Effect of selective 3-ketoacyl coenzyme A thiolase inhibition on glucose metabolism in cardiac patients

Gabriele Fragasso, Altin Palloshi and Amarild Cuko
Heart Failure Clinic, Istituto Scientifico/Universita' San Raffaele, Milan, Italy

Correspondence: Gabriele Fragasso, Heart Failure Clinic, Istituto Scientifico/ Universita' San Raffaele, Via Olgettina 60, 20132 Milan, Italy.
Tel: +39-02-26437395; fax: +39-02-26437395; e-mail: gabriele.fragasso@hsr.it

Abstract

It has recently been shown that trimetazidine, a 3-ketoacyl coenzyme A thiolase inhibitor, improves overall glucose metabolism in diabetic patients with left ventricular dysfunction. Forearm glucose and lipid metabolism and forearm release of endothelial vasodilator and vasoconstrictor factors during prolonged partial inhibition of fatty acid oxidation by trimetazidine have recently been evaluated in patients with postischemic left ventricular dysfunction. Trimetazidine significantly improved both insulin-induced forearm oxidation of glucose and release of cyclic guanosine monophosphate, whereas forearm release of endothelin-1 was decreased. Although these findings need further confirmation, the combined beneficial effects of trimetazidine on left ventricular function and glucose metabolism make the use of this drug particularly attractive, especially in those cardiac patients in whom abnormalities of both myocardial and glucose metabolism coexist.
■ *Heart Metab.* 2006;30:21–24.

Keywords: Trimetazidine, diabetes, glucose metabolism, left ventricular function, endothelial function, 3-ketoacyl coenzyme A thiolase inhibition

Introduction

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 a need to increase insulin concentrations in order to maintain normal glycemic conditions. Recent studies have identified a direct relationship between endothelial dysfunction and insulin resistance [1]. Endothelin-1 (ET-1)* concentrations have been shown to correlate significantly with fasting insulin concentrations, systolic and diastolic blood pressure, visceral obesity, and triglyceride concentrations, confirming a close relationship between insulin resistance and endothelial function [2]. When present, insulin resistance has been found to be operative in both cardiac and skeletal muscles [3]. Different degrees of endothelial dysfunction associated with a state of insulin resistance have been reported in most cardiovascular diseases, such as hypertension [4], coronary artery disease [5,6], microvascular angina [7], and heart failure [8]. In contrast, insulin resistance is a pathological condition that is rarely diagnosed as a distinct entity. In a recent study, our group showed that more than 50% of patients submitted to coronary stenting for ischemic heart disease and with normal baseline blood glucose concentrations exhibit abnormal hyperglycemia after an oral glucose tolerance test [9]. This abnormality is associated with a higher probability of restenosis [9]. Our results are supported by previous studies showing

that individuals with impaired glucose tolerance not only run the risk of developing overt diabetes and its associated microvascular complications, but also have an increased risk of cardiovascular morbidity and mortality compared with healthy glucose-tolerant patients [10]. Therefore, early detection of impaired glucose tolerance would permit initiation of secondary preventive treatment measures in such patients.

Uptake of glucose in heart and arm skeletal muscle is inversely related to serum free fatty acid (FFA) concentrations [11], and increased FFA flux from adipose tissue to non adipose tissue amplifies metabolic derangements that are characteristic of the insulin resistance syndrome [12]. In addition, new findings suggest that increased FFA concentrations 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 [13].

Effects of selective 3-ketoacyl coenzyme A thiolase inhibition on glucose metabolism

Decreasing increased plasma triglyceride and FFA concentrations could be the first therapeutic option for decreasing the reliance of the heart on fatty acids and overcoming the fatty acid inhibition of myocardial glucose utilization. Indeed β-blockers, by reducing peripheral lipolysis, should reduce FFA availability. Interestingly enough, a recent study has shown that one of the main effects of the β-blocker, carvedilol, is the reduction of FFA utilization in favor of greater utilization of glucose in patients with stable New York Heart Association functional class III heart failure [14]. This change in myocardial energetics could provide a potential mechanism for the decreased myocardial oxygen consumption and improved energy efficiency that is seen with β-adrenoreceptor blockade in the treatment of heart failure.

