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Review

Ketone bodies for the failing heart: fuels that can fix the engine?

Salva R. Yurista, [1,2] Christopher T. Nguyen, [1,2] Anthony Rosenzweig, [1] Rudolf A. de Boer, [3] and B. Daan Westenbrink [3,*]

Accumulating evidence suggests that the failing heart reverts energy metabolism toward increased utilization of ketone bodies. Despite many discrepancies in the literature, evidence from both bench and clinical research demonstrates beneficial effects of ketone bodies in heart failure. Ketone bodies are readily oxidized by cardiomyocytes and can provide ancillary fuel for the energy-starved failing heart. In addition, ketone bodies may help to restore cardiac function by mitigating inflammation, oxidative stress, and cardiac remodeling. In this review, we hypothesize that a therapeutic approach intended to restore cardiac metabolism through ketone bodies could both refuel and 'repair' the failing heart.

Highlights

Neurohormonal activation, pro-inflammatory cytokines and natriuretic peptides may play roles in stimulating ketogenesis in heart failure.

Targeting ketone body metabolism in heart failure holds significant promise and current evidence from animal and human studies support the use of ketone bodies in heart failure setting.

Ketone bodies may restore cardiac function of the failing heart by improving the myocardial energetics and directly target inflammation, oxidative stress and cardiac remodeling in a way that may be beneficial for heart failure.

Clinical trials utilizing ketone supplementation in heart failure are currently under investigation.

Further studies are needed to ascertain the benefits and understand the mechanisms of actions of ketone bodies in heart failure.

Introduction

Heart failure (HF) is a major global health problem that is reaching epidemic proportions [1–3]. According to American Heart Association, more than 6 million adults in the United States are living with HF [4]. Despite the large range of pharmacological and device-based therapies available to treat HF, morbidity and mortality remain high [5–7]; thus, new treatment strategies are urgently needed. Because of its high energy consumption and limited ability to store ATP, the heart is highly dependent on a continuous supply and efficient oxidation of exogenous substrates. In patients with HF, metabolic roadblocks in fatty acid (FA) and glucose metabolism occur, which reduce the myocardial capacity to generate ATP [8,9]. This results in myocardial energy deficiency, and the failing heart is often likened to an 'engine out of fuel' [10]. Ketone bodies have long been recognized as an efficient metabolic substrate as they have higher phosphate-to-oxygen ratio than FAs (2.5 for ketone bodies vs 2.3 for FAs) and release more free energy per two-carbon moiety than glucose [11,12]; with the heart being one of the largest energy-consuming organs in the body, ketone bodies could be advantageous metabolic substrates for patients with HF.

Ketones, metabolism, and the heart

Metabolic regulation of ketone metabolism: ketogenesis and ketolysis

In a fed state, few ketone bodies are present in the circulation. During fasting, a reduced insulin-to-glucagon ratio fosters the mobilization of FAs from peripheral stores to be converted into ketone bodies by the liver through a series of enzymatic steps. Ketones are then transferred from the liver, which cannot oxidize ketones by itself, to peripheral tissues where they generate ATP within mitochondria. This physiological mechanism provides an alternative fuel for multiple organs, including the heart, in particular under conditions of prolonged fasting, insulin deprivation, and extreme exercise [13–16].

In this section, we provide a brief overview of ketogenesis and ketolysis (Figure 1).

Ketogenesis is a biochemical process that includes a series of reactions that produce three ketone bodies: acetoacetate (AcAc), beta-hydroxybutyrate (βOHB), and acetone. Ketogenesis

[1]Cardiovascular Research Center, Cardiology Division, Corrigan Minehan Heart Center, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[2]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA
[3]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

*Correspondence: b.d.westenbrink@umcg.nl (B.D. Westenbrink).

