ORIGINAL RESEARCH

Left Ventricular Unloading Increases the Coronary Collateral Flow Index Before Reperfusion and Reduces Infarct Size in a Swine Model of Acute Myocardial Infarction

Natalia Briceno, BSc, MRCP;* Shiva K. Annamalai, MD;* Lara Reyelt, BS; Paige Crowley, BS; Xiaoying Qiao, PhD; Lija Swain, PhD; Robert Pedicini, BS; Sina Foroutanjazi, BS; Lena Jorde, BA; Gemini Yesodharan, MD; Divaka Perera, MD, FRCP; Navin K. Kapur, MD

***Background*—**Unloading the left ventricle and delaying reperfusion reduces infarct size in preclinical models of acute myocardial infarction. We hypothesized that a potential explanation for this effect is that left ventricular (LV) unloading before reperfusion increases collateral blood flow to ischemic myocardium.

***Methods and Results*—**Acute myocardial infarction was induced by balloon occlusion of the left anterior descending artery for 120 minutes in adult swine, followed by reperfusion for 180 minutes. After 90 minutes of occlusion, animals were assigned to 30 minutes of continued occlusion (n=6) or to 30 minutes of support with either an Impella CP (n=4) or venoarterial extracorporeal membrane oxygenation (n=5) with persistent occlusion. The primary end point was measures of microcirculatory blood flow including the collateral flow index (CFI) during left anterior descending artery occlusion as $(P_w-RA)/(P_a-RA)$, where P_a, P_w, and RA are aortic, coronary wedge, and right atrial pressure, respectively. Infarct size was quantified using triphenyltetrazolium chloride. Compared with continued occlusion, Impella, not venoarterial extracorporeal membrane oxygenation, reduced infarct size relative to the area at risk. Before reperfusion, Impella reduced LV stroke work by 25% and increased the CFI by 75%, but venoarterial extracorporeal membrane oxygenation did not. Among all groups, the change in CFI between 90 and 120 minutes correlated inversely with the change in LV stroke work (r^2=0.44, P=0.01) and infarct size (r^2=0.41, P=0.02).

***Conclusions*—**We report for the first time that 30 minutes of LV unloading during coronary occlusion increases the CFI, which correlates inversely with LV stroke work and infarct size. Venoarterial extracorporeal membrane oxygenation failed to increase the CFI and did not reduce infarct size. **(*J Am Heart Assoc*. 2019;8:e013586. DOI: 10.1161/JAHA.119.013586.)**

Key Words: acute myocardial infarction • collateral flow • mechanical circulatory support • ventricular unloading

Acute myocardial infarction (AMI) is a leading cause of heart failure, with an annual incidence of over 700 000 in the United States alone.[1] Infarct size in AMI is determined by the duration of coronary occlusion, the size of the myocardial area at risk, and the collateral circulation.[2] Recent clinical data support that collateral blood flow is an independent determinant of myocardial salvage in acute ST-segment–elevation myocardial infarction.[3,4] To interrogate microcirculatory physiology in vivo, pressure and Doppler sensor–tipped guide wires can obtain phasic coronary pressure and flow profiles beyond a coronary occlusion and correlate with myocardial damage in AMI.[5,6] These data can be used to quantify the pressure-derived collateral flow index (CFI), which includes a measure of the distal coronary wedge pressure (Pw). Increasing CFI and Pw values have independently been reported as markers of increasing microcirculatory blood flow, reduced myocardial ischemia, and improved clinical outcomes in AMI.[6–8]

The use of acute mechanical circulatory support devices such as transvalvular axial flow pumps (Impella, Abiomed Inc) or venoarterial extracorporeal membrane oxygenation (VA-ECMO) circuits during high-risk coronary intervention or AMI complicated by cardiogenic shock is increasing.[9,10]

From the British Heart Foundation Centre of Excellence and National Institute for Health Research Biomedical Research Centre, School of Cardiovascular Medicine and Sciences, King's College London, London, United Kingdom (N.B., D.P.); Molecular Cardiology Research Institute, Surgical and Interventional Research Laboratories, and The CardioVascular Center, Tufts Medical Center, Boston, MA (S.K.A., L.R., P.C., X.Q., L.S., R.P., S.F., L.J., G.Y, N.K.K.).

An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013586

*Dr Briceno and Dr Annamalai contributed equally to this work.

Correspondence to: Navin K. Kapur, MD, Tufts Medical Center, 800 Washington Street, Box # 80, Boston, MA 02111. E-mail: nkapur@tuftsmedicalcenter.org

Received June 27, 2019; accepted August 29, 2019.

Clinical Perspective

What Is New?

- Mechanically unloading the left ventricle before reperfusion in acute myocardial infarction increases the collateral flow index and reduces infarct size as compared with continued occlusion without support or support with venoarterial extracorporeal membrane oxygenation before reperfusion.
- The results suggest a mechanistic role of the collateral circulation in the reduction of ischemia reperfusion injury during mechanical left ventricular unloading.

What Are the Clinical Implications?

- Future clinical studies are required to explore the impact of left ventricular unloading on collateral flow in patients during acute myocardial infarction.

However, our understanding of how these devices impact coronary blood flow or infarct size during AMI remains limited. We recently reported that compared with reperfusion alone, mechanically unloading the left ventricle and delaying reperfusion by 30 minutes reduces myocardial damage and promotes myocardial recovery 30 days in a preclinical model of AMI.[11–13] This approach is under current clinical investigation.[14] Whether changes in microcirculatory blood flow during left ventricular (LV) unloading and delayed reperfusion influence infarct size remains unknown. The main objectives of the present study were: (1) to quantify the CFI during left anterior descending artery (LAD) occlusion without mechanical circulatory support, as compared with support with Impella LV unloading and VA-ECMO before reperfusion, and (2) to test whether the combination of VA-ECMO and delayed reperfusion reduces infarct size in a swine model of AMI.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files.

