The progression of myocardial ischemia is profoundly influenced by reperfusion, but the effects of reperfusion are complex (1-8). Reperfusion initiated within the first 2 to 3 hours after the onset of coronary occlusion limits the extent of myocardial necrosis. This is now routinely accomplished clinically by thrombolysis and various percutaneous coronary interventions (PCI). However, reperfusion also changes the pattern of myocardial injury by producing damaged cardiomyocytes with contraction bands and calcification (Baroldi’s coagulative myocytolysis) (9,10), coupled with reduced reflow (“no-reflow phenomenon”) and hemorrhage in the core of the ischemic zone (1-8). Although reperfusion can clearly salvage ischemic myocardium, reperfusion also can cause additional injury (Janus-like effect, the double-edged sword of reperfusion). This phenomenon is termed reperfusion injury and is manifest as functional impairment, arrhythmias and progression to cell death (lethal reperfusion injury). Reperfusion is mediated by bursts of Ca\(^{2+}\) and oxygen radical generation, compounded by accumulation of neutrophils in the microvasculature (1-8). While this basic information is established, there are a number of unresolved issues or uncertainties which are stimulating active research in the field, as discussed below.

Three major modes of cell injury and death have now been identified, i.e., oncosis (unprogrammed cell death, with cell swelling), apoptosis (programmed cell death type I, with cell shrinkage), and autophagy (programmed cell death type II, with cell inclusions) (5,11-15). Further work is needed to define the exact contributions of these modes of cell injury and death in evolving myocardial infarction, with and without reperfusion. This ongoing analysis requires careful attention to methodological issues involved in cytochemical and biochemical detection of these modes of cell death (5,11-15). Results with caspase inhibitors and mutant mouse models suggest approximate contributions of 50% each from oncosis and apoptosis to the extent of acute myocardial ischemia-reperfusion injury (16-18). However, documentation of classical cytological features of apoptosis in ischemic cardiomyocytes is problematic when apoptotic morphology in ischemic non-myocytes is readily demonstrable in evolving myocardial infarcts (15). The current published work leaves open several possibilities, including the concept of simultaneous activation of apoptotic and oncotic pathways, with the rate and magnitude of ATP depletion influencing the initial response of the
ischemic cardiomyocytes, and with the ultimate outcome being a hybrid mode of injury, best designated as myocardial ischemic cell death (5). In chronic heart failure, the three mechanisms of oncosis, apoptosis and autophagy appear to be simultaneously operative (12,13,18).

Modulation of myocardial ischemic injury can occur not only by reperfusion but by other phenomena, including myocardial stunning, preconditioning, postconditioning and remodeling (4,5,19). The extent to which these phenomena share similar and dissimilar mechanisms is uncertain. However, the interaction of these phenomena is key to the long-term outcome of a myocardial ischemic event.

Since lethal reperfusion injury may contribute up to 50% of the final size of a myocardial infarct, strategies to reduce the extent of reperfusion injury are clinically important (8). Considerable experimental work has explored pharmacological and other adjuncts for combination with coronary artery opening. However, translation of promising animal work to the clinical setting has been disappointing. Nevertheless, some promising new approaches are receiving active investigation. These approaches include:

- postconditioning, a process of series of brief, interrupted reperfusion episodes prior to full reperfusion, producing a graded reperfusion with salvaging effects on ischemic myocardium;
- approaches to promote the recently discovered reperfusion salvage kinase (RISK) pathway which promotes cell survival;
- and blockade of the mitochondrial permeability transition pore (PTP) aimed at preserving mitochondrial function and restitution of oxidative phosphorylation (8).

Finally, the potential role of precursor and stem cell therapy in combination with reperfusion is a very active area of research, as investigators pursue the quest for myocardial regeneration, which is the holy grail of cardiovascular medicine (20). There are more questions than answers in this field at this point (21-25). However, preliminary results to date indicate that delayed introduction of cell therapy is preferable to early intervention in ameliorating unregulated myocardial remodeling in an attempt to avoid chronic heart failure following a major acute ischemic event. Interesting possibilities exist in determining factors that may convert the toxic environment of acutely damaged myocardium into a more fertile soil for the nurturing of stem cells as well as ways to shore up the stem cells as they enter the battle for myocardial salvage and repair (21-25).

**Bullet Points:**
While experimental evidence indicates that oncosis and apoptosis each contribute about 50% to the extent of myocardial ischemic-reperfusion injury, the exact interplay of these mechanisms in the evolving myocardial infarct is open to interpretation and needed clarification.

Reperfusion, stunning, preconditioning, postconditioning, and remodeling can individually act as modulators of myocardial ischemic injury, but the intricacies of their interactions is determinative in producing a spectrum of favorable and unfavorable outcomes following an acute ischemic event.

Potential new approaches to successfully combining adjuvant therapy with coronary artery opening are postconditioning, activation of the reperfusion salvage kinase (RISK) pathway and blockade of the mitochondrial permeability transition pore (PTP).

If the use of precursor and stem cell therapy can be successfully combined with reperfusion, myocardial repair to prevent chronic heart failure may become a reality.

REFERENCES:


