*. 2020;98:391–399.

18. Tang TWH, Chen HC, Chen CY, et al. Loss of gut microbiota alters immune system composition and cripples postinfarction cardiac repair. *Circulation*. 2019;139:647–659.

19. Zhang L, Du J, Yano N, et al. Sodium butyrate protects against high fat diet-induced cardiac dysfunction and metabolic disorders in type II diabetic mice. *J Cell Biochem*. 2017;118:2395–2408.

20. Patel BM. Sodium butyrate controls cardiac hypertrophy in experimental models of rats. *Cardiovasc Toxicol*. 2018;18:1–8.

21. Russo M, Guida F, Paparo L, et al. The novel butyrate derivative phenylalanine-butyramide protects from doxorubicin-induced cardiotoxicity. *Eur J Heart Fail*. 2019;21:519–528.

22. Ganesh BP, Nelson JW, Eskew JR, et al. Prebiotics, probiotics, and acetate supplementation prevent hypertension in a model of obstructive sleep apnea. *Hypertension*. 2018;72:1141–1150.

23. Arpaia N, Campbell C, Fan X, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature*. 2013;504:451–455.

24. Aguilar EC, Leonel AJ, Teixeira LG, et al. Butyrate impairs atherogenesis by reducing plaque inflammation and vulnerability and decreasing NFkappaB activation. *Nutr Metab Cardiovasc Dis*. 2014;24:606–613.

25. Cui X, Ye L, Li J, et al. Metagenomic and metabolomic analyses unveil dysbiosis of gut microbiota in chronic heart failure patients. *Sci Rep*. 2018;8:635.

26. Kummen M, Mayerhofer CCK, Vestad B, et al. Gut microbiota signature in heart failure defined from profiling of 2 independent cohorts. *J Am Coll Cardiol*. 2018;71:1184–1186.

27. Luedde M, Winkler T, Heinsen FA, et al. Heart failure is associated with depletion of core intestinal microbiota. *ESC Heart Fail*. 2017;4:282–290.

28. Kim S, Goel R, Kumar A, et al. Imbalance of gut microbiome and intestinal epithelial barrier dysfunction in patients with high blood pressure. *Clin Sci (Lond)*. 2018;132:701–718.

29. Guo Y, Zou J, Xu X, et al. Short-chain fatty acids combined with intronic DNA methylation of HIF3A: potential predictors for diabetic cardiomyopathy. *Clin Nutr*. 2021;40:3708–3717.

30. Liao HY, Wang CY, Lee CH, Kao HL, Wu WK, Kuo CH. Development of an efficient and sensitive chemical derivatization-based LC-MS/MS method for quantifying gut microbiota-derived metabolites in human plasma and its application in studying cardiovascular disease. *J Proteome Res*. 2021;20:3508–3518.

31. Puchalska P, Crawford PA. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. *Cell Metab*. 2017;25:262–284.

32. Gonzalez Hernandez MA, Canfora EE, Pasmans K, Astrup A, Saris WHM, Blaak EE. The relationship between circulating acetate and human insulin resistance before and after weight loss in the DiOGenes study. *Nutrients*. 2020;12:339.

33. Olsson A, Gustavsen S, Nguyen TD, et al. Serum short-chain fatty acids and associations with inflammation in newly diagnosed patients with multiple sclerosis and healthy controls. *Front Immunol*. 2021;12:661493.

34. Trend S, Leffler J, Jones AP, et al. Associations of serum short-chain fatty acids with circulating immune cells and serum biomarkers in patients with multiple sclerosis. *Sci Rep*. 2021;11:5244.

35. Linares R, Fernandez MF, Gutierrez A, et al. Endocrine disruption in Crohn's disease: bisphenol A enhances systemic inflammatory response in patients with gut barrier translocation of dysbiotic microbiota products. *FASEB J*. 2021;35:e21697.

36. Si X, Shang W, Zhou Z, et al. Gut microbiome-induced shift of acetate to butyrate positively manages dysbiosis in high fat diet. *Mol Nutr Food Res*. 2018;62(3).

37. Sato FT, Yap YA, Crisma AR, et al. Tributyrin attenuates metabolic and inflammatory changes associated with obesity through a GPR109A-dependent mechanism. *Cells*. 2020;9:2007.

