Ketone bodies in acute heart failure: fuel for thought

Yosef Manla, MD[1], William Kuan, PharmD [2], Andrew L Clark MA, MD, FRCP [3], John GF Cleland MD, PhD, FRCP, FACC, FESC [4], Pierpaolo Pellicori, MD, FESC [4]

Author affiliations:

[1] Heart, Vascular & Thoracic Institute, Cleveland Clinic Abu Dhabi, United Arab Emirates

[2] Department of Pharmacy Services, University of Kentucky Albert B. Chandler Hospital, Lexington, KY, USA

[3]Department of Cardiology, Hull University Hospitals Trust, Castle Hill Hospital,

[4] School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow

Corresponding author:
Dr Pierpaolo Pellicori
School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow
Email: Pierpaolo.pellicori@glasgow.ac.uk
Twitter handle for Pierpaolo Pellicori: @PierpaoloPel
Twitter handle for Yosef Manla: @Manlayosef

Conflict of interest: PP has received consultancy honoraria and/or sponsorship support from Boehringer Ingelheim, Pharmacosmos, Novartis, Vifor, AstraZeneca, and Caption Health, and research support from Bristol Myers Squibb in the past 5 years, not connected with this editorial. JGFC reports research grants and honoraria from Abbott, Amgen, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Medtronic, NI Medical, Pharmacosmos, Servier, Torrent, and Vifor Pharma. WK, YM and ALC have no conflict of interest.

Neuro-hormonal activation due to cardiac dysfunction results in renal water and salt retention, a key pathophysiological feature of heart failure (HF).[1] Loop diuretics are the mainstay of treatment for water overload in patients with HF, but the addition of other classes of diuretics, such as carbonic anhydrase inhibitors or thiazides, might provide synergistic effects for the management of worsening congestion.[2,3] Sodium-glucose cotransporter 2 inhibitors (SGLT2-i) were originally developed for diabetes to reduce blood glucose by blocking its reabsorption in the proximal tubule of the nephron and increasing urinary glucose excretion. However, initiation of an SGLT2-i is associated with a rapid decrease in body weight and an increase in hematocrit, which is consistent with osmotic diuresis. Mechanistic studies also suggest that SGLT2-i enhances natriuresis and potentiates the effects of loop diuretics.[4,5] In patients with acute heart failure (AHF), use of SGLT2-i after clinical stabilization is safe, reduces symptoms and signs of congestion, and improves outcomes.[6] For patients with chronic HF (CHF), SGLT2-i reduce hospitalizations for worsening HF regardless of phenotype and improve survival for those with a reduced (HFrEF) left ventricular ejection fraction (LVEF).[7]

Although much of the benefit of SGLT2-i is likely to be mediated by diuresis and the reduction of clinical or sub-clinical congestion, other mechanisms may be involved. There is growing evidence that SGLT2-i reduce inflammation, oxidative stress, and ischemia/reperfusion injury. They protect the kidneys and lower left ventricular-end diastolic volume in those with HFrEF.[8] SGLT2-i might also alter cardiac energetics and metabolism by increasing circulating ketone bodies (KB).[9] KB are synthesized by the liver from fatty acids and used as metabolic substrates in many organs, including the heart, to maintain energy production in stressful situations.[9,10]

In healthy individuals, KB (mostly acetone, β-hydroxybutyrate, and acetoacetate) concentrations are low but may be increased, physiologically, by fasting, when carbohydrate intake is restricted, or in situations of stress or prolonged exercise. Large increases in KB suggest a pathological problem, such as diabetic or alcoholic ketoacidosis or, indeed, heart failure. In patients with CHF, circulating KB are usually high, and their concentration increases with worsening systolic function and neurohormonal activation, as well as with higher atrial pressures and with the presence of venous congestion.[11] It might be, then, that

KB are a useful marker of the severity of HF and congestion (*central figure*). Acetone can be measured reliably in exhaled breath and acetoacetate in urine using portable devices, which makes them attractive for routine clinical use. Exhaled acetone is several-fold higher in patients with HF than controls and correlates with circulating KB. In patients with CHF, exhaled acetone increases with worsening NYHA class, with extent of peripheral edema, with more severe left and right ventricular systolic dysfunction, and with higher plasma concentrations of natriuretic peptides. Those with higher exhaled acetone have a worse prognosis.[12,13] In those hospitalized with water retention due to HF, initially, high levels of exhaled acetone decline substantially after a week or so of effective diuretic treatment.[14]

