Inhibition of Fatty Acid Oxidation to Treat Heart Failure in Patients

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Abstract Heart failure is a major cause of morbidity and mortality in the world. Cardiac energy metabolism, specifically fatty acid and glucose metabolism, is altered in heart failure and has been considered a contributing factor in the impaired heart function observed in patients with heart failure. Emerging evidence demonstrates that correcting these changes in energy metabolism by modulating mitochondrial oxidative metabolism may be effective treatment for heart failure. Promising strategies include the downregulation of fatty acid oxidation and increased coupling of glycolysis to glucose oxidation. Fatty acid β-oxidation enzymes carnitine palmitoyl transferase I and pyruvate dehydrogenase kinase are examples of metabolic targets for the treatment of heart failure. This article reviews the existing evidence for inhibition of fatty acid oxidation to treat heart failure. Further studies are needed to confirm the potential benefit of modulating these metabolic targets as an approach to treating heart failure in clinical settings.

Keywords Fatty acid • Oxidation • Heart failure • Treatment

1 Introduction

To preserve normal cardiac ejection, the myocardium requires more energy than do other tissues. Under the normal state, the major source of adenosine triphosphate (ATP) production is fatty acid oxidation (FAO), and others come from glucose and some amino acids. When heart failure occurs, the myocardial energy metabolism appears abnormal, which includes the downregulation of glucose and FAO,

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dependent more on glucose as its preferential substrate [1, 2]. In the early stage of heart failure, the abnormality may be inconspicuous; an animal experiment found that moderate or severe heart failure exhibited normal myocardial FAO [3]. This situation may be caused by elevated fatty acid concentration in heart failure. As failure progresses, mitochondrial oxidative metabolism is reduced and glycolysis is increased with the downregulation of glucose and FAO, and the shift of the preferential substrate is more significant. Considering that fatty acids are an inefficient energy substrate as compared with glucose, theoretically requiring 11–12 % more oxygen for identical ATP produced as carbohydrates [1], the change may be an important compensatory or protective mechanism for heart failure [4], which would improve "energy starvation". The decrease in FAO and increase in glycolysis observed in pressure-overload hypertrophied hearts is accompanied by changes in expression and activity of metabolic enzymes involved in these pathways.

Because of insufficient energy metabolism in heart failure, the modulation of cardiac metabolism may be a new approach to the treatment of heart failure. One important strategy is inhibition of FAO, which modifies fatty acid β-oxidation, decreases levels of circulating fatty acids, and increases the utilization of glucose. The pathway of fatty acid metabolism includes many enzymes, with gene transcription perhaps controlled by peroxisome proliferator-activated receptor (PPAR) and regulated by the sympathetic nerve. So FAO can be inhibited in many ways and used to treat heart failure (Fig. 1).

2 Inhibitors of FA Beta-Oxidation

2.1 Trimetazidine

Trimetazidine (TMZ) is a piperazine derivative (1-(2,3,4-trimethoxybenzyl)-piperazine dihydrochloride) that optimizes energy metabolism presumably by partial inhibition of long-chain 3-ketoacyl CoA thiolase (3-KAT), with subsequent decrease in FAO and stimulation of glucose oxidation [5]. TMZ can relieve angina pectoris in patients with coronary artery disease [6–11], and these benefits do not depend on the change in heart rate, blood pressure [10], and rate-pressure product at rest, during submaximal and peak exercise [9, 11]. Some clinical trials have demonstrated the effect of TMZ in heart failure, including ischemia or nonischemia. One trial of 50 patients with ischemic cardiomyopathy indicated that in addition to conventional treatment, TMZ could improve exercise tolerance, reduce the plasma bone natriuretic protein (BNP) and cardiac troponin T levels without improving New York Heart Association (NYHA) class and left ventricular ejection fraction (LVEF) after 6-month follow-up [12]. Some other studies demonstrated that TMZ could improve NHYA class, LVEF, endothelium-dependent relaxation, and quality of life; prolong 6-min walk distance; increase cardiac phosphocreatine and adenosine triphosphate (PCr/ATP) ratio; and even reduce all-cause mortality and heart-failure hospitalization mortality [13–18]. In patients with diabetes and idiopathic dilated