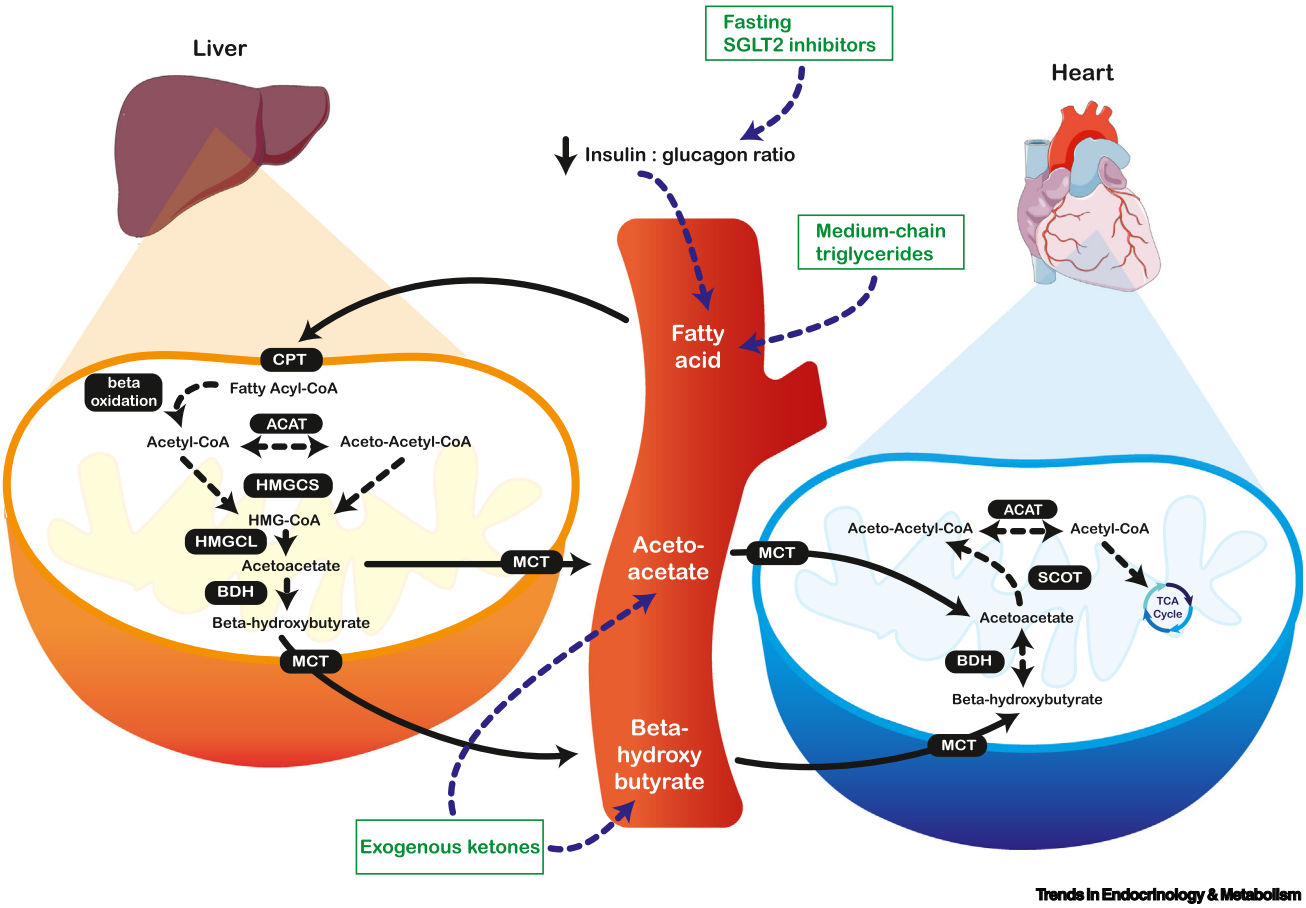

Figure 1. Contribution of therapeutic ketosis to hepatic ketogenesis and myocardial ketolysis. Fasting, sodium–glucose co-transporter 2 (SGLT2) inhibitor treatments (via reduced insulin/ glucagon secretion), and medium-chain triglycerides increase circulating free fatty acids that are readily absorbed directly into the portal circulation and transported to the liver for rapid beta-oxidation. Exogenous ketones (i.e., ketone salts or ketone ester) introduce two mature ketone bodies into circulation: acetoacetate or beta-hydroxybutyrate that can be internalized and oxidized by the heart. Part of illustration elements courtesy of Servier Medical Art. Abbreviations: ACAT, acetoacetyl-CoA thiolase; BDH, beta-hydroxybutyrate dehydrogenases; CPT, carnitine palmitoyl transferase; HMGCL, HMG-CoA lyase; HMG-CoA, hydroxymethylglutaryl-CoA; HMGCS, HMG-CoA synthase; MCT, monocarboxylate transporter; SCOT, succinyl-CoA:3-ketoacid-CoA transferase; SGLT2, sodium–glucose co-transporter 2; TCA, tricarboxylic acid.

primarily takes place in hepatocyte mitochondria, and to a lesser extent ketogenesis has also been observed in kidney epithelia, astrocytes, and enterocytes. As the first step, FAs are transported to mitochondria by carnitine palmitoyl transferase and then broken down into acetyl-CoA via beta-oxidation. The sequential metabolic process generates AcAc, which can be converted to βOHB (the most abundant ketone body in circulation) by beta-hydroxybutyrate dehydrogenase (BDH). The remaining AcAc can also be spontaneously converted into acetone through non-enzymatic decarboxylation [11,17–19].

The process of ketone body oxidation to redeem energy is called ketolysis. Unlike ketogenesis, ketolysis can occur in almost every cell, except hepatocytes. AcAc and βOHB in the circulation are avidly transported to extrahepatic tissues by monocarboxylate transporter. The mitochondrial enzyme beta-hydroxybutyrate dehydrogenase (BDH) catalyzes the oxidation of βOHB to AcAc. AcAc is then activated to acetoacetyl-CoA by the enzyme succinyl-CoA:3-ketoacid-CoA transferase (OXCT/SCOT). Next, ACAT cleaves acetoacetyl-CoA into two molecules of acetyl-CoA. Acetyl-CoA then passes through the citric acid cycle (TCA cycle) to be turned into ATP through

oxidative phosphorylation. Acetone does not convert back to acetyl-CoA, so it is either excreted through urine or exhaled [11,17–19].