In this issue, Voorrips and colleagues assessed longitudinal changes in KB in 79 patients hospitalized with worsening breathlessness and clinical or radiological signs of congestion due to HF enrolled in the EMPA-RESPONSE-AHF trial.[15] Patients were randomized within 24 hours of their initial hospital presentation to empagliflozin or placebo, which were given for 30 days. Compared to placebo, empagliflozin did not improve symptoms, diuretic response, plasma NT-proBNP or length of stay, the main outcomes of interest. In the present, post-hoc analysis, [16] total plasma KB fell by about 20% between enrolment and the end of the trial with no additional effect of empagliflozin. The reduction of KB was mostly driven by a fall in the concentration of acetone, which was positively correlated with changes in plasma NT-proBNP, which almost halved within 48 hours of the start of the trial. Therefore, the fall in acetone might reflect decongestion rather than any specific effects of empagliflozin.

Patients with HF might have high cardiac utilization of ketones, but it is unclear whether this reflects greater abundance and, therefore, myocardial availability of KB or greater myocardial avidity and preference for KB; it could be both. [17] In animal models, genetic or dietary induction of ketosis, as well as administration of KB, caused inconsistent improvements in cardiac structure and function.[18] In humans, little is known about the effects of exogenous KB on cardiac function. Using a cross-over design, Nielsen and colleagues found that, compared to saline-placebo, a three-hour infusion of 3-hydroxybutyrate in 16 patients with HFrEF increased left ventricular stroke volume, heart rate, and therefore cardiac output by a large amount (from a mean of 4.8 to 6.8 L/min, $P<0.001$). Systemic arterial pressure did not change, but systemic and pulmonary resistances dropped by ~20-30%, mean LVEF increased from 35% to 43% ($P<0.001$) and right ventricular function improved. [19] In healthy volunteers, within 30 minutes of inducing a modest ketosis, an increase in LVEF,

tricuspid annular planar systolic excursion, left atrial contraction, heart rate and systolic blood pressure, and a decrease in systemic vascular resistance have also been reported.[20] Ongoing mechanistic trials are testing the effects of exogenous KB on cardiac structure, function, and hemodynamics in patients with AHF (NCT04698005, NCT04442555) and CHF, of different phenotypes (NCT03560323, NCT04703361, NCT04633460).

The current study fuels interest in the role of KB in HF. KB might be a marker of cardiac and hemodynamic stress, with a fall in KB related (whether directly or indirectly) to effective diuresis (and not with SGLT2-i). More work needs to be done to establish the clinical and therapeutic relevance of KB in patients with HF. For the time being, managing congestion effectively and implementing guideline-recommended therapy after stabilization are two of the best strategies to improve well-being and prognosis in patients with AHF and, at the same time, perhaps reduce the need for alternative sources of fuel for the failing myocardium.

Acknowledgment

The authors of this editorial participated as mentees (YM, WK) and mentor (PP) in the first Journal of Cardiac Failure (JCF)'s one-on-one reviewer mentorship program. This program was a pilot endeavor encompassing a diverse group of junior and experienced cardiovascular researchers, with the goal of making peer-reviewing an interactive learning process.[21] The authors are grateful to JCF for this opportunity.

