Can Myocardial Infarct Size be Reduced by Mechanically Unloading the Left Ventricle?

Running title: Kloner; Infarct size and unloading the left ventricle

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Oxygen Supply/Demand Approach to Reducing Infarct Size

Great strides have been made in the treatment of acute myocardial infarction (MI). Improved outcomes and reduced mortality are largely the result of opening the occluded infarct artery as soon as possible and by keeping it open. Early reperfusion consistently reduces myocardial infarct size in both experimental animal models and in patients.

Despite advances in stenting of the occluded coronary artery and shortening of the “door-to-balloon” time, 1 month mortality post infarction still hovers around 15% and post myocardial infarction heart failure remains problematic. Therefore, there is still a need to try to further reduce myocardial infarct size in 2013. Initial concepts focused on reducing myocardial infarct size by improving the imbalance between O₂/nutrient supply and O₂/nutrient demand of the heart (Table 1). Improving O₂ supply by inducing early reperfusion with thrombolytic therapy, then angioplasty, and now stenting has been successful and dual antiplatelet therapy and possibly addition of anticoagulant therapy has further improved clinical outcomes, maintained vessel patency, and reduced stent thrombosis. Other techniques to improve O₂/nutrient supply such as hyperoxemia and erythropoietin have shown benefit in some but not all studies. Antianginal agents that vasodilate the coronary arteries and may improve coronary flow such as nitrates and calcium blockers in general have failed to reduce myocardial infarct size in clinical trials.

While restoring O₂ supply reduces ischemic cardiac damage due to myocardial infarction, attempts at reducing myocardial infarct size by reducing O₂ demand have yielded mixed results. Early clinical studies with beta blockers in the pre-reperfusion era were negative. However chronic beta blockers post MI were suggested to reduce fatal ventricular arrhythmias, reduce reinfarction and limit LV remodeling and post-MI heart failure and death. Some beta blockers combined with reperfusion were shown to reduce myocardial infarct size¹ and limit
microvascular damage, and in TIMI IIb immediate intravenous metoprolol coupled with thrombolysis reduced recurrent chest pain and reinfarction compared to delayed beta blockade. There has been a lack of large contemporary studies testing the effect of beta blockers coupled with angioplasty/stenting to determine whether in this setting they further reduce ischemic necrosis. Some studies suggested that other drugs that reduce oxygen demand, such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers are capable of reducing myocardial infarct size.

However, again there is little data from large contemporary studies combining these agents with early reperfusion achieved by percutaneous coronary intervention to determine whether they are capable of further reducing infarct size. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers given chronically after myocardial infarction have been shown to reduce post-MI remodeling, heart failure, and for ACE-inhibitors, reduce mortality. Another approach to reduce O₂ demand is by making the heart hypothermic. In experiments in our laboratory, this approach has consistently worked to reduce myocardial infarct size.

Hypothermia slows the reduction of myocardial ATP during ischemia and this appears to us to be a logical mechanism of action; however, recent studies suggest that hypothermia also may preserve certain signal transduction pathways including extracellular signal – regulated Kinase, which could be another mechanism of action. Clinical studies with hypothermia in patients with acute myocardial infarction have shown variable results, largely due to technical difficulties, such as inability to cool the heart great enough and quick enough prior to reperfusion. In clinical studies of anterior wall myocardial infarction in which temperature is reduced to ≤ 35°C prior to reperfusion there has been a positive signal for reduction in
myocardial infarct size. Heat exchange catheters have been tried but may not be adequate to reduce rapid and sufficient cooling, in all patients. Recently, a cooling “ThermoSuit” (Life Recovery Systems Napa, CA), was developed that induces systemic cooling very rapidly, achieving core temperatures of ~33.0 degrees C within 5-12 minutes. Such approaches are already being applied to cardiac arrest patients, in which therapy is begun in the field. This method of inducing hypothermia has yet to be applied to a myocardial infarct size reducing clinical trial. Other pharmacologic agents that have shown promise for reducing infarct size are adenosine infusions and ivabradine. Adenosine agonists and adenosine infusions can slow heart rate, vasodilate and in both some experimental and 2 large clinical trials showed reduction of anterior wall myocardial infarctions. Ivabradine, the If sodium channel blocker that slows heart rate without dropping blood pressure, appears promising in experimental models of infarct size reduction, but has not been tested clinically.

Mechanical Unloading for Reducing Infarct Size

Mechanical unloading is another approach that has been tried for reduction of myocardial oxygen demand and infarct size. While some experimental myocardial infarct size studies using intra-aortic balloon counterpulsation (IABP) showed reductions, in infarct size, this technique, that primarily reduces afterload, was unsuccessful in reducing myocardial infarct size in humans or in reducing death from cardiogenic shock. The reason for the negative clinical trials is unclear, as discussed by Kapur et al.

