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Effect of next generation pulsatile mechanical circulatory support on cardiac mechanics - The PULSE trial

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ABSTRACT

Objectives: To describe hemodynamic effects of iVAC2L mechanical circulatory support (MCS).
Background: MCS is increasingly used in the context of high-risk percutaneous coronary intervention (PCI). The effect of the pulsatile iVAC2L MCS on left ventricular loading conditions and myocardial oxygen consumption (MVO_2) is unknown.
Methods: This prospective single-arm two-center study included 29 patients who underwent high-risk PCI with iVAC2L MCS using simultaneous invasive pulmonary pressure monitoring and left ventricular pressure-volume analysis. Hemodynamic recordings were performed during steady state conditions with MCS off and on before and after PCI. Pressure-volume variations were analyzed to denote responders and non-responders.
Results: The mean age was 74 (IQR: 70–81) years and the mean SYNTAX score was 31 ± 8.3. Left ventricular unloading with iVAC2L MCS was demonstrated in 22 out of 27 patients with complete PV studies. Patients with moderate or severe mitral regurgitation or presenting with acute coronary syndrome (ACS) had higher filling pressures and volumes and were most responsive to iVAC2L unloading (9/10 patients with moderate or severe MR and 11/11 patients with ACS). Pulsatile MCS activation reduced MAP (−4%), SBP (−9%), ESP (−11%), ESV (−15%) and EDV (−4%) among responders but not among non-responders. Responders experienced significant reductions in afterload (Ea: −19%) with increases in stroke volume (+11%) and cardiac output (+11%).
Conclusions: Pulsatile iVAC2L MCS in patients with advanced coronary artery disease at high to prohibitive operative risk resulted in LV unloading and reduced myocardial oxygen consumption particularly in patients with ACS or significant MR with higher filling pressures at baseline.
Clinical trial registration: NCT03200990.

1. Introduction

Percutaneous mechanical circulatory support (MCS) can be used to facilitate high risk percutaneous coronary interventions (PCI). MCS adoption in clinical practice is increasing. Main goals are to assure hemodynamic stability, reduce myocardial oxygen consumption (MVO_2) and left ventricular (LV) afterload, while enhancing coronary and end-organ perfusion [1]. Efficacy has been demonstrated in several studies [1–8].

Multiple MCS technologies are commercially available (Fig. 1). The intra-aortic balloon pump (IABP) is placed in the ascending aorta and provides up to 0.5 L/min of output. Impella and Heartmate PhP are microaxial-flow devices that are retrogradely placed with the tip inside the LV. They eject LV blood in the aorta at rates between 2.5 and 5.0 L/

Abbreviations: ACS, acute coronary syndrome; CO, cardiac output; CPO, cardiac power output; Ea, effective arterial elastance; EDP, end-diastolic pressure; EDV, end-diastolic volume; Ees, end-systolic elastance; ESP, end-systolic pressure; ESV, end-systolic volume; IABP, intra-aortic balloon pump; LV, left ventricle; MAP, mean arterial pressure; MCS, mechanical circulatory support; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; MR, mitral regurgitation; MVO_2, myocardial oxygen consumption; PCI, percutaneous coronary intervention; PV, pressure-volume; PVA, pressure-volume area; SV, stroke volume; SW, stroke work.

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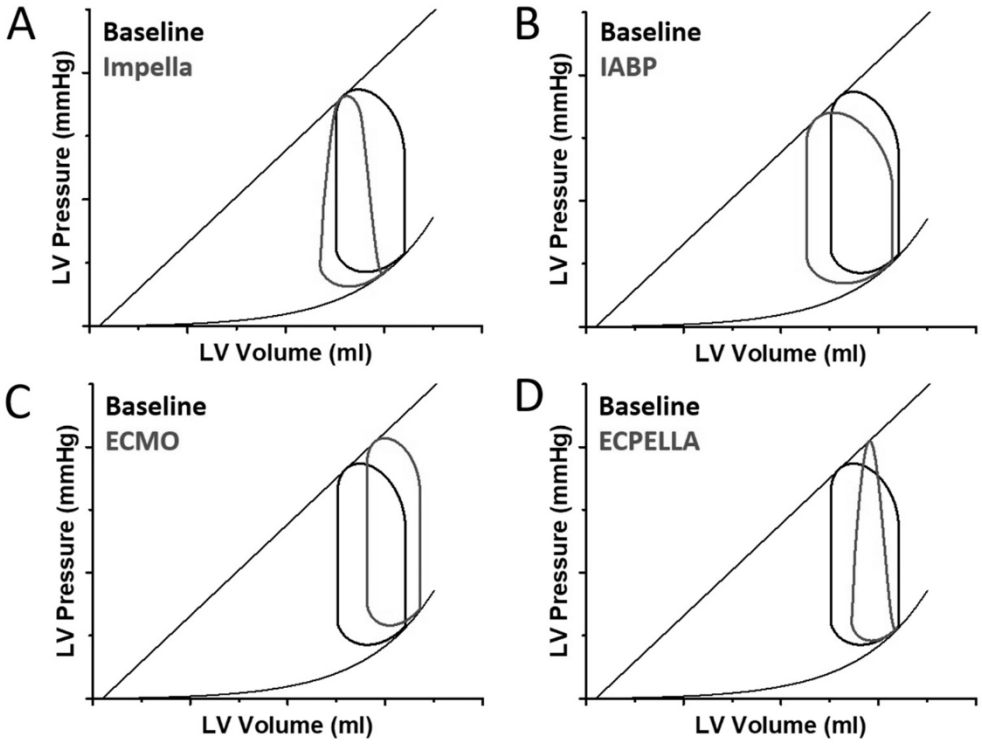

Fig. 1. Different effects of various mechanical support devices on cardiac mechanics.

min. Impella has been associated with high rates of hemolysis [9]. TandemHeart and V-A ECMO both apply centrifugal pumps that draw blood from the left and right atrium respectively, and eject it on the ilio-femoral system at the expense of higher vascular complications. With the exception of the IABP, all devices provide continuous flow.

The randomized PROTECT II trial reported improved clinical outcomes at 90 days with micro-axial flow MCS over the conventional intra-aortic balloon pump (IABP) in the context of high-risk PCI. More potent MCS resulted in more comprehensive lesion preparation and a reduction in repeat revascularization [2]. Conversely, recent large US based registry data pointed in the opposite direction [10] and due to the lack of evidence from randomized controlled trials, MCS remains only partially endorsed by current guidelines [3].

The iVAC2L system (PulseCath B.V., Amsterdam, The Netherlands) is a next generation pulsatile MCS that consists of an extracorporeal pump driven by a standard IABP console and delivers a stroke volume (SV) of 21 mL in synchrony with the underlying cardiac performance. The pulsatile support outperforms what can be generated by IABP [11]. The effect of the iVAC2L on cardiac mechanics is unclear but can be evaluated through real-time in vivo pressure-volume (PV) analysis with conductance catheters [4]. The PULsecath mechanical Support Evaluation (PULSE) trial aimed to study the effects of iVAC2L on cardiac mechanics through changes in the LV PV relationship in patients undergoing elective high-risk PCI requiring MCS.

