From recurrent ischemia to ischemic heart failure: new data on trimetazidine

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Abstract

Over recent years, the management of chronic coronary disease has improved markedly as a result of the increased use of surgical and percutaneous revascularization procedures. However, the prevalence of recurrent ischemia, together with the growing population of individuals surviving acute coronary syndromes but with serious myocardial damage, increases the prevalence of ischemic left ventricular cardiomyopathy and heart failure. The management of heart failure is currently based on the use of angiotensin converting enzyme inhibitors, β-adrenolytic agents and aldosterone inhibitors, but cardioprotective metabolic intervention is an interesting novel approach. Trimetazidine, an anti-ischemic metabolic agent, reduces fatty acid β-oxidation by selective inhibition of 3-ketoacyl coenzyme A thiolase activity, which can decrease the consequences of recurring ischemia, facilitating the maintenance of myocardial function and enhancing left ventricular performance. This paper reviews the recent data regarding the therapeutic effects of trimetazidine in various populations with left ventricular dysfunction.
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Recurrent ischemia after revascularization

The current approach to the treatment of chronic ischemic heart disease is focused on two basic targets: prolongation of total or event-free survival, and symptomatic relief of angina. Despite the increasing role of revascularization, there remain a substantial number of patients who will require intense medical treatment as a result of failed, incomplete, or unachieved interventional or surgical revascularization of the myocardium. With prolonged survival even in advanced stages of coronary disease, a growing number of patients exist who suffer from recurrent episodes of ischemia or have a history of acute coronary syndromes, or both, resulting in an accumulating burden of myocardial damage. This population of patients is at increased risk of developing ischemic cardiomyopathy and heart failure. Recent developments in revascularization techniques have not changed the outlook significantly and even relatively low-risk populations undergoing percutaneous intervention with stenting or surgical coronary artery bypass grafting rarely remain asymptomatic or symptom free [1] (*Figure 1*).

This problem is even more apparent in patients with multivessel disease, as revealed by data from the Arterial Revascularization Therapy Study [2]. The available body of evidence suggests that revascularization fails to eliminate recurrent ischemia in 30–40% of patients with single-vessel disease and 60–70% of those with multivessel coronary disease. Thus effective medical treatment of ischemia or prevention of its deleterious effects remains an essential element of treatment.

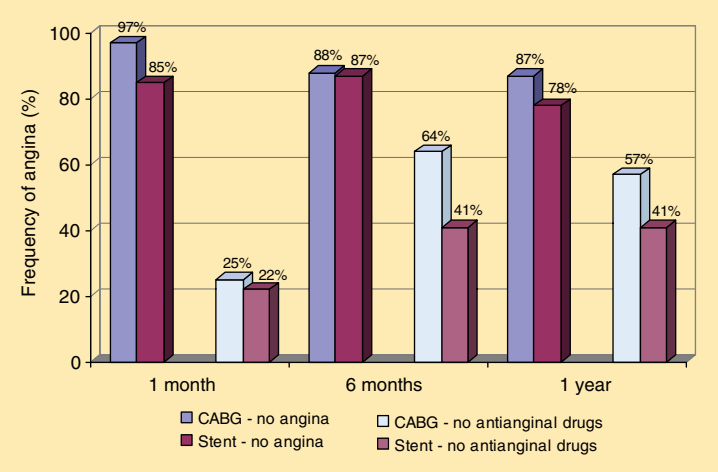

Figure 1. Angina after current revascularization techniques. CABG, coronary artery bypass grafting. (Data from Eefting et al [1].)

The introduction of trimetazidine has expanded the treatment of myocardial ischemia beyond hemodynamic intervention and offers a potential alternative for improvement of function in the ischemic myocardium. Trimetazidine is an effective antianginal drug, both in monotherapy and in combination with traditional antianginal drug groups such as calcium antagonists or β-adrenolytic agents [3].

Effects of trimetazidine in patients with left ventricular dysfunction

Over the past few years, there have been several interesting reports on the use of trimetazidine in patients with various degrees and types of left ventricular dysfunction.

The first observation of functional benefit in patients with ischemic cardiomyopathy treated with trimetazidine came from Brottier *et al* [4]. In their small 6-month double-blind placebo-controlled study of 20 patients with severe ischemic cardiomyopathy (New York Heart Association [NYHA] class III/IV), left ventricular ejection fraction increased by 9.3% in the group treated with trimetazidine and decreased by 15.6% in the placebo group ($P < 0.018$). More recently, very similar results were obtained by Sisakyan [5], who used a sustained-release preparation of trimetazidine given 35 mg twice daily in NYHA class II/III patients. An improvement of ejection fraction from 32% to 41% ($P < 0.05$) was demonstrated in the trimetazidine group, compared with a non significant change from 30% to 35% in the placebo group.

