HHS Public Access

Author manuscript

J Cardiovasc Transl Res. Author manuscript; available in PMC 2020 November 03.

Published in final edited form as:

J Cardiovasc Transl Res. 2019 April ; 12(2): 87–94. doi:10.1007/s12265-019-09876-3.

Mechanical Left Ventricular Unloading to Reduce Infarct Size during Acute Myocardial Infarction: Insight from Preclinical and Clinical Studies

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Abstract

Acute myocardial infarction (AMI) remains a leading cause of morbidity and mortality, Pioneering preclinical work reported by Peter Maroko and Eugene Braunwald in 1971 identified oxygen supply and demand are primary determinants of myocardial infarct size in the setting of a heart attack Since the 1950's, advances in mechanical engineering led to the development of short-term circulatory support devices that range from pulsatile to continuous flow pumps. The primary objective of these pumps is to reduce native heart work, enhance coronary blood flow, and sustain systemic perfusion. Whether these pumps could reduce myocardial infarct size in the setting of AMI became an intense focus for preclinical investigation with variable animal models, experimental algorithms, and pump platforms being tested. In this review, we discuss the design of these preclinical studies, the evolution of mechanical support platforms, and attempts to translate these experimental methods into clinical trials.

Keywords

Acute myocardial infarction; ischemia-reperfusion injury; cardioprotection; mechanical circulatory support; preclinical models

Myocardial Ischemia-Reperfusion Injury Remains a Major Unresolved Target of Therapy

Acute myocardial infarction (AMI) remains a leading cause of morbidity and mortality, with an annual incidence of over 805,000 in the United States alone [1]. Beginning with the "open artery theory" in the 1970s, the field of STEMI management has been ruled by the

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All other authors do not have a conflict of interest. No animal or human studies were performed in this report.

fundamental principle that “time is muscle,” indicating that prolonged coronary occlusion leads to myocardial injury [2, 3]. For this reason, the well-established paradigm of contemporary management for STEMI focuses on rapid coronary reperfusion via balloon angioplasty and stenting to limit myocardial injury. However, despite timely reperfusion, nearly 10% of patients with acute myocardial infarction (MI) die during their index hospitalization, and 25% of survivors progress to develop chronic heart failure [4]. One explanation for these poor outcomes is that reperfusion of ischemic myocardium accelerates myocardial ischemia-reperfusion injury (IRI) leading to additional myocardial damage. Prior attempts to limit IRI via vascular conditioning or pharmacologic approaches have failed to show clear clinical benefit. Once a coronary artery becomes occluded, heart rate and myocardial contractility increase to compensate for reduced stroke volume, which decreases the myocardial oxygen supply-to-demand ratio and creates a vicious cycle of progressive myocardial damage.

Preclinical models of myocardial oxygen supply and demand mismatch in AMI

Pioneering preclinical work reported by Peter Maroko and Eugene Braunwald in 1971 identified oxygen supply and demand are primary determinants of myocardial infarct size in the setting of a heart attack [5]. Using an anesthetized canine model, these investigators performed a left thoracotomy, opened the pericardium, and surgically ligated the left anterior descending artery. Serial 20 minute occlusions of the artery were performed with one-hour intervals between occlusions to assess ischemic burden and myocardial damage by quantifying ST-segment elevations. To explore whether increasing myocardial oxygen consumption during coronary occlusion increases myocardial damage, they employed: 1) pharmacologic agents to drive heart rate and contractility (isoproterenol), 2) right atrial pacing, 3) inotropes (glucagon and ouabain), 4) sympathomimetics (bretylium), and 5) acute arterial hemorrhage. To test the effects of reduced myocardial oxygen consumption, investigators administered either methoxamine to increase systemic blood pressure or the negative inotrope propranolol. Compared to controls, all methods that increased myocardial oxygen consumption increased ST-segment elevations, whereas reducing myocardial oxygen consumption with either propranolol or methoxamine reduced ST-segment elevations and CPK levels. Major limitations of this study included: 1) the need for surgical thoracotomy to access the coronary vessel, 2) the inability to quantify myocardial infarct size, 3) the inability to assess myocardial oxygen consumption directly, and 4) the inability to test late term effects of initial drug therapy on infarct size and cardiac function. The investigators concluded that “measures designed for *reduction of myocardial oxygen demands* and *improvement of coronary perfusion*, when effected promptly after a patient has been brought to the hospital, might potentially reduce the ultimate size of the infarction.” At the time, 2 other cardiovascular pioneers, Charles Dotter and Andreas Greuntzig, were developing techniques for peripheral and coronary vascular angioplasty respectively. In 1977, the first coronary angioplasty was performed in Zurich and henceforth, coronary reperfusion to restore myocardial oxygen supply during an AMI became the cornerstone focus of STEMI management for the next 40 years.

