The role of trimetazidine in heart failure

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Abstract

Shifting the energy substrate preference away from free fatty acids (FFA) and toward glucose metabolism by FFA oxidation inhibitors, such as trimetazidine, may be an effective adjunctive treatment in terms of myocardial metabolism and left ventricular function improvement. These effects seem operative in heart failure syndromes regardless of their aetiopathogenetic cause and not confined to those of ischaemic origin. Additionally, abnormalities of glucose homeostasis are consistently present in patients with heart failure, definitely contributing to the progression of the primary disease. Apart from a meticulous metabolic control of frank diabetes, special attention should also be paid to insulin resistance, a condition that is generally under-diagnosed as a distinct clinical entity. The observed combined beneficial effects of trimetazidine on left ventricular function and glucose metabolism represent an additional advantage of this drug. In this paper, the recent literature on the beneficial therapeutic effects of trimetazidine on left ventricular dysfunction and glucose metabolism is reviewed and discussed.

Key words: trimetazidine, free fatty acid inhibitors, heart failure, left ventricular function, myocardial metabolism.

Introduction

Several aspects of myocardial metabolism of the failing heart resemble that of the diabetic heart. Fasting blood ketone bodies [1] as well as fat oxidation during exercise [2] have been shown to be increased in patients with heart failure. Insulin resistance has been found to be associated with heart failure [3] and the consequent impaired suppression of lipolysis could determine the development of ketosis. A number of different approaches have been used to manipulate energy metabolism in the heart. These involve both indirect measures and the use of agents which directly act on the heart to shift energy substrate utilization away from fatty acid metabolism and towards glucose metabolism, which is more efficient in terms of ATP production per mole of oxygen utilized. Recent studies have outlined the potential benefits of these agents on regional and global myocardial dysfunction. These beneficial effects can be explained by the fact that by increasing utilization of glucose and lactate, which are more efficient fuels for aerobic respiration, the oxygen consumption efficiency of the myocardium can be improved by 16 to 26% [4]. Additionally, heart and arm skeletal muscle glucose uptakes are inversely related to serum free fatty acid (FFA) levels [5] and increased FFA flux from adipose tissue to non-adipose tissue amplifies metabolic derangements that are

characteristic of the insulin resistance syndrome [6]. New findings also suggest that raised FFA levels not only impair glucose uptake in heart and skeletal muscle but also cause alterations in the metabolism of vascular endothelium, leading to premature cardiovascular disease [7]. Therefore, FFA inhibitors could also play a beneficial role in terms of glucose metabolism homeostasis. Among them, trimetazidine is the most extensively studied agent.

The aim of this paper is to review and summarize the reported evidence on the protective effects of trimetazidine on left ventricular function and glucose metabolism, and its clinical application in heart failure patients.

Effects of metabolic modulation with trimetazidine on left ventricular dysfunction

Trimetazidine, an inhibitor of 3-ketoacyl coenzyme A thiolase (3-KAT), the last enzyme involved in β-oxidation [8], has been shown to affect myocardial substrate utilization by inhibiting oxidative phosphorylation and by shifting energy production from FFA to glucose oxidation [9]. Experimental evidence indicates that this effect is predominantly caused by a selective block of long chain 3-KAT [8]; however, this issue is still under debate [10, 11]. Based on the hypothesis that trimetazidine could act as a metabolic modulator in the protection of ischaemic myocardium, Brottier et al. assessed the value of long-term treatment with this 3-KAT inhibitor in patients with severe ischaemic cardiomyopathy, who were already receiving conventional therapy [12]. Twenty patients were randomized to either placebo or trimetazidine. All patients on trimetazidine, at 6 months follow-up, reported a clinically considerable improvement in symptoms and showed a higher ejection fraction compared to patients on placebo. The authors concluded their study by recommending the use of trimetazidine as a complementary therapeutic tool in patients with severe ischaemic cardiomyopathy.

On this basis, the effects of trimetazidine on dobutamine-induced left ventricular dysfunction in patients with angiographically proven coronary artery disease were assessed [13]. Patients were blindly and randomly assigned to a 15-day treatment period with either placebo or trimetazidine. They were then crossed over to the other regimen for an additional 15 days. At the end of each treatment period, a stress echo with dobutamine was performed. Both in resting condition and at peak dobutamine infusion, wall motion score index was significantly lower on trimetazidine therapy than on placebo. Furthermore, trimetazidine induced an increase in dobutamine infusion time and an increase of the administered dobutamine dose to the development of ischaemia. These results indicated that trimetazidine may not only protect from dobutamine-induced ischaemic dysfunction, but could also improve resting regional left ventricular function, as shown by the significantly decreased peak and resting wall motion score index, during the active treatment period. A subsequent study confirmed these preliminary results [14].