Another approach is to induce muscles directly to reduce FFA utilization in favor of glucose oxidation. In this context, the use of a partial fatty acid inhibitor could have a very specific role. Trimetazidine [1-(2,3,4 trimethoxybenzyl-piperazine dihydrochloride)] has been reported to exert several beneficial effects in cardiac patients, without affecting myocardial oxygen consumption and blood supply [15]. This agent has been shown to preserve intracellular concentrations of phophocreatine and ATP [16] and to reverse the harmful effects of increased triglyceride concentrations, normalizing the impaired myocardial recovery from low-flow ischemia by decreasing myocardial oxidation of lipid and release of citrate [17]. These effects could be a consequence of the main mechanism of action of trimetazidine – ie, inhibition of oxidative phosphorylation by shifting energy production from FFA to glucose oxidation [3]. This beneficial metabolic adaptation is predominantly caused by a selective block of long-chain 3-ketoacyl coenzyme A thiolase activity, the final enzyme involved in β-oxidation [18]. Partial inhibition of fatty acid oxidation may therefore explain the beneficial effects of trimetazidine in cardiac patients.

Therapeutic approach to abnormal glucose metabolism in cardiac patients

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. In patients with ischemic left ventricular dysfunction, trimetazidine has been shown to exert significant beneficial effects [19,20]. These beneficial effects of the molecule have been incidentally observed to be mainly operative in patients who, in addition to ischemic cardiomyopathy, also have diabetes [21,22] (*Figures 1–3*). After trimetazidine, there was a clear trend towards a decrease in blood glucose, although the difference compared with placebo was not statistically significant. Conversely, both glycosylated hemoglobin and endothelin were significantly reduced after treatment with trimetazidine. Together, these data indicate a significant trimetazidine-induced improvement in glucose metabolism in cardiac patients.The mechanism of action is related to the property of trimetazidine to facilitate myocardial utilization of glucose instead of FFAs which, in the context of malfunctioning myocardial cells, appear to be deleterious. Interestingly, compounds such as dichloroacetate, which stimulate pyruvate dehydrogenase activity, thereby facilitating glucose oxidation

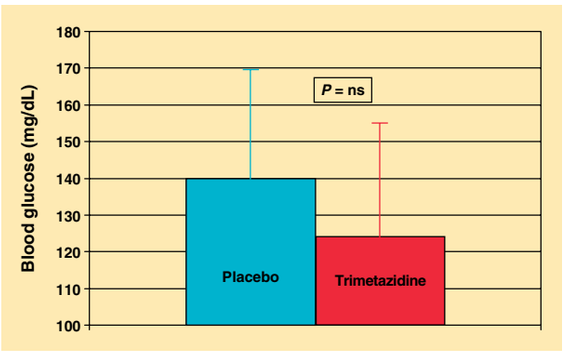

Figure 1. Long-term effects of trimetazidine and placebo on (mean ± SD) blood glucose concentrations in diabetic patients with postischemic cardiomyopathy. (From Fragasso et al [21], with permission.)

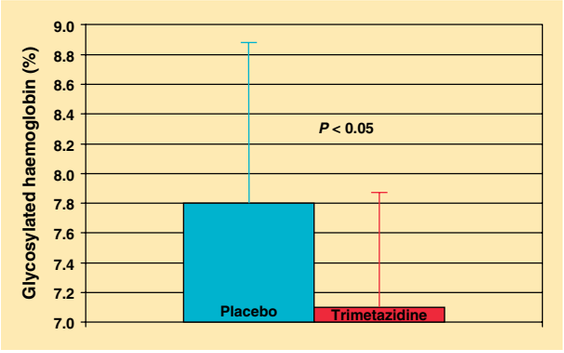

Figure 2. Long-term effects of trimetazidine and placebo on (mean ± SD) glycosylated hemoglobin concentrations in diabetic patients with postischemic cardiomyopathy. (From Fragasso et al [21], with permission.)

and inhibiting FFA oxidation, have also been shown to improve left ventricular function in patients with heart failure [23].

Bearing in mind the concept that trimetazidine should, therefore, be able to promote the utilization of glucose and nonfatty substrates by the mitochondria, attention has been focused on this specific issue.

Effects of trimetazidine on endothelial function

It has recently been observed that trimetazidine was able to reduce the release of endothelin in cardiac patients (*Figure 3*) [21,24]. Growth factors, vasoactive substances, and mechanical stress are involved in the increase in ET-1 concentrations in patients with heart failure. Despite the known adaptive aspect of supporting contractility of the failing heart, persistent increases in cardiac expression of ET-1 in the failing heart have a pathophysiological maladaptive aspect and are associated with the severity of myocardial dysfunction [25].

