There have been many resounding victories in the war against coronary artery disease. Among those are antiarrhythmic drugs, pacemakers, coronary bypass surgery, coronary angioplasty, reperfusion therapy, and statins. But the one goal that has continuously eluded us has been the clinical availability of an effective cardioprotective agent. Although reperfusion therapy has partially achieved the goal of limiting infarct size in the setting of acute myocardial infarction, the logistics usually prevent restoration of perfusion until after a significant amount of myocardium has been lost to infarction. In 1974, when Braunwald1 proposed that priority should be given to the identification of interventions that would make the myocardium resistant to infarction, nobody knew what an arduous task that would be. In the beginning, “big pharma” was a strong partner in this quest, and many drugs were evaluated. The first wave of drugs like β-blockers and calcium antagonists were examined because it was believed that they would reduce oxygen consumption and that an improvement in the supply-demand relationship in the heart would suppress infarction. Unfortunately, the determinants of oxygen consumption in the ischemic heart are very different from those in the well-perfused heart, and not surprisingly, these drugs were ineffective. Then, the focus shifted to antioxidants and antiinflammatory agents. Their preclinical performance was inconsistent, and the clinical trials that they spawned were all decidedly negative. Most recently, a great deal of money was spent on the development of the sodium–hydrogen exchange blocker cariporide, which again failed in clinical trials. Adenosine and insulin suffered similar fates. With each negative trial, the industry has become increasingly leery of cardioprotective interventions, and most companies are now very reluctant to include primary cardioprotectants in their development pipelines. Nobody knows for sure why there has been such a dismal track record in the cardioprotection trials. One possibility may be that the animal models do not accurately mimic ischemia/reperfusion in humans. It is our opinion, however, that it was probably a case of the wrong drugs being tested because all of the above agents yielded very discrepant results in animal models.

The one glimmer of hope has been the odd phenomenon of ischemic preconditioning. Exposing the heart to a short sublethal period of ischemia causes it to become very resistant to infarction from a subsequent ischemic insult. The protected phenotype is transient, lasting only for 1 to 2 hours after the preconditioning ischemia. Discovered in 1986, ischemic preconditioning was the first demonstration that it was unambiguously possible to make the heart resistant to ischemia.2 Importantly, all who tried to reproduce it could. Investigators have dissected the mechanism of preconditioning over the following 2 decades and have learned a great deal about it. For example, the protection is the result of autacoids, including adenosine, bradykinin, and opioids, that are released during the preconditioning ischemia and activate complex signal transduction pathways that trigger entrance into the protected phenotype.

One particularly significant discovery was the finding that the actual protection from preconditioning occurs in the first minutes of reperfusion. We now know that a large amount of cell death caused by ischemia/reperfusion actually occurs when many of the mitochondria in the heart are destroyed by the formation of permeability transition pores in the first minutes of reperfusion. Although many refer to this as a reperfusion injury, we should remember that the mitochondrial injury that prompts pore formation is actually a product of the duration of the preceding ischemia. Reperfusion without prolonged ischemia is a benign event. Nevertheless, the ramification is that the protection given by preconditioning can be instituted right up to the time of reperfusion by activating appropriate signaling pathways, and numerous animal studies confirm that a number of interventions instituted just before reperfusion can duplicate the salvage of ischemic preconditioning. Unfortunately, despite the great strides that have been made in understanding the origin of infarction and the established strategies for preventing it, the industry seems to no longer be willing to gamble its money on cardioprotective agents. So, what is the cardiologist to do?

Several articles over the years have proclaimed that ischemic preconditioning in a remote region of the heart3 or even a remote organ like the intestine4 or kidney5,6 causes the heart to assume a preconditioned-like state. This “preconditioning at a distance” or “remote preconditioning” has been a scientific curiosity, but it recently was extended to humans when Loukogeorgakis et al7 demonstrated that ischemic preconditioning of one arm with a simple blood pressure cuff protected the endothelium of the contralateral arm from a mild ischemic insult. Of course, if one wants to apply this kind of protection to the setting of acute myocardial infarction, remote preconditioning is not an option because patients present only after ischemia has already begun. The attractiveness of remote preconditioning is that it is simple and safe and does not involve a drug that the industry must supply. Hausenloy et al8 recently tested a remote arm preconditioning protocol in patients undergoing coronary artery bypass sur-
gery and found that the release of the biomarker troponin-t was greatly attenuated in the preconditioned patients. Iliodromitis and colleagues tested intermittent arm ischemia in patients presenting with acute myocardial infarction and treated with primary coronary angioplasty. Unfortunately, their protocol did not protect and paradoxically caused an increase in the biomarkers of infarction. Either remote preconditioning is ineffective when performed after ischemia has begun, or perhaps the wrong preconditioning protocol was used.

In the present issue of Circulation, Loukogeorgakis and colleagues shed light on the above question by instituting remote preconditioning during the ischemic insult in their model of arm ischemia. They examined brachial artery diameter with ultrasound during the reactive hyperemia after a 5-minute brachial artery occlusion. The hyperemic flow causes an endothelial-dependent dilation called flow-mediated dilation. That dilation is greatly attenuated after an ischemic insult of 20 minutes of brachial artery occlusion followed by 20 minutes of reperfusion, but ischemic preconditioning of the contralateral limb prevents that loss of function. When the contralateral arm was exposed to ischemia/reperfusion cycles during the 20 minutes of ischemia of the other arm (postconditioning), no protection was seen. Although most investigators would have stopped there and published the negative data, these authors went 1 step further. They asked whether the failure to protect might have been related to insufficient tissue being made ischemic with the arm cuff during the repetitive ischemia/reperfusion cycles. So, they used a leg cuff. Interestingly, leg postconditioning preserved the flow-mediated dilation response. Their results suggest that the failure to limit infarction in the study by Iliodromitis et al may have been caused by their attempt to remotely postcondition too little tissue.

Whether leg postconditioning would be as effective against myocardial infarction is unknown. Obviously, it is impossible to extrapolate from endothelial protection to protection against myocardial infarction, but one encouraging observation emerges from the Loukogeorgakis study. They found that the ATP-sensitive potassium channel blocker glibenclamide abrogated the protection from leg postconditioning. Interestingly, opening of this channel is central to protection from ischemic preconditioning and postconditioning, and these new data indicate that the endothelial protection from leg postconditioning occurs by a similar mechanism. Clinical testing in patients with acute myocardial infarction is needed to determine whether leg postconditioning will be protective. This article follows a recent trend in which investigators are attempting to bypass industry by looking for protective strategies that do not depend on proprietary drugs. Foremost among these is ischemic postconditioning in which the coronary artery undergoes alternating reperfusion/occlusion cycles in the first minutes of reperfusion. All available evidence indicates that postconditioning targets the same permeability transition pores that preconditioning does. Post-conditioning can be accomplished in primary coronary angioplasty, and Staat et al recently showed that postconditioning of such patients caused a dramatic reduction in infarct size as assessed by creatine kinase release. If leg postconditioning proves to be effective, then this protection also could be extended to patients receiving thrombolytic drugs. A clear advantage of such studies is that the investigator no longer has to wait until a well-heeled pharmaceutical company decides to make a drug available for testing. Remote preconditioning or postconditioning is available to any investigator who can convince the local institutional review board to permit it. The downside, of course, is that the deep pockets of industry are not likely to be available for funding such research.

Disclosures

None.

References


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