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THERAPEUTIC IMPLICATIONS OF METABOLIC DERANGEMENTS IN HEART FAILURE

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Abstract

Heart failure is a prevalent disease with an adverse prognosis. Several factors characterize different heart failure clinical manifestations. Among the others, the mechanisms and pathways that regulate cardiac and global *metabolic states in patients with heart failure definitely play an important role. In fact , several drug classes used to treat patients with heart failure have been shown to induce changes in myocardial and global metabolism. These changes may be of special interest for both potential beneficial and deleterious effects and should be well understood and known by all providers managing patients with heart failure. Additionally, pharmacological modulation of cardiac energy metabolism may be considered as an adjunctive therapeutic option in heart failure. This paper reviews the metabolic derangements in heart failure and the metabolic effects of medications used for the treatment of patients with heart failure.*

Keywords: *. Metabolism, heart failure, adenosine triphosphate, renin–angiotensin–aldosterone system , Mineralocorticoid receptor antagonists*

Introduction

Metabolic derangements have long been recognized as playing an important role in the pathophysiology of heart failure [1]. Metabolic impairment in heart failure is not just a feature of the heart, but rather a global issue with important contributions from organs and peripheral tissues [2]. Prescription of heart failure medications is aimed towards the pathophysiological mechanisms underlying the disease process. For instance, inhibition of the renin–angiotensin–aldosterone and sympathetic nervous systems is directed towards ameliorating abnormal neurohormonal activation which leads to worsening left ventricular remodeling and progression of heart failure [3]. However, apart from their primary therapeutic actions, the drugs used for the treatment of patients with heart failure may affect the global and cardiac metabolism [4]. These additional pharmacological actions may be of special interest for both potential beneficial and deleterious effects and should be well understood and known by all providers managing patients with heart failure. This paper reviews the metabolic derangements in heart failure and the metabolic effects of the most common medications used for the treatment of patients with heart failure.

Changes in cardiac metabolism in heart failure

Proper heart function relies on a high efficiency of energy conversion. Mitochondrial oxygen-dependent processes transfer the chemical energy from metabolic substrates into adenosine triphosphate (ATP). Healthy myocardium uses mainly fatty acids as its major energy source; beta-oxidation generates 60–90 % of the total ATP production [5]. The remaining 10–40% of the ATP comes from the oxidation of pyruvate that is derived from glycolysis and lactate oxidation [6]. Under certain circumstances, amino acid and ketone oxidation may contribute to ATP production [6].

Heart failure is associated with perturbation in cardiac energy metabolism [1, 5]. The myocardial capacity to extract energy from substrate is globally depressed in heart failure [7], determining decreased

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oxidative phosphorylation, decreased high pluse energy phosphate content, generation of reactive oxygen species, and mitochondrial dysfunction [8, 9].

In addition, metabolic derangements in heart failure include changes in metabolic pathways that regulate essential cellular processes such as growth, redox homeostasis, and autophagy [10].

Changes in global metabolic state in heart failure

Insulin resistance has been recognized as a key metabolic derangement in heart failure [11]. Insulin resistance reflects a disturbance of glucose metabolism and potentially worsens metabolic efficiency of both skeletal muscle and cardiac muscle [12]. Multiple factors contribute to insulin resistance in heart failure including neurohormonal activation, increased circulating inflammatory cytokines, oxidative stress, and tissue hypoperfusion [11]. Impaired insulin sensitivity progresses in parallel to heart failure severity and is a prognostic marker independent of other established prognostic factors [13].

Impaired glucose oxidation and a switch towards anaerobic glycolysis also occurs in heart failure and is related to insulin resistance, increased circulating catecholamines, and tissue hypoxia [11]. Other important peripheral metabolic changes that occur in heart failure include impairments in beta-oxidation of fatty acids leading to accumulation of intermediates of fatty acid oxidation in the circulation [14].

Heart failure is also characterized by growth hormone resistance [15] and anabolic hormone depletion [16]. Coupled with insulin resistance, excess catecholamines, and cytokine abnormalities, these hormonal changes can alter the metabolic balance between catabolism and anabolism, leading to tissue wasting [17].

To overcome it
is possible, due to the
uniting the knowledge and
will of all doctors in the world

Metabolic effects of medications in patients with heart failure

Apart from their primary therapeutic action, some of the medications used to treat patients with heart failure also have additional pharmacological effects. Among these effects, those primarily affecting global and cardiac metabolism deserve special attention. In addition to coronary artery disease, diabetes mellitus is a major antecedent of heart failure [18]. Since the majority of heart failure patients are being treated in parallel for diabetic, vascular, renal, and psychiatric conditions, it will also be important to consider the metabolic impact of these non-cardiac treatments.

