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Hemodynamic Effects of Reducing LV Afterload With Impella or Intra-Aortic Balloon Counterpulsation During Veno-Arterial Extracorporeal Membrane Oxygenation in Cardiogenic Shock: HERACLES Trial

Running title: *Ezad et al., IABP vs Impella for LV Unloading in VA-ECMO*

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Abstract

Background: Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) provides organ support in cardiogenic shock but increases left ventricular (LV) afterload, potentially impairing cardiac recovery. LV unloading with an intra-aortic balloon pump (IABP) or micro-axial flow pump (mAFP) may mitigate this effect. HERACLES compared their effects on myocardial oxygen supply and demand.

Methods: Patients receiving VA-ECMO for cardiogenic shock were randomized to LV unloading with IABP or mAFP, stratified by ischemic/non-ischemic etiology. Distal coronary, aortic and LV pressures and coronary flow (inverse mean transit time, T_{mn}) were measured with and without unloading. Myocardial oxygen demand was estimated as the area under the LV pressure curve in systole (TTI) x heart rate (HR). The primary endpoint was the change in myocardial oxygen supply-demand ratio calculated as $[(T_{mn} * TTI*HR)_{off} / (T_{mn} * TTI *HR)_{unload}]$. Secondary endpoints included changes in coronary flow [device flow ratio (DFR) $=(T_{mn})_{off}/ (T_{mn})_{unload}$], oxygen demand per beat (DTTI), contractility (DdP/dt_{max}) and filling pressure (DLVEDP).

Results: Twenty-four patients were enrolled (age 51 [46-57]; 46% male; 96% SCAI D/E; 38% ischemic). At randomization, lactate was 4.3 mmol/L [IQR 2.5 to 8.4], LV ejection fraction 10% [10 to 17], LVEDP 18 mmHg [14 to 24]. The myocardial oxygen supply-demand ratio improved with IABP but not mAFP (1.48 [1.23 to 2.10] vs 0.97 [0.92 to 1.39]; P=0.036), driven predominantly by differential reduction of TTI. Coronary pressure increased but flow was unchanged with mAFP (DFR 1.00 [0.86 to 1.13]). Coronary flow increased marginally with IABP (DFR 1.16 [1.00 to 1.51]). LV pressures decreased with both devices and contractility with IABP only, with no between-group differences. Thirty-day mortality was similar (38% vs 45%, p=0.84).

Conclusions: In VA-ECMO supported SCAI D/E cardiogenic shock, IABP improved myocardial oxygen supply-demand balance, whereas mAFP did not. Further research is needed to determine whether these mechanistic differences translate to clinical outcomes.

Clinical Trial Registration Information: https://www.isrctn.com/ISRCTN82431978

Key words: Cardiogenic shock, Impella, IABP, VA-ECMO

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Nonstandard Abbreviations and Acronyms

DFR	device flow ratio
DPTI	diastolic pressure–time index
IABP	intra-aortic balloon pump
LV	left ventricle / left ventricular
LVEDP	left ventricular end-diastolic pressure
LVESP	left ventricular end-systolic pressure
mAFP	micro-axial flow pump
MCS	mechanical circulatory support
SCAI	Society for Cardiovascular Angiography and Interventions
T_{mn}	mean coronary transit time
TTI	tension time index
VA-ECMO	veno-arterial extracorporeal membrane oxygenation
VIS	vasoactive-inotropic score

Clinical Perspective

What is Known

- VA-ECMO maintains systemic perfusion in severe cardiogenic shock, however retrograde aortic flow may increase left ventricular afterload and impair myocardial recovery by worsening the balance between myocardial oxygen supply and demand.
- The intra-aortic balloon pump and micro-axial flow pump are commonly used to unload the left ventricle during VA-ECMO. Their effects on coronary flow and myocardial oxygen demand in this setting have not been previously evaluated or compared.

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What the Study Adds

- In this randomized mechanistic trial of patients with SCAI D/E cardiogenic shock supported with VA-ECMO, unloading with an intra-aortic balloon pump improved the myocardial oxygen supply-demand ratio but the micro-axial flow pump did not.
- Both devices lowered left ventricular pressures to a similar degree; however, only the intra-aortic balloon pump significantly reduced myocardial oxygen demand.
- Coronary flow was not significantly augmented with either device despite the micro-axial flow pump increasing distal coronary pressure, suggesting preserved coronary auto-regulation despite severe cardiogenic shock.

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Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly used to provide hemodynamic support in refractory cardiogenic shock. Although VA-ECMO restores systemic perfusion, retrograde aortic flow increases left ventricular (LV) afterload and may exacerbate myocardial injury by increasing LV wall stress and myocardial oxygen demand [1]. In some patients this can lead to complications such as non-opening of the aortic valve, left ventricular distension, intracardiac thrombus formation and pulmonary edema. Even in the absence of overt clinical sequelae increased afterload may jeopardize the chances of myocardial recovery by maintaining an unfavorable balance between myocardial oxygen supply and demand.

Increasing interest has therefore developed in strategies to "unload" the left ventricle in order to prevent or treat complications and potentially facilitate myocardial recovery. Observational data suggest that LV unloading may improve successful weaning from VA-ECMO and short-term survival despite an increased risk of complications [2,3]. The intra-aortic balloon pump (IABP) and micro-axial flow pump (mAFP) represent two of the most commonly used adjunctive mechanical circulatory support (MCS) devices to unload the LV.

Despite widespread adoption of LV unloading, the mechanisms by which different unloading strategies may influence myocardial recovery remain poorly understood. A key determinant of myocardial recovery is likely to be the balance between myocardial oxygen supply and demand. The IABP and mAFP have distinct mechanisms of action and may therefore have differing physiological effects with respect to coronary blood flow and left ventricular pressures. Whether one strategy results in a more favorable myocardial oxygen supply demand ratio during VA-ECMO support is unknown.

The HERACLES trial was therefore designed to compare the physiological effects of IABP and mAFP unloading on myocardial oxygen supply demand balance in patients with cardiogenic

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shock supported with VA-ECMO. We hypothesized that compared with IABP support, the active LV unloading provided by mAFP would increase coronary flow and reduce LV pressures, producing a more beneficial myocardial oxygen supply demand ratio.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Study Design and Population

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HERACLES (ISRCTN82431978) was an investigator-initiated multicenter randomized mechanistic trial conducted at two tertiary National Health Service cardiac centers in the United Kingdom (St Thomas' Hospital and Harefield Hospital). Consecutive patients receiving VA-ECMO for cardiogenic shock were screened for inclusion between October 2022 and July 2026. The study protocol was approved by the United Kingdom Health Research Authority (21/LO/0853).

