

JACC REVIEW TOPIC OF THE WEEK

Mechanical Unloading in Heart Failure



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ABSTRACT

Myocardial injury induces significant changes in ventricular structure and function at both the cellular and anatomic level, leading to ventricular remodeling and subsequent heart failure. Unloading left ventricular pressure has been studied in both the short-term and long-term settings, as a means of preventing or reversing cardiac remodeling. In acute myocardial infarction, cardiac unloading is used to reduce oxygen demand and limit infarct size. Research has demonstrated the benefits of short-term unloading with mechanical circulatory support devices before reperfusion in the context of acute myocardial infarction with cardiogenic shock, and a confirmatory trial is ongoing. In chronic heart failure, ventricular unloading using mechanical circulatory support can reverse many of the cellular and anatomic changes that accompany ventricular remodeling. Ongoing research is evaluating the ability of left ventricular assist devices to promote myocardial recovery and remission from clinical heart failure. (J Am Coll Cardiol 2018;72:569-80)

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Acute myocardial infarction (AMI) remains a leading cause of morbidity and mortality, with >650,000 cases reported in the United States annually. Over the past 3 decades, early revascularization and AMI management have had a significant impact on early mortality, and 30-day survival for ST-segment elevation myocardial infarction is now 95%. However, 1 in 4 patients surviving a first AMI will develop heart failure (HF) within 1 year, and 75% will develop HF within 5 years from the index event (1). As more people survive the initial AMI, an increasingly heavy burden is placed on our health care system in the form of new HF patients. Additional therapeutic approaches focusing on HF prevention should be developed.

For patients with established HF, either following myocardial infarction or in the setting of idiopathic cardiomyopathy, therapies aim to interrupt the cycle of progressive dilation and dysfunction; a process called remodeling. Medical therapies, cardiac

resynchronization therapy, and mitral repair/replacement can interrupt this process to a certain degree, but are insufficient to halt disease progression, and most patients ultimately succumb to HF. Additional therapies that reverse or at least halt disease progression are needed for these patients as well.

Evidence is mounting concerning the impact of left ventricular (LV) unloading with mechanical circulatory support on reverse remodeling, and the accompanying changes at the cellular level. Recent studies demonstrated the clinical benefits of LV unloading in acute HF in the setting of AMI. In the short term, LV unloading using mechanical circulatory support aims to reduce infarct size, limit ventricular remodeling, and prevent the development of the HF syndrome. The physical and molecular mechanisms underlying the effects of unloading in the short- and long-term settings are similar. The purpose of this review is to describe the anatomic and cellular changes occurring



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**ABBREVIATIONS
AND ACRONYMS****AMI** = acute myocardial infarction**ATP** = adenosine triphosphate**EDPVR** = end-diastolic pressure-volume relationship**ESPVR** = end-systolic pressure-volume relationship**HF** = heart failure**LV** = left ventricular**LVAD** = left ventricular assist device**mPTP** = mitochondrial permeability transition pore**MVO₂** = myocardial oxygen consumption**PE** = potential energy**PVA** = pressure-volume area**RISK** = reperfusion injury salvage kinases**ROS** = reactive oxygen species**SDF1 α** = stromal derived factor 1 α **SW** = stroke work

during reverse remodeling due to unloading in the settings of chronic and acute LV dysfunction.

VENTRICULAR REMODELING

Acute or chronic myocardial injury precipitates metabolic derangement, followed by myocyte death. The remaining viable myocardium responds to cell loss through myocyte hypertrophy and development of fibrosis in the interstitial space (2,3). A reduction in contractile force activates neurohormonal compensatory mechanisms aimed at maintaining systemic perfusion such as the sympathetic nervous and renin-angiotensin systems. Over time, the LV undergoes structural changes including an increase in ventricular volume, rightward shift of the end-diastolic pressure-volume relationship (EDPVR) and development of a more spherical shape (4–6). These anatomic changes are accompanied by alterations in gene expression, metabolic substrate preference and utilization, and the composition of the extracellular matrix (7–9). Together, these structural, biochemical, and molecular changes are termed ventricular remodeling.

ACUTE HEART FAILURE FOLLOWING AMI

Infarct size correlates with mortality and development of HF (10). The larger the infarct, the higher the burden on remaining viable myocardium and the greater the adaptive cardiomyocyte hypertrophy. Myocardial infarction initiates the process of ventricular remodeling as described in the preceding text. Accordingly, limiting myocardial injury is the primary target of clinical investigations aimed at preventing HF after an AMI. Two primary approaches have been pursued. The first is to minimize the overall ischemic time experienced by the myocardium. The adage “time is muscle” suggests that the faster an occluded coronary artery can be reperfused and myocardial oxygen supply restored, the smaller the infarct size. This has led to adoption of a benchmark door-to-balloon time, the time from arrival to a medical facility to primary reperfusion, of 90 min or less. However, recent reports demonstrate no effect on mortality or post-AMI HF incidence with additional reduction in the door-to-balloon time below 90 min (11). The second approach to limit infarct size in AMI has been to employ interventions and pharmacotherapy to reduce reperfusion injury. These methods have been

reviewed extensively and are founded on solid pre-clinical data, but none have successfully translated into routine clinical practice (12).