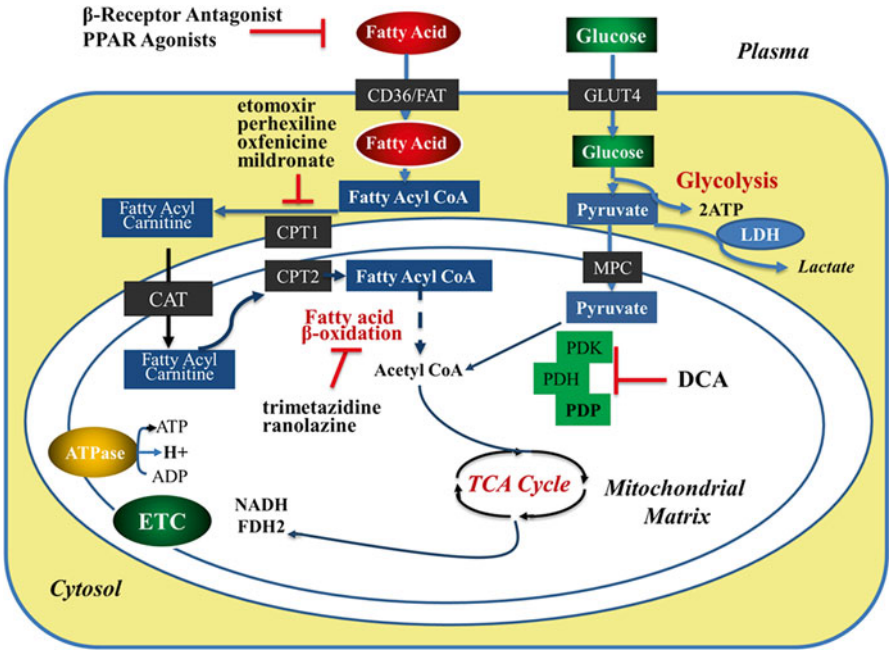

Fig. 1 Inhibition of fatty acid oxidation for the treatment of heart failure. β-Adrenoreceptor antagonists and peroxisome proliferator-activated receptor (PPAR) agonists decrease the level of circulating fatty acids. Carnitine palmitoyltransferase I (CPT-1) inhibitors decrease fatty acid β-oxidation and increase glucose oxidation by decreasing fatty acid transport into the mitochondria. Trimetazidine and ranolazine can directly inhibit fatty acid β-oxidation. Dichloroacetate (DCA) increases glucose oxidation by inhibiting pyruvate dehydrogenase kinase (PDK) activity, thereby stimulating pyruvate dehydrogenase (PDH)

cardiomyopathy, TMZ could also significantly improve cardiac function and physical tolerance [19–21]. At the same time, in patients with TMZ, inflammatory response was decreased [21]. Especially, LVEF was greater in diabetic than nondiabetic patients [22]. Although some trials provided encouraging results, some controversies remained. To solve the problem of inconsistent results of different clinical trials, Gao et al. and Zhang et al. contributed to meta-analyses in 2010 and 2012, respectively [23, 24]. The two integrated analyses suggested that TMZ improves LVEF, improves subjective and objective measures of functional status in heart failure, simultaneously ameliorates LV remodeling, and reduces hospitalization. Zhang et al. noted a significant association of gender and LVEF improvement. Otherwise, there were some disputes on all-cause mortality.

TMZ may contribute to the shift of energy production from free fatty acids (FFAs) to glucose oxidation, preservation of intracellular levels of phosphocreatine and ATP; reduction of cell acidosis, calcium overload and free radical-induced injury, and cardiac fibrosis; and improvement of endothelial function, which benefit heart failure. However, direct measurement of cardiac FAO in patients with chronic

non-ischemic heart failure revealed no changes in FFA uptake and only a 10 % decrease in FAO with TMZ. This finding challenges the concept that the beneficial effect of TMZ is mediated primarily by FAO inhibition [25]. Otherwise, researchers demonstrated that TMZ did not inhibit any component of β-oxidation in an isolated human cardiomyocyte cell line in 2003 [26]. Recently, some evidence indicated that the benefits of TMZ also came from its effect on the whole metabolism modulation. According to Fragasso and Tuunanen [18, 19], TMZ reduced the whole-body resting energy expenditure, regardless of the etiology and diabetic status of heart failure, reduced the cardiac FFA oxidation and improved whole-body insulin sensitivity in heart failure without diabetes. These data suggest that the metabolic effect of TMZ may also take place in other organs and tissues, to reduce the whole-body energy demand. Then, the improvement in insulin resistance, which contributes to the development of LV dysfunction by reducing cardiac efficiency through a metabolic shift toward fatty acid utilization would also decrease whole-body FFA oxidation.