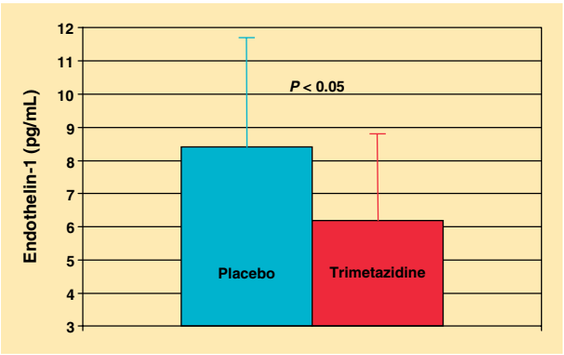

Figure 3. Long-term effects of trimetazidine and placebo on (mean ± SD) endothelin-1 concentrations in diabetic patients with postischemic cardiomyopathy. (From Fragasso et al [21], with permission.)

Trimetazidine-induced reduction in intracellular acidosis in ischemic myocardium [26] could influence, not only myocardial, but also endothelial, membranes. By decreasing endothelial damage, trimetazidine could inhibit ET-1 release – which, in turn, will ultimately decrease myocardial damage. A second hypothesis is that, simply by decreasing the effects of chronic myocardial ischemia, trimetazidine could inhibit the release of ET-1. The observed decrease in ET-1 release that is associated with trimetazidine may therefore be linked to the trimetazidine-induced reduction in myocardial ischemia. Finally, keeping in mind the close relationship between endothelium and insulin sensitivity, the observed effects of trimetazidine on endothelial function could also explain the beneficial action of trimetazidine on glucose metabolism.

Effects of trimetazidine on glucose metabolism

It has recently been shown that, apart from improving left ventricular function in cardiac patients, trimetazidine also improved overall glucose metabolism in the same patients (*Figure 1*), indicating an attractive ancillary pharmacological property of this class of drug [21]. 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, as a major factor in the development and progression of heart failure is an already reduced availability of ATP, alterations in glucose metabolism could further impair the efficiency of cardiomyocytes in producing 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 on improved cardiac efficiency, and on improved peripheral extraction and utilization of glucose. Finally, in view of the known relationship between ET-1 concentration and abnormalities of glucose metabolism [1], the observed beneficial effects of trimetazidine on glucose metabolism could also be partly ascribed to the positive effect of the drug on the reduction in ET-1 concentrations.

Animal studies have also suggested that trimetazidine improves blood glucose utilization in rats with fasting hyperglycemia [27]. In this respect, we have recently evaluated both forearm metabolism of glucose and lipid and forearm release of endothelial vasodilator and vasoconstrictor factors during prolonged

inhibition of β-oxidation by trimetazidine in patients with postischemic left ventricular dysfunction. Trimetazidine increased both insulin-induced forearm glucose oxidation and release of cyclic guanosine monophosphate, whereas forearm release of ET-1 was decreased [28]. 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 ischemic heart disease and type 2 diabetes.

Conclusions

Most cardiac diseases are associated with abnormalities of glucose homeostasis, which undoubtedly contribute to the progression of the primary disease. If not adequately treated, in most cardiac patients glucose metabolism abnormalities will contribute heavily to the occurrence of complications, among which severe left ventricular dysfunction is at present one of the most frequent and insidious. In addition to meticulous metabolic control of frank diabetes, special attention should be also paid to insulin resistance, a condition that is generally underdiagnosed as a distinct clinical entity. The combined beneficial effects of trimetazidine on left ventricular function and glucose metabolism make the use of this drug particularly attractive, especially in those cardiac patients in whom myocardial and glucose metabolism abnormalities coexist. ■

* See glossary for definition of these terms.