A key pathophysiological feature that determines the extent of necrosis during AMI is the balance between the residual supply of oxygen to the myocardium at risk and myocardial metabolic demands. Although the current paradigm—early reperfusion therapy—focuses on restoring oxygen supply to the myocardium at risk, strategies to reduce myocardial oxygen demand to achieve a more favorable supply-demand ratio as a means of limiting infarct size have not been clinically tested. Extensive preclinical and some clinical evidence suggest that immediately reducing the mechanical workload (unloading) of the heart before reperfusion leads to a smaller infarct size. Short-term cardiac unloading reduces oxygen demand and preconditions myocardium at risk to oppose reperfusion injury, and may limit irreversible necrosis, allowing the heart to more fully recover once coronary flow is restored. Here, we provide an overview of the hemodynamic principles and physiological mechanisms underlying short- and long-term unloading, and discuss emerging preclinical data supporting translation of this approach to limiting infarct size and preventing the development of HF.

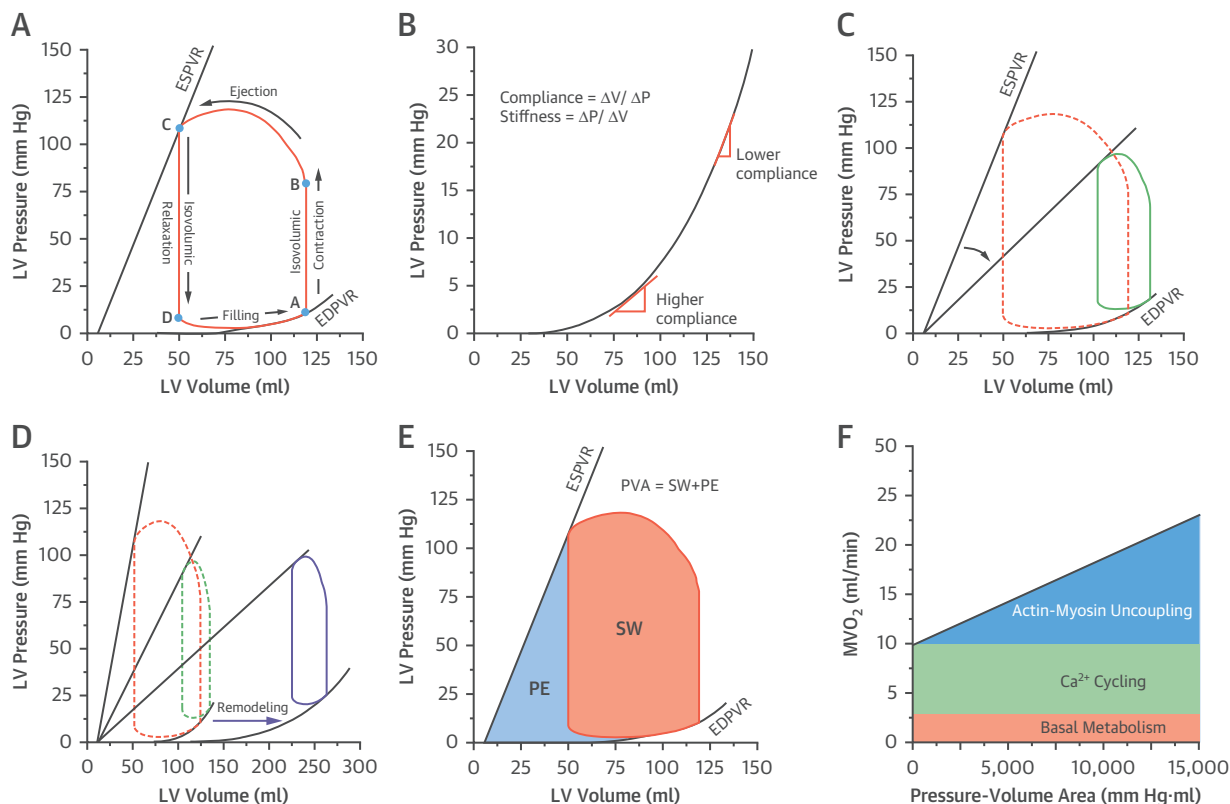
SHORT-TERM CARDIAC UNLOADING

Cardiac unloading can be defined as the reduction of mechanical power expenditure of the ventricle to minimize myocardial oxygen consumption (MVO₂) and reduce hemodynamic forces that lead to ventricular remodeling and, in MI, to reduce infarct size.

Ventricular hemodynamics, work, power, and energy demands can be understood within the framework of ventricular pressure-volume analysis (Figure 1) (13). The pressure-volume loop falls within the boundaries of the end-systolic pressure-volume relationship (ESPVR) and EDPVR (Figure 1A). The ESPVR is linear with a slope, E_{es} , that is considered a load-independent index of ventricular contractility. The EDPVR is nonlinear and characterizes passive ventricular properties (i.e., at a point when all actin-myosin bonds are uncoupled). Ventricular compliance (or stiffness, the mathematical reciprocal of compliance) is determined by the slope of the EDPVR. Because the EDPVR is nonlinear, ventricular compliance decreases as filling pressure increases (Figure 1B). The location of the pressure-volume loop within the ESPVR and EDPVR boundaries is determined by the ventricular preload and afterload.