2. Methods

2.1. Patient eligibility

Eligible patients were deemed clinically stable with no overt signs of fluid overload. A multidisciplinary heart team including cardiologists and cardiac surgeons deemed all patients at very high or prohibitive operative risk based on comorbidities and frailty and at high risk for hemodynamic instability during PCI warranting MCS because of complex target coronary artery disease (unprotected left main stem disease, multivessel disease, single remaining vessel) with or without LV dysfunction (Fig. 2A). Procedural planning included invasive coronary angiography, transthoracic echocardiography (TTE) and assessment of the ilio-femoral arterial system by invasive (angiography) or non-invasive methods (computed tomography angiography). Major exclusion criteria were cardiogenic shock as defined in the SHOCK trial [12], moderate or severe aortic valve disease, presence of LV thrombus, extensive peripheral arterial disease or common femoral/iliac artery size < 6 mm (Table 1).

All patients provided written informed consent. The study was approved by the respective local institutional review boards and was conducted in accordance with the declaration of Helsinki. The trial was registered on clinicaltrials.gov (NCT03200990). PulseCath BV provided an unrestricted grant for the study. The authors were responsible for the data acquisition and analysis and take full responsibility for the content of this work.

2.2. iVAC2L MCS

A detailed description of the iVAC2L can be found elsewhere [11]. In brief, the iVAC2L has three essential components: 1) the membrane pump, 2) a bi-directional flow catheter and 3) a patented rotating 2-way valve (Supplement, Fig. 1). The transparent extracorporeal membrane pump contains a blood chamber and an air chamber divided by a thin flexible membrane. The blood chamber is connected to the bi-directional flow catheter and the air chamber to a genuine IABP console, which acts as pneumatic driver for the pump. The total chamber volume is 40 mL, and the pump can expel 21 mL of blood per beat. The bi-directional flow catheter is composed of nitinol-wire-reinforced polyurethane, measures 95 cm and has a 17Fr (5.9 mm) outer diameter. The inlet tip is made of stainless steel. The catheter has an integrated two-way valve that pivots around 2 axes at 6 cm from the inlet. A connector piece at the other end of the catheter connects to the membrane pump. The flow catheter is percutaneously inserted through the common femoral artery (CFA) and advanced across the aortic valve.

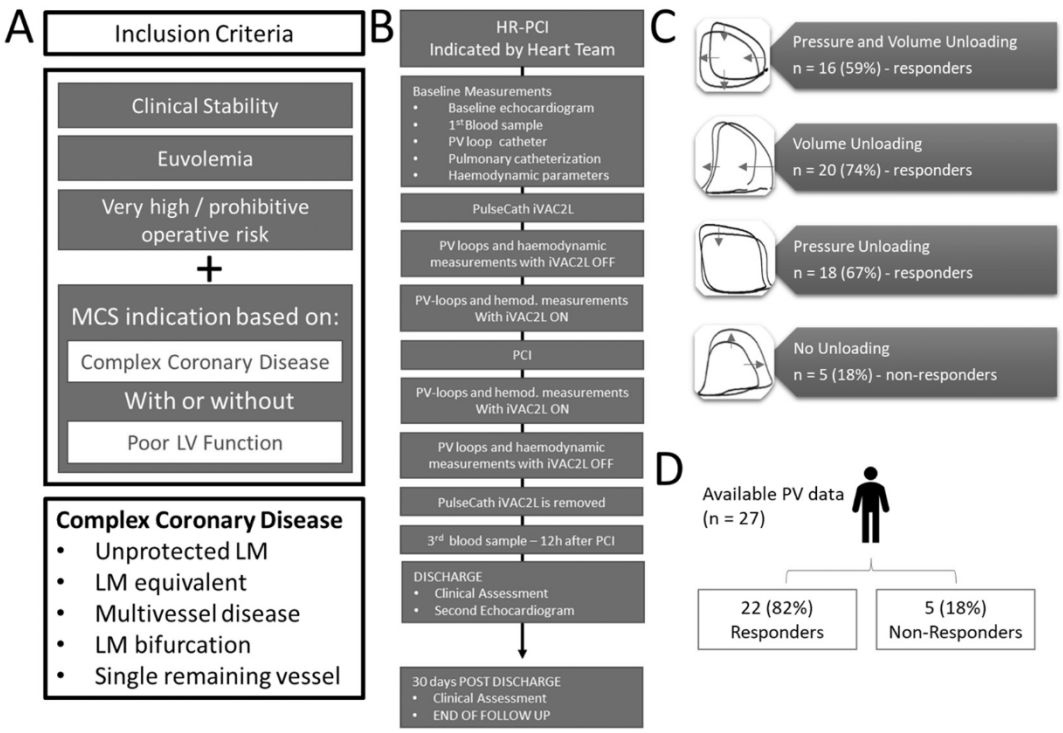

Fig. 2. (A) Inclusion criteria. Patients were defined as high-risk based on the presence of complex coronary disease (bottom) with or without significant left ventricular dysfunction. (B) Study Flowchart. (C and D) Adjudication of Left ventricular unloading based on the occurrence of net negative variations in pressure, volume or both altogether, resulting in an 82% rate of responders (LM: left main coronary artery. HR-PCI: high-risk PCI. PV: pressure-volume. PCI: percutaneous coronary intervention. TNV: total net variation. ESV: end-systolic volume. EDV: end-diastolic volume. ESP: end-systolic pressure. EDP: end-diastolic pressure).

The iVAC2L operates in synchrony with the cardiac cycle. Through the tip, arterialized blood is drained from the LV in systole and expelled into the ascending aorta through the integrated 2-way valve in diastole.

Optimal performance is achieved at 70–80 bpm. During tachycardia, asynchronous pumping can generate a pulsatile device output of 1.2 L/min albeit at the cost of increased afterload [11].

2.3. Study procedure

First, transfemoral venous and double arterial access was obtained. A pulmonary artery catheter was placed in the right pulmonary artery. A 7Fr conductance catheter (ConductNT, CDLeycom, Hengelo, The Netherlands) and the iVAC2L (through an 18F sheath) were positioned across the aortic valve with their distal extremities inside the LV. By default, the PCI required a transradial approach. The conductance catheter was calibrated using volume data obtained from recent echocardiography or cardiac magnetic resonance imaging studies and PV analysis relied on single beat algorithms [4]. Pre-PCI, two complete sets of hemodynamic measurements, including cardiac output (CO), pulmonary pressures and LV PV loops were taken, with iVAC2L OFF and ON (ECG-triggered 1:1 assist ratio). Another ON-OFF pair of sets was recorded post-PCI. Deflation was set to end-diastole (R-wave) and inflation to end-systole (T-wave). The flow produced by iVAC2L was measured using a "clamp-on" flowmeter which was placed on the catheter just distal to the membrane chamber. Femoral arteriotomy closure was performed with percutaneous suture or plug based closure devices. Blood samples were drawn pre-PCI, post-PCI and 12–24 h post-PCI. Echocardiograms were obtained within 24 h prior to the PCI and predischarge to rule out device induced injury to the aortic valve or myocardium. A 30-day clinical follow up was organized through telemedicine (Fig. 2B).