An increasing number of studies have indicated that the cardioprotective effect of TMZ may occur via different mechanisms possibly involving regulation of mitochondrial function. In hypertrophied hearts, TMZ normalized post-ischemic function and fractional glucose oxidation via inhibiting glycolysis, possibly in response to reduced energy reserve and/or low rates of FAO. In ischemia-reperfusion, TMZ could decrease the infarct size of myocardium as with ischemia preconditioning, whose cardioprotective effect was represented by inhibiting mitochondria permeability transition pore (mPTP) opening, a critical event leading to cell death [27]. In myocytes of the failing heart, mPTP opening could also be antagonized by TMZ, which benefitted heart failure related to reduced complex II- and uncoupled oxidative stress mediated by mitochondrial nitric oxide synthase [25]. In a rat model *of ex vivo* perfusion with glucose, TMZ had a positive impact on mitochondrial homeostasis, which significantly increased the respiration control rate and respiratory chain complex I activity, thus leading to decreased reactive oxygen species (ROS) production, maintained mitochondrial electrical potential, and improved mitochondrial membrane integrity [28]. These effects may be attributed to the antioxidation of TMZ. When acute ischemia occurs, the positive effects of TMZ occur by increasing complex I activity, with decreased futile O_2 consumption and reduced ROS production, rather than depending on an increase in ATP production.

2.2 Ranolazine

Ranolazine is similar to TMZ, a piperazine derivative, ((±)-N-(2,6-dimethyl-phenyl-4-[2-hydroxy-3-(2-methoxy-phenoxy)-propyl]-1-pi-perazine acetamide; RS-43285)) [37]. It is an anti-ischemia drug and approved in the United States and some European countries for treatment, combined with amlodipine, beta-blockers or nitrates, of chronic stable angina in patients [29]. Some clinical evidence has demonstrated that ranolazine could improve ischemia symptoms and quality of life of patients with chronic stable or severe angina; it increased the exercise capacity,

time to angina and time to ≥1-mm ST-segment depression, and reduced angina frequency without clinically meaningful hemodynamic effects [30–34]. In non–ST-elevated acute coronary syndrome, ranolazine could increase exercise duration, reduce worsening angina and the incidence of arrhythmias, and thus decrease the risk of cardiovascular death, myocardial infarction and recurrent ischemia with elevated BNP accompanied by acute coronary syndrome [34–39]. Ranolazine has benefits in anti-ischemia, but the mechanism is not completely clear. One proposed mechanism is metabolic modulation. *In vitro* studies suggested that ranolazine inhibits FAO in skeletal muscle, and in isolated working rat hearts, ranolazine stimulated glucose oxidation, which may be a primary effect and concomitantly decrease FAO. This metabolic modulation would have some advantages for cells exposed to conditions of oxygen limitation or heart failure, including increased efficiency of ATP production, reduced production of lactate and H+, and reduction of other adverse effects from increased fatty acid metabolites. In guinea-pig hearts during low-flow ischaemia, ranolazine could improve pyruvate dehydrogenase activity, which was inhibited by global low-flow ischaemia [40]. Subsequent studies indicated no effects of ranolazine on pyruvate dehydrogenase kinase or phosphatase or on pyruvate dehydrogenase catalytic activity, which suggests that ranolazine activates pyruvate dehydrogenase indirectly [41]. Some evidence supported ranolazine attenuating calcium overload and ROS generation, thus preserving mitochondrial function [42, 43]. Therefore, ranolazine should partially inhibit β-oxidation, but the main mechanism does not appear to be through inhibition of myocardial FAO.

A few reports have described the effects of ranolazine on human metabolism. In the MERLIN TIMI-36 trial, ranolazine improved hyperglycemia control, with lower haemoglobin A1c level and fasting plasma glucose in diabetic patients [44, 45]. A few registered clinical trials have studied the effect of ranolazine in heart-failure patients, but most are not completed, and the results of the complete RALI-DHF trial have not been published [46]. However, animal experiments have given some inspiring results. Studies of acute intravenous infusion of ranolazine previously indicated improved LVEF, LV end-diastolic pressure (LVEDP), LV end-systolic volume, stroke volume, and cardiac output without an increase in myocardial oxygen consumption and thus improve mechanical efficiency in dogs with chronic heart failure [47, 48]. Another study of long-term ranolazine monotherapy in dogs with heart failure demonstrated significantly decreased LVEDP, accompanied by increased LVEF, stroke volume, and cardiac index [49].