In the setting of AMI (Figure 1C), ventricular contractility is decreased (decreased slope of the

FIGURE 1 PV Analysis of LV Hemodynamics During AMI and Following LV Unloading



ESPVR) resulting in decreases of stroke volume (width of the loop) and pressure generation (height of the loop); the pressure-volume loop shifts rightward towards larger volumes (initially along the original EDPVR) due to the increased filling pressure. Changes in diastolic properties, both active and passive aspects, play a key role in the pathophysiology in the acute and chronic phases following AMI. With the onset of diminished oxygen supply and onset of ischemia, the rate of relaxation is decreased, and especially at high heart rates, uncoupling of actin-myosin bonds may be incomplete between contractions (incomplete relaxation) (14). Under such conditions, the pressure-volume loop may fail to

reach the EDPVR, potentially decreasing ventricular compliance beyond that due to the increased filling pressure. Over time, however, with the hypertrophic response (elongation and widening) of surviving myocytes, increased extracellular matrix turnover (caused by the inflammatory response, necrosis, etc.) and increased diastolic wall stress, the EDPVR can shift rightward towards larger volumes, a phenomenon called ventricular remodeling (Figure 1D) (15). Rightward shifts of the EDPVR are also associated with further rightward sloping of the ESPVR; thus, remodeling results, not only in chamber enlargement, but also in further reductions of LV contractility beyond that caused by loss of myocytes.

Insights into myocardial energetics are also obtained from pressure-volume analysis. There are 2 components to the total mechanical work of the heart: stroke work (SW) and potential energy (PE) (**Figure 1E**). SW is the area inside the pressure-volume loop and represents the mechanical energy transferred from the myocardium to the blood to propel it through the cardiovascular system. PE is the area on the pressure-volume diagram bounded by the ESPVR, the EDPVR, and the diastolic portion of the pressure-volume loop and is residual energy stored in the myofilaments not released as external energy. The sum of SW and PE is the total mechanical work of the heart per beat and is referred to as the pressure-volume area (PVA) ($PVA = SW + PE$). PVA directly correlates with MVO₂ (**Figure 1F**) (16). Three major processes contribute to MVO₂: basal metabolism, calcium sequestration by the sarcoplasmic reticulum (SERCA2a adenosine triphosphatase activity), and actin-myosin cross-bridge uncoupling during relaxation by myosin adenosine triphosphatase. These processes are fueled by adenosine triphosphate (ATP) hydrolysis which is principally generated through aerobic metabolism and reflected by MVO₂ per minute. With changes in contractility, heart rate, and loading conditions, calcium cycling and cross-bridging vary significantly, whereas basal metabolism is relatively constant. The amount of calcium cycled is linked with myocardial contractility; changes in contractility, therefore, induce changes in oxygen consumption independent of concomitant changes in workload (i.e., parallel upward and downward shifts of the MVO₂-PVA relationship). The number of actin-myosin bonds created during contraction is related to the total mechanical work performed by the muscle so that the greater the work the greater the oxygen consumption.

Minimization of the work-related oxygen consumption can be achieved by ventricular unloading (defined in the preceding text and detailed further later in the text) by reducing both SW and PE through reductions of ventricular peak systolic and end-diastolic pressures. Reductions of heart rate and contractility (when possible) are very effective means of reducing MVO₂.

Heart rate is a critical determinant of oxygen consumption because both calcium cycling and mechanical work occur with each beat. Thus, the oxygen required to fuel these processes increases linearly with increases of heart rate. Accordingly, myocardial oxygen demand can be decreased by reducing heart rate, contractility, and/or total mechanical work. Each component should be considered when attempting to achieve maximal cardiac unloading.

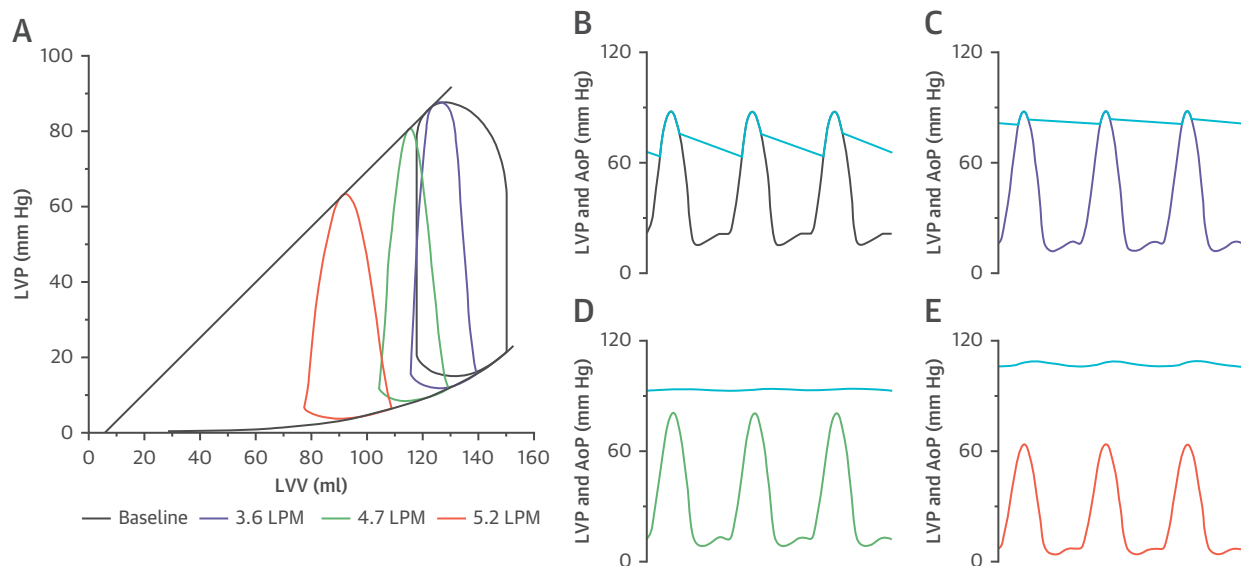
The forces resulting in ventricular remodeling are similar to those that determine MVO₂. With ventricular remodeling, the ESPVR and EDPVR shift rightward towards increased volumes. Persistently increased systolic wall stress leads to myocellular hypertrophy and drives apoptosis. Persistently elevated diastolic ventricular pressure causes ventricular dilation, manifest as rightward shifts of the EDPVR and ESPVR. Ischemic, newly infarcted, and stunned myocardium during acute MI and after reperfusion therapy are particularly vulnerable to remodeling due to the markedly increased stresses and active cytokines and enzymes (matrix metalloproteinases) that break down extracellular matrix. Thus, minimization of PVA decreases oxygen demand and limits remodeling.