Mechanically unloading the left ventricle and delaying coronary reperfusion limits infarct size

Prior attempts to limit ischemia-reperfusion injury via vascular conditioning or pharmacologic approaches have failed to show clear clinical benefit [6–7]. A critical barrier to these strategies is the mandate for rapid coronary reperfusion and therefore insufficient time for any beneficial impact prior to reperfusion. While these strategies were being tested in preclinical and clinical trials, a few investigators continued working on the first arm of Maroko and Braunwald's conclusion, namely, reducing myocardial oxygen demand to reduce infarct size. Since the 1950's, advances in mechanical engineering led to the development of short-term circulatory support devices that range from pulsatile to continuous flow pumps. The primary objective of these pumps is to reduce native heart work, enhance coronary blood flow, and sustain systemic perfusion. Whether these pumps could reduce myocardial infarct size in the setting of AMI became an intense focus for preclinical investigation with variable animal models, experimental algorithms, and pump platforms being tested (Table 1). Intra-aortic balloon counterpulsation pumps (IABPs) were among the first percutaneously delivered circulatory support pumps to be studied in preclinical models of infarct reduction. IABPs function by inflating during diastole and deflating during systole to create higher diastolic pressures in the aortic root and to reduce ventricular afterload during systole. The net effect of IABP activation is a reduction in LV pressure with minimal change in LV volume, thereby leading to minimal change in net PVA or myocardial oxygen consumption (Figure 1A) [8–9] Several studies have confirmed that intact native ventricular function is a major determinant of IABP effects [10–11]. For this reason, the more dysfunctional the LV, the less function an IABP becomes. The challenge with IABP studies in preclinical models is that major determinants of IABP function including aortic length, diameter, and compliance may vary considerably between species and relative to humans. Early preclinical studies with IABPs generated mixed results with respect to altering infarct size (Table 1). All 4 of the referenced IABP studies were performed using an open thoracotomy and a surgical ligature around the left anterior descending artery (LAD), which may alter intra-cardiac loading conditions once the pericardium is incised [12–15]. Furthermore, with the exception of the study by Ledoux and Smalling, all prior studies initiated IABP support after LAD ligation. Ledoux and Smalling were the first to identify that IABP insertion before, not after, LAD reperfusion reduced infarct size. Based largely on the findings of this study, the Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction (CRISP-AMI) study explored the utility of initiating IABP therapy immediately before coronary reperfusion in patients with acute anterior myocardial infarction [16]. The study failed to demonstrate any reduction in myocardial infarct size measured by cardiac MRI among IABP recipients compared to subjects receiving coronary reperfusion without IABP therapy. One explanation for this observation is that in CRISP AMI, a majority of patients were treated beyond 3 hours from time of symptom onset to IABP insertion and/or reperfusion, which may have impacted any potential for infarct salvage with IABP therapy [17–18].

Another mechanical circulatory support platform studies in the early 1980's was left atrial-to-femoral artery bypass. Using an extracorporeal rotary flow pump, a drainage cannula was

