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Evaluating the metabolic approach to treatment of diabetic coronary patients

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ABSTRACT

Diabetic patients with coronary artery disease have an altered myocardial metabolism of glucose and free fatty acids (FFA) and accelerated and diffuse atherogenesis with involvement of peripheral coronary segments that causes chronic hypoperfusion and hibernation. Therefore, in coronary diabetic patients the ischaemic metabolic changes that occur as a consequence of the mismatch between blood supply and cardiac metabolic requirements are heightened by the diabetic metabolic alterations.

Important metabolic alterations in diabetic patients are the decreased utilization of glucose and the increase in muscular and myocardial FFA uptake and oxidation. These metabolic changes are responsible for the increased susceptibility of the diabetic heart to myocardial ischaemia and to a greater decrease of myocardial performance for a given amount of ischaemia compared to non diabetic hearts.

A therapeutic approach aimed at an improvement of cardiac metabolism through manipulations of the utilization of metabolic substrates should result in an improvement of myocardial ischaemia and of left ventricular function. The inhibition of FFA oxidation improves cardiac metabolism at rest, increases the cardiac resistance to ischaemia and therefore reduces the decline of left ventricular function due to chronic hypoperfusion and repetitive episodes of myocardial ischaemia in patients with and without diabetes.

Modulation of myocardial FFA metabolism should be the key target for metabolic interventions in diabetic patients with coronary artery disease.

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1. Introduction

Diabetic patients without overt coronary artery disease have a prognosis that is similar to that of non-diabetic patients with coronary disease and coronary diabetic patients have a cardiovascular death rate double than that of non-diabetic patients with coronary artery disease [1–3]. In addition, diabetic patients with ischaemic heart disease have an increased incidence of heart failure than non diabetic patients because of the altered myocardial metabolism and accelerated and diffuse atherogenesis. The diffuse distribution of atherosclerosis in patients with type 2 diabetes mellitus is related in part to the metabolic derangements of diabetes and in part to the clustering of different risk factors such as elevated blood pressure, central obesity and altered lipid profile.

In patients with diabetes mellitus and coronary artery disease the metabolic changes occurring as a consequence of the mismatch between blood supply and cardiac metabolic requirements are heightened by the diabetic metabolic changes. The presence of myocardial insulin resistance has been demonstrated in diabetic patients with and without coronary artery disease suggesting that even early stages of altered glycaemic control may affect myocardial metabolism and predispose to the diabetic cardiomyopathy [4–7]. Several metabolic alterations occur in the pre-diabetic and in the diabetic state that may heighten the effect of myocardial ischaemia and contribute to the development of diabetic cardiomyopathy [8,9]. The lack of insulin and the state of insulin resistance may influence cardiac function through several different mechanisms such as decreased glucose transport and carbohydrate oxidation, increase in free fatty acid (FFA) utilization, decrease in sarcolemmal calcium transport and alterations in myofibrillar regulatory contractile proteins. In diabetic patients, myocardial glucose uptake, availability and utilization are blunted in both fasting condition and after insulin stimulation [10].

In diabetics and in subjects with insulin resistance the abnormalities in glucose uptake and utilization are coupled with an increase in FFA oxidation not only in the skeletal myocytes but also in the cardiomyocytes. These metabolic changes of the diabetic heart and skeletal myocytes lead to a diminished production of high energy phosphate since the beta-oxidation of FFA is less efficient than the glycolysis in generating energy. The heart uses ATP (adenosine triphosphate) as the main source of energy. ATP is mainly produced by the oxidation of acetyl coenzyme A into the mitochondria. The two main metabolic pathways for energy supply in the heart are FFA oxidation and breakdown of glucose and carbohydrates in the glycolysis. Both pathways, in the presence of oxygen produce acetil-CoA that enters the Krebs cycle. In aerobic conditions

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the main source of myocardial energy comes from FFA. However, glucose oxidation produces the required energy for the normal functioning of the Na^+/K^+-ATPase and the Ca^{2+}-ATPase pumps that are crucial for the preservation of membrane potential and calcium transport. Since the glycolitic and pyruvate pathways require less oxygen per mole of ATP generated than FFA oxidation during increased myocardial requirement or decreased oxygen availability glucose and lactate become the main source of energy and the myocardial glucose uptake may increase by 30 fold.

