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REVIEW

Metabolic approach to heart failure: The role of metabolic modulators

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Abstract Heart failure (HF) is a systemic and multiorgan syndrome with metabolic failure as fundamental mechanism. As a consequence of its impaired metabolism, other processes are activated in the failing heart, further exacerbating the progression of HF.

Metabolic agents are a relatively new class of drugs that act through optimisation of cardiac substrate metabolism. Among the metabolic modulators, Trimetazidine (TMZ) and perhexiline are the only two agents with proven anti-ischaemic effect currently available. However, due to its major side effects, perhexiline is not yet approved in the US or Europe.

Clinical trials have demonstrated that the adjunct of TMZ to optimal medical therapy improves symptoms and prognosis of HF without exerting negative hemodynamic effects. Due to its anti-ischaemic/anti-anginal effect and excellent tolerability, the modulation of cardiac metabolism with TMZ represents a promising approach for the treatment of patients with HF.

Contents

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1. Introduction

Opie L. Lancet 1999;353:768–769 "The heart is more than a pump. It is also an organ that needs energy from metabolism. A metabolic disease, ischaemia, should ideally be treated by metabolic therapy".

Heart failure (HF) is a growing cardiovascular disease affecting 1–2% of the population in developed countries,[1] with a noteworthy impact in terms of human and economic resources.[2,3] HF is complex syndrome characterised by a continuous spectrum of changes, ranging from the subtle loss of normal function to the presence of symptoms refractory to medial therapy. It may be associated with different changes in cardiac physiology, including ventricular dilatation, regional wall motion abnormalities, and decreases in the left ventricular ejection fraction and other parameters of ventricular function.

Recently, there has been a growing appreciation of the complex metabolic processes underlying HF pathophysiology and symptoms.[4] As a consequence, HF is currently conceived as a systemic and multiorgan syndrome with metabolic failure as basic mechanism. In fact, the failing heart may be defined as "an engine out of fuel".[5] Beyond myocardial metabolic failure, systemic (peripheral) metabolic regulation has been found to contribute both to major symptoms (muscle weakness, fatigue, exercise limitation, and dyspnoea) and to disease progression.[4]

Taking into account these issues, we will review the role of metabolic modulators, in particular trimetazidine (TMZ), in HF focusing on their therapeutic implications.

2. Metabolic processes in the normal and failing heart

Fatty acid oxidation represents the major source of energy for myocardium, up to 80%. Glucose metabolism provides for the remaining quantity of energy. At rest, the myocardium uses 15–20% of its maximal oxidative capacity[6] and adapts the substrate utilisation during increased demands. A net increase in glucose and lactate uptake has been demonstrated during low to moderate intensity exercise, without change in free fatty acid metabolism.[7] Glucose utilisation drops during high intensity exercise compared to lower intensity exercise.[8] When the myocardium is stressed beyond the limits of its metabolic reserve, an aerobic limit is reached. As a consequence, anaerobic metabolism begins and ventricular performance declines.[9]

Therefore, it is not surprising that altered energetics play an important role in the pathophysiology of the failing heart. In particular, chronic HF may be conceived as "a ketosis-prone state", given the evidence that blood ketone bodies are increased in this syndrome. In fact, blood ketone body and free fatty acid levels are higher during the fast and also remain higher after glucose infusion in patients with chronic HF than controls.[10] Also, it has been found[11] that blood ketone bodies are elevated in chronic HF in proportion to the severity of cardiac dysfunction and neurohormonal activation. A possible mechanism is augmented supply of free fatty acids for ketogenesis due to increased stress hormone-related lipolysis. Increased mobilisation of free fatty acids could augment ketogenesis.

Other metabolic abnormalities that characterise HF range from testosterone deficiency, insulin resistance and a metabolic shift favouring catabolism and impairment in skeletal muscle bulk and function.[12] Notably, changes in substrate utilisation to mitochondrial dysfunction lead to ATP deficiency and impaired contractility.[13] In fact, other processes implicated in the progression of HF such as structural remodelling and oxidative stress are also activated. All these metabolic alterations are defined with the term "metabolic remodelling", i.e. remodelling of cardiac energy metabolism, which causes a decrease in energy production and a switch in energy substrate use. Thus, beyond structural remodelling, metabolic remodelling can contribute to the progression of HF.[14,15] Also, given that the myocardium has low ATP levels, it is not able to effectively sustain its contractile function,[16] leading to a disorder of cardiac contractility and to the progression of left ventricular remodelling.[6] This represents the so-called "metabolic vicious circle".[14] However, the exact effects of metabolic impairment in HF still need to be fully elucidated.

