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SHORT REPORT

Energetics and Metabolism

The medium-chain fatty acid octanoate is a beneficial fuel for the failing heart

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Abstract

The failing heart displays marked alterations of energy substrate metabolism, with a reduced oxidation of long-chain fatty acids (FA) associated with increased glucose oxidation. Recent preclinical and human studies have shown that the delivery of ketone bodies as an alternative substrate reduces pathological cardiac remodeling and dysfunction in heart failure. However, chronic administration of ketone bodies is challenging. Therefore, using a clinically relevant canine model of tachypacing-induced dilated cardiomyopathy, we tested the hypothesis that other shorter-chain FA may also be beneficial. Seven dogs received cardiac tachypacing and continuous infusion of sodium octanoate, a medium-chain FA, starting after 2 wk of pacing when cardiac dysfunction was still moderate. Six dogs received cardiac pacing with no octanoate infusion. Octanoate did not significantly alter circulating levels of ketone bodies, whereas it still exerted protection, resulting in a delayed progression of systolic and diastolic cardiac dysfunction and normalized myocardial metabolism. These results identify the delivery of medium-chain FA as a potential actionable therapeutic for heart failure with reduced ejection fraction. Octanoate has translational promise due to proven methods of dietary supplementation with no need for parenteral administration.

NEW & NOTEWORTHY Provision of the medium-chain fatty acid octanoate prevented or reversed key metrics of cardiac functional and metabolic deterioration in a large animal model of dilated cardiomyopathy. Our results demonstrate the cardiac benefits of supplementing a medium-chain FA independent of ketosis in a translational model of heart failure. These findings encourage mechanistic and next-stage translational studies into metabolic interventions for the treatment of heart failure.

cardiac metabolism; heart failure; ketones; octanoate; tachypacing

INTRODUCTION

The impressive ATP turnover of the heart, estimated to be kilograms/day, is supported by the oxidation of multiple energy substrates. In vivo quantifications of cardiac substrate consumption indicate that the healthy heart primarily obtains energy from the oxidation of long-chain fatty acids (FA), with the remainder derived from oxidation of carbohydrates and, to a lesser extent, amino acids and short-chain fuels (1). Among the latter, ketone bodies have received considerable attention as cardioprotective metabolites. Recent preclinical and human studies have shown that ketone body supplementation reduces pathological cardiac remodeling and dysfunction in heart failure (HF) (2, 3). In a canine model of tachypacing-induced dilated cardiomyopathy, characterized by cardiac metabolic alterations similar to those found in patients and in engineered human myocardium (4–6), we identified profound beneficial effects of a continuous infusion of β-hydroxybutyrate (3OHB), the most naturally abundant circulating ketone body (2). Treatment with 3OHB enhanced its cardiac uptake, improved cardiac function, and reduced pathological remodeling. First in human trials to assess the impact of intravenous administration of 3OHB or oral ketone esters in HF have been launched

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with early promising results (3, 7–9). However, the challenge of administering ketone preparations demands studies to identify practical ancillary approaches.

The mechanisms through which ketone bodies rescue cardiac function in HF are incompletely understood. However, multiple studies support a likely benefit through the provision of an ancillary cardiac fuel in the setting of dysfunctional long-chain FA oxidation, as well as reduced afterload and suppressed inflammasome activation, thereby promoting cardiomyocyte survival (2, 7, 10–12). In support of a fuel mechanism, cardiac uptake of 3OHB is proportional to supply and increases in HFrEF (13, 14). Loss of Bdh1, the enzyme responsible for the first step of 3OHB oxidation, exacerbates cardiac dysfunction in a pressure overload ischemic HFrEF model (2). In addition, cardiac-specific overexpression of Bdh1 improves left ventricular (LV) function and remodeling in pressure overload HFrEF (10). If 3OHB acts as an ancillary fuel, it stands to reason that other short- and medium-chain FA may also be beneficial. Butyrate, for example, is voraciously consumed in pressure overload HF (15). Medium-chain fatty acids offer a compelling rationale as they bypass the CPT1-dependent carnitine shuttle and are well studied as a component of dietary interventions to treat long-chain FA oxidation disorders (16). However, no studies have investigated, in vivo, the cardiac metabolic and hemodynamic effects of chronic administration of medium-chain FA in large animal models of HF. Therefore, we addressed this void of knowledge by testing a chronic infusion of octanoate, a medium-chain FA, in canines subjected to cardiac tachypacing. We chose octanoate to reduce predicted signaling overlap between short-chain FAs and 3OHB while anticipating that an 8-carbon FA may bypass the disrupted long-chain FA oxidation pathway in the diseased heart (17).