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Patients over the age of 18 receiving VA-ECMO for cardiogenic shock were eligible if they were due to undergo clinically indicated cardiac catheterization and LV unloading. Key exclusion criteria were post cardiotomy cardiogenic shock, LV thrombus, pregnancy or post-partum cardiomyopathy, contraindication to either IABP or mAFP insertion and mechanical aortic valve replacement.

Where participants lacked capacity to consent, written assent was obtained from an independent treating physician and retrospective consent sought if capacity was subsequently regained.

Randomization and Study Procedures

Participants were randomized in a 1:1 ratio to LV unloading with either an IABP or mAFP using an online randomization system administered by the King's College London Clinical Trials Unit. Randomization was stratified by the etiology of cardiogenic shock (ischemic versus non-ischemic).

Diagnostic coronary angiography was performed and where indicated percutaneous coronary intervention completed before randomization. The Impella CP (Abiomed, Danvers, USA) was used as the mAFP in all participants. The allocated unloading device was inserted via the femoral artery contralateral to the ECMO arterial return cannula.

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Coronary and Ventricular Physiology Assessment

Following insertion of the assigned unloading device, coronary physiological assessment was performed using a PressureWire™ X guidewire (Abbott Vascular, Santa Clara, CA, USA) connected to the CoroFlow™ system (Coroventis Research, Uppsala, Sweden). The left anterior descending artery was used preferentially, unless it was the infarct related artery in which case measurements were undertaken in either the left circumflex or right coronary arteries.

Baseline coronary transit time (T_{mn}) was recorded as the mean of three thermodilution measurements using 3-5 mL boluses of normal saline. Baseline measurements ($T_{mn(off)}$) were obtained with the IABP on standby or the mAFP operating at power level P1. Repeat measurements

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($T_{mn(unload)}$) were obtained during unloading (IABP 1:1 augmentation or mAFP P5). Additional measurements were acquired at P3 in the mAFP group to assess the effect of varying mAFP flow. All measurements were performed following a minimum stabilization period of 60 seconds after any change in device settings (Figure S1).

The PressureWire X was then placed in the left ventricle with a guiding catheter in the aortic root to allow simultaneous measurement of aortic and left ventricular pressures. LV end-diastolic pressure (LVEDP), LV end-systolic pressure (LVESP) and dP/dt_{max} were recorded and analyzed using CoroFlow software. Measurements were recorded in the same device-off and on states as described above. Offline analysis of the left ventricular and aortic pressure signals was undertaken to calculate the tension time index (TTI) for each cardiac cycle as the area under the left ventricular pressure curve during systole (Figures S2-4) and averaged over 5 consecutive cardiac cycles. The diastolic pressure–time index (DPTI) was calculated as the area between the aortic and left ventricular pressure curves during diastole, averaged over the same 5 consecutive cardiac cycles. The Buckberg index, a pressure-derived estimate of the myocardial oxygen supply:demand ratio, was calculated as DPTI/TTI[4].

During the course of coronary and ventricular physiological measurements VA-ECMO flow rates, vasoactive medication doses and ventilator settings were kept constant. Following completion of the catheterization laboratory protocol, usual clinical care was continued with decisions on unloading device settings, weaning and inotropes at the discretion of the treating physician.

Sample Size

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We hypothesized that IABP would have no significant effect on the myocardial oxygen supply demand ratio whilst mAFP would increase it. Assuming a mean myocardial oxygen supply demand ratio of 1.25 in the mAFP group and 1.0 in the IABP group, with a common standard deviation of 0.20, a total sample size of 24 patients (12 per group) would provide 80% power to detect this difference using a two-sided test (two sided α=0.05). A sample size of 36 patients would provide approximately 95% power and allow for the possibility that physiological measurements might not be obtainable in all participants. Therefore, the recruitment target was set at 36 patients, with 24 participants considered the minimum sample size required for adequate power.

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Study Outcomes

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The primary outcome measure was the change in myocardial oxygen supply demand ratio following activation of the unloading device.

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Myocardial oxygen supply was estimated as the inverse of the coronary transit time and myocardial oxygen demand from the product of TTI and heart rate. A flow derived index was chosen in preference to the pressure-derived DPTI for estimating myocardial oxygen supply, as pressure based indices do not account for changes in coronary microvascular resistance.

The supply-demand ratio was calculated as:

$$[(T_{mn} \times TTI \times HR)_{off} / (T_{mn} \times TTI \times HR)_{unload}].$$

Values >1 indicate an improvement in myocardial oxygen supply demand balance following device activation.

Key secondary physiological endpoints included:

- Device flow ratio (DFR) calculated as $T_{mn(off)}/ T_{mn(unload)}$ (no units)
- Change in LVEDP (mmHg)

- Change in LVESP (mmHg)
- Change in TTI (mmHg.s)
- Change in dP/dt_{max} (mmHg/s)

Exploratory clinical outcomes included 30-day mortality, successful VA-ECMO decannulation, lactate clearance in the first 24 hours, change in mean arterial pressure, pulse pressure and vasoactive inotropic score (VIS) in the first 72 hours post randomization.

Statistical Analysis

All analyses were performed using R statistical software version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). Given the small sample size non-parametric methods were specified a priori for all analyses. Continuous variables are presented as median [interquartile range] and categorical variables are presented as counts (percentages). Between group comparisons used the 2-sided Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Within group comparisons used the Wilcoxon signed rank test. For the myocardial oxygen supply demand ratio device off vs on was tested against a null value of 1 using a 1-sample Wilcoxon signed rank test. Between group comparison of the supply demand ratio used the within patient ratio as the unit of analysis.

Time to death was estimated by the Kaplan–Meier method with groups compared by the log-rank test. Serial measures of lactate, VIS, pulse pressure and mean arterial pressure were analyzed by linear mixed effects models with patient as a random effect. A p value of <0.05 was considered significant for all comparisons. As a mechanistic study the trial was not powered for clinical endpoints, no adjustment was made for multiple comparisons, and therefore these findings should be considered exploratory and hypothesis-generating only. The primary analysis for clinical

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outcomes is as per the intention to treat principle. A sensitivity analysis was performed of clinical outcomes, in the as-treated population, to account for crossovers that may occur during the index catheterization laboratory visit, but after collection of primary outcome data.