Experimental Protocol of Myocardial Infarction and Mechanical Circulatory Support

Studies were conducted in adult, male Yorkshire swine. The study protocol was approved by the Institutional Animal Care and Use Committee at Tufts Medical Center. All experiments were performed according to the committee's guidelines. Animals were premedicated with Telazol (0.8 mL/kg IM). General anesthesia was induced and maintained with isoflurane (1–2%). All animals were intubated and mechanically ventilated (Harvard Apparatus Inc) with room air and supplemented oxygen to maintain physiologic pH and oxygen saturation. Surface ECG leads, an orogastric tube, peripheral 18G venous catheters, and a rectal thermistor were placed in all animals. Heating pads were used as needed to maintain a core body temperature >99°F. Vascular access sheaths were then deployed into the right internal jugular vein (10F), left carotid artery (7F), and both femoral arteries (7F) and veins (10F). Unfractionated heparin boluses with a goal activated clotting time of 300 to 400 seconds, continuous lidocaine infusion (1 mg/kg), and noradrenaline (0.16 μg/min) were initiated in all animals. A 6F Judkins right coronary catheter (Boston Scientific) engaged the left coronary artery via the right femoral artery, and baseline angiograms were recorded. A pressure wire was delivered into the distal LAD and a 3.0×8-mm angioplasty balloon (Boston Scientific) was deployed in the mid-LAD after the first diagonal branch with angiographic confirmation of LAD occlusion. Coronary angiography performed immediately after reperfusion and again after the end of the study protocol confirmed patency of the LAD. Following reperfusion, the LAD balloon was left in position for repeat balloon occlusion during Evans Blue counterstaining.

To explore the effects of mechanical support with Impella or VA-ECMO before reperfusion in AMI, 15 swine underwent 120 minutes of LAD occlusion followed by 180 minutes of reperfusion. Following 90 minutes of LAD occlusion, subjects were randomly assigned to have continued occlusion alone for 30 minutes (n=6), continued occlusion for 30 minutes with activation of an Impella CP (n=4), or continued occlusion for 30 minutes with activation of VA-ECMO (n=5) (Figure 1A). In the 2 device arms, pumps remained active throughout the 180 minutes after reperfusion. The Impella CP was inserted via a 14F sheath in the right carotid artery and activated at maximal support (44 000 RPM or P-level 8). VA-ECMO was initiated using a 19F arterial cannula and 21F multistage venous cannula in the left femoral artery and right femoral vein, respectively. VA-ECMO was activated at 7500 RPM using an extracorporeal centrifugal flow pump (CardiacAssist Inc) and a membrane oxygenator (Quadrox, Maquet Inc).

Myocardial Infarct Quantification

After 180 minutes of reperfusion the LAD was balloon occluded, followed by intracoronary delivery of Evans Blue. The animals were then immediately euthanized and myocardial infarct size quantified using digital photography across LV cross-sectional slices incubated in 1% triphenyltetrazolium chloride as previously described.[13] Three blinded reviewers (XQ, GY, and RP) quantified the total myocardial area, area at risk, and infarct zone using digital planimetry to identify the infarct percentage relative to the area at risk.

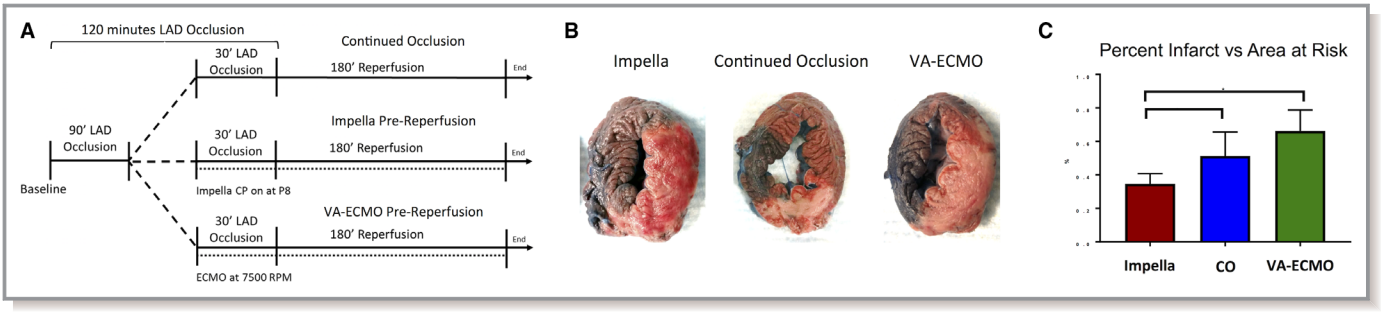

Figure 1. Infarct size associated with Impella or venoarterial extracorporeal membrane oxygenation (VA-ECMO) plus delayed reperfusion. **A**, Illustration of the study design; (**B**) Representative pathologic specimens of the left ventricle with triphenyltetrazolium chloride and Evans Blue counterstaining; (**C**) Bar graph quantifying infarct size normalized to the area at risk for the continued occlusion (CO), Impella, and VA-ECMO groups (n=5 per group). Red=Impella, blue=continued occlusion, green=VA-ECMO. LAD indicates left anterior descending artery.

Coronary Hemodynamic Assessment

Using a coronary guide catheter and pressure wire (Radi Systems; Abbott Vascular Inc) positioned in the distal LAD beyond the area of balloon occlusion, the CFI was calculated between 90 and 120 minutes at 10-minute intervals in all 3 groups (with a total of 4 CFI measurements per subject) during the period of LAD balloon occlusion with or without Impella or VA-ECMO support. CFI was calculated as (Pw−RA)/(Pa−RA), where Pa, RA, and Pw are aortic, right atrial, and coronary wedge pressure, respectively.[15,16] Concurrently, a dual pressure and Doppler flow wire (Combowire XT, Phillips Inc) was inserted into the left circumflex artery and measured average peak velocity between 90 and 120 minutes of LAD occlusion in all 3 groups.

Right Heart and LV Hemodynamic Assessment

Pulmonary artery catheter indices and LV pressure and volume were recorded throughout the study protocol. For LV pressure and volume measurements, a 5F-conductance catheter system (Sigma M, CD Leycom) deployed via the left carotid was used as we have previously described.[11–13] Absolute LV volumes were measured by subtracting parallel conductance from total conductance volumes. Stroke volume is calculated as the difference in conductance volumes at $+dP/dt_{max}$ and $-dP/dt_{min}$. LV stroke work (SW) was calculated as the product of peak LV peak systolic pressure and stroke volume. A pulmonary artery catheter was inserted via the right internal jugular vein.