2.3 Dichloroacetate

Dichloroacetate (DCA) inhibits pyruvate dehydrogenase (PDH) kinase activity, thereby stimulating PDH and carbohydrate oxidation, the rate-limiting enzyme of glucose oxidation. DCA treatment could increase glucose uptake and cardiac energy reserves and ameliorate chronic heart failure [50]. When DCA was administered intravenously for 30 min, myocardial lactate consumption and forward stroke

volume were elevated, myocardial oxygen consumption was reduced, and LV mechanical efficiency was improved in heart failure patients with NYHA functional class III–IV [51]. However, another clinical trial demonstrated that intravenous infusion of DCA with the same dose over 15 min did not significantly protect heart-failure patients with LVEF ≤ 40 %, which increased LV diastolic and systolic volumes and did not increase LVEF and stroke volume significantly [52]. Recently, some data suggested that DCA may be useful for treating pulmonary hypertension by increasing the mitochondria-dependent apoptosis of pulmonary artery smooth muscle cells and right ventricular failure.

3 Carnitine Palmitoyltransferase/Carnitine System Inhibitors

The rate-limiting enzyme for fatty acid β-oxidation and thus a potential drug target for regulating mitochondrial fatty acid uptake is carnitine palmitoyltransferase (CPT). Drugs targeting CPT-1 include etomoxir, an irreversible CPT-1 inhibitor; perhexiline; oxfenicine; and mildronate.

3.1 Etomoxir

Carnitine palmitoyltransferase 1(CPT-1) is the first limiting-rate enzyme for mitochondrial β-oxidation of long-chain fatty acids, which is located on the outer membrane of mitochondria. Etomoxir is a CPT-1 inhibitor.. This inhibition of mitochondrial CPT-1 is common to a number of oxirane carboxylic acid derivatives and is both irreversible and stereospecific. Etomoxir has been developed for treating diabetes mellitus type 2 but has been rarely explored for heart failure. A small clinical trial of heart-failure patients with NYHA class II-III indicated that etomoxir had neither a positive inotropic effect nor vasodilatory properties in acute studies; however, long-term treatment with etomoxir reduced resting heart rate, elevated LVEF, with increased CO and stroke volume during exercise [53]. However, in the ERGO study, etomoxir induced unacceptably high liver transaminase levels, which caused premature study termination. Then, according to the ERGO data, etomoxir produced no improvement of 6-min corridor walk test or echocardiographical values [54]. Long-term etomoxir treatment improved the performance of the hypertrophied ventricle in rats with ascending aorta constriction, including increased maximal developed pressure, LV pressure-volume area, and ±dP/dt(max) [55]. Yet, in a similar animal experiment with shorter treatment time and smaller drug dose, etomoxir could not affect cardiac function *in vivo* but improved function associated with a substrate switch in the isolated heart [56]. This evidence suggested that the effects of etomoxir on heart failure were still indistinct, and the effectiveness and safety required further investigation. In isolated working hearts with ischemia-reperfusion,

low-dose etomoxir decreased long-chain acylcarnitine and long-chain acyl-coenzyme A (CoA) levels but did not prevent depressed function. In contrast, a high dose of etomoxir prevented the palmitate-induced depression of function but did not decrease myocardial long-chain acylcarnitine or long-chain acyl-CoA levels, accompanied by decreased oxygen consumption per unit work during reperfusion recovery and increased ATP and creatine-phosphate levels. Thus, the potential protection of etomoxir was unrelated to changes in levels of long-chain acylcarnitines but might be due to increased glucose use by the reperfused heart. Moreover, this CPT-1 inhibitor increased the sarcoplasmic reticulum (SR) Ca2+ uptake rate. In rats with hypertrophied hearts by aortic constriction, etomoxir could prevent the reduced SR Ca2+-ATPase (SERCA2) gene expression and thus may prevent the transition of cardiac hypertrophy into heart failure [57, 58].