In the following paragraphs different therapeutic agents used for the treatment of patients with heart failure and most cardiovascular diseases will be outlined, with a special emphasis at their metabolic effects. Potential beneficial and deleterious influences on cardiac and global metabolism will be reported. Table 1 shows a brief summary of the main metabolic effects of medications used for the treatment of patients with heart failure.

Beta adrenergic receptor blockers

Beta-blockers reduce mortality and morbidity in patients with heart failure with reduced ejection fraction [19-21]. This class of drugs targets the beta adrenergic receptors of the sympathetic nervous system. Sympathetic stimulation of the cardiovascular system increases heart rate, blood pressure and myocardial contractility. This results in increased myocardial energy metabolic requirements that can cause myocardial ischemia. Beta blockers blunt the cardiovascular response to adrenergic stimulation, thus reducing ischemia [22].

Beta blockers have also been shown to directly affect myocardial energetics, independently from their hemodynamic effects [23]. By blocking the beta-1 receptor located on adipose tissue, beta-blockers reduce peripheral lipolysis. This results in a reduction in circulating levels of free fatty acids and contributes to the shift of myocardial substrate utilization towards a greater glucose utilization due to substrate competition [24]. Beta-blockers decrease myocardial

Table 1

Main metabolic effects of medications used for the treatment of patients with heart failure.

Medications	Metabolic effects
Beta adrenergic receptor blockers	• Reduction of peripheral lipolysis • Reduction of circulating levels of free fatty acids • Increased carbohydrates utilization • Improved insulin sensitivity (carvedilol)
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	• Improved glucose homeostasis • Reduction in the incidence of diabetes
Mineralocorticoid receptor antagonists	• Detrimental effects on glucose and lipid homeostasis by increased cortisol levels through blockade of the glucocorticoid receptors • However, eplerenone appears devoid of metabolic effects
Angiotensin receptor-neprilysin inhibitors	• Improved insulin sensitivity • Grater reduction in HbA1c compared to ACE-inhibitor enalapril
I_f-channel inhibitor (Ivabradine)	• Reduced mitochondrial reactive oxygen species formation • Increased ATP production and calcium retention capacity
Diuretics	• Induced dyslipidemia (thiazide diuretics) • Induced insulin resistance (thiazide diuretics) • Elevated parathyroid hormone level (loop diuretics) • Induced electrolyte depletion (thiazide and loop diuretics) • Activation of neuro-hormonal systems (loop diuretics)
Sodium–glucose cotransporter-2 inhibitors	• Increased glucosuria triggers lipolysis and fatty acid oxidation and ketone body synthesis in the liver • Increased diuresis resulting in reduction in plasma volume and blood pressure
Glucagon-like peptide 1 agonists	• Augmentation of insulin and inhibition of glucagon secretion • Improved insulin resistance • Promoted weight loss
Acetylsalicylic acid	• Reduction of circulating FFA, by activating AMP-activated protein kinase • Activation of catabolic pathways (glucose uptake and FFA oxidation) • Inhibition of the transcription factor NF-kappa B (improved glucose tolerance)
Statins	• Pravastatin decreases the risk of development of diabetes • Other statins including simvastatin, atorvastatin, and rosuvastatin increase the risk of development of diabetes • All statins reduce serum testosterone levels
Trimetazidine	• Reduction in fatty acid oxidation • Improved glycolysis and glucose oxidation • Antioxidant activity • Reduced endothelin-1 release
Ranolazine	• Modulation of late sodium current, thereby reducing the accumulation of intracellular Ca++ • Increased glucose oxidation • Lowered plasma glucose and HbA1c levels
CPT-I inhibitors	• Reduction of FFA oxidation • Increased glucose oxidation • Up-regulation of the expression of various enzymes involved in fatty acids betabeta-oxidation
Vitamin D	• Stimulation of insulin secretion • Improvement in insulin resistance
Psychotropic drugs	• Induced weight gain and insulin resistence • Decreased insulin secretion