METHODS

All animal studies were performed in accordance with NIH guidelines for the humane treatment of animals and approved by the Institutional Animal Care and Use Committee of Temple University and the University of Pennsylvania.

Heart Failure Protocol and Treatment Randomization

Thirteen male mongrel hounds underwent chronic instrumentation. A Doppler blood flow probe was placed around the left circumflex coronary artery, and a solid-state pressure transducer was inserted into the left ventricle through the apex. In addition, external pacing leads were secured to the pericardium and saline-filled lines positioned in the aorta, left atrium, and right ventricle. External ventricular pacing was initiated and maintained at the rate of 210 beats/min for 3 wk, followed by 240 beats/min for an additional week to

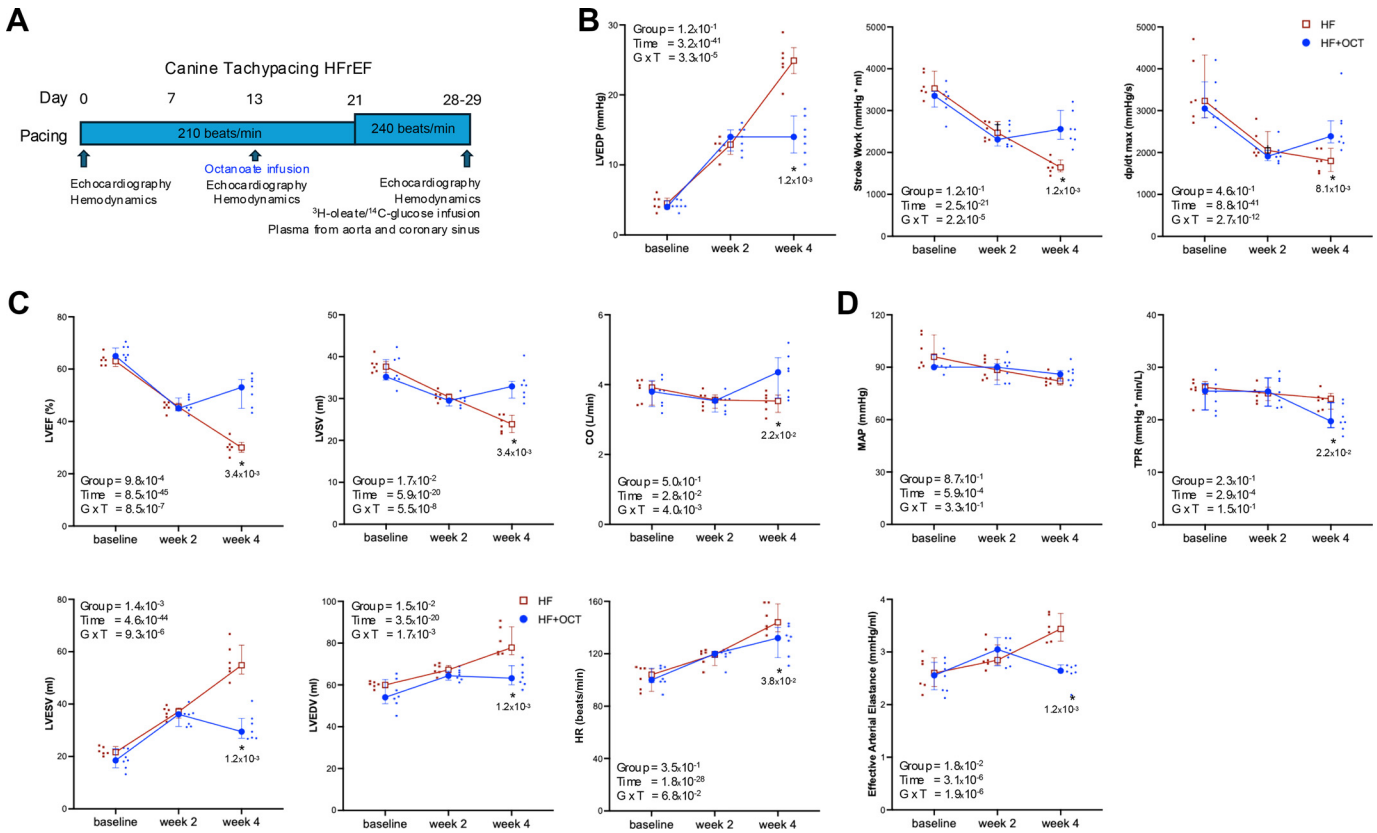

Figure 1. Infusion of octanoate attenuates cardiac dysfunction and pathological remodeling in a tachypacing model of heart failure with reduced ejection fraction. *A*: experimental protocol. Left ventricular hemodynamics (*B*), echocardiography (*C*), and systemic hemodynamics (*D*) at baseline, *week 2*, and *week 4* in HF and HF + Oct ($n = 6$ or 7 per group). Data are presented as median ± interquartile range (IQR). Comparisons were made with a nonparametric