The fate of circulating ketones

In general, ketosis is defined as having blood ketone levels of 0.5 mmol/l or more. Plasma concentrations of circulating ketone body can range from 0.1 to 0.25 mmol/l in non-fasting healthy subjects but increase to more than 1 mM during fasting or prolonged exercise [20]. Interestingly, it has been demonstrated that circulating βOHB concentrations are also increased after bariatric surgery, which is most likely explained by increased lipolysis [21,22]. Under physiological dietary conditions, the rate of ketogenesis from FAs is usually low. This is associated with relatively high levels of insulin and low levels of glucagon. Insulin has been recognized as the primary antiketogenic hormone, whereas glucagon is considered as ketogenesis promoting [23]. Approximately 80% of the circulating ketones will be taken up and utilized for energy by extrahepatic tissues including the brain, heart, kidney, and skeletal muscle; the rest are excreted in the urine or exhaled as acetone [20].

Myocardial metabolism in the healthy heart and heart failure

Cardiac metabolism has been described in detail elsewhere [12,24]. Here, we provide a brief summary of cardiac fuel utilization in the healthy and failing heart.

Myocardial energetics defined the energy that is produced and utilized by cardiomyocytes to generate the contraction and active relaxation of the beating heart. An adult mammalian heart requires more than 6 kg of ATP per day to maintain its continuous work [10]. The majority of ATP is generated from oxidative phosphorylation in mitochondria (~90–95%) and myocardial metabolism has the highest oxygen consumption rate per unit weight basis [25,26]. FA is the major fuel for the healthy heart in humans on a balanced diet (~40–60%) and more recently, it has been proposed that the heart only consumes a small amount of glucose [27]. In the normal heart, the contribution of lactate, ketone bodies, and amino acids to myocardial oxidative metabolism is minor [8,14,28,29].

Data from human biopsies demonstrated that the failing heart had an approximately 30% lower ATP compared with its healthy controls [30]. The failing heart loses its metabolic flexibility and manifests a reduction in oxidative metabolism and a switch in the substrate from FA to glucose [31,32]. In the advanced stage of HF, glucose oxidation is also reduced and a shift toward an increased reliance on ketone metabolism occurs [33–35]. Similar metabolic reprogramming has also been demonstrated in mice with cardiomyocyte-specific knockout of the ketolytic enzyme SCOT or BDH1. These mice display enhanced cardiac hypertrophy and accelerated pathologic cardiac remodeling following myocardial stress [34,36]. Moreover, increased circulating ketone concentrations and/or myocardial ketone utilization have also been reported in both HF patients with reduced (HFrEF) and preserved ejection fraction (HFpEF), and patients with diabetic heart disease [33,35,37–39].

Ancillary mechanisms responsible for increased ketone concentrations in heart failure

Neurohormonal regulation

The circulating ketone concentration is determined by hepatic ketone production, ketone utilization by extrahepatic organs, and ketone excretion. In addition to insulin, several other factors may contribute to ketogenesis [11]. In patients with HF, neurohormonal activation contributes to cardiac mechanical and metabolic inefficiency, impairs mitochondrial energy production, and undermines cardiac function [40,41]. High levels of catecholamines in patients with HF have been shown to increase lipolysis and stimulate insulin resistance, which may further contribute to

increased circulating free fatty acids (FFAs) [41,42]. Catecholamine-induced lipolysis is achieved through direct protein kinase A-mediated phosphorylation and deactivation of the lipid droplet-associated protein perilipin-1. This pathway is at least partially responsible for catecholamine-induced docking of phosphorylated hormone-sensitive lipase to the lipid droplet and the resultant lipolysis [43]. In addition, elevated concentrations of cortisol and growth hormone in patients with congestive HF may promote lipolysis and FFA release [37]. Since the production of ketone bodies is dependent on the amount of FFA supplied to the liver, lipolysis stimulated by neurohormonal activation would be expected to result in increased ketogenesis in patients with HF. Of note, norepinephrine has been reported to directly activate ketogenesis in the liver and reduce ketone body excretion as well, suggesting that reduced clearance could also contribute to increased ketogenesis in HF [44,45].

Role of cytokines

A large number of studies have consistently shown elevation of proinflammatory cytokines e.g., tumor necrosis factor and interleukin-6 (IL-6)] in HF patients. Increased concentrations of these cytokines have been associated with sarcopenia and lower fat tissue content [37,46]. Cytokines may cause chronic generalized inflammation, including in the gastrointestinal tract, and may negatively affect the absorption of nutrients and micronutrients that contribute to cardiac cachexia [46]. As cardiac cachexia is related to malnutrition, it will also promote lipolysis by depleting the glycogen stores which in turn augment ketogenesis. Interestingly, a study in advanced HF patients demonstrated that insulin-to-glucagon ratio is decreased with increasing HF severity, resembling a prolonged fast [47]. A direct link between the degree of cachexia and ketone concentrations has not been established yet.