Notes: *ACE: angiotensin-converting enzyme; AMP: adenosine monophosphate; ATP: adenosine triphosphate; CPT-I: Carnitine palmitoyltransferase I; FFA: free fatty acids; HbA1c: glycated hemoglobin, NF-kappa B: nuclear factor-kappa B.*

uptake of free fatty acids [25], and increase glucose utilization [26]. A higher rate of carbohydrate utilization induced by beta blockade may result in a greater cardiac energy production at similar levels of oxygen consumption. This change in myocardial energetics could provide a potential mechanism for the decreased myocardial oxygen consumption and improved energy efficiency seen with beta blockade in the treatment of heart failure [27]. It appears that nonselective beta-blockers are more efficient in shifting total body substrate utilization from lipids to glucose oxidation [28]. Better metabolic effects of the nonselective beta-blockers could be one of the reasons of better survival rates observed with their use in patients with chronic heart failure [29]. Nonselective beta-blockade has also been shown to be superior in improving glucose and lipid metabolism and in reducing lipid peroxidation in patients with diabetes and hypertension [30].

Renin–angiotensin–aldosterone system (RAAS) inhibitors

Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce morbidity and mortality in heart failure with reduced ejection fraction [31-33]. ACE inhibitors also inhibit kininase and increase levels of bradykinin, which can induce cough and angioedema but also may contribute to their beneficial effect through vasodilation.

Angiotensin receptor blockers (ARBs) do not inhibit kininase and are associated with a much lower incidence of cough and angioedema than ACE inhibitors [34]. Long-term therapy with ARBs has been shown to reduce morbidity and mortality [35, 36], especially in ACE inhibitor–intolerant patients.

Angiotensin II is an important regulator of cardiac energy metabolism and function. There are several mechanisms through which angiotensin II may directly contribute to cardiac dysfunction [37]. Angiotensin II increases mitochondrial reactive oxygen species in cardiomyocytes [38], and affects mitochondrial oxidative phosphorylation, including fatty acid oxidation [39]. In addition, by decreasing oxidative metabolism, angiotensin II can reduce ATP levels, thus compromising ATP production [40].

There is also evidence that angiotensin II regulates glucose oxidation [41]. Angiotensin II-induced hypertrophy and diastolic dysfunction is associated with reduced glucose oxidation [37]. In fact, apart from their effect on left ventricular function and outcomes and as a prove that the renin-angiotensin axis is definitely implicated in glucose regulation, ACE inhibitors and ARBs have also been shown to improve glucose homeostasis and prevent diabetes in heart failure patients, [42, 43].

Mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, block receptors that bind aldosterone and, with different degrees of affinity, other steroid hormone receptors (e.g., corticosteroid, androgen). This pharmacological activity makes MRAs effective in treating hypertension, particularly resistant hypertension, and in reducing the risk of morbidity and mortality among patients with systolic heart failure [44, 45].

It has been shown that spironolactone may affect glucose and lipid homeostasis. Spironolactone was shown to impair glucose tolerance and to increase glycated hemoglobin (HbA1c) [46, 47]. The potential cause of this negative effect is that spironolactone increases cortisol levels through its blockade of the glucocorticoid receptors. In contrast to spironolactone, the selective mineralocorticoid receptor blocker eplerenone has a very low activity on other steroid receptors and does not affect plasma levels of cortisol or HbA1c [48]. A recent systematic review of the impact of MRAS on glucose homeostasis has indeed confirmed that spironolactone may induce disease-specific and modest alterations on glycemia, while eplerenone did not seem to influence glycemia [49]. Further prospective studies might provide insight onto the effects of MRAs on glucose metabolism and their clinical implications.

Spironolactone may also have adverse effects on serum lipoprotein levels by increasing low-density lipoprotein (LDL) cholesterol and decreasing high density lipoprotein (HDL) cholesterol [50].

Angiotensin receptor-neprilysin inhibitors (ARNI)

ARNI are a combination of an ARB and a neprilysin inhibitor, which are enzymes that degrade na-

triuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides [51]. In the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial, the first approved ARNI sacubitril-valsartan was proven superior to the ACE-inhibitor enalapril in reducing the risks of death and of hospitalization for heart failure in symptomatic patients with heart failure with a reduced ejection fraction (HFrEF) [52]. The initiation of sacubitril-valsartan therapy also led to a greater reduction in the N-terminal-prohormone B-type natriuretic peptide (NT-proBNP) concentration compared to enalapril therapy among patients with HFrEF who were hospitalized for acute decompensated heart failure [53].