RESULTS

Study Population

Sixty patients receiving VA-ECMO for cardiogenic shock were screened, of whom 24 underwent randomization; 13 were assigned to IABP and 11 to mAFP respectively (Figure 1). The predominant reason for exclusion was a clinical decision that there was no need for cardiac catheterization and/or LV unloading. All patients received the allocated unloading device. One patient in the mAFP arm did not have any physiology measurements recorded due to the inability to access radial arteries and advance a guiding catheter, two patients had uninterpretable pressure traces precluding calculation of TTI.

Median age was 51 years [46 to 57], 46% were male and the median ejection fraction was 10% (10 to 17). Twenty-three participants (96%) presented with SCAI D or E shock, 15 (63%) had a non-ischemic etiology and 14 (58%) had suffered a cardiac arrest prior to randomization. The median interval between onset of cardiogenic shock and VA-ECMO support being established was 5.3 hours [1.5 to 9.7]. Time to LV unloading was 6.4 hours [4.8 to 14.5] and the median index ECMO flow rate during measurements was 1.66 L/min/m^2 [1.44 to 1.85]. Baseline characteristics are presented in Tables 1 and 2.

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Four patients in the IABP arm crossed over to mAFP after completion of the catheter laboratory protocol as per treating physician preference.

Primary Endpoint

Compared to baseline, activation of the IABP improved myocardial oxygen supply-demand balance, resulting in a median supply-demand ratio of 1.48 [1.23 to 2.10] (p=0.005 versus unity). In contrast, activation of the mAFP did not alter myocardial oxygen supply-demand balance (0.97 [0.92 to 1.39], p=0.64). When comparing the two groups, the improvement in myocardial oxygen supply-demand ratio was significantly greater with IABP than with mAFP unloading (1.48 versus 0.97, p=0.036) (Figure 2). To explore the differences in supply and demand between devices we compared the percentage change in these variables separately. Myocardial oxygen supply increased numerically more with IABP (18% [-3 to 54%] vs -6% [-15 to 9%], p=0.19). Oxygen demand fell with IABP as compared to mAFP (-25% [-30 to -16] vs -6% [-11 to 4], p=0.05) (Figure 3).

In the mAFP arm, supply and demand fell by similar proportions (median -6% [-15 to 9] and – 6% [-11 to 4] respectively) and changed concordantly across participants (Spearman rho 0.62, p=0.09) (Figure 4). In the IABP arm supply increased by 18% [-3 to 54] whilst demand fell by 25% [-30 to -16] (Spearman rho -0.38, p=0.22).

The Buckberg index (DPTI/TTI) increased with IABP activation (on/off ratio 1.31 [1.28 to 1.52], p<0.001 versus unity) but not with mAFP (1.19 [1.10 to 1.65], p=0.07), with no significant difference between groups (p=0.35) (Table S1).

Secondary Physiological Endpoints

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Coronary Physiology

Coronary transit time decreased numerically with IABP activation (from 0.7 (0.4, 1.4) to 0.6 (0.3, 1.0) p=0.078), translating to a small increase in coronary flow with the device (DFR 1.16 [1.00 to 1.51]) (Table S2, Figure S5). IABP did not consistently change distal coronary pressure. In contrast, mAFP activation at P5 did not affect coronary flow (DFR 1.00 [0.86 to 1.13]) but increased mean distal coronary pressure by 3 mmHg, p=0.02 (Table S3). There was no significant difference in device flow ratio between treatment groups (1.16 vs 1.00, p=0.23) (Table S4, Figure S5). The change in coronary flow on device activation was not correlated with the change in DPTI in either arm (IABP Spearman rho −0.22, p=0.50; mAFP rho −0.45, p=0.22); in particular, mAFP increased DPTI without a corresponding increase in coronary flow (Figure S6).

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Aortic Pressure

At baseline, pulse pressure was lower in the IABP group (6 versus 20 mmHg, p=0.009), whereas mean arterial pressure was similar between groups (Table 3). IABP activation led to reduction in both assisted systolic (-12 mmHg [-17 to -5 mmHg]) and end diastolic blood pressure (-12 mmHg [-16 to -10 mmHg]). (Table S2). Peak diastolic augmentation was 14.5% [3.3 to 25.9%] above unassisted systolic pressure.

Left Ventricular Pressure

At baseline, LVEDP was higher in participants randomized to IABP than mAFP (23 versus 14 mmHg, p=0.031) (Table 3). IABP activation reduced LVEDP by 4 mmHg [-6 to -4] and LVESP by 12 mmHg [-16 to -9] (Table S2). Activation was also associated with reductions in TTI and LV

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dP/dt_{max} (Figure S7). mAFP activation also reduced LVEDP and LVESP, with progressively greater reductions observed at higher pump speeds (Table S3). However, neither TTI nor dP/dt_{max} changed significantly. No difference was observed between groups with respect to change in LVEDP (-4 vs -5 mmHg, p=0.92) nor LVESP (-12 vs -7mmHg, p=0.19). Both devices reduced dP/dt max by a similar amount with a trend towards greater reduction in TTI observed with IABP (-3.03 vs -1.36, p=0.07) (Table S4, Figure S7).

Exploratory Clinical Outcomes

At 30 days 10 participants (42%) had died of whom 9 died during the index intensive care unit admission. Thirty-day mortality did not differ between groups (log-rank p=0.84) (Figure S8).

There were no differences in frequency of successful VA-ECMO decannulation, duration of VA-ECMO support or length of intensive care unit stay between groups. Similarly, there were no differences in bleeding or vascular complications, however those randomized to mAFP did require numerically more units of blood transfusion (Table S5). In the as treated analysis, no difference was observed in mortality, VA-ECMO weaning nor complications (Table S6).

Serial measures analyzed by linear mixed effect models showed mean arterial pressure trajectories differed between groups (device by time interaction p=0.02) driven by the immediate post unloading time point with no difference thereafter (Table S7). Absolute lactate and VIS did not differ at any time point (Figure S9). Lactate trajectory differed however due to a numerically higher baseline in the IABP arm. Similarly pulse pressure differed at baseline resulting in a significant interaction (p=0.034) reflecting convergence rather than a device effect. Findings were unchanged in the as treated analysis (Figure S10).

