New Insights Into the Open Artery Hypothesis

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Factors Affecting Left Ventricular Remodeling

Early coronary artery reperfusion is clearly the most important therapy for acute ST segment elevation myocardial infarcts. Early reperfusion reduces myocardial infarct size and in so doing helps to prevent or minimize deleterious consequences of a large myocardial infarction, including infarct expansion (thinning and dilation of the infarct), subsequent eccentric hypertrophy and dilation of the noninfarcted ventricular muscle, and global dilation of the left ventricle. These processes encompass the phenomenon of ventricular remodeling. One of the major determinants of death at 1 year after a myocardial infarction is the degree of dilation of the left ventricle (LV). However, suppose early reperfusion is not available. A number of manipulations and pharmacological therapies can be administered beyond the time frame of reducing myocardial infarct size and still reduce the extent of infarct expansion and LV remodeling (Table 1). Angiotensin converting enzyme inhibitors and angiotensin receptor blockers have been shown to reduce LV dilation and remodeling and in some studies reduce major cardiovascular events. Cell therapy and even some noncellular therapies (collagen, alginate) may thicken the infarct scar and prevent ventricular wall dyskinesis and certain suturing techniques have been attempted to prevent infarct expansion and remodeling. Late reperfusion—too late to reduce myocardial infarct size, but early enough to favorably affect infarct healing—also appears to limit infarct expansion and limit LV remodeling, and is the subject of the accompanying article.

Certain features are associated with worse LV remodeling (Table 2), including a large myocardial infarct, lack of any reperfusion, a large zone of no reflow, and certain antiinflammatory agents (such as steroids and a host of nonsteroidal antiinflammatory agents) introduced early enough to inhibit the healing phase of myocardial infarction.

Benefit of Late Reperfusion in Preclinical Studies

The concept that late reperfusion resulting in a patent infarct artery causes benefit beyond myocardial salvage (also referred to as the open artery hypothesis) remains somewhat controversial. Experimental studies and various thrombolytic and observational studies have supported the concept that late reperfusion may have certain therapeutic benefits. Hochman and Choo published a landmark study in 1987 demonstrating the benefit of late reperfusion. Rats were subjected to left coronary artery ligation for 30 minutes followed by reperfusion, or coronary occlusion of 2 hours followed by reperfusion, or permanent coronary artery ligation without reperfusion; the hearts were examined by histology 2 weeks later. The investigators used an “expansion index” calculation that took into account both the degree of LV cavity dilation as well as the degree of thinning of the infarct wall in relationship to the noninfarcted LV wall thickness. Rats reperfused at 30 minutes after coronary occlusion demonstrated smaller myocardial infarcts, less transmurality of the infarct, and less infarct expansion compared to rats with permanent coronary occlusion. However, although rats reperfused late (after 2 hours of coronary occlusion) did not differ in infarct size nor transmurality of the infarct compared to rats subjected to a permanent coronary occlusion, those reperfused late did demonstrate less infarct expansion. In a study by Hale and Kloner, the effects of early versus later reperfusion on long term left ventricular topography were assessed. Rats were subjected to proximal coronary artery occlusion for 30 minutes followed by reperfusion (early reperfusion) or 90 minutes of occlusion followed by reperfusion (late reperfusion), or permanent coronary occlusion, and then the rats were allowed to survive for 6 weeks. Early reperfusion reduced scar circumference and thinning of the infarcted wall and prevented LV cavity dilation. Late reperfusion still thickened the scar without significantly affecting scar circumference; late reperfusion resulted in a nonsignificant trend toward smaller LV cavity diameter and area compared to permanent coronary occlusion and did reduce expansion index compared to permanent coronary occlusion.

New Information on Late Reperfusion

The present article by Nakagawa et al extends these early observations of late reperfusion on several fronts. Using the rat coronary artery occlusion model, the investigators observed a benefit of reperfusion as late as 24 hours postcoronary occlusion on infarct wall thickness, infarct length, LV diameter, and LV function—suggesting that even reperfusion at 24 hours can prevent infarct expansion and remodeling. Furthermore, they extended our knowledge of the benefit of late reperfusion by examining the biological characteristics of the thickened wall over a period of 4 weeks. They showed that the increased infarcted ventricular wall thickness with late reperfusion was attributable to greater cellularity, including more myofibroblasts and endothelial cells—major components of granulation tissue. During the subacute phase of...
infarction, the proliferation rate of cells was greater and the incidence of apoptosis lower within the granulation tissue of hearts that received late reperfusion versus permanent coronary occlusion. Collagen fibers appeared earlier and were thicker and myocardial debris disappeared earlier with late reperfusion. Alterations in matrix metalloproteinase (MMP) 2 and 9 were implicated; there was less expression of these MMPs in the late reperfusion compared to the permanently occluded group. All of these observations point to the concept that late reperfusion enhanced the healing process. This makes sense in that late reperfusion would allow access to the infarct by those cells crucial to the scavenging of debris, laying down collagen, and forming new blood vessels.