Figure legend

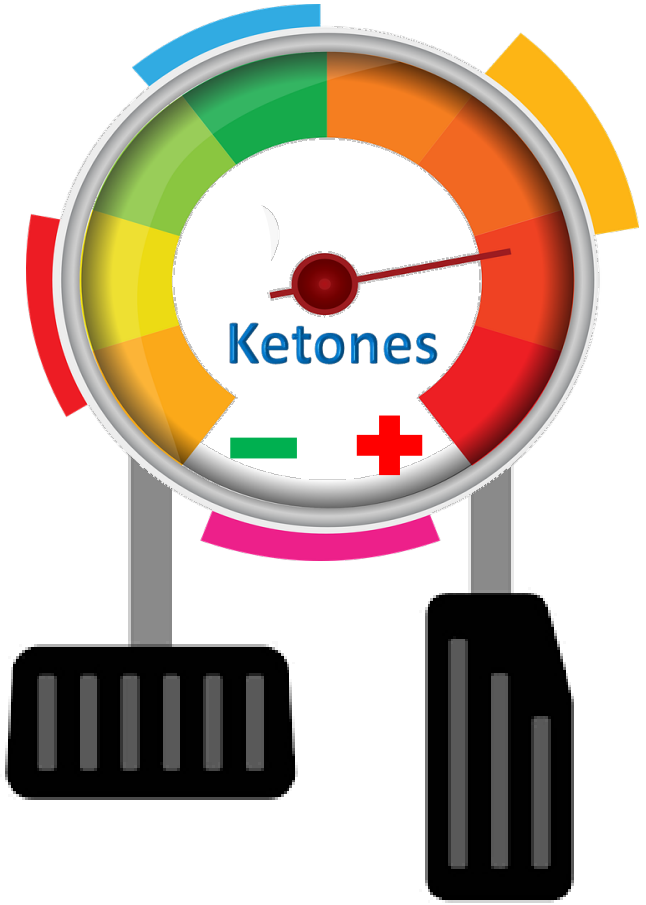
Ketone bodies (KB) might increase in response to physiological situations, usually after glycogen stores have been exhausted (fasting, prolonged exercise) or due to pathological causes (cardiac dysfunction and development of congestion); in patients with acute heart failure, diuresis might reduce KB. Therefore, KB might be a marker of cardiac and hemodynamic stress in heart failure (*left panel*). Preliminary experimental and human studies suggest that augmentation of KB might have beneficial effects on cardiac hemodynamics and function; for instance, KB might increase heart rate (HR), left ventricular ejection fraction (LVEF) and stroke volume (SV), and atrial contraction, and cause a fall in systemic (SVR) and pulmonary (PVR) vascular resistance (*right panel*). Abbreviations: SGLT2-i - sodium-glucose cotransporter 2 inhibitors.

References

1. Cleland JGF, Pfeffer MA, Clark AL, et al. The struggle towards a Universal Definition of Heart Failure—how to proceed? *Eur Heart J*. 2021;42(24):2331-2343. doi:10.1093/eurheartj/ehab082
2. Mullens W, Dauw J, Martens P, et al. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. *New England Journal of Medicine*. 2022;387(13):1185-1195. doi:10.1056/NEJMoa2203094
3. Trullàs JC, Morales-Rull JL, Casado J, Ramírez AF, Manzano L, Formiga F. Rationale and design of the "Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC) Trial:" a double-blind, randomized, placebo-controlled study to determine the effect of combined diuretic therapy (loop diuretics with thiazide-type diuretics) among patients with decompensated heart failure. *J Card Fail*. 2016;22(7):529-536.
4. Inzucchi SE, Zinman B, Fitchett D, et al. How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial. *Diabetes Care*. 2017;41(2):356-363. doi:10.2337/dc17-1096
5. Griffin M, Rao VS, Ivey-Miranda J, et al. Empagliflozin in Heart Failure. *Circulation*. 2020;142(11):1028-1039. doi:10.1161/CIRCULATIONAHA.120.045691
6. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. 2022;28(3):568-574. doi:10.1038/s41591-021-01659-1
7. Vaduganathan M, Docherty KF, Claggett BL, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *The Lancet*. 2022;400(10354):757-767.
8. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. *Basic to Translational Science*. 2020;5(6):632-644.
9. Lopaschuk GD, Karwi QG, Ho KL, Pherwani S, Ketema EB. Ketone metabolism in the failing heart. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*. 2020;1865(12):158813. doi:https://doi.org/10.1016/j.bbalip.2020.158813
10. 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(5):1190-1195. doi:10.2337/db15-1356
11. Lommi J, Kupari M, Koskinen P, et al. Blood ketone bodies in congestive heart failure. *J Am Coll Cardiol*. 1996;28(3):665-672. doi:https://doi.org/10.1016/0735-1097(96)00214-8
12. Kupari M, Lommi J, Ventilä M, Karjalainen U. Breath acetone in congestive heart failure. *Am J Cardiol*. 1995;76(14):1076-1078. doi:https://doi.org/10.1016/S0002-9149(99)80304-X
13. Marcondes-Braga FG, Gioli-Pereira L, Bernardez-Pereira S, et al. Exhaled breath acetone for predicting cardiac and overall mortality in chronic heart failure patients. *ESC Heart Fail*. 2020;7(4):1744-1752. doi:https://doi.org/10.1002/ehf2.12736
14. Yokokawa T, Sato T, Suzuki S, et al. Change of exhaled acetone concentration levels in patients with acute decompensated heart failure a preliminary study. *Int Heart J*. 2018;59(4):808-812.
15. Damman K, Beusekamp JC, Boorsma EM, et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes

in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). *Eur J Heart Fail*. 2020;22(4):713-722. doi:https://doi.org/10.1002/ejhf.1713
16. Voorrips SN BEBJ et al. Longitudinal changes in circulating ketone body levels in patients with acute heart failure: A post-hoc analysis of the EMPA-Response-AHF Trial. *J Card Fail*. Published online 2022.
17. Murashige D, Jang C, Neinast M, et al. Comprehensive quantification of fuel use by the failing and nonfailing human heart. *Science (1979)*. 2020;370(6514):364-368.
18. Takahara S, Soni S, Maayah ZH, Ferdaoussi M, Dyck JRB. Ketone therapy for heart failure: current evidence for clinical use. *Cardiovasc Res*. 2022;118(4):977-987. doi:10.1093/cvr/cvab068
19. Nielsen R, Møller N, Gormsen LC, et al. Cardiovascular Effects of Treatment With the Ketone Body 3-Hydroxybutyrate in Chronic Heart Failure Patients. *Circulation*. 2019;139(18):2129-2141. doi:10.1161/CIRCULATIONAHA.118.036459
20. Selvaraj S, Hu R, Vidula MK, et al. Acute Echocardiographic Effects of Exogenous Ketone Administration in Healthy Participants. *Journal of the American Society of Echocardiography*. 2022;35(3):305-311. doi:10.1016/j.echo.2021.10.017
21. Lala A, Mentz RJ. The JCF Reviewer Mentorship Program. *J Card Fail*. 2022;28(1):1-2.

Ketone Bodies in Heart Failure

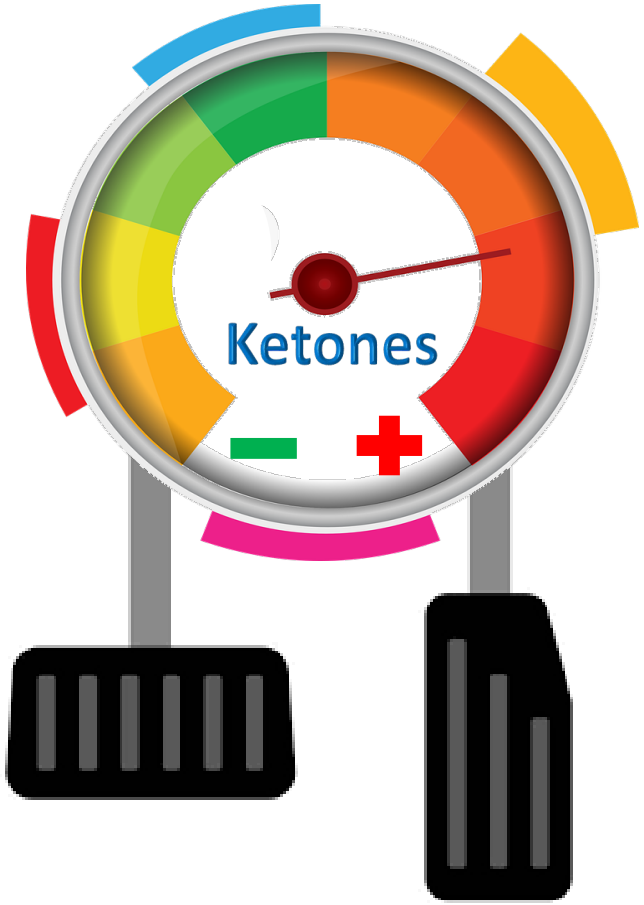


Reduced by
Diuresis &
Relief of
Congestion

Increased by
Fasting
Worsening Congestion
Cardiac dysfunction
SGLT2-i?