placed into the left atrium and a return cannula placed in the femoral artery. Oxygenated blood was removed from the left atrium and delivered to the systemic arterial circulation. The net effect of this support system is minimal change in LV pressure, but a significant reduction in LV volume leading to reduced PVA and myocardial oxygen consumption (Figure 1B) [19–20]. Catinella and Spencer tested this approach by applying the LA-FA bypass circuit 15 minutes after surgical LAD ligation [21]. Four hours later, compared to controls, myocardial infarct size was reduced in the LA-FA bypass group. The clinical utility of LA-FA bypass was further explored in a porcine model where balloon occlusion of the LAD for 120 minutes was followed by 120 minutes of reperfusion without mechanical support [22]. In the mechanically supported group, percutaneous LA-FA bypass was initiated after 120 minutes of ischemia, and LAD occlusion was prolonged for an additional 30 minutes (total of 150 minutes of LAD occlusion), followed by 120 minutes of reperfusion with device support. Compared to controls, LA-FA bypass significantly reduced infarct size in the group despite 30 additional minutes of LAD occlusion (Figure 2). These findings extended the observations of Ledoux and Smalling by suggesting that mechanical unloading of the LV and *delaying* coronary reperfusion reduces infarct size. In 2014, the TandemHeart to Reduce Infarct Size (TRIS) trial was initiated and proposed insertion of the TandemHeart LA-FA bypass circuit before reperfusion in patients presenting with anterior STEMI. The trial was terminated in 2015 due to lack of enrollment. While the TandemHeart is able to effectively unload the LV, the failure of this trial reflected concerns among the interventional community about the feasibility of trans-septal puncture prior to reperfusion in STEMI.

Over the same time period, a third class of acute circulatory support devices, known as trans-valvular pumps were being developed. Trans-valvular pumps employed micro-axial impellers to transfer rotational kinetic energy to blood and thereby generate flow. These pumps were deployed across the aortic valve and displace blood directly from the LV to the aorta. In contrast to LA-FA bypass, trans-valvular pumps reduce both LV pressure and volume, thereby significantly reducing PVA and myocardial oxygen consumption. The magnitude of PVA reduction is determined, in part, b the magnitude of flow generated by the trans-valvular pump (Figures 1C-D) [23]. One of the earliest trans-valvular pumps was the Hemopump (Nimbus Inc), which was a micro-axial impeller attached by a driveline to an *extracorporeal* motor (Figure 2). Initial preclinical testing in a canine model of surgical LAD ischemia and reperfusion showed reduced cardiac workload due to systolic and diastolic unloading with a concomitant increase in perfusion to ischemic myocardium [24]. Based on these preliminary studies, Smalling and colleagues compared the effect of IABPs versus the Hemopump in a canine model of surgical LAD ischemia and reperfusion [25]. The IABP and Hemopump were active throughout the entire period of LAD occlusion and reperfusion. Compared to controls without mechanical support, both the IABP and Hemopump reduced infarct size by 57% and 65% respectively. A follow up study in 2005 using a similar canine model of surgical LAD ischemia and reperfusion injury confirmed that initiation of Hemopump support within 15 minutes before, not after, reperfusion reduced infarct size [26] (Figure 3). Clinical translation of these exciting studies was limited by a risk of potential adverse effects of the Hemopump including vascular complications, hemolysis, and the need for a driveline and externalized motor.

In 2015, the SHIELD 1 trial tested the clinical utility of the HeartMate Percutaneous Heart Pump (HM-PHP) device in 50 patients undergoing high risk PCI (Figure 2). In this study, the HM-PHP increased cardiac index and mean arterial pressure [27]. The HM-PHP shares the external motor and drive-line connected to a trans-valvular impeller from the Hemopump design. However, in contrast the Hemopump, the HM-PHP device can be deployed into the LV via a 14Fr sheath and employs a self-expanding 24Fr impeller across the aortic valve, which allows the device to achieve flows above 4 liters/minute without the need for surgical access. The HM-PHP is under investigation in the United States as part of the SHIELD-2 trial. However, this study was paused in 2017 due to isolated instances of pump stoppage. The HM-PHP device is not currently available for commercial use.

