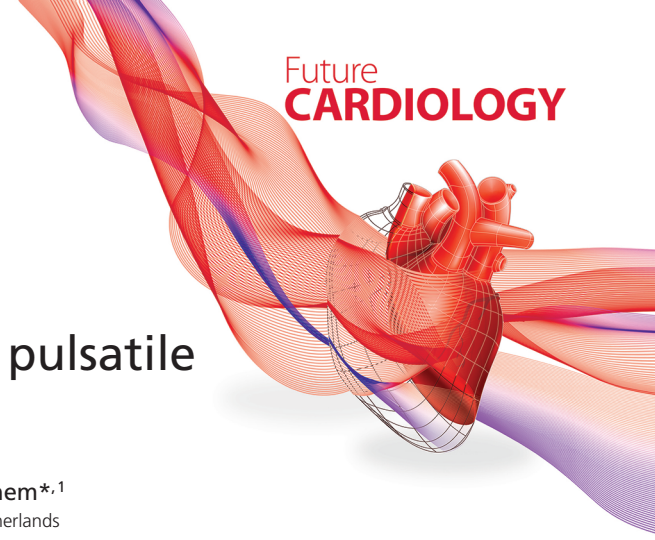
Device Evaluation

Future CARDIOLOGY



PulseCath iVAC2L: next-generation pulsatile mechanical circulatory support

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Contemporary state of the art percutaneous coronary intervention techniques offer treatment strategies and solutions to an increasing number of patients with heart failure and complex coronary artery disease. Percutaneous mechanical circulatory support is intended to alleviate the mechanical and energetic workload imposed to a failing ventricle by reducing left ventricle pressures and volumes and potentially also increasing coronary blood flow. The PulseCath iVAC2L is a transaortic left ventricular assist device that applies a pneumatic driving system to produce pulsatile forward flow. Herein, the essential aspects regarding iVAC2L are discussed with focus on its mechanisms of action and the available clinical experience.

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Keywords: coronary disease • heart failure • high-risk percutaneous coronary interventions • mechanical circulatory support • PulseCath iVAC2L

Contemporary state of the art percutaneous coronary intervention (PCI) techniques offer treatment strategies and solutions to an increasing number of patients with heart failure (HF) and complex coronary artery disease. Patients deferred from surgery due to left ventricle (LV) dysfunction, complex anatomies and significant comorbidities may be eligible for percutaneous therapeutics [1,2]. However, PCI in such conditions remains a procedure at high risk for major complications and even death.

Percutaneous mechanical circulatory support (MCS) is intended to alleviate the mechanical and energetic workload imposed to the failing ventricle by reducing LV pressures and volumes and potentially also increasing coronary blood flow (CBF) [3,4]. MCS may provide a back-up against the spiral of hemodynamical deterioration that occasionally occurs during coronary manipulation and instrumentation. Patients with advanced HF and significant compromise of the LV systolic function may be most vulnerable and thus benefit most from MCS [5].

The intra-aortic balloon pump (IABP) was introduced over five decades ago as a pulsatile MCS able to generate diastolic augmentation and increase diastolic CBF through early-diastole triggered balloon inflation in the descending aorta and unload the left ventricle through pre-systolic balloon deflation. Other percutaneous MCS rely on continuous flow to evacuate oxygenated blood from the left atrium or ventricle and deliver at some level in the aorta. Veno-arterial extracorporeal membrane oxygenation transfers de-oxygenated blood from the right atrium over an oxygenator to the iliac artery or abdominal aorta. Continuous flow systems may be prone to hemolysis [6].

The percutaneous PulseCath iVAC2L introduces a pulsatile alternative by evacuating blood from the left ventricle and expelling it into the ascending aorta in synchrony with the cardiac cycle [7,8]. This review describes the iVAC2L principles and its introduction into clinical practice.