For these reasons, improving cardiac metabolism may be an appealing approach in HF, with significant clinical implications that go beyond the mere energetic supply.

3. Treatment of HF with metabolic agents

On the basis of the aforementioned evidence, therapeutic strategies targeted to the metabolic processes have been developed in the last decades.[2] According to the European Society of Cardiology guidelines,[17] the neurohormonal antagonists (ACE-inhibitors, beta-blockers, mineralocorticoid receptor antagonists and angiotensin receptor blockers) are used to modify the progression of systolic dysfunction in chronic HF, often in combination with a diuretic to relieve symptoms and signs of congestion. However, despite these pharmacotherapies can improve clinical symptoms of HF, the prognosis remains poor.

Conversely, metabolic agents may be particularly efficacious, when added to standard therapies, because they act through optimisation of cardiac substrate metabolism without exerting negative hemodynamic effects.[6] Fig. 1 shows the different mechanisms of action of metabolic modulators.

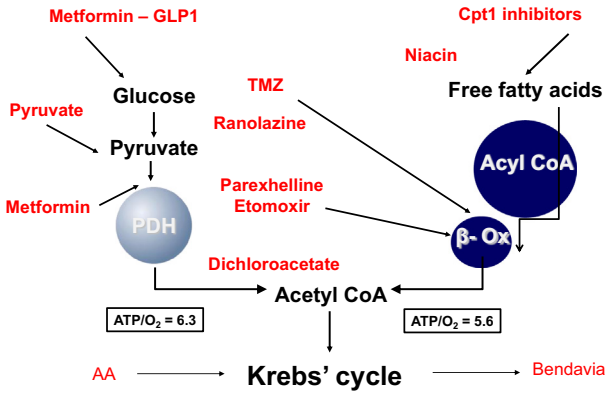

Figure 1 Targets of cardiac metabolic agents. The figure depicts the site of action of modulators of cardiac metabolism. Inhibition of free fatty acid oxidation favours glucose oxidation and consequently increases the amount of high energy phosphates produced/mole of oxygen. AA = amino acids; β-Ox = beta-oxidation; Cpt1 inhibitors = carnitine palmitoyltransferase 1 inhibitors; GLP1 = Glucagon-like peptide-1; PDH = pyruvate dehydrogenase kinase; TMZ = Trimetazidine.

Table 1 Modulators of cardiac metabolism.

	Metabolic effect at pharmacological doses	Anti-ischaemic effect	Major side effects	Marketed
Trimetazidine	FFA inhibitor	++++	Gastrointestinal	Worldwide
Perhexiline	CPI inhibitor	+++	Liver toxicity	Australia
Etomoxir	CPI inhibitor	−−−−	Left ventricular hypertrophy	No
Niacin	Uptake inhibitor	−−−−	Lymphoma	Worldwide
Ranolazine	None	+−−−	QT prolongation, Liver toxicity	US/Europe
Dichloroacetate	Inhibitor of PDH kinase	+++		No

CPI = C-kinase potentiated Protein phosphatase-1 Inhibitor; FFA = free fatty acids; PDH = pyruvate dehydrogenase complex.

Nicotinic acid (niacin) is a broad-spectrum antiatherogenic compound involved in the pathway of lipid metabolism. Beyond its beneficial effects on ischaemic heart disease (i.e. decreased atherosclerotic lesion progression and increased lesion regression),[18] it can also alter energy metabolism acting on arterial FFA concentrations and uptake, and β-oxidation.

Ranolazine is an antianginal drug approved in the United States for the treatment of chronic stable angina, which also reduces myocardial stunning and infarct size.[15] It mainly acts through a shift in myocardial energy metabolism from fatty acid β-oxidation towards glucose oxidation, therefore increasing ATP generation and, ultimately, improving contractile function.