Experimental studies with a catheter mounted axial flow pump (moving blood from left ventricle (LV) to aorta) that reduced preload, did reduce infarct size in experimental models. R.W. Smalling et al. subjected anesthetized dogs to 2 hours of left anterior descending coronary artery occlusion followed by 1 hour of reperfusion and compared the effect of a
Hemopump transvalvular axial-flow LV assist device to intra-aortic balloon counterpulsation on LV unloading, coronary collateral blood flow and reduction of infarct size. The Hemopump device was placed through a laparotomy into the common iliac arteries and then it was advanced under fluoroscopic control across the aortic valve. Comparator animals received an intra-aortic balloon catheter placed by cutdown into the femoral artery and advanced to the descending aorta. Hemopump animals had a maximum flow increase of 3-3.5 Liters/min. During coronary artery occlusion, with the Hemopump LV support but not intra-aortic balloon counterpulsation, there was improvement (reduction) in LV segmental end-diastolic dimensions measured with ultrasonic crystals, suggesting diastolic LV unloading. The Hemopump also reduced systolic paradoxical motion. Mean aortic pressure was maintained, while LV systolic pressure and end-diastolic pressures were reduced with the Hemopump on during coronary occlusion. The intra-aortic balloon pump, when turned on during coronary occlusion, resulted in no change in mean arterial pressure, had a trend toward a modest decrease in LV systolic pressure and did not reduce LV diastolic pressure except at 1 hour after reperfusion. Control animals without LV mechanical support shared values similar to those in the treated groups when the devices were turned off.

With Hemopump LV assistance during coronary artery occlusion, regional myocardial blood flow in the risk region increased slightly from .05 to 0.1 ml/min/gm. There was no change with intra-aortic counterpulsation compared to controls. Myocardial infarct size, expressed as a percentage of the risk zone was 63% in control animals versus 27% (p=0.01 vs. controls) with intra-aortic balloon counterpulsation, and 21.7% in the Hemopump group (p=0.01 vs. controls; p=ns vs. intra-aortic balloon).

The authors concluded that the Hemopump device provided better LV systolic and
diastolic unloading compared to the intra-aortic balloon counterpulsation device; both techniques reduced myocardial infarct size greater than reperfusion alone.

Achour et al.\textsuperscript{15} assessed LV unloading just prior to reperfusion in dogs subjected to 2 hours of left anterior descending coronary artery occlusion plus 4 hours of reperfusion. A left ventricular assist device, placed transvalvularly was activated just prior to reperfusion. Myocardial infarct size was reduced in the LV assist device group and transmural regional myocardial blood flow was improved in this group compared to controls. End diastolic wall thickness at reperfusion returned to baseline with LV assist started pre-reperfusion. Another group, treated with LV assist activated \textit{after} reperfusion did not show benefit. The authors concluded that LV unloading prior to reperfusion, but not after reperfusion decreased the extent of myocardial necrosis compared to reperfusion alone or LV unloading that occurs after reperfusion has occurred. This group suggested that a potential mechanism by which LV unloading prior to reperfusion reduced infarct size was by reducing the release of endothelin-1 and reducing calcium overload.\textsuperscript{16}

Another group of researchers\textsuperscript{17} showed in a canine model that a catheter-mounted micro-axial blood pump (Impella, Aachen, Germany) turned on during 60 min. of ischemia and 120 min. of reperfusion in sheep, significantly reduced infarct size compared to controls (67\% to 18\%). The pump produced 4.1 L/min. flow at full support.

The pump increased diastolic and mean arterial pressure, decreased LV end-diastolic pressure, and improved reperfusion blood flow. It had partial benefits when used during reperfusion only. Importantly, the micro-axial blood pump was observed to reduce myocardial oxygen consumption during ischemia and reperfusion and the reduction in O\textsubscript{2} consumption correlated with the decrease in myocardial infarct size (r=0.9).
Other studies by other researchers have suggested that unloading the LV with an LV assist device reduces infarct size.\textsuperscript{18, 19} One study suggested an added benefit of unloading the LV plus administering an ultra short acting beta blocker.\textsuperscript{19}

Clinical studies using these newer LV support devices for infarct size reduction are not available, but these devices have shown promise in stabilizing patients with cardiogenic shock.\textsuperscript{20}

**The Present Study**

Kapur et al.\textsuperscript{13} provide an intriguing study in this issue of *Circulation*, suggesting that a circulatory support device that reduces left ventricular preload with a left atrial to femoral artery pumping approach decreased LV wall stress and LV stroke work after reperfusion and limited infarct size even when treated animals received an additional 30 minutes of ischemia, during which left ventricular unloading was activated. The benefit of this type of unloading may be secondary to reduction in oxygen demand, but also intriguing was their observation that phosphorylation of Reperfusion Injury Salvage Kinase pathway proteins (pERK and pAkt) was increased in samples of the left ventricle obtained from the non-infarct zone (but not the infarct zone). Since this non-infarcted tissue was neither ischemic nor reperfused, the significance of this finding remains to be determined.