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DISCUSSION

In this randomized mechanistic study of LV unloading during VA-ECMO support, IABP improved oxygen supply-demand balance whereas mAFP did not. Two key physiological observations underpin this finding. First, coronary flow increased marginally with IABP but was unchanged with mAFP. Second, whilst both devices reduced left ventricular pressures, and hence provided LV venting, only the IABP significantly unloaded the LV by reducing oxygen demand as well as contractility.

The rationale for LV unloading during VA-ECMO support in those without overt clinical complications is to reduce myocardial work and allow the injured ventricle to rest and promote recovery[5]. In contrast LV venting lowers ventricular pressures without reducing myocardial work or myocardial oxygen consumption, hence such methods may not promote myocardial recovery[1]. Pre-clinical work has shown that VA-ECMO support may increase infarct size in ischemic shock supporting the concept that MCS can influence myocardial injury and recovery beyond restoration of systemic perfusion[6]. However, the mechanisms through which different unloading devices might impact myocardial energetics remain poorly understood[7]. We had hypothesized that active unloading with an mAFP would result in a more favorable myocardial oxygen supply-demand ratio through greater reductions in LV pressures and improved coronary perfusion. Contrary to this hypothesis, mAFP activation did not significantly improve the myocardial oxygen supply-demand ratio whereas IABP activation resulted in a 48% improvement despite comparable reductions in left ventricular pressures.

Although mAFP increased distal coronary pressure and reduced LVEDP this did not translate to an increase in coronary flow. In contrast, there was a numerical trend towards improved

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coronary flow with IABP consistent with the device producing diastolic augmentation. One explanation for the minimal impact of either device on coronary flow may be that there is residual coronary autoregulation capacity despite the presence of cardiogenic shock. Autoregulation matches supply to demand in addition to maintaining flow over a range of perfusion pressures[8]. Animal models support this hypothesis with increases in perfusion pressure offset by increased microvascular resistance in response to reduced demand[9]. Moreover, a sheep model demonstrated coupling between reduced oxygen supply in response to reduced demand during mAFP unloading[10]. In patients undergoing high-risk percutaneous coronary intervention those with more disordered auto-regulation improved coronary perfusion efficiency with IABP [11]. We observed a trend towards a proportional change in supply relative to demand in the mAFP group but not the IABP suggesting supply and demand may become uncoupled in those unloaded with an IABP. These observations suggest that improvements in myocardial oxygen supply are not the dominant physiological effect of unloading during VA-ECMO. Rather the principal mechanism appears to be modulation of myocardial oxygen demand.

The differential effects of IABP and mAFP on myocardial oxygen demand likely reflect fundamentally different mechanisms of ventricular unloading. Whilst both devices reduced LVEDP and LVESP to a similar degree only IABP significantly reduced TTI leading to the observed difference in oxygen supply demand ratio. Previous pressure-volume analyses have shown that IABP unloading reduces effective arterial elastance and LVESP with a proportionally greater effect on potential energy than stroke work[12,13]. In contrast, mAFP reduces pressure volume area predominantly through a reduction in stroke work whilst exerting less effect on arterial resistance[10]. Our findings suggest these distinct hemodynamic signatures may translate into meaningful differences in myocardial energetics in patients supported with VA-ECMO. Results

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were directionally consistent when supply–demand balance was assessed using the pressure-derived Buckberg index, which improved significantly with IABP but not mAFP, although the between-group difference did not reach significance. The attenuated difference likely reflects the limitations of a pressure-based estimate of myocardial oxygen supply, which does not account for autoregulation. Consequently, the increase in coronary pressure with mAFP is interpreted as increased supply despite the absence of a corresponding increase in measured coronary flow. Indeed, changes in coronary flow were unrelated to changes in DPTI in either arm and with mAFP, tended to parallel changes in demand, suggesting that flow may reflect changes in demand rather than perfusion pressure.

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Our findings differ from Goffer et al who observed greater reductions in myocardial work with mAFP compared to IABP in a porcine model of ischemic cardiogenic shock [14]. Several physiological differences between the studies may explain this. First, participants in our study had more severe cardiac dysfunction reflected by lower pulsatility meaning the IABP may have had a greater physiologic effect. Second mAFP support was evaluated at clinically achievable pump speeds in our study. In contrast animal studies often employ higher pump speeds which are not achievable in clinical practice due to suction events and ventricular collapse. Third, in our present study mAFP insertion was always performed after VA-ECMO support was established; experimental studies suggest that the hemodynamic effects of combined VA-ECMO and mAFP support may depend on the sequence of deployment, with greater reductions in myocardial work observed when mAFP support precedes initiation of VA-ECMO[7].

The present work also supports the concept that effective diastolic augmentation with an IABP requires a degree of residual ventricular ejection and arterial pressure and therefore findings should not be extended to those with no native cardiac output. In a model of ventricular fibrillation

cardiac arrest supported with VA-ECMO IABP reduced coronary flow[15]. The absence of native ventricular contraction required asynchronous balloon counter pulsation which could obstruct flow to the aortic root from the ECMO circuit. In contrast, experimental models with residual ventricular ejection have demonstrated improvements in the myocardial oxygen supply-demand balance with IABP unloading similar to the present study [13].

These observations may have important clinical implications as contemporary practice frequently assumes greater mechanical unloading may lead to improved clinical outcomes and myocardial recovery. Observational data suggest IABP provides a similar mortality benefit as mAFP but with lower complication rates[3,16]. Our findings provide a potential mechanistic explanation for this observation and suggest that physiological effects most relevant to myocardial recovery are not captured by measures of ventricular decompression alone. Strategies that reduce myocardial oxygen demand may be more beneficial than those that simply lower ventricular filling pressures. Whether the observed improvement in myocardial oxygen supply-demand balance with IABP translates into improved myocardial recovery or clinical outcomes requires further investigation. Ongoing randomized trials are comparing either mAFP (UNLOAD-ECMO, NCT05577195) or IABP (EULODIA, NCT07027202; EASE-ECMO, NCT06872021; REMAP-ECMO, NCT05913622; ANCHOR, NCT04184635) unloading with VA-ECMO alone, but none directly compares the two devices.