38. Egorin MJ, Yuan ZM, Sentz DL, Plaisance K, Eiseman JL. Plasma pharmacokinetics of butyrate after intravenous administration of sodium butyrate or oral administration of tributyrin or sodium butyrate to mice and rats. *Cancer Chemother Pharmacol*. 1999;43:445–453.

39. Le Poul E, Loison C, Struyf S, et al. Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. *J Biol Chem*. 2003;278:25481–25489.

40. Saddik M, Lopaschuk GD. Myocardial triglyceride turnover and contribution to energy substrate utilization in isolated working rat hearts. *J Biol Chem*. 1991;266:8162–8170.

41. Peterson LR, Herrero P, Schechtman KB, et al. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. *Circulation*. 2004;109:2191–2196.

42. Rijzewijk LJ, van der Meer RW, Lamb HJ, et al. Altered myocardial substrate metabolism and decreased diastolic function in nonischemic human diabetic cardiomyopathy: studies with cardiac positron emission tomography and magnetic resonance imaging. *J Am Coll Cardiol*. 2009;54:1524–1532.

43. Buchanan J, Mazumder PK, Hu P, et al. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. *Endocrinology*. 2005;146:5341–5349.

44. Sorokina N, O'Donnell JM, McKinney RD, et al. Recruitment of compensatory pathways to sustain oxidative flux with reduced carnitine palmitoyltransferase I activity characterizes inefficiency in energy metabolism in hypertrophied hearts. *Circulation*. 2007;115:2033–2041.

45. Akki A, Smith K, Seymour AM. Compensated cardiac hypertrophy is characterised by a decline in palmitate oxidation. *Mol Cell Biochem*. 2008;311:215–224.

46. Sack MN, Rader TA, Park S, Bastin J, McCune SA, Kelly DP. Fatty acid oxidation enzyme gene expression is downregulated in the failing heart. *Circulation*. 1996;94:2837–2842.

47. Murashige D, Jang C, Neinast M, et al. Comprehensive quantification of fuel use by the failing and nonfailing human heart. *Science*. 2020;370:364–368.

48. Lewandowski ED, Fischer SK, Fasano M, et al. Acute liver carnitine palmitoyltransferase I overexpression recapitulates reduced palmitate oxidation of cardiac hypertrophy. *Circ Res*. 2013;112:57–65.

49. Pellieux C, Aasum E, Larsen TS, et al. Overexpression of angiotensinogen in the myocardium induces downregulation of the fatty acid oxidation pathway. *J Mol Cell Cardiol*. 2006;41:459–466.

50. Lionetti V, Linke A, Chandler MP, et al. Carnitine palmitoyl transferase-I inhibition prevents ventricular remodeling and delays decompensation in pacing-induced heart failure. *Cardiovasc Res*. 2005;66:454–461.

51. Halestrap AP. Pyruvate and ketone-body transport across the mitochondrial membrane. Exchange properties, pH-dependence and mechanism of the carrier. *Biochem J*. 1978;172:377–387.

52. Lewandowski ED, Kudej RK, White LT, O'Donnell JM, Vatner SF. Mitochondrial preference for short chain fatty acid oxidation during coronary artery constriction. *Circulation*. 2002;105:367–372.

53. Aubert G, Martin OJ, Horton JL, et al. The failing heart relies on ketone bodies as a fuel. *Circulation*. 2016;133:698–705.

54. Carley AN, Maurya SK, Fasano M, et al. Short-chain fatty acids outpace ketone oxidation in the failing heart. *Circulation*. 2021;143:1797–1808.

55. Bedi KC Jr, Snyder NW, Brandimarto J, et al. Evidence for intramyocardial disruption of lipid metabolism and increased myocardial ketone utilization in advanced human heart failure. *Circulation*. 2016;133:706–716.

56. Hallows WC, Lee S, Denu JM. Sirtuins deacetylate and activate mammalian acetyl-CoA synthetases. *Proc Natl Acad Sci U S A*. 2006;103:10230–10235.

57. Fujino T, Kondo J, Ishikawa M, Morikawa K, Yamamoto TT. Acetyl-CoA synthetase 2, a mitochondrial matrix enzyme involved in the oxidation of acetate. *J Biol Chem*. 2001;276:11420–11426.

58. Ho KL, Karwi QG, Wagg C, et al. Ketones can become the major fuel source for the heart but do not increase cardiac efficiency. *Cardiovasc Res*. 2021;117:1178–1187.

