Cardiac substrate utilization in heart failure: Where is the relevance of SGLT2 inhibition?

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Heart failure is a steadily increasing clinical problem attributable to an aging population with accumulation of predisposing comorbidities and improved cardiovascular care. The most relevant consequence of myocardial infarction has shifted from mortality to ischemic cardiomyopathy and heart failure.¹ Structural and/or functional abnormalities of the heart reduce cardiac output and lead to elevation of left ventricular filling pressure as a hypertrophic stimulus and cause for adverse cardiac remodeling.²

The terminology of heart failure is based on left ventricular ejection fraction (LVEF), categorizing patients as those with preserved LVEF (HFpEF, with LVEF $\geq 50\%$), mid-range LVEF (HFmrEF, with LVEF 40%-49%), or reduced LVEF (HFrEF, with LVEF $<40\%$).³ The most relevant causes for HFrEF are ischemic and dilative cardiomyopathy, whereas HFpEF combines different clinical etiologies resulting in impaired diastolic relaxation and myocardial stiffness, including age, hypertension, diabetes, and chronic kidney disease.⁴ Heart failure treatment has been successful for HFrEF, with renin-angiotensin-aldosterone system inhibition, beta-blockers, mineralocorticoid receptor antagonists, neutral endopeptidase inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors associated with improved prognosis.^{3,5} In contrast, HFpEF remains an unmet clinical need limited to symptomatic diuretic treatment and management of comorbidities.⁴

There is long-term interest in the use of metabolic interventions to improve heart failure outcomes.⁶ This is based on observations of energetic deficits limiting cardiac contractility in stages of advanced heart failure attributable to mitochondrial dysfunction and insufficient substrate supply.⁷ The relevance of substrate supply has been suggested by a shift in cardiac fuel utilization toward glucose metabolism occurring in early stages of heart failure.⁸⁻¹⁰ This is followed by impairment of fatty acid oxidation as the most relevant metabolic alteration of heart failure.¹⁰ Recent evidence further suggests ketone body utilization to provide an alternative energetic substrate in advanced heart failure.^{11,12} Therefore, metabolic reprogramming is an integral component of heart failure pathogenesis.

SGLT2 inhibition reprograms cardiac signaling in heart failure.

CENTRAL MESSAGE

Metabolic reprogramming by SGLT2 inhibition is attributable to a fasting-like response leading to reduced cardiac insulin and/or adrenergic signaling.

This Invited Expert Opinion provides a perspective on the following paper: Source article: *J Am Coll Cardiol.* 2019 Apr 23;73(15):1931-1944. <https://doi.org/10.1016/j.jacc.2019.01.056>.

See Commentaries on pages 900 and 901.

Recent success of SGLT2 inhibition in improving heart failure outcomes has brought renewed interest in metabolic interventions for heart failure therapy.¹³ SGLT2 inhibitors were originally developed to lower blood glucose in patients with diabetes.¹⁴ Inhibition of SGLT2 prevents glucose reabsorption in the proximal renal tubule, causing glucosuria and osmotic diuresis, resulting in caloric loss and reduced body weight in conjunction with decreased blood pressure. Unexpectedly, SGLT2 inhibition was also found to markedly reduce heart failure hospitalization in patients with diabetes, an observation that was recently extended to patients with HFpEF independent of diabetes.^{13,15} The mechanisms relevant for these beneficial effects remain incompletely understood but include modulation of cardiac metabolism. Loss of urinary glucose by SGLT2 inhibition reduces systemic carbohydrate availability and shifts substrate provision to other energetic sources.^{16,17} SGLT2 inhibition lowers circulating glucose and insulin availability while increasing levels of free fatty acids, ketone bodies, and glucagon, mimicking a fasting-like response.¹⁸ This change of systemic substrate availability shifts cardiac substrate utilization from glucose to fatty acid and ketone body oxidation while simultaneously reducing adverse cardiac remodeling and improving left ventricular function in

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Received for publication Jan 15, 2021; revisions received Feb 17, 2021; accepted for publication Feb 18, 2021; available ahead of print March 3, 2021.

