REPERFUSION INJURY - CHALLENGES TO REDUCE IT

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Reperfusion achieved through pharmacological agents or mechanical angioplasty is associated with reperfusion injury. This implies several events associated with reperfusion, some transitory like reperfusion arrhythmias mostly ventricular arrhythmias and stunning of myocardium and permanent known as lethal reperfusion injury inferring death of myocardium induced by reperfusion. Whereas transitory effects have been accepted and documented, 'lethal reperfusion injury' following reperfusion in STEMI has long been a matter of deliberation.[1,2] This has been essentially due to lack of definitive clinical demonstration in spite of convincing experimental evidence. There has been a gap between well-defined and controlled experimental models and unclear human proofs - clinical models.[3] 'Lethal reperfusion injury' is defined as a potentially preventable death of myocardium that was viable at the time of reperfusion, which is consequence of events triggered or exaggerated by reperfusion. The fact that preventive maneuvers like post-conditioning limit infarct size without affecting ischemic injury is the best demonstration of the reality of lethal reperfusion injury.The idea of lethal reperfusion injury has since won progressive acceptance on the basis of evidence coming from clinical and basic science studies.[4]

The concept of reperfusion is based on four landmark studies conducted more than 30 years ago, two experimental and two clinical. These trials changed the course of STEMI treatment in less than a decade, encouraging development of strategies to reduce ischemic injury. First was the demonstration of a spatial progression of necrosis during an infarction by Reimer et al.[5,6] They demonstrated progression of a wave front of myocardial necrosis from the central subendocardial layers, where ischemia is most severe, to the less ischemic lateral boundaries of the AAR and the subepicardium. Second, was the demonstration of the reduced infarct size with reperfusion, first demonstrated the existence of myocardial salvage by reperfusion at 3 hr after coronary occlusion ("time is muscle").[7,8] Third, was the unequivocal demonstration that coronary thrombosis is present in most cases of ongoing STEMI by DeWood, reporting angiographic findings in patients studied shortly after the onset of STEMI.[9] Fourth, was successful experience with the administration of intracoronary thrombolytics (streptokinase), and later, in a larger group of patients.[10,11]

Emergence of reperfusion therapy for limiting ischemic damage during STEMI is one of the greatest success stories in the world of medicine. Mortality has

gradually reduced from close to 20% to around 5% due to employment of newer agents and strategies involving pharmacological and mechanical revascularization.[12] Progressive decrease in time between STEMI diagnosis and reperfusion contributed importantlyto this reduced mortality. It is widely accepted that the shortening of door-to-balloon time - the time between first medical contact and mechanical reperfusion results in greater myocardial salvage and better outcomes. Huge multidisciplinary efforts have resulted in a significant reduction in door-to-balloon times over the last 10 years as observed in all registries. In spite of these improvements in-hospital mortality has remained unchanged in the recent past, indicating the need to find other targets like components of total ischemic time and factors that contribute to infarct size.[13] The use of adjunctive antithrombotic agents with thrombolyticswas to enhance the effect of thrombolysis and this reflects a competition between lysis and ongoing thrombosis.[14] Aspirin as an effective adjunctive agent was established in the ISIS-2 - Second International Study of Infarct Survival trial in which the benefits of aspirin and streptokinase were additive.[15] Further evidence has been offered of clinical benefits by supplementing aspirin with new antiplatelet agents such as clopidogrel, ticagrelor, or prasugrel. Given the clear beneficial effect of optimal antiplatelet therapy in STEMI, it should be implemented in the testing of any cardio-protective strategy.[16]

Though reperfusion therapy - pharmacological and mechanical claimed rapid successes, development of therapies to reduce reperfusion injury has been rather disappointing. This disparity reveals the contrast between the forthright problem presented by restoration of blood flow and more complex processes associated with containment of reperfusion injury. Various pharmacological and non-pharmacological strategies have been explored to reduce reperfusion injury.

Definition of "*ischemic pre-conditioning*" was the first breakthrough in non-pharmacological interventions in 1986. This reported that brief cycles of ischemia and reperfusion performed *before* a prolonged coronary artery occlusion with reperfusion could dramatically reduce final infarct size in dogs. [17] Given that total ischemic time was unaltered rather increased by this intervention; it was proposed that there was more to limiting infarct size than a shorter duration of ischemia. This study ushered in a new era and stimulated research that increased our understanding of the pathophysiology of ischemia reperfusion (I/R) injury at the molecular level. This identified new targets for future novel therapies. Many years later, the infarct-limiting effects of ischemic pre-conditioning were shown to be due to a large extent to a reduction in reperfusion injury although it is also plausible that pre-conditioning can reduce ischemic damage.[18]

Ischemic pre-conditioning can never be applied in the clinical setting of STEMI due to unpredictability of coronary artery occlusion but it can have an important role in planned procedures like cardiac surgery.[19,20] The next breakthrough was concept of "*ischemic post-conditioning*" in 2003, demonstrating that brief episodes of ischemia and reperfusion performed immediately after reflow following prolonged ischemia could reduce final infarct size in dogs by 30% to 40%.[21] This effect was even more surprising than pre-conditioning, as the intervention was being applied after reflow; thus, it has no connection to the duration of ischemia or any associated event and must be related to the prevention of events occurring after reperfusion. This experiment demonstrated that lethal reperfusion injury is a reality;it is quite significant in an experimental setting (30% to 40% of final infarct size), and moreover it is amenable to timely intervention.[1]