Natriuretic peptides

Natriuretic peptides are produced within the heart and secreted in response to cardiac stress. Natriuretic peptides are invaluable as biomarkers to determine the diagnosis and prognosis of HF, and increasing natriuretic peptide levels through neprilysin inhibition is a central component of evidence-based treatment for this condition [48]. Interestingly, natriuretic peptides have recently also been shown to poses lipolytic activity [49–51]. For instance, natriuretic peptides have been found to stimulate lipolysis in isolated human adipose tissue [51]. Intravenous infusion of human atrial natriuretic peptide at concentrations that mimic those seen in HF induced lipid mobilization [49] and increased circulating ketone levels threefold versus placebo [50]. Furthermore, a different study demonstrated that elevated ketone concentrations in HF were strongly related to the increase in brain natriuretic peptide [52].

Building upon these observations, increases in circulating ketone concentrations in HF are most probably explained by the universal response to cardiac stress, mediated by release of neurohormones, proinflammatory cytokines, and natriuretic peptides (Figure 2).

Ketone bodies as a potential biomarker for HF

Ketone bodies have also recently emerged as potential biomarkers of HF. Some authors proposed breath acetone as a non-invasive biomarker for the diagnosis of HF following the discovery of increased breath acetone concentrations in patients with acute decompensated HF [53–57]. Increased acetone concentrations are also associated with a poor prognosis and hemodynamic severity in non-ischemic chronic HF [56,58]. Urinary ketones have also been shown to be associated with HF severity [59]. A prospective population-based cohort study in general Dutch population demonstrated that elevated βOHB concentrations are associated with an increased risk of HFrEF, particularly in women [60]. In another study, increased plasma βOHB in patients with arrhythmogenic cardiomyopathy predicted adverse outcomes and disease progression [61]. Thus,