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J Thorac Cardiovasc Surg 2022;164:895-9

0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2021.02.092>

experimental models of heart failure.^{16,17} Although it currently remains unknown whether this modulation of cardiac metabolism by SGLT2 inhibition is a cause or a consequence of improved left ventricular function, it demonstrates the integral relevance of cardiac metabolism as part of heart failure progression and raises questions about the underlying mechanisms.

Cardiac metabolism of the healthy heart is flexible and depends on a complex network of numerous pathways ensuring constant adenosine triphosphate (ATP) production to fuel the contractile demand. Cardiomyocytes metabolize fatty acids, glucose, ketone bodies, and amino acids in a supply-dependent manner.¹⁹ ATP production relies mostly on mitochondrial oxidative phosphorylation, with fatty acids providing 60% to 90% of the required substrate.⁸ The remaining energy demand is derived from glycolysis and pyruvate oxidation, with little relevance of ketone body or branched-chain amino acid metabolism in the healthy heart.²⁰ Increasing workload and early stages of heart failure alter substrate utilization and increase glucose uptake and glycolysis while leaving glucose oxidation capacity relatively unaffected.²¹ This response provides immediate energy supply in a stressed environment and can be attributed to adrenergic stimulation causing translocation of the insulin dependent glucose transporter type 4 (GLUT4) to the cell membrane.²² Therefore, adrenergic signaling mimics the cellular response to insulin, with both pathways merging on glucose uptake, metabolic regulation, and mechanistic target of rapamycin (mTOR) activation.²³ mTOR is a master regulator of cell growth, metabolic control, and autophagy. There are 2 different complexes of mTOR, mTORC1 and mTORC2. Whereas mTORC1 interacts with raptor (regulatory-associated protein of mTOR), and is inhibited by rapamycin, mTORC2 binds to rapamycin-insensitive companion of mTOR (RIC-TOR) and is not directly responsive to rapamycin.²⁴ Activation of mTORC1 promotes cellular protein synthesis and hypertrophy to allow workload-dependent cardiac adaptation; however, sustained mTORC1 activation overwhelms the cellular protein synthesis machinery, causing an unfolded protein response with endoplasmic reticulum stress and apoptotic cell death.^{25,26} Importantly, partial mTORC1 inhibition prevents adverse cardiac remodeling and preserves left ventricular function in different models of cardiomyopathy.^{27,28} This also can be attributed to reduced energy demand in conjunction with more dynamic cellular protein turnover by partial mTORC1 inhibition. Regulation of myocardial glucose uptake has been attributed to mTORC2 activation, leading to protein kinase B (Akt) stimulation as an integral part of the insulin receptor cascade.^{29,30} Both mTOR complexes are activated in response to adrenergic signaling, with β_2 -receptors increasing G_s adenyl cyclase-dependent cyclic adenosine monophosphate (cAMP) with protein kinase A-dependent

mTORC2 activation.^{31,32} Furthermore, sustained β_2 -receptor stimulation causes G_i -dependent extracellular regulated kinase 1/2 (ERK1/2) and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) activation as components of the insulin receptor cascade with downstream mTORC1/C2 stimulation.³¹ In addition, myocardial α_1 adrenoceptors activate both mTOR complexes in an PI3K/Akt pathway-independent manner.³³ Similarly, mTOR is activated in response to insulin signaling, with insulin receptor activation causing PI3K/Akt activation with downstream translocation of the insulin-dependent glucose transporter GLUT4 in addition to tuberous sclerosis complex 1/2 (TSC1/2) inhibition to allow mTOR activation.³⁴ The metabolic relevance of mTOR signaling for cardiac glucose uptake is demonstrated by similar impairment of adrenergic- or insulin-dependent cardiomyocyte glucose uptake by mTORC2 inhibition.³³ These observations demonstrate that myocardial glucose uptake occurs as a direct consequence of adrenergic or insulin signaling and in parallel with mTOR activation as the main regulator of cardiomyocyte hypertrophy, endoplasmic reticulum stress, and adverse cardiac remodeling.^{24,25} Therefore, resting myocardial glucose uptake may be an indicator of left ventricular stress and cardiac adrenergic activation.²¹ High myocardial glucose uptake in patients with dilated cardiomyopathy thereby predicts improvement of left ventricular function in response to beta-blocker therapy.³⁵ The overlap of adrenergic signaling and the insulin receptor cascade suggests comparable consequences of both signaling pathways for heart failure outcome and left ventricular remodeling.³⁴ Indeed, sustained insulin signaling was found to deteriorate heart failure in experimental models, whereas depletion of insulin or its myocardial receptor improved pressure overload-induced cardiac dysfunction. Furthermore, treatment of type 1 diabetic mice with insulin promoted cardiomyocyte death and heart failure despite improvement of systemic glucose metabolism.³⁶ In addition, insulin treatment independently predicted adverse prognosis in heart failure trials.³⁷ Therefore, reducing circulating insulin concentrations by SGLT2 inhibition might explain some of the cardiac benefits of the drug class. Indeed, SGLT2 inhibition reduces myocardial glucose utilization in heart failure models, which was paralleled by improved left ventricular function and reduced adverse remodeling.^{16,17} In addition, SGLT2 inhibition has been found to reduce myocardial glucose uptake in patients with diabetes but without heart failure.³⁸