Table 1
Inclusion and exclusion criteria applied in the PULSE trial.

Inclusion and exclusion criteria
Inclusion criteria
• Patient is ≥18 years.
• Informed Consent must be signed by the patient, prior to HR-PCI.
• Multidisciplinary heart team consensus for high-risk PCI. Anatomical criteria: Intervention to an unprotected left main, left main equivalent or single remaining vessel; multivessel disease; intervention in a distal left main bifurcation.
Exclusion criteria
• No written informed consent.
• Left ventricular thrombus.
• Interventricular septal defect.
• Significant peripheral arterial disease or arterial lumen size < 6 mm at the level of the common femoral artery.
• Significant aortic valve disease (moderate or severe aortic valve stenosis/-regurgitation).
• Cardiogenic shock.
• Previous stroke within the last 3 months.
• Major bleeding event within last 3 months.
• Chronic kidney disease with an eGFR < 25 mL/min.

2.4. Study endpoints

The main study endpoint was the PV variations with iVAC2L ON vs OFF. The Pressure-volume Area (PVA) was used as a proxy for MVO_2. Additional endpoints were major bleeding defined as Bleeding Academic Research Consortium (BARC) 3–5 [13]; major vascular complications defined by the 2nd Valve Academic Research Consortium (VARC) definitions, acute kidney dysfunction using the AKIN classification [14]; increase in aortic regurgitation by more than one grade on TTE; cardiogenic shock requiring inotropic/vasopressor support and/or MCS escalation. Clinical endpoints were adjudicated by an independent Clinical Events Committee.

2.5. Pressure volume analysis

End-systole was defined as the point of maximum time-varying elastance. End-diastole was defined at the R-wave. Contractility was assessed using a single-beat algorithm. End-systolic elastance (Ees) was defined by the slope of the end-systolic pressure-volume relationship. Effective arterial elastance (Ea) was derived from ESP/SV as a measure of overall afterload. The ventricular-arterial coupling (VAC) ratio Ees/Ea reflected the energy transfer from the LV to the arterial system. The PVA was calculated as previously described [4]. Forward CO was obtained with thermodilution (CO_{FRD}) and global CO was derived from the conductance volumetric signal (CO_{GLB}). CO_{GLB} is more sensitive to subtle changes in cardiac mechanics, and hence was the preferred method for calculating cardiac output while CO_{FRD} was used to derive vascular resistances. Stroke work (SW) was calculated as the area within the PV loop.

LV unloading was ascertained based on the net change in ESP, EDP, ESV and EDV with the iVAC2L on and off. Changes in ESP and EDP taken together defined pressure unloading if there was a netto shift to lower pressures. Changes in ESV and EDV taken together defined volume unloading if there was a netto shift to lower volumes. The loops analyzed were either pre or post-PCI, whichever showed the most reliable PV loop tracings with the most clear changes. Responders had pressure and/or volume unloading (Fig. 2C–D). Non-responders had no LV unloading at all.

Missing data on mPAP (14%) and mPCWP (39%) were imputed using univariate linear regression models derived from the relationship of the existing data with the conductance catheter-derived EDP. EDP correlated with mPAP (r: 0.60, CI95%: 0.50 to 0.69, $p < 0.001$) and mPCWP (r: 0.67 CI95%: 0.57 to 0.76, $p < 0.001$). For illustrative purposes, averaged PV loops [15] with the device OFF and ON were plotted.

2.6. Statistical analysis

Data is expressed as mean ± SD and compared using Student's *t*-test for unpaired samples, or median (25th–75th percentile) and Mann-Whitneys *U* test if skewed. Categorical data is reported as percentage, and tested using Fisher's exact test. For hemodynamic variables, the percent variation from ON vs OFF mode was tested with one-sample t-test or Wilcoxon's Signed Rank test. Biochemical parameters pre, post and 24 post-PCI were compared using Friedman's test.

A two-sided alpha level of 5% defined statistical significance for all tests. All calculations were performed in the R statistical package v.4.0.2.

3. Results

3.1. Baseline characteristics

29 patients were enrolled between January 2017 and December 2018. Two patients had no reliable PV loop measurements and were excluded from the PV analysis. The first suffered a fatal retroperitoneal bleeding and had a cardiac arrest before the conductance signal could be acquired. The second had no radial access and had its conductance catheter removed in order to allow the PCI to be performed via femoral access.

Median (25th–75th percentile) age was 74 (70–81) years, 65% were male. The estimated in-hospital mortality following open heart surgery as estimated by the Euroscore II was 3.9% (1.9–5.2) (Table 2). Eleven patients had a semi-elective PCI after they presented with an acute coronary syndrome and 10 patients had moderate or severe mitral regurgitation. The mean SYNTAX score was 31 ± 8.3. Left Main (LM) disease was present in 59%. A median of 4 [4–6] significant lesions were treated per patient. Rotational atherectomy (RA) and invasive imaging were used in 17% and 26% respectively. Procedural time was 92 (77–109) minutes and support time was 68 (53–80) minutes. Hospital stay was 4 (2–10) days (Table 3). Thirty-day follow up was complete for all subjects.

Hemodynamic measurements in OFF and ON states with the corresponding percent changes are depicted in Tables 4 and 5 for responders and non-responders. Table 1 of the Supplement shows the percent changes for the aggregate data. At baseline, mean arterial pressure

Table 2
Baseline demographics from the whole sample and from responders compared to non-responders. p-Values refer to Student's *t*-tests for unpaired samples, Mann-Whitney's *U* test (continuous data) or Fisher's exact test (categorical data) comparing responders and non-responders. Frequencies are shown as percentages (counts). Continuous measurements are shown as mean ± SD or median (25th–75th quartiles). ACS: acute coronary syndrome. BMI: body mass index. BSA: body surface area COPD: chronic pulmonary obstructive disease. EF: ejection fraction. MI: myocardial infarction. MR: moderate or severe mitral regurgitation. PCI: percutaneous coronary intervention.