The CPT inhibitor etomoxir was found to protect heart from fatty acid-induced ischaemic injury independent of changes in long chain acylcarnitine.[19]

Dichloroacetate stimulates the mitochondrial pyruvate dehydrogenase complex by directly inhibiting the activity of pyruvate dehydrogenase kinase, and it may improve postischaemic recovery of cardiac function.[15] Nevertheless, among the several metabolic modulators, TMZ and perhexiline are the only two agents with proven anti-ischaemic effect currently available on the market (Table 1). They both directly inhibit myocardial fatty acid oxidation and improve regional and global myocardial function.[20] CPT inhibitor perhexiline is used in Australia and some parts of Asia for the treatment of chronic stable angina and has growing evidence of its efficacy in HF.[21,22] However, it is not yet approved in the US or Europe, due to major side effects such as hepatotoxicity and peripheral neuropathy.[23]

4. Efficacy of TMZ in HF

TMZ is an inhibitor of free fatty acid oxidation that shifts cardiac and muscle metabolism from free fatty acids to glucose utilisation resulting into a greater production of high-energy phosphates and into an anti-ischaemic effect.[24–27] Since the early 70s, there has been growing evidence that TMZ lessens ischaemic injury, and myocardial ischaemia and improves cardiac function both in animals[28–31] and in humans.[32–42]

In particular, there are consistencies on the efficacy of TMZ in ischaemic cardiomyopathy across studies. The efficacy of TMZ added to standard therapy has been found in improving symptoms (e.g. dyspnoea,[37] and ischaemic symptoms[43]), left ventricular ejection fraction,[36–40,44] cardiac volume,[37,44] inflammation,[45] contractility,[46] fasting blood glucose and endothelial function.[40,47] Taken all together, these studies suggest that TMZ may be used to improve left ventricular function and to relieve symptoms in patients with post-ischaemic HF. A randomised clinical trial[39] further demonstrated the effect of TMZ added to conventional therapy in improving functional class, left ventricular end-systolic volume and ejection fraction in patients with HF of various origins. As shown by an international multicentre retrospective cohort study data on 669 patients with chronic HF,[41] the adjunct of TMZ to conventional therapy is effective in reducing mortality and improves long term survival. A meta-analysis of randomised controlled trials in HF,[48] has confirmed that TMZ ameliorates cardiac function for ischaemic and non-ischaemic HF, and reduces mortality, cardiovascular events and hospitalisation. Another meta-analytic study,[49] in chronic HF patients, has shown that TMZ decreases hospitalisation for cardiac causes and improves clinical symptoms, cardiac function and left ventricular remodelling.

Finally, TMZ has no deleterious effect on heart rate or blood pressure.[43]

5. Mechanisms of action of TMZ

The efficacy of TMZ in improving HF may be mainly explained considering the effect of the modulation of free fatty acids metabolism on cardiac function. It acts on the formation of reactive oxygen species leading to improved reperfusion mechanical function.[50] It has been observed that TMZ counteracts stress-induced atrophy in skeletal muscle myotubes.[51] This may explain the effect of TMZ on functional capacity in cardiovascular patients.[35,52,53] The positive action of TMZ on exercise performance could be ascribed to a cytoprotective mechanism exerted by TMZ on skeletal muscle integrity. Also, unpublished data from our group further indicate that TMZ reduces size loss and cytoskeleton alterations caused by Tumour Necrosis Factor α, and that TMZ increases glucose consumption and reduces glycogen content in murine skeletal muscle myotubes (Ferraro, personal communication).

Also, the effect of TMZ may be mediated through a reduction of metabolic demand at the level of the peripheral muscles. A study[42] has demonstrated TMZ to reduce the whole-body rate of energy expenditure in patients with HF. Thus, TMZ could improve symptoms and left ventricular function in patients with HF through the reduction of whole-body energy demand.

6. Conclusions

Patients with HF have metabolic disturbances that reduce the ATP production, which also causes a reduction in contractile reserve. Optimisation of cardiac metabolism should be ideally obtained with inhibition of FFA oxidation, improvement in insulin sensitivity and fuelling of the Krebs cycle with amino acids.

TMZ has been shown to exert a cytoprotective effect. The inhibition of free fatty acid oxidation with TMZ improves cardiac metabolism at rest and during stress, therefore ameliorating symptoms and prognosis in HF patients. Because of its effectiveness, excellent tolerability, and unique metabolic mechanisms of action, TMZ represents a promising drug for the treatment of patients with HF. The effect of a comprehensive metabolic approach to HF should be tested in future clinical trials.

Conflict of interest

The authors have no conflict of interest.

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