longitudinal model (nparLD, F1-LD-F1) using R. *P* values are time and group × time (G × T) by ANOVA-type statistic (ATS) and group by Box-modified ATS. *$P < 0.05$ HF vs. HF + OCT at *week 4* by two-sided Wilcoxon rank-sum. CO, cardiac output; dP/dt_{max}, maximum first derivative of left ventricular pressure; HF, heart failure; HR, heart rate; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; LVESV/LVEDV, left ventricular end systolic/diastolic volume; LVSV, left ventricular stroke volume; MAP, mean arterial pressure; TPR, total peripheral resistance.

induce dilated cardiomyopathy. Dogs were randomized using the GraphPad QuickCalcs online randomization generator to receive vehicle (saline) infusion (HF, $n = 6$) or octanoate infusion (HF + Oct, $n = 7$). Additional metabolic comparisons were made against nonfailing controls randomly drawn from a historic pool (control, i.e., chronically instrumented and not paced, $n = 5$). Octanoate (2.9 μmol/kg/min, isocaloric dose relative to ketones administered in Ref. 2) was administered via external infusion pumps after 2 wk of pacing, at a time when cardiac parameters were already altered, but cardiac failure was still in a compensated stage (Fig. 1*A*). Functional and metabolic measurements were obtained and analyzed independently by two investigators blinded to treatment.