Baseline characteristics				
	All	Responders	Non-responders	p
n	29[a]	22	5	
Age (years)	74 (70–81)	74.5 (70.3–8)	74 (72–76)	0.51
BMI	27 (26–30)	26 (25–30)	30 (27–31)	0.44
Height (cm)	175 (165–182)	173 (165–182)	181 (178–187)	0.07
BSA (m^2)	2.0 (1.8–2.2)	2.0 (1.8–2.1)	2.2 (2.2–2.3)	0.07
Gender (M) (%)	65.5 (19)	59.1 (13)	100 (5)	0.14
Diabetes mellitus (%)	31 (9)	31.8 (7)	20 (1)	1
Hypertension (%)	72.4 (21)	72.7 (16)	60 (3)	0.62
Smoking (%)	62.1 (18)	63.6 (14)	40 (2)	0.37
Stable angina (%)	55.2 (16)	45.5 (10)	80 (4)	0.33
Unstable angina (%)	20.7 (6)	27.3 (6)	0 (0)	0.56
Acute coronary syndrome (%)	37.9 (11)	50 (11)	0 (0)	0.06
Previous MI (%)	58.6 (17)	68.2 (15)	40 (2)	0.33
Previous PCI (%)	41.4 (12)	50 (11)	0 (0)	0.06
Ischemic stroke (%)	27.6 (8)	22.7 (5)	60 (3)	0.14
Chronic kidney disease (%)	44.8 (13)	40.9 (9)	60 (3)	0.63
COPD (%)	24.1 (7)	27.3 (6)	20 (1)	1
Mitral regurgitation (%)	34.5 (10)	40.9 (9)	20 (1)	0.62
Aortic regurgitation (%)	17.2 (5)	18.2 (4)	0 (0)	0.56
Atrial fibrillation (%)	20.7 (6)	22.7 (5)	20 (1)	1
EF < 40% (%)	37.9 (11)	40.9 (9)	40 (2)	1
EF (%)	43 ± 14	38 ± 13	47 (44 to 48)	0.014
SYNTAX score	31 ± 8	32 (27–38)	29 (28–30)	0.40
EUROSCORE II	3.9 (1.9–5.2)	4.1 (2.5–6.6)	3.1 (1.9–5.2)	0.57

[a] 2 patients did not have pressure-volume loop assessment.

Table 3
Procedural and baseline hemodynamical characteristics according to response to mechanical circulatory support. Frequencies are shown as percentages. Continuous measurements are shown as mean ± SD or median (25th–75th quartiles). p-values are derived from or Fisher's exact test between responders and non-responders. LAD: left anterior descendant. LCX: left circumflex. LM: left main. RCA: right coronary artery.

Procedural characteristics				
Procedural characteristics	Total	Responders	Non-responders	p
	29	22	5	
Number of significant stenoses	4 (4–6)	4.5 (4–6)	4 (4–5)	0.80
Severe LM disease	62.1 (18)	63.6 (14)	40 (2)	0.37
Unprotected LM	37.9 (11)	50 (11)	60 (3)	1
Multivessel disease	76 (22)	82 (18)	60 (3)	1
3-Vessel disease	41 (12)	41 (9)	60 (3)	0.63
LM equivalent	31 (9)	27 (6)	60 (3)	0.62
RCA treated	41.4 (12)	45.5 (10)	40 (2)	1
LM treated	44.8 (13)	50 (11)	20 (1)	0.34
LAD treated	79.3 (23)	90.9 (20)	80 (4)	0.47
LCX treated	48.3 (14)	50 (11)	60 (3)	1
IV fluids	37.9 (11)	36.4 (8)	60 (3)	0.37
IV sedation	24.1 (7)	31.8 (7)	0 (0)	0.28
Rotablation	17 (5)	18 (4)	20 (1)	1

Table 4
Effect of iVAC2L among responders. Absolute measurements with iVAC2L on OFF and ON states, and the percent variation in hemodynamic variables between these states. Continuous measurements are shown as mean ± SD or median (25th–75th quartiles). HR: heart rate. CO_{GLOBAL}: global cardiac output. CPO: cardiac power output. SBP: systolic blood pressure. DBP: diastolic blood pressure. MAP: mean arterial pressure. ESP: end-systolic pressure. ESV: end-systolic volume. EDP: end-diastolic pressure. EDV: end-diastolic volume. SV_{GLOBAL}: global stroke volume. mPCWP: mean pulmonary wedge pressure. mPAP: mean pulmonary artery pressure. TPR: Total Pulmonary Resistance; EF_{GLOBAL}: global ejection fraction. Ees: end-systolic elastance. SW: stroke work. PVA: pressure-volume area. Ea: effective arterial elastance. TSR: Total Systemic Resistance.

Percent changes among responders (n = 22)			
	OFF	ON	% variation
GENERAL LV FUNCTION			
$HR_{(bpm)}$	76 ± 18	76 ± 14	+1 (−1; +5)
$CO_{GLOBAL(L/min)}$	4.56 ± 0.85	5.12 ± 0.89	+11 (+3; +18)§
$CPO_{(W)}$	0.80 ± 0.20	0.96 ± 0.25	+21 ± 20§
LV PRESSURES AND VOLUMES			
SBP (mmHg)	115 ± 24	128 ± 25	+13 ± 21‡
DBP (mmHg)	52 ± 14	60 ± 12	+22 ± 37†
MAP (mmHg)	74 ± 17	82 ± 15	+15 ± 26†
ESP (mmHg)	119 ± 24	106 ± 23	−11 ± 9§
ESV (mL)	90 (67; 140)	72 (56; 117)	−15 ± 10§
EDP (mmHg)	19 ± 7	22 (13; 27)	+13 ± 28†
EDV (mL)	155 (142; 213)	149 (139; 189)	−4 (−11; +0.01)‡
$SV_{GLOBAL(mL)}$	62 ± 16	69 ± 15	+11 (+3; +16)‡
PULMONARY CIRCULATION			
mPCWP (mmHg)	19 ± 9	21 (14; 24)	+12 ± 34
mPAP (mmHg)	24 ± 8	26 ± 9	+4 (−5; +12)
TPR (mmHg·min/mL)	434 ± 143	437 (325; 562)	+7 ± 28
LV CONTRACTILITY			
$EF_{GLOBAL(\%)}$	38 ± 13	45 ± 14	+13 (+8; +24)§
Ees (mmHg/mL)	1.42 ± 0.67	1.27 ± 0.47	−4 ± 24
$V100_{(mL)}$	59 (50; 125)	57 (50; 117)	−4 ± 18
$+dP/dt_{MAX(mmHg/s)}$	943 ± 281	900 ± 257	−4 ± 8†
LV ENERGETICS			
$SW_{(mmHg.mL)}$	6271 ± 2243	6518 ± 2051	+6 ± 17
$PVA_{(mmHg.mL)}$	12,063 ± 3187	11,500 ± 3053	−8 (−15; −0.3)*
SW/PVA	0.52 ± 0.11	0.57 ± 0.11	+9 (+7; +13)‡
LV AFTERLOAD			
$Ea_{(mmHg/mL)}$	1.79 (1.66; 2.32)	1.47 (1.31; 1.85)	−19 (−24; −14)‡
Ees/Ea	0.71 ± 0.25	0.82 ± 0.32	+19 ± 21§
TSR (mmHg·min/mL)	1278 (1203; 1653)	1189 (1048; 1619)	−5 ± 18

* $p < 0.1$ versus baseline.
† $p < 0.05$ versus baseline.
‡ $p < 0.01$ versus baseline.
§ $p < 0.001$ versus baseline.

(MAP) for the whole cohort was 82 (74–92) mm Hg and global cardiac power output (CPO_{GLOBAL}) was 0.93 (0.72–1.05) W. The mean global ejection fraction (EF_{GLOBAL}) was 47% (33–54), and mPAP was 20 (17–26) mm Hg. Baseline LV end-diastolic pressure (EDP) was 18 (12–24) mm Hg. During support, the median flow of iVAC2L was 1.42 (1.30–1.46) L/min at an underlying heart rate of 71 (63–81) bpm.