Principles of action

Pumping mechanism & driving modes

The iVAC2L is a 17F 100 cm nitinol-wire-reinforced polyurethane by-directional flow catheter and features a rotating two-way valve positioned 6 cm proximally to the tip that pivots around two axes. The tip and the valve are composed of stainless steel and act as inlet and outlet, respectively. The catheter is connected to an extracorporeal pump that contains two chambers divided by a thin flexible membrane. One chamber accepts blood from the catheter; the other chamber is filled with helium and is connected to a genuine IABP console. The flexible membrane bounces back and forth in synchrony with the cardiac cycle (Figure 1A). Timing is similar to IABP operations.

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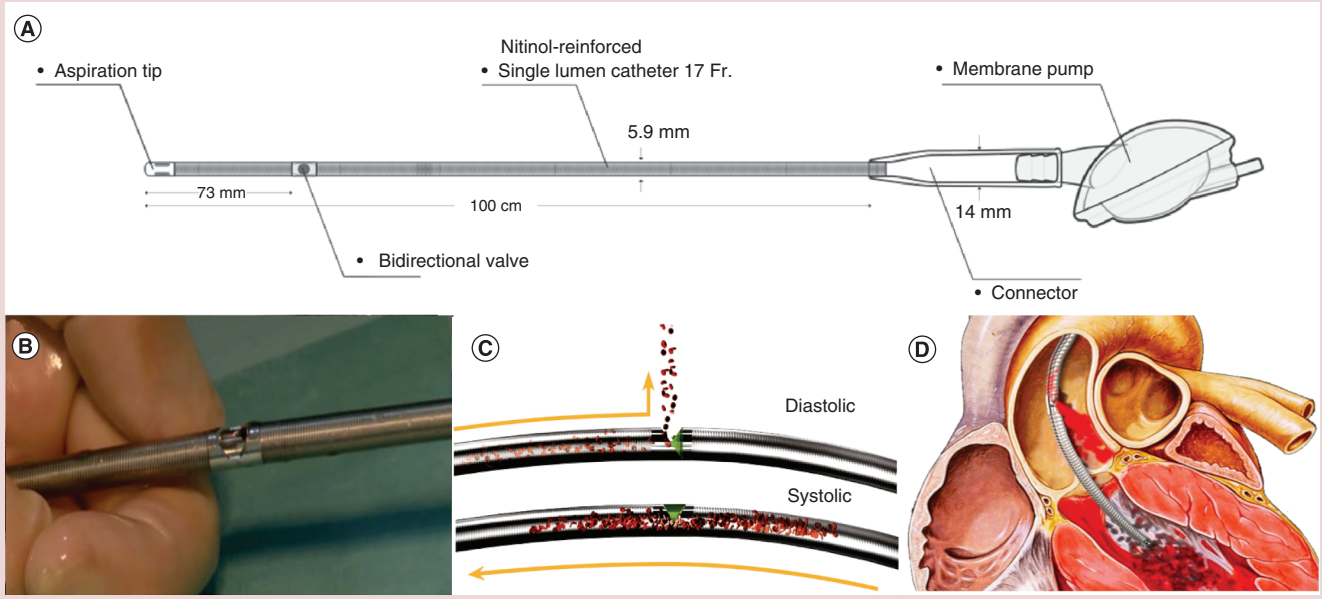

Figure 1. The PulseCath iVAC2L. (A) Design of PulseCath iVAC2L. The extracorporeal pneumatic dual chamber is located outside the patient and the intraventricular inlet is located at the tip, both 73 cm apart. **(B)** The two-way valve is located 6 cm from the catheter tip. **(C)** The two-way valve closes in systole (iVAC2L aspiration phase) and opens during diastole (iVAC2L ejection phase). **(D)** The ejection jet produced by iVAC2L is directed at an angle of 45° relative to the catheter, toward the coronary ostia. The aortic valve should be aligned with the point between the two orifices.
Figure 1A & D is reproduced from PulseCath BV and Figure 1B & C is adapted with permission from [26].