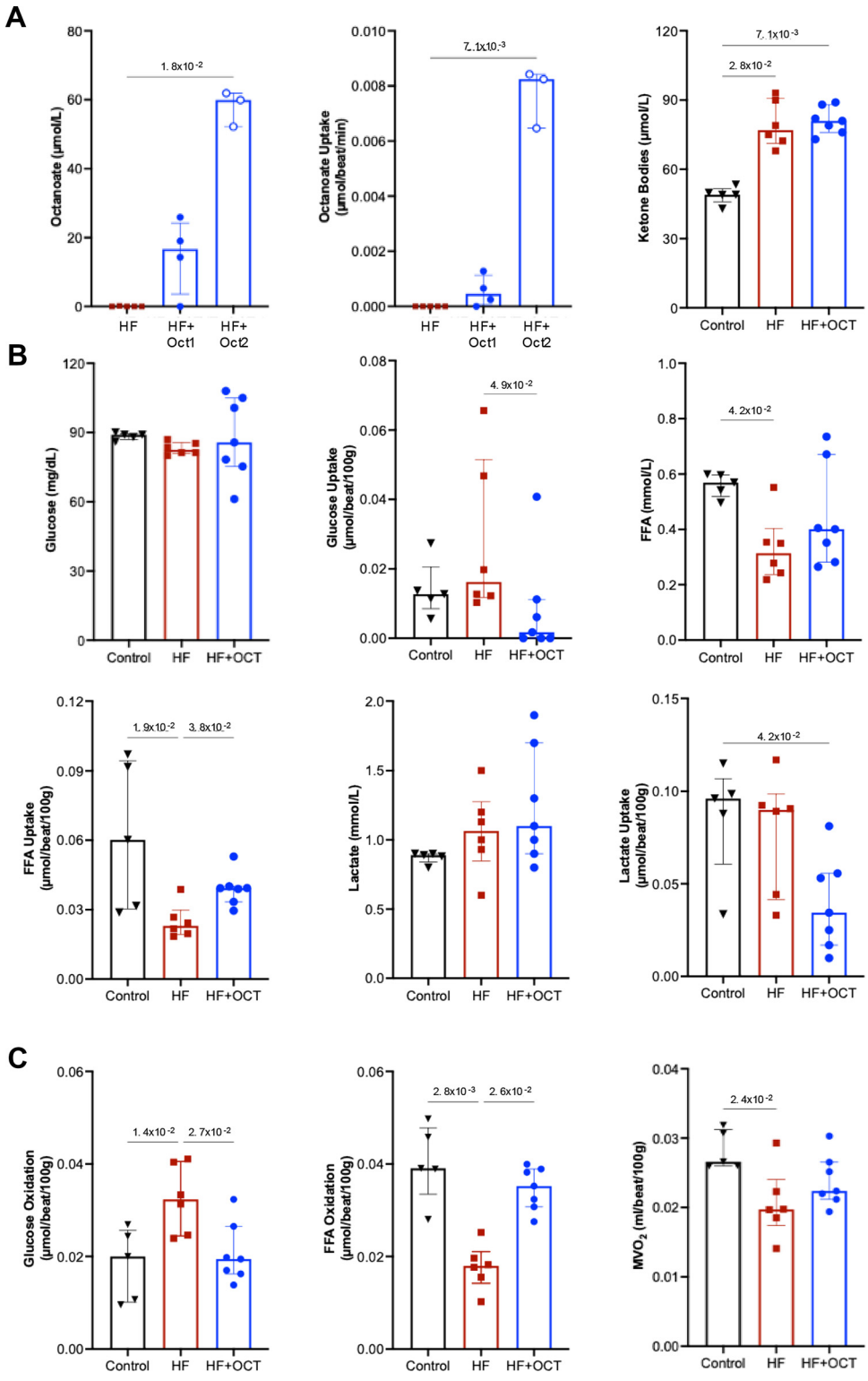

Figure 2. Infusion of octanoate restores critical metabolic characteristics in a tachypacing model of heart failure with reduced ejection fraction. *A*: arterial plasma concentrations and cardiac uptake of octanoate (n = 3–5 per group) and ketone bodies (n = 5–7 per group). *B*: arterial plasma concentrations and cardiac uptake of the primary energy substrates glucose, free fatty acids, and lactate (n = 5–7 per group). *C*: cardiac oxidation of glucose and oleate, and myocardial oxygen consumption (n = 5–7 per group). Measurements were obtained on the final day of the pacing protocol in HF and HF + Oct groups compared with nonfailing controls (control, $n = 5$). Data are presented as median ± IQR. $P < 0.05$ shown for Kruskal–Wallis followed by Dunn's multiple comparison test using Prism 10. FFA, long-chain free fatty acids; HF, heart failure; $M\dot{V}O_2$, myocardial oxygen consumption.