Modulation of myocardial metabolism by trimetazidine in post-ischaemic heart failure

By keeping in mind the concept that trimetazidine should, therefore, be able to promote the utilization of glucose and non-fatty substrates by the mitochondria, attention was focused on heart failure, where maintenance of metabolic efficiency is a crucial issue.

The effects of the addition of trimetazidine to standard treatment of diabetic patients with ischaemic dilated cardiomyopathy on symptoms, exercise tolerance and left ventricular function were assessed [15]. Thirteen such patients on conventional therapy were randomly allocated in a double blind fashion to either placebo or trimetazidine, each arm lasting 15 days, and then again with placebo or trimetazidine for 2 additional 6-month periods. Both in the short and long terms, trimetazidine showed a significant beneficial effect on left ventricular function and control of symptoms, compared to placebo. The observed short-term trimetazidine benefit was maintained in the long term and contrasts with the natural history of the disease, as shown by the mild but consistent decrease of EF when on placebo (Figure 1). These results paved the way to additional studies, that have invariably confirmed the positive effects of trimetazidine in patients with post-ischaemic left ventricular dysfunction [16-18].

Modulation of myocardial metabolism by trimetazidine in heart failure of different aetiologies

The beneficial effect of trimetazidine on left ventricular function has been attributed to preservation of phosphocreatine (PCr) and adenosine triphosphate (ATP) intracellular levels [19]. Previous clinical studies using phosphorus-31 magnetic resonance spectroscopy to measure PCr/ATP ratios in human myocardium have shown that this ratio is reduced in failing human myocardium [20]. The PCr/ATP ratio is a measure of myocardial energetics and its reduction may depend on imbalance of myocardial oxygen supply and demand [21], and reduction of the total creatine pool, a phenomenon known to occur in heart failure [22]. In a recent study performed in patients with heart failure of different aetiologies on full standard medical therapy, it was observed that the trimetazidine-induced improvement of functional class and left ventricular function is associated with an improvement of PCr/ATP ratio, supporting the hypothesis that trimetazidine probably

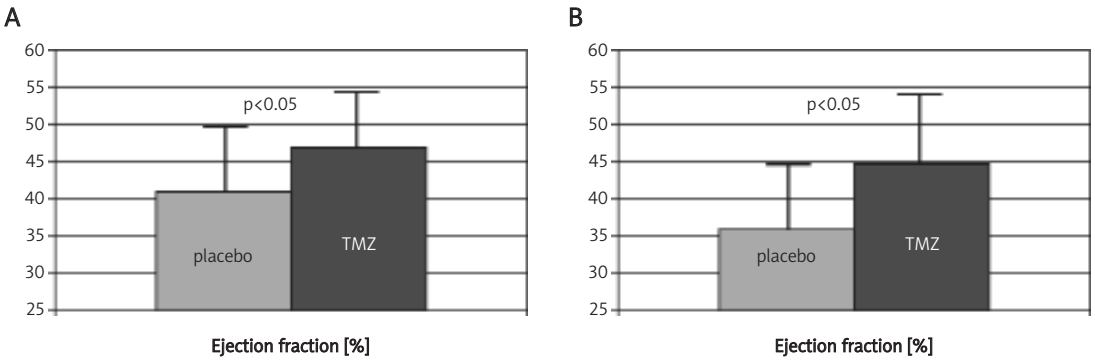

Figure 1. Short (figure 1A) and long-term (figure 1B) effects of trimetazidine and placebo on ejection fraction, in diabetic patients with post-ischaemic cardiomyopathy. Histograms (mean±1 standard deviation) show the significant beneficial effects of trimetazidine compared to placebo, in both short and long term studies (adapted from ref. 15)

preserves myocardial high energy phosphate intracellular levels [23]. These results appear particularly interesting, especially in view of previous evidence indicating the PCr/ATP ratio as a significant predictor of mortality [24].

Based on the results of this pilot study, it has also been tested whether trimetazidine added to usual treatment could also be beneficial in a more consistent group of patients with systolic-dysfunction heart failure of various aetiologies [25]. Compared to patients on conventional therapy alone, those on trimetazidine improved functional class, exercise tolerance, quality of life and left ventricular function, and used less diuretics and less digoxin. Plasma B-type natriuretic peptide (BNP) level was also significantly reduced in patients on trimetazidine, compared to conventional therapy alone.

Overall, these data confirm that selective inhibition of 3-KAT by trimetazidine represents a new therapeutic option in the treatment of patients with heart failure of various aetiologies, and not only secondary to ischaemic heart disease. A recent statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology indicated partial fatty acid oxidation inhibitors, such as trimetazidine, as potential new tools in the treatment of advanced heart failure [26]. The time has come to test this therapeutic approach in a multicentre, randomized trial in patients with heart failure.