Another smaller study demonstrated improvement in resting left ventricular function and reduction in the severity of dobutamine-induced ischemic myocardial dysfunction [6]. This was followed by a study by Belardinelli and Purcaro [7], who demonstrated the positive influence of trimetazidine therapy on contractile reserve in 38 patients with postinfarction ischemic cardiomyopathy. The resting ejection fraction in the trimetazidine-treated group increased from $33.1 \pm 4.5\%$ to $39.5 \pm 5.9\%$ ($P = 0.001$), and the number of dysfunctional segments was reduced from 147 to 137. Only the trimetazidine group showed improved contractility during low-dose dobutamine testing; there was no significant change in patients receiving placebo. Thus metabolic intervention with trimetazidine has the potential to help preserve contractile reserve and protect viable myocardium, possibly through the mechanism of decreasing the amount of hibernated myocardium. Importantly, peak VO_2 was also significantly increased in patients taking trimetazidine (by 15% compared with controls; $P = 0.001$).

A study by Vitale and colleagues [8] was focused on the effect of 6 months of treatment with trimetazidine on left ventricular function in elderly patients (mean age 78 years) with ischemic cardiomyopathy. Trimetazidine, added to standard medical therapy, produced a significant improvement in left ventricular contractility after 6 months: left ventricular ejection fraction increased from 29% at baseline to 34.4% in trimetazidine group, compared with a decrease to 27% in the placebo group ($P < 0.0001$); left ventricular cavity size decreased and, interestingly, there was an improvement in diastolic function as a result of enhanced early diastolic relaxation in the trimetazidine group alone. These benefits were paralleled by improvement in NYHA class and overall quality of life in patients receiving trimetazidine 20 mg three times daily.

Very similar changes in left ventricular ejection fraction were reported by Rosano et al [9], who studied the beneficial effects of trimetazidine in 32 patients with diabetic cardiomyopathy, over a period of 6 months. An increase in left ventricular ejection fraction of $5.4 \pm 0.5\%$ ($P < 0.05$) was observed in the

trimetazidine group, and a small, non significant, decrease in the placebo group (2.4%, NS; $P < 0.01$ between groups). Similarly, significant improvements in regional wall motion score and in the efficacy of left ventricular relaxation were induced by trimetazidine

More recently, Di Napoli *et al* [10] have shown that long-term treatment with trimetazidine is beneficial in patients with ischemic left ventricular dysfunction. Sixty-one patients were allocated randomly to receive additional treatment with trimetazidine for 18 months. Persistent improvement in left ventricular performance was seen, starting at 6 months (left ventricular ejection fraction 30% at baseline, 32% at 6 months, and 37% at 18 months – an 11% difference compared with the deteriorating placebo group), together with a significant effect on ventricular remodeling. Plasma concentrations of C-reactive protein remained stable throughout the study in trimetazidine group, but increased significantly in the controls, suggesting that trimetazidine may curb deleterious inflammatory processes.

An important recent contribution came from El-Kady *et al* [11], who studied 200 patients aged 55 ± 12 years with ischemic left ventricular dysfunction resulting from multivessel coronary artery disease. The patients were allocated randomly to groups for 2 years to receive either treatment with trimetazidine 20 mg three times daily or placebo, after a background period of standard treatment over 24 months. This well treated, postinfarction (96%) symptomatic population (92% receiving angiotensin converting enzyme inhibitors, 72% receiving β-adrenolytic agents) presented with a mean baseline left ventricular ejection fraction of 36% and a mean wall motion score index of 2.2. Stress-gated single photon emission computed tomography using ^{99m}technetium-labeled methoxyisobutyl isonitrile was used to evaluate the perfusion and function of the left ventricle. Compared with baseline values, mean maximum work at peak exercise improved by 2 metabolic equivalents with trimetazidine, and ejection fraction improved from 36% to 44% (a change of 23%; $P < 0.001$), with no change in placebo group (37% and 37%). Wall motion score index improved significantly only in the trimetazidine group (from 3.1 to 1.6; $P < 0.001$). Interestingly, there was a distinct and significant ($P < 0.0001$) difference in survival between the groups, in favor of those receiving trimetazidine: their 2–year mortality rate was 8%, compared with 38% in those receiving placebo.