A recent study confirmed that treatment with sacubitril-valsartan improves insulin sensitivity and leads to a metabolic benefit in patients with obesity and hypertension and supports the relevance of neprilysin inhibition along with angiotensin 1-receptor blockade in the regulation of human glucose and lipid metabolism [54]. In paradigm-HF trial, sacubitril-valsartan did not reduce the prespecified exploratory outcome of new onset diabetes in comparison with enalapril, although the number of patients with new-onset diabetes during the course of the trial was very small [55]. In a post-hoc analysis of the PARADIGM-HF trial, patients with diabetes and HFrEF who received sacubitril-valsartan had a greater long-term reduction in HbA1c than those receiving enalapril. These data suggest that sacubitril/valsartan might enhance glycemic control in patients with diabetes and HFrEF [55].

I_f-channel inhibitor

Elevated heart rate is a significant marker for mortality and morbidity in cardiovascular disease including heart failure [56, 57]. Ivabradine is a new therapeutic agent that selectively inhibits the I_f current in the sinoatrial node, providing heart rate reduction. A randomized clinical trial demonstrated the efficacy of ivabradine in reducing the composite endpoint of cardiovascular death or heart failure hospitalization among symptomatic patients with HFrEF who are in sinus rhythm with a resting heart rate of ≥70 beats per minute [58]. The benefit of ivabradine was driven by a reduction in heart failure hospitalization.

Myocardial cellular energy reserve is inversely associated with heart rate [59]. At high heart rates, myocardial oxygen requirement is increased whereas the time available for perfusion, which occurs predominantly during diastole, is reduced potentially causing myocardial ischemia [60]. Heart rate reduction may therefore have a role in preserving myocardial energy levels and preventing myocardial ischemia. In an experimental study, heart rate reduction by ivabradine selectively reduced heart rate while preserving myocardial energy substrate metabolism [61]. In another animal study, ivabradine reduced infarct size independently of a reduction in heart rate and improved ventricular cardiomyocyte viability, possibly by reducing mitochondrial reactive oxygen species formation, increasing ATP production and calcium retention capacity [62].

Diuretics

Diuretics are recommended to reduce the signs and symptoms of congestion in patients with heart failure [3]. Diuretics inhibit the reabsorption of sodium or chloride at specific sites in the renal tubules. Loop diuretics have emerged as the preferred diuretic agents for use in most patients with heart failure. Thiazide diuretics may be considered in hypertensive patients with heart failure and mild fluid retention because they confer more persistent antihypertensive effects [63].

Thiazide diuretics may cause several vascular and metabolic abnormalities that increase cardiovascular risk. They do not reduce oxidative stress, improve endothelial function, or prevent the expression of pro-atherogenic molecules [64]. Thiazide diuretics can impair glucose tolerance and increase the potentially atherogenic serum low-density lipoprotein (LDL) cholesterol fraction and triglycerides [65]. They worsen insulin resistance and deteriorate lipoprotein metabolism [66, 67].

Loop diuretics are known to increase renal calcium losses compensated for by a parathyroid hor-

mone-dependent increase in 1,25-dihydroxy vitamin D levels [68]. Treatment with furosemide or bumetanide may cause hypocalcemia, resulting in elevation of parathyroid hormone. The increased concentration of alkaline phosphatase may indicate accelerated bone remodeling [69].

The principal adverse effects of diuretics include electrolyte and fluid depletion, as well as hypotension and increased blood urea nitrogen [63]. The diuretic-induced loss of salt and water activates several hormonal systems such as vasopressin, the renin-angiotensin-aldosterone system or the sympathetic nervous system[70]. Diuretics also cause the depletion of potassium and magnesium, which can predispose patients to serious cardiac arrhythmias [71].

Sodium–gucose cotransporter-2 inhibitors

Clinical trials involving patients with type 2 diabetes mellitus have shown that inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of hospitalization for heart failure. DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial evaluated the efficacy and safety of the SGLT2 inhibitor dapagliflozin in patients with heart failure and a reduced ejection fraction, and showed that the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes [72].

Sodium-glucose cotransporter-2 is selectively expressed in the human kidney, where it causes reabsorption of a large proportion of filtered glucose [73]. Inhibition of SGLT2 decreases renal glucose reabsorption causing increased glycosuria with related metabolic and hemodynamic consequences. The metabolic effects of SGLT2 inhibitors are due to relative plasma glucose deficiency which triggers lipolysis in adipose cells and fatty acid oxidation and ketone body synthesis in the liver [74]. The hemodynamic effects of SGLT2 inhibitors are secondary to increased diuresis resulting in reduction in plasma volume and blood pressure 74. In addition, SGLT2 inhibitors also exert beneficial effects on renal function, myocardial metabolism, ion transporters, fibrosis, adipokines, and vascular function [75-77]. As a result, SGLT2 inhibitors not only improve glycemic control in patients with type 2 diabetes, they also improve long-term cardiovascular and renal outcomes in patients with and without diabetes [72, 75-77].