Modulation of glucose metabolism by trimetazidine

Regulation of glucose metabolism is an important target in the control of cardiovascular risk factors. Abnormalities of glucose homeostasis range from frank diabetes to a state of insulin resistance, a definition used to indicate the necessity to increase insulin levels in order to maintain normal glycaemic levels. Recent studies have identified a direct relation between endothelial dysfunction and insulin resistance [27]. Endothelin-1 levels have been shown to significantly correlate with fasting insulin levels, systolic and diastolic blood pressure, visceral obesity and triglyceride levels, confirming a close relationship between insulin resistance and endothelial function [28]. When present, insulin resistance has been found to be operative in both cardiac and skeletal muscles [29]. Different degrees of endothelial dysfunction associated with a state of insulin resistance have been evidenced in most cardiovascular diseases such as hypertension [30], coronary artery disease [31, 32], microvascular angina [33] and heart failure [3]. On the other hand, insulin resistance is a pathological condition that is rarely diagnosed as a distinct entity. In a recent study, our group has shown that more than 50% of patients submitted to coronary stenting for ischaemic heart disease and with normal baseline blood glucose levels present abnormal hyperglycaemia after an oral glucose tolerance test [34]. These abnormalities are associated with a higher probability of restenosis [34]. These results are supported by previous studies showing that impaired glucose tolerance not only runs the risk of developing overt diabetes and its associated microvascular complications but also has an increased risk of cardiovascular morbidity and mortality compared with healthy glucose-tolerant patients [35]. Therefore, early detection of impaired glucose tolerance would permit initiation of secondary preventive treatment measures in such patients.

In diabetes, ischaemic heart disease and heart failure, lowering raised plasma triglyceride and FFA levels could be the first therapeutic option to decrease the heart's reliance on fatty acids and overcome the fatty acid inhibition of myocardial glucose utilization. Indeed beta-blockers, by reducing peripheral lipolysis, should reduce FFA availability. Interestingly enough, a recent study has shown that one of the main effects of the beta blocker carvedilol is the reduction of FFA utilization in favour of greater glucose utilization in patients with stable NYHA functional class III heart

failure [36]. This change in myocardial energetics could indicate a potential mechanism for the decreased myocardial oxygen consumption and improved energy efficiency seen with β-adrenoreceptor blockade in the treatment of heart failure. Nevertheless, only non-selective, compared to selective, β-adrenoreceptor blockers appear to shift total body substrate utilization from lipid to glucose oxidation [37]; this could be one of the reasons for better survival rates observed with non-selective β-adrenoreceptor blockers [38]. Additionally, central inhibition of sympathetic nervous activity with moxonidine in heart failure has been associated with increased mortality [39]. In fact, despite a significant reduction of catecholamine spillover, moxonidine has been shown to increase FFA utilization and increase myocardial oxygen consumption [40]. This could be the reason for the failure of central sympathetic inhibition to prevent deaths in long-term studies in patients with heart failure and also indicates that the predominant mechanism of action of beta blockers is probably related to their peripheral anti-lipolytic action.

Another possibility is to directly induce muscles to reduce FFA utilization in favour of glucose oxidation. In this context, the use of a partial fatty acid inhibitor could play a very specific role. In fact, as previously outlined, most cardiac diseases are associated with combined insulin resistance and endothelial dysfunction. In these contexts, improving the cardiac metabolic milieu by partially inhibiting FFA utilization could be particularly effective.

By keeping in mind the concept that 3-KAT inhibitors should, therefore, be able to promote the utilization of glucose and non-fatty substrates by the mitochondria, attention has been focused on this specific issue. In fact, apart from improving left ventricular function in cardiac patients, it has been recently shown that trimetazidine could also improve overall glucose metabolism in the same patients, indicating an attractive ancillary pharmacological property of this class of drugs [15]. In fact, the known insulin resistant state in most cardiac patients is certainly aggravated in those patients with overt diabetes. This is particularly relevant in patients with both diabetes and left ventricular dysfunction. In this context, the availability of glucose and the ability of cardiomyocytes and skeletal muscle to metabolize glucose are grossly reduced. Indeed, since a major factor in the development and progression of heart failure is already a reduced availability of ATP, glucose metabolism alterations could further impair the efficiency of cardiomyocytes to produce energy. By inhibiting fatty acid oxidation, trimetazidine stimulates total glucose utilization, including both glycolysis and glucose oxidation. The effects of trimetazidine on glucose metabolism could therefore be dependent by a) improved cardiac efficiency; b) improved peripheral glucose extraction and utilization. Finally, considering the known relation between ET-1 concentration and glucose metabolism abnormalities [27], the observed beneficial effects of trimetazidine on glucose metabolism could also be partly ascribed to the positive effect of the drug on ET-1 levels reduction.