Statistical Analysis

Results are presented as mean±SD. An unpaired Student *t* test or 1-way ANOVA were used to compare continuous variables between groups, with a Bonferroni correction performed. Simple linear regression analysis was used to evaluate for a correlation between 2 parameters.

To account for treatment group differences, univariate correlations were additionally adjusted for Impella and extracorporeal membrane oxygenation as covariates in a multivariate linear regression. R^2 and *P* values are reported for univariate analyses in the figures and for multivariate analyses in Table S1. Statistical analyses were performed with GraphPad Prism (GraphPad Software, Inc.) and IBM SPSS Statistics 25.0.0.2 (for the multivariate analysis).

A *P* value of ≤0.05 was considered to indicate a significant effect or between-group difference.

Results

Reducing LVSW Reduces Infarct Size

Compared with continued occlusion, LV unloading with the Impella CP device for 30 minutes before reperfusion reduced myocardial infarct size (52±15% versus 34±6%, *P*=0.03) (Figure 1B and 1C). Venoarterial-continued occlusion did not reduce LVSW (2812±832 versus 2950±896 mm Hg-mL, *P*=0.14) or LV end-diastolic pressure (12±6 versus 13±5 mm Hg, *P*=0.21). Impella CP activation at P8 generated estimated flows of 3.1±0.1 L/min and when compared with preactivation levels significantly reduced LVSW by 25% (3014±1005 versus 2245±1428 mm Hg-mL, *P*=0.04) and LV end-diastolic pressure by 50% (8±1 versus 4±3 mm Hg, *P*=0.01) (Table 1; Figure 2A). VA-ECMO generated flows of 5.1±0.8 L/min without significantly reducing LVSW (2202±689 versus 2422±335 mm Hg-mL, *P*=0.52) or LV end-diastolic pressure (11±5 versus 10±7 mm Hg, *P*=0.28). VA-ECMO, not Impella CP, reduced right atrial pressure (RAP) before reperfusion (change in RAP: 6±4 versus 4±3 mm Hg, *P*=0.009). Compared with Impella CP, VA-ECMO resulted in a nonsignificant reduction in total cardiac output after 30 minutes of activation quantified by thermodilution (2.1±1.1 versus 3.3±0.5 L/min, *P*=0.10).

LV Unloading Increases Coronary CFI

No difference in the CFI was observed between groups after 90 minutes of LAD occlusion. Compared with predevice

Table 1. Hemodynamic Values

	Continued Occlusion (n=6)				Impella Before Reperfusion (n=4)				VA-ECMO Before Reperfusion (n=5)			
		LAD Occlusion				LAD Occlusion				LAD Occlusion		
	Baseline	90 min	120 min	Reperfusion	Baseline	90 min	120 min	Reperfusion	Baseline	90 min	120 min	Reperfusion
Heart rate, beats per min	75±8	77±11	73±9*	83±9	76±16	74±14	75±10	88±10	77±19	67±12	72±28	82±7
MAP, mm Hg	84±9	81±16	82±81	77±78	83±9	87±16	84±18	68±15	92±12	80±11	86±17	93±20
LVEDP, mm Hg	9±3	12±6	13±5	13±4†‡	6±4	8±1	4±3*	5±2	9±8	11±5	10±7	2±1
LVSW, mm Hg	2891±1020	2812±832	2950±896	2710±1092	2831±739	3014±1005	2245±1428*†§	1668±988	2992±783	2202±689	2422±335	1631±789
RA, mm Hg	7±3	8±2	9±3	7±2	6±2	7±6	5±2	6±1	4±3	6±4	4±3*	3±2
Mean PA, mm Hg	23±6	23±6	22±4	22±3	17±3	19±5	18±3	20±1	22±9	20±5	16±3	18±2
TDCO, L/min	3.5±0.6	3.3±0.5	3.3±0.6	3.6±0.4	3.2±0.8	3.3±0.5	3.3±0.5	2.8±0.3	3.9±0.7	3.4±0.6	2.1±1.1‡§	2.9±0.4
Pump flow, L/min	N/A	N/A	N/A	N/A	N/A	N/A	3.1±0.1	3.1±0.1	N/A	N/A	5.1±0.8	4.9±1.1

LAD indicates left anterior descending artery; LVEDP indicates left ventricular end-diastolic pressure; LVSW, left ventricular stroke work; MAP, mean arterial pressure; N/A, not available; PA, pulmonary artery; RA, right atrium; TDCO, thermodilution cardiac output; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

* $P\leq0.05$: 90 minutes vs 120 minutes.

† $P\leq0.05$: continued occlusion vs Impella.

‡ $P\leq0.05$: continued occlusion vs extracorporeal membrane oxygenation.

§ $P\leq0.05$: Impella vs extracorporeal membrane oxygenation.

activation levels, 30 minutes of LV unloading with Impella increased the CFI by 75% (absolute CFI: 0.08±0.08 versus 0.14±0.05, pre- versus post-Impella; P=0.03) (Figure 2B; Table 2). After 30 minutes of VA-ECMO activation with persistent LAD occlusion, the CFI did not change compared with preactivation levels (absolute CFI: 0.08±0.02 versus 0.06±0.02, pre– versus post–VA-ECMO; P=0.27). No change in CFI was observed in the continued occlusion group (absolute CFI: 0.08±0.05 versus 0.08±0.06, 90 minutes versus 120 minutes of occlusion; P=0.95). In all groups, no change in average peak velocity was observed in the left circumflex artery between 90 and 120 minutes of LAD occlusion. A change in LVSW between 90 and 120 minutes of LAD occlusion inversely correlated with a corresponding change in CFI (P=0.01, R^2=0.44) (Figure 2C, see Table S1 for Multivariate Regression Analysis).

LV Unloading Increases Pw

The Pw reflects pressure in the microcirculation during a period of coronary occlusion and is a central component of the CFI. Representative Pa and Pw tracings are shown in Figure 3A. Compared with VA-ECMO, activation of Impella CP for 30 minutes increased Pw systolic (−4±3 versus 4±5 mm Hg, P=0.01), Pw mean (−2±1 versus 2±2 mm Hg, P=0.03), and Pw pulse pressures (−2±3 versus 4±3 mm Hg, P<0.01) (Figure 3B, Table 2).

