Lethal Reperfusion Injury: Does Anyone Still Care?

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In the early 1980s, the introduction of percutaneous transluminal coronary angioplasty (PTCA) and the reintroduction and adoption of thrombolysis demonstrated definitively the benefits of restoring blood flow to the ischemic myocardium. The potential merits of these procedures derived, in part, from the experiments of Jennings, Reimer, and colleagues [1] on the temporal progression of necrosis during ischemia, and the work of the group of Braunwald, Ross, Maroko, and others [reviewed in 2] showing that the benefits of reperfusion were significantly greater than anything achieved using pharmacological agents to minimize the extent of injury. In parallel to the advent of clinical reperfusion, experimentalists were beginning to suggest that reperfusion might not be without some deleterious consequences, and the spectre of a “reperfusion injury” arose [3]. Fifteen years later, while clinical cardiology has undergone a dramatic revolution thanks to widespread use of agents/procedures that promote coronary reflow, and despite general acceptance that reperfusion injury probably occurs to some extent, experimentalists continue to engage in arcane arguments over the precise definition, nature, and relevance of this concept.

Definitions and Evidence

Lethal reperfusion injury is defined as the death of myocytes, alive at the time of reperfusion, as a direct result of some aspect of the process of reperfusion. Based on this definition, Hearse [4] proposed criteria for the unequivocal demonstration of reperfusion injury, founded on the administration of a drug solely at the time of reperfusion, resulting in the limitation of infarct size, and the differentiation between accelerated recovery and absolute protection, that have been met with studies on adenosine [5], yet skeptics remain. The hallmark study of Engler and associates [6] that concluded reperfusion induces apoptosis of cardiomyocytes is further evidence for cell death provoked by reperfusion. Although the pattern of nuclear chromatin condensation was distinctly different in reperfused than in persistently ischemic tissue [6], purists will claim that the time course of apoptosis in cardiomyocytes is unknown and perhaps reperfusion merely accelerates this form of cell death, which would have occurred anyway. Certainly, it is not yet possible to look at a viable cell and predict if it will undergo apoptosis in the ensuing couple of hours. But while these intellectual critics remain on the fence, the practical cardiology revolution of the last 15 years continues.

It was probably Rosenkranz and Buckberg [7] who provided the first definition of reperfusion injury as a singular entity with “those metabolic, functional, and structural consequences of restoring coronary arterial flow...that can be avoided or reversed by modification of the conditions of reperfusion.” This broader definition, which embraces all cell types in the heart and all forms of injury, plausibly is more apt to the clinical setting and will be used in this commentary.

Clinical Significance

Any concept of lethal reperfusion injury is only relevant if it has some practical application to clinical cardiology and cardiac surgery. In the clinical literature there is evidence suggestive of reperfusion injury. For example,

- **Early hazard.** There is a small, but consistent increase in mortality in the first 24 hours for patients with acute myocardial infarction (AMI) receiving thrombolytic therapy when compared with those who do not receive a lytic agent [8].
- **Extent of reflow.** In the GUSTO angiographic sub-study [9], mortality in the first 6 hours did not differ between patients with TIMI 3 flow (complete reflow) and those with grade 0 or 1 (little or no reflow). However, mortality was three- to fourfold higher in patients with grade 2 flow, indicating that partial reperfusion is detrimental. Even beyond the first day, the GUSTO and TEAM studies provide convincing evidence that only AMI patients who achieve complete reperfusion (TIMI 3 flow) benefit from thrombolytic therapy, and that partial reflow (grade 2) is no better than no reperfusion, and may actually be harmful [10]. Lincoff and Topol [8] estimated that optimal reperfusion occurred in only 25% or less of patients with AMI that underwent thrombolysis.
- **Immediate PTCA.** It was thought that immediate percutaneous transluminal coronary angioplasty (PTCA) after thrombolysis would improve reperfusion and consequently reduce adverse events, such as recurrent angina and mortality, while improving myocardial performance. However, several clinical trials have failed to support this assumption, and
there was actually an increased incidence of complications, including reinfarction and death [11].