However, because cardiac output and blood pressure are intimately linked with ventricular work, there are limits to which PVA and heart rate can be reduced during AMI without compromising perfusion of vital organs, including the brain, kidneys, liver, and the heart itself. Thus, pharmacotherapies aimed at reducing myocardial work load and minimizing PVA (e.g., beta blockers) are inherently limited as they run the risk of compromising end-organ perfusion due to a reduction in cardiac output. By contrast, a mechanical LV assist device (LVAD) that draws blood directly from the LV and pumps it to the arterial system can uncouple LV pressure and flow generation from pressure and flow in the arterial system. Increases in LVAD flow left-shifts the pressure-volume loop to lower end-diastolic volumes and pressures, reducing the PVA (**Figure 2A**). In the time domain (**Figures 2B to 2E**), progressive increases in LVAD flow reduce peak LV pressure, increase aortic diastolic and mean pressures, and allow for uncoupling of LV pressure generation from aortic pressure. Concomitantly, there is an increase in total cardiac output (i.e., the sum of native heart and LVAD flow), thereby shifting oxygen demand/supply balance within the heart, minimizing demand while maximizing supply.

MOLECULAR BIOLOGY OF UNLOADING IN THE SETTING OF ISCHEMIA-REPERFUSION INJURY

In 1985, Eugene Braunwald and Robert Kloner (17) described myocardial reperfusion in AMI as a “double-edged sword” due to the fact that reperfusion of ischemic myocardium also promotes cardiomyocyte death and microvascular damage through a process referred to as myocardial ischemia-reperfusion injury. Since then, multiple studies have defined several key mechanisms that drive myocardial

FIGURE 2 Hemodynamic Changes During LV Unloading by Mechanical Circulatory Support



(A) During acute myocardial infarction or in chronic heart failure, the PV loop shifts to the right along the EDPVR, resulting in elevated end-diastolic pressures (**black loop**). With LV unloading by a continuous-flow left ventricular assist device (LVAD), the isovolumic contraction and relaxation periods are lost, and the PV loop assumes a triangular shape. Increases in LVAD support result in progressive leftward shifting of the PV loop to lower points on the EDPVR curve, with a reduction in LV volume (LVV). **(B to E)** Increases in LVAD flow result in uncoupling of LV pressure (LVP) and aortic pressure (AoP). LPM = liters per minute; other abbreviations as in [Figure 1](#).

damage during ischemia and reperfusion (18-22). From the onset of ischemia, mitochondrial oxidative phosphorylation becomes uncoupled and synthesis of ATP is reduced within cardiomyocytes. This loss of ATP generation has 2 effects. First, intracellular calcium and lactate levels increase, whereas intracellular pH decreases. Second, reduced ATP synthesis provides the substrate for generation of reactive oxygen species (ROS) that promote a feed-forward process known as ROS-induced ROS-release. The net effect of increased ROS levels is the opening of a hole in the mitochondrial membrane known as the mitochondrial permeability transition pore (mPTP), which accelerates loss of mitochondrial integrity and subsequent cardiomyocyte death within the ischemic myocardium. The magnitude of myocardial damage correlates directly with the duration of myocardial ischemia, hence the development of the door-to-balloon benchmark. However, reperfusion also promotes mPTP opening by triggering an influx of calcium, alterations in cellular pH, ROS, and increasing microcirculatory obstruction.

In 1983, ground-breaking studies using intermittent periods of ischemia in a nonischemic myocardial territory reduced infarct size in an ischemic myocardial zone (23). This early preclinical observation introduced the field of ischemic preconditioning,

whereby episodic myocardial or skeletal muscle ischemia reduced myocardial infarct size. Over the next 20 years, investigators identified that ischemic preconditioning activates phospho-inositol-3 kinase, Akt, and Erk, which limited formation of the mPTP and reduced myocardial infarct size. Independent of these reperfusion injury salvage kinases (RISK), other investigators identified that activation of the survivor activating factor enhancement pathway mediated by tumor necrosis factor alpha and STAT3 also limited ischemia reperfusion injury (24-26). Over the same time period, a growing body of evidence supported the cardioprotective role of a circulating cytokine known as stromal derived factor (SDF)-1 α . More recent evidence supports that increased expression of SDF-1 α promotes Akt-mediated phosphorylation and inactivation of glycogen synthase kinase 3-beta, which limits mPTP formation and myocardial infarct size (27-30). On the basis of these sentinel studies, multiple investigators have attempted to target various aspects of the RISK, survivor activating factor enhancement, and SDF-1 α signaling pathways using pharmacological and ischemic conditioning approaches without clear benefit.