Hemodynamics and Cardiac Morphofunctional Assessments

Hemodynamic parameters were obtained by connecting the chronically implanted probes and lines to recorders. Measured hemodynamic parameters included heart rate, coronary blood flow in the circumflex artery, and aortic and LV pressures. From these data, mean aortic pressure (MAP), mean left circumflex flow, and the first derivative of LV pressure (dP/dt_{max}) were calculated. Cardiac remodeling and contractile function were evaluated by echocardiography. In addition, two standard afterload indices, total peripheral resistance and effective arterial elastance (E_a), were calculated by dividing MAP by cardiac output or stroke volume, respectively.

All assessments were performed at baseline (before pacing) and at 2 and 4 wk of pacing (terminal study). Data collection was conducted on conscious animals to minimize the impact of sedatives or anesthetics on physiological parameters. Custom-made cotton/nylon jackets were used to shield the exteriorized wires, catheters, infusion pumps, and external pacemakers.

Cardiac Metabolism and Radiolabeled Isotope Tracing

Cardiac metabolism was assessed on the final day of the experimental protocol. Access to the coronary sinus via a peripheral approach was established under fluoroscopic guidance. Oxygen partial pressure (P_{O_2}) and oxygen concentration were measured in paired arterial and coronary sinus (AO/CS) blood samples, and coronary blood flow was recorded to calculate myocardial oxygen consumption ($M\dot{V}O_2$). To trace the metabolic fate of the major cardiac energy substrates, free fatty acids (FFA) and glucose, radiolabeled oleate (0.7 µCi/min) and glucose (20 µCi as a bolus followed by 0.3 µCi/min) were infused via a peripheral vein. After steady-state concentrations of the infused tracers were achieved, paired AO/CS blood samples were collected. Radiolabeled FFA and glucose, ^3H_2O, and $^{14}CO_2$ were measured with a scintillation counter, whereas total FFA, glucose, lactic acid, and ketone bodies were measured spectrophotometrically in arterial and coronary sinus samples, as previously described (2). Octanoic acid was measured spectrophotometrically in plasma after removing albumin-bound long-chain FFA by ultrafiltration at a 30-kDa cutoff. The rates of cardiac substrate uptake and oxidation were calculated using coronary blood flow. Substrate uptake, oxidation rates, and $M\dot{V}O_2$ were normalized to heart rate and heart weight.

Stable Isotope Tracing

Stable isotope tracing was performed in isolated adult mouse cardiomyocytes with ^{13}C sodium octanoate. Cardiomyocytes were isolated from the hearts of adult male C57BL/6NJ mice (Jackson Laboratory) via collagenase digestion and gravity sedimentation (18). Cardiomyocytes were cultured for 24 h in conventional media (M199, Thermo Fisher) containing 5 mM glucose (Sigma), 100 µM palmitate (Sigma), and 200 µM 1,2,3,4-^{13}C octanoate (Cambridge Isotopes). Cells were harvested to evaluate the contribution of octanoate to tricarboxylic acid (TCA) cycle intermediates via gas chromatography-mass spectrometry. Each heart was treated as a biological replicate ($n = 3$) measured in technical triplicate.

Statistical Analysis

Time course comparisons use a rank-based longitudinal model (nparLD R package, F1-LD-F1: group × time). We report group [Box-modified ANOVA-type statistic (ATS)], time (ATS), and group × time (ATS) P values from this model. A single planned pairwise comparison (HF vs. HF + OCT at *week 4*, 2-sided Wilcoxon rank-sum) was reported without multiplicity adjustment; no other pairwise tests were performed. The final day comparisons use the Kruskal–Wallis test followed up by the Dunn's test.