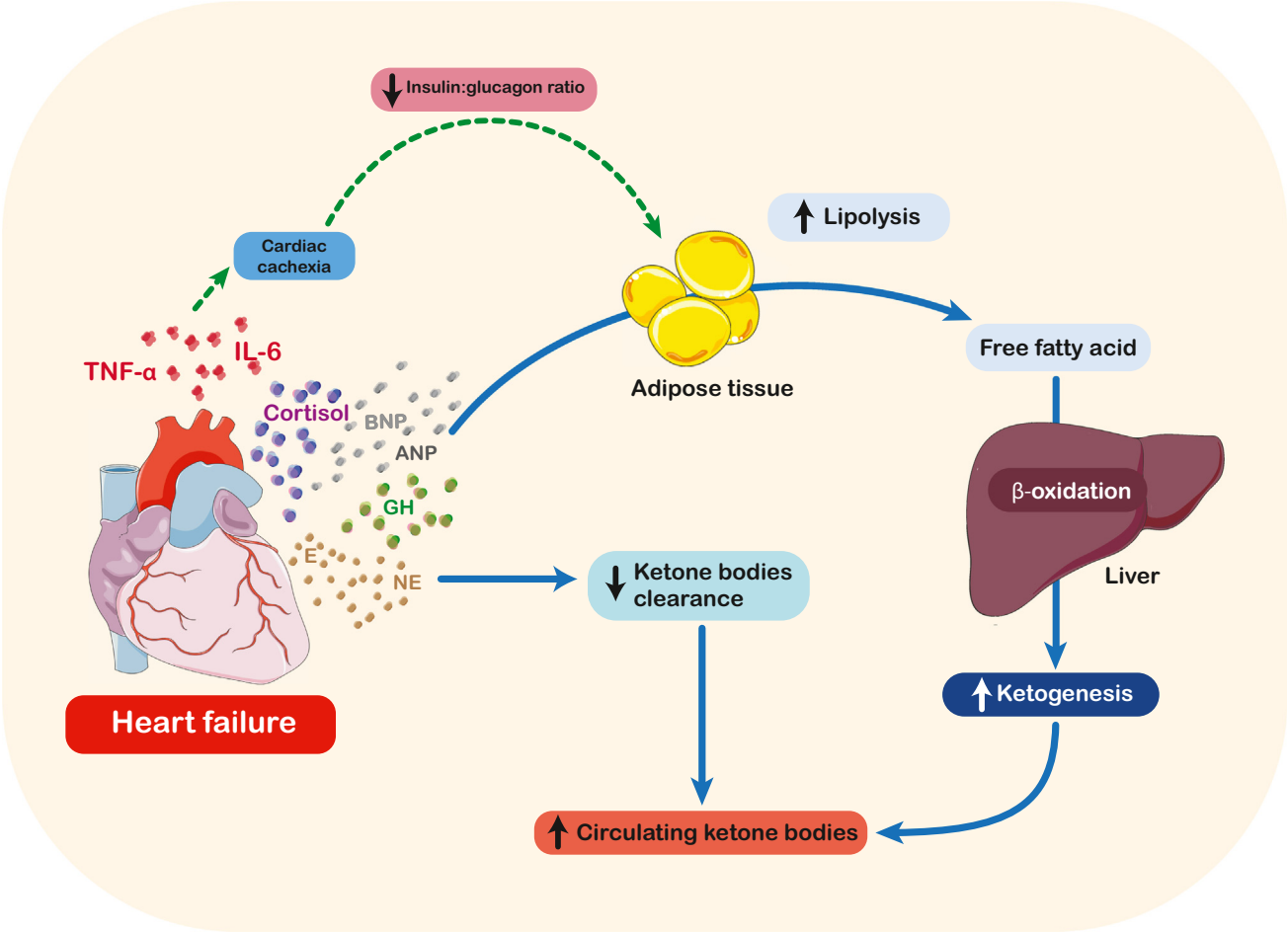

Figure 2. Ancillary mechanisms responsible for ketogenesis in heart failure. Heart failure is associated with neurohormonal activation, elevated proinflammatory cytokines, and increased natriuretic peptides. Neurohormones and natriuretic peptides may have a direct effect on lipolysis, whereas cytokines promote ketogenesis indirectly (via reduced insulin/glucagon ratio). Increased lipolysis in turn stimulates hepatic ketogenesis and increases circulating ketone bodies in heart failure. In addition, norepinephrine decreases the renal clearance of ketone bodies. Part of illustration elements courtesy of Servier Medical Art. Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; E, epinephrine; GH, growth hormone; IL, interleukin; NE, norepinephrine; TNF, tumor necrosis factor.

it is tempting to speculate that increased ketogenesis is a common response to cardiac stress. Although it is intriguing to consider that ketone bodies can be biomarkers in HF, the incremental utility of this approach needs to be validated before clinical use.

Roles of ketones in heart failure

Fuels for the failing heart

In the regular fed state, the contribution of ketone bodies to the cardiac energy provision in the healthy heart is modest. This contribution can, however, dramatically increase when hearts are exposed to higher ketone concentrations. A recent study in the working mouse heart model demonstrated that in the presence of normal concentrations of carbohydrates and FAs, ketone bodies become the predominant cardiac fuel source for the heart at βOHB concentrations above 2.0 mM [62]. A recent study in humans also revealed that both healthy and failing hearts efficiently extracted ketones from the circulation, and that failing hearts consumed more ketones than healthy

controls [27]. Importantly, myocardial ketone oxidation was proportional to the circulating concentrations as well. It therefore appears that the circulating ketone levels are the chief determinant of myocardial ketone body oxidation rates [27,63]. It also suggests that the heart has a marked overcapacity to utilize ketones and may suggest an attractive therapeutic opportunity [34,64,65]. In mice that underwent pressure-overload surgery for over 4 weeks, ketone bodies have been shown to contribute to cardiac energy production up to 20% [66]. Furthermore, nutritional ketosis induced by ketone ester (KE) has been shown to increase ketone oxidation [63,65] and increase myocardial ATP accordingly [65]. Interestingly, a positron emission tomography study demonstrated that βOHB infusion suppressed myocardial glucose uptake, which indicates a substrate competition in humans [67]. However, more studies in isolated perfused mouse hearts did not detect substrate competition with glucose and ketone supplementation increased ATP production, but did not improve cardiac efficiency [62,68]. In patients with HFrEF, βOHB infusion caused significant improvement in left ventricular ejection fraction (~8%) and cardiac output [64]; nevertheless, further research is clearly required to ascertain whether these benefits are associated with direct effects of increased cardiac energetics or via improvement of systemic vascular resistance.

Pleiotropic roles of ketone bodies

In addition to its role as (cardiac) substrate metabolism, several pleiotropic roles of ketone bodies in HF setting, that could potentially have benefits in the failing heart, have been reported.

NLRP3 inflammasome

The NOD-, LRR-, and pyrin domain-containing 3 (NLRP3) inflammasome has recently emerged as a new promising therapeutic target in HF [69]. Its activation mediates chronic inflammation and promotes HF progression [70]. Intriguingly, a previous study showed that βOHB reduced the NLRP3 inflammasome-mediated IL-1β and IL-18 production in human monocytes. Mechanistically, βOHB-attenuated K^+ efflux from macrophages inhibited the apoptosis-associated Speck-like protein containing a caspase-1 recruitment domain (ASC) polymerization, speck formation, and inflammasome assembly [71]. Furthermore, a ketogenic diet (KD) reduced circulating inflammatory markers in humans [72], and sodium–glucose co-transporter 2 inhibitors (SGLT2is) ameliorate NLRP3 inflammasome activity in patients with diabetes and high cardiovascular risk. It has been suggested that this is at least partially mediated by the associated increase in circulating ketone concentrations [73]. In an experimental HFpEF setting, ketosis induced by SGLT2is or KE suppressed NLRP inflammasome activity and reversed the HFpEF phenotype [74].

Oxidative stress

Oxidative stress has been implicated in the development and progression of HF [75]. βOHB has been recognized as an endogenous and specific inhibitor of class I histone deacetylases, resulted in a significant suppression of mitochondrial oxidative stress via activation of Foxo3a and Mt2 promoter genes [76]. The protective effects of ketone bodies against oxidative stress in HF have been based on indirect evidence in mice with cardiac-specific overexpression of Bdh1. These mice display increased ketone body utilization, reduced oxidative stress, and resistance to pathologic cardiac remodeling after transverse aortic constriction [77]. In experimental diabetic cardiomyopathy, a KD improved mitochondrial function and reduced cardiac oxidative stress [78].