In parallel to the growing body of published reports exploring biological mechanisms of cardioprotection,

multiple investigators in the late 1980s were beginning to identify that reducing myocardial wall stress and oxygen consumption using mechanical pumps could also reduce infarct size. Various approaches employed counterpulsation pumps, extracorporeal centrifugal flow pumps, and large transvalvular axial flow pumps. These investigators identified that early and effective LV unloading reduced MVO₂, which correlated directly with reduced infarct size. However, few of these studies explored the impact of LV unloading on myocardial biology. In 2003, Meyns et al. (31) identified a reduced myocardial lactate extraction ratio in sheep unloaded with a transvalvular axial flow pump before reperfusion, suggesting a potential beneficial impact on myocardial metabolism. In 2005, Achour et al. (32) identified that ischemia and reperfusion increased contraction band necrosis, mitochondrial calcium deposits, and mitochondrial swelling. By contrast, activation of a transvalvular axial flow pump before, not after, reperfusion was associated with normal mitochondrial integrity and cardiomyocyte ultrastructure. For the next decade, there were no further advances in the field of LV unloading and myocardial biology.

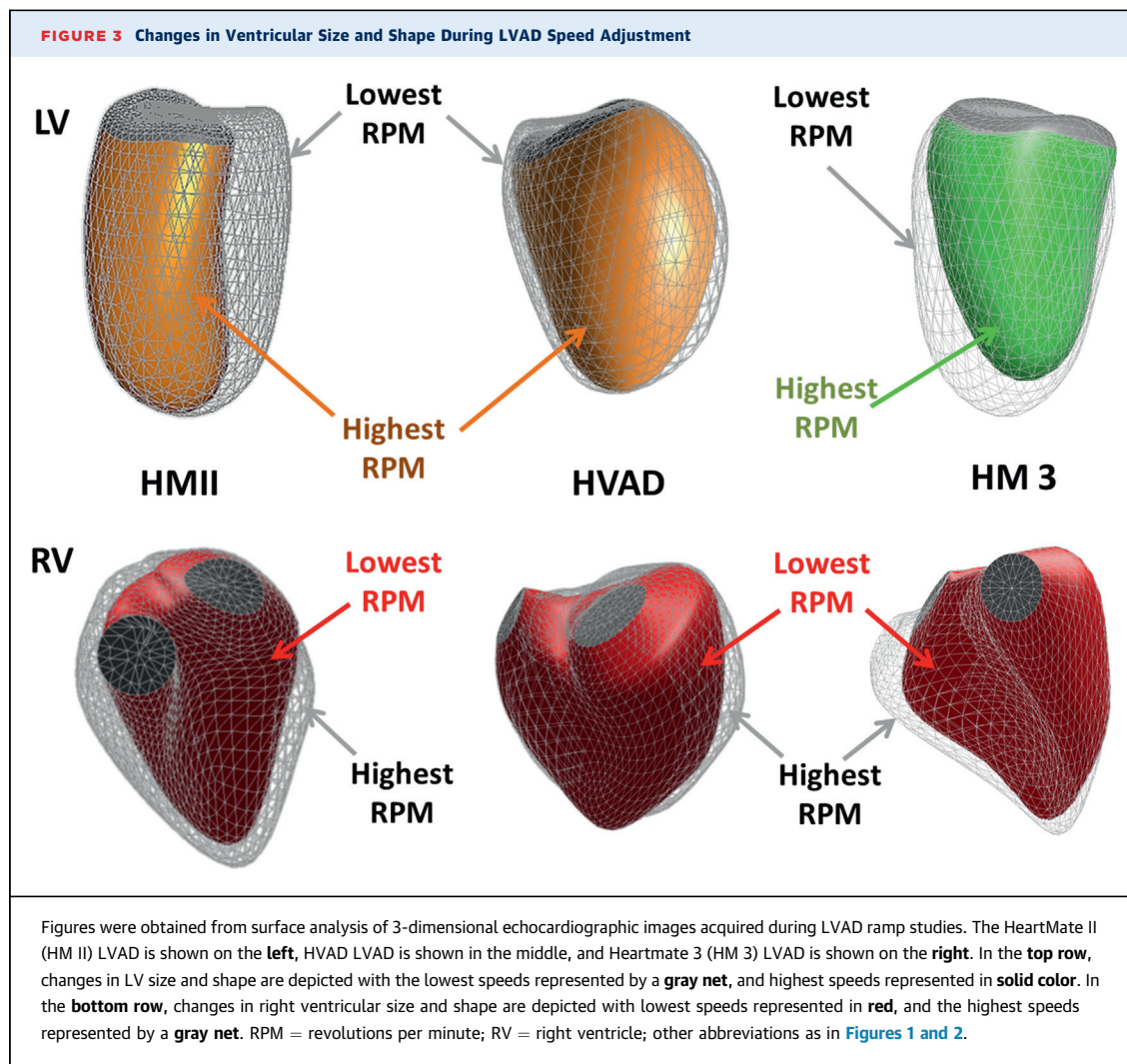
In 2015, Kapur et al. (33) employed a contemporary transvalvular axial flow pump and identified that first mechanically unloading the LV and delaying reperfusion reduced infarct size in a swine model of AMI. These authors further identified that LV unloading activated the RISK pathway within the infarct zone and increased myocardial levels of SDF-1 α and its downstream effector glycogen synthase kinase 3- β . This study was the first to link LV unloading directly to the ischemic conditioning biology first introduced in the 1980s. More recently, using a genomic approach, the same authors reported that LV unloading and delayed reperfusion, known as primary unloading, triggers a global shift in gene expression that primarily involves preserved cellular respiration and mitochondrial integrity (34). These observations are consistent with the findings of Achour et al. (32) and suggest that the field of mechanobiology and cardioprotection remain largely unexplored and future investigation may identify novel approaches to limit ischemia-reperfusion injury.