RESULTS

Octanoate infusion prevented further elevation of left ventricular end-diastolic pressure (LVEDP) and improved stroke work (SW) and the peak derivative of LV pressure (Fig. 1*B*). Consistent beneficial effects were exerted on echocardiographic parameters of cardiac function and remodeling. Compared with HF, HF + Oct increased LV ejection fraction, stroke volume, and cardiac output with decreased LV volumes and heart rate (Fig. 1*C*). Octanoate reduced total peripheral resistance and effective arterial elastance, two indexes of ventricular afterload, with no statistically significant difference observed in mean arterial pressure (Fig. 1*D*).

In the HF + Oct group, octanoate was chronically infused from *week 2* to *week 4* and either discontinued (HF + Oct1) 1 h before or continued (HF + Oct2) during terminal arterial-venous blood sampling. Octanoate infusion dramatically increased concentration and cardiac uptake of water-soluble short-/medium-chain FA, which were undetectable in the absence of infusion, with no statistically significant differences observed in the concentration of 3OHB (Fig. 2*A*).

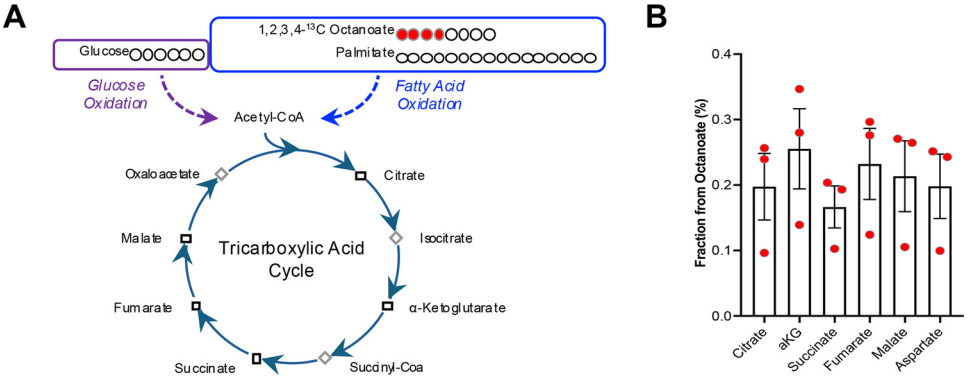

Figure 3. ^{13}C isotope labeling confirms octanoate oxidation in isolated adult mouse cardiomyocytes. *A*: schematic of ^{13}C stable isotope tracing in isolated mouse cardiomyocytes. *B*: fractional enrichment of tricarboxylic acid intermediates from ^{13}C-octanoate ($n = 3$ biological replicates). Data are presented as means ± SE.

Compared with HF, HF + Oct decreased cardiac uptake of glucose and lactate and increased uptake of free FA (Fig. 2*B*). During HF, cardiac glucose oxidation increased and FA oxidation and $M\dot{V}O_2$ decreased compared with control (Fig. 2*C*). HF + Oct decreased cardiac glucose oxidation and increased FA oxidation compared with HF with no significant differences compared with control (Fig. 2*C*).

To confirm myocardial oxidation of the infused octanoate substrate, stable isotope tracing was performed in isolated adult mouse cardiomyocytes. To simulate physiologic conditions, glucose and the long-chain fatty acid palmitate were provided in the media in addition to ^{13}C-labeled octanoate (Fig. 3*A*). ^{13}C-octanoate-enriched tricarboxylic acid (TCA) cycle intermediates confirming octanoate oxidation by cardiomyocytes (Fig. 3*B*).