The change in LVSW between 90 and 120 minutes of occlusion inversely correlated with the corresponding change in Pw pulse pressure (P=0.04, R^2=0.30) (Figure 4A and 4B). Infarct size relative to the area at risk correlated inversely with changes in CFI (P=0.02, R^2=0.41) and Pw pulse pressure (P=0.002, R^2=0.60) between 90 and 120 minutes of LAD occlusion (Figure 4C and 4D). See Table S1 for multivariate regression analysis.

Discussion

Mechanically unloading the left ventricle reduces ventricular wall stress, SW, and myocardial oxygen consumption during AMI.[17–20] The concept of mechanically unloading the left ventricle and delaying reperfusion for 30 minutes as an approach to reduce infarct size is under active clinical investigation; however, no studies have explored the impact of ventricular unloading on microcirculatory blood flow during LAD occlusion. We introduce data showing for the first time that activation of a transvalvular pump during persistent coronary occlusion reduces LVSW and increases the pressure-derived CFI to the ischemic myocardium in AMI and further that a higher pressure-derived CFI is associated with smaller infarct size (Figure 5). We also show for the first time that initiation of VA-ECMO did not reduce LVSW, increase the CFI,

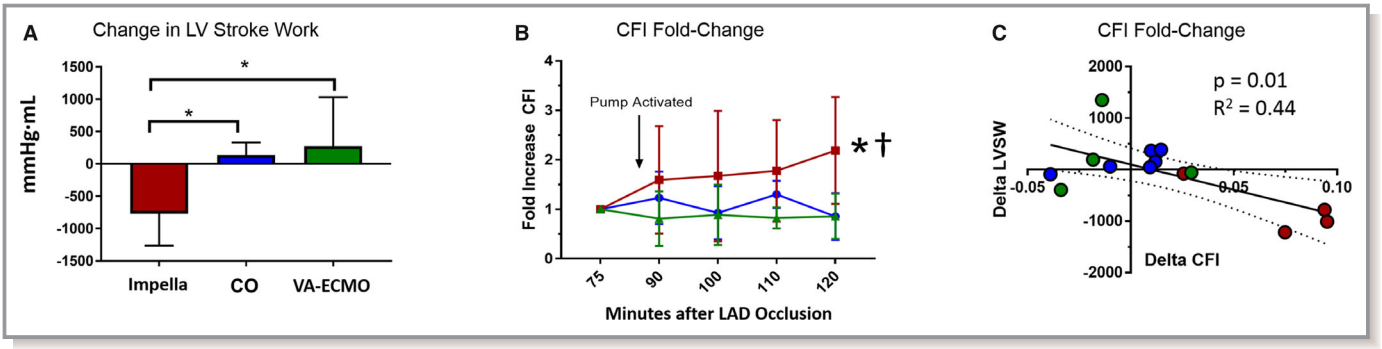

Figure 2. Hemodynamic association between left ventricular stroke work (LVSW) and the collateral flow index (CFI). **(A)** Changes in LVSW between groups (*, $P<0.05$ for comparisons shown); **(B)** Changes in the CFI between groups (*, $P<0.05$ vs 90 minutes, †, $P<0.05$ vs Continued occlusion (CO) and veno-arterial extracorporeal membrane oxygenation (VA-ECMO); **(C)** Correlation between changes in LVSW vs changes in the CFI. Red= Impella, blue=continued occlusion, green=VA-ECMO. Solid line: linear regression, Dotted line: 95% CI.

or reduce infarct size. These data support the concept that by reducing ventricular workload, LV unloading during a period of LAD occlusion may partially attenuate myocardial ischemia by providing a graded increase in microcirculatory collateral blood flow to myocardium at risk. These findings have potentially important clinical implications for the selection of acute mechanical circulatory support for high-risk coronary intervention or AMI complicated by cardiogenic shock, whereby Impella or VA-ECMO may be used and may have opposing effects on infarct size. We further provide new mechanistic insight into the rationale for ongoing clinical trials exploring LV unloading and delayed reperfusion as an approach to reduce infarct size in AMI. Future clinical studies exploring the impact of LV unloading on myocardial blood flow are required.

Beginning in the late 1980s, preclinical work with *surgically implanted* transvalvular circulatory support pumps introduced the concept of "functional reperfusion," whereby mechanically reducing LV wall stress causes a favorable redistribution of myocardial blood flow such that perfusion to an ischemic

Table 2. Pressure-Derived CFI Values

	Continued Occlusion (n=6)		Impella Before Reperfusion (n=4)		VA-ECMO Before Reperfusion (n=5)	
	LAD Occlusion		LAD Occlusion		LAD Occlusion	
	90 min	120 min	90 min	120 min	90 min	120 min
CFI	0.08±0.05	0.08±0.06	0.08±0.06	0.14±0.05*†‡	0.08±0.02	0.06±0.02
RA, mm Hg	8±2	9±3	7±6	5±2	6±4	4±3*
Pa—systolic, mm Hg	100±13	98±14	100±23	93±22	95±7	102±20
Pa—diastolic, mm Hg	74±13	70±15	73±14	77±20	66±9	78±17
Pa—mean, mm Hg	87±12	83±14	89±20	84±24	81±8	89±19
Pa—pulse width, mm Hg	26±6	27±9	27±10	16±6	29±7	24±3
Pw—systolic, mm Hg	18±5	18±4	19±10	22±6‡	22±14	18±13*
Pw—diastolic, mm Hg	8±4	10±4	12±5	11±3	7±5	5±9
Pw—mean, mm Hg	13±5	13±4	14±7	16±6‡	10±2	8±2*
Pw—pulse width, mm Hg	10±2	8±3	7±6	11±3†‡	15±15	13±17
APV-LCx, cm/s	12±5	12±5	14±2	15±5	14±4	14±5

APV-LCx indicates average peak velocity in the left circumflex artery; CFI, collateral flow index; LAD, left anterior descending artery; Pa, proximal aortic pressure; Pw, coronary wedge pressure; RA, right atrium.
CFI=[(Pw mean−RA)/(Pa mean−RA)].
Pulse width=systolic−diastolic.
*$P\leq0.05$: 90 minutes vs 120 minutes.
Comparing magnitude of change between 90 and 120 minutes.
†$P<0.05$: continued occlusion vs Impella.
‡$P<0.05$: Impella vs VA-ECMO.