Glucagon-like peptide 1 (GLP-1) agonists

Apart from SGLT-2 inhibitors, several new drug classes have emerged as efficacious anti-diabetic agents. These include the incretin-based therapies: dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) agonists [78]. A recent meta-analysis showed that the use of SGLT-2 inhibitors or GLP-1 agonists was associated with lower mortality than DPP-4 inhibitors or placebo or no treatment [79]. Use of DPP-4 inhibitors was not associated with lower mortality than placebo or no treatment [79]. Incretin based treatments and SGLT-2 inhibitors are recommended in people with type 2 diabetes not achieving target glycemic control with metformin [80].

Glucagon-like peptide-1 (GLP-1) is released from gut enteroendocrine cells and controls meal-related changes in plasma glucose levels through augmentation of insulin and inhibition of glucagon secretion [81]. Thus, GLP-1 agonists improve postprandial glycemia and overall glycemic control [82]. In addition to the glucose-lowering effect, GLP-1 agonists activate brown fat and decrease lipid storage via direct modulation of adipocyte metabolism [83]. They decrease insulin resistance and promote weight loss through delayed gastric emptying and appetite suppression [84]. The GLP-1 analog, liraglutide, has been approved for the treatment of obesity [85].

GLP-1 agonists were also shown to lower liver inflammation, ameliorate nonalcoholic fatty liver disease, and protect from diabetes-related kidney dysfunction [86]. They also lower blood pressure, improve cardiovascular function, and prevent cardiovascular disease and mortality [87]. Cardiovascular benefits of GLP-1 analogs could be influenced by direct actions of these medications on the cardiovascular system or indirectly through intermediary actions on metabolism, energy transfer, inflammation or thrombosis [88]. GLP-1 agonists have also been suggested to reduce generation of reactive

oxygen species [89], decrease the levels of the inflammatory cytokines, increase the levels of the anti-inflammatory adipokine adiponectin, and reduce the frequency of inflammatory macrophages [90]. Furthermore, GLP-1 receptor agonists inhibit platelet function and prevent thrombus formation [91]. All these ancillary mechanisms definitely extend the beneficial effects of these drugs well beyond their primary glucose lowering action as possible contributors to their cardioprotective effects. New clinical experimental studies to address the mechanisms of vascular action of the various members of this drug class should be encouraged.

Acetylsalicylic acid

Acetylsalicylic acid (aspirin) inhibits platelet function by acetylation of the platelet cyclooxygenase, resulting in an irreversible inhibition of platelet-dependent thromboxane formation [92]. Aspirin reduces vascular events and improves long-term prognosis in patients with ischemic heart disease [93]. Apart from its principal antithrombotic therapeutic effect, aspirin also reduces circulating free fatty acids and triacylglycerols [94]. These changes in lipid metabolism are consistent with the reported inhibitory effects of salicylates on peripheral lipolysis [95] and liver fatty acid synthesis [96]. These metabolic effects can potentially be explained by the observation that aspirin may directly activate adenosine monophosphate-activated protein kinase (AMPK), a central regulator of cell growth and metabolism [97]. AMPK is a key regulator of metabolism: its activation determines the phosphorylation of numerous metabolic enzymes, acutely decreasing anabolic pathways that consume ATP, such as fatty acid, triacylglycerol, phospholipid, and protein biosynthesis, while activating catabolic pathways that generate ATP, such as glucose uptake and fatty acid oxidation [98].

Aspirin has also been shown to inhibit activation of the transcription factor nuclear factor-kappa B (NF-kappa B) [99]. Nuclear factor-κB (NF-κB) represents a family of inducible transcription factors, which regulates a large array of genes involved in different processes of the immune and inflammatory responses [100]. More recently, aspirin has been shown to improve glucose tolerance due to a combination of its anti-inflammatory properties and enhanced nitric oxide levels which facilitates insulin signaling and energy utilization in target tissues [101].

Statins

There is a wealth of evidence that hydroxymethyl glutaryl-coenzyme A reductase inhibitors (statins) lower cholesterol levels and reduce vascular events and death in patients with atherosclerotic cardiovascular disease[102-104]. Despite significant statin-induced improvement in endothelial function and decreases in circulating pro-inflammatory markers, statins either do not alter insulin sensitivity or may actually promote insulin resistance[105]. Overall, statin therapy is associated with a slightly increased risk of development of diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events 106. Statins do not appear to demonstrate a 'class effect' on insulin sensitivity and development of diabetes. Differences between individual statins likely exist, with pravastatin decreasing the risk[107] and other statins including simvastatin [105], atorvastatin[108], and rosuvastatin[109] increasing in the risk of development of diabetes. This may be due to the "off-target" effects of some statins to cause insulin resistance by diverse mechanisms unrelated to endothelial dysfunction. Indeed, there is evidence of other differential metabolic actions of distinct statins including effects on glucose transport, insulin secretion, and insulin resistance [107].

