

# Reperfusion injury: reduction by Vastarel MR

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## Abstract

Ischemia-reperfusion syndrome is defined as myocardial injury caused by the restoration of coronary flow. This phenomenon has a complex pathophysiology and results in a paradoxical reduction of the beneficial effect of myocardial reperfusion. Studies suggest that ischemia-reperfusion injury may account for up to 50% of the final size of a myocardial infarct. Vastarel MR (trimetazidine) is a pharmacological agent that shifts the preference for energy substrate away from fatty acid metabolism and towards glucose metabolism. Furthermore, it reduces intracellular acidosis, and protects against the toxicity induced by oxygen free radicals, which are key participants in ischemia-reperfusion injury. Accordingly, in animal studies a reduction in ischemia-reperfusion injury has been observed in association with the use of trimetazidine. These protective properties of trimetazidine over ischemia-reperfusion have also been suggested in clinical studies.

■ *Heart Metab.* 2008;40:23–25.

**Keywords:** Acute myocardial infarction, percutaneous coronary intervention, infarct size, ischemia reperfusion, cardiac energy metabolism, oxygen paradox

## Introduction

The technique of reperfusion during acute myocardial infarction has led to a dramatic decrease in the morbidity and mortality associated with coronary artery disease in recent decades. Restoration of blood flow within the “golden hours” has resulted in a reduction in myocardial infarct size [1]. Although greatly beneficial overall, the abrupt restoration of blood flow in the coronary arteries after occlusion was also, surprisingly, found to be associated with an additional and accelerated myocardial injury beyond that generated by ischemia alone, an observation first reported by Jennings et al [2]. This phenomenon has been called “ischemia-reperfusion injury” [3]. The process has a complex pathophysiology leading to cardiomyocyte death that is distinct from that associated with ischemic injury. Because of the deleterious

effects of ischemia-reperfusion injury, several treatments aiming to prevent or limit this process have been proposed [2]. Vastarel MR (trimetazidine) is an antianginal drug that acts by switching the energy substrate from fatty acid metabolism to glucose metabolism, thus making possible the increased formation of ATP with a decreased need for oxygen [4]. These properties are of great potential interest to the reduction of ischemia-reperfusion injury.

## Pathophysiology of ischemia-reperfusion injury

The pathophysiology of ischemia-reperfusion injury is complex. In this process, the re-oxygenation of ischemic myocardium generates a high degree of myocardial injury as a result of the generation of

potent oxygen-derived free radicals. This phenomenon is known as the "oxygen paradox". The oxidative stress also reduces the bioavailability of nitric oxide, which is critical to the improvement of coronary blood flow and inactivation of superoxide radicals.

Reperfusion is also associated with an abrupt increase and overload of intracellular calcium, which cause hypercontracture of cardiomyocytes, leading to cell death.

Activation and accumulation of polymorphonuclear neutrophils occur in the damaged myocardium, and contribute to the ischemia-reperfusion injury. Neutrophils are important for the development of reperfusion injury, releasing oxygen free radicals, proteases, and proinflammatory mediators that further amplify the infiltration of neutrophils into the jeopardized myocardium. Other processes involving platelets and complement also participate in ischemia-reperfusion injury. Acting together, these effects may last hours or months after reperfusion, and participate in sustained cardiomyocyte death [2,5].

### The impact of ischemia-reperfusion injury

The exact contribution of ischemia-reperfusion injury to infarct size is difficult to determine. However, on the basis of the observed reduction in infarct size associated with treatments preventing ischemia-reperfusion injury, it is postulated that up to 50% of the final size of the myocardial infarct is linked to the ischemia-reperfusion injury [3]. Reduction of this phenomenon should provide great clinical benefit, and is therefore currently the subject of extensive experimentation.