Animal studies have also suggested that trimetazidine improves blood glucose utilization in rats with fasting hyperglycaemia [41]. On this ground, both forearm glucose and lipid metabolism and forearm release of endothelial vasodilator and vasoconstrictor factors have been evaluated during prolonged inhibition of β-oxidation by trimetazidine in patients with post-ischaemic left ventricular dysfunction. Trimetazidine increased both insulin-induced forearm glucose oxidation and forearm cyclic guanosine monophosphate release, while forearm ET-1 release was decreased [42]. Although these findings need further confirmation, the effects of trimetazidine at the skeletal muscle level add a new therapeutic window in the treatment of patients with ischaemic heart disease and type 2 diabetes.

Based on these data, the Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD) has included metabolic agents such as trimetazidine as potential medical aids in the treatment of cardiac patients with diabetes [43].

Effects of trimetazidine on endothelial function

It has recently been observed that trimetazidine could reduce endothelin release in cardiac patients [15, 42, 44]. Growth factors, vasoactive substances and mechanical stress are involved in the endothelin-1 (ET-1) increase in heart failure patients. Despite the known adaptive aspect of supporting contractility of the failing heart, persistent increases in cardiac ET-1 expression in the failing heart have a pathophysiological maladaptive aspect and are associated with the severity of myocardial dysfunction [45].

Trimetazidine-induced reduction of intracellular acidosis in ischaemic myocardium could not only influence myocardial but also endothelial membranes [46]. By decreasing endothelial damage, trimetazidine could inhibit ET-1 release which, in turn, will finally decrease myocardial damage. A second hypothesis is that, by just decreasing the effects of chronic myocardial ischaemia, trimetazidine could inhibit ET-1 release. Therefore, the observed decrease in ET-1 release with trimetazidine could likely be linked to trimetazidine-induced reduction of myocardial ischaemia. Finally, keeping in mind the close relation between endothelium and insulin sensitivity, the observed effects of trimetazidine on endothelial function could also explain the beneficial action of trimetazidine on glucose metabolism.

Myocardial protection with trimetazidine

Clinical studies have shown that partial FFA inhibition may exert cardioprotective effects in the setting of myocardial ischaemia including acute myocardial infarction [47-49]. In patients undergoing cardiac surgery, Fabiani et al. demonstrated that trimetazidine may reduce ischaemia-reperfusion damage during cardiac surgery and that pretreatment with trimetazidine allows the patient to face the operation with better ventricular function [49]. Kober et al. have demonstrated that trimetazidine reduces pre-procedural myocardial cell ischaemia as assessed by the duration and amplitude of ST elevation during percutaneous coronary interventions [50]; however, whether its cytoprotective effects could translate into a reduction of myocardial necrosis is unknown. A recent study has indeed shown that pretreatment with a 60 mg acute oral loading dose of trimetazidine before elective percutaneous coronary interventions limits myocardial damage, as shown by a lower total amount of cardiac troponin I release after coronary angioplasty [51]. Trimetazidine is also beneficial in preventing ischaemia-reperfusion injury. In fact, a recent animal experiment demonstrated that trimetazidine could limit lethal ischaemia-reperfusion injury by inhibiting mitochondrial permeability transition pore opening, which represents a crucial event in cardiomyocyte death following myocardial ischaemia-reperfusion [52, 53]. Altogether, these effects could explain the reduction of cardiac myonecrosis in patients pretreated with trimetazidine before cardiac surgery or angioplasty. The question of whether the observed beneficial effects of trimetazidine could translate into an improved post-procedural outcome needs further investigation. Clearly, these results warrant large-scale longitudinal studies to investigate the effects of pre-procedural trimetazidine treatment on late outcome in patients undergoing elective myocardial revascularization.

In conclusions inhibitors of fatty acid oxidation such as trimetazidine could have an important role in the therapeutic strategy of patients with heart failure. More specifically, shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism may be an effective adjunctive treatment in patients with heart failure, in terms of left ventricular metabolism and function improvement. These effects seem operative in heart failure syndromes regardless of their aetiopathogenetic cause and not confined to those of ischaemic origin.

Additionally, most cardiac diseases are associated with abnormalities of glucose homeostasis, which definitely contribute to the progression of the primary disease. If not adequately treated, in most cardiac patients glucose metabolism abnormalities will heavily contribute to the occurrence of complications, of whom severe left ventricular dysfunction is at present one of the most frequent and insidious. Apart from meticulous metabolic control of frank diabetes, special attention should also be paid to insulin resistance, a condition that is generally underdiagnosed as a distinct clinical entity. The observed combined beneficial effects of the 3-KAT inhibitor trimetazidine on left ventricular function and glucose metabolism represent an additional advantage of these drugs, especially in those cardiac patients in whom myocardial and glucose metabolism abnormalities coexist.

Although highly suggestive, whether these benefits would translate into improved survival should be ascertained by a multicentre trial.

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