In diabetic and pre-diabetic states a reduced glucose uptake and utilization coupled with a preferential FFA oxidation occur as a consequence of inadequate insulin receptor signalling or decreased insulin levels [10,11]. An important metabolic alteration of diabetes is the increased FFA concentrations and increased muscular and myocardial FFA uptake and oxidation. The increased uptake and utilization of FFA during increased metabolic demands or during ischaemia is responsible for greater decrease of myocardial performance for given amount of ischaemia compared to non diabetic hearts and for the increased susceptibility of diabetic heart to myocardial ischaemia [10,12–14]. The preferential increased uptake of FFA during stress or ischaemia also causes a parallel increase of intermediate metabolic products that are toxic for the cells especially during ischaemia or increased workload [14]. Therefore, the abnormal increase in FFA uptake and utilization contributes to both the development of contractile dysfunction and to the increased sensitivity of the heart to injury during ischaemia. Furthermore, the decreased energy production of the diabetic heart related to the decreased glucose utilization and preferential FFA oxidation leads to important alterations in calcium homeostasis that are responsible for the impaired systolic and diastolic function of the diabetic heart. The impairment of systolic and diastolic function of the diabetic heart may remain subclinical in some cases, while in the presence of reduced coronary blood flow (such as during acute myocardial ischaemia or chronic coronary artery disease) or during increased myocardial energy requirement (such as in presence of arterial hypertension) it may facilitate the development of overt heart failure.

2. Metabolic approach to coronary artery disease in diabetics

In diabetic patients with coronary artery disease a therapeutic approach aimed at an improvement of cardiac metabolism through manipulations of the utilization of metabolic substrates should result in an improvement of myocardial ischaemia and of left ventricular function.

Modulation of myocardial FFA metabolism is an important target for metabolic interventions in patients with coronary artery disease with and without diabetes. In diabetic patients the effects of modulation of FFA metabolism should be even greater that those observed in patients without diabetes.

It is well known that the improvement of glucose metabolism in patients with acute ischaemic syndromes improves cardiovascular outcome. The administration of the glucose–insulin–potassium (Sodi Pallares or GIK solution) induces a reduction of FFA oxidation in the ischaemic heart. In the DIGAMI and in the ECLA studies the long-term mortality in diabetic patients admitted for acute MI was reduced by a 24 h GIK infusion [15,16]. A meta-analysis of the trials on GIK infusion in patients with acute MI showed a 28% reduction in mortality at one-year follow-up and this therapeutic regimen has been recommended for all diabetic patients suffering acute MI [17].

In chronic conditions, improvement of cardiac metabolism can be obtained by both an aggressive control of glucose metabolism with anti-diabetic agents and insulin and through the modulation of FFA metabolism. Trimetazidine is an effective anti-anginal agent that shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase [18,19]. The benefits of increased glycolytic substrate utilization are attributed to several mechanisms. The expected number of moles of ATP produced per mole of oxygen consumed is 12% higher for glucose than for FFA oxidation although it is reasonable to believe that the improvement of glucose metabolism may increase ATP production up to 30%. By decreasing fatty acid oxidation, trimetazidine stimulates glucose utilization, restoring coupling between glycolysis and carbohydrate oxidation, and leading to ATP production with less oxygen consumption [18]. By stimulating membrane phospholipid turnover during ischaemia and reperfusion, trimetazidine redirects fatty acids towards phospholipids, increasing cell tolerance to ischaemia–reperfusion damage. The anti-ischaemic properties of trimetazidine are independent from haemodynamic changes and are associated with a greater recovery of mechanical function after ischaemia. The cardioprotective effects of trimetazidine have been confirmed in human models of ischaemia–reperfusion including patients undergoing PTCA and CABG [20–22].

Several studies have shown that trimetazidine is as effective as classic haemodynamic agents in improving myocardia ischaemia along with an improved tolerance profile [23,24]. In stable effort angina, trimetazidine improves exercise tolerance and elevates ischaemic threshold as much as b-blockers or Ca-channel blockers [23,24]. In particular, the VASCO-angina study [25] has recently shown that trimetazidine improves effort-induced myocardial ischaemia and functional capacity in patients with chronic stable angina receiving beta-blockers. Also, when given in association to b-blockers, trimetazidine has a greater anti-ischaemic effect than nitrates and calcium-channel blockers [26,27]. The mechanism of action of trimetazidine, based on a switch from fatty acids to glucose utilization [18] makes this drug the ideal treatment of myocardial ischaemia in diabetic patients with and without left ventricular dysfunction. The TRIMPOL-1 study showed that four weeks of treatment with trimetazidine significantly decreased the number of anginal episodes and improved myocardial ischaemia and exercise capacity in diabetic patients [28]. Our group has shown that, in diabetics with chronic stable angina, the adjunct of trimetazidine to standard medical therapy reduces the number of episodes of ST segment depression (Fig. 1), the episodes of silent ischaemia and the total ischaemic burden [29].