Their experimental design was unusual. Anesthetized pigs in the control group were subjected to 120 minutes of left anterior descending balloon coronary artery occlusion, followed by 120 minutes of reperfusion. In the treated group, mechanical unloading (percutaneous left atrial to femoral artery bypassing which utilizes a centrifugal flow pump that achieved 3.2 liters/minute flow) was initiated after 120 minutes of coronary artery occlusion and the coronary occlusion was then extended for an additional 30 minutes with the device on, followed by 120 minutes of coronary reperfusion with the mechanical support device working. Despite the fact
that the treated group was subjected to an additional 30 minutes of ischemia compared to the control group, unloading the left ventricle during this time period and throughout reperfusion was associated with an impressive reduction in infarct size (28% of the left ventricle infarcted in the treated group, versus 52% in the control group). The authors conclude “that first unloading the left ventricle despite delaying coronary reperfusion during an acute MI reduces myocardial injury,” a unique and fascinating observation. If this finding holds true it could have important clinical implications. It would suggest that inducing a phase of unloading of the left ventricle may be more important than simply aiming for a specific “door-to-balloon” time. It would suggest that a 30 minute delay of “door to balloon time” associated with unloading of the left ventricle salvages more myocardium than not delaying door to balloon time without unloading the left ventricle. Whether interventional cardiologists would be willing to buy into delaying door to balloon time in order to unload the left ventricle prior to reperfusion remains to be seen. I suspect additional experimental and clinical trials will be needed before they are convinced.

The authors point out several limitations of their study. Perhaps the biggest concern is the small n values. An n of 4 in each group is small for this type of study and when the n value is that small a single outlier can have major impact. Future studies in which the n values are considerably larger are needed. There should be some type of risk zone assessment. Although the authors showed that there was no difference in coronary length or left ventricular mass distal to the occlusion site, a more traditional anatomic risk zone that assesses the mass of the left ventricle that was ischemic is preferable. Strengths of the study include the unique experimental design and findings regarding infarct size, the success of their mechanical unloading device that reduced LV end-diastolic pressure, provided 3.2 liters/minute flow, decreased LV stroke work, circumferential LV strain, and LV wall stress during reperfusion while maintaining systemic
arterial pressure, and measuring both anatomic myocardial infarct size as well as enzymatic estimates of necrosis during reperfusion. The concept of further reduction of infarct size by reducing $O_2$ demand by unloading the left ventricle is worthy of future studies.

Of course there are other potential therapies that are being developed that do not primarily rely on favorably altering the balance between oxygen supply and demand by utilizing hemodynamic maneuvers. Examples of some of these other types of therapies under study include various conditioning regimens (pre, post, remote conditioning, perconditioning); administration of conditioning mimetic pharmaceuticals; membrane stabilizing agents (glucose-insulin-potassium); mitochondrial protective agents – cyclosporine, Bendavia; agents that primarily work along the reperfusion injury salvage kinase (RISK) pathway– although it is interesting that 2 therapies that reduce $O_2$ demand may also involve this pathway (including hypothermia and the mechanical device used in Kapur’s study); certain antidiabetic agents; and the late sodium current inhibitor, ranolazine. Review articles that cover these agents as well as other cardioprotective agents and maneuvers have recently been published.1,21

**Conflict of Interest Disclosures:** None.

**References:**


Table 1. Therapies That May Reduce Infarct Size by Either Improving O₂ Supply or Demand

<table>
<thead>
<tr>
<th>Increasing O₂ Supply</th>
</tr>
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<tbody>
<tr>
<td>1) Early coronary reperfusion</td>
</tr>
<tr>
<td>a) Thrombolytic Therapy</td>
</tr>
<tr>
<td>b) Angioplasty</td>
</tr>
<tr>
<td>c) Stenting</td>
</tr>
<tr>
<td>d) Coronary Artery Bypass Surgery</td>
</tr>
<tr>
<td>e) Thrombus Aspiration</td>
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<tr>
<td>2) Agents to keep the infarct artery patent, once reperfused</td>
</tr>
<tr>
<td>a) Dual Antiplatelet Therapy: aspirin plus clopidogrel or prasugrel or ticagrelor</td>
</tr>
<tr>
<td>b) Addition of antithrombin agent (rivaroxaban)</td>
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<tr>
<td>c) Adenosine (has been shown to have antiplatelet features; coronary vasodilator)</td>
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<tr>
<td>d) Statins (may stabilize the plaque)</td>
</tr>
<tr>
<td>3) Hyperoxemia</td>
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<tr>
<td>4) Increasing erythrocytes (erythropoietin)</td>
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<tr>
<td>5) Ranolazine</td>
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<table>
<thead>
<tr>
<th>Decreasing O₂ Demand</th>
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<tbody>
<tr>
<td>1) Beta Blockers</td>
</tr>
<tr>
<td>2) Angiotensin Converting Enzyme Inhibitor</td>
</tr>
<tr>
<td>3) Angiotensin Receptor Blocker</td>
</tr>
<tr>
<td>4) Adenosine (decrease heart rate, decrease blood pressure)</td>
</tr>
<tr>
<td>5) Hypothermia</td>
</tr>
<tr>
<td>6) Mechanical Circulator Support Devices (preload, after load reduction)</td>
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