Another intriguing feature of the present analysis was that late reperfusion did not affect the incidence of apoptosis of cardiomyocytes, which has been one theory regarding how late reperfusion might help prevent heart failure. Instead, these authors state that true apoptosis of cardiomyocytes is a very rare event. However, the authors did note a reduction of degenerative ultrastructural changes (myofibrillar loss, increased numbers of mitochondria) within surviving cardiomyocytes in the late reperfusion group compared to the permanently occluded group.

The present study as well as the earlier works by Hochman and Choo and Hale and Kloner support the open artery hypothesis. These studies suggest that reperfusion too late to reduce myocardial infarct size may still improve healing of the infarct, resulting in a thicker infarct wall, less infarct expansion, less LV dilation, and improved cardiac function. What remains unanswered by these preclinical studies is the determination of the exact duration of the window of opportunity during which late reperfusion can still enhance healing and at what time it is too late for reperfusion to benefit the healing and remodeling process.

**Recent Clinical Trials**

The enthusiasm for late reperfusion in the clinical setting was diminished by the Occluded Artery Trial or OAT trial, published in 2006. This was a large, multicenter, randomized study of 2166 patients with acute myocardial infarction who had total occlusion of the infarct related artery 3 to 28 days after myocardial infarction and qualified as high risk, with a left ventricular ejection fraction of less than 50% or a proximal coronary artery occlusion with a large risk region. Patients were randomized to routine percutaneous coronary intervention and stenting plus optimal medical therapy (n=1082) or optimal medical therapy without invasive opening of the infarct-related vessel (n=1084). The primary end point of this study was a composite of “death from any cause, reinfarction, or NYHA Class IV heart failure with hospitalization or admission...to a short-stay unit.” There was no significant difference in the primary end point between groups over 4 years, with 17.2% reaching it in the PCI group versus 15.6% in the medical group (hazard ratio = 1.16; 95% confidence interval of 0.92 to 1.45; P = 0.20). Why were these results negative? One possibility was that reinfarction rates tended to be higher in the PCI groups, so it is possible that reinfarction might have negated any benefit of reduced LV remodeling. In the design of the study, patients were randomized from 3 to 28 days after onset of acute myocardial infarction, and the median interval between myocardial infarction and randomization was 8 days. However, in the early description of myocardial infarct expansion in humans the process was well underway within the first week of acute myocardial infarction. Therefore initiating reperfusion at 8 days may simply have been too late to have a beneficial effect on remodeling. That reperfusion at this time may have been too late to prevent infarct expansion and left ventricular dilation was also suggested by an ancillary study of OAT, the TOSCA-2 study (The Total Occlusion Study of Canada-2), from the same investigators. Three hundred eighty-one patients who presented with an acute myocardial infarction and had an occluded infarct related artery at 3 to 28 days were randomized to either PCI with stenting or optimal medical therapy alone. After 1 year patients underwent repeat coronary and left ventricular angiography. Over the course of 1 year left ventricular ejection fraction increased in both groups without a significant difference between them. The PCI group showed an increase in ejection fraction of 4.2±8.9% (n=150) and the medical group showed an increase of 3.5±8.2% (n=136; P = 0.47). There was no significant difference in median change in LV end-systolic volume index or end-diastolic volume index between groups. Again, in this study PCI could be initiated 3 to 28 days after MI; the median was 10 days. The authors concluded that based on the OAT and TOSCA-2 study “routine PCI is not recommended for stable patients with a persistently occluded infarct related artery after myocardial infarction.” However, if reperfusion is not begun until 10 days after onset of acute myocardial infarction, the chances of interfering with LV remodeling may be very small as infarct expansion and LV dilation are already well underway.

**Table 1. Factors That May Improve or Lessen Post-MI LV Remodeling**

| 1. Early reperfusion (reduction of infarct size) |
| 2. Late reperfusion (no reduction of infarct size) |
| 3. Angiotensin converting enzyme inhibitors |
| 4. Angiotensin receptor blockers |
| 5. Cell therapy |
| 6. Non-cellular therapy—alginate, collagen, other noncellular matrix |
| 7. Aneurysmectomy |
| 8. Suturing the infarct |
| 9. ? Afterload or preload reduction in general |

**Table 2. Factors That May Worsen Post-MI LV Remodeling (Increasing Infarct Expansion and LV Dilation)**

| 1. Large infarcts |
| 2. No reperfusion (permanent coronary occlusion) |
| 3. A large no-reflow zone |
| 4. Antiinflammatory agents (steroids and certain nonsteroidal antiinflammatory agents) |
| 5. Over exertion or hypoxic exertion during infarct healing phase (swimming) |
| 6. ? Hypertension |
Conclusions

The preclinical studies consistently show a reduction of infarct expansion and left ventricular dilation when reperfusion is initiated late—meaning too late to reduce myocardial infarct size. However, it is likely that there is only a finite time window of opportunity in which late reperfusion can be initiated and still have a benefit; if reperfusion is induced beyond this window of opportunity, then LV remodeling is not affected. The present article by Nakagawa suggests that reperfusion even at 24 hours after coronary occlusion has benefit in a rat model. Their study suggests that the open artery hypothesis is alive and well and suggests that there is a need to revisit the issue with an OAT-like trial in which PCI is initiated at an earlier time point, such as 24 hours, rather than 8 to 10 days, after onset of acute myocardial infarction.

Disclosures

None.

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