59. Nielsen R, Moller N, Gormsen LC, et al. Cardiovascular effects of treatment with the ketone body 3-hydroxybutyrate in chronic heart failure patients. *Circulation*. 2019;139:2129–2141.

60. Bergman EN. Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. *Physiol Rev*. 1990;70:567–590.

61. Shimazu T, Hirschey MD, Newman J, et al. Suppression of oxidative stress by beta-hydroxybutyrate, an endogenous histone deacetylase inhibitor. *Science*. 2013;339:211–214.

62. Kimura I, Inoue D, Maeda T, et al. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). *Proc Natl Acad Sci U S A*. 2011;108:8030–8035.

63. Taggart AK, Kero J, Gan X, et al. (D)-beta-Hydroxybutyrate inhibits adipocyte lipolysis via the nicotinic acid receptor PUMA-G. *J Biol Chem*. 2005;280:26649–26652.

64. Miyamoto J, Ohue-Kitano R, Mukouyama H, et al. Ketone body receptor GPR43 regulates lipid metabolism under ketogenic conditions. *Proc Natl Acad Sci U S A*. 2019;116:23813–23821.

65. Natarajan N, Hori D, Flavahan S, et al. Microbial short chain fatty acid metabolites lower blood pressure via endothelial G protein-coupled receptor 41. *Physiol Genomics*. 2016;48:826–834.

66. Brown AJ, Goldsworthy SM, Barnes AA, et al. The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J Biol Chem*. 2003;278:11312–11339.

67. Gormsen LC, Svart M, Thomsen HH, et al. Ketone body infusion with 3-hydroxybutyrate reduces myocardial glucose uptake and increases blood flow in humans: a positron emission tomography study. *J Am Heart Assoc*. 2017;6:e005066.

68. McCarthy CG, Chakraborty S, Singh G, et al. Ketone body β-hydroxybutyrate is an autophagy-dependent vasodilator. *JCI Insight*. 2021;6:e149037.

69. Lewandowski ED, Chari MV, Roberts R, Johnston DL. NMR studies of beta-oxidation and short-chain fatty acid metabolism during recovery of reperfused hearts. *Am J Physiol*. 1991;261:H354–H363.

70. Yang T, Santisteban MM, Rodriguez V, et al. Gut dysbiosis is linked to hypertension. *Hypertension*. 2015;65:1331–1340.

71. Durgan DJ, Ganesh BP, Cope JL, et al. Role of the gut microbiome in obstructive sleep apnea-induced hypertension. *Hypertension*. 2016;67:469–474.

72. Vijay A, Astbury S, Panayiotis L, et al. Dietary interventions reduce traditional and novel cardiovascular risk markers by altering the gut microbiome and their metabolites. *Front Cardiovasc Med*. 2021;8:691564.

73. Chen L, He FJ, Dong Y, et al. Modest sodium reduction increases circulating short-chain fatty acids in untreated hypertensives: a randomized, double-blind, placebo-controlled trial. *Hypertension*. 2020;76:73–79.

74. Pluznick JL, Protzko RJ, Gevorgyan H, et al. Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation. *Proc Natl Acad Sci U S A*. 2013;110:4410–4415.

75. Santisteban MM, Qi Y, Zubcevic J, et al. Hypertension-linked pathophysiological alterations in the gut. *Circ Res*. 2017;120:312–323.

76. Onyszkiewicz M, Gawrys-Kopczynska M, Konopelski P, et al. Butyric acid, a gut bacteria metabolite, lowers arterial blood pressure via colon-vagus nerve signaling and GPR41/43 receptors. *Pflugers Arch*. 2019;471:1441–1453.

77. Gambhir D, Ananth S, Veeranan-Karmegam R, et al. GPR109A as an anti-inflammatory receptor in retinal pigment epithelial cells and its relevance to diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2012;53:2208–2217.

78. Fu SP, Li SN, Wang JF, et al. BHBA suppresses LPS-induced inflammation in BV-2 cells by inhibiting NF-kappaB activation. *Mediators Inflamm*. 2014;2014:983401.

79. Youm YH, Nguyen KY, Grant RW, et al. The ketone metabolite beta-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nat Med*. 2015;21:263–269.