3.2. Pressure volume analysis

3.2.1. Left ventricular unloading

LV unloading with iVAC2L was demonstrated in 22 patients (82% of the analyzed cohort). Unloading was more common at end-systole and early diastole, indicated by significant reductions in ESP and ESV (Fig. 3A and B). These changes were expressed in the PV loops as a downward shift of the ventricular ejection phase and left shift of the isovolumetric relaxation phase of the cardiac cycle (Fig. 4A and Supplement, Fig. 2). Significant reductions also occurred in the EDV. There was a significant 11% increase in CO_{GLOBAL} and SV_{GLOBAL} (Tables 4 and 5). SW numerically increased (ΔSW: +6 ± 17%, p = 0.1) PVA reduction (as a surrogate for MVO_2) was observed in 78% of all the cases (ΔPVA of −8.2% (p = 0.064)). The ΔSW/PVA ratio increased (+9.4%, $p < 0.01$). A significant 19% reduction in Ea occurred, and the Ees/Ea ratio increased by 18%. Contractility and PVA remained unchanged.

Overall, 5 individuals were classified as non-responders as they showed no significant changes in cardiac mechanics in the ON vs OFF state. Only one of these subjects had more than mild MR and all had stable CAD. Unlike responders, non-responders had no significant change in LV pressures and volumes with the exception of a significant increase in the EDP after activation of iVAC2L. MAP and DBP significantly increased during MCS (Table 5).

3.2.2. Mitral regurgitation

Patients with mitral regurgitation (MR, n = 10) had higher baseline EDP (23 ± 7 vs 15 ± 7 mm Hg, p = 0.01) and filling volumes (EDV: 194 (170–200) vs 138 (120–159) mL, $p < 0.01$, ESV: 128 (106–152) vs 61 (46–76) mL, $p < 0.001$). Contractility was significantly lower (Ees: 1.09 ± 0.49 vs 1.51 ± 0.42 mm Hg/mL, p = 0.04; V100: 113 (84–165) vs 40 (29–54) mL, $p < 0.001$; EF_{GLOBAL}: 34 ± 11 vs 52 ± 13 < 0.001). Other baseline and hemodynamic subgroup characteristics are summarized in Supplement, Tables 2–4.

Nine out of 10 patients with more than mild mitral regurgitation (MR) experienced unloading with significant reductions in EDV (−5.8 ± 7.5 mL, p = 0.038). PVA significantly decreased (−9.4 ± 7.3%, $p < 0.01$) (Fig. 4B).

3.2.3. Acute coronary syndrome

At baseline, patients with ACS had higher LV volumes (ESV: 103 (74–127) vs 60 (45–127), p = 0.06; EDV: 169 (159–194) vs 137 (120–196) mL, p = 0.08) and EDP (22 ± 8 vs 15 ± 7 mm Hg, p = 0.02). Among the 11 patients with ACS unloading was seen in all patients. Individuals with ACS experienced both pressure and volume unloading with iVAC2L, with reductions in EDP, EDV, ESP and ESV (Fig. 4C) and a ΔPVA of −9% (p = 0.084).

Table 5
Effect of iVAC2L among non-responders. Absolute measurements with iVAC2L on OFF and ON states, and the percent variation in hemodynamic variables between these states. Continuous measurements are shown as mean ± SD or median (25th–75th quartiles). HR: heart rate. CO_{GLOBAL}: global cardiac output. CPO: cardiac power output. SBP: systolic blood pressure. DBP: diastolic blood pressure. MAP: mean arterial pressure. ESP: end-systolic pressure. ESV: end-systolic volume. EDP: end-diastolic pressure. EDV: end-diastolic volume. SV_{GLOBAL}: global stroke volume. mPCWP: mean pulmonary wedge pressure. mPAP: mean pulmonary artery pressure. TPR: Total Pulmonary Resistance; EF_{GLOBAL}: global ejection fraction. Ees: end-systolic elastance. SW: stroke work. PVA: pressure-volume area. Ea: effective arterial elastance. TSR: Total Systemic Resistance.

Percent changes among non-responders (n = 5)			
	Off	On	% variation
GENERAL LV FUNCTION			
HR $_{bpm}$	67 (55; 72)	70 (54; 74)	+2 (+2; +4)
$CO_{GLOBALL/min}$	5.29 (4.84; 6)	4.98 (4.87; 5.44)	+3 (+3; +11)
CPO $_{W}$	0.82 (0.74; 0.90)	1.01 (0.94; 1.23)	+47 (+26; +50)
LV PRESSURES AND VOLUMES			
SBP $_{mmHg}$	110 (105; 115)	130 (110; 153)	+24 (−4; +39)
DBP $_{mmHg}$	60 (53; 60)	80 (54; 82)	+31 (+2; +33)*
MAP $_{mmHg}$	71 (65; 75)	92 (70; 97)	+29 (+5; +42)*
ESP $_{mmHg}$	114 (112; 127.6)	106 (103; 122)	−6 (−7; −3)
ESV $_{mL}$	73 (63; 120)	71 (70; 118)	+3 (+2; +10)
EDP $_{mmHg}$	16 (14; 24)	20 (19; 27)	+15 (13; +27)*
EDV $_{mL}$	178 (152; 226)	202 (143; 226)	+0.04 (−2; +4)
$SV_{GLOBAL\ mL}$	85 (72; 98)	80 (73; 100)	+1 (−2; +6)
PULMONARY CIRCULATION			
mPCWP $_{mmHg}$	14 (14; 16)	20 (19; 22)	+32 (23; 59)
mPAP $_{mmHg}$	22 (20; 23)	26 (24; 27)	+15 (13; +20)
TPR $_{mmHg\cdot min/mL}$	299 (283; 338)	369 (355; 395)	+19 (+9; +33)
LV CONTRACTILITY			
$EF_{GLOBAL\%}$	47 (44; 48)	46 (44; 50)	+1 (−0.2; +2)
Ees $_{mmHg/mL}$	1 (1; 2)	1 (1; 2)	+4 (+2; +16)
V100 $_{mL}$	58 (52; 80)	67 (61; 92)	+16 (+4; +30)
$+dP/dt_{maxmmHg/s}$	968 (886; 1115)	951 (871; 957)	−1.7 (−1.8; −1.6)
LV ENERGETICS			
SW $_{mmHg.mL}$	7,394 (7,328; 9,297)	7,993 (7,881; 9,231)	+7 (−3; +12)
PVA $_{mmHg.mL}$	12,747 (11,751; 16,705)	11,963 (11,175; 13,658)	−6 (−7; +2)
SW/PVA	0.58 (0.47; 0.63)	0.66 (0.54; 0.68)	+5 (+4; +16)
LV AFTERLOAD			
Ea $_{mmHg/mL}$	1.34 (1.07; 1.34)	1.17 (1.03; 1.32)	−4 (−13)
Ees/Ea	0.9 (0.62; 0.99)	1.08 (0.72; 1.16)	+9 (9; +16)
TSR $_{mmHg\cdot min/mL}$	1127 (1087; 1193)	1028 (950; 1101)	−8 (−9; −7)

* $p < 0.1$ versus baseline.