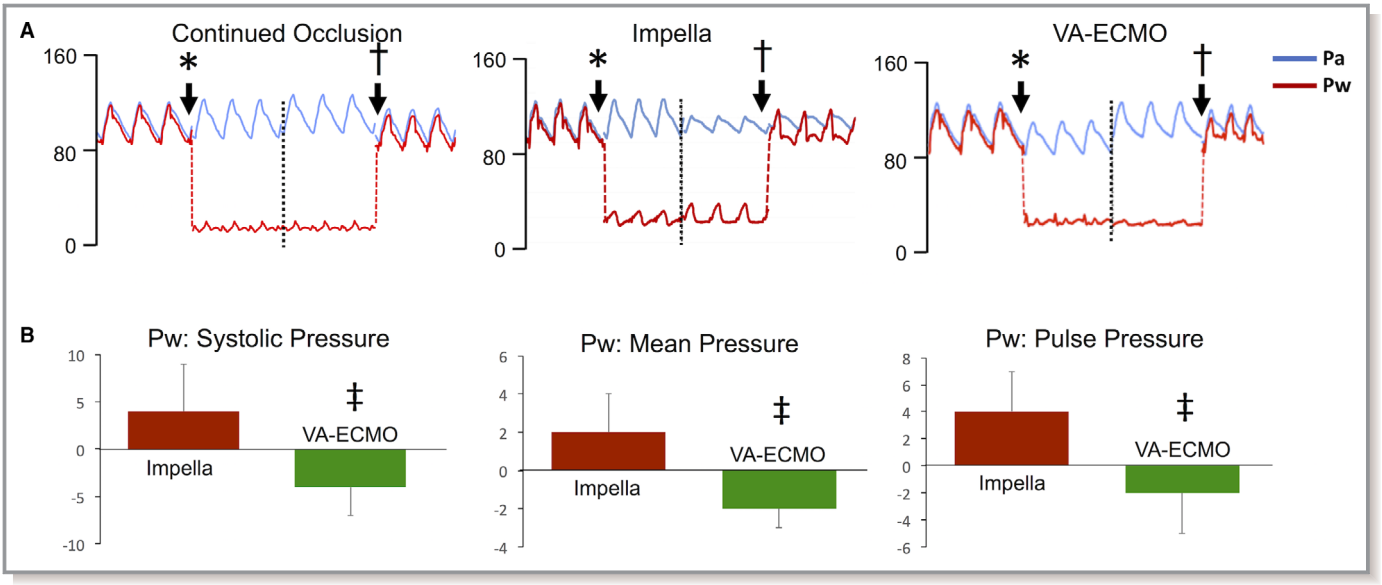

Figure 3. Collateral flow index tracing analysis. **A**, Representative pressure tracings are shown from the continued occlusion (CO), Impella, and venoarterial extracorporeal membrane oxygenation (VA-ECMO) groups. Blue and red tracings represent aortic pressure (Pa) and the distal coronary pressure, respectively. Onset of left anterior descending artery (LAD) balloon occlusion (*), followed by activation of either an Impella or VA-ECMO after 90 minutes (vertical hashed line), and coronary reperfusion at 120 minutes (†) are shown. The red tracing between onset of LAD occlusion and coronary reperfusion represents the coronary wedge pressure (Pw). **B**, Changes between Impella and VA-ECMO for the coronary wedge systolic, mean, and pulse pressures are shown (‡$P<0.05$ between groups).

coronary bed increases significantly despite persistent occlusion of the coronary artery supplying that territory.[21] These early studies identified that ischemic injury may be reduced before reperfusion, known as functional reperfusion, by reducing myocardial SW, oxygen consumption, and wall stress.[21–24] However, these studies did not test the impact of first unloading the left ventricle then delaying reperfusion on blood flow or infarct size. Since 2003, we and others have reported that mechanically unloading the left ventricle and delaying reperfusion significantly reduces myocardial infarct size.[11–13,25,26] To date, the mechanisms of benefit with LV unloading and delayed reperfusion have focused on activation of a cardioprotective signaling program or reducing myocardial oxygen consumption by decreasing LV workload. We now introduce data that support a third mechanism, whereby LV unloading directly increases myocardial microcirculatory blood flow.

First, to test whether LV unloading is required to reduce infarct size, we compared the effect of Impella CP activation to VA-ECMO on ventricular hemodynamics. VA-ECMO withdraws deoxygenated venous blood into a centrifugal pump that delivers blood through an oxygenator into the arterial circulation, which increases mean arterial pressure and, depending on native ventricular function, may increase LVSW. We observed that VA-ECMO had no significant impact on LVSW and reduced total cardiac output, whereas Impella CP reduced LVSW and maintained total cardiac output between 90 and 120 minutes of LAD occlusion. After 180 minutes of reperfusion, both support platforms reduced LVSW, which may reflect progressive unloading versus progressive myocardial damage with Impella CP versus VA-ECMO, respectively. This possibility was supported by infarct quantification, which showed less myocardial infarct size normalized to the area at risk with Impella CP compared with VA-ECMO. VA-ECMO did not significantly increase infarct size compared with continued occlusion followed by delayed reperfusion. Collectively, these data support that irrespective of which mechanical configuration is employed to unload the left ventricle, reducing LVSW may be required to reduce infarct size in AMI.