Cholesterol is the principal compound of all steroid hormones, including androgens and estrogens. Statins, by reducing cholesterol levels, may impact the capacity of steroidogenic tissues to produce adrenocortical hormones and sex steroids. A meta-analysis of placebo-controlled randomized trials suggests that statins lower serum concentration of testosterone [110]. The magnitude of the decrease in testosterone levels is directly proportional to the dosage of statin therapy and duration of treatment [111]. The clinical relevance of this association needs further investigation, especially that lower levels of endogenous testosterone have been associated with a higher risk of developing

atherosclerosis [112].

In contrast, statins do not appear to affect serum estrogen concentrations. In a study of menopausal women with hyperlipidemia, pravastatin lowered lipid levels without decreasing endogenous estrogen levels [113]. Another study showed that long-term administration of statins had no effect on serum estrogen levels in postmenopausal women irrespective of whether they were receiving or not receiving oral estrogen therapy [114].

Specific Metabolic Drugs

Given the above-described metabolic derangements and the difficulty of standard treatment to control the symptomatic and prognostic burden in patients with heart failure, pharmacological manipulation of cardiac energy metabolism could be considered as an adjunctive therapeutic option [115]. Stimulation of myocardial glucose oxidation may improve cardiac energy metabolism and can be achieved either directly with stimulation of glucose metabolism, or indirectly through inhibition of fatty acid beta-oxidation. Several pharmacological agents have been shown to optimize cardiac energy metabolism and may be considered as potential therapeutic options in heart failure.

Trimetazidine. Trimetazidine is a piperazine derivative drug with a primary metabolic mechanism of action which has been reported to exert several beneficial effects in patients with cardiac conditions including heart failure. The main mechanism of action of trimetazidine is related to inhibition of the long-chain 3-ketoacyl CoA thiolase activity, the last enzyme involved in beta-oxidation, which results in a reduction in fatty acid oxidation and a stimulation of glucose oxidation [116]. By inhibiting fatty acid oxidation, trimetazidine stimulates total glucose utilization, including both glycolysis and glucose oxidation [4]. The effects of trimetazidine on glucose metabolism could therefore improve peripheral glucose extraction and utilization and the overall myocardial energy metabolisglucosem [117, 118]. Trimetazidine has also been shown to reduce membrane damage induced by oxygen free radicals in human red cells [119] and to reduce endothelin-1 release in patients with coronary artery disease[120].

Trimetazidine is a clinically effective antianginal agent that has no negative inotropic or vasodilator properties [116] and has beneficial effects in heart failure. We have previously demonstrated that trimetazidine improves left ventricular systolic function and exercise tolerance in patients with heart failure [121] and that these effects are associated with an increase in the cardiac phosphocreatine and adenosine triphosphate (PCr/ATP) ratio, indicating preservation of the myocardial high-energy phosphate levels [122]. Trimetazidine has also been shown to improve left ventricular function, symptoms, glucose metabolism, and endothelial function in patients with diabetes and ischemic cardiomyopathy [123] and to improve prognosis in patients with heart failure of different etiologies [124, 125]. It has therefore been advocated that trimetazidine may be included in the guidelines dealing with heart failure [126].

Ranolazine. Ranolazine is another piperazine derivative that reduces anginal symptoms by preventing ischemia-induced sodium and calcium overload in myocardial cells through the inhibition of the late phase of the inward sodium current ($I_{Na,late}$) during cardiac repolarization [127-129]. In addition to its antianginal actions, ranolazine may possess antiarrhythmic activity by suppressing early afterdepolarizations and reducing transmural dispersion of repolarization [129]. Thus, this drug is commonly used to treat stable angina pectoris or to suppress arrhythmia [130-132]. Ranolazine may also affect active relaxation and passive diastolic compliance [133] and improve cardiac diastolic dysfunction through modulation of myofilament calcium sensitivity [134]. The MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary-Thrombolysis In Myocardial Infarction 36 trial demonstrated the efficacy of ranolazine in reducing adverse outcomes in high-risk patients with acute coronary syndromes identified by increased B-type natriuretic peptide (BNP) level [135].

