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Reperfusion Injury in Acute Myocardial Infarction Shock- Role of Mechanical Circulatory Support Devices

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Abstract

The efficacy of mechanical circulatory support in acute myocardial infarction is dependent upon the size of the infarct. If applied early, mechanical support to reduce reperfusion injury appears to be effective in reducing infarct size in animal studies. The optimal timing of reperfusion is uncertain and requires further investigation. Efficient unloading appears to be essential in increasing the efficacy of the type of mechanical support and may favor one over another.

Keywords: myocardial infarction, cardiogenic shock, mechanical circulatory support

Background

When considering the management of shock, the topic of reperfusion injury in acute myocardial infarction (AMI) is challenging. Management must balance preventative cardiology and critical care, as the initial problem lies with the infarction rather than the shock.

There is a clear relationship between the size of an infarct and the prognosis after myocardial infarction. Data from ten randomized clinical trials where magnetic resonance imaging was done after an infarction show a clear correlation between all-cause mortality and heart failure hospitalization with the size of the infarction.[1] Importantly, in patients where the final size was 8% or less of area at risk, there was little to no mortality and very little morbidity.

The management solution for patients with AMI shock is to re-perfuse early in the treatment process. However, even if the patient presentation, treatment plan, and procedure are the same, patients can have very different hearts after reperfusion, and this is a consequence of reperfusion injury.

The pathophysiology behind reperfusion injuries is complex, but there is an understanding that cardiomyocyte death due to necrosis and apoptosis is important in the process. Changes in microcirculation, such as microvascular stasis and hemorrhage, tissue edema, and capillary compression, are also important. Clearly, strategies to address these mechanisms and minimize reperfusion injury would have a great impact on outcomes in AMI and, in turn, the development and prognosis of cardiogenic shock in this setting. There have been several studies that aimed to reduce reperfusion injury utilizing pharmacological strategies and remote ischemia by the use of blood pressure cuffs in ambulances en route to the hospital. Thus far, the results have been inconsistent.[2]

Use of Mechanical Circulatory Support

These inconsistencies led to the proposal that mechanical circulatory support (MCS) might be an efficient way to reduce reperfusion injury. In the setting of an AMI, MCS increases collateral coronary perfusion pressure and decreases left ventricular pressure, diastolic pressure, wall stress, and, consequently, myocardial oxygen consumption. The efficacy is dependent on the size of the infarct. Because of this, the question becomes: can MCS in AMI shock reduce reperfusion injury **and** infarct size? If so, how does it do it? How should reperfusion be timed with respect to the onset of unloading?

Animal Studies

MCS and infarct size were investigated in a study on sheep with left anterior coronary artery (LAD) occlusion.[3] The control group had reperfusion after 60 minutes of ischemia, while the group treated with an Impella CP (Abiomed) had immediate reperfusion. The group with full support from the onset had a lower myocardial oxygen extraction than the control group; however, both groups showed decreased infarct size.[3]

Another study in a pig model investigated MSC efficacy after 90 minutes of LAD occlusion with a balloon.[4] Four groups were evaluated: a reperfusion-only group (Group 1), a group that received an Impella CP device for 15 minutes before reperfusion (Group 2), a group that had an Impella CP on for 30 minutes before reperfusion (Group 3), and a group that had immediate reperfusion followed by circulatory support (Group 4). Group 3 had the smallest infarction.[4]

This same study also investigated different molecules related to the reperfusion process.[4] Specifically, stromal cell-derived factor 1-alpha (SDF1-alpha) was reduced in the group that did not receive MCS (Group 1). The group treated with unloading before reperfusion (Group 2) had a more normal level of SDF1-alpha. In addition, scar tissue formation was negatively associated with plasma SDF1-alpha, indicating that the molecule might be secreted by the heart to reduce reperfusion injury. This was further investigated in a model where SDF1-alpha was blocked, showing an attenuated effect of reperfusion.[4] The results challenge the understanding that "time is muscle," as a strong indication that delaying reperfusion by 30 minutes with circulatory unloading onboard was associated with improved outcomes.

A similar study using a pig model contested these results.[5] The effects of 60 minutes of ischemia and MCS were investigated in 3 groups: Group 1 with conventional ischemia with reperfusion, Group 2 with upfront unloading with an Impella for 30 minutes before reperfusion, and Group 3 where unloading and reperfusion were done simultaneously after 60 minutes of ischemia. Group 3 had the smallest infarct size, but no difference existed between Groups 1 and 2.[5] While there may be differences between these studies, the most important being the duration of ischemia, there is still a need for further understanding.

In a meta-analysis of several animal studies investigating the effects of MCS and unloading in AMI, there appears to be a 2.2% absolute reduction in infarct size, which corresponds to a relative reduction of ~10%.[6]

With the understanding that MCS works in the setting of AMI, the next step is to investigate which type of support works best. A study involving LAD occlusion for 120 minutes in pigs explored MCS type and efficacy in reducing infarct size in 3 groups.[7] Group 1 had continued occlusion with Impella support, Group 2 had re-perfusion, and Group 3 had veno-arterial extracorporeal membrane oxygenation (V-A ECMO) re-perfusion. Group 3 was associated with the largest infarct size, while Group 1 showed a decreased infarct size. Group 1 also showed a reduction in left ventricular (LV) stroke work, while Group 3 showed no change.[7] The study also examined collateral coronary perfusion by measuring the coronary collateral flow index and focusing on wedge pressure. Wedge pressure was positively influenced by unloading with an Impella.[7] No change was noticed with V-A ECMO, suggesting that collateral perfusion is essential and may improve the microvascular environment, leading to smaller infarcts.

It is essential to acknowledge the limitations of using animal models. These studies use 100% controlled occlusion with no disease of other vessels, and the time of occlusion is known. In contrast, patients often have partial reflow due to heparin administration, and occlusion time is rarely known for certain. In addition, reocclussion or distal embolization are always risks. Concomitant coronary disease must be considered as it can limit collateral flow and induce preconditioning that can potentially be beneficial for reperfusion injury. Arrhythmias can also play a significant role in these patients.

Clinical Studies

There is limited clinical data available exploring AMI shock and MCS efficacy. The CRISP AMI randomized trial compared percutaneous coronary intervention (PCI) alone to PCI with an intra-aortic balloon pump (IABP) in 337 patients not in cardiogenic shock.[8] The primary endpoint was infarct size. There was no difference between the two groups; in fact, there was a trend toward a larger infarct in the group with the IABP.[8]

The DTU STEMI pilot trial included 50 patients unloaded with an Impella CP and tested the hypothesis that delaying reperfusion by 30 minutes after starting unloading with an

Impella CP was feasible.[9] The trial results showed that this strategy was feasible and did not increase infarct size. However, there appeared to be no difference in the outcomes.[9] The DTU STEMI trial is ongoing, testing whether unloading with an Impella and delaying reperfusion compared to conventional therapy will help.

Conclusion

In conclusion, if applied early in animal studies, percutaneous MCS to reduce reperfusion injury can effectively reduce infarct size. Effective unloading appears essential so that left ventricular assist devices, such as the Impella, are more efficient than ECMO and possibly balloon pumps. The optimal timing of reperfusion is uncertain and is being further investigated in clinical trials. There is still little information on the development of acute heart failure and cardiogenic shock. However, MCS serves other purposes for cardiogenic shock patients, such as supplying blood flow to the brain and kidneys.

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