TRANSLATING SHORT-TERM UNLOADING TO A CLINICAL THERAPY

Dating back to the 1970s, ex vivo and in vivo experimental models of AMI demonstrated that unloading before, during, or after an index ischemic event positively affects cardiac function post-infarction

(35–38). However, unloading the ventricle in the clinical setting was previously infeasible from a technological perspective. The development of percutaneous ventricular assist devices in the early 2000s allowed for clinically relevant investigations into the effect of unloading on infarct size. With this background in mind, Kapur et al. (39) hypothesized that first reducing myocardial oxygen demand by limiting LV PVA (primary unloading), followed by coronary reperfusion would decrease myocardial infarct size compared with reperfusion alone (primary reperfusion). Activation of a percutaneous left atrial-to-femoral artery bypass pump (TandemHeart, Cardiac Assist, Pittsburgh, Pennsylvania) in a swine model of anterior myocardial infarction reduced LV PVA and, despite delaying coronary reperfusion, reduced myocardial infarct size by over 40% (39). Primary unloading (initiating mechanical support and reducing LV myocardial oxygen demand first while maintaining systemic perfusion) slows myocardial injury, enabling coronary reperfusion while reducing reperfusion injury. The reproducibility of primary unloading has been established in several laboratories worldwide using swine, canine, and bovine AMI models and a less invasive transvalvular axial-flow catheter (Impella CP, Abiomed, Danvers, Massachusetts), which decreased LV wall stress, activated a myocardial protection program involving up-regulation of the cardioprotective RISK pathway, and limited myocardial infarct size (33,40–42).

Clinical findings have mimicked these preclinical developments. In the USpella registry, among 154 consecutive patients with AMI complicated by cardiogenic shock, mechanical circulatory support with the Impella device before coronary reperfusion was associated with higher in-hospital and 30-day survival (43). In a separate registry study of 287 consecutive patients with AMI complicated by cardiogenic shock, Basir et al. (44) demonstrated that initiation of Impella support before percutaneous coronary intervention and before the administration of vasopressors or inotropes was independently associated with increased survival to discharge compared with patients receiving late mechanical support. It is important to remember that none of these studies were randomized. Furthermore, in-hospital survival was higher among patients supported within 60 min before reperfusion, compared with those supported later in the course of treatment (45). Interestingly, intra-aortic balloon pump counterpulsation without any delay to coronary reperfusion in the CRISP-AMI (Counterpulsation Reduces Infarct Size Pre-PCI for AMI) trial failed to reduce infarct size (46), which may have been due



to both the lesser hemodynamic effects of the intra-aortic balloon pump compared with Impella as well as the minimal period of unloading before revascularization.

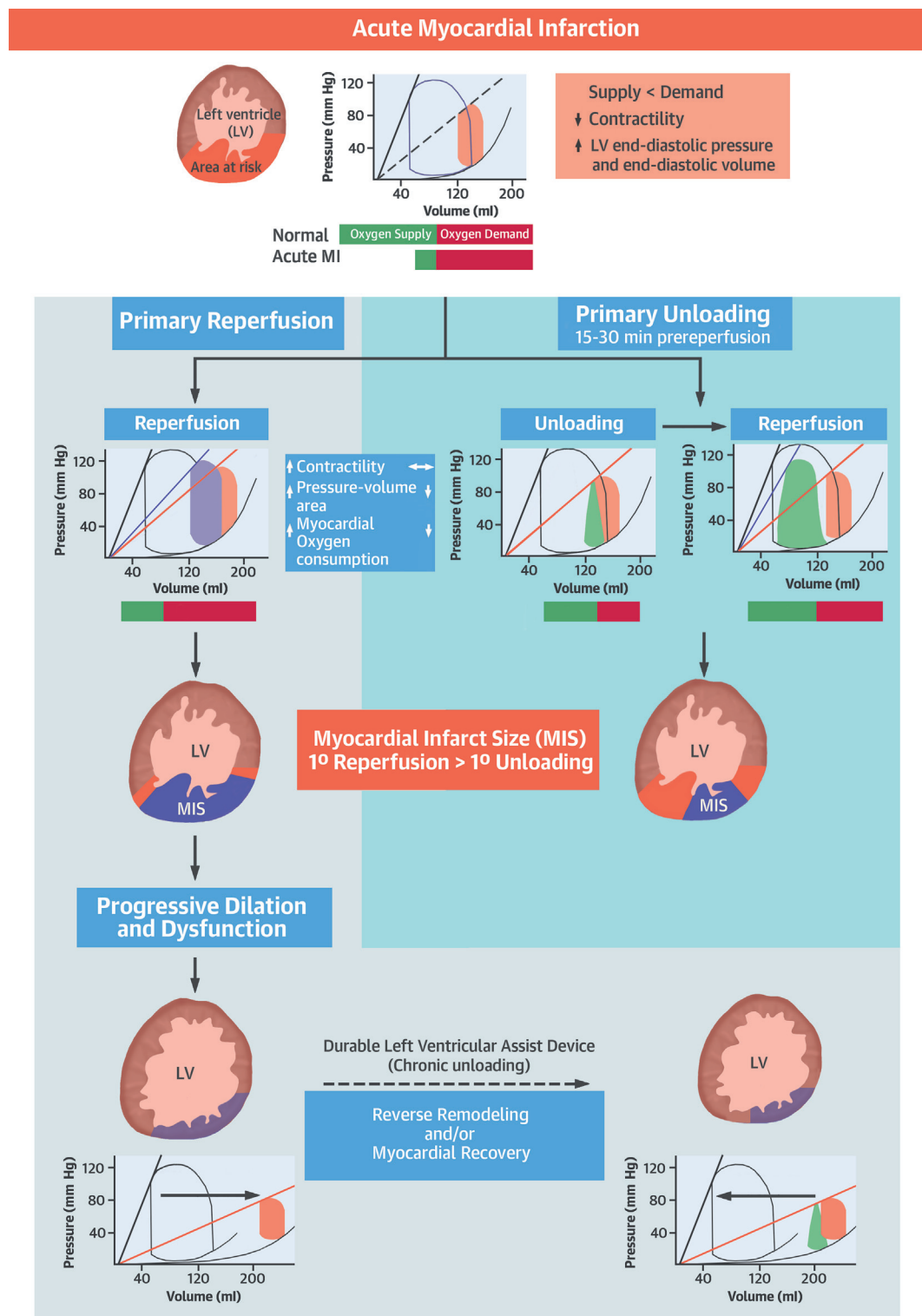
Contemporary AMI management includes first restoring myocardial oxygen supply (reperfusion) then attempting to pharmacologically reduce myocardial oxygen demand. The concept of primary unloading in ST-segment elevation myocardial infarctions alters the sequence of therapy by first significantly reducing myocardial oxygen demand (unloading) while maintaining systemic perfusion, and then restoring myocardial oxygen supply (reperfusion). The Food and Drug Administration has recently granted approval to initiate a safety and feasibility human trial of primary unloading in patients presenting with ST-segment elevation myocardial infarction (Door To Unloading with IMPELLA CP System in Acute Myocardial Infarction

