Cardioprotective therapy in reperfusion injury: lessons from the European Myocardial Infarction Project – Free Radicals (EMIP-FR)

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Abstract

Early and successful myocardial reperfusion improves clinical outcomes of patients presenting with acute myocardial infarction (AMI). However, reperfusion itself can exacerbate myocardial injury beyond that caused by ischemia. The European Myocardial Infarction Project – Free Radicals trial (EMIP-FR) was one of the first studies that tested the hypothesis that a cardioprotective agent, such as trimetazidine, could reduce mortality from reperfusion injury in AMI. Compared with placebo, no benefit of such cardioprotection was observed for the population as a whole with respect to mortality. However, a significant benefit was observed in patients who had not undergone thrombolysis and were receiving trimetazidine, confirming the powerful anti-ischemic properties of trimetazidine, even in the setting of AMI.

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Introduction

It is now well established that early and successful myocardial reperfusion by either thrombolysis or primary percutaneous coronary intervention (PCI) represents the most effective strategy for improving clinical outcomes in patients presenting with acute myocardial infarction (AMI) [1–3]. However, soon after recognition of the crucial role of early coronary reperfusion in AMI [4–7], it became evident that reperfusion itself could potentially exacerbate myocardial damage above that produced by the initial ischemic insult – the so-called ''reperfusion injury'' [8–10]. Several strategies are currently under scrutiny to limit the ischemia-reperfusion injury that is associated with coronary recanalization in AMI, including administration of cardioprotective agents, mechanical prevention of distal coronary embolization, intermittent reperfusion, and thrombus aspiration.

The European Myocardial Infarction Project – Free Radicals (EMIP-FR)

The clinical relevance of protecting the ischemic myocardium from ischemia-reperfusion injury had been anticipated many years ago by a group of European investigators who, in the early 1990 s, designed the European Myocardial Infarction Project – Free Radicals (EMIP-FR) trial [11]. At that time, reactive oxygen species (ROS) were considered the major factors in ischemia-reperfusion injury, and benefits

observed in animal models were mostly attributed to a reduction in ROS [12]. Furthermore, in the setting of coronary revascularization, an anti-ischemic agent, trimetazidine, had been shown to have anti-ischemic and potentially cardioprotective effects that had been attributed to its antioxidant effects on membrane activity [13–15].

In this context, the EMIP-FR trial, recognizing reperfusion injury as an important determinant of the outcome of myocardial perfusion therapy, was designed to test the hypothesis that trimetazidine could reduce mortality resulting from reperfusion injury in patients with AMI. It was a double-blind, multicenter study, conducted from 1992 to 1996, that included a total of 19 725 patients presenting with AMI, undergoing either thrombolysis or conservative therapy in cases of contraindication to reperfusion. Patients were allocated randomly to groups to receive either trimetazidine or placebo therapy with either the thrombolysis or the conservative therapy. Treatment comprised an intravenous bolus injection of 40 mg of trimetazidine followed by a continuous infusion of 60 mg/24 h for 48 h and was started before or simultaneously with the thrombolysis, and as soon as possible for those not undergoing thrombolysis. The primary endpoint was total mortality at 35 days. Secondary endpoints were death while in hospital, long-term mortality, cardiovascular mortality, and a combined endpoint of major adverse cardiovascular events. The results showed that, compared with placebo, trimetazidine did not confer any benefit on 35-day, hospital, or long-term mortality for the population as a whole. However, in those patients not undergoing thrombolysis, a non significant reduction in mortality was observed in those receiving trimetazidine in the intention-to-treat analysis, which became significant in the per-protocol population analysis.

EMIP-FR was therefore considered a disappointing clinical trial, adding to the list of other such trials with drugs that were very effective in animal models, but ineffective in humans. Although several years have past since the termination of EMIP-FR, we are still left with an unresolved conundrum: why have clinical studies failed to confirm the beneficial effects of pharmacological interventions that were observed in experimental models?