In parallel to the development of the Hemopump, another trans-valvular pump known as the Impella (Abiomed Inc) was introduced into clinical practice in the early 2000's. In contrast to the Hemopump, the Impella microaxial impellers were connected to an *intracorporeal* motor without the need for an externalized driveline (Figure 2). In 2003, Meyns and colleagues employed a sheep model of surgical LAD ischemia and reperfusion injury to test whether full or partial trans-valvular support with a surgically implanted Impella 5.0 LP pump reduced infarct size [28] (Figure 3). These investigators observed that initiation of full support at the time of reperfusion with flow rates of over 4 liters/minutes had a greater reduction in infarct size compared to partial support (2.5 liters/minute). Using aortic and coronary sinus blood samples, they further reported that reduced myocardial oxygen consumption during Impella support correlated directly with reduced myocardial infarct size. In 2012, a percutaneously delivered Impella CP pump was introduced into clinical practice and allowed for flows of 3.5 liters/ minute without the need for surgery. In 2015, this novel Impella device was employed in a non-surgical swine model of LAD ischemia and reperfusion to test whether first unloading the LV and *extending the delay to reperfusion* by 60 minutes (primary unloading) would reduce infarct size [29] (Figure 3). Compared to animals receiving primary reperfusion alone, primary unloading reduced infarct size, increased signaling through the reperfusion injury salvage kinase (RISK) pathway and increased levels of the cardioprotective cytokine stromal derived factor one alpha (SDF1a). This was the first report to introduce the concept of mechanical conditioning whereby LV unloading and delayed reperfusion activates a cardioprotective signaling program within the myocardium. Since then, several laboratories have confirmed that primary unloading with variable periods of 'mechanical conditioning' before reperfusion in swine and canine models [30–31]. Furthermore, compared to primary reperfusion, primary unloading with the Impella CP for 30 minutes before reperfusion in swine triggers a cardioprotective shift in myocardial gene expression, preserves mitochondrial integrity, and leads to a durable reduction in LV scar size as quantified by cardiac magnetic resonance imaging 28 days after the initial ischemic injury [32]. Collectively, these preclinical studies led to a clinical first-in-human study known as the Door To Unloading With Impella CP System in Acute Myocardial Infarction to Reduce Infarct Size (DTU): A Prospective Feasibility Study (NIH CLINICAL TRIAL: NCT03000270). This is a multi-center, prospective, randomized, two-arm feasibility trial to assess the potential role of unloading with the Impella CP prior to revascularization in reducing infarct size. The study design includes 1:1 randomization between: 1) 30 minutes of unloading with Impella CP prior to primary percutaneous

coronary intervention (PPCI); and 2) initiation of Impella CP unloading followed immediately by PPCI. In addition to evaluating safety, infarct size at 3–5 days and 30 days will be evaluated using cardiac magnetic resonance imaging. This study is actively underway in the United States.

In conclusion, reducing myocardial infarct size remains a major unmet need with broad-reaching implications for long-term survival and morbidity associated with heart failure after an acute myocardial infarction. Over the past 50 years, mechanical circulatory support devices have evolved from balloon counterpulsation pumps to extracorporeal rotary flow pumps to intracorporeal micro-axial flow pumps that can be rapidly implanted without the need for surgery (Figure 4). Cumulative experience from laboratories around the world testing these devices in preclinical models of ischemia-reperfusion injury suggest that LV unloading prior to reperfusion (Primary Unloading) may be the most efficient method to achieve the two objectives proposed by Maroko and Braunwald in 1971 to reduce infarct size, namely "*reduction of myocardial oxygen demands* and *improvement of coronary perfusion.*" Whether Primary Unloading translates to improved clinical outcomes remains to be determined.

Acknowledgements

This work was supported by a grant from the National Institutes of Health (RO1HL139785-01) to N.K.K.

Disclosures:

Institutional research grants, consulting, and speaker honoraria to N.K.K. from Abbott, Abiomed, Boston Scientific, Maquet, Medtronic, and MD Start

Compliance with Ethical Standards

No funding was received for this report. Conflict of interest: Navin Kapur, MD has received institutional grant support from Abbott, Abiomed, Boston Scientific, Maquet/Getinge, Medtronic and MD Start. Dr. Kapur receives consulting/speaking honoraria from Abbott, Abiomed, Boston Scientific, and MD Start.