3.2 Perhexiline

Perhexiline is an antianginal agent that inhibits rat cardiac mitochondrial CPT-1 and CPT-2 levels [59]. Perhexiline inhibits FAO by reducing mitochondrial fatty acid uptake. However, in working rat hearts, perhexiline increased the efficiency of myocardial oxygen utilization by approximately 30 % without significant effects on palmitate oxidation, which suggested that the mechanism of perhexiline with improvement of myocardial efficiency was largely or entirely independent of its effects on CPT [60]. The use of this agent decreased because of the acute and chronic potential toxicity. Recently, some investigators conducted a re-evaluation of perhexiline. They collated the retrospective clinical data for patients with chronic heart failure and/or refractory angina and found that perhexiline therapy offered symptom relief for most patients, with only a small minority showing any side effects or abnormal liver function test results, and patients with refractory angina were more likely to be responders [61]. With careful plasma drug level monitoring for dose titration, perhexiline was effective and safe, with admirable results in chronic heart failure and especially refractory angina. A short-term, placebo-controlled clinical study of 56 patients with ischemic or nonischemic heart failure reported that perhexiline improved the quality of life, peak exercise oxygen consumption and LVEF [62]. However, perhexiline therapy in LV dysfunction after myocardial infarction failed to demonstrate an improvement in echocardiographical parameters and function of viable segments by dobutamine echocardiography [63]. Another clinical trial indicated that in symptomatic patients with hypertrophic cardiomyopathy, perhexiline improved diastolic dysfunction and exercise capacity and increased the myocardial ratio of phosphocreatine to ATP as measured by nuclear magnetic resonance, which is consistent with a metabolic mechanism of action [64]. Although these small clinical studies suggest that perhexiline should have beneficial effects in heart failure patients, more large-scale pivotal trials should be conducted in patients with heart failure or hypertrophic cardiomyopathy to further confirm the findings.

3.3 Oxfenicine

Oxfenicine (S-4-hydroxyphenyl glycine) is a selective inhibitor of cardiac mitochondrial CPT-1. It has not been used in human clinical studies, but some animal experiments have explored its effects on metabolism, myocardiac ischemia and heart failure. Oxfenicine could increase glucose metabolism and insulin sensitivity in mice with diet-induced obesity and insulin resistance via reduced FAO [65]. As well, early and sustained treatment with this CPTI inhibitor prevented by almost 1 week LV chamber dilation, wall thinning and delayed onset of decompensation in dogs with pacing-induced heart failure [66]. This finding is consistent with the drug's prevention of various changes in protein phenotype, especially metalloproteinase-2 and -9. In rats with diet-induced obesity, chronic oxfenicine treatment improved post-ischemic cardiac function and reduced myocardial infarct size by approximately 40 % after ischemia-reperfusion [67]. However, oxfenicine also affected myocardial hypertrophy in dogs and rats after 1 or 2 years, which might be caused by inhibition of FAO. However, 8-week administration of oxfenicine did not result in cardiac hypertrophy or contractile dysfunction in normal rats, even combined with a high-fat diet [68]. Otherwise, oxfenicine significantly blocked cell death induced by the combination of palmitate and carnitine, which suggests that oxfenicine could reduce palmitate-induced cardiac apoptosis [69].

3.4 Mildronate

Mildronate (3-(2,2,2-trimethylhydrazine)) propionate, also named THP and MET-88, could inhibit the uptake of long-chain fatty acids into mitochondria by reducing the level of carnitine biosynthesis, which is required by CPT-1, and inhibit FAO ultimately. In the mouse, long-term mildronate treatment significantly decreased carnitine concentration in plasma and heart tissue and increased the rate of insulin-stimulated glucose uptake by 35 %, accompanied by upregulated expression of related genes, including glucose transporter 4, hexokinase II, and insulin receptor proteins. These findings suggested that mildronate has benefits by decreasing FAO but also increasing glucose oxidation, prompting the shift of substrate preference. Mildronate has benefits on cardioprotection. In ischemia-reperfusion, mildronate could reduce the infarct size significantly, improve the recovery of cardiac function and decrease the incidence of ventricular fibrillation, thus preventing the accumulation of long-chain acylcarnitine induced by ischemia [70, 71]. Interestingly, mildronate did not affect cardiac function and energy metabolism without ischemia. In addition, long-term mildronate treatment attenuated the development of atherosclerosis in apoE/low-density-lipoprotein receptor double-deficient mice [72]. Mildronate prolonged survival with a median 50 % survival of 103 days as compared with 79 days for rats with heart failure following myocardial infarction as compared with control rats and attenuated the dilatation of the left ventricle and