However, it needs to be considered that augmentation of myocardial glucose uptake is an early and temporal phenomenon in the pathogenesis of heart failure. It occurs as an immediate response to workload and precedes cardiac hypertrophy, persisting throughout the hypercontractile phase of 4 to 8 weeks in the pressure overload model.^{21,39} This is followed by a continuous decline in myocardial

glucose utilization thereafter, which is paralleled by deterioration of left ventricular function and has been attributed to the occurrence of insulin resistance.⁴⁰ It currently remains unknown how SGLT2 inhibition effects cardiac glucose utilization in these advanced stages of heart failure characterized by insulin resistance and limited glucose supply. However, models of diabetic cardiomyopathy featuring pronounced cardiac insulin resistance suggests SGLT2 inhibition to restore myocardial glucose utilization under these conditions. This also led to improved survival and cardiac energetics.⁴¹ These observations suggest that SGLT2 inhibition may be able to decrease or increase myocardial glucose utilization in an environment- and disease-dependent manner while independently improving heart failure outcome. Along these lines, it currently remains inconclusive whether heart failure-dependent augmentation of myocardial glucose uptake only indicates myocardial stress and adrenergic signaling or contributes by itself to the progression of disease.²¹ A backlog of glucose metabolites created by insufficient mitochondrial glucose oxidation has been suggested to initiate adverse cardiac signaling events and oxidative stress.³⁹ Among these, glucose-6-phosphate serves as an intrinsic mTOR activator while also providing a substrate for hexosamine biosynthesis and posttranscriptional modifications leading to cell stress and mitochondrial impairment.^{39,42} In contrast, increasing myocardial glucose availability by overexpression of glucose transporter GLUT1 prevented left ventricular remodeling in models of pressure overload cardiomyopathy.^{43,44} The latter finding suggests augmented intracellular glucose availability to provide cellular protection, although this might depend on the cellular capacity for glucose metabolism. Therefore, augmentation of cardiac glucose utilization in early stages of heart failure might be primarily an adaptive response to cope with increased energetic demand while the underlying signaling events drive adverse left ventricular remodeling.³⁹

Additional metabolic consequences of heart failure include impairment of myocardial fatty acid utilization. Although less affected by acute changes in myocardial workload, a decline in fatty acid oxidation capacity is readily detectable by 2 weeks after a pressure overload procedure.^{10,45,46} This has been linked to the accumulation of nonoxidized toxic intermediates, such as ceramides and diacylglycerol, termed lipotoxicity.⁴⁷ Furthermore, the energetic depletion observed in advanced stages of heart failure has been attributed mainly to reduced fatty acid oxidation capacity.^{7,48} Regulation of fatty acid oxidation occurs on a transcriptional level with down-regulation of the transcriptional coactivators peroxisome proliferator-activated receptor gamma coactivator 1 alpha/beta (PGC-1 α/β) and their interconnected transcription factors, including peroxisome proliferator-activated receptor alpha, estrogen-related receptor alpha, and nuclear respiratory

factor 1.^{7,49} PGC-1 α functions as a master regulator of mitochondrial biogenesis and respiration, and its down-regulation is indicative for heart failure progression.⁵⁰ This might be the consequence of sustained adrenergic signaling with Akt and/or mTOR activation.⁴⁰ Importantly, SGLT2 inhibition increases cardiac expression of PGC-1 α in conjunction with fatty acid oxidation capacity, mitochondrial integrity, and cellular ATP content.^{16,17} Interestingly, no change in myocardial fatty acid uptake capacity has been recorded in patients with diabetes without heart failure in response to SGLT2 inhibition, demonstrating disease-dependent regulation of cardiac metabolism.³⁸

