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CROSSTALK

CrossTalk proposal: Ketone bodies are an important metabolic fuel for the heart

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The heart must produce a very large amounts of ATP to maintain contractile function. However, the heart has limited energy stores along with a negligible capacity for glycogenesis, lipogenesis, ketogenesis or gluconeogenesis. Therefore, it utilizes a variety of circulating fuels to generate the ATP needed to support its contractile machinery and maintain ionic homeostasis. The heart is an omnivore that has a remarkable metabolic flexibility that allows it to swiftly shift its preference between different fuels depending on its work demands, neurohormonal status and the availability of oxidative substrates. The normal heart is mainly reliant on fatty acids as a major source of acetyl-CoA (40–60% of the total cardiac acetyl-CoA production), while carbohydrates (glucose and lactate) represent the second largest contributor to cardiac acetyl-CoA production (20–40%). Ketone bodies (β-hydroxybutyrate, acetoacetate and acetone) are also important sources of cardiac ATP production. Using myocardial oxygen consumption as an indicator of energy substrate utilization, it has been shown that ketone bodies contribute 5–10% of the total cardiac ATP production in healthy individuals (Funada *et al.* 2009). In line with this, Horton *et al.* (2019) measured cardiac ketone uptake in dogs, and if all of these ketones were oxidized, they would contribute about 10–15% of the heart's ATP production. By directly measuring ketone oxidation rates in the mouse heart, we showed that ketone oxidation contributes 15–20% of the total cardiac ATP production (Fig. 1*A*), with the remainder originating from fatty acid and glucose oxidation (Ho *et al.* 2019). Therefore, ketones are a significant fuel for ATP production in the normal heart.

In mammals, ketogenesis predominantly occurs in the liver, which converts fatty acid-derived acetyl-CoA into ketone bodies and releases them into the extrahepatic tissues to support energy production. The concentration of ketone bodies in the blood is governed by nutritional, physical and hormonal status. Circulating ketone levels in humans can range from <0.1 mM in a fed state (Owen *et al.* 1969), up to 6 mM following a prolonged fast (Owen *et al.* 1969), and could reach 25 mM in uncontrolled diabetes (diabetic ketoacidosis) (Bobo *et al.* 1991). Adherence to a ketogenic diet (a high fat, low carbohydrate diet) also enhances circulating ketone body levels by stimulating adipose tissue lipolysis, mobilization of fatty acids, hepatic ketogenesis, and ultimately, induction of a mild to moderate ketosis (0.6–1.5 mM) (Veech, 2004; Wang *et al.* 2014). These increases in circulating ketone body levels have the potential to stimulate cardiac ketone oxidation on the basis of increasing oxidative substrate supply to the heart. Indeed, we showed in mouse hearts perfused in the presence of 0.6 mM β-hydroxybutyrate, ketone oxidation provides ∼25% of the acetyl-CoA for the TCA cycle (Ho *et al.* 2019) (Fig. 1*B*), and in the presence of 2 mM β-hydroxybutyrate, ketone oxidation becomes the major source of energy for the heart (70%) (Ho *et al.* 2021) (Fig. 1*C*). Whether similar results could be recapitulated *in vivo* under the same conditions has yet to be determined.

It is important to note that insulin plays a pivotal role in regulating cardiac energy metabolism. Insulin stimulates glucose oxidation rates and inhibits fatty acid oxidation rates in the heart (Ho *et al.* 2019; Karwi *et al.* 2019*a*,*b*; Ho *et al.* 2021). Despite earlier suggestions that insulin also stimulates ketone oxidation in the Langendorff perfused rat heart (Sultan, 1992), recent studies using isolated working heart have shown that insulin does not influence cardiac ketone oxidation rates in murine models of normal heart (Ho *et al.* 2021), post-myocardial infarction (Karwi *et al.* 2019*b*), diabetes (Verma *et al.* 2018) and pressure-overload-induced heart failure (Ho *et al.* 2019). These data suggest that cardiac ketone oxidation is not regulated by insulin, unlike glucose and fatty acid oxidation.

While the contribution of glucose and fatty acid to ATP production in the heart is mainly orchestrated by Randle cycle phenomena (Randle *et al.* 1963), how ketones interact with these other oxidative substrates in the healthy heart is not fully understood. Earlier *in vivo* studies showed that acute infusion of ketones reduces cardiac fatty acid uptake and oxidation rates in the normal pig heart (Stanley *et al.* 2003). However, a recent study showed that acute enhancement of ketone oxidation

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did not have a significant effect on either fatty acid or glucose oxidation rates in the isolated working heart (Ho *et al.* 2021). While these contradictory data could be due to the differences between the animal models and/or experimental settings, whether chronic enhancement of ketone body use in the normal heart is beneficial or detrimental has yet to be determined, which warrants further investigation. This is important since there has been the assumption that ketone bodies are a more efficient fuel for the heart compared to glucose and fatty acids (Sato *et al.* 1995; Veech, 2004; Ferrannini *et al.* 2016; Mudaliar *et al.* 2016). These assumptions are primarily based on the observation that ketone bodies release more energy in the form of heat compared to glucose (243.6 *vs.* 223.6 kcal/mol for 2-carbon units) and generate more ATP per oxygen consumed compared to fatty acids (P/O ratio = 2.5 for ketone bodies *vs.* 2.33 for fatty acid). However, glucose (P/O = 2.58) is, in fact, a more oxygen-efficient substrate compared to ketone, and fatty acid is a more energy-dense substrate than ketone (palmitate releases 298 kcal/mol of 2-carbon units), suggesting that ketone is not a more thrifty fuel than either fatty acids or glucose. In support of this, direct measurement of cardiac efficiency (cardiac work/myocardial oxygen consumption) in the mouse heart demonstrates that stimulating cardiac ketone oxidation rates does not enhance cardiac efficiency (Verma *et al.* 2018; Ho *et al.* 2019, 2021). These findings were recently confirmed in patients with heart failure where ketone body infusion to enhance ketone body delivery to the heart does not increase cardiac efficiency (Nielsen *et al.* 2019). Of importance is that some of the beneficial effects of augmented levels of circulating ketone bodies in heart failure have been proposed to be due to the anti-inflammatory effect of ketone bodies (Deng *et al.* 2020), although this proposal has recently been challenged (Chriett *et al.* 2019). Another challenge with the chronic enhancement of ketone body use is the potential alteration in acid–base balance that could be critical for patients with long term metabolic complications as well as patients in critical care (Fischer *et al.* 2018).

There has been an increasing interest in the role of ketone bodies in the failing heart. Earlier study by Funada *et al.* (2009) suggested that ketone utilization could be enhanced in patients with heart failure with reduced ejection fraction (HFrEF). In 2016, two independent investigations simultaneously proposed an increase in the ketolytic capacity in human and murine failing hearts (Aubert *et al.* 2016; Bedi *et al.* 2016). Subsequent studies in human (Du *et al.* 2014; Voros *et al.* 2018) and murine models (Nagao *et al.* 2016; Ho *et al.* 2019; Horton *et al.* 2019) showed evidence that the circulating ketone body levels and cardiac ketone body uptake are increased in HFrEF. Nevertheless, evidence of increased circulating levels of ketone bodies and/or cardiac ketone body uptake was not observed in all murine models of HFrEF (Aubert *et al.* 2016; Byrne *et al.* 2020), which may be explained by the type, severity or stage of heart failure. While there is an increasing body of evidence that supports an increase in circulating ketone body levels and cardiac ketone body use in HFrEF, a recent study suggested that circulating ketone body levels and cardiac ketone oxidation are decreased in murine models of heart failure with preserved ejection fraction (HFpEF) (Deng *et al.* 2020). Whether these enhancements in the availability and/or cardiac uptake of ketone bodies are accompanied by increased ketone oxidation in the failing heart is an important area of investigation. While ketones are not directly regulated by insulin, a major metabolic perturbation in the failing heart is the development of cardiac insulin resistance (Ciccarelli *et al.* 2011; Aroor *et al.* 2012; Chokshi *et al.* 2012;

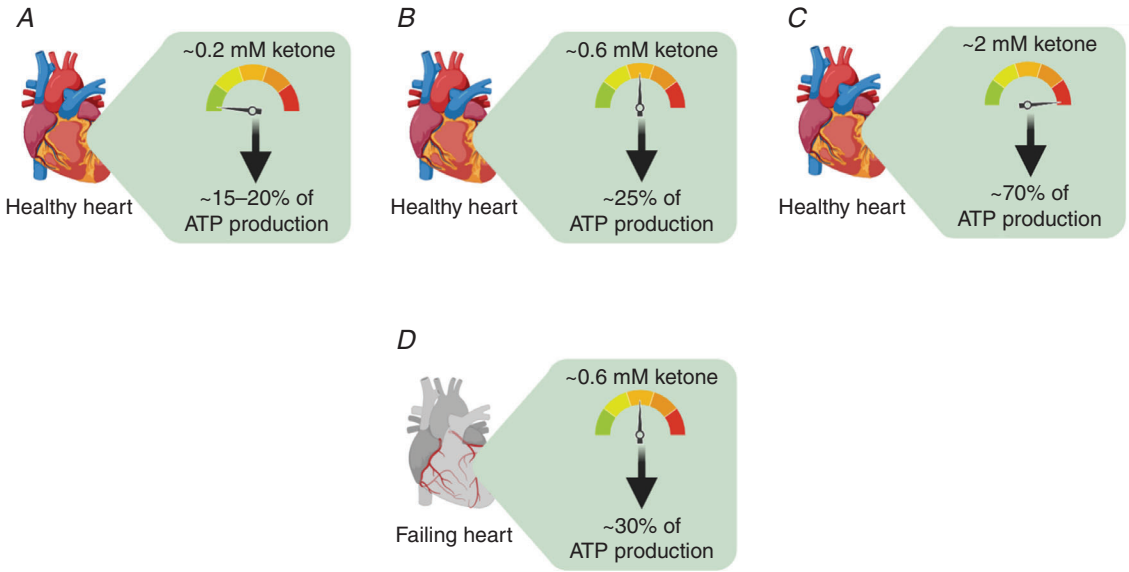

Figure 1. Illustration of different circulating ketone levels and ketone contribution to cardiac ATP production in the healthy and the failing heart
A and *B*, under low–moderate circulating ketone levels (0.2–0.6 mM), ketone contributes to ∼15–25% of the healthy heart's total ATP production. *C*, ketone could become the primary source of acetyl-CoA (∼70% contribution) under severe ketosis (i.e. ketone levels ∼2 mM). *D*, in the failing heart and under moderate ketone levels (0.6 mM), ketone could contribute to almost a third of the cardiac ATP production.

Zhang *et al.* 2013; Fu *et al.* 2015; Riehle & Abel, 2016; Ho *et al.* 2019; Karwi *et al.* 2019*a*,*b*). This reduction in the metabolic effects of insulin in the heart favours a decrease in glucose oxidation and an increase in fatty acid oxidation (Ciccarelli *et al.* 2011; Aroor *et al.* 2012; Chokshi *et al.* 2012; Zhang *et al.* 2013; Fu *et al.* 2015; Riehle & Abel, 2016; Ho *et al.* 2019; Karwi *et al.* 2019*a*,*b*). Enhanced ketone contribution as a source of acetyl-CoA and reduced equivalents in the failing heart has the potential to reduce the contribution of glucose and/or fatty acids to acetyl-CoA and reduced equivalent production. However, a recent study by our group showed that augmented delivery of ketone to the failing heart increases ketone oxidation and its contribution to cardiac ATP production to ∼30% (Fig. 1*D*), with no significant effect on either glucose or fatty acid oxidation rates (Ho *et al.* 2019). Consistent with these findings, a recent study showed that ketone body infusion in humans does not reduce cardiac fatty acid oxidation (Gormsen *et al.* 2017). Taken together, these findings indicate that enhanced ketone oxidation is an important fuel that provides an ancillary supply of acetyl-CoA and reducing equivalents to the failing heart instead of interfering with the contribution of glucose or fatty acid to cardiac ATP production.

Increased preference for a particular oxidative substrate and its impact on cardiac efficiency (cardiac work/cardiac oxygen consumption) is important in the failing heart (Lopaschuk *et al.* 2020). This is because there is an increase in myocardial oxygen consumption in heart failure (Olson & Schwartz, 1951; Blain *et al.* 1956), which in the presence of reduced contractile function, makes the failing heart an inefficient pump. This decrease in cardiac efficiency is often accompanied by an enhanced contribution of fatty acid to cardiac ATP production compared to glucose (Blain *et al.* 1956; Paolisso *et al.* 1994). These alterations in cardiac preference in the failing heart are consistent with increased myocardial oxygen consumption, since fatty acid is a less oxygen-efficient substrate compared to glucose (Karwi *et al.* 2018). In line with this, an increased reliance on fatty acid oxidation in the failing heart is associated with an increase in cardiac oxygen consumption (How *et al.* 2005). In this context, it has been widely proposed that ketone bodies could serve as a 'thrifty fuel' for the failing heart (Ferrannini *et al.* 2016). Despite enhancing cardiac ATP production, recent studies by our group showed that enhancing cardiac ketone oxidation does not improve cardiac efficiency in heart failure due to accelerating myocardial oxygen consumption, but rather provides an extra source of ATP production for the heart (Ho *et al.* 2019). In further support of these findings, a recent study in heart failure patients showed an improved cardiac output following acute infusion of ketone bodies, yet cardiac efficiency did not change (Nielsen *et al.* 2019). Taken together, it seems plausible that enhanced ketone contribution provides an extra source of energy to the failing heart but does not improve cardiac efficiency.

In conclusion, ketone bodies are an important source of ATP in the normal heart, and their contribution to total cardiac ATP production positively correlates with their circulating levels. An acute increase in ketone use in the normal heart has the potential to influence the use of other oxidative substrates as competing fuels. Future studies need to focus on delineating the interplay between ketone bodies and other oxidative substrates in the normal heart and understanding whether chronic enhancement of ketone body use in the normal heart is beneficial or detrimental.

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Additional information

Competing interests

None.

Author contribution

Q.G.K. and G.D.L. designed the literature search strategies. Q.K. performed the literature search and wrote the manuscript. G.D.L. edited the manuscript. Both authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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