When the console detects end-systole, it inflates the gas chamber and propels the blood in the adjacent chamber back into the catheter. With the sudden increase in flow, the two-way valve (Figure 1B) changes its position driving blood to the aorta (ejective inflation). When systole begins, the inverse occurs as the gas chamber is deflated and LV blood is aspirated out of the left ventricle by the negative pressure in the blood chamber (aspirative deflation). End-systole may coincide with the dicrotic notch of the aortic pressure waveform (pressure triggering) or with the t-wave on the ECG (ECG triggering). End-diastole is preferably set at the start of pressure build-up or at the start of the QRS complex.

An assist ratio of 1:1 in synchronous mode (pump stroke:heart stroke) produces a flow of 1.5–1.8 l/min (Figure 2 & Table 1) [9,10]. In the absence of proper ECG or pressure triggering, the internal mode of the IABP console will trigger the system at a fixed rate (e.g., 70 per min) to deliver asynchronous support.

The internal mode can provide support during tachy (or bradi) arrhythmias [7,11].

Hemodynamic effects

The effects of the iVAC system are depicted in Table 1. Clinical human experience with iVAC2L is limited to high-risk PCI where it increases mean arterial pressure, cardiac index, cardiac power index and SVO_2 with concomitant reduction of mean pulmonary arterial pressure [9]. An invasive pressure volume study demonstrated a reduction in myocardial oxygen consumption as represented by smaller pressure–volume (PV) area, less wall stress, improvement in ventricular-arterial coupling and overall left shifting of the PV loop demonstrating unloading [10].

Pulsatile support by iVAC2L features a fundamentally different mechanistic concept as compared to continuous axial flow MCS. Continuous flow MCS will remove blood throughout the entire cardiac cycle from the LV and expel it into the ascending aorta uninterruptedly. This consistently elevates aortic impedance and systemic vascular resistance [12]. The arterial system stiffens compromising the Windkessel effect. As a consequence, increased backward propagation of reflected waves augments LV afterload [13]. These changes can be detrimental to ischemic myocardial tissue unable to cope with additional mechanical workload.

Conversely, pulsatile support offers intuitively a more effective way to propel blood forward and potentially spare ischemic myocardium [14]. Hemodynamic studies with counterpulsation support the hypothesis of benefit

Table 1. Current *in vivo* experience with the iVAC system in synchronic mode at 1:1 assist ratio (full support).