Therapeutic ketosis in heart failure: what we know so far

In Table 1, we summarize evidence from animals and human studies evaluating cardiac effects of therapeutic ketosis in a dedicated HF setting. The pros and cons from each method to induce ketosis have been discussed and reviewed elsewhere [20].

Table 1. Animal and human studies on the effects of ketone administration in heart failure[a]

Refs	Study	Ketone source	Outcomes
Animal studies			
Horton *et al.* [34]	Transaortic constriction/ myocardial infarction mice and tachypacing-induced dilated cardiomyopathy dogs	• Ketogenic diet in mice (5 weeks) • Infusion of βOHB in dogs (2 weeks)	• Ketogenic diet ameliorated pathological LV remodeling in mice. • βOHB infusion improved LV function and remodeling in dogs.
Yurista *et al.* [93]	Non-diabetic rats with postmyocardial infarction heart failure	Oral SGLT2is empagliflozin (10–12 weeks)	• Empagliflozin significantly improved cardiac function, attenuated LV hypertrophy and fibrosis, reduced myocardial oxidative stress. • Empagliflozin also increased myocardial expression of the ketone body transporters and ketogenic enzymes and normalized myocardial ATP levels.
Santos-Gallego *et al.* [94,95]	Non-diabetic pigs with heart failure	Oral SGLT2i empagliflozin (8 weeks)	Empagliflozin improved both systolic and diastolic function, ameliorated adverse cardiac remodeling (reduced LV mass, LV dilatation, and less LV sphericity), increased myocardial ATP content, and enhanced myocardial work efficiency.
Ho *et al.* [66]	Isolated working heart from mice underwent transverse aortic constriction surgery over 4 weeks	Perfusion of βOHB	Perfusion with βOHB increased ketone oxidation rates and increased ketone contribution to the total energy production in the failing heart.
You *et al.* [83]	Spontaneous hypertensive rats	Ketogenic diet (4 weeks)	Ketogenic diet promoted interstitial fibrosis and cardiac remodeling.
Yurista *et al.* [65]	Transaortic constriction/ myocardial infarction mice and rats with postmyocardial infarction heart failure	Ketone ester-enriched diet (4 weeks)	• Ketone ester ameliorated LV dysfunction and remodeling in two preclinical animal models. • Ketone ester supplementation resulted in smaller LV mass and atrial natriuretic peptide reduction in rats. • Ketone ester increased myocardial expression of the ketone body transporters and ketogenic enzymes and normalized myocardial ATP levels in rats.
Nakamura *et al.* [81]	Transaortic constriction mice	Ketogenic diet (4 weeks)	Ketogenic diet suppressed the development of pathological cardiac hypertrophy
Zhang *et al.* [79]	Mice with cardiac-specific deletion of Mpc1 (CS-MPC1$^{-/-}$)	• Ketogenic diet • High-fat diet • Exogenous ketones (ketone ester-enriched diet and ketone salts in drinking water)	• KD ameliorated cardiac structural, metabolic, and functional remodeling of non-stressed hearts • 3 weeks' pretreatment with KD reversed the outcome after transaortic constriction surgery • High-fat diet fully rescued cardiac hypertrophy • Exogenous ketones preserved ejection fraction and reduced cardiac hypertrophy
McCommis *et al.* [80]	Mice with cardiac-specific deletion of Mpc2 (CS-MPC2$^{-/-}$)	• Ketogenic diet • Diets with higher fat content (40% MCTs) • 24-h fasting • Exogenous ketones: βOHB intraperitoneal injection (2 weeks) or ketone ester-enriched diet (5 weeks)	• Ketogenic diet significantly reversed HF. • Diets with higher fat content prevented cardiac remodeling and dysfunction. • 24-h fasting ameliorated cardiac remodeling. • Exogenous ketones moderately attenuated cardiac remodeling.
Deng *et al.* [74]	'3-Hit' mice model of HFpEF	• Oral ketone ester (30 days) • Oral SGLT2i empagliflozin (30 days)	Both treatments improved hypertension, reduced cardiac brain natriuretic peptide, reduced interstitial fibrosis, ameliorated lung edema, improved exercise performance, and decreased cardiac stiffness.

Table 1. (continued)

Refs	Study	Ketone source	Outcomes
Guo *et al.* [78]	db/db mice	Ketogenic diet (8 weeks)	Ketogenic diet improved glycemic control and prevented the development of diabetic cardiomyopathy by inhibiting apoptosis, improving mitochondria function, and reducing oxidative stress.
Xu *et al.* [82]	Adult healthy rats	• Ketogenic diet (16 weeks) • Intraperitoneal injection of βOHB or AcAc (16 weeks) • Frequent deep fasting (16 weeks)	Ketogenic diet and βOHB injection impaired cardiac function and induced cardiac fibrosis.
Human studies			
Nielsen *et al.* [64]	16 patients with HFrEF	Na-βOHB infusion (3 hours)	βOHB infusion improved cardiac output and reduced systemic vascular resistance without impairing myocardial external energy efficiency
Monzo *et al.* [63]	19 patients with HFrEF and nine controls	Oral ketone ester supplementation	Acute ketosis induced by ketone ester (80 min after ingestion) increased the heart ability to utilize ketone bodies

[a]Abbreviation: LV, left ventricle.