In contrast to other antianginal drugs, ranolazine appears to act via a non-hemodynamic mechanism [136]. It has therefore been proposed that ranola-

zine may act as a metabolic modulator [137]. The metabolic mechanism of action of ranolazine is the partial inhibition of fatty acid oxidation that determines an increase in glucose oxidation, with a subsequent shift in substrate utilization (from fatty acid to glucose), which reduces the cardiac oxygen supply needed to support a given level of myocardial work [138]. In an experimental rat model, the beneficial effects of ranolazine in cardiac ischemia/reperfusion was shown to be due, at least in part, to a stimulation of glucose oxidation and a reduction in fatty acid oxidation, allowing improved ATP production per oxygen consumed and reduction in the build-up of protons, lactate, and harmful fatty acyl intermediates [139]. In patients with cardiovascular disease and diabetes, ranolazine was shown to lower plasma glucose and glycated hemoglobin (HbA_{1C}) concentrations [140, 141]. The exact mechanism by which ranolazine improves glycemic control is not understood; however, it is proposed to inhibit glucagon secretion, increase insulin secretion, and preserve pancreatic β-cell function [141, 142].

Carnitine palmitoyl transferase I (CPT-I) inhibitors. Etomoxir, perhexiline and oxfenicine are CPT-I inhibitors. CPT-I is the key enzyme for the transfer of long-chain fatty acids into the intramitochondrial matrix. Its inhibition, therefore, reduces fatty acid oxidation and their inhibitory effect on pyruvate dehydrogenase. As a result, glucose oxidation is increased[143, 144]. Etomoxir, initially developed as an anti-diabetic agent, has been observed to improve left ventricular performance of pressure-overloaded rat hearts[145]. These effects have been considered due to a selective modification of gene expression of hypertrophic cardiomyocytes[146]. Etomoxir could also increase phosphatase activation, have a direct effect on peroxisome proliferator activated receptor-alpha and up-regulate the expression of various enzymes involved in fatty acid beta-oxidation[146]. The first clinical trial employing etomoxir in patients with heart failure showed a significant improvement in cardiac function[147]. In experimental animal studies, etomoxir has also been shown to improve glucose metabolism[148], but its use may be limited by the observation that it may cause cardiac hypertrophy[149], oxidative stress[150] and increased liver transaminase levels[151].

Analogously to etomoxir, oxfenicine and perhexiline, originally classified as calcium antagonists, reduce cardiac utilization of long chain fatty acids by inhibiting CPT-I [152-155]. They have been initially developed as anti-anginal agents [156]. However, they have been subsequently employed in patients with heart failure [157]. Metabolic modulation with perhexiline has been shown to improve maximal oxygen consumption (VO2 max), left ventricular ejection fraction, symptoms, resting and peak stress myocardial function, and skeletal muscle energetics [157]. Perhexiline was also shown to improve cardiac energetics and symptom status in heart failure due to dilated cardiomyopathy with no evidence of altered cardiac substrate utilization [158]. However, perhexiline was reported to cause hepatotoxicity and peripheral neuropathy [159, 160]. Thus, while CPT-I inhibitors could provide an important ancillary metabolic and functional effect in patients with heart failure, their potential toxicities at present limit their routine clinical use.

Vitamin D. Preclinical studies indicated multiple pathways through which vitamin D may affect cardiovascular function and the risk for heart failure[161]. Vitamin D receptor is expressed in the cardiovascular system and is increased in the hypertrophic heart[162]. Experimental studies showed that vitamin D receptor activator paricalcitol prevents fibrosis and diastolic dysfunction in a murine model of pressure overload[163]. Epidemiological studies showed that vitamin D deficiency is associated with incident cardiovascular disease[164, 165], leftventricular dilation[166] and the risk of heart failure[167, 168]. While substantial observational evidence has associated low vitamin D status with the risk of heart failure, ventricular remodeling, and clinical outcomes in heart failure, prospective trials powered for clinical outcomes are lacking[161]. There is therefore insufficient data to recommend routine assessment or supplementation of vitamin D for the prevention or treatment of heart failure[161].

Nonetheless, vitamin D appears to be implicated in the regulation of glucose metabolism[169]. vitamin D receptor is present in most tissues and cells, including pancreatic β-cells[170]. 1,25-Dihy-

droxy vitamin D3 may have a direct protective effect on β-cells, contributing to prevention of diabetes[171]. Vitamin D deficiency impairs glucose -stimulated insulin secretion and increases insulin resistance[172]. Supplementation with 1,25-dihydroxyvitamin D improved free fatty-acid-induced insulin resistance in muscle cells[173]. However, whereas vitamin D deficiency has been associated with the risk of diabetes [168, 174], vitamin D supplementation has not been consistently shown to improve glycemic control[169, 175].