Year	n	Study	Indication	Device	Reported findings	Flow (l/min)	Vascular complications	Instability	Aortic valve lesion	Hemolysis	Death	Major complications	Ref.
1999	4	Mihaylov	Acute LV failure (calves)	PUCA (25F prototype) at 1:2 mode	– 12% ↓ MVO_2 – ↔ CO – ↑ CBF (diastolic) – ↑ SBP – ↑ DBP	2.94 ± 0.54 l/min	Not reported	Not reported	Not reported	Not reported	No	No	[7]
2006	7	Li	Acute LV failure (sheep)	PUCA II (21F prototype) in asynchronous mode	– ↔ LCT – ↑ MAP – ↑ SBP – ↑ DBP – ↔ CO – ↔ EDP – ↔ LAP – ↔ RVEDP – ↔ CVP – ↑SO_2 †	N/A	No	Yes (n = 1) (14%)	Not reported	Not reported	Yes (n = 1) Refractory VF under support	Refractory VF (n = 1)	[8]
2007	14	Mariani *et al.*	Left ventricular support during off-pump CABG	LV21 (iVAC3L)	– Provided LV assistance without any eventualities	2.4 ± 0.2 l/min	No	No	No	Mild	No	No	[25]
2008	1	Amico *et al.*	Left ventricular support during off-pump CABG	LV21 (iVAC3L)	– ↑ SBP, ↑ MAP – ↔ DBP – ↑ HR	N/A	No	No	No	Not reported	No	No	[33]
2011	1	Anastasiadis	ECMO venting in cardiogenic shock due to acute left ventricular failure	LV21 (iVAC3L)	– Transitory improvement but subsequent deterioration	N/A	No	Persistent cardiogenic shock while on support	No	Mild	Yes, from multiple organ failure	– Escalation of support – Death	[23]
2011	2	Arrigoni	Right ventricular support in cardiogenic shock + IABP on the LV	LV21 (iVAC3L)	– ↑ SBP, ↑ MAP – ↑ CO – Improvement in metabolic acidosis – Transient improvement followed by refractory deterioration	N/A	No	Yes, postoperatively (n = 1)	No	Not reported	Yes (1 individual)	– Persistent mediastinal bleeding (n = 1) – Death (n = 1)	[24]
2017	14	Den Uil	High-risk PCI	LV17 (iVAC2L)	– ↑ MAP – ↓ MPAP – ↑ CI – ↑ SVO_2 – ↑ CPI	1.4 l/min (IQR: 1.1–2.0)	Yes (n = 1)	Yes (n = 1)	No	No	No	– AKI and intubation (n = 1)	[9]
2017	1	Samol	High-risk PCI	LV17 (iVAC2L)	– Uneventful procedure	N/A	No	No	No	N/A	No	No	[34]
2018	1	Samol	High-risk PCI	LV17 (iVAC2L)	– Provided support during massive vasospasm causing bradycardia and hypotension with good outcome – ↑ MAP by 10 mmHg	N/A	No	Yes (n = 1)	N/A	N/A	No	No	[35]
2018	1	Bastos	High-risk PCI	LV17 (iVAC2L)	– ↓ Innate CO by 33% – ↓ TSR by 17% – ↓ WSes by 15% – ↓ PVA by 14% – Left and downward shifting of the PV loop	1.28 ± 0.04 l/min	No	No	No	No	No	No	[10]

† In the carotid artery.

AKI: Acute kidney injury; CABG: Coronary artery bypass graft; CBF: Coronary blood flow; CI: Cardiac index; CO: Cardiac output; CPI: Cardiac power index; DBP: Diastolic blood pressure; ECMO: Extracorporeal membrane oxygenation; EDP: End diastolic pressure; fCO: Total forward CO; HR: Heart rate; IABP: Intra-aortic balloon pump; LAP: Left atrial pressure; LV: Left ventricle; MAP: Mean arterial pressure; MPAP: Mean pulmonary artery pressure; MVO_2: Myocardial oxygen consumption; N/A: Not applicable; PCI: Percutaneous coronary intervention; PV: Pressure–volume; PVA: Pressure–volume area; RVEDP: Right ventricle EDP; SBP: Systolic blood pressure; TSR: Total systemic resistance; VF: Ventricular fibrillation.

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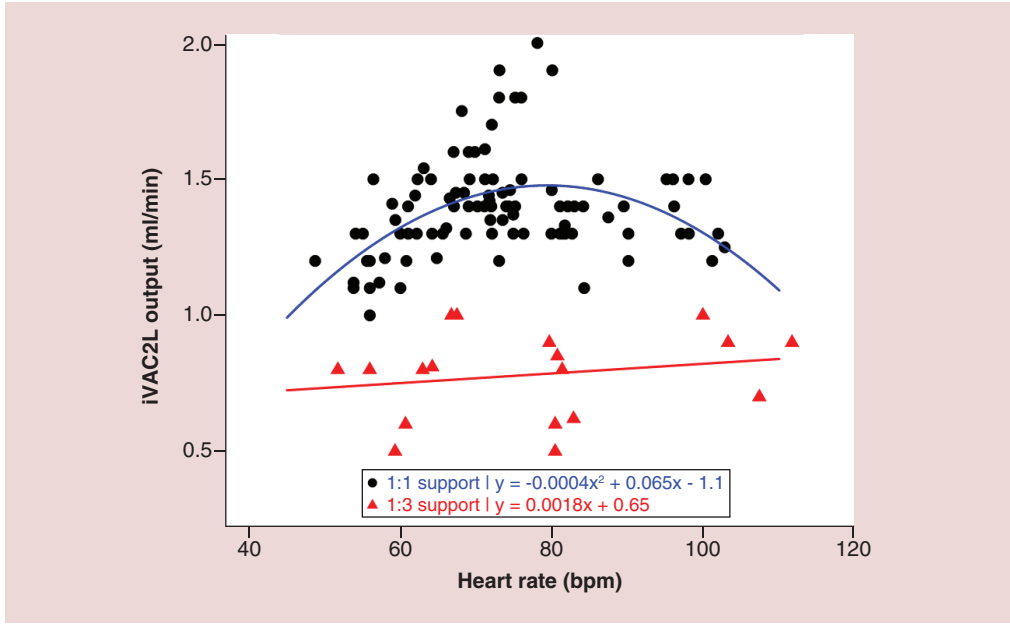