Next, to test whether LV unloading impacts collateral blood flow to ischemic myocardium, we quantified the pressure-derived CFI after activation of Impella CP or VA-ECMO for 30 minutes before reperfusion. The basis for quantifying the CFI is rooted in the fact that perfusion pressure distal to an occluded coronary artery originates from microcirculatory blood flow.[27] To account for changes in coronary venous pressure, both aortic root and distal coronary pressures are normalized to RAP. Furthermore, to account for potential increases in aortic root pressure leading to enhanced blood flow through nonculprit vessels, we quantified average peak velocity of coronary blood flow in the nonoccluded left circumflex artery. Theoretically, VA-ECMO should reduce RAP and increase aortic root pressure, thereby increasing blood flow through nonoccluded coronary vessels and increasing the distal Pw and hence the CFI. However, we observed that after 30 minutes of device activation, VA-ECMO reduced RAP, but did not increase aortic root pressure, flow through the left

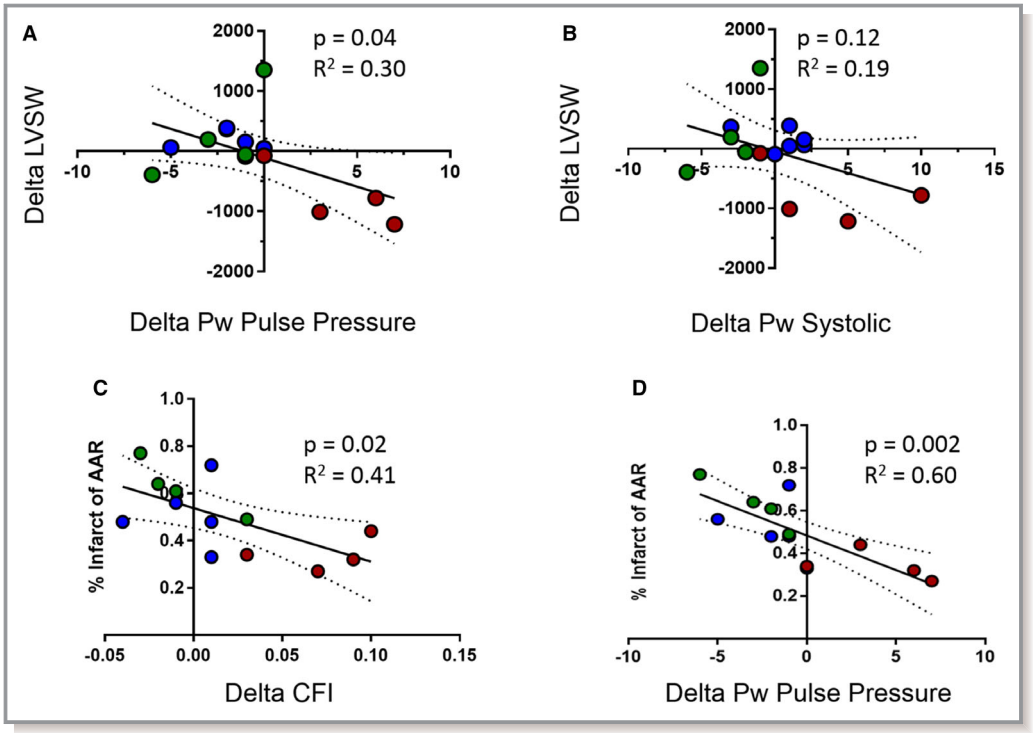

Figure 4. Scatter plots illustrating correlations between ventricular and coronary indices and infarct size. **A**, Changes in left ventricular stroke work (LVSW) correlate with changes in coronary wedge (Pw) pulse pressure; (**B**) Changes in LVSW correlate with changes in Pw systolic pressure; (**C** and **D**) Infarct size normalized to the area at risk (AAR) correlate with changes in the collateral flow index (CFI) and Pw pulse pressure, respectively. Red=Impella, blue=continued occlusion, green=venoarterial extracorporeal membrane oxygenation. Solid line: linear regression line, dotted lines: 95% CI.

circumflex artery, Pw, or CFI. In contrast, the Impella CP did not reduce RAP, aortic root pressure, or flow through the left circumflex artery, but did reduce LVSW, which correlated significantly with an increase in the Pw and CFI. Changes in the CFI inversely correlated with infarct size. The lack of increased flow through the nonculprit left circumflex artery may reflect the minimal observed changes in aortic root pressure and the impact of intact coronary autoregulation and microcirculatory resistance in regions of nonischemic myocardium. These findings suggest that LVSW may be an important determinant of the CFI and microcirculatory blood flow especially in regions of ischemic myocardium where autoregulation may be uncoupled.

Several reports have shown that Pw can be used to predict recruitment of collateral blood flow in patients undergoing balloon angioplasty.[28] Although the coronary wedge pulse pressure has not been validated as an independent measure of coronary blood flow, it describes the degree of pulsatility within the microcirculation and may be a surrogate of increased energy within the collateral circulation.[29] To better understand whether LV unloading recruits blood flow to ischemic myocardium during LAD occlusion, we interrogated tracings from the pressure wire and identified that mean Pw was higher after 30 minutes of Impella CP unloading compared with VA-ECMO. Furthermore, reductions in LVSW significantly correlated with increased coronary wedge pulse pressure. Increases in total CFI or coronary wedge pulse pressure were associated with reduced infarct size. Overall, these findings are consistent with prior reports suggesting that low Pw is associated with increased LV wall tension[30] and further support the concept that mechanically unloading the left ventricle during coronary occlusion may be an important method to both reduce myocardial oxygen consumption[12,13,25] and enhance microcirculatory blood flow to ischemic myocardium during an AMI.

Study Limitations

Limitations of the current study include the small numbers of animals studied; however, this was driven by a mortality rate of 40% and cost associated with these studies. Therefore, numbers in each group were low. Another limitation included the use of the swine model, which is known to have limited myocardial collateral circulation compared with human hearts. For this reason, the absolute CFI values reported in this study may not correlate with absolute values in humans. However, despite the limited collateral circulation in swine we were able