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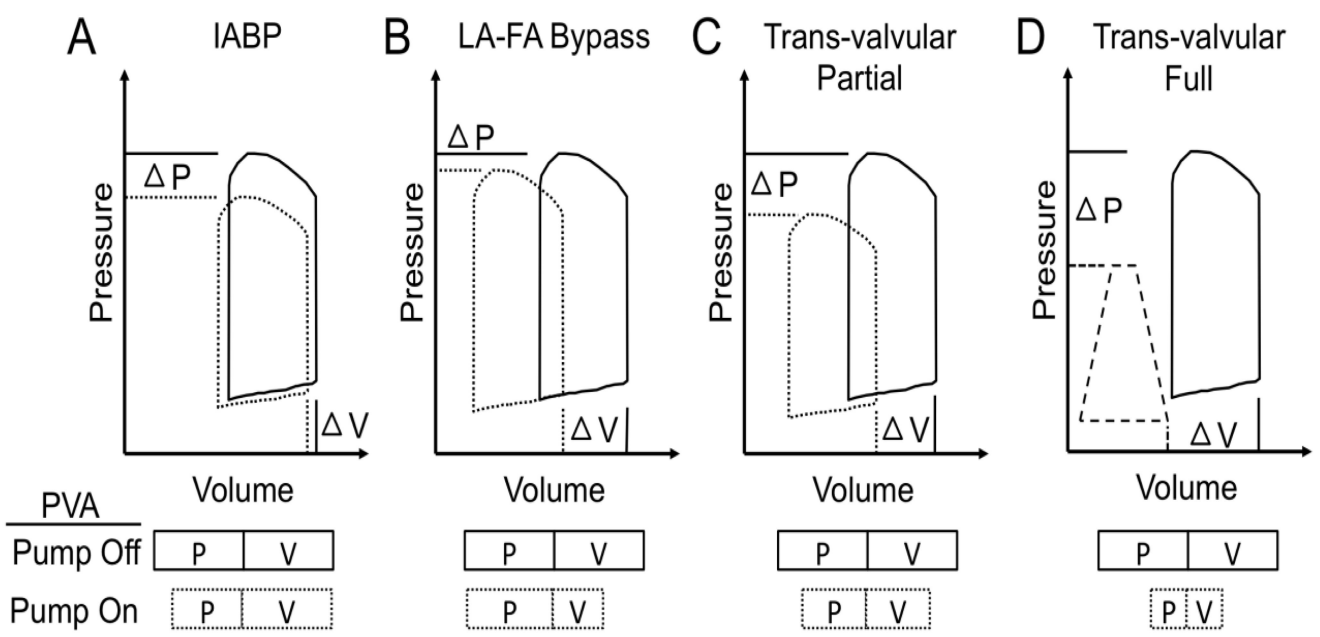

Figure 1.

Impact of acute mechanical circulatory support pumps on myocardial oxygen consumption. A) Compared to baseline, intra-aortic balloon pumps reduce LV pressure, not volume, thereby creating a small reduction in pressure-volume area (PVA), which directly correlates with myocardial oxygen consumption; B) Left atrial to femoral artery (LA-FA) bypass pumps such as the TandemHeart device reduce PVA by significantly decreasing LV volume, not pressure; C-D) Trans-valvular pumps such as the Hemopump, Impella, or HeartMate percutaneous heart pump, reduce PVA by decreasing both LV pressure and volume. The magnitude of PVA reduction directly correlates with the magnitude of flow through a trans-valvular pump. Full lines represent 'Pump Off'. Hashed lines represent 'Pump On'. PVA is illustrated by the boxes encompassing the product of LV pressure (P) and volume (V).