Ketogenic diet and fasting

The classic KD, consisting of a high-fat and low-protein and carbohydrate diet, is a way of eating pattern that mimics the fasting state. A sustained KD can increase blood ketone levels to 2–4 mmol/l, yet the long-term compliance is often low because it is unpalatable, requires lifestyle changes, and causes gastrointestinal symptoms [20]. To date, no clinical trials have been done in humans utilizing KD in specific cardiac/HF setting.

However, recent animal studies have found significant positive effects of KD and fasting in HF. Five weeks of a KD led to significant amelioration of pathological cardiac remodeling in mice following transaortic constriction/myocardial infarction surgery [34]. In a mouse model of cardiac genetic deletion of MPC1 (CS-MPC1$^{-/-}$), KD ameliorated cardiac structural, metabolic, and functional remodeling of non-stressed hearts and 3 weeks pretreatment with KD reversed the outcome after transverse aortic constriction surgery [79]. In mice with cardiac-specific deletion of mitochondrial pyruvate carrier (CS-MPC2$^{-/-}$), KD significantly prevented cardiac remodeling and dysfunction and completely reversed remodeling of the failing hearts. Interestingly, 24-h fasting also reduced cardiac remodeling in these animals [80]. KD also has been shown to attenuate cardiac remodeling in a mouse model of pressure overload [81] and exert antiapoptotic effects and protect against diabetic cardiomyopathy in db/db mice [78].

Surprisingly, in non-HF animals, the opposite was recently reported. Compared with the normal diet, healthy adult rats fed a KD for 16 weeks developed impaired cardiac function and increased cardiac fibrosis [82]. The authors also observed that 16 weeks of frequent deep fasting as an alternative method to induce ketosis resulted in cardiac fibrosis [82]. In another study, 4 weeks' feeding of a diet consisting of 10% protein and 90% fat promoted cardiac fibrosis in spontaneous hypertensive rats [83].

Medium-chain triglycerides

Another common way to increase circulating ketones is by ingesting the ketone precursors medium-chain triglycerides (MCTs) that generally provide FA with aliphatic tail of 6–12 carbon atoms. MCT can increase blood ketone levels to 1–2 mM in humans; however, it may also cause some

digestive symptoms at high doses [84,85]. Similar to KD, no clinical study has been done on this topic in HF patients.

A high-fat diet (with ~42% MCTs) significantly improved cardiac remodeling and dysfunction in CS-MPC2$^{-/-}$ mice [80]. General positive results have also been demonstrated in spontaneous hypertensive rats as long-term feeding with MCTs demonstrated improved cardiac function and remodeling [86–88] as well as preserved cardiac energy status [87].

Exogenous ketone supplementation: ketone salts and ketone ester

Both ketone salts (KSs) and KE have been tested in humans and are commonly used as alternatives to achieve sustained ketosis. KSs are generally cheaper and more palatable but less ketogenic than KE (1–3 mmol/l for KS vs 2–6 mmol/l for KE) [20,89]. KSs typically use sodium, potassium, calcium, or magnesium as the cation. This raises concerns about possible cation overload related to the doses required to achieve ketosis, and may limit the chronic use of KS in HF patients [12]. Gastrointestinal distress has also been reported after ingestion of KSs or KE [20].

Feeding a KE, R,S-butanediol diacetoacetate, enriched diet and supplementation of potassium βOHB in drinking water preserved ejection fraction and attenuated cardiac hypertrophy in non-stressed CS-MPC1$^{-/-}$ hearts [79]. Daily intraperitoneal injection of βOHB for 2 weeks or feeding a normal diet supplemented with 16.5% kcal of D-β-hydroxybutyrate-(R)-1,3-butanediol monoester for 5 weeks moderately improved cardiac remodeling in CS-MPC2$^{-/-}$ mice [80]. In the canine tachypacing HF model, continuous infusion of Na-βOHB significantly reduced pathologic cardiac remodeling [34]. In another study, we demonstrated that KE-enriched diets [both ~19% kcal hexanoyl-hexyl-3-hydroxybutyrate or ~33% kcal D-β-hydroxybutyrate-(R)-1,3-butanediol monoester] reduced pathological cardiac remodeling and enhanced ventricular function in both mice and rats model of HFrEF, associated with increased myocardial markers of ketone uptake and oxidation and normalization of myocardial ATP levels [65]. Oral administration of KE (1 mg/g body weight) for 30 days was reported to improve cardiac mitochondrial function and inflammation, and rescued HFpEF phenotypes in a small animal models [74]. By contrast, a recent study demonstrated that a 16-week injection of βOHB in adult healthy rats resulted in impaired cardiac function and cardiac fibrosis [82].