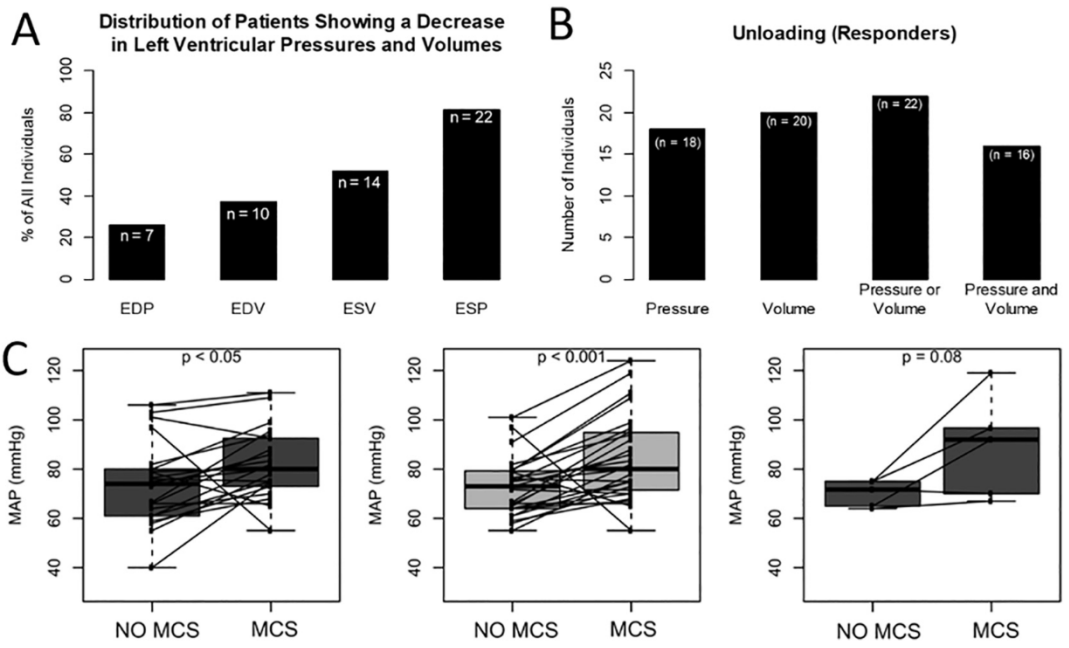

Fig. 3. (A) Quantification of patients in the group of responders that exhibited pressure unloading, volume unloading, pressure or volume unloading (i.e., one or the other), and pressure and volume unloading (i.e., both simultaneously). The majority of responders showed reduction in LV pressures and volumes simultaneously, but some of them had only either pressure or volume unloading. (B) Breakdown of the unloading response to iVAC2L in the entire study population regardless of responder status. Overall, the most frequently observed unloading pattern produced by iVAC2L occurred during systole. Although less frequently, the device can also lead to left ventricular unloading in diastole. (C) iVAC2L significantly increased the MAP in the ascending aorta.

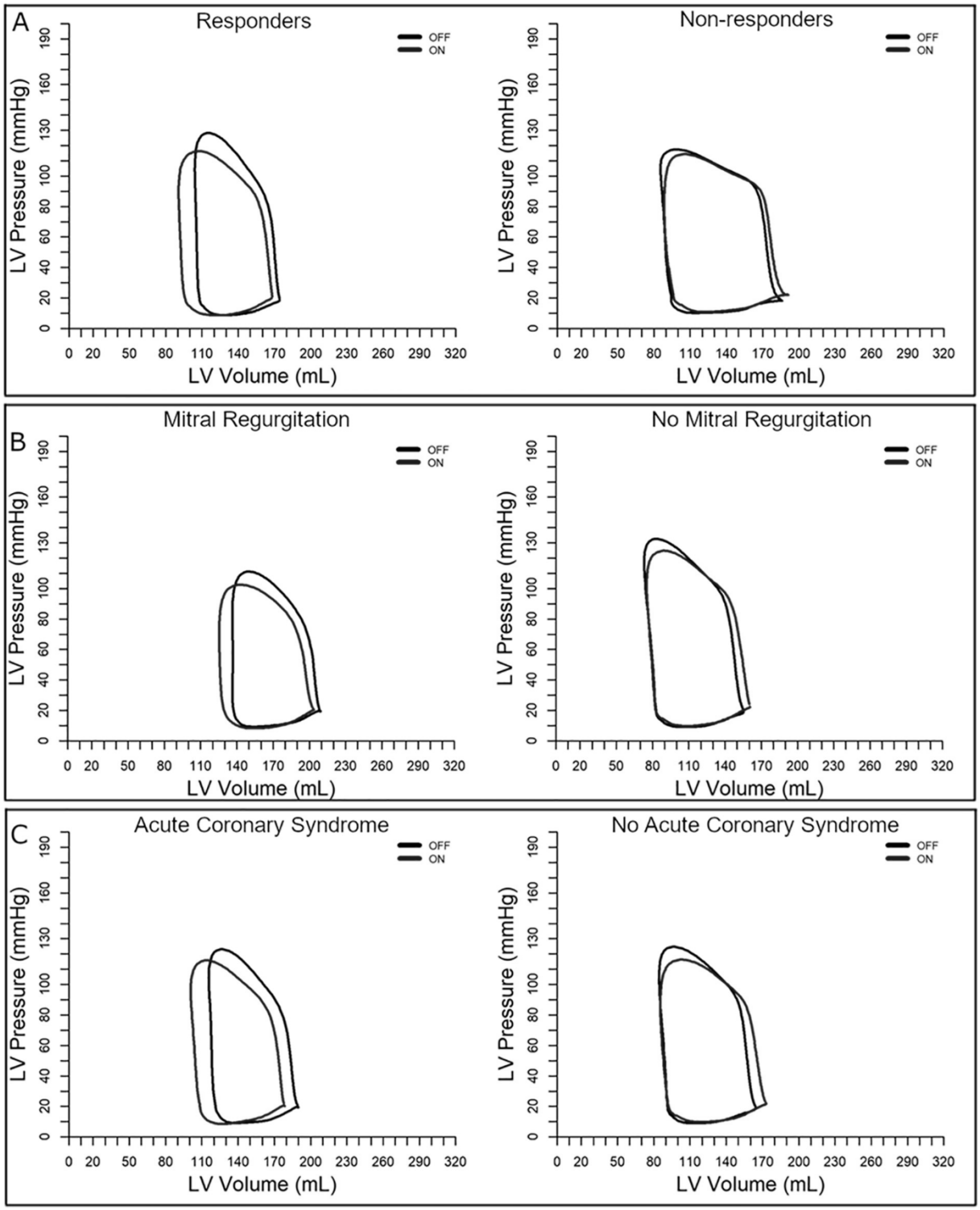

Fig. 4. Representative left ventricular PV loops invasively recorded with iVAC ON and OFF. (A) Left ventricular unloading is demonstrated in the group of responders through left and downward shift of the PV loop in ON state (blue) relative to OFF. The magnitude of the shift is greater at the end of the ejection phase (upper left corner of the PV loop) and at the isovolumetric relaxation phase (left side of the PV loop), but can also occur at the isovolumetric contraction phase in early systole (right side of the PV loop). In contrast, PV loops from non-responders showed practically no change from baseline. The unloading pattern observed among responders was emulated by patients with moderate or severe MR (B, left side) and ACS (C, left side). In the absence of MR or ACS, post-activation PV loops behaved in a similar way as non-responders (A, B and C, right side). MR: Mitral Regurgitation. ACS: Acute Coronary Syndrome. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.3. Clinical outcomes