80. Bae HR, Kim DH, Park MH, et al. β-Hydroxybutyrate suppresses inflammasome formation by ameliorating endoplasmic reticulum stress via AMPK activation. *Oncotarget*. 2016;7:66444–66454.

81. Deng Y, Xie M, Li Q, et al. Targeting mitochondria-inflammation circuit by β-hydroxybutyrate mitigates HFpEF. *Circ Res*. 2021;128:232–245.

82. Sun M, Wu W, Chen L, et al. Microbiota-derived short-chain fatty acids promote Th1 cell IL-10 production to maintain intestinal homeostasis. *Nat Commun*. 2018;9:3555.

83. Macia L, Tan J, Vieira AT, et al. Metabolite-sensing receptors GPR43 and GPR109A facilitate dietary fibre-induced gut homeostasis through regulation of the inflammasome. *Nat Commun*. 2015;6:6734.

84. Nastasi C, Candela M, Bonefeld CM, et al. The effect of short-chain fatty acids on human monocyte-derived dendritic cells. *Sci Rep*. 2015;5:16148.

85. Millard AL, Mertes PM, Ittelet D, Villard F, Jeannesson P, Bernard J. Butyrate affects differentiation, maturation and function of human monocyte-derived dendritic cells and macrophages. *Clin Exp Immunol*. 2002;130:245–255.

86. Nagao M, Toh R, Irino Y, et al. β-Hydroxybutyrate elevation as a compensatory response against oxidative stress in cardiomyocytes. *Biochem Biophys Res Commun*. 2016;475:322–328.

87. Machado RA, Constantino Lde S, Tomasi CD, et al. Sodium butyrate decreases the activation of NF-kappaB reducing inflammation and oxidative damage in the kidney of rats subjected to contrast-induced nephropathy. *Nephrol Dial Transplant*. 2012;27:3136–3140.

88. Huang W, Guo HL, Deng X, et al. Short-chain fatty acids inhibit oxidative stress and inflammation in mesangial cells induced by high glucose and lipopolysaccharide. *Exp Clin Endocrinol Diabetes*. 2017;125:98–105.

89. Aguilar EC, Santos LC, Leonel AJ, et al. Oral butyrate reduces oxidative stress in atherosclerotic lesion sites by a mechanism involving NADPH oxidase down-regulation in endothelial cells. *J Nutr Biochem*. 2016;34:99–105.

90. Wu J, Jiang Z, Zhang H, et al. Sodium butyrate attenuates diabetes-induced aortic endothelial dysfunction via P300-mediated transcriptional activation of Nrf2. *Free Radic Biol Med*. 2018;124:454–465.

91. Robles-Vera I, Toral M, de la Visitacion N, et al. Probiotics prevent dysbiosis and the rise in blood pressure in genetic hypertension: role of short-chain fatty acids. *Mol Nutr Food Res*. 2020;64:e1900616.

92. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of

heart failure with preserved ejection fraction. *Circulation*. 2017;136:6–19.

93. Bello NA, Cheng S, Claggett B, et al. Association of weight and body composition on cardiac structure and function in the ARIC study (Atherosclerosis Risk in Communities). *Circ Heart Fail*. 2016;9:e002978.

94. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med*. 2002;347:305–313.

95. Savji N, Meijers WC, Bartz TM, et al. The association of obesity and cardiometabolic traits with incident HFpEF and HFrEF. *J Am Coll Cardiol HF*. 2018;6:701–709.

96. Ingelsson E, Sundstrom J, Arnlov J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. *JAMA*. 2005;294:334–341.

97. Vardeny O, Gupta DK, Claggett B, et al. Insulin resistance and incident heart failure the ARIC study (Atherosclerosis Risk in Communities). *J Am Coll Cardiol HF*. 2013;1:531–536.

98. Ho JE, Lyass A, Lee DS, et al. Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction. *Circ Heart Fail*. 2013;6:279–286.

99. Fontes-Carvalho R, Ladeiras-Lopes R, Bettencourt P, Leite-Moreira A, Azevedo A. Diastolic dysfunction in the diabetic continuum: association with insulin resistance, metabolic syndrome and type 2 diabetes. *Cardiovasc Diabetol*. 2015;14:4.

100. Nakamura M, Sadoshima J. Cardiomyopathy in obesity, insulin resistance and diabetes. *J Physiol*. 2020;598:2977–2993.