In healthy humans, a 390-min infusion of Na-βOHB (at 0.18 g/kg/h) decreased glucose uptake in the heart and improved myocardial blood flow [67], whereas a 3-h infusion of Na-βOHB (at 0.18 g/kg/h) improved cardiac output and reduced systemic vascular resistance in patients with HFrEF [64]. Acute nutritional ketosis induced by oral supplementation of 25 g D-β-hydroxybutyrate-(R)-1,3-butanediol monoester increased the ability of the heart to extract ketones, and it correlates with degree of cardiac function and remodeling in HFrEF patients [63].

Sodium–glucose co-transporter 2 inhibitors

SGLT2is gained basic and clinical research attention due to their cardiovascular benefits in HF regardless of the patient's glycemic status [90,91]. It has been postulated that the mechanism underlying the cardiovascular benefits of SGLT2is could include ketogenesis [92]. Studies from us and from others have indicated that oral administration of SGLT2is empagliflozin in small and large animal models of HFrEF improved systolic function, increased circulating ketone levels, associated with enhanced cardiac ketone oxidation, and increased cardiac ATP production [93,94]. Furthermore, chronic oral treatment with SGLT2is empagliflozin improved diastolic function and cardiac strain parameters in a large animal model of HFrEF [95,96]. In a small animal model of HFpEF, oral administration of SGLT2is for 30 days improved HFpEF phenotypes [74]. In patients with HFrEF, SGLT2i improved cardiac remodeling in both diabetic and non-diabetic setting

Table 2. Ongoing clinical trials of exogenous ketones evaluating heart failure outcomes

Trial registration	Study	Ketone source	Outcome
NCT04442555	12 patients with acute heart failure	Oral ketone ester supplementation	Awaiting study outcome
NCT04698005	24 patients with acute decompensated heart failure	Oral ketone ester supplementation	Awaiting study outcome
NCT04633460	20 patients with HFpEF	Oral ketone ester supplementation	Awaiting study outcome
NCT04443426	28 patients with chronic heart failure with reduced ejection fraction	Oral βOHB salt supplementation	Awaiting study outcome
NCT04703361	12 patients with heart failure with reduced ejection fraction	βOHB infusion	Awaiting study outcome
NCT04379934	Biopsy of human atrial tissue in 40 patients with and without heart failure	βOHB perfusion	Awaiting study outcome
NCT04370600	16 NYHA Class II–III ambulatory heart failure patients	Oral ketone ester supplementation	Awaiting study outcome
NCT04594265	8 patients with heart failure with reduced ejection fraction	Oral ketone ester supplementation	Awaiting study outcome
NCT03560323	36 diabetic subjects with heart failure with reduced ejection fraction	Racemic βOHB infusion	Awaiting study outcome

[97,98]. SGLT2is therapy also reduced insulin and increased circulating ketone levels, as well as led to a decline in NLRP3 inflammasome activity in diabetic patients [73]. It is worth mentioning that it is difficult to explain the cardiovascular benefits of SGLT2is solely based on increased ketogenesis. Further mechanistic studies are required to shed a light on the modes of action and mechanisms mediating these effects, which may be related to substrate metabolism or other pleiotropic effects of ketone bodies.

Concluding remarks and future perspectives

Our understanding of cardiac metabolism has advanced greatly in the last years and in particular, ketone bodies have emerged as an important substrate with additional pleiotropic effects that may treat and restore cardiac function of the failing heart. Limited data in animals and humans suggest that ketone bodies may be beneficial for HF patients regardless of the method used to increase the ketone delivery to the heart. Nevertheless, the results should be interpreted cautiously, as the available data from preclinical studies are not fully harmonized and so far, only a few clinical trials have been conducted to evaluate the cardiac effects of ketone bodies in patients with HF. In addition, it is worth noting that beneficial acute cardiac or hemodynamic effects have not consistently translated into improved clinical outcomes.

The exact mechanism of cardiac benefit with ketone therapy is yet to be established and additional mechanisms may arise over time. Moreover, there are several concerns that should be addressed before moving forward into the clinical application (see Outstanding questions). The effect of inducing ketosis in HF through supplementation or other means has been the focus of intense preclinical investigation and is being investigated in multiple ongoing clinical studies (Tables 1 and 2) that we anticipate will clarify its potential therapeutic benefits and provide insight into possible underlying mechanisms.

Outstanding questions

Evidence from animal and human studies suggests that enhancing circulating ketone levels can increase ketone oxidation in the myocardium and improve cardiac function. Important topics that merit further investigation are listed below:

An important step would be to determine the 'true' contribution of ketone bodies to the cardiac diet in a fed state.

The mechanism of increased ketogenesis in HF needs to be investigated.

Further studies are required to assess the safety, feasibility, and efficacy of ketone therapy, including the exact mechanism of benefits of ketone therapy in HF.

Most positive evidence of ketone therapy comes from studies in HFrEF (experimental and clinical). This reinforces the need to include more studies in HFpEF.

There is scarce evidence to recommend whether modulating endogenous ketosis (i.e., fasting, KD) or ingesting exogenous ketone supplementation is preferable in HF.

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Declaration of interests

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