decreased ATP level, thus preventing the increase in right atrial pressure [73]. The mildronate improvement in cardiac function in rats with heart failure induced by coronary artery ligation was attributed to increased SR Ca2+ pump activity. In LV myocardial homogenates, SERCA2 protein content was 32 % lower in the myocardial infarction group than the sham-operated group. However, in the mildronate group with myocardial infarction, SERCA2 content was the same as in the sham-operated group [74]. In another similar model, mildronate significantly prevented the decrease in Vmax for SR Ca2+ uptake activity and improved myocardial high-energy phosphate [75]. Mildronate prevented the cardiopathologic changes and reduced the increased expression of nuclear factor kBp65 induced by azidothymidine. Subsequent experiments indicated that mildronate acted at the level of complex I, mainly by reducing H_2O_2 to protect mitochondria in liver [76]. However, mildronate pre-treatment of rats at 100 or 200 mg/kg/day for 1 or 2 weeks did not prevent ischemia-reperfusion–induced mitochondrial dysfunction and liver injury [77]. Recently, mildronate was found to have beneficial effects in diabetes and neuroprotective properties. In conclusion, mildronate has greater protective action than inhibition of carnitine biosynthesis and thus would be an extremely potential drug.

4 Beta-Blocker

When heart failure occurs, β-adrenergic overdrive increases the level of circulating fatty acids, caused by enhanced fatty acid mobilization, inhibited myocardial uptake of glucose, and promoted onset of insulin resistance. Then, excess plasma fatty acid and insulin resistance could result in abnormalities of myocardial function. Therefore, an indirect therapeutic approach to inhibit FAO in the failing heart would be to reduce the circulating levels of fatty acids via a β-blocker. Long-term therapy with b-adrenergic receptor antagonists (metoprolol and carvedilol) can improve cardiac performance and survival in patients with heart failure. In cultured mouse C2C12 cells, carvedilol could inhibite palmitate oxidation and increase glycolysis by nearly 50 %. A few small clinical trials assessed the metabolic modulation of β-blockers. Carvedilol or bisoprolol treatment in heart failure patients could improve NYHA class and LVEF and increase mean cardiac phosphocreatine and ATP (PCr/ATP) ratio by 33 % on *in vivo* 31P-magnetic resonance spectroscopy [78]. Carvedilol treatment for 6 months for heart failure also reduced total body resting energy production rate and increased glucose oxidation. In another trial of nine patients with ischemic cardiomyopathy, carvedilol treatment in patients with heart failure resulted in a 57 % decrease in myocardial FFA use without a significant change in glucose use [79]. Metoprolol also caused a significant decrease in basal plasma FFA levels in patients with heart failure and decreased CPTI activity and increase in triglyceride content in dogs with coronary microembolism-induced heart failure [80]. A model of dogs with pacing-induced dilated cardiomyopathy was used for evaluating the effects of carvedilol and metoprolol on myocardial metabolism. Short-term treatment with carvedilol had superior hemodynamic and

metabolic effects as compared with metoprolol and included increasing plasma insulin levels and suppressing nonesterified fatty acids and glucagon levels [81]. These findings suggested that carvedilol had a more pronounced ability of shifting the substrate preference from FFAs to glucose. Not unsurprisingly, carvedilol treatment caused a 20 % reduction in myocardial FFA extraction, whereas metoprolol had a neutral effect in patients with chronic heart failure after 4 months of therapy [82]. Meanwhile, carvedilol treatment tended to increase cardiac lactate extraction, so it caused a shift from FFA utilization to lactate utilization in heart failure. The differences in these two agents on cardiac sympathetic activity and energy metabolism may be related to the differential effects of these drugs on clinical outcomes.

5 Conclusions

Although some small clinical trials showed surprisingly efficacious effects of inhibition of fatty acid metabolism on heart failure, some other studies did not support the approach for heart failure. For example, in a review published in 1994, cardiomyopathy often develops in children with genetic defects in FAO enzymes, which forces the heart to rely on glucose. This finding suggested that FAO may be indispensable for myocytes. Acipimox, a nicotinic-acid derivative that could decrease the FFA level of plasma, was used for heart failure, without profound benefits in cardiac efficiency [83]. The peroxisome proliferator-activated receptor alpha (PPARα) agonist, which would prevent changes in myocardial substrate metabolism in the failing heart treated with fenofibrate in pigs with pacing-induced heart failure, increased the expression of PPARα-regulated genes, prevented LV hypertrophy, and delayed the development of LV dilation and dysfunction [84]. In addition, new evidence supports that metabolic abnormalities in the failing heart post-infarction revealed that the heart was not energetically starved but rather inefficient in energy utilization for mechanical function [85]. Thus, we regret that we cannot state clearly that inhibition of FAO is an adaptive or a maladaptive process based on existing evidence. In conclusion, although energy metabolic modulation is an important and effective approach in heart failure, some questions remain but are worth more efforts to search for evidence to verify further mechanisms and clinical effects.

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