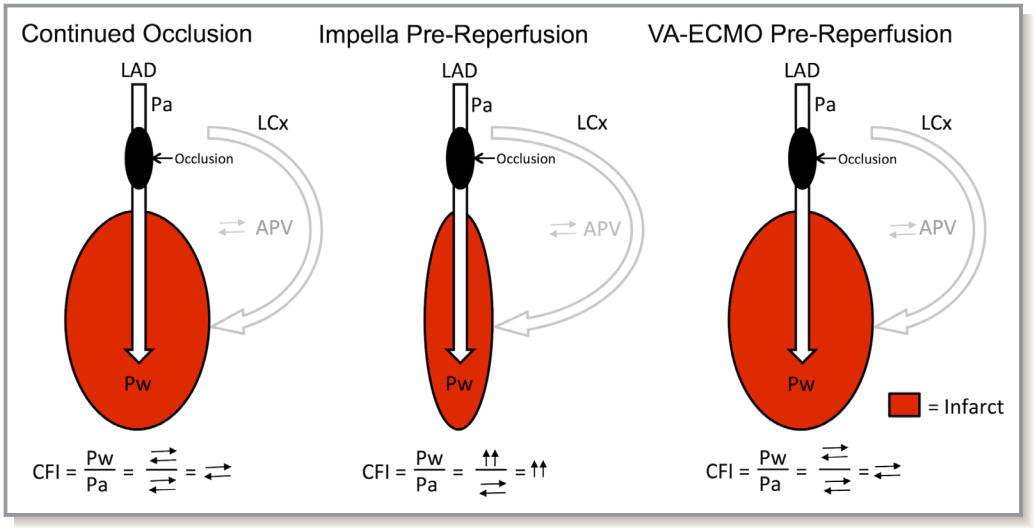

Figure 5. Impella activation promotes functional reperfusion. Illustration representing changes in infarct size and associated changes in the pressure-derived collateral flow index (CFI) between groups. Compared with continued occlusion or venoarterial extracorporeal membrane oxygenation (VA-ECMO), Impella activation before reperfusion increased the CFI and reduced infarct size without affecting average peak velocity (APV) in the left circumflex artery (LCx). Pa (aortic pressure), Pw (coronary wedge pressure), and ⇄(no change). LAD indicates left anterior descending artery.

to identify clear changes in the CFI, which supports our observation that unloading may directly increase microcirculatory blood flow in ischemic myocardium. Adenosine was not administered during Pw measurement in this study. Measurement of wedge pressure and subsequent calculation of CFI without the use of adenosine has been shown to overestimate the CFI value in patients with well-developed collaterals.[31] However, the CFIs in this model were all low, suggesting a poorly collateralized coronary circulation (as demonstrated by CFIs <0.25 and all subjects having ST elevation on their ECG during LAD occlusion), therefore negating the requirement for hyperemia. Finally, the control group was not usual care, as occlusion continued in this group during the additional interventions performed during occlusion in the other 2 groups. However, matching total LAD occlusion times among study groups was required to test our hypothesis by enabling the calculation of CFI during LAD occlusion. Reperfusion at 90 minutes in the control arm would have been a confounder for subsequent CFI measurements (with transient balloon occlusion) and the true effect of each device on this would not have been elucidated. In addition to published reports,[11–13] future studies confirming whether infarct size is smaller with LV unloading and delayed reperfusion versus no LV unloading with immediate reperfusion may be needed.

Conclusions

We have introduced novel data supporting the concept that mechanically unloading the left ventricle is necessary and sufficient to increase microcirculatory blood flow and, in addition to reducing myocardial oxygen consumption, may represent a viable approach to improve myocardial oxygen supply to ischemic myocardial before epicardial coronary reperfusion, referred to as functional reperfusion. These findings have potentially important implications for the management of patients and for clinical trials evaluating the utility of acute mechanical circulatory support devices for high-risk coronary intervention, AMI, or cardiogenic shock by suggesting that LV unloading may directly attenuate myocardial ischemia. Future studies are required to determine whether LV unloading alters myocardial ischemia and microcirculatory blood flow in patients during AMI.

Sources of Funding

This work was supported by a grant from the National Institutes of Health (RO1HL139785-01) to Kapur and from Abiomed Inc to Tufts Medical Center.

Disclosures

Kapur receives institutional grant support and consulting and speaker honoraria from Abiomed Inc, Abbott Inc, Boston Scientific Inc, Medtronic Inc, MD Start, and Precardia. The remaining authors have no disclosures to report.

References

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA,

Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation*. 2018;137:e67–e492.