Lethal reperfusion injury reduction concept was first tested in 2005 showing that ischemic post-conditioning can reduce infarct size in STEMI. In this proof-of-concept trial, ischemic post-conditioning was applied within one minute after reflow by inflating/deflating angioplasty balloon (low-pressure, upstream of the stent) in 4 one-minute cycles. This resulted in a 36% reduction of the area under the curve for creatine kinase release, a surrogate marker of infarct size.[22] Though many but not all, of the small trials performed showed infarct size reduction in patients undergoing post-conditioning.[19] However, the largest randomized clinical trial POST (Effects of Postconditioning on Myocardial Reperfusion in Patients With ST-Segment Elevation Myocardial Infarction) of post-conditioning in STEMI was neutral.[23] Remote ischemic conditioning - conditioning performed in a distant organ has been described as another form of myocardial conditioning well described in animal models.[24] In human scenario remote ischemic pre-conditioning 4 five-minute brachial cuff inflations applied during ongoing STEMI, during ambulance transfer to the PCI center and before PCI reperfusion resulted in increased myocardial salvage compared with regular PCI,with a potential for fewer long-term clinical events.[25,26]

Numerous pharmacological interventions have been investigated to reduce reperfusion injury. During the last decade past, many phase II clinical trials have been performed to find co-adjuvant pharmacological interventions to reduce myocardial damage associated with reperfusion in STEMI. As ischemic pre and post-conditioning during PCI cannot be applied, pharmacological agents that trigger similar pathways to ischemic conditioning have been extensively employed at the pre-clinical level and then translated into pilot clinical trials.[27] Cyclosporine-A is the paradigm pharmacological post-conditioning agent, which acts by inhibiting the opening of the MPTP, an event also seen with post- conditioning. In a randomized study, 58 patients received a single bolus of cyclosporine A or placebo immediately before PCI. Infarct size, measured by the area under the curve of creatine kinase, was significantly smaller in the cyclosporine-A group. [28]

Different Beta-blocking agents were tested in many STEMI trials before reperfusion became established practice in the 1970s to 1980s with suggestion but no definite evidence of their cardio-protective effect. The mechanism for this infarct-limiting effect is probably related to a decrease in reperfusion injury due to the effect of metoprolol on circulating cells (neutrophils/platelets) rather than cardiomyocytes; this is contrary to the old classical theory of reduced myocardial oxygen consumption.[29] METOCARD-CNIC (Effect of Metoprolol in Cardio- protection During an Acute Myocardial Infarction) trial evaluates 270 anterior STEMI patients undergoing PCI, randomized to early IV metoprolol or control before reperfusion. Infarcts, measured by CMR, were significantly smaller in the IV metoprolol group.[30] The effect was more noticeable in patients recruited during ambulance transfer to the PCI center.[31] Six-month CMR follow-up of more than 200 patients showed that the IV metoprolol group had a significantly higher mean LVEF and had significantly less cases of severe LVEF depression.[32] COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial), a much larger trial did not endorse the encouraging results of earlier trial due to various technical reasons like late administration of lytic agent, enrolment of Killip class 3 and inclusion of patients with borderline blood pressure.[33]

Possible therapeutic use of glucose to protect cardiomyocytes from energy depletion during AMI was described long time ago; combined administration of glucose/insulin/potassium (GIK) during ongoing myocardial infarction has been tested in several trials with some encouraging results.[34] IMMEDIATE (Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care) trial studied patients with ACS randomizing them to GIK or placebo during transfer to the hospital. In patients presenting with STEMI, GIK significantly reduced CMR-evaluated infarct size.[35] However, these promising results need to be confirmed in an adequately powered prospective trial. Glucagon- like peptide-1 (GLP1) analogs, after promising pre-clinical results, was studied in 172 STEMI patients to receive IV injection of the GLP1 analog exenatide or placebo. Myocardial salvage on CMR was significantly higher in the exenatide group.[36]

Glycoprotein IIb/IIIa inhibitors have been shown to reduce thrombotic events due to their potent effect on platelets and platelet-leukocyte aggregates. The INFUSE-AMI trial studied 452 anterior STEMI patients undergoing PCI in 2 by 2 factorial randomization to test the effect of abciximab and/or thrombectomy on infarct size, as evaluated by CMR. Thrombus aspiration had no effect on infarct size, but intracoronary administration of abciximab significantly reduced infarct size. Now that the current standard of care for STEMI patients includes use of potent oral antiplatelet agents, glycoprotein IIb/IIIa inhibitors are left for a selected STEMI population.[37]

Over the past decades, important progress has been made in phase II trials evaluating protective interventions against lethal reperfusion injury. The challenge for the future is to design larger trials to evaluate clinical outcomes employing newer therapies to contain lethal reperfusion injury. It is believed that the advances in the next decade will emerge from refining the current day therapies rather that identifying new drugs.

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