Clinical outcomes at 30 days are summarized in Table 6. Two patients died within 30 days. One patient suffered a major vascular complication and died from an uncorrectable retroperitoneal hemorrhage. A second patient developed refractory ventricular fibrillation during the PCI and required escalation to extracorporeal membrane oxygenation. After successful weaning the patient declined further

Table 6
Clinical outcomes 48 h and 30 days after the interventions. Frequencies are exposed as percent (count). MI: myocardial infarction. TIA: transient ischemic attack. CPR: cardio-pulmonary resuscitation. N/A: not available.

Clinical outcomes		
Outcomes	48 h	30 days
All-cause mortality	3.4 (1)	6.9 (2)
Stroke or TIA	6.9 (2)	10.3 (3)
MI	6.9 (2)	10.3 (3)
Repeat revascularization	0 (0)	0 (0)
Major bleeding	3.4 (1)	3.4 (1)
Major vascular complications	6.9 (2)	6.9 (2)
Acute renal dysfunction	6.9 (2)	6.9 (2)
Aortic regurgitation	0 (0)	0 (0)
Ventricular tachyarrhythmias	3.4 (1)	3.4 (1)
Need for CPR	3.4 (1)	3.4 (1)
Atrial fibrillation	17.2 (5)	17.2 (5)
Prolonged hypotension	3.4 (1)	N/A
Cardiogenic shock	3.4 (1)	N/A

treatment and died on day 23. Additionally, two patients with a prior history of cerebrovascular disease experienced an ischemic stroke in the first 48 h post-procedurally.

3.4. Laboratory data

Biochemistry parameters are shown in Table 7. Median NT-pro-BNP and cardiac biomarkers of myocardial injury were above the upper limit of normal at baseline, and increased after the PCI. Haptoglobin decreased and total bilirubin showed a minor increase. Lactate levels and serum creatinine remained unchanged.

4. Discussion

This is the first mechanistic study to assess LV unloading with iVAC2L using real-time invasive PV analysis in hemodynamically stable patients undergoing high-risk PCI. The main findings are: 1) pulsatile iVAC2L MCS provides demonstrable LV unloading and reductions in MVO_2 in the majority of patients. 2) Cardiac mechanics improved particularly in patients with significant MR or ACS who had higher filling pressures at baseline. 3) High-risk PCI with iVAC2L MCS was feasible in patients with advanced coronary artery disease at very-high to prohibitive operative risk.

The goal of using MCS with high-risk PCI is to achieve and maintain a hemodynamic state that optimizes myocardial oxygen demand/supply ratio, preserves end-organ perfusion and prevents pulmonary venous congestion. Importantly, patients in the PULSE trial were deemed hemodynamically stable with no overt clinical signs of cardiac decompensation or elevated cardiac filling pressures.

Table 7
Biochemical parameters. Continuous measurements are shown as mean ± SD or median (25th–75th percentile). NS: non-significant.

Biochemical parameters (n = 29)				
Variable	Pre-PCI	Post-PCI	24 h post-PCI	p
Troponin (ng/L)	66 ± 193	162 ± 159	170 ± 159	<0.01
CK (U/L)	79 (51–121)	85 (53–153)	121 (71–216)	0.18
CK-MB(μg/L)	3 (2–3)	5 (3–7)	6 (3−10)	<0.001
NT-proBNP (pmol/L)	362 (104–437)	282 (134–518)	336 (159–628)	<0.05
LDH(U/L)	249 (189–252)	234 (206–267)	230 (211–269)	NS
Ht (%)	40 (35–44)	35 (31–39)	33 (31–37)	<0.001
Hb (mmol/L)	8.4 (7.3–9.1)	7 (6.4–8.1)	7 (6.5–7.6)	<0.001
Haptoglobin (g/L)	2 (1.5–2.5)	1.6 (1.2–2)	1.3 (0.9–2)	<0.001
Thrombocytes (109/L)	254 (205–286)	234 (187–273)	222 (172–291)	<0.01
Total bilirubin (μmol/L)	9 (6–13)	9 (8–14)	10 (8–13)	0.06
Creatinine (μmol/L)	100 (83–130)	105 (80–118)	104 (87–140)	NS
Lactate (mmol/L)	1.4 (1.3–1.8)	1.5 (1.1–1.8)	1.8 (1.2–2.7)	NS

Invasive PV analysis with a conductance catheter allows monitoring beat-to-beat cardiac mechanics and energetics [4]. It has been previously applied to demonstrate immediate hemodynamic effects in interventions such as transcatheter atrial septum closure and mitral edge-to-edge repair [16]. We applied real-time invasive PV assessment to study the effects of the pulsatile iVAC2L MCS on LV performance in hemodynamically stable patients undergoing high-risk PCI and identified responders and non-responders. Activation of iVAC2L provided unloading in 82% of cases, particularly in patients with more than mild MR or ACS who were characterized by higher loading conditions at baseline and lower cardiac contractility. Non-responders tended to have lower cardiac load and better ventricular-arterial coupling at baseline.

Multiple factors determine the acute response to left ventricular assist devices. Device-related factors include peak flow rate and circuit configuration. Patient-related factors involve the cardiovascular substrate and hemodynamic filling status. Studies with IABP have demonstrated improved performance under increased systemic vascular resistance, increased right filling pressures and low RA:mPCWP ratio. In line with the present study, one report documented greater benefit in the presence of ischemic cardiomyopathy and severe MR [17]. The hemodynamic gain is inversely correlated with baseline contractility [5]. Other factors such as baroreflexes, use of medications, metabolic factors, and interventricular interactions can also play a role [1].

Systolic aspiration of LV blood by the iVAC2L typically reduced systolic LV pressure and the Ea, which is indicative of reduced overall afterload. Ventricular arterial coupling also improved (Ees/Ea) generating more efficient energy transfer from the LV to the arterial system. Furthermore the 8% PVA reduction reflected decreased MVO_2 and suggested that the observed increase in CO_{GLOBAL} and in aortic MAP occurred with no additional energetic costs to the innate myocardium. We did not find lower pulmonary and wedge pressures with iVAC2L support contrary to previous reports [11]. In the PULSE trial, it may have been challenging to demonstrate manifest LV unloading because 1) - patients were deemed clinically euvolemic at baseline and 2) administration of fluids, dye and pharmacological agents during the PCI may affect filling patterns (including pulmonary pressures) and change loading conditions beyond the MCS.