REFERENCES

1. Piatti PM, Monti LD, Galli L, et al. Relationship between endothelin-1 concentrations and the metabolic alterations typical of the insulin resistance syndrome. *Metabolism*. 2000;49:748–752.
2. Piatti PM, Monti LD, Zavaroni I, et al. Alterations in nitric oxide/cyclic-GMP pathway in nondiabetic siblings of patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2000;85:2416–2420.
3. Stanley WC, Lopaschuk GD, Hall JL, McCormack JG. Regulation of myocardial carbohydrate metabolism under normal and ischemic conditions: potential for pharmacological interventions. *Cardiovasc Res*. 1997;33:243–257.
4. Natali A, Taddei S, Quiñones Galvan A, et al. Insulin sensitivity, vascular reactivity, and clamp-induced vasodilatation in essential hypertension. *Circulation*. 1997;96:725–726.
5. Despres JP, Lamarche B, Mauriege P, et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med*. 1996;334:952–957.
6. Yoshimura T, Hisatomi A, Kajihara S, et al. The relationship between insulin resistance and polymorphisms of the endothelial nitric oxide synthase gene in patients with coronary artery disease. *J Atheroscler Thromb*. 2003;10:43–47.
7. Piatti PM, Fragasso G, Monti LD, et al. Endothelial and metabolic characteristics of patients with angina and angiographically normal coronary arteries. *J Am Coll Cardiol*. 1999;34:1452–1460.
8. Paolisso G, De Riu S, Marrazzo G, Verza M, Varricchio M, D'Onofrio F. Insulin resistance and hyperinsulinemia in patients with chronic heart failure. *Metabolism*. 1991;40:972–977.
9. Piatti P, Di Mario C, Monti LD, et al. Association of insulin resistance, hyperleptinemia, and impaired nitric oxide release with in-stent restenosis in patients undergoing coronary stenting. *Circulation*. 2003;108:2074–2081.
10. The Decode Study Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet*. 1999; 354:617–621.
11. Nuutila P, Knuuti MJ, Raitakari M, et al. Effect of antilipolysis on heart and skeletal muscle glucose uptake in overnight fasted humans. *Am J Physiol Endocrinol Metab*. 1994; 267:E941–E946.
12. Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr Rev*. 2002;23:201–229.
13. Steinberg HO, Baron AD. Vascular function, insulin resistance and fatty acids. *Diabetologia*. 2002;45:623–634.
14. Wallhaus TR, Taylor M, DeGrado TR, Russell DC. Myocardial free fatty acid and glucose use after carvedilol treatment in patients with congestive heart failure. *Circulation*. 2001; 103:2441–2446.
15. Chierchia S, Fragasso G. Metabolic management of ischaemic heart disease. *Eur Heart J*. 1993;14 (suppl G):2–5.
16. Fragasso G, De Cobelli F, Perseghin G, et al. Improved myocardial high-energy phosphate metabolism induced by partial fatty acid inhibition in patients with heart failure. *J Am Coll Cardiol*. 2004;43:190A.
17. Monti LD, Allibardi S, Piatti PM, et al. Triglycerides impair postischemic recovery in isolated hearts: roles of endothelin-1 and trimetazidine. *Am J Physiol Heart Circ Physiol*. 2001; 281:H1122–H1130.
18. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res*. 2000;86:580–588.
19. Brottier L, Barat JL, Combe C, Boussens B, Bonnet J, Bricaud H. Therapeutic value of a cardioprotective agent in patients with severe ischemic cardiomyopathy. *Eur Heart J*. 1990;11:207–212.
20. Lu C, Dabrowski P, Fragasso G, Chierchia SL. Effects of trimetazidine on ischemic left ventricular dysfunction in patients with coronary artery disease. *Am J Cardiol*. 1998; 82:898–901.
21. Fragasso G, Piatti PM, Monti L, et al. Short and long term beneficial effects of partial free fatty acid inhibition in diabetic patients with ischemic dilated cardiomyopathy. *Am Heart J*. 2003;146:E1–E8.
22. Rosano GMC, Vitale C, Sposato B, Mercuro G, Fini M. Trimetazidine improves left ventricular function in diabetic patients with coronary artery disease: a double-blind placebo-controlled study. *Cardiovasc Diabetol*. 2003;2:16/1–16/9.
23. Bersin RM, Wolfe C, Kwasman M, et al. Improved hemodynamic function and mechanical efficiency in congestive heart failure with sodium dichloroacetate. *J Am Coll Cardiol*. 1994;23:1617–1624.
24. Fragasso G, Piatti P, Monti L, et al. Acute effects of heparin administration on the ischemic threshold of patients with coronary artery disease: evaluation of the protective role of the metabolic modulator trimetazidine. *J Am Coll Cardiol*. 2002;39:413–419.
25. Yamauchi-Kohno R, Miyauchi T, Oshino T, et al. Role of endothelin in deterioration of heart failure due to cardiomyopathy in hamsters: increase in endothelin production in the heart and beneficial effect of endothelin A antagonist on survival and cardiac function. *Circulation*. 1999;99:2171–2176.
26. Maridonneau-Parini I, Harpey C. Effects of trimetazidine on membrane damage induced by oxygen free radicals in human red cells. *Br J Clin Pharmacol*. 1985;20:148–151.
27. Cano C, Bermúdez VJ, Medina MT, et al. Trimetazidine diminishes fasting glucose in rats with fasting hyperglycemia: a preliminary study. *Am J Ther*. 2003;10:444–446.
28. Monti LD, Setola E, Fragasso G, et al. Metabolic and endothelial effects of trimetazidine on forearm muscle in patients with type 2 diabetes and ischemic cardiomyopathy. *Am J Physiol Endocrinol Metab*. 2006;290:E54–E59.