Trimetazidine effects on cardiac biomarkers in acute coronary syndrome

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Abstract
Trimetazidine acts at the cellular level, increasing myocardial glucose oxidation and shifting substrate utilization from fatty acid to carbohydrate metabolism. In an ischemic situation, this promotes the formation of adenosine triphosphate, the main source of cardiac energy, at less oxygen cost. The benefit on myocyte necrosis can be judged by reduction in release of biomarkers such as cardiac troponin, myocardial creatine kinase, brain natriuretic peptide, and interleukin 6. These beneficial effects of trimetazidine have been recorded in patients with acute coronary syndrome, treated medically or by percutaneous intervention or coronary artery bypass graft surgery. What is most gratifying is that these effects on cellular protection are associated with clinical improvement in symptoms, left ventricular function, cardiac events, and even mortality.  ■ Heart Metab. 2015;67:26-29

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Trimetazidine is a drug which treats myocardial ischemia through a metabolic pathway without having any hemodynamic effects. The metabolic effect is mediated by inhibition of mitochondrial long-chain 3-ketoacyl CoA thiolase, an enzyme that operates in the free fatty acid (FFA) β-oxidative chain. Its key function is increasing myocardial glucose oxidation and shifting from fatty acid to carbohydrate metabolism. This allows adenosine triphosphate (ATP) formation using less oxygen, which is deficient in ischemia. Although FFAs are a major source of ATP production in the heart, they require more oxygen than glucose to produce an equivalent amount of ATP. As a result, during ischemia, fatty acids are not as efficient a source of energy as glucose. Furthermore, during ischemia, the products of glycolysis such as lactate and protons accumulate and promote an increase in intracellular sodium and calcium, which in turn require more ATP to reestablish ionic homeostasis. By reducing cytosolic concentrations of FFAs and hydrogen ions, the cell membrane is protected from irreversible damage. Trimetazidine also reduces reactive oxygen species, improving myocardial integrity. The protection of cellular integrity translates into cell survival and improved cardiac efficiency.

Benefits of trimetazidine have been documented for stable angina, acute coronary syndromes (ACS), heart failure (HF), and in stent restenosis. It potenti-
ates the beneficial effects of exercise training on functional capacity, left ventricular ejection fraction, and endothelial-dependent relaxation. On top of optimal medical therapy, it is effective in reducing event-free survival in HF.

Effects of trimetazidine on cardiac biomarkers

Cardiac biomarkers such as cardiac troponin (cTn), high-sensitivity (hs) troponin, myocardial creatine kinase (CK-MB), and brain natriuretic peptide (BNP) have been well established in the diagnosis, management, and prognosis of cardiac diseases. The release of these markers can be used as a guide to determine the benefits of medical or interventional therapy. This article presents the effects of trimetazidine on biomarker release and demonstrates how this can be used to judge the efficacy of metabolic management of ischemia.

Biomarkers post–myocardial infarction

Pudil et al studied a population (average age 56 years) with acute myocardial infarction (AMI), admitted within 6 hours of onset of symptoms and treated with streptokinase. The trimetazidine group showed lower plasma E-selectin levels, and a significant reduction of plasma C-reactive protein level (CRP). In another study, 100 diabetic patients with AMI were prospectively enrolled and randomized to receive trimetazidine (group A, 50 patients) or placebo (group B, 50 patients), starting before thrombolysis. After 24 hours, 45 patients (90%) in group A vs 10 patients (20%) in group B showed peaking of cTn and CK-MB levels (P<0.05), suggesting less myocardial damage. Both biomarker levels were significantly higher in the placebo group at different sampling times (Figure 1).

Complete resolution of ST-segment elevation was recorded in 70% of patients in group A vs 36% in group B (P<0.05). Six months later, group A showed a higher left ventricular ejection fraction (LVEF) and fewer cardiac adverse events (P<0.05). They concluded that in patients with AMI receiving thrombolytic therapy, trimetazidine was associated with less myocardial damage, earlier successful reperfusion, improvement of LVEF, and fewer cardiac adverse events.

Biomarkers post–percutaneous coronary intervention

Percutaneous coronary intervention (PCI) provides an ideal opportunity to study the effects of trimetazidine prior to induction and relief of ischemia. In a study of patients with non–ST-segment elevation myocardial infarction (NSTEMI), Demirel showed that trimetazidine treatment, commenced prior to PCI and continued after PCI, improved left ventricular end-diastolic volume and decreased BNP levels.

Bonello et al, in a study of 582 patients, demonstrated that trimetazidine resulted in a significant reduction in the postprocedural cardiac troponin I (cTnI) levels and in the total amount of cTn released (Figure 2). He concluded that preprocedural administration of trimetazidine significantly reduces PCI-induced myocardial infarction.