Metabolomic analysis of human nondiabetic, end-stage failing hearts have further identified myocardial ketone metabolism to serve as an alternative energetic fuel to compensate for reduced cardiac fatty acid oxidation. Myocardial expression of ketone-metabolizing enzymes is increased in heart failure, whereas their disruption impairs cardiac function and causes adverse cardiac remodeling.^{11,12,51} Interestingly, supplementation of ketone bodies in patients with HFrEF acutely increases cardiac output and reduces left ventricular filling pressure.⁵² Whether this is mediated solely by provision of additional energy or is based on independent signaling events remains to be established. Interestingly, ketones were found to inhibit mTOR signaling in diabetic kidney disease as a mechanism for SGLT2 inhibition-mediated renoprotection.⁵³ Signaling and utilization of ketone bodies are further facilitated by up-regulation of circulating ketone body concentrations in response to heart failure.⁵⁴ This can be attributed to adrenergic signaling providing adipose tissue lipolysis and hepatic ketone body production.⁵⁵ The mechanisms relevant for heart failure-dependent induction of cardiac ketone body-catabolizing enzymes remains to be established. Importantly, SGLT2 inhibition increases circulating ketone body concentrations while also augmenting cardiac expression of ketone-catabolizing enzymes. A consequential increase in myocardial ketone body utilization might explain, at least partially, the improved myocardial energetics with SGLT2 inhibition.^{16,17} The increased production of ketone bodies in response to SGLT2 inhibition can be attributed to reduced adipose tissue insulin signaling, providing lipolysis, while increased hepatic glucagon signaling favors ketone body generation, providing a fasting-like response.¹⁸ The relevant mechanism for induction of cardiac ketone body-catabolizing enzymes remains obscure and, interestingly, has been detected only in nondiabetic conditions.^{56,57}

In conclusion, heart failure is a state of metabolic reprogramming that initially can be attributed to adrenergic signaling and in advanced stages leads to energetic deficits. Overlap of the adrenergic- and insulin-signaling pathways suggests similar consequences for adverse cardiac remodeling. Reducing cardiac adrenergic and/or insulin signaling in

FIGURE 1. SGLT2 inhibition reprograms cardiac signaling in heart failure. Increased adrenergic and/or insulin signaling augments cardiac glucose uptake during early heart failure, most likely as an adaptive response to maintain energetic demands. Both pathways merge on mTOR activation and downstream maladaptive remodeling. SGLT2 inhibition shifts substrate availability from glucose to other energetic sources to reduce cardiac insulin signaling and downstream maladaptive pathways. BCAA, Branched-chain amino acid; GLUT4, glucose transporter type 4; PI3K/Akt, phosphatidylinositol 3-kinase/protein kinase B; ERK, extracellular regulated kinase; mTOR, mechanistic target of rapamycin; PGC-1, peroxisome proliferator-activated receptor gamma coactivator 1; SGLT2, sodium-glucose cotransporter 2.

response to SGLT2 inhibition might explain some of the beneficial effects of this drug class (Figure 1).

Conflict of Interest Statement

Dr Lehrke has received grants and personal fees from Boehringer Ingelheim, MSD, and Novo Nordisk and personal fees from Amgen, Sanofi, Astra Zeneca, Bayer, and Lilly. P.A. Mann reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

This study was supported by the Deutsche Forschungsgemeinschaft (TRR 219, Project-ID 322900939 M-03) and Interreg V-A grant EURlipids to Dr Lehrke.

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Key Words: heart failure, cardiac substrate metabolism, SGLT2 inhibition, insulin signaling, adrenergic signaling, mTOR signaling