

EDITORIAL COMMENT

Cyclosporine A Prior to Primary PCI in STEMI Patients



The Coup de Grâce to Post-Conditioning?*

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One major predictor of morbidity and mortality after a myocardial infarction is infarct size (IS). Early revascularization, with the aim of re-establishing coronary flow, is indeed the best available treatment, provided that it is implemented early enough after coronary artery occlusion. However, in the process of myocardial salvage via reperfusion, the heart is also subjected to reperfusion injury (RI), whose unfavorable manifestations include both transient (myocardial stunning, arrhythmias) and irreversible components (microvascular obstruction and lethal RI) (1).

More specifically, lethal RI occurs when cells reversibly damaged by an ischemic insult are induced to die by the subsequent reperfusion. The technical inability to assess the relative injurious consequences of ischemia and reperfusion in the same biological sample has led to skepticism in many cardiologists, who for several years have underestimated, or even refused to believe in the existence of RI. This controversy is not merely academic, but has important clinical consequences because it implies that reperfusion itself triggers injurious events, independent from those occurring during the preceding ischemic period, which can be attenuated, or even prevented, by specific interventions delivered only at the time of reperfusion. The dispute seemed to be settled in favor of the “believers” with the seminal discovery of

ischemic post-conditioning (PC), that is repeated cycles of brief reperfusion/reocclusion, resulting in substantial salvage of ischemic myocardium from infarction. The fact that procedures performed during reperfusion and after conclusion of ischemia could significantly reduce IS validated conceptually the existence of lethal RI. PC, ischemic pre-conditioning, and remote ischemic conditioning (in which cycles of brief ischemia and reperfusion are applied to the heart itself before ischemia or to a remote organ, respectively) are cardioprotective interventions sharing common signaling pathways, whose activation minimizes IS by triggering ischemic conditioning (IC) (2). Mitochondria are reportedly the most important mediators of IC, carrying the “structural gear” of cardioprotection, such as the mitochondrial permeability transition pore (MPTP) and adenosine triphosphate-sensitive potassium channels, which are true points of convergence of multiple signaling molecules involved in IC. MPTP, for instance, is a mega-channel in the inner mitochondrial membrane, whose opening upon reperfusion spawns a lethal chain of events (including oxidative phosphorylation uncoupling, matrix swelling, rupture of the outer mitochondrial membrane and cytosolic release of cytochrome c), finally resulting in caspase activation and apoptotic cell death. Inhibition of MPTP opening at the onset of reperfusion is deemed the single most powerful event resulting in IC. Hence, with the final goal of mimicking pharmacologically endogenous IC, several inhibitors of MPTP opening have been developed and tested.

Despite the dramatic shortening of the time elapsing between diagnosis and revascularization (door-to-balloon time was reduced from 83 min in 2005 through 2006 to 67 min in 2008 through 2009), in-hospital mortality of patients with ST-segment

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elevation myocardial infarction (STEMI) has remained virtually unchanged (3). As such, novel interventions capable of reducing IS beyond the extent provided by early coronary reperfusion are stringently needed. Because of the inability to affect retroactively damage initiated during ischemia, attention has turned to reducing the extent of RI, the only component of the overall damage amenable to intervention. One promising pharmacological agent with the expectation to reduce RI and thus lessen IS is cyclosporine A (CsA), the epitome of the cardiovascular drugs that pharmacologically mimic the effects of ischemic PC. CsA inhibits cyclophilin D, which decreases the threshold for MPTP opening in response to calcium and inorganic phosphate, both of which accumulate during ischemia and, even more so, during reperfusion (4).

Indeed, CsA has been shown to reduce myocardial RI in animal studies and small clinical trials. A pilot study by Piot et al. (5), for instance, showed a significant reduction in IS and creatine kinase (CK) release in acute STEMI patients randomized to CsA therapy (5). Six-month follow-up of 28 patients from this study documented persistent IS reduction, attenuation of left ventricular (LV) dilation, and improvement in LV ejection fraction by cardiac magnetic resonance (CMR) imaging in the CsA group (6).

However, the subsequent phase III clinical trial, CIRCUS (Cyclosporine to ImpRove Clinical oUtcome in STEMI patients), an international, prospective, multicenter, randomized, double-blinded, placebo-controlled trial of 975 patients, reported no significant difference between the CsA and placebo groups in the primary endpoint, a composite of 1-year all-cause mortality, rehospitalization for heart failure (HF) or HF worsening, and LV adverse remodeling (7).

Similarly, other clinical trials testing the cardioprotective role of CsA in acute STEMI patients did not disclose beneficial effects. In a double-blinded, randomized clinical trial of 101 patients with acute anterior STEMI receiving thrombolytic therapy, Ghaffari et al. (8) reported that an intravenous bolus injection of CsA administered immediately before thrombolysis did not result in IS reduction (evaluated by peak troponin and CK release) or improvement in clinical outcomes (i.e., occurrence of major arrhythmias, HF, LV ejection fraction, in-hospital, and 6-month mortality rates).