3. Modulation of cardiac metabolism in diabetic patients with heart failure

Due to the preferential promotion of glucose and pyruvate oxidation, trimetazidine improves the activity of the sodium-potassium ATPase and the calcium uptake pump of the sarcoplasmic reticulum, that are respectively responsible of left ventricular systolic depolarization and diastolic relaxation. Furthermore, the metabolic effects of Trimetazidine translate into a reduced total ischaemic burden and into a better utilization of metabolic substrates that translates into a greater mechanical efficiency [29–35]. Our group has shown that trimetazidine added to standard medical therapy improves left ventricular systolic and diastolic function in diabetic patients with ischaemic cardiomyopathy suggesting that the adjunct of targeted cardiac metabolic therapy to usual care improves cardiac metabolism especially in the areas of hybernated myocardium (Fig. 2) [29]. The observed improvement of left ventricular

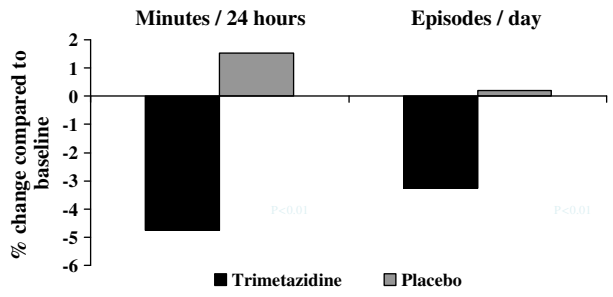

Fig. 1. Effect of trimetazidine on episodes of myocardial ischaemia and total ischaemic burden in patients with coronary artery disease. Trimetazidine added to standard anti-anginal therapy significantly reduced the episodes of silent and symptomatic myocardial ischaemia and the total ischaemic burden compared to placebo.

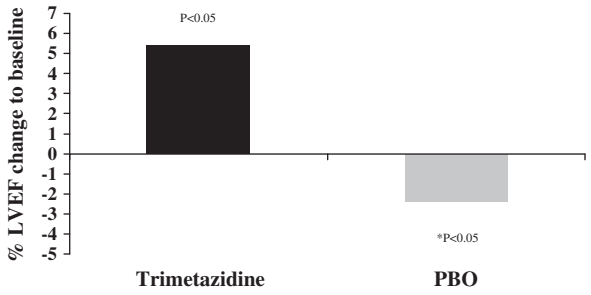

Fig. 2. Effect of trimetazidine on left ventricular function in diabetic patients with coronary artery disease. Trimetazidine added to standard therapy for heart failure significantly improved left ventricular function compared to placebo.

function was paralleled by a similar improvement of left ventricular diastolic compliance suggesting that the experimental evidence of an improvement of sarcoplasmic Ca^{+2} pump does translate into an effect of trimetazidine on diastolic function. Similar findings have been obtained by Fragasso et al. who have also reported an improvement in glucose metabolism and a decrease in endothelin-1 after chronic trimetazidine therapy in patients with diabetic cardiomyopathy [36]. These findings suggest that the improvement of cardiac and muscular glucose metabolism through FFA inhibition improves overall glucose metabolism as shown by a significant decrease of HbA1c. The effect of trimetazidine on endothelin-1 suggests that the drug may also have an effect on the vascular endothelium.

Whether the effects of trimetazidine on myocardial ischaemia and left ventricular function have prognostic importance is still unclear. However, we have reported a reduction in cumulative events in patients with ischaemic heart failure in whom trimetazidine was added on top of standard therapy further supporting the importance of this drug in the treatment of patients with heart failure [37]. Finally, our group has recently demonstrated that trimetazidine on top of medical therapy reduces mortality and morbidity in heart failure with impaired left ventricular function [38].

4. Conclusion

The metabolic changes of diabetes alter myocardial metabolism reducing cardiac susceptibility to ischaemic stimuli and cardiac performance. In diabetic coronary patients, the episodes of transient myocardial ischaemia coupled with the chronic myocardial hypoperfusion cause a progressive decline of left ventricular function. The inhibition of FFA oxidation improves cardiac metabolism at rest, increases the cardiac ischaemic and therefore reduces the decline of left ventricular function due to chronic hypoperfusion and repetitive episodes of myocardial ischaemia.

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