Our findings must be considered in light of some limitations. Firstly, this was a small mechanistic study and therefore clinical outcomes can only be considered exploratory. Secondly, although randomization reduces selection bias baseline imbalances in LVEDP and pulse pressure were observed between treatment groups and may have influenced the magnitude of physiological response; however, as our outcome measure inherently meant that each participant acted as their

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own control, the influence of baseline heterogeneity is mitigated to some extent. Third, myocardial oxygen supply and demand were estimated using invasively measured surrogates. Simultaneous measurement of ventricular volume and pressure may have enabled more accurate estimation of wall tension, but as the latter is directly related to the cube root of volume (and directly related to pressure by Laplace's Law), the omission of volume in our method is likely to have had a minimal impact on the associations we have found. Fourth, physiology measurements were obtained acutely following activation of the unloading device and may not reflect longer-term hemodynamic adaptation. In addition, minor drift of the pressure wire sensor relative to the guide catheter transducer cannot be excluded in this critically unwell population; however, as each endpoint was a paired within patient comparison recorded within minutes, any systematic offset is likely to have largely cancelled. Fifth, the mAFP was not tested at its highest power level; however, P4 is the most commonly used starting power level in real world practice and we tested at P5[17]. Finally, the participants represent a selected cohort where the treating physician felt there was a clinical requirement for LV unloading and therefore the results may not be generalizable to all patients supported with VA-ECMO.

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Conclusion

In patients with cardiogenic shock supported with VA-ECMO, LV unloading with an IABP improved the myocardial oxygen supply-demand ratio whilst unloading with an mAFP did not. Despite similar reductions in ventricular pressures the two devices exhibited distinct physiological effects on myocardial energetics and systemic hemodynamics. These findings suggest the IABP may be physiologically advantageous and the oxygen supply-demand ratio could represent a

mechanistic target for therapy. Larger clinical outcome trials are warranted to assess whether this physiological premise translates into improved clinical outcomes.

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Supplemental Material:
Tables S1-S7
Figures S1-S10

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Tables

Table 1. Baseline Participant Demographics

		Randomized device			
Characteristic	**N**	**Overall**, N = 24	**IABP**, N = 13	**mAFP**, N = 11	**p**
Age, years	24	51.3 (46.2, 56.6)	49.1 (43.4, 52.3)	56.3 (49.9, 61.8)	0.020
Sex	24				0.682
Female		13 (54%)	8 (62%)	5 (45%)	
Male		11 (46%)	5 (38%)	6 (55%)	
BMI, kg/m²	24	28.1 (25.7, 33.2)	27.3 (25.6, 33.0)	30.2 (26.9, 32.8)	0.524
BSA, m²	24	2.0 (1.8, 2.2)	2.0 (1.8, 2.1)	2.0 (1.8, 2.2)	0.728
Diabetes	24	4 (17%)	2 (15%)	2 (18%)	>0.999
Hypertension	24	6 (25%)	3 (23%)	3 (27%)	>0.999
Prior stroke	24	2 (8.3%)	1 (7.7%)	1 (9.1%)	>0.999
Smoker	24	7 (29%)	4 (31%)	3 (27%)	>0.999
Atrial fibrillation	24	1 (4.2%)	0 (0%)	1 (9.1%)	0.458
SCAI shock stage	24				0.827
C		1 (4.2%)	0 (0%)	1 (9.1%)	
D		13 (54%)	7 (54%)	6 (55%)	
E		10 (42%)	6 (46%)	4 (36%)	
Etiology	24				>0.999
Ischemic		9 (38%)	5 (38%)	4 (36%)	
NSTEMI		*1 (11%)*	*0 (0%)*	*1 (25%)*	
STEMI		*8 (89%)*	*5 (100%)*	*3 (75%)*	
Non-ischemic		15 (63%)	8 (62%)	7 (64%)	
Cardiac arrest	24	14 (58%)	9 (69%)	5 (45%)	0.408
eCPR	14	6 (43%)	5 (56%)	1 (20%)	0.301
Ejection fraction, %	19	10.0 (10.0, 16.5)	10.0 (9.3, 15.0)	13.0 (10.0, 20.0)	0.299
Presenting lactate, mmol/L	24	8.5 (5.2, 14.0)	11.8 (5.0, 20.0)	6.3 (5.4, 9.5)	0.258
Randomization lactate, mmol/L	23	4.3 (2.5, 8.4)	5.1 (2.5, 10.8)	4.1 (2.2, 5.4)	0.559
Intubated	24	13 (54%)	7 (54%)	6 (55%)	>0.999
On inotropes at baseline	24	23 (96%)	13 (100%)	10 (91%)	0.458
Vasoactive-inotropic score	24	13.3 (6.5, 24.1)	12.0 (7.0, 15.5)	22.0 (8.8, 31.5)	0.324

Data are presented as median (interquartile range) or n (%). Percentages were calculated using the number of patients with available data for each variable. P values compare patients randomized to intra-aortic balloon pump (IABP) or microaxial flow pump (mAFP) unloading. BMI, body mass index; BSA, body surface area; eCPR, extracorporeal cardiopulmonary resuscitation; IABP, intra-aortic balloon pump; mAFP, microaxial flow pump; NSTEMI, non–ST-segment–elevation myocardial infarction; SCAI, Society for Cardiovascular Angiography and Interventions; STEMI, ST-segment–elevation myocardial infarction; and VIS, vasoactive-inotropic score.

