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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.

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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.

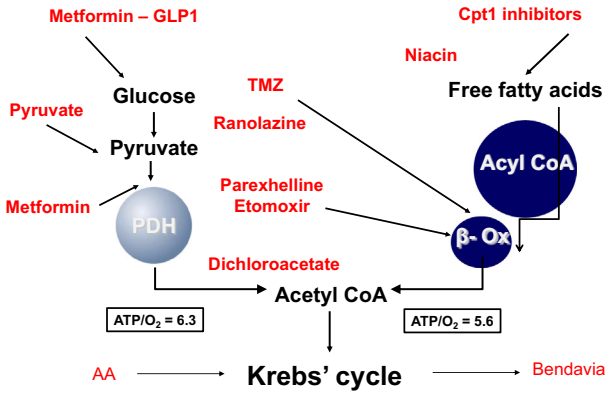

Figure 1 Targets of cardiac metabolic agents. The figure depicts the site of action of modulators of cardiac metabolism. Inhibition of free fatty acid oxidation favours glucose oxidation and consequently increases the amount of high energy phosphates produced/mole of oxygen. AA = amino acids; β-Ox =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