[DTU]; [NCT03000270](#)) as a first step before conducting a large-scale pivotal efficacy trial.

REVERSE REMODELING AND MYOCARDIAL RECOVERY IN LONG-TERM HF

Long-term HF represents a challenge that is different than what is encountered in AMI, because the ventricular remodeling has already occurred, and as such, the goal is to reverse the remodeling process. Reverse remodeling is defined as the return of the ventricular size and shape, genotype, metabolism, and myocardial function towards normal. Normalization of cellular and intracellular myocardial properties is required to achieve improved myocardial function and, ultimately, myocardial recovery. Neurohormonal blockade serve as the mainstay therapy to achieve those goals. The primary objective of medical therapy is to: 1) unload excess pressure to which the LV is

CENTRAL ILLUSTRATION Following Acute Myocardial Infarction, There Is a Decrease in Contractility and a Rightward Shift of the Pressure-Volume Loop



exposed, by reducing preload volume (i.e., diuresis); 2) reduction in afterload utilizing vasodilator medications; and 3) promote restoration of beta-responsiveness and improve ventricular contractility (beta-blocker therapy). Animal models demonstrated that angiotensin-converting enzyme inhibitors achieved marked reductions in LV pressures, accompanied by a decrease in LV mass and volume (47,48). Similar unloading properties have been demonstrated in human studies, and the benefits of angiotensin-converting enzyme inhibitors have been repeatedly demonstrated in randomized, clinical trials (49-51). Reverse remodeling was also shown with administration of beta-blockers and aldosterone blockers (52-54). Cardiac resynchronization therapy induces further reverse remodeling by achieving electrical optimization of myocardial contraction. However, the most dramatic reverse remodeling has been reported with LVADs. LVADs remove blood from the LV, providing direct mechanical unloading of the heart while also restoring systemic perfusion (Figure 2). The hemodynamic effects of LVADs include reduction in the LV end-diastolic pressure and volume, elimination of the isovolumic contraction and relaxation periods, and significant reduction in the energetic requirements of the heart (55). Unloading was more profound with the first-generation pulsatile-flow LVADs than the current continuous-flow LVADs; however, the hemodynamic benefits of earlier LVADs were overshadowed by their adverse effect profile and limited durability (56).

Reverse remodeling induced by the LVAD is dependent on the operating speed of the LVAD and the flow generated in response to the pressure gradient between the LVAD inflow cannula and the ascending aorta. Each device has a unique relationship between flow and pressure, as represented by device-specific pressure-flow (H/Q) curves. Short-term changes in LV shape can be demonstrated by changing the LVAD operating speed (ramp study). As previously shown, increases in LVAD speed at fixed intervals result in progressive linear decreases in LV size as assessed by 2-dimensional echocardiography, or transition from a spherical to a conical shape with

significant reduction in LV volumes as shown by 3-dimensional echocardiography (57-59) (Figure 3). Furthermore, the reverse remodeling process is device specific. Intrathoracic devices, such as the HeartWare HVAD (Medtronic, Minneapolis, Minnesota) and the HeartMate 3 (Abbott, Abbott Park, Illinois) compress the LV apex, bringing it closer to the base of the heart. As a result, the heart remains more spherical, with volumetric changes occurring globally throughout the LV. By contrast, intra-abdominal devices, such as the HeartMate II (Abbott), pull the LV apex downward, resulting in a more conical shape with the most pronounced changes in size at the base of the heart. Regardless of the form of reverse remodeling that occurs, hemodynamic changes are comparable for the 2 device types, indicating equivalent degrees of pressure unloading (60). Significant reductions in LV volumes have been demonstrated as early as 30 days post-implantation, and are accompanied by marked reductions in LV mass as well as sustained improvement in LV ejection fraction (61).