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Table 2. Comparison of VA-ECMO Parameters Between Patients Randomized to IABP or mAFP Left Ventricular Unloading

VA-ECMO parameter	**Overall**, N = 24	**IABP**, N = 13	**mAFP**, N = 11	p
Time from shock onset to VA-ECMO, h	5.3 (1.5, 9.7)	3.4 (0.9, 9.5)	5.4 (2.0, 9.3)	0.602
VA-ECMO flow, L/min	3.35 (2.98, 3.50)	3.29 (2.91, 3.49)	3.42 (3.06, 3.74)	0.417
Indexed ECMO flow, L/min/m²	1.66 (1.44, 1.85)	1.57 (1.44, 1.76)	1.73 (1.50, 1.85)	0.685
Oxygenator FiO_2, %	63 (59, 70)	60 (60, 70)	70 (58, 73)	0.724
Sweep gas flow, L/min	2.0 (2.0, 3.0)	2.0 (1.5, 3.0)	3.0 (2.0, 3.5)	0.161
Time from VA-ECMO to unloading device, h	6.4 (4.8, 14.5)	6.3 (4.7, 13.7)	6.7 (4.8, 14.5)	0.728

Data are presented as median (IQR). FiO_2, fraction of inspired oxygen delivered through the oxygenator; IABP, intra-aortic balloon pump; mAFP, microaxial flow pump; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

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Table 3. Baseline Coronary and Ventricular Physiology of Patients Randomized to IABP or mAFP Left Ventricular Unloading

Baseline physiology	**Overall**, N = 24	**IABP**, N = 13	**mAFP**, N = 11	p
LVEDP, mmHg	18.0 (14.0, 24.3)	23.0 (17.0, 29.0)	14.0 (14.0, 19.5)	0.031
LVESP, mmHg	79.0 (71.5, 90.0)	74.0 (61.0, 81.0)	82.5 (79.0, 96.0)	0.050
Systolic BP, mmHg	81.0 (72.0, 90.0)	73.0 (63.0, 85.0)	84.0 (81.0, 92.0)	0.088
Diastolic BP, mmHg	66.5 (62.0, 75.0)	67.0 (62.0, 75.0)	65.0 (62.0, 75.0)	0.713
Pulse pressure, mmHg	9.5 (4.5, 19.5)	6.0 (3.0, 16.0)	20.0 (10.0, 26.0)	0.009
Mean arterial pressure, mmHg	70.2 (65.8, 78.5)	70.0 (62.0, 77.7)	70.3 (69.0, 78.7)	0.316
Heart rate, bpm	91.5 (75.8, 114.3)	94.0 (90.0, 115.0)	81.0 (71.0, 112.0)	0.300
dP/dt max, mmHg/s	887.0 (491.8, 1,048.3)	567.0 (445.5, 1,012.5)	983.0 (682.0, 1,112.0)	0.362
dP/dt min, mmHg/s	-656.5 (-859.3, -385.0)	-448.0 (-816.5, -362.0)	-712.0 (-911.0, -620.0)	0.197
TTI, mmHg·s	16.2 (14.1, 17.7)	15.6 (11.9, 17.8)	16.2 (15.6, 16.7)	0.456
Pd, mmHg	65.0 (51.5, 69.5)	63.0 (51.0, 67.0)	67.5 (64.5, 79.8)	0.100
Pa, mmHg	69.0 (59.0, 72.5)	64.0 (52.0, 70.0)	71.5 (69.3, 77.8)	0.058
Transit time, s	0.7 (0.5, 1.3)	0.7 (0.4, 1.4)	0.8 (0.5, 1.1)	0.620
Resting full-cycle ratio (RFR)	0.9 (0.9, 1.0)	0.9 (0.9, 1.0)	0.9 (0.9, 0.9)	0.713
Supply-demand index (baseline)	1,213.9 (598.6, 1,744.2)	1,047.7 (569.0, 1,661.8)	1,325.7 (848.1, 1,779.4)	0.456

Data are presented as median (interquartile range). P values compare patients randomized to intra-aortic balloon pump (IABP) or microaxial flow pump (mAFP) unloading. BP, blood pressure; dP/dt, rate of left ventricular pressure change; LVEDP, left ventricular end-diastolic pressure; LVESP, left ventricular end-systolic pressure; Pa, aortic pressure; Pd, distal coronary pressure; RFR, resting full-cycle ratio and TTI, tension–time index.

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Figure Legends

Figure 1. Study CONSORT Diagram

IABP – Intra-aortic balloon pump; mAFP – micro-axial flow pump

Figure 2. Effect of left ventricular unloading on myocardial oxygen supply-demand balance

(A) Within-patient supply-demand index (transit time (T_{mn}) x tension time index (TTI) x heart rate (HR)) with the unloading device off and on; thin lines are individual participant trajectories. (B) The primary endpoint, the within-patient supply-demand ratio (off/on); each point is one participant, the bar is the median and box the interquartile range, and the dashed line marks the null value of 1, above which myocardial oxygen supply-demand balance improved on device support. Median supply demand ratio in the IABP arm 1.48 [IQR 1.23 to 2.10] and 0.97 [IQR 0.92 to 1.39] in the mAFP arm. IABP - intra-aortic balloon pump; mAFP – micro-axial flow pump.

Figure 3. Proportional change in myocardial oxygen supply and demand with LV unloading, by randomized device

Box plots show the percentage change from the device-off state in estimated myocardial oxygen supply (left panel; inverse of coronary transit time) and myocardial oxygen demand (right panel; product of tension time index and heart rate) after activation of the intra-aortic balloon pump (IABP) or micro-axial flow pump (mAFP). Each point represents an individual participant; boxes show the median and interquartile range (IQR), with whiskers extending to 1.5 × IQR. The dashed line at 0% indicates no change from baseline; values above the line denote an increase in supply (left) or demand (right) during unloading.

