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W(h)ither Myocardial Reperfusion Injury?

Kim P. Gallagher

Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan, Department of Physiology, The University of Michigan Medical School, Ann Arbor, Michigan

The title of this article is an intentionally egregious pun. *Whither* is one of those words you might expect to hear on "Masterpiece Theater." It means "to what place, result or condition" (*Webster's II, New Riverside University Dictionary*, Houghton Mifflin, Boston, 1984, p. 1316) is something or other headed. So the title of this article is meant, in part, to convey the question, Where are we going with reperfusion injury? The word *wither*, of course, means something else entirely, and it betrays my bias regarding reperfusion injury and where it is going. From the standpoint of a researcher in the pharmaceutical industry, the bottom line for any concept is therapeutic utility and efficacy, that is, does it translate into something useful in human patients? For the concept of irreversible myocardial reperfusion injury, unfortunately, I think the answer to this question is no.

Regarding reperfusion, clinical data indicate one thing with certainty: Restoring blood flow to previously ischemic myocardium is better than not restoring blood flow [1]. It limits the extent of damage ("time is muscle" idea) and may, even after relatively prolonged ischemic intervals, be beneficial [2]. The idea behind irreversible reperfusion injury, however, is that reperfusion itself exacts a price. As shown in Figure 1, infarct size due to ischemia per se is shown in black. The crosshatched portion (filled with question marks, again my bias) depicts an additional portion of irreversible injury due to restoration of blood flow. Had there been no reperfusion, the extent of infarction would have been larger still, potentially extending from the endocardium to the epicardium. Thus, the crosshatched area represents the potential target for pharmacologic intervention directed at reperfusion injury.

Given the scenario depicted in Figure 1, it is not surprising that both academic and pharmaceutical researchers have been very interested in reperfusion injury. An intervention given to every patient reperfused with a thrombolytic agent or angioplasty catheter could have enormous impact on public health (and stock prices) if it reduced the ultimate extent of damage in the patient. There is not much question that it is better to have smaller infarcts than larger infarcts.

Herein, however, lies the problem from the standpoint of a bottom-line industry scientist: We do not know if significant reperfusion injury actually occurs in human patients and, despite 20 years or so of experimental work on reperfusion injury, no anti-reperfusion intervention has had an impact on the problem of myocardial infarction in humans. Consequently, it is also not surprising that the pharmaceutical industry's interest in myocardial reperfusion injury (and acute myocardial ischemia, in general) has been waning of late. It is not enough for a concept to be scientifically intriguing to sustain it in industrial basic science labs. The concept has to be backed up by consistent preclinical data. Then it has to be demonstrable in human patients. On neither count does myocardial reperfusion injury look particularly strong from the standpoint of a bottom-line–oriented pharmaceutical researcher.

There is some irony here, because the number of experimental reports focused on myocardial reperfusion injury is enormous. Hundreds of papers have reported experimental infarct size reductions varying from 30% to 90%, depending on species and experimental circumstances. A variety of interventions have been used to evaluate different mechanisms proposed to explain reperfusion injury, with particular emphasis on oxygen free radicals, calcium overload, and neutrophils [3]. Consequently, the phrases *reperfusion injury* or *ischemia/reperfusion injury* are well entrenched in the myocardial researchers' vernacular.

Most of the evidence supporting the importance of irreversible reperfusion injury was obtained in acute experiments, involving open-chest, anesthetized animals in which reperfusion intervals were measured in hours rather than days. For example, superoxide dismutase and catalase seemed to work fine in short-term experiments but in conscious animals with longer reperfusion intervals, efficacy was not reproducible [4]. Even though there have been reports that demonstrated reperfusion injury distinct from ischemic injury [5], other studies have come up with different results and opposite conclusions [6]. Such disparate results suggest that the degree of myocardial reperfusion injury may depend mainly on the experimental species and circumstances in which it is measured. Which experimental species and circumstances

Address for correspondence: Kim P. Gallagher, Ph.D., Parke-Davis Pharmaceutical Research Division, 2800 Plymouth Road, Ann Arbor, MI 48105.