2. Reimer KA, Ideker RE, Jennings RB. Effect of coronary occlusion site on ischaemic bed size and collateral blood flow in dogs. *Cardiovasc Res*. 1981;15:668–674.
3. Kim EK, Choi JH, Song YB, Hahn JY, Chang SA, Park SJ, Lee SC, Choi SH, Choe YH, Park SW, Gwon HC. A protective role of early collateral blood flow in patients with ST-segment elevation myocardial infarction. *Am Heart J*. 2016;171:56–63.
4. Ortiz-Pérez JT, Lee DC, Meyers SN, Davidson CJ, Bonow RO, Wu E. Determinants of myocardial salvage during acute myocardial infarction: evaluation with a combined angiographic and CMR myocardial salvage index. *JACC Cardiovasc Imaging*. 2010;3:91–500.
5. Cuculi F, De Maria GL, Meier P, Dall'Armellina E, de Caterina AR, Channon KM, Prendergast BD, Choudhury RP, Forfar JC, Kharbanda RK, Banning AP. Impact of microvascular obstruction on the assessment of coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve after ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2014;64:1894–1904.
6. Sezer M, Nisanci Y, Umman B, Umman S, Okcular I, Olcay A, Bilge A, Ozcan M, Meric M. Pressure-derived collateral flow index: a strong predictor of late left ventricular remodeling after thrombolysis for acute myocardial infarction. *Coron Artery Dis*. 2006;17:139–144.
7. Billinger M, Kloos P, Eberli FR, Windecker S, Meier B, Seiler C. Physiologically assessed coronary collateral flow and adverse cardiac ischemic events: a follow-up study in 403 patients with coronary artery disease. *J Am Coll Cardiol*. 2002;40:1545–1550.
8. De Bruyne B, Meier B, Finci L, Urban P, Rutishauser W. Potential protective effect of high coronary wedge pressure on left ventricular function after coronary occlusion. *Circulation*. 1988;78:566–572.
9. Stretch R, Sauer CM, Yuh DD, Bonde P. National trends in the utilization of short-term mechanical circulatory support: incidence, outcomes, and cost analysis. *J Am Coll Cardiol*. 2014;64:1407–1415.
10. Doshi R, Patel K, Decter D, Gupta R, Meraj P. Trends in the utilisation and in-hospital mortality associated with short-term mechanical circulatory support for heart failure with reduced ejection fraction. *Heart Lung Circ*. 2019;28:e47–e50.
11. Esposito ML, Zhang Y, Qiao X, Reyelt L, Paruchuri V, Schnitzler GR, Morine KJ, Annamalai SK, Bogins C, Natov PS, Pedicini R, Breton C, Mullin A, Mackey EE, Patel A, Rowin E, Jaffe IZ, Karas RH, Kapur NK. Left ventricular unloading before reperfusion promotes functional recovery after acute myocardial infarction. *J Am Coll Cardiol*, 2018;72:501–514.
12. Kapur NK, Qiao X, Paruchuri V, Morine KJ, Syed W, Dow S, Shah N, Pandian N, Karas RH. Mechanical pre-conditioning with acute circulatory support before reperfusion limits infarct size in acute myocardial infarction. *JACC Heart Fail*. 2015;3:873–882.
13. Kapur NK, Paruchuri V, Urbano-Morales JA, Mackey EE, Daly GH, Qiao X, Pandian N, Perides G, Karas RH. Mechanically unloading the left ventricle before coronary reperfusion reduces left ventricular wall stress and myocardial infarct size. *Circulation*. 2013;128:328–336.
14. Kapur NK, Alkhouli MA, DeMartini TJ, Faraz H, George ZH, Goodwin MJ, Hernandez-Montfort JA, Iyer VS, Josephy N, Kalra S, Kaki A, Karas RH, Kimmelstiel CD, Koenig GC, Lau E, Lotun K, Madder RD, Mannino SF, Meraj PM, Moreland JA, Moses JW, Kim RL, Schreiber TL, Udelson JE, Witzke C, Wohns DHW, O'Neill WW. Unloading the left ventricle before reperfusion in patients with anterior ST-segment–elevation myocardial infarction. *Circulation*. 2019;39:337–346.
15. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation*. 1993;87:1354–1367.
16. Perera D, Biggart S, Postema P, Patel S, Lambiase P, Marber M, Redwood S. Right atrial pressure: can it be ignored when calculating fractional flow reserve and collateral flow index? *J Am Coll Cardiol*. 2004;44:2089–2091.
17. Uriel N, Sayer G, Annamalai S, Kapur NK, Burkhoff D. Mechanical unloading in heart failure. *J Am Coll Cardiol*. 2018;72:569–580.
18. Burkhoff D, Sayer G, Doshi D, Uriel N. Hemodynamics of mechanical circulatory support. *J Am Coll Cardiol*. 2015;66:2663–2674.
19. Kapur NK, Paruchuri V, Pham DT, Reyelt L, Murphy B, Beale C, Bogins C, Wiener D, Nilson J, Esposito M, Perkins S, Perides G, Karas RH. Hemodynamic effects of left atrial or left ventricular cannulation for acute circulatory support in a bovine model of left heart injury. *ASAIO J*. 2015;61:301–306.
20. Esposito ML, Shah N, Dow S, Kang S, Paruchuri V, Karas RH, Kapur NK. Distinct effects of left or right atrial cannulation on left ventricular hemodynamics in a swine model of acute myocardial injury. *ASAIO J*. 2016;62:671–676.
21. Laschinger JC, Grossi EA, Cunningham JN Jr, Krieger KH, Baumann FG, Colvin SB, Spencer FC. Adjunctive left ventricular unloading during myocardial reperfusion plays a major role in minimizing myocardial infarct size. *J Thorac Cardiovasc Surg*. 1985;90:80–85.
22. Achour H, Boccalandro F, Felli P, Amirian J, Uthman M, Buja M, Smalling RW. Mechanical left ventricular unloading prior to reperfusion reduces infarct size in a canine infarction model. *Catheter Cardiovasc Interv*. 2005;64:182–192.
23. Smalling RW, Cassidy DB, Barrett R, Lachterman B, Felli P, Amirian J. Improved regional myocardial blood flow, left ventricular unloading, and infarct salvage using an axial-flow, transvalvular left ventricular assist device. A comparison with intra-aortic balloon counterpulsation and reperfusion alone in a canine infarction model. *Circulation*. 1992;85:1152–1159.
24. Merhige ME, Smalling RW, Cassidy D, Barrett R, Wise G, Short J, Wampler RK. Effect of the hemopump left ventricular assist device on regional myocardial perfusion and function. Reduction of ischemia during coronary occlusion. *Circulation*. 1989;80:III158-III166.
25. Saku K, Kakino T, Arimura T, Sunagawa G, Nishikawa T, Sakamoto T, Kishi T, Tsutsui H, Sunagawa K. Left ventricular mechanical unloading by total support of Impella in myocardial infarction reduces infarct size, preserves left ventricular function, and prevents subsequent heart failure in dogs. *Circ Heart Fail*. 2018;11:e004397.
26. Sun X, Li J, Zhao W, Lu S, Guo C, Lai H, Wang C. Early assistance with left ventricular assist device limits left ventricular remodeling after acute myocardial infarction in a swine model. *Artif Organs*. 2016;40:243–251.
27. Seiler C, Fleisch M, Garachemani A, Meier B. Coronary collateral quantitation in patients with coronary artery disease using intravascular flow velocity or pressure measurements. *J Am Coll Cardiol*. 1998;32:1272–1279.
28. Meier B, Luethy P, Finci L, Steffenino GD, Rutishauser W. Coronary wedge pressure in relation to spontaneously visible and recruitable collaterals. *Circulation*. 1987;75:906–913.
29. Davies JE, Whinnett ZI, Francis DP, Manisty CH, Aguado-Sierra J, Willson K, Foale RA, Malik IS, Hughes AD, Parker KH, Mayet J. Evidence of a dominant backward-propagating "suction" wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. *Circulation*. 2006;113:1768–1778.
30. Eng C, Kirk ES. Flow into ischemic myocardium and across coronary collateral vessels is modulated by a waterfall mechanism. *Circ Res*. 1984;55:10–17.
31. Perera D, Patel S, Blows L, Tomsett E, Marber M, Redwood S. Pharmacological vasodilatation in the assessment of pressure-derived collateral flow index. *Heart*. 2006;92:1149–1150.

SUPPLEMENTAL MATERIAL

Table S1. Multivariate Regression Analysis.

Correlation Variables		R^2	P
Change in LVSW	Change CFI	0.38	0.05
Change in LVSW	Pw Pulse Pressure	0.34	0.08
Change in LVSW	Pw Systolic	0.36	0.06
% Infarct of AAR	Change in CFI	0.42	0.05
% Infarct of AAR	Change in Pw Pulse Pressure	0.55	0.02

AAR - Area at risk, CFI - collateral flow index, LVSW - Left ventricle stroke work, Pw - Coronary wedge pressure