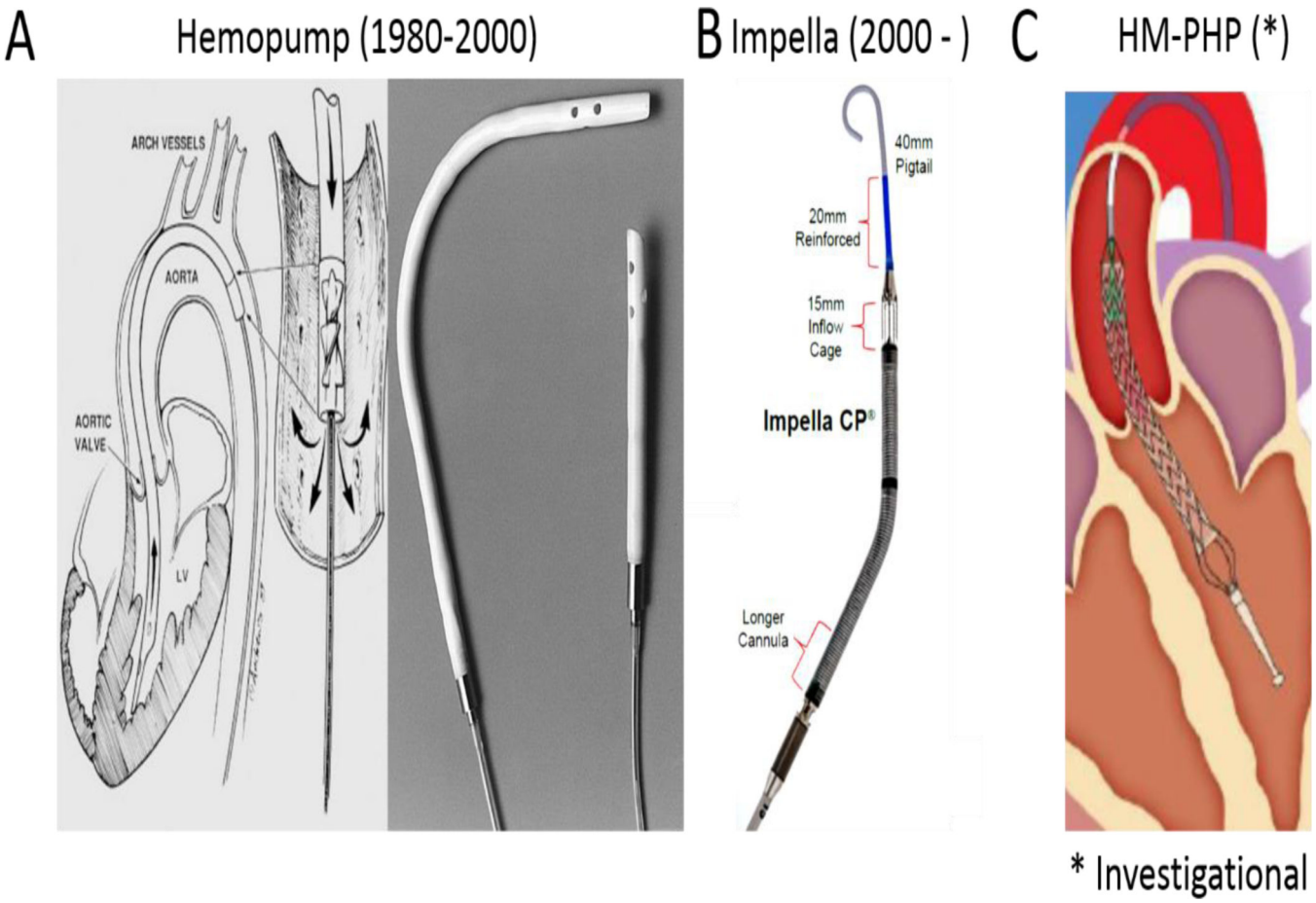

Figure 2.

Transvalvular Pumps. A) The Hemopump has a trans-valvular impeller connected to an extra-corporeal motor by a driveline; B) The Impella has a trans-valvular impeller connected to an intracorporeal motor without a driveline; C) The investigational HeartMate Percutaneous Heart Pump (HM-PHP) has a self-expanding trans-valvular impeller connected to an extra-corporeal motor by a driveline.