- **Infarct extension.** Also known as early recurrent infarction, it is thought to occur in ~20% of patients after successful thrombolysis and is considered to be a major complication that contributes up to 25% of the cumulative infarct size [12].

- **Antithrombotic agents.** ISIS-2 demonstrated that the use of aspirin as an adjunct to thrombolysis decreased mortality and reinfarction by ~50% [13]. Similar results were obtained independently in the GISSI study. The EPIC trial showed that blockade of platelet IIb/IIIa receptors with the c7E3 antibody (RheoPro) in high risk patients undergoing PTCA reduced the incidence of nonfatal myocardial infarction and emergency (repeat) PTCA [14].

It can be argued that many of these incidents might represent recurrence of ischemia or inadequate reperfusion. For example, platelet activation after PTCA probably is a consequence of plaque compression and rupture, rather than a consequence of establishing reflow per se. Nevertheless, these events represent "... consequences of restoring coronary flow ... that can be avoided ..." [7], and thus fit into the broader context of reperfusion injury. Moreover, the clinical situation is much more heterogenous and complex than the laboratory experiment. Successful thrombolysis restores perfusion not to normal tissue, but to a tissue comprised of a variety of cells, including cardiomyocytes, fibroblasts, vascular smooth muscle cells, endothelial cells, etc., each subjected to a mix of ischemic severities with differing vulnerabilities and responses, against a background of vascular disease, endothelial injury/dysfunction, intramural mast cell and macrophage activation, hyper-responsive circulating platelets and leukocytes, and a plethora of other factors. Attempting to define the proportion of injury that truly represents damage provoked by reperfusion is probably of minor significance (and limited clinical value) when many other critical factors contribute to the clinical outcome, including

- Time to reflow
- Severity, site (anterior vs. posterior), and extent of ischemia
- Presence or absence of antecedent angina that can precondition the heart and/or reduce the time for thrombolysis
- Pattern of reflow
  - TIMI grade flow
  - Epiacardial reflow without adequate myocardial tissue perfusion
  - Intermittent patency
  - Reocclusion
  - Vasoaspassm
- Platelet activation, thrombin production, tissue factor expression, endogenous procoagulant versus anticoagulant balance, production of a systemic lytic state
- Leukocyte activation (both circulating cells and intramural leukocytes of the coronary arteries) and cytokine production

Against this panoply of factors, it is unlikely that a single component that can be labeled "reperfusion injury" will be identified that demonstrably contributes to the incidence of cardiac morbidity or mortality (these being the relevant endpoints for this type of study, rather than infarct size). Because of the complexity of the clinical picture, no one drug is likely to resolve all the concerns of achieving optimal reperfusion. Therefore, I would propose that the concept of lethal reperfusion injury is unhelpful, outdated, and redundant when viewed in isolation. Essentially, reperfusion is inseparable from the preceding ischemia because it does not occur in the absence of ischemia, and it is part of the continuum of myocardial injury initiated by occlusion of a coronary artery. The key question is whether there is preventable cell death during ischemia-reperfusion. Studies on the phenomenon of ischemic preconditioning clearly imply that the answer is positive [15]. Of value is the identification of the mechanisms of preconditioning, the production of a pharmacological mimic as a therapeutic agent, and the definition of the temporal limits to the cardioprotective effects within the ischemia-reperfusion continuum. Practical considerations would prompt administration of a cardioprotective agent as early as possible, hoping to limit any cell death possible, whether it be provoked by ischemia or reperfusion.

New revolutions in cardiology will continue, perhaps recognizing the importance of apoptosis, or inducing long-term preconditioning, inhibiting cytokine formation and leukocyte activation post-cardiopulmonary bypass, or preventing restenosis, despite continuing debate about whether any problem provoked by reperfusing the ischemic myocardium actually exists. Potential issues surrounding reperfusion and cardioprotection will be resolved by these other approaches, rather than further attempts to define reperfusion injury.

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Due to reference limitations, many important citations have been omitted. Hopefully, the cited bibliography will enable the interested reader to find most of the key references.