Unloading LV pressure reduces neurohormonal activation and improves the responsiveness of β -adrenergic receptors (62-64). The addition of standard HF pharmacotherapy to LVAD support augments the suppression of neurohormonal activity, further promoting a reversal of LV structural changes (65). However, since the initial studies on reverse remodeling and myocardial unloading following LVAD, there were concerns that complete normalization of both the anatomic shape and function along with reversal of the molecular changes could not be achieved. Margulies et al. (7) studied the transcriptional adaptations in 199 failing and LVAD-supported hearts. The authors reported that over 3,000 genes exhibit dysregulation in HF. Among these dysregulated genes, a relatively small number exhibit a pattern of normalization, partial recovery, or overshoot after LVAD support. The authors concluded that mechanical unloading with LVAD does not normalize the dysregulated genes in the failing myocardium and more likely results in the expression of a new gene expression profile (7). On the cellular level, Diakos et al. (66) reported a decrease in cardiomyocyte size after LVAD unloading, without any

CENTRAL ILLUSTRATION Continued

Primary reperfusion increases cardiac output, but does not relieve the increase in left ventricular (LV) pressure and wall stress, resulting in infarct expansion and adverse ventricular remodeling. Primary unloading reduces LV pressure, wall stress, and myocardial oxygen consumption, preventing infarct expansion and decreasing subsequent ventricular remodeling. In the chronically remodeled heart, implantation of a durable left ventricular assist device results in a leftward shift of the pressure-volume loop, which promotes reverse remodeling, and in some cases, myocardial recovery. MI = myocardial infarction; MIS = myocardial infarct size.

sign of atrophy. From this small study of 44 patients, the authors concluded that LVAD unloading is sufficient to induce cardiomyocyte normalization. However, the extracellular changes were not consistent across different reports. In their original report on 15 patients, the Utah group reported: 1) 33% increase in capillary density; 2) 36% decrease in microvascular lumen area; 3) endothelial cell activation; and 4) significant increase in interstitial and total collagen content (67). On the other hand, a recent paper by Farris et al. (68) failed to show any differences in myocardial fibrosis and/or capillary density following mechanical unloading. Interestingly, the authors reported a reduction of fibroblast-specific collagen expression. The final answer on the extracellular changes occurring following LVAD support is still not clear.

From the metabolic standpoint, LVAD implantation induces only partial normalization in amino acid utilization. Specifically, the failing myocardium demonstrates a decrease in glucose utilization. Following mechanical unloading, there is an increase of glycolysis; however, there is not a significant change in oxidative metabolism. Furthermore, citric acid cycle abnormalities persist despite mechanical unloading with LVAD therapy (69).

The concerns about partial normalization raised by the above reports were further supported by Topkara et al. (70). In this seminal study, the authors reported the genetic and epigenetic changes during the failing and recovery phases in a transgenic mouse model. They found that suppression of the transgene was associated with a reversal of cardiac hypertrophy and improved cardiac myocyte contractile function. Those changes occurred concurrently with improved LV contractility and reverse LV remodeling. However, the normalization of LV structure and function was accompanied by only partial normalization (~60%) of gene expression.

Although the recovery of myocardial function is often sustained, cellular studies of both animal and human tissue have shown a persistence of abnormalities in genetic expression and properties of the extracellular matrix, indicating that reversal of the HF phenotype is not always matched by a reversal of the genotypic, metabolic, and molecular changes that accompany ventricular remodeling (7,70).

TRANSLATING LONG-TERM UNLOADING TO A CLINICAL THERAPY

Many studies have evaluated the effect of long-term unloading, utilizing LVAD therapy, on myocardial

recovery and the rate of LVAD explantation (71). The Harefield group, Birks et al. (72), pioneered the study of myocardial recovery in LVAD patients, demonstrating that device explantation can be achieved in 73% of selected patients with the combination of medical therapy, clenbuterol, and a pulsatile-flow LVAD. The same group demonstrated similar results with the HeartMate II continuous-flow LVAD (73). However, a study in the United States failed to replicate these studies, and was discontinued due to lack of efficacy. Investigators continued to evaluate the rate of myocardial recovery in large datasets and eventually identified a patient profile that is associated with myocardial recovery in response to long-term unloading (74,75). Young age, nonischemic etiology of HF, LV size <6.5 cm, creatinine \leq 1.2 g/dl, lack of implantable defibrillator, and a short duration of HF before LVAD implantation were associated with higher incidence of LVAD explantation for recovery. A scoring system was developed that predicts the chance of myocardial recovery in response to long-term unloading in LVAD patients. The results of the much-anticipated RESTAGE-HF (Remission From Stage D Heart Failure; NCT01774656) study, evaluating the rate of LVAD explantation among patients with a good profile for myocardial recovery, were recently presented, and found that 36% of the patients enrolled underwent LVAD explantation, with sustainable remission from the HF syndrome (76). This study highlights the importance of actively attempting to achieve myocardial recovery through aggressive medical management and systematically looking for evidence of recovery during LVAD support. Importantly, the LV should be evaluated in a reloaded state (i.e., during minimal degrees of LVAD support) to fully assess function, although it remains debatable whether it is important to slowly recondition the heart through gradually increased loading over time (77).

CONCLUSIONS

Cardiac unloading reduces mechanical power expenditure of the LV, minimizing MVO₂ and reducing ventricular remodeling (Central Illustration). Unloading can be achieved both in AMI and chronic HF. There is a significant body of evidence demonstrating that initiation of cardiac unloading leads to anatomic, cellular, molecular, and genetic changes in both the short- and long-term setting. Current studies are focusing on the clinical applications of early unloading in the setting of

myocardial infarction as a tool to reduce infarct size (DTU trial), and late unloading to achieve partial or complete myocardial recovery in chronic HF to test the degree to which partial or complete myocardial recovery can be achieved in patients with chronic HF (RESTAGE-HF study).

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