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Acute mechanical LV unloading in ischemia reperfusion injury: Be prepared

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In the last decade, a strong focus on reducing door-to-balloon time in acute myocardial infarction (MI) has improved acute and in-hospital survivals. On the other hand, better acute survival has led to increased number of patients with late-onset heart failure (HF), which contributes to current pandemic increase in HF prevalence (1). Realization of injury associated with reperfusion of the occluded coronary artery, which can account for up to 50% of final infarct size (2), prompted search for new therapies to reduce reperfusion injury and prevent late-onset HF. Various approaches have been proposed to reduce reperfusion injury including pharmacological approaches, remote pre- and post-conditioning, hypothermia, and neuro-modulation (3,4). Unfortunately, so far, none of them has become the clinical standard. Particularly, recent clinical trials using pharmacological approaches have reported disappointing results (5–7). This is presumably due to the lack of perfusion in the ischemic myocardium until reperfusion, which precludes efficient delivery of any drugs, proteins, or biological molecules. Because large part of reperfusion injury is expected to occur rapidly after restoration of coronary flow, approaches that can directly intervene ischemic tissue without (before) reperfusion may be necessary. Mechanical left ventricular (LV) unloading using LV assist devices is one of the few approaches that can directly modulate ischemic tissue prior to reperfusion. For example, LV unloading leads to reduced LV wall stress (8), improved oxygen supply-demand (9), and potentially improved perfusion to the ischemic border tissue.

In this issue of JACC, Kapur et al. (*JACC Kapur et al.*) reports the efficacy of acute mechanical LV unloading as an approach to reduce infarct size in a pig model of ischemic reperfusion injury. Specifically, they examined the impact of LV unloading using the Impella, a percutaneously deployable LV assist device, at different time points before and after reperfusion of the occluded coronary artery. The results were that LV unloading initiated 30 minutes prior to reperfusion, but not immediately before or after reperfusion, reduced acute infarct size. This was associated with increased tissue expression of SDF-1α, a key molecule that has been reported to promote protective effects through several mechanisms (10). Most importantly, reduced acute infarct size was also associated with smaller scar size at the chronic stage of MI with better-preserved cardiac function.

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In 2003, Meyns lab reported first preclinical evidence that mechanical LV unloading can reduce infarct size in a sheep ischemic reperfusion model (9). This concept was not clinically well accepted at the time due to the lack of efficient, low-invasive, and rapidly deployable cardiac unloading devices. Recent emergence of new generation powerful percutaneous LV support devices brought this approach in reality in a clinically applicable manner. Several recent preclinical studies reproduced the effects of mechanical LV unloading on reducing ischemic reperfusion injury (11–13). Additionally, early clinical data on the use of Impella in US supports this concept by exhibiting better survival in patients who received Impella prior to percutaneous coronary intervention than those receiving after the percutaneous coronary intervention (*Analysis of Outcomes for 15,259 U.S. Patients with Acute Myocardial Infarction Cardiogenic Shock (AMICS) Supported with the Impella Device, O'Neill et al, American Heart Journal, In Press*). The manuscript by Kapur et al is in line with these data and extends the demonstration of beneficial effects of acute LV unloading to more chronic stage, suggesting potential prevention of late-onset HF after MI.

Although previous preclinical studies of acute mechanical LV unloading suggested its efficacy in reducing infarct size, the mechanisms leading to reduced infarct size remained unclear. To address this point, Kapur et al focused on SDF-1α pathway in the infarct tissue based on their previous data (12) and found that SDF-1α expression was indeed increased and correlated with reduced infarct size. Because 30 minutes is too rapid for many of the proteins to be translated and then activate downstream pathways, they instead looked at its degradation. They found suppressed expression and activities of proteases that are known to degrade SDF-1α. Moreover, they showed that inhibition of SDF-1α-CXCR4 pathway using AMD3100 (CXCR-4 antagonist) abolishes the benefit of acute mechanical LV unloading. These data strongly support the key roles of SDF-1α and its downstream pathway in reducing the infarct size.

It is interesting that the beneficial effect of acute LV unloading could be seen only when it was initiated 30 minutes before reperfusion, but not within 15 minutes or after reperfusion (*JACC Kapur et al.*). This suggests that simple acute reduction in LV wall stress or improved oxygen supply-demand is not sufficient to pose beneficial effect. It rather seems that mechanical LV unloading needs some time to prepare the heart for ischemic reperfusion, requiring waiting period. However, it is expected that the ischemic tissue continues to increase infarct size gradually during the 30 minutes period, although the net effect of LV unloading may be the reduction in final infarct size by limiting the reperfusion injury. Approaches that can be combined with mechanical LV unloading to more quickly prepare the heart for reperfusion injury, for example, therapies that can rapidly increase SDF-1α, may further increase the benefit of LV unloading.

A recent meta-analysis of infarct size and patient outcomes revealed that with every 5% increase in infarct size, there is approximately 20% increase in both mortality and HF hospitalization per year (14). In Kapur et al (*JACC Kapur et al.*), acute mechanical LV unloading reduced the infarct size by half compared to the conventional primary reperfusion approach. If this is reproducible in humans, primary mechanical LV unloading will have enormous benefit on reducing future HF events in patients with acute MI. Having said that, several questions easily arise when considering clinical translation of this approach. Is 30

minutes, not 25 minutes or 35 minutes, the best time to prepare the heart for reperfusion? Do patients presenting to the hospital after several hours still gain benefit? How much degree of LV unloading is required to achieve the benefit? What is the effect of collateral circulation (not present in the animal models) on the underlying mechanism? How can the appropriate unloading be evaluated in MI patients? How long do the hearts need to be unloaded after reperfusion? These questions indicate how less we know about this new approach that takes the advantage of emerging percutaneous LV assist devices, and there is a critical need for further preclinical and clinical researches to address these questions. Additionally, waiting for 30 minutes without reperfusion after initiating the LV assist device may be counter-intuitive for clinical interventionists who have been working long time under the concept of "time is muscle". Solid evidence that can convince interventionists to change their practice needs to be established. Lack of rodent-sized LV support devices limits preclinical research to large animal experiments, but many experts are gaining their interests in this new field. Meanwhile, a clinical trial aiming at testing the impact of primary unloading in acute MI is on its way (The Door to Unloading Trial: NCT03000270;35). So far, the existing data on primary LV unloading against acute MI are promising and its future seems to be bright.

As Benjamin Franklin said,

- "By failing to prepare, you are preparing to fail"

It could be that we have been failing to prepare the heart for reperfusion injury, making the heart prone to fail. Acute mechanical LV unloading could be a vital approach to prepare the heart and prevent its failure. If the ongoing early-phase clinical trial proves positive, interventional cardiologists may also need to "Be prepared" to modify their therapeutic strategies against acute MI.

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