Collectively, hemodynamic effects with iVAC2L were more pronounced than what could be achieved with IABP in prior studies. IABP had only a modest impact in 15 heart failure patients undergoing cardiac surgery and in a subset of patients with advanced heart failure which was characterized by low right heart filling pressures and high systemic vascular resistance [5,6]. Our results suggest that iVAC2L generates more LV unloading by means of enhanced reductions in filling pressures and volumes.

With the device on, SW had a numerical increase and was proportionally higher relative to the PVA compared to off state. In contrast, SW reportedly decreased with the IABP [5,6]. Different from the IABP, iVAC2L actively displaces LV blood during systole in addition to the blood already displaced by the LV itself. While the IABP creates a pressure drop in the aorta, iVAC2L reduces pressure directly in the LV. This creates a larger SV, which leads to higher SW. Therefore, the increased SW reflects the combined mechanical energy generated by the LV and iVAC2L whereas in the IABP context SW is solely determined by the LV contribution while assisted by a transitorily enhanced gradient. The higher CO and aortic MAP with reductions in end-systolic pressures and volumes as well as afterload markers attest to the efficacy of iVAC2L as a cardiac pump.

Simulations on continuous flow MCS also suggested LV unloading with an increase in MAP and reduction in PVA [1] but invasive PV studies are lacking. There are at least theoretical advantages with maintained pulsatility over continuous flow. Pulsatility maintains physiological vascular responses and endothelial function at the level of systemic and microcirculation. It also provides more energy at a given mean arterial pressure than continuous flow. Its generation depends more on

energy gradients than on pressure gradients. Thus, under similar values of mean arterial pressure, pulsatile MCS can project higher amounts of energy over the arterial tree than continuous flow [18].

We reported 2 deaths and 3 strokes in a cohort of 29 patients. The clinical event rate reflected the overall patient profile and seemed somewhat higher than reported in the PROTECT II trial (30-day mortality 6.9% vs 7.6%) and the USPELLA Registry (2%) [2,7]. Despite having higher baseline Ejection Fraction (43 ± 14% vs 23.4 ± 6.3%), patients in PULSE were older with more extensive and complex coronary artery disease than in other studies (SYNTAX score 31 vs 29 in PROTECT II). In PROTECT II patients received on average 3 stents and rotational atherectomy was used in 9% and 14% of the IABP and Impella cohorts respectively as compared to 3.8 ± 1.6 stents per patient and rotational atherectomy in 19% in PULSE. Duration of MCS support in PULSE was shorter (1.1 h) than the Impella (2.9 h) and IABP cohorts of PROTECT II (8.4 h).

Careful access management is effective in preventing complications. In the PULSE trial, while iVAC2L has demonstrated to satisfactorily augment MAP while unloading the LV, bleeding and vascular complications were in line with previous data, with rates that were lower than in previous reports on Impella and IABP (Supplement, Figs. 3 and 4). Operators must implement routine use of pre-procedural planning with multi-slice CT scanning and ultrasound-guided punctures. Anticoagulation should be closely monitored with a target ACT ≥ 200 s and watch for clot formation in the blood chamber as well as in the catheter lumen after explantation [11]. In the PULSE trial, no macroscopic thrombus formation was noted on the iVAC2L upon retrieval. We did not see damage to the aortic valve and no clinically overt hemolysis.

4.1. Strengths and limitations

The multi-disciplinary heart team deemed all patients in the PULSE trial at very high to prohibitive operative risk. The risk profile may not be fully appreciated by conventional surgical risk scores. The study population was heterogeneous and complex. Improved identification of MCS responders may refine patient selection in the future.

PULSE was a pilot study with a limited sample size. Our findings were collected in elderly patients at high or prohibitive operative risk with extensive coronary artery disease and hence may not be generalizable. The sample size was too small to elaborate on clinical outcomes, and it was not possible to perform long-term follow up. Nevertheless, the clinical event rate was in line with the patient risk profile and is put in perspective of other MCS studies in Supplemental Fig. 3.

PV assessment was performed with iVAC2L ON and OFF. However, loading conditions changed throughout procedures because fluid administration, dye and sedatives were administered per operator's discretion. Fluids and sedatives may alter cardiac mechanics and have affected our measurements. We tried to minimize these “bystander” effects by waiting for steady state conditions prior to study related hemodynamic recordings and by making analyses ON and OFF MCS support before PCI (41% of responders and 80% of non-responders) and after PCI (59% of Responders and 20% of Non-responders). Furthermore, the effect of the PCI and the presence of individuals with preserved LV function may have confounded the effect of the device. Finally, we used single-beat algorithms to infer PV relations as opposed to preload modulation maneuvers such as Inferior vena-cava balloon occlusion.

Further research should address the need for translating hemodynamic effects of iVAC2L MCS into clinical outcomes in different populations, as well as comparing the results with other devices.

5. Conclusion

Pulsatile iVAC2L MCS in patients with advanced coronary artery disease at high to prohibitive operative risk resulted in LV unloading and reduced myocardial oxygen consumption particularly in patients with ACS or significant MR with higher filling pressures at baseline.

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CRediT authorship contribution statement

Marcelo Barros Bastos, MD M.H.Sc. (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Investigation: Lead; Methodology: Lead; Project administration: Lead; Software: Lead; Validation: Lead; Visualization: Lead; Writing – original draft: Lead; Writing – review & editing: Lead).

Hannah Mcconkey (Data curation: Equal; Investigation: Supporting; Project administration: Equal; Writing – review & editing: Equal).

Oren Malkin (Funding acquisition: Supporting; Project administration: Supporting; Resources: Supporting).

Corstiaan Den Uil (Writing – review & editing: Supporting).

Joost Daemen (Investigation: Equal; Project administration: Supporting; Writing – review & editing: Supporting).

Tiffany Patterson (Project administration: Supporting; Writing – review & editing: Supporting).

Quinten Wolff (Writing – review & editing: Supporting).

Isabella Kardys (Formal analysis: Supporting; Methodology: Supporting; Writing – review & editing: Supporting).

Jan Schreuder (Data curation: Supporting; Methodology: Equal; Supervision: Supporting; Writing – original draft: Supporting; Writing – review & editing: Supporting).

Mattie Lenzen (Project administration: Supporting; Writing – review & editing: Supporting).

Felix Zijlstra (Project administration: Supporting; Writing – review & editing: Supporting).

Simon Redwood (Investigation: Equal; Project administration: Supporting; Writing – review & editing: Supporting).

Nicolas Van Mieghem (Conceptualization: Lead; Funding acquisition: Lead; Investigation: Lead; Methodology: Equal; Project administration: Lead; Resources: Lead; Supervision: Lead; Writing – review & editing: Equal).

Declaration of competing interest

Dr Van Mieghem is advisor and received research grant support from PulseCath B.V. He received institutional research grant support from Abbott Vascular, Boston Scientific, Medtronic, Edwards Lifesciences, Daiichi Sankyo.

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Dr Schreuder is an employee of CD Leycom.

Mr Malkin is an employee of PulseCath BV.

The other authors report no conflicts.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2022.03.013.

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