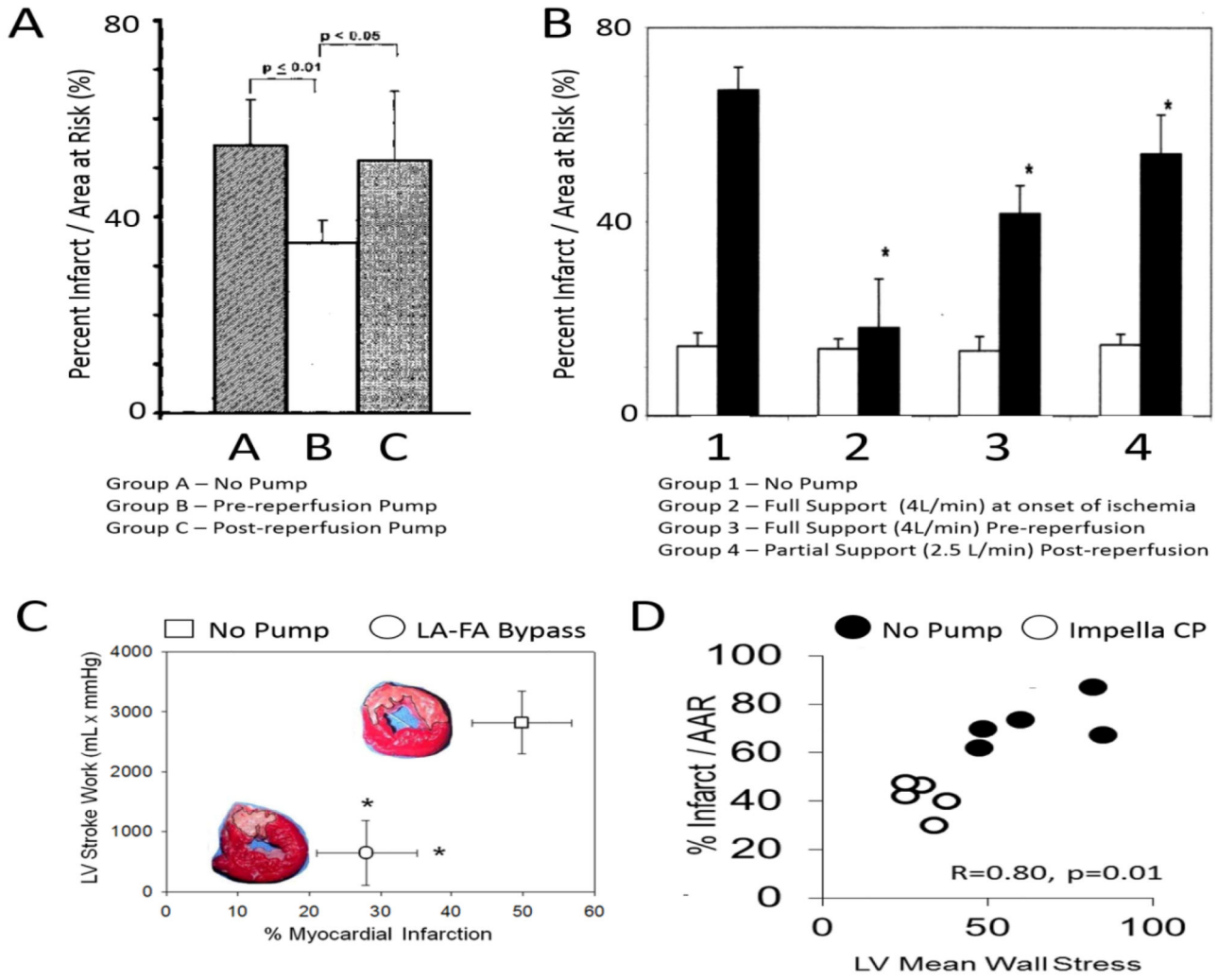

Figure 3.

A) Infarct reduction before, not after, reperfusion with the Hemopump; B) Infarct reduction before, not after, reperfusion with full Impella support (>4 liters/minute of flow); C) Infarct reduction with the TandemHeart LA-FA bypass pump before reperfusion; D) Infarct reduction with the Impella CP before reperfusion.