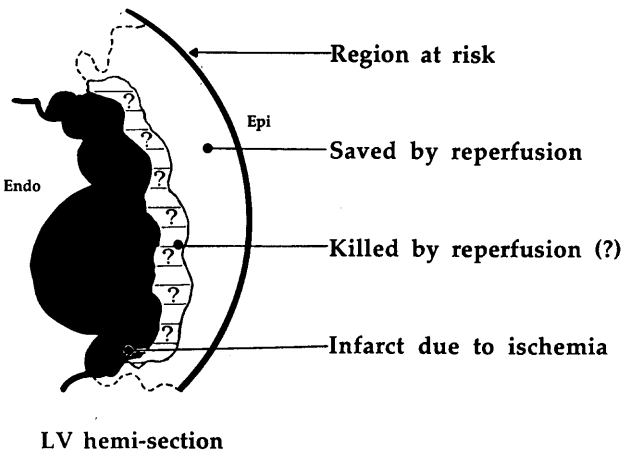

Fig. 1. Schematic depiction of irreversible reperfusion injury in a left ventricular (LV) hemisection. The region at risk is demarcated with dashed lines. Within the region at risk, ischemia alone produces an infarct (solid black), the size of which is determined largely by the duration and severity of ischemia. Reperfusion saves some of the myocardium (open portion) within the region at risk. Without reperfusion, the infarct may have extended from the endocardium (Endo) to the epicardium (Epi). The idea behind irreversible reperfusion injury, however, is that reperfusion exacts an additional increment of cell death (crosshatched portion filled with question marks) beyond that produced by ischemia alone.

best simulate myocardial infarction in human patients? Those that are associated with a lot of reperfusion injury or those that are not? It is not clear cut. A conceptual leap is needed to believe reperfusion injury is an important player in human myocardial injury, given that the experimental interventions, such as superoxide dismutase (SOD) and catalase, among others [4], have not been effective consistently.

The second concern is how to demonstrate that an intervention is useful in human patients. To define an intervention as "useful" requires that it produce an effect that is detectable, but measuring infarct size in humans is not easy or particularly accurate. Distinguishing infarction due to ischemia from that due to reperfusion may not be possible at all given the technical limitations of clinically applicable techniques. Thus, demonstrating significant reductions in the extent of myocardial damage, unequivocably attributable to a particular pharmacologic intervention, represents a daunting obstacle in human patients. The more noise there is in measurement of a clinical endpoint, the larger the size of a clinical trial required to demonstrate a statistically significant effect. Clinical trials are expensive and time consuming, so they represent a big risk for pharmaceutical companies. Small mistakes in study design can compound the problems associated with inherently noisy measurements, and the FDA is not a particularly forgiving agency. Combine these concerns with a concept backed up by conflicting experimental results, and it is easy to see why pharmaceutical companies are not exactly lining up to do reperfusion injury trials.

Despite my remarks, I suspect that research on interventions to modify reperfusion injury will continue. For those of you so inclined, please bear in mind that reports demonstrating that infarct size is reduced by 50% in animals by reperfusion intervention XYZ or son-of-XYZ or cousin-of-XYZ have been published, presented, discussed, and debated for quite a while. So much so, in fact, that a "50% reduction in infarct size due to ischemia/reperfusion injury" hardly raises a yawn anymore (much less stimulates a drug development program in a pharmaceutical company), especially if cousin-of-XYZ is a pretreatment. If the idea is to show an intervention works by reducing reperfusion injury, then the compound has to work if it is administered at reperfusion not just as a pretreatment. Admittedly, some compounds, such as adenosine [7], have worked in experiments when administered at reperfusion, but such results have not been followed up by clinical trials. The choice of animal species is also important because of the importance of native collaterals on ultimate infarct size [8]. Rabbits and pigs have negligible collateral investment so they may be better than dogs, who are characterized by quite variable levels of collateral perfusion animal to animal. One might argue that using dogs is warranted if careful measurements of collateral perfusion are performed. Unfortunately, the usual cutoff value for collateral perfusion is often set at 0.15–0.20 ml/min/g, which is probably much too high, but even that is not known with certainty.

One could also argue that definitive infarct studies should only be done in subhuman primates, not only because they are closer to humans phylogenetically but because of the intriguing evidence that infarcts are smaller in monkeys than pigs and dogs at comparable durations and intensities of ischemia [9]. Is there something unique about the myocardium of primates that makes infarct predictions based on dogs and pigs questionable? Questions like this one are important but may not ever get answered because of their cost and the dwindling number of laboratories that can afford to answer them.

In conclusion, an enormous effort has gone into studying myocardial reperfusion injury with the ultimate objective of modifying ischemic injury in human patients, an objective that has not been achieved. I'm not arguing that reperfusion injury does not exist. I think it very clearly does in a lot of experimental circumstances, but this does not mean the same thing happens in people. Doing the same kind of laboratory investigation that has been done for the last 20 years or so is not going to help us much. Yet another novel inhibitor of another novel cause of reperfusion injury reduces infarct size by 50% in anesthetized dogs? Does it matter? We still do not know with any degree of certainty that irreversible reperfusion injury is impor-

tant in humans, so I return to the original question: Whither myocardial reperfusion injury? In terms of human therapeutic utility, I think the answer is "wither" without the "h."

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