Editorial Comment

Reperfusion Injury

Putting the Genie Back in the Bottle?*

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Genie. A supernatural creature which occupies a parallel world to that of mankind . . . Possessing free will, . . . can be either good or evil.

—Wikipedia (1)

In this issue of the Journal, Newton et al. (2) describe a rare event: a negative study with potentially enormous impact. Their work, using cardiac magnetic resonance, demonstrates that administration of a single dose of cyclosporine at the time of percutaneous coronary intervention for ST-segment elevation myocardial infarction (STEMI), which prevents or reduces reperfusion injury, does not have adverse consequences for left ventricular (LV) remodeling in the post-infarction period (2). To put this in context requires consideration of a long line of basic research and clinical frustration on the subject of reperfusion injury in myocardial infarction.

Contemporary understanding of acute myocardial infarction is grounded in the classic experimental infarct studies of Jennings et al. (3) starting in the 1970s. By the mid-1970s, recognition of the significance of reperfusion injury in reperfused myocardial infarction had also come into focus in experimental work (4). Subsequent work, stimulated initially by both the advent of intracoronary mechanical and thrombolytic reperfusion and the emergence of intravenous thrombolytic therapy, systematically evaluated multiple potential mechanisms of reperfusion injury and explored potential approaches to the prevention or reduction of reperfusion injury (5–14). These mechanisms now include oxidative stress, increased intracellular calcium, rapid restoration of myocardial pH, inflammatory processes, metabolic modulation, and opening of the mitochondrial permeability transition pore (MPTP) (13–27).

Studies in animal models have shown that 50% of infarct size may be related to reperfusion injury, and a number of strategies reduce infarct size in such models (28). Currently, 3 interrelated approaches are of particular interest: prevention of MPTP opening, ischemic post-conditioning, and activation of the reperfusion injury salvage kinase (RISK) pathway. Ischemia alters the MPTP, whereas calcium overload and excessive production of reactive oxygen species in the early minutes of reperfusion trigger the opening of the MPTP (29–32). During reperfusion, the open MPTP allows free entry of proteins into the mitochondria, which results in an osmotic load and mitochondrial swelling and rupture as well as ionic gradient disruption across the mitochondrial membrane leading to hydrolysis of adenosine triphosphate (29,30,33). Ischemic post-conditioning decreases infarct size by limiting reperfusion injury through repetitive interruption of myocardial perfusion during primary percutaneous coronary intervention (34). The effect is linked to the activation of protein kinases, which in turn mediate their cardioprotective actions through the MPTP (35,36). RISKs are protein kinases that prevent lethal myocardial reperfusion injury. The RISK pathway can be activated through mechanical as well as pharmacologic agents, including ischemic post-conditioning and preconditioning. Pharmacologic activators include glucagon-like peptide, erythropoietin, atorvastatin, and atrial natriuretic peptide (34,37–39).

However, clinical implementation of strategies to prevent reperfusion injury has not been very successful to date (28). Thus, guidelines for the management of STEMI remain silent on the subject, and a potentially important approach to reducing morbidity and mortality of myocardial infarction remains unused.

Cyclosporine is a known blocker of MPTP opening, which can reduce infarct size in experimental models (40–43). Cyclosporine inhibits MPTP opening via its binding to the peptidylprolyl isomerase cyclophilin D located in the mitochondrial matrix. Recently, Piot et al. (44) reported a successful clinical demonstration of the prevention of reperfusion injury in patients, showing a reduction of the infarct size by roughly 20% (by cardiac magnetic resonance) to 40% (by troponin curve) with administration of a single dose of intravenous cyclosporine at the time of primary percutaneous coronary intervention for STEMI, resulting in reductions in LV end-systolic and -diastolic volumes, in a small randomized trial reported in the New England Journal of Medicine.

However, cyclosporine is not specific for cyclophilin D and also binds to cyclophilin A (45–47). This complex could have a detrimental effect on post-myocardial infarction myocardial remodeling because it inhibits calcineurin, which is essential for compensatory hypertrophy. Remodeling...
ing, with chamber dilation and an element of compensatory hypertrophy is, of course, a common result of moderate- to large-size myocardial infarctions. The hypertrophic component may be, at least initially, considered to be beneficial, offsetting the increased workload on the myocardium imposed after myocardial infarction (45). Hypertrophy in this setting is associated with increased intracellular calcium or enhanced sensitivity to calcium, and the calcium/calcmodulin-dependent protein phosphatase calcineurin seems to be central to translation of elevated intracellular calcium levels to trophic signals mediating hypertrophy (46). In consequence, development of cardiac hypertrophy in experimental infarct models is prevented by calcineurin inhibition, which can result from administration of cyclosporine. Experimental studies using high doses of cyclosporine and prolonged treatment after infarction have clearly demonstrated such effects (47).

Thus, a need existed to determine whether the cyclosporine protocol developed by Piot et al. (44), using only a single dose of the agent, would also affect post-infarction remodeling. In the original study, 58 patients with acute STEMI were randomized to receive a single 2.5-mg/kg dose of intravenous cyclosporine or placebo, and infarct size was assessed using cardiac enzymes and, in 27 patients, using delayed enhancement cardiac magnetic resonance infarct imaging on day 5. To address the remodeling issue, the same group has now imaged patients from the original cohort (13 controls, 15 treated with cyclosporine) 6 months after infarction. The results showed persistent reduction in infarct size with persistently reduced LV end-systolic volume and a strong trend toward reduced end-diastolic volume at 6 months in the cyclosporine group. There was no difference between groups in global LV mass or regional wall thickness in remote, noninfarcted myocardium at 6 months. The authors conclude that cyclosporine can significantly decrease the infarct size during reperfusion without any detrimental effect on myocardial remodeling over 6 months.

Clearly, these are small pilot studies and larger multicenter, randomized clinical trials will be needed to obtain more definitive results. In addition, there are other potential agents for the prevention of MPTP opening, such as minocycline, that merit evaluation (48). Further, there are other strategies for the prevention of reperfusion injury that merit further exploration (e.g., ischemic post-conditioning and RISK activation). Nonetheless, this is an important advance and seems to be the first practical step toward putting the genie of reperfusion injury back in the bottle.

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Key Words: myocardial infarction • reperfusion injury • cardiac MRI • cyclosporine.