Figure 2. Scatterplot showing the relation between device output and heart rate at 1:1 assist ratio (black circles). Highest output is obtained between 70 and 90 bpm. Below 60 bpm, performance is limited by the low-heart rate itself and above 90 bpm the shortened filling times become the major limiting factor. 1:3 support (red triangles) results in lower output that however remains consistent at higher heart rates.

with iVAC2L by showing afterload reductions, LV unloading and improved intraventricular synchronicity [5,15]. iVAC2L operates in synchrony with the cardiac cycle and the exclusive expulsion of blood into the ascending aorta during diastole may preserve the innate systolic function.

In the arterial system, pulsatile flow restores cyclic strain in the wall of the peripheral vessels. This process involves a higher amount of energy applied to the vasculature than with continuous support [12]. As a consequence, continuous flow devices tend to transfer less energy to the cardiovascular system than pulsatile devices do while operating in the same conditions. This effect may sensitize baroceptors, reducing the sympathetic tone and promoting peripheral vasodilation, with less catecholaminergic stress, and reduced fluid overload. The net effect is improved blood flow to vital organs, as already demonstrated in the stomach, liver and renal cortex [16,17].

Importantly, iVAC2L – alike most continuous MCS – provides partial support and does not necessarily increase total forward cardiac output (fCO) when applied in healthy or compensated states [18]. Partial LV assistance gradually downregulates the autonomic stimulus to the innate cardiac function resulting in only minor changes to the total fCO [4,9,18,19]. Alternatively, in acute decompensated HF and in cardiogenic shock when pump function is considerably affected by insufficient blood supply, impaired myocardial contractility or mechanical factors, small additions to the deficient innate CO are likely to increase total fCO [7,11].

Invasive PV analysis corroborates this paradigm: cardiac cycles that are assisted by iVAC show PV loops progressively shifting to the left and occasionally downward with time (Figure 3). The width of the PV loop, indicating SV, is expected to shrink as iVAC2L, working as a parallel pump, provides part of the total SV. The PV area tends to decrease [10,20]. The overall shape of the PV loop may show variations depending on device output, anatomical features, LV systolic function, valvular disease and conduction disturbances. The effective arterial elastance (E_a) is likely to decrease due to reduced afterload, which may improve ventricular–arterial coupling. This new configuration facilitates blood ejection into the arterial system and reduces wall stress (Figure 4) [10].

The hemodynamic effects are proportional to the device output. Pressure levels and gradients across the catheter play a major role in determining output [21]. Consequently, situations when the afterload is abnormally high such as in hypertensive states can reduce performance [22]. Conversely, low preload may compromise iVAC2L performance and precipitate suction.

