Adjunctive Therapy to Reduce Infarct Size: Current and Future Challenges

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ST elevated myocardial infarction needed to primary coronary intervention within 90 minutes occurred when coronary artery is totally occluded. When coronary artery flow was recovered, myocardium could be injured by restoration of blood flow, defined as reperfusion injury. To reduce the size of myocardial injury during reperfusion is great challenge and many clinicians try to discover the best way to protect myocardium from reperfusion injury. Lethal reperfusion injury is one type of cardiac dysfunction and it is considered to accelerate the myocardial injury during myocardial reperfusion period. There are three paradoxical mechanisms which induce lethal reperfusion injury : (1) oxygen paradox, (2) Ca2+ paradox and (3) pH paradox. All of these factors open mitochondrial permeability transition pore(mPTP), which results in loss of ATP and cell death. Therefore, the mPTP is a cornerstone of lethal reperfusion injury mechanism. Furthermore, it is one of new targets to prevent ischemic mycocardium from reperfusion injury. The mitochondrial permeability transition pore (MPTP) is a non-specific pore that opens in the inner mitochondrial membrane (IMM) when matrix [Ca2+] is high, especially when accompanied by oxidative stress, high [Pi] and adenine nucleotide depletion. Such conditions occur during ischemia and subsequent reperfusion, when MPTP opening is known to occur and cause irreversible damage to the heart. Matrix cyclophilin D facilitates MPTP opening and is the target of its inhibition by cyclosporin A that is cardioprotective. Less certainty exists over the composition of the pore itself, with structural and/or regulatory roles proposed for the adenine nucleotide translocase, the phosphate carrier and the FoF1 ATP synthase. Under conditions favouring MPTP opening, calcium-triggered conformational changes in these proteins may perturb the interface between themgenerating the pore. Proteins associated with the outer mitochondrial membrane (OMM), such as members of the Bcl-2 family and hexokinase (HK), whilst not directly involved in pore formation, may regulate MPTP opening through interactions between OMM and IMM proteins at "contact sites". Cardioprotective protocols such as preconditioning inhibit MPTP opening at reperfusion by preventing the loss of mitochondrial bound HK2 that stabilizes these contact sites. Contact site breakage both sensitises the MPTP to [Ca2+] and facilitates cytochrome loss from the intermembrane space leading to greater ROS production and further MPTP opening. The central role of MPTP opening in causing reperfusion injury appears well established as is the cardioprotection offered by its inhibition. Indeed, pharmacological interventions targeting CyP-D have been proven effective in a wide range of models including a small proof of principle clinical trial. Nevertheless, the effects are modest and not observed in all species. One reason for this may be that CyP-D only facilitates MPTP

opening which can occur in its absence when the stimulus is sufficient. Development of new drugs that target the pore forming component of the MPTP would be preferable, but uncertainties over the molecular identity of the MPTP make this difficult. Clearly, a major priority must be to clarify the molecular identity of the proteins that make up the MPTP and how they interact. Since the "front runners", the ANT, PiC and FoF1 ATP synthase, all have essential roles in oxidative phosphorylation, it is possible that knock down or knockout experiments will not be a suitable approach to provide unequivocal evidence for their role. This is especially true if the pore is formed from a novel conformation of one or more of these proteins or at an interface between them.

The animal studies about pharmacologic suppression of mPTP opening with using cyclosporine or sanglifehrin A during reperfusion reported that the myocardial infarct size was reduced by up to 50%, suggesting that mPTP opening might contribute to the final decision of infarct size. However, these approach showed no benefit in clinical trials. Intravenous cyclosporine did not reduce the primary end point, composite of all-cause death, worsening of heart failure during the initial hospitalization, rehospitalizaion for heart failure, or adverse left ventricular remodeling at 1 year.

Whether it will be effective when drugs are added just prior to reperfusion of an occluded vessel, as required in the treatment of myocardial infarction by PCI, remains to be established.