Mechanisms of action

There is evidence that heart failure is accompanied by increased extraction of plasma free fatty acids and decreased utilization of glucose in patients with congestive heart failure [12,13], with the exception of those with idiopathic dilated cardiomyopathy [14,15]. The ability to improve mechanical function without increasing metabolic demand and risk of ischemia was demonstrated both for trimetazidine and for ranolazine, another metabolic drug of the same class [16,17], and seems to be a critical mechanism responsible for the improvement observed in patients with heart failure. This is attributable to the ability of these agents to shift substrate utilization from fatty acid to glucose, by inhibiting 3-ketoacyl coenzyme A thiolase. However, recent studies provided novel data regarding ancillary actions of trimetazidine in heart failure. The findings of a study by Tabbi-Anneni *et al* [18] showed that another action of trimetazidine – an increase in phospholipid synthesis, leading to stabilization of cell membranes – may be another feature of its protective activity in heart failure, as demonstrated by their experimental model.

The anti-inflammatory effect of trimetazidine that manifests as a reduction in C-reactive protein concentrations (*Figure 2*), described in the study by Di Napoli [10], may be clinically relevant according to current understanding of atherogenesis and the complications of atherosclerosis. Other mechanisms, important in patients with diabetes and ischemic cardiomyopathy, were suggested by the findings of Fragasso *et al* [19], who showed that treatment with trimetazidine (20 mg three times daily) not only influenced the ejection fraction, but also reduced the concentrations of fasting blood glucose, glycated hemoglobin, and endothelin-1* (8.8 ± 3.8 compared with 10.9 ± 3.8; $P < 0.001$). Fragasso and colleagues also confirmed a reduced release of endothelin during physical exercise [20]. The same mechanism may play a significant part in skeletal muscle metabolism: Monti *et al* [21] recently reported that trimetazidine increased insulin-induced forearm uptake of glucose and glucose oxidation and decreased the release of endothelin-1, paralleled by a significant increase in forearm release of cyclic guanosine monophosphate. This is particularly interesting in view of the growing interest in the peripheral muscular deconditioning and cachexia that are present in heart failure.

Summary

Even though chronic coronary disease is nowadays the target of aggressive revascularization strategies, the problem of ischemic left ventricular dysfunction is growing. With a significant number of patients not qualifying for intervention (up to 30%, even in developed regions [22]), novel therapies for improving

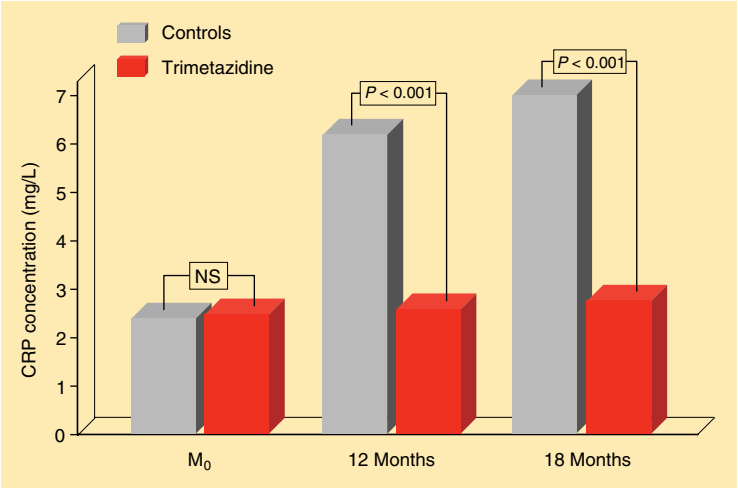

Figure 2. Changes in plasma concentrations of C-reactive protein (CRP) in patients with heart failure treated with or without (controls) trimetazidine in addition to their usual medication. (Data from Di Napoli et al [10].)

outcomes in such patients are necessary. There is increasing evidence that trimetazidine, a metabolic drug with proven antianginal and cardioprotective efficacy, can improve left ventricular function in the chronically ischemic myocardium. Novel important actions of the drug, such as reducing the release of endothelin, are under investigation, and the findings of preliminary randomized studies suggest that adjunctive therapy with trimetazidine may translate into improved survival in patients with ischemic cardiomyopathy. The available body of evidence indicates the need for a larger, clinical outcomes directed prospective, double-blind randomized trial of trimetazidine in ischemic heart failure. ■

* See glossary for definition of these terms.

