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Commentary: “The weight” will be worth it: Avoiding premature judgment on the success or failure of left ventricular unloading in mitigating reperfusion injury

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Mortality following acute myocardial infarction (AMI) has declined substantially with the advent of primary reperfusion therapy, but the incidence of new-onset heart failure remains stubbornly high. A long list of therapies and treatment paradigms like ischemic preconditioning and novel pharmacology showed promise in preclinical models but have failed to reduce infarct size in clinical trials. In this issue of the *Journal*, Goodwin and Selzman¹ rigorously describe the recent literature surrounding left ventricular (LV) unloading and its innovative application to mitigate reperfusion injury following AMI.

Preclinical models of LV unloading with a transvalvular axial flow pump like the Impella family of devices (Abiomed Inc, Danvers, Mass) have shown compelling

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CENTRAL MESSAGE

LV unloading has the potential to limit injury associated with myocardial infarction and reperfusion therapies. More work remains to translate these benefits from the bench to the bedside.

results with respect to reperfusion injury. Recently, Esposito and colleagues² demonstrated activation of a cardioprotective cascade led by the signaling protein stromal-derived factor-1 α in a swine model where reperfusion was delayed for at least 30 minutes after unloading with an Impella device. These findings provide a mechanistic explanation for the improved ventricular performance observed in previous large animal studies. Smalling and colleagues³ almost 3 decades ago and Meyns and colleagues⁴ almost 2 decades ago showed that an axial flow device significantly reduced ventricular filling pressures and infarct size when applied during ischemia before reperfusion. These improvements correlated with decreases in myocardial oxygen consumption created by unloading.⁴ However, Goodwin and Selzman astutely remind us that ischemic time cannot be controlled as it can in the preclinical setting, and that animal models fail to replicate the mix of comorbidities shared by

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FIGURE 1. Cellular, organ, and systematic level benefits associated with left ventricular unloading. The favorable effects of LV unloading in preclinical models are wide-ranging but have yet to extend to clinical outcomes in patients with AMI. At the cellular level, LV unloading induces a cardioprotective program characterized by increased expression of SDF-1 α and a reduction in MMPs. At the organ level, as seen in the pressure-volume loops in the left-most box, unloading reduces LV end-diastolic pressure and volume. These benefits translate, at the systemic level, to increases in cardiac output and systolic blood pressure. Whether these benefits of unloading reduce infarct size, and ultimately, the incidence of heart failure and mortality after AMI remains to be seen. SDF-1 α , Stromal-derived factor-1 α ; MMP, matrix metalloproteinase; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; SBP, systolic blood pressure; CO, cardiac output.

many survivors of AMI that contribute to phenomena like microvascular dysfunction, which can also impact infarct size and clinical outcomes.

This extensive background work set the stage for in vivo studies, prompting the groundbreaking Door-to-Unload in ST-segment elevation MI (DTU-STEMI) trial.⁵ Informed by preclinical work establishing the minimum time required to trigger the cardioprotective cascade of LV unloading, Kapur and colleagues⁵ designed a feasibility study randomizing patients to 30 minutes of unloading with an Impella device before reperfusion versus immediate unloading and reperfusion. Average infarct size trended lower (not statistically significantly) in patients with the 30 minutes of unloading before reperfusion. Thus, while this study was statistically neutral with respect to infarct size, it is critical to remember that it was not designed for this purpose. Rather, DTU-STEMI was intended to demonstrate the feasibility and safety of the DTU concept, and, indeed, there was no significant difference in the frequency of complications with delayed versus immediate reperfusion and that total door-to-balloon time remained less than 90 minutes in both groups.

Thus, it remains to be seen whether the benefits of unloading identified in preclinical settings can be replicated

in the real world and usher in a new paradigm of care for patients with AMI (Figure 1). The recently initiated Primary Unloading and Delayed Reperfusion in ST-Elevation Myocardial Infarction: The STEMI-DTU Trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03947619) Identifier: NCT03947619) is designed precisely to address this question. Our job, in the meantime, is to keep an open mind and, if possible, contribute to the speedy completion of this pivotal study.

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