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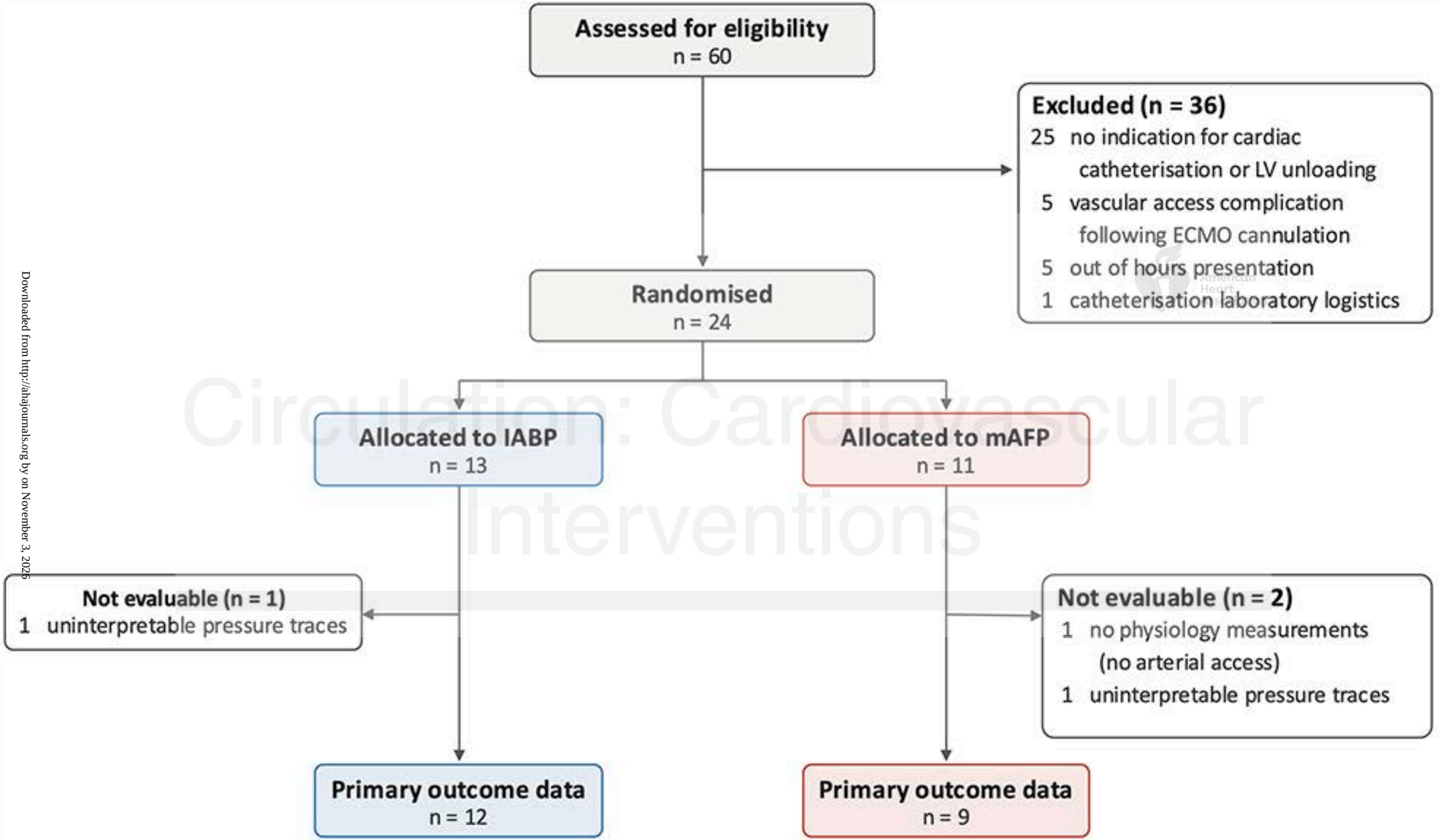
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Figure 4. Coupling of myocardial oxygen supply and demand on activation of the randomized unloading device

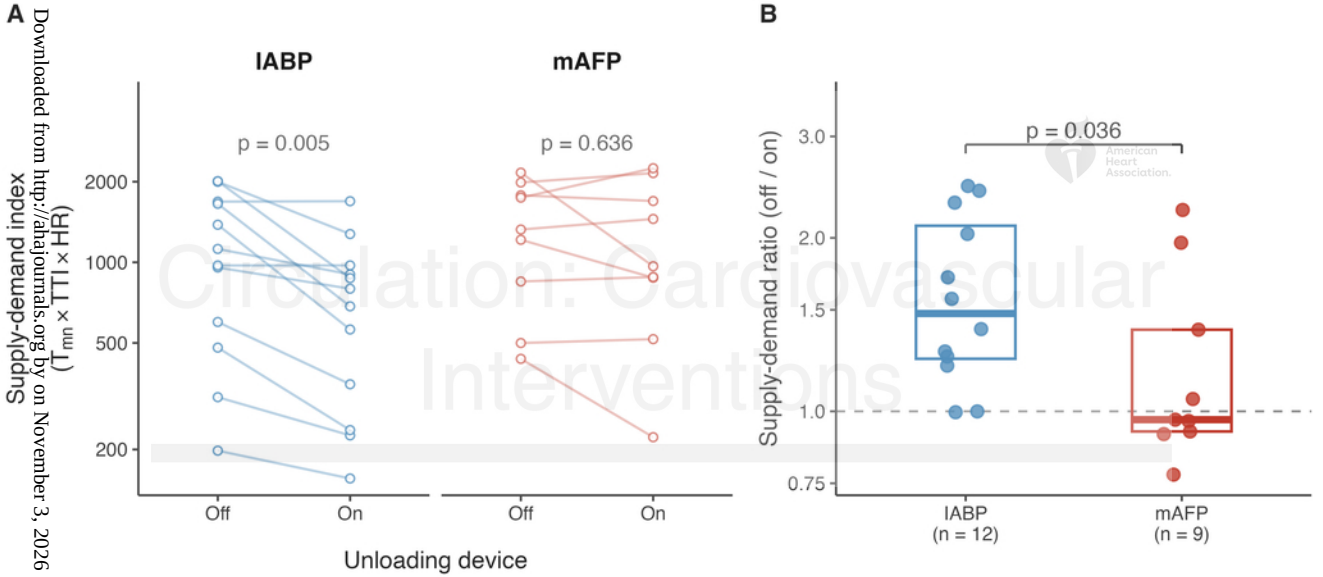
Proportionate (natural log) change in myocardial oxygen supply, estimated as the inverse of coronary transit time, plotted against the proportionate change in demand, estimated as the product of the tension-time index and heart rate, for participants randomized to Intra-aortic balloon pump (IABP) (**A**) and micro-axial flow pump (mAFP) (**B**). The dashed line is the line of identity, on which supply falls in exact proportion to demand and the supply-demand ratio is unity. Points above this line indicate a favorable shift in the balance between supply and demand.