REFERENCES

1. Eefting F, Nathoe H, van Dijk D, et al. Randomized comparison between stenting and off-pump bypass surgery in patients referred for angioplasty. *Circulation*. 2003;108:2870–2876.
2. Legrand VM, Serruys PW, Unger F, et al. Arterial Revascularization Therapy Study (ARTS) Investigators. Three-year outcome after coronary stenting versus bypass surgery for the treatment of multivessel disease. *Circulation*. 2004;109:1114–1120.
3. Szwed H, Sadowski Z, Elikowski W, et al. Combination treatment in stable effort angina using trimetazidine and metoprolol: results of a randomized, double-blind, multicentre study (TRIMPOL II). TRIMetazidine in POLand. *Eur Heart J*. 2001;22:2267–2274.
4. Brottier L, Barat JL, Combe C, Boussens B, Bonnet J, Bricaud H. Therapeutic value of a cardioprotective agent in patients with severe ischaemic cardiomyopathy. *Eur Heart J*. 1990;11:207–212.
5. Sisakyan HS. New therapeutic approach in chronic heart failure: metabolic intervention with trimetazidine. *Heart Metab*. 2005;26:23–26.
6. 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.
7. Belardinelli R, Purcano A. Effect of trimetazidine on the contractile response of chronically dysfunctional myocardium to low-dose dobutamine in ischemic cardiomyopathy. *Eur Heart J*. 2001;22:2164–2170.
8. Vitale C, Wajngaten M, Sposato B, et al. Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease. *Eur Heart J*. 2004;25:1814–1821.
9. 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.
10. Di Napoli P, Taccardi AA, Barossti A. Long term cardioprotective action of trimetazidine and potential effect on the inflammatory process in patients with ischaemic dilated cardiomyopathy. *Heart*. 2005;91:161–165.
11. El-Kady T, El-Sabban K, Gabaly M, Sabry A, Abdel-Hady S. Effects of trimetazidine on myocardial perfusion and the contractile response of chronically dysfunctional myocardium in ischemic cardiomyopathy: a 24-month study. *Am J Cardiovasc Drugs*. 2005;5:271–278.
12. Paolisso G, Gambardella A, Galzerano D, et al. Total-body and myocardial substrate oxidation in congestive heart failure. *Metabolism*. 1994;43:174–179.
13. Taylor M, Wallhaus TR, DeGrado TR, et al. An evaluation of myocardial fatty acid and glucose uptake using PET with [18F] fluoro-6-thia-heptadecanoic acid [F] FDG in patients with congestive heart failure. *J Nucl Med*. 2001;42:55–62.
14. Yazaki Y, Isobe M, Takahashi W, et al. Assessment of myocardial fatty acid metabolic abnormalities in patients with idiopathic dilated cardiomyopathy using 123I BMIPP SPECT: correlation with clinicopathological findings and clinical course. *Heart*. 1999;81:153–159.
15. Dávila-Román VG, Vedala G, Herrero P, et al. Altered myocardial fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy. *J Am Coll Cardiol*. 2002;40:271–277.
16. Sabbah HN, Chandler MP, Mishima T, et al. Ranolazine, a partial fatty acid oxidation (pFOX) inhibitor, improves left ventricular function in dogs with chronic heart failure. *J Card Fail*. 2002;8:416–422.
17. Chandler MP, Stanley WC, Morita H, et al. Short-term treatment with ranolazine improves mechanical efficiency in dogs with chronic heart failure. *Circ Res*. 2002;91:278–280.
18. Tabbi-Anneni I, Helies-Toussaint C, Morin D, Bescond-Jacquet A, Lucien A, Grynberg A. Prevention of heart failure in rats by trimetazidine treatment: a consequence of accelerated phospholipid turnover? *J Pharmacol Exp Ther*. 2003;304:1003–1009.

19. Fragasso G, Piatti PM, Monti L, et al. Short and long-term effects of trimetazidine in patients with diabetes and ischemic cardiomyopathy. *Am Heart J*. 2003;146:E18.
20. Fragasso G, Piatti PM, 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;39:413–439.
21. Monti LD, Setola E, Fragasso G, et al. Metabolic and endothelial effects of trimetazidine on forearm skeletal muscle in patients with type 2 diabetes and ischemic cardiomyopathy. *Am J Physiol Endocrinol Metab*. 2006;290:E54–E59.
22. Hemingway H, Crook AM, Feder G, et al. Underuse of coronary revascularization procedures in patients considered appropriate candidates for revascularization. *N Engl J Med*. 2001;344:645–654.