101. Balasse E, Ooms HA. Changes in the concentrations of glucose, free fatty acids, insulin and ketone bodies in the blood during sodium beta-hydroxybutyrate infusions in man. *Diabetologia*. 1968;4:133–135.

102. Mikkelsen KH, Seifert T, Secher NH, Grondal T, van Hall G. Systemic, cerebral and skeletal muscle ketone body and energy metabolism during acute hyper-D-beta-hydroxybutyratemia in post-absorptive healthy males. *J Clin Endocrinol Metab*. 2015;100:636–643.

103. den Besten G, Bleeker A, Gerding A, et al. Short-chain fatty acids protect against high-fat diet-induced obesity via a PPARγ-dependent switch from lipogenesis to fat oxidation. *Diabetes*. 2015;64:2398–2408.

104. Gao Z, Yin J, Zhang J, et al. Butyrate improves insulin sensitivity and increases energy expenditure in mice. *Diabetes*. 2009;58:1509–1517.

105. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.

106. Inzucchi SE, Kosiborod M, Fitchett D, et al. Improvement in cardiovascular outcomes with empagliflozin is independent of glycemic control. *Circulation*. 2018;138:1904–1907.

107. Joubert M, Jagu B, Montaigne D, et al. The sodium-glucose cotransporter 2 inhibitor dapagliflozin prevents cardiomyopathy in a diabetic lipodystrophic mouse model. *Diabetes*. 2017;66:1030–1040.

108. Lee TM, Chang NC, Lin SZ. Dapagliflozin, a selective SGLT2 inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. *Free Radic Biol Med*. 2017;104:298–310.

109. Verma S, Garg A, Yan AT, et al. Effect of empagliflozin on left ventricular mass and diastolic function in individuals with diabetes: an important clue to the EMPA-REG OUTCOME trial? *Diabetes Care*. 2016;39:e212–e213.

110. Ferrannini E, Baldi S, Frascerra S, et al. Shift to fatty substrate utilization in response to sodium-glucose cotransporter 2 inhibition in subjects without diabetes and patients with type 2 diabetes. *Diabetes*. 2016;65:1190–1195.

111. Tan Y, Yu K, Liang L, et al. Sodium-glucose cotransporter 2 inhibition with empagliflozin improves cardiac function after cardiac arrest in rats by enhancing mitochondrial energy metabolism. *Front Pharmacol*. 2021;12:758080.

112. Pietschner R, Kolwelter J, Bosch A, et al. Effect of empagliflozin on ketone bodies in patients with stable chronic heart failure. *Cardiovasc Diabetol*. 2021;20:219.

113. Verma S, Rawat S, Ho KL, et al. Empagliflozin increases cardiac energy production in diabetes: novel translational insights into the heart failure benefits of SGLT2 inhibitors. *J Am Coll Cardiol Basic Trans Science*. 2018;3:575–587.

114. Abdurrachim D, Teo XQ, Woo CC, et al. Empagliflozin reduces myocardial ketone utilization while preserving glucose utilization in diabetic hypertensive heart disease: a hyperpolarized ^{13}C magnetic resonance spectroscopy study. *Diabetes Obes Metab*. 2019;21:357–365.

115. Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD clinical practice consensus guidelines 2018: diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2018;19(suppl 27):155–177.

116. Qiu H, Novikov A, Vallon V. Ketosis and diabetic ketoacidosis in response to SGLT2 inhibitors: basic mechanisms and therapeutic perspectives. *Diabetes Metab Res Rev*. 2017;33(5).

117. Nordmann AJ, Nordmann A, Briel M, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2006;166:285–293.

118. Holloway CJ, Cochlin LE, Emmanuel Y, et al. A high-fat diet impairs cardiac high-energy phosphate metabolism and cognitive function in healthy human subjects. *Am J Clin Nutr*. 2011;93:748–755.

119. Goldberg IJ, Ibrahim N, Bredefeld C, et al. Ketogenic diets, not for everyone. *J Clin Lipidol*. 2021;15:61–67.

120. Shaw DM, Merien F, Braakhuis A, Plews D, Laursen P, Dulson DK. The effect of 1,3-butanediol on cycling time-trial performance. *Int J Sport Nutr Exerc Metab*. 2019;29:466–473.

KEY WORDS heart failure, HFpEF, HFrEF, short-chain fatty acids, ketones