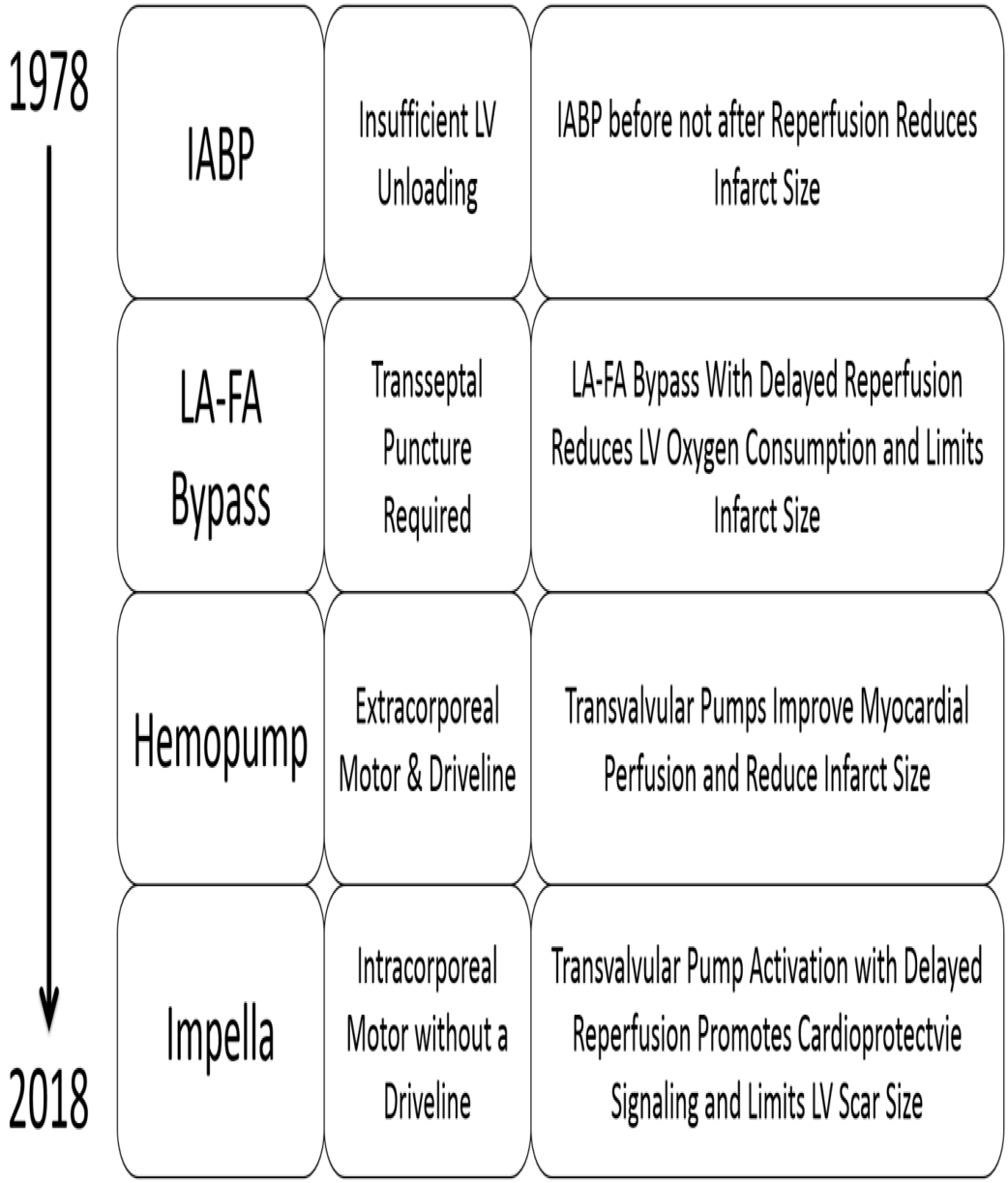

Figure 4.
Summary of key lessons over the past four decades of preclinical studies exploring infarct reduction with acute mechanical left ventricular support devices

Table 1.

Summary of preclinical studies of acute mechanical left ventricular support devices to reduce infarct size

Animal Model	Year	Duration of Ischemia (min)	Duration of Reperfusion (min)	Mechanical Support Before or After Reperfusion	Occluded Vessel	Method of Occlusion	Device	Reduction in Infarct Size?	Reference
Canine	1978	480	X	Before	LAD	Ligation	IABP	Yes	Roberts & Gay [6]
Baboons	1979	1440	X	Before	LAD	Ligation	IABP	No	Haston & McNamara [7]
Porcine	1980	1440	X	Before	LAD	Ligation	IABP	No	Laas & Replogle [8]
Porcine	2008	60	240	Before vs After	LAD	Ligation	IABP	Yes / No	Ledoux & Smalling [9]
Canine	1983	240	X	Before	LAD	Ligation	LA-FA Bypass	Yes	Catinella & Spencer [12]
Porcine	2013	120	120	Before	LAD	Balloon angioplasty	TandemHeart	Yes	Kapur & Karas [13]
Canine	1989	120	60	Before	LAD	Ligation	Hemopump	Yes	Merhige & Wampler [14]
Canine	1992	120	60	Before	LAD	Snare ligation	Hemopump/ IABP	Yes	Smalling & Amirian [15]
Canine	2005	120	240	Before vs After	LAD	Snare ligation	Hemopump	Yes / No	Achour & Smalling [16]
Sheep	2003	60	120	Before vs After	LAD	Ligation	Impella 5.0	Yes	Meyns & Flameng [17]
Porcine	2015	90	120	Before	LAD	Balloon angioplasty	Impella CP	Yes	Kapur & Karas [18]
Porcine	2015	120	120	Before	LCx	Ligation	Impella LD	Yes	Sun & Wang [20]
Porcine	2018	90	120	Before	LAD	Balloon angioplasty	Impella CP	Yes	Esposito & Kapur [21]