Psychotropic drugs. Over 1 in 6 community-based patients with heart failure suffers from depression[176]. In longitudinal studies, people with severe mental illnesses such as schizophrenia, bipolar disorder and major depressive disorder had significantly higher incidence of cardiovascular disease[177]. The incidence was also higher for coronary heart disease, cerebrovascular disease and congestive heart failure[177]. People with severe mental illnesses also have worse physical health and reduced life expectancy compared to the general population [178] and are at increased risk of cardiovascular disease related death[177]. The excess cardiovascular mortality associated with schizophrenia and bipolar disorder is attributed in part to an increased risk of the modifiable coronary heart disease risk factors; obesity, smoking, diabetes, hypertension and dyslipidemia[178].

Psychotropic medications can induce weight gain or worsen other metabolic cardiovascular risk factors[178]. Although, psychotropic drugs do not strictly belong to a specific cardiovascular drug class, clinical cardiologists should be aware of their potential interference with energy metabolism, considering their widespread use in cardiac patients. Both antidepressant and antipsychotic drugs may adversely affect global energy metabolism.

Antidepressants may induce alterations of glucose metabolism, and some antidepressants such as amitriptyline, mirtazapine, and paroxetine are associated with a greater risk of weight gain which may contribute to insulin resistance [179]. The mechanisms underlying this association are poorly defined. The noradrenergic nortriptyline and selective serotonin reuptake inhibitors have been reported to worsen glycemic control in diabetic patients [180, 181], whereas tricyclic antidepressants induce hyperglycemia in humans[182] and hyperinsulinemia in mice[183].

Both first- and second-generation antipsychotics, may determine various metabolic dysregulations. Antipsychotic-induced weight gain is considered as an indirect pathway to development of glucose intolerance via progressive peripheral insulin resistance and decreases in insulin secretion[184]. The risk of new-onset type 2 diabetes mellitus is particularly increased with second-generation antipsychotics treatment[85]. Experimental studies on cultured cell models of adipocytes showed that second-generation antipsychotics directly induce insulin resistance and alter lipogenesis and lipolysis in favor of progressive lipid accumulation and adipocyte enlargement. These effects of second-generation antipsychotics on adipocytes could explain, in part, the association of second-generation antipsychotics with weight gain and diabetes[186]. The atypical antipsychotic clozapine has been reported to be associated with metabolic adverse effects, including type-2 diabetes mellitus[187].

Some antipsychotic medications are associated with proatherogenic conditions including insulin resistance and dyslipidemia. In particular, olanzapine and clozapine have been consistently demonstrated to promote insulin resistance and dyslipidemia[188]. Ziprasidone and amisulpiride may be associated with more favorable metabolic effects[188]. The mechanism by which anti-psychotic drugs bring about dyslipidemia is poorly understood. These drugs have been shown to increase lipogenesis, reduce lipolysis and enhance the antilipolytic effects of insulin in adipocytes. This has the net effect of lipid accumulation in adipocytes[188].

On this basis, and considering the metabolic risk associated with psychotropic medications, healthcare providers should be aware of the potential changes in glucose and lipid metabolism in their patients. Appropriate clinical and laboratory monitoring will reduce the incidence of adverse events in patients at risk. This allows for a more optimized treatment selection in patients predisposed to cardiovascular disease.

CONCLUSIONS

Heart failure is associated with changes in global and cardiac metabolism. Metabolic derangements in heart failure include progressive impairments in myocardial substrate utilization and a shift from fatty acids to glucose oxidation as the predominant source of myocardial energy production. The failing myocardium is also characterized by decreased oxidative phosphorylation, decreased high-energy phosphate content, generation of reactive oxygen species, and mitochondrial dysfunction. On the systemic level, heart failure is characterized by insulin resistance, impaired glucose oxidation, impairments in beta-oxidation of fatty acids and metabolic imbalance between catabolism and anabolism. Most medications routinely used for the treatment of patients with heart failure yield ancillary effects on cardiac and/or global metabolism. These effects can either be beneficial or detrimental and should be well understood and known by all providers managing patients with heart failure. On the other hand, pharmacological modulation of cardiac energy metabolism may be considered as a potential adjunctive therapeutic option in heart failure.

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