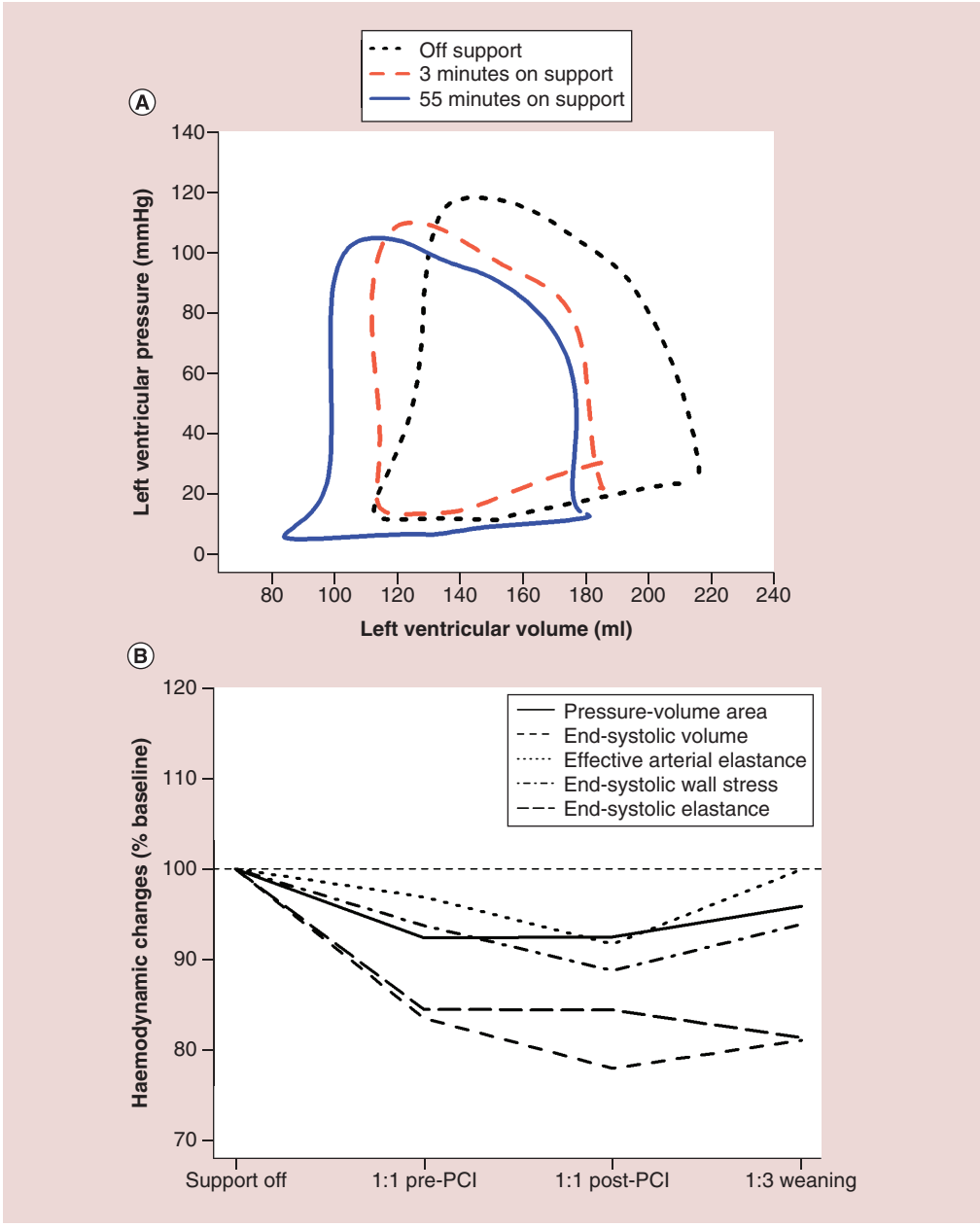

Figure 3. Left ventricular pressure-volume analysis during a high-risk percutaneous coronary intervention showing the effects of iVAC2L. (A) Pressure–volume loops from a patient with ischemic cardiomyopathy and ejection fraction of 40%. Pressure–volume loops pre-support, immediately after activation and 55 min postactivation show progressive shifting of the PV loops to the left and downward, denoting left ventricle unloading. **(B)** Activation results in reduction in the pressure–volume area, which is a surrogate for myocardial oxygen consumption. Left ventricular volume and wall stress fall at end-systole, and contractility (end-systolic elastance) also decrease.