DISCUSSION

The present study shows that a continuous infusion of octanoate markedly attenuates the progressive hemodynamic and metabolic deterioration in canines with tachypacing-induced dilated cardiomyopathy. The beneficial effects were particularly evident for LVEDP, an index of central congestion, but also impacted other critical parameters of cardiac contractile work, such as cardiac output, ejection fraction, and LV volumes. Octanoate infusion was started after 2 wk of pacing, corresponding to the phase of compensated HF. Therefore, the intervention we tested was not preventive, but simulated a clinical scenario in which patients are treated at a mildly symptomatic stage of HF. Octanoate delivery did not revert all changes, yet it prevented further derangement and restored many metabolic parameters to control values.

The heart consumes a variety of energy substrates based on their availability. Octanoate is a potential cardiac fuel, yet the physiologic blood concentration of this medium-chain FA is negligible. By infusing octanoate, an additional substrate was supplied at sufficiently high concentration to favor myocardial uptake. Although octanoate oxidation was not directly measured, it is plausible that cardiac extraction indicates oxidation, considering the absence of known pathways of medium-chain FA storage in cardiomyocytes. This is supported by robust enrichment of ^{13}C-labeled octanoate into TCA metabolites in isolated mouse cardiomyocytes. However, the beneficial effects of octanoate infusion may also be mediated by extracardiac mechanisms unrelated to the provision of a fuel. Reduced afterload, as we also found with 3OHB infusion, could improve cardiac dynamics, reduce myocardial energy demand, and decrease ventricular remodeling (2). In mice, acute administration of sodium octanoate has been shown to attenuate sepsis-induced cardiac dysfunction in part through G protein-coupled receptor 84-dependent anti-inflammatory signaling (19). Octanoate infusion also has the potential to activate ghrelin, a major metabolic hormone, via octanoylation. Administration of the active hormone acyl-ghrelin induced cardiac functional and metabolic improvements in tachypacing heart failure, similar to the present findings (20). Acyl-ghrelin also improved cardiac output in HFrEF patients and increased fractional shortening in isolated mouse cardiomyocytes (21). Although potential signaling mechanisms were not interrogated in the current study, these pleiotropic effects could be complementary to the benefits of fuel provision and broaden the therapeutic relevance of short-/medium-chain fuels. Importantly, however, octanoate infusion was not ketogenic, suggesting the effects are independent of ketone bodies. Octanoate has translational promise for future clinical trials, due to proven methods of dietary supplementation, well-tolerated and devoid of the side effects caused by ketone bodies (22).

Taken together, these results indicate that octanoate rescues cardiac function and delays pathological remodeling in nonischemic HF and identify medium-chain FA delivery as a potential actionable therapeutic for acute and chronic heart failure. Similar to ketone bodies, the increased circulating levels of a medium-chain FA in HF oppose the progression toward decompensation, perhaps in part due to provision of an alternate cardiac fuel. It remains to be tested if recovery of physiological metabolism, indicative of improved cardiac health, precedes or follows hemodynamic improvements related to peripheral octanoate signaling. Future investigations should identify overlapping and unique characteristics of short- and medium-chain fuels as well as test practical approaches to administer octanoate as a therapeutic for the failing heart, including early-stage treatment.

DATA AVAILABILITY

Data will be made available upon reasonable request.

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DISCLOSURES

D.P.K. is a consultant for Amgen and Pfizer. None of the other authors has any conflicts of interest, financial or otherwise, to disclose.

AUTHOR CONTRIBUTIONS

N.G., T.R.M., D.P.K., and F.A.R. conceived and designed research; N.G., T.R.M., N.N., R.B., A.R., A.W., T.W., and S.H. performed experiments; N.G., T.R.M., and K.B. analyzed data; N.G., T.R.M., D.P.K., and F.A.R. interpreted results of experiments; T.R.M. prepared figures; T.R.M. drafted manuscript; N.G., T.R.M., D.P.K., and F.A.R. edited and revised manuscript; N.G., T.R.M., N.N., R.B., A.R., A.W., T.W., K.B., S.H., D.P.K., and F.A.R. approved final version of manuscript.

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