Ketone Bodies in Heart Failure

Biomarker

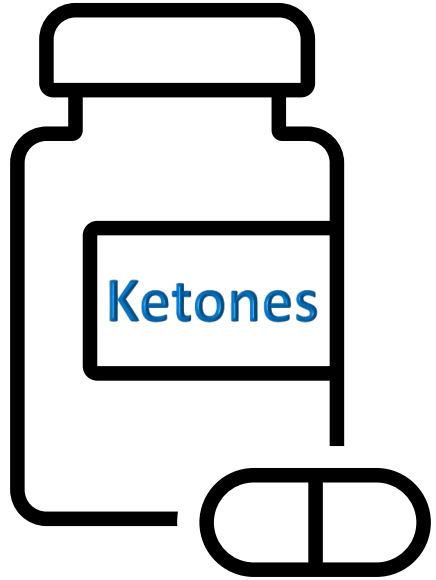


Reduced by
Diuresis &
Relief of
Congestion

Increased by
Fasting
Worsening Congestion
Cardiac dysfunction
SGLT2-i?

Thrifty Fuel?

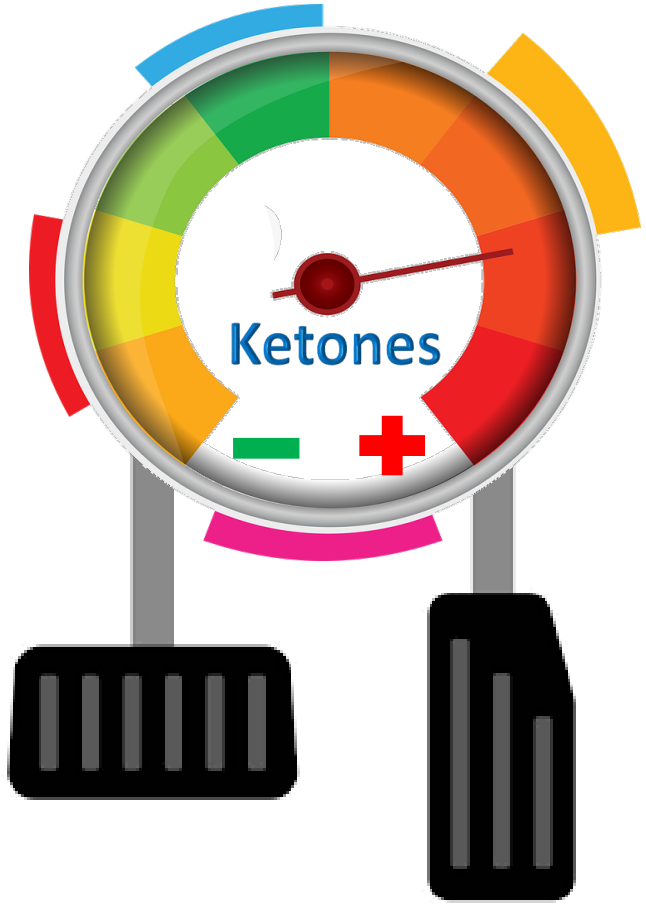
Novel Treatment?



↑ HR, SV, LVEF and left atrial contraction
↓SVR and PVR

Ketone Bodies in Heart Failure

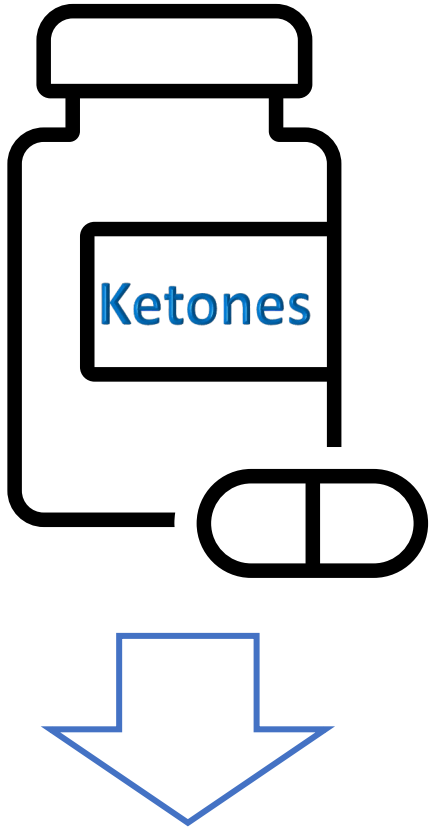
Biomarker



Reduced by
Diuresis &
Relief of
Congestion

Increased by
Fasting
Worsening Congestion
Cardiac dysfunction
SGLT2-i?

Novel Treatment?



↑ HR, SV, LVEF and left atrial contraction
↓SVR and PVR