Clinical efficacy

iVAC3L and iVAC2L obtained Conformité Européenne (CE) mark for LV circulatory support up to 24 h in 2009 and 2014, respectively. iVAC2L is currently approved in 28 countries and under review in 5 others (Figure 5). It has been used in nearly 200 patients worldwide. The vast majority of iVAC2L-supported cases were high-risk PCI. A small number of cases pertain venting purposes in combination with extracorporeal membrane oxygenation and LV support postcardiotomy [23]. Case reports documented use of iVAC3L for right ventricular (RV) support via

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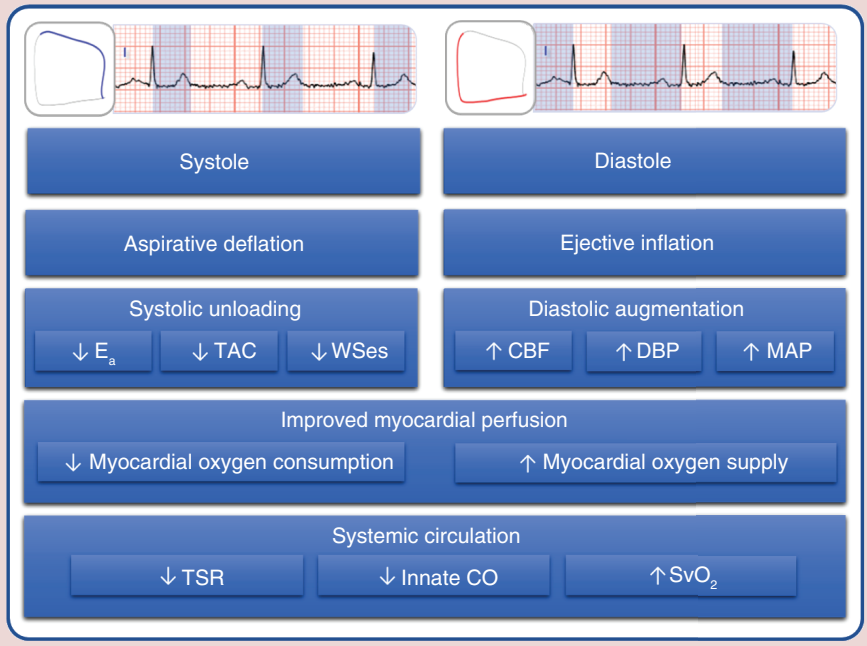