To reconsider the EMIP-FR study, although the investigators are to be congratulated for having promptly addressed the role of reperfusion injury in the clinical outcome of patients undergoing reperfusion therapy in STEMI, it has to be recognized that they committed a common mistake observed in the design of this kind of trials: the choice of the intravenous route of administration. Cardioprotective agents have been shown to prevent reperfusion injury if delivered by the intracoronary route or administered before reperfusion, but to be ineffective when given intravenously or after reperfusion. Besides permitting the drug to reach the ischemic area, intracoronary delivery also makes it possible to achieve a dosage of the drug that is optimal to carry out the specific action. This may be one of the reasons for the negative results of EMIP-FR and similar trials. However, there are other differences in methodology and biology between experimental and clinical studies, including: comorbid conditions, concomitant medication, preconditioning, severity and duration of ischemia, mode of occlusion and reperfusion, treatment-related factors, timing of drug administration, and choice of endpoint. A detailed analysis of these factors goes beyond the aims of this paper, but they should be kept in mind.

What needs to be emphasized is the clear demonstration of the anti-ischemic properties of trimetazidine. In the study design for EMIP-FR, trimetazidine was presumed to improve patient outcomes mostly on the basis of its anti-oxidant effects. However, although the anti-ischemic properties of trimetazidine had been noted previously, its mechanism of action was elucidated only later. Trimetazidine inhibits the enzyme 3-ketoacyl coenzyme A thiolase (3-KAT), and thus reduces fatty acid oxidation and stimulates glucose oxidation [16]. In this way it directly modulates the use of energy substrates in the heart, increases the production of ATP, limits ischemic injury, and thus improves cardiac performance. Moreover, during ischemia, it limits the increase in blood concentrations of free fatty acids, which augment lactate and proton accumulation, decrease cellular pH, and impair calcium handling [17].

In the EMIP-FR study, trimetazidine was tested in two distinct groups of patients: one undergoing reperfusion therapy (thrombolysis) and one not reperfused. As mentioned before, the final infarct size is determined by ischemic necrosis and reperfusion injury (*Figure 1*). The angiographic equivalent of reperfusion injury is the no-reflow phenomenon, and is observed in up to 35% of patients undergoing successful PCI [18].

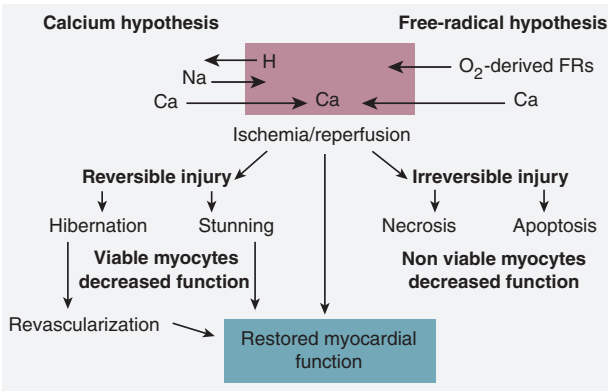

Figure 1. Cellular mechanisms involved in ischemia-reperfusion injury. FRs, free radicals.

Even though, in animal models, reperfusion injury accounts for up to 50% of the final infarct size [19], the burden of each major determinant (ischemia and reperfusion injury) is hard to determine in clinical practice, and this was so in the case of the thrombolysis group in EMIP-FR. In contrast, except for cases of spontaneous reperfusion, the non reperfused group experienced only the ischemia-related injury and, thus, any benefit obtained in this group of patients can be attributed to the anti-ischemic properties of the drug under investigation. Long-term mortality was greater in the non reperfused group (25.5%) than in the thrombolysis group (17.1%), and this is consistent with other findings that support prompt revascularization [20]. In addition, patients in the non reperfused group tended to have more previous myocardial infarction, and to have histories of angina, atherosclerotic disease, or diabetes mellitus. However, despite being at greater risk, patients in this group who received trimetazidine experienced a significant reduction in mortality in the per-protocol population analysis.

Summary

The EMIP-FR trial highlights the powerful anti-ischemic properties of trimetazidine in the setting of AMI. However, the study design for the trial prevented demonstration of the postulated cardioprotective effects of trimetazidine compared with reperfusion injury. Other factors may also have contributed to the lack of benefit in this context. Paradoxically, reperfusion injury is relevant in patients who undergo very early reperfusion, when a sizeable part of salvageable myocardium is present. The efficacy of cardioprotective agents is barely evident when the total ischemic time exceeds 2 h and the ischemic damage is complete and irreversible [21]. Given the negative results of subsequent clinical trials testing other cardioprotective agents (adenosine, cariporide, calcium channel blockers), it must be admitted that we are still far from correctly translating the findings from animal studies into clinical practice. In fact, even within acceptable time intervals for reperfusion therapy, the incidence of cardiac failure in AMI survivors is increasing progressively, reaching almost 25% [22]. ■

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