In a study by Lin et al, 475 patients with ACS undergoing PCI were treated with trimetazidine and atorvastatin, or atorvastatin alone. Twenty-four hours post-PCI, cTnI concentration and myeloper...
oxidase activity were significantly lower ($P<0.05$) in the trimetazidine group; however, CK-MB and high-sensitivity CRP levels of the two groups did not differ (Table I). The administration of conventional doses of atorvastatin plus trimetazidine three days before PCI is able to protect PCI patients from myocardial injury.  

Recently, Shehata showed that trimetazidine given 72 hours before PCI in diabetic patients with renal dysfunction resulted in a decrease of contrast-induced nephropathy measured by rise in creatinine, and a decrease in myocardial injury measured by rise in cTnI. This could be an effective way of reducing contrast-induced nephropathy during interventions. 

Wang showed that biomarker levels above the upper limit of normal were significantly less in patients receiving trimetazidine seven days before PCI (12% vs 23% for CK-MB and 16% vs 35% for cTnI; $P<0.05$ for both). Myocardial infarction determined by CK-MB levels was detected post-PCI in fewer trimetazidine patients than controls (7% vs 12%; $P<0.05$). The benefit of pretreatment was so great that the incidence of periprocedural MI was reduced by nearly 42%. Periprocedural MI, a strong predictor of long-term adverse prognosis, can now be easily reduced and at relatively low cost. 

### Biomarkers post–coronary artery bypass graft surgery

In a prospective, double-blind, randomized, placebo-controlled study, the effects of trimetazidine on the inflammatory response was studied in patients undergoing coronary artery bypass graft surgery (CABG). Interleukin 6 levels were significantly lower in the treatment group compared with control at all time points assessed. This suggests that trimetazidine can reduce the inflammatory response in patients undergoing (CABG). 

Reperfusion injury is common during CABG with cardiopulmonary bypass, the critical moment happening at the end of surgery, when there is declamping of the aorta and release of hyperoxic radicals causing the injury. Martins et al studied 60 patients with mild left ventricular dysfunction undergoing CABG, treated with trimetazidine 15 days prior to the procedure. Cardiac troponin T (cTnT) and CK-MB were measured before and 5 minutes after aortic declamping, and 12, 24, and 48 hours later. There was a highly significant difference in favor of trimetazidine showing that it was effective in reducing ischemic reperfusion injury. 

### Biomarkers in ischemic cardiomyopathy

In a study involving 50 patients with ischemic cardiomyopathy, 25 patients were assigned to receive conventional treatment plus trimetazidine. The group receiving trimetazidine demonstrated a reduction in BNP levels ($135 \pm 22$ vs $252 \pm 44$ pg/mL; $P=0.001$) and cTnT ($P=0.001$), while the control group showed increased plasma BNP levels ($288 \pm 46$ vs $239 \pm 59$ pg/mL; $P=0.02$), with no change in cTn levels. Trimetazidine administration also resulted in a significant improvement in exercise tolerance assessed with a 6-minute walk test ($P=0.01$). 

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>cTnI (pg/ml)</th>
<th>CK-MB (zB/UL)</th>
<th>Δ MPO (cB/pmol/L)</th>
<th>Δ hs-CRP (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>238</td>
<td>0.63±0.47</td>
<td>25.1±3.6</td>
<td>38.8±19.5</td>
<td>5.60±6.33</td>
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<tr>
<td>Experiment</td>
<td>237</td>
<td>0.38±0.52*</td>
<td>25.7±2.6</td>
<td>15.7±25.2*</td>
<td>5.29±8.17</td>
</tr>
</tbody>
</table>

Table I Myocardial injury markers and inflammatory markers 24 hours after percutaneous coronary intervention. *$P<0.05$, compared with the control group. 

Abbreviations: CK-MB, myocardial creatine kinase; cTnI, cardiac troponin I; MPO, myeloperoxidase; hs-CRP, high-sensitivity C-reactive protein. 

Conclusion

A large amount of data is now available to show the beneficial effects of trimetazidine in improving myocardial ischemia, and reducing myocardial necrosis as deduced by a reduction in cardiac biomarkers. This is specially seen when trimetazidine is given preprocedure or as early as possible after the event, as metabolic manipulation shows maximum benefit before permanent myocyte damage occurs. The biomarker improvements have been shown in patients with ACS, both STEMI and NSTEMI with thrombolysis, PCI, or CABG. Importantly, the reduction in ischemic cellular damage as seen by biomarker improvements has translated into clinical benefits for these patients.

REFERENCES