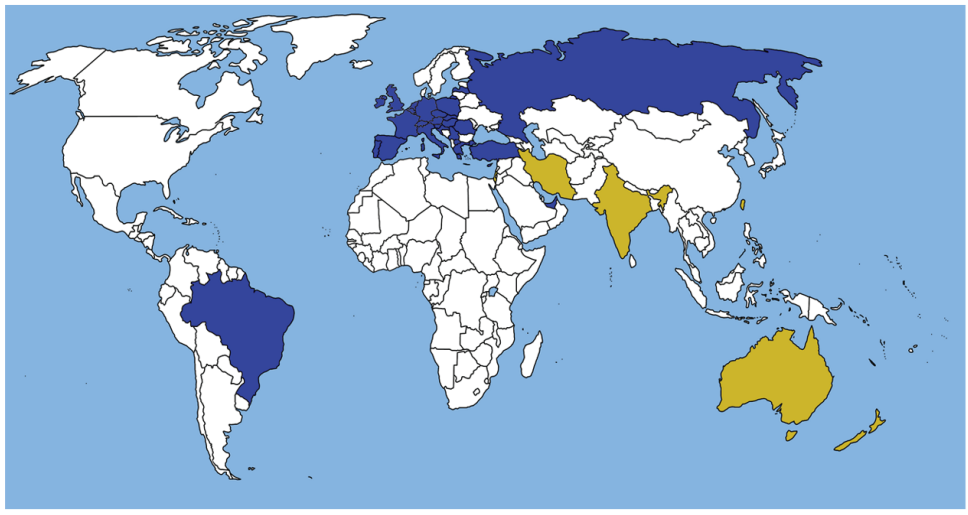
Figure 4. Summary of the hemodynamic effects of iVAC2L. In systole, aspirative deflation is most commonly set to occur between the QRS complex and the end of the T wave in the electrocardiogram. Left ventricular blood is aspirated and systolic unloading reduces the E_a, TAC and end-systolic WSes. Myocardial oxygen consumption decreases as a consequence of reduced afterload. In diastole, iVAC2L ejects the volume of blood stored in the extracorporeal dual chamber back into the aorta (ejective inflation) increasing the aortic DBP and the MAP. CBF increases in diastole and improves myocardial oxygen supply. The cardiac output of the native heart (innate CO) decreases as iVAC2L assumes part of the systolic workload. The optimized hemodynamic setting induces improvements in TSR and in the SvO_2.
CBF: Coronary blood flow; CO: Cardiac output; DBP: Diastolic blood pressure; E_a: Effective arterial elastance; MAP: Mean arterial pressure; SvO_2: Mixed venous oxygen saturation; TAC: Total arterial compliance; TSR: Total systemic resistance; WSes: Wall stress.

surgical access to the pulmonary artery, for example, via a supraclavicular incision with the catheter tip seated in the RV [24].

The first-generation 21F iVAC3L MCS which requires surgical cut-down and axillary/subclavian artery access, was initially tested during and after coronary bypass surgery. Mariani *et al.* reported successful use of iVAC3L in a series of 14 patients with poor LV function undergoing off-pump coronary artery bypass graft, with mean age of 69 years. The iVAC3L produced a flow ranging from 2.2 to 2.8 l/min. There were no major adverse cardiovascular/cerebral events. One patient experienced clinically significant hemolysis [25].

The experience in high-risk PCI is exclusively conducted with iVAC2L. Two studies have tested the use of this device in elective high-risk PCI, and one trial is ongoing. The Erasmus Medical Center has been actively testing the performance of iVAC2L in high-risk PCI [9,10,26]. In 2015, den Uil *et al.* prospectively enrolled 14 patients with LV failure undergoing high-risk PCIs supported by iVAC2L. iVAC2L improved diastolic arterial pressure, mean arterial pressure and cardiac output, with an angiographic PCI success of 100%. There was one major access complication related to the 19F access sheath [9].

A recent retrospective propensity matched analysis compared outcomes of elective high-risk PCI in 198 patients with complex coronary disease and LVEF <45% including 69 patients under next-generation MCS (percutaneous heart pump [n = 25], Impella CP [n = 18] or iVAC2L [n = 26]). Survival at 30 days in MCS protected PCI was superior to unprotected PCI despite a lower EF and more complex coronary artery disease per SYNTAX score at baseline. Outcome was similar for different MCS technologies [27]. This study corroborated earlier notion that MCS might catalyse more comprehensive PCI execution with more lesions treated, less incomplete revascularization and application of more complex PCI techniques like rotational atherectomy and bifurcation stenting [28–30].



Currently approved in:

The Netherlands	Italy	Romania	Macedonia
Ireland	Spain	Slovakia	Turkey
United Kingdom	Portugal	Slovenia	Greece
Belgium	Brazil	Russia	Latvia
France	Austria	Croatia	Poland
Germany	Hungary	Serbia	Switzerland
Czech Republic	Turkey	Hong Kong	UAE

Awaiting approval:

India
Australia
New Zealand
Iran
Taiwan
Israel

Figure 5. Regulatory situation of iVAC2L. iVAC2L is Conