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EDITORIAL

Exogenous ketones in the healthy heart: the plot thickens

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This editorial refers to 'Ketones can become the major fuel source for the heart but do not increase cardiac efficiency' by K.L. Ho *et al.*, pp. 1178–1187.

Interest in the myocardial effects of exogenous ketones in both healthy and disease states has grown significantly in recent years.[1] The human myocardium requires 35 L of oxygen to pump approximately 7200 L of blood per day against systemic vascular resistance to produce the requisite kilogram quantities of adenosine triphosphate (ATP) daily.[2] Therefore, the prospect of leveraging ketones as an alternative fuel source, particularly in heart failure where insulin resistance and down-regulation of fatty acid oxidation have been reported,[1,3] has generated significant interest.[4–7] However, the interplay of exogenous ketones on competing substrate oxidation rates and cardiac efficiency is not well characterized. Such information provides necessary insight going forward as the ketogenic diet and exogenous ketosis become increasingly popular.

Ho *et al.*[8] present novel and interesting data to address these important aims. The authors exposed isolated working murine hearts to glucose (at a fixed concentration), palmitate (using two concentrations), and beta-hydroxybutyrate (using three increasing concentrations), with and without the addition of insulin. The two concentrations of palmitate allowed inferences to be drawn regarding myocardial substrate use in the presence of high fat states, such as seen with the ketogenic diet. Use of glucose not only served as a substrate comparison, but also provided a source for anaplerosis, which is necessary to the continued utilization of cataplerotic ketones.[1] Interestingly, myocardial ketone oxidation increased with increasing concentrations of ketones, even at the highest level studied. These results indicate that ketone oxidation occurs commensurately to their availability. In these studies, increasing ketones did not appear to *significantly* hinder oxidation of competing substrates.

Notably, the increase in myocardial ketone oxidation and tricyclic acid (TCA) cycle activity with higher concentrations of exogenous ketones was not accompanied by increases in cardiac ATP content or cardiac work. Furthermore, oxygen consumption continued to increase, with a resulting decrease in cardiac efficiency. The uncoupling between reducing equivalents and ATP production rates led the authors to speculate on several possible mechanisms including the role mitochondrial uncoupling proteins and the mitochondrial permeability transition pore. It seems plausible, that in the absence of increased demand and/or activation of stress signalling pathways, mitochondrial uncoupling may prevent ATP generation in the setting of excess fuel (including ketones, lactate, or palmitate).

Importantly, the decrease in myocardial efficiency with increasing ketone delivery might only be relevant to healthy myocardium under non-stressful conditions, and extrapolation to disease states may be limited. While exogenous ketone delivery in healthy myocardium may result in a 'ceiling effect' of cardiac work in the absence of heightened cardiac demand, pathologic conditions, and metabolic dysregulation that constrain cardiac work may favour improved pump function when supplemental fuels, including ketones, are available. Thus, states such as heart failure may afford the greatest clinical benefit.[1] Further proof-of-concept stems from the authors' previous work in heart failure, whereby oxygen consumption and TCA activity matched cardiac work,[9] and clinical models of heart failure mirror these results.[7] Yet, mild discordance between pre-clinical and clinical models of 'healthy' myocardium exists, as patients with mild cardiovascular comorbidities and no overt heart failure also seem to also augment oxygen consumption proportionately to stroke work, preserving myocardial efficiency.[7]

As with any novel data, this study generates more questions than it answers (Figure 1). For example, how does healthy myocardium respond in stressful situations to high concentrations of exogenous ketones with substrate oxidation and myocardial efficiency, considering benefit in exercise capacity has been observed with exogenous ketones?[10] Is it possible that myocardial efficiency may normalize in this setting. Furthermore, how does the regulation of ketone metabolism and excretion influence these findings? At high levels of ketones, urinary excretion or exhalation of ketones may decrease myocardial exposure to supraphysiologic levels ketones, potentially acting as another safety mechanism to avoid unregulated ketone oxidation with resulting decreased myocardial efficiency. Do the potential vasodilatory effects of ketones actually augment cardiac work?[1,7] Finally, the effects of chronic exposure of the myocardium to high concentrations of ketones (as may be seen with the ketogenic diet) on substrate competition are unknown,

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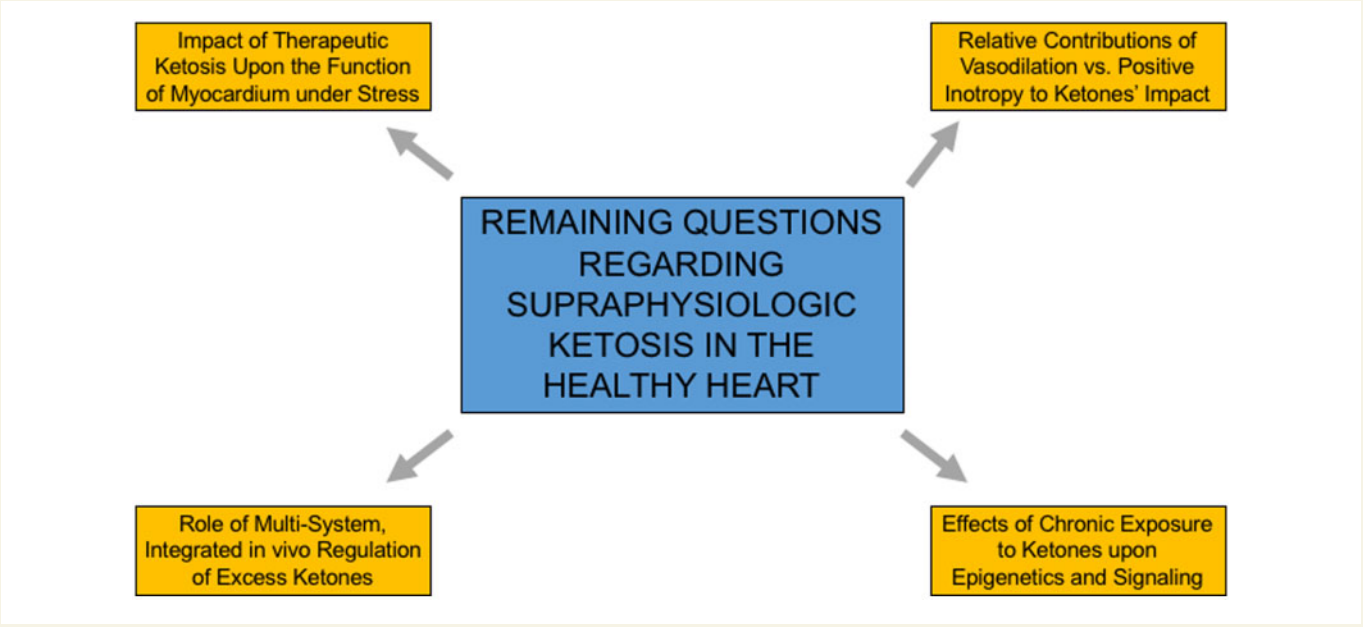

Figure 1 Remaining questions regarding the effect of supraphysiologic ketosis in the healthy heart.

where transcriptional and epigenetics effects of ketones can add layers of complexity.

Therapeutic ketosis is a burgeoning field in cardiovascular disease, yet deeply in need of studies defining the effects of supraphysiologic ketone levels on myocardial metabolism. As such, we congratulate the authors for sharing their interesting findings that provide novel data on the complex interplay of ketones, competing substrate oxidation, and cardiac efficiency.

Disclosures

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