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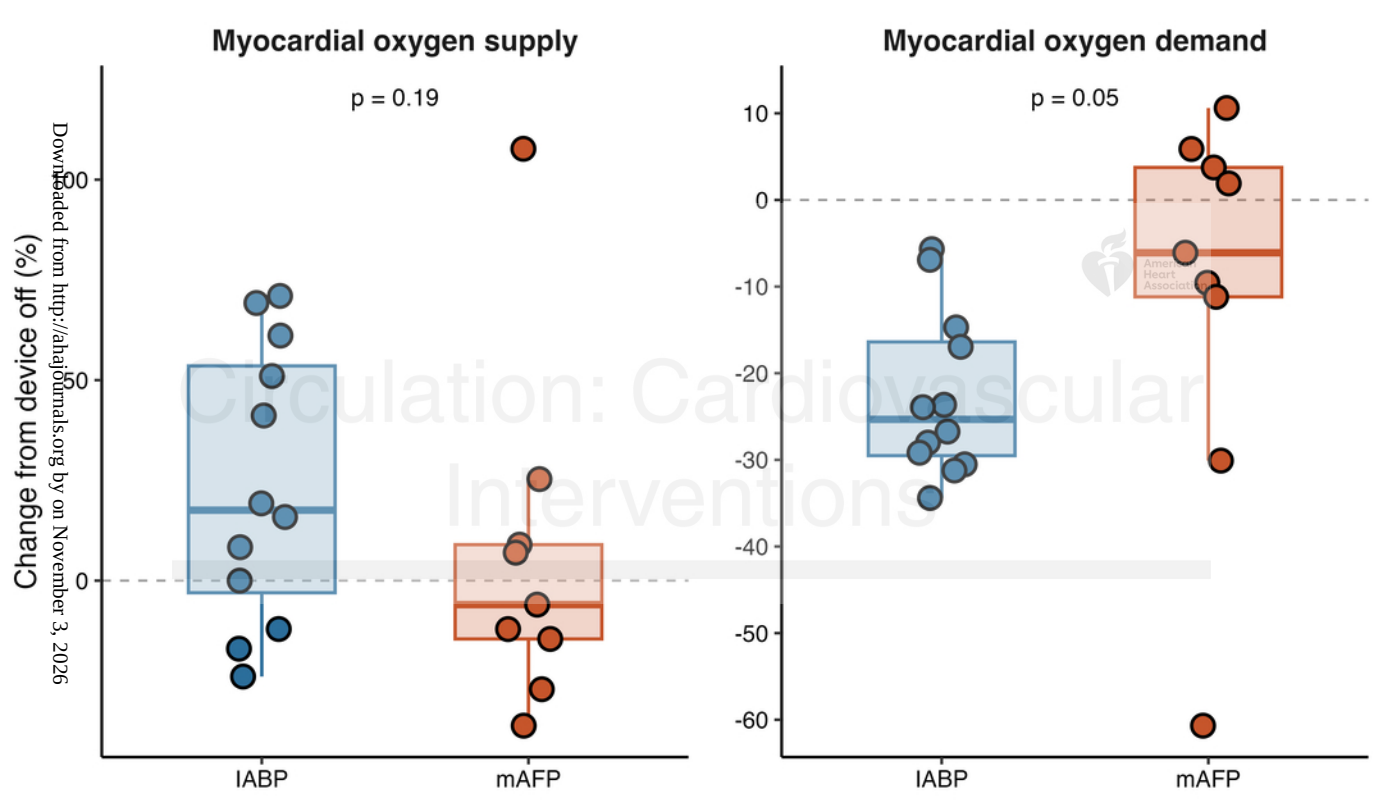


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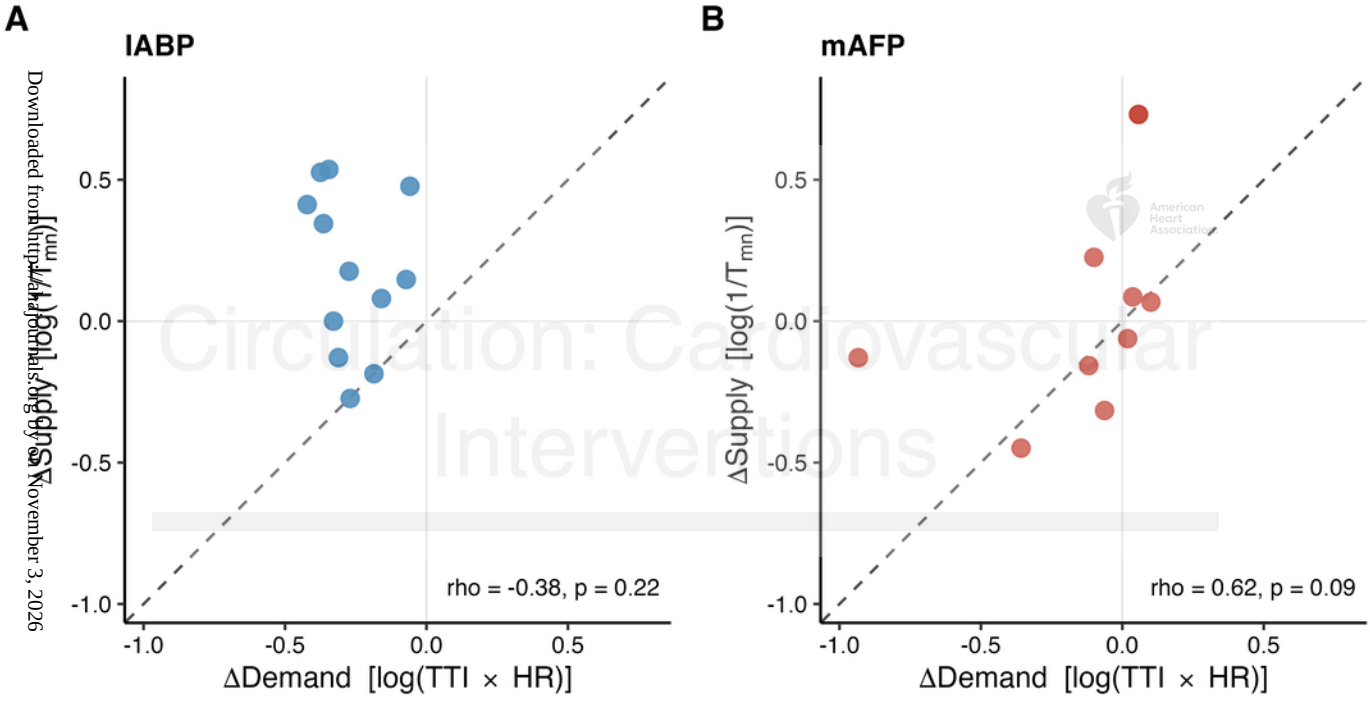
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