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In this issue of the *Journal*, the latest clinical trial, CYCLE (CYClosporinE A in reperfused myocardial infarction), by Ottani et al. (9) reinforces the lack of

success of CsA in improving $\geq 70\%$ ST-segment resolution (STR) at 1 h after percutaneous coronary intervention (PCI) (primary endpoint), high-sensitivity troponin T (hs-TnT) release on day 4, as well as LV remodeling and clinical events at 6 months (secondary endpoints). Of note, the CYCLE investigators adopted the usage of Sandimmun, the CsA formulation chosen by Piot et al. (5) in the original pilot study, instead of CycloMulsion, the newer formulation of CsA to which the negative outcome of the CIRCUS trial was erroneously attributed.

Although resolution of the sum of ST-segment elevation (sum STR) after reperfusion therapy by fibrinolysis was used in prior studies to predict IS, LV function, epicardial vessel patency, and mortality, new work raised the possibility that successful reperfusion and IS reduction may occur without any appreciable change in STR. In a clinical study of 180 first acute STEMI patients (10), no association was found between STR and IS, LV function, and microvascular injury, as assessed by CMR. Further questions regarding STR as a marker of reperfusion have been raised by 2 recent reports from the INFUSE-AMI (Intracoronary Abciximab and Aspiration Thrombectomy in Patients with large anterior MI) clinical trial, enrolling anterior STEMI patients treated with PCI. Although a significant correlation between STR and 30-day IS by magnetic resonance imaging was initially reported, a subsequent study from the same clinical trial comparing IS between 2 myocardial blush grade (MBG) groups (final MBG 0/1 vs. MBG 2/3, with MBG 2/3 considered successful myocardial reperfusion) documented that the MBG 2/3 group exhibited significantly greater final Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 (reflecting successful epicardial reperfusion), along with remarkably smaller IS and infarct mass, although not a significant difference in STR, as compared with the MBG 0/1 group (11). Hence, the use of STR in the CYCLE trial as the primary endpoint to assess the efficacy of reperfusion therapy may be inappropriate. Moreover, the use of single hs-TnT peaks at day 4, in the absence of definite validation, is hardly acceptable as a surrogate enzymatic estimate of IS and should have been replaced, or at least combined with the anatomic estimate of IS provided by CMR, currently the test of choice to assess the cardioprotective efficacy of different drugs used to curb RI. Although CMR may involve logistic and financial hassles, its use would also have been warranted, considering that CsA was not reported to exert any direct effect on myocardial edema, which plays a major role in the overall quantification of CMR-measured IS.

Another concern was raised by the CYCLE trial with regard to the safety of CsA. Although the trial was not powered to evaluate safety, and the investigators reported no statistically significant difference in adverse events between the CsA and placebo groups, the 2-fold incidence of 6-month mortality (4.4% CsA vs. 2.0% control), as well as the incidence of cardiogenic shock (2.9% CsA vs. 1.5% control) and the trend toward larger LV volumes raise the ominous possibility that CsA might even exert harmful effects. Because anaphylaxis, the potential side effect of the CsA formulation used in the CYCLE trial, did not occur, it is unlikely that the choice of the original formulation has played any role.

Despite some reservations regarding study design (open-label instead of double-blind, placebo-controlled) and the use of sub-optimally informative endpoints (i.e., STR, and assessment of single hs-TnT peaks as surrogate markers of IS instead of CMR), the CYCLE trial is unmistakably neutral. PC has been extensively investigated in STEMI patients. The enthusiasm raised by the landmark study of Staat et al. (12), which reports successful PC of the human heart, was subsequently curtailed by the negative findings of additional, relatively large all-comers trials, including the POST (Effects of Postconditioning on Myocardial Reperfusion in Patients With ST-Segment Elevation Myocardial Infarction) trial (13) and the most recent LIPSIA CONDITIONING trial (14), both of which did not disclose any benefit of PC combined with PCI.

Thus, what are the translational implications of these disappointing findings? Although the negative outcome of the CYCLE trial should not be seen as the ultimate coup de grâce to PC, it would be myopic to assert that the translational applicability of MPTP-opening inhibition to mimic PC has remained unscathed. However, there is more to PC than MPTP. Indeed, mitochondria are central, although not the only effectors of the conditioning phenomenon.

Several other players, including unknown intracellular mediators, can be targeted to improve the degree of myocardial salvage secondary to early reperfusion. The limited, or rather incomplete, understanding of the molecular mechanisms powering PC may be a chief reason for failure of the translational efforts. An alternative possibility is that we perceive as a macroscopic failure what is really a microscopic success. Because ischemia is the prerequisite, although not the ultimate cause, of cell death, its overall duration is sort of binding, in that it can be neither too short (a situation in which the cumulative damage caused by ischemia and reperfusion may not be enough to pass the threshold of irreversibility), nor too long (which would generate an ischemic event sufficient to start and complete the cell death process, independently of reperfusion). In practical terms, a 90-min period from the occurrence of coronary occlusion, namely the stringent door-to-balloon time advocated by the guidelines to achieve revascularization, may be an inadequate ischemic time to set the stage for the development of RI, particularly for the human heart, in which ischemic injury has a slow progression. If this is the case, PC may be successful in reducing microscopically an injury, whose extent is too small to be detected and quantified by current techniques. Even if this minimalist theory is correct, the translational implication of PC would still be low, unless future studies identify the ideal subpopulation of STEMI patients (possibly those exposed to ischemic times longer than 90 min) who can receive maximum benefit, not only from primary PCI, but also from pharmacological intervention aimed at reducing lethal RI.

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