### Mechanism of action of trimetazidine

Trimetazidine is an antianginal drug that has no hemodynamic effect and thus does not affect cardiac myocyte oxygen demand or supply in the same way as other antianginal drugs [6]. The mechanism of action of trimetazidine is related to the inhibition of the enzyme long-chain 3-ketoacyl coenzyme A thiolase, which is critical to the  $\beta$ -oxidation pathway. This inhibition decreases the utilization of free fatty acids as a source of energy for the myocardium, resulting in an increase in glucose oxidation. This metabolic switch acts to improve cardiac energy metabolism by switching ATP production from lipid to glucose oxidation, thus enhancing intramitochondrial coupling and favoring a more efficient mode of ATP production per mole of oxygen. Moreover, trimetazidine reduces intracellular acidosis and protects against the toxicity induced by oxygen free radicals.

The drug therefore directly protects myocyte structure and function, and increases cell resistance to hypoxic stress [4,5,7–9].

### Trimetazidine in the treatment of ischemia-reperfusion injury

A number of experimental studies have demonstrated that trimetazidine exerts direct anti-ischemic effects, limiting the accumulation of calcium and acidosis, inflammation, and the production of oxygen-derived free radicals after reperfusion [10]. Animal studies have investigated the potential impact of this drug on ischemia-reperfusion injury on the basis of these metabolic properties. They have constantly observed that trimetazidine was able to limit lethal ischemia-reperfusion injury by inhibiting the opening of mitochondrial permeability transition pores, which represents a crucial event in cardiomyocyte death after myocardial ischemia-reperfusion [11–15].

The potential benefit associated with the use of trimetazidine in ischemia-reperfusion injury during percutaneous revascularization in humans has been evaluated in patients with stable coronary artery disease. A study recently published suggested that this metabolic agent could decrease the ischemia-reperfusion injury associated with the procedure. In this prospective randomized study in patients undergoing contemporary percutaneous coronary intervention using direct stenting, we have observed that trimetazidine reduced myocardial ischemia-reperfusion injury as assessed by the release of troponin I<sub>c</sub> [16] (Figure 1). Importantly, such increases in biomarkers after percutaneous coronary intervention have been associated with long-term outcome [17,18].

Steg et al [19] used a multicenter randomized double-blind study to evaluate intravenous trimetazidine in patients undergoing primary percutaneous

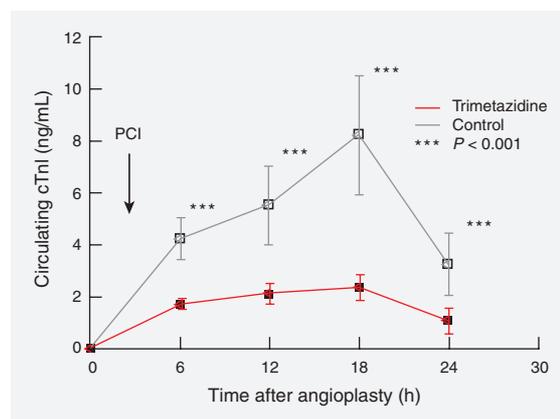


Figure 1. Time course of release of cardiac troponin I<sub>c</sub> (cTnI). Values are mean  $\pm$  SD. \*\*\* $P < 0.001$ .

coronary intervention in the setting of acute myocardial infarction. Although this study was small and underpowered to detect statistical differences in global or regional wall motion or clinical outcome, it was able to detect an earlier and more complete return of the ST-segment toward baseline in patients treated with trimetazidine. ST-segment normalization has been associated with improved coronary reperfusion and outcome. It therefore supports a beneficial effect of the infusion of trimetazidine during reperfusion in acute myocardial infarction, mediated by a reduction in ischemia-reperfusion injury [19].

## Conclusion

Ischemia-reperfusion is a complex process that is responsible for a large part of the size of the myocardial infarct after coronary artery occlusion. Trimetazidine exhibits metabolic properties that could be of particular interest in reducing ischemia-reperfusion injury. Accordingly, clinical studies have shown promising findings with this drug in reducing ischemia-reperfusion injury in patients undergoing percutaneous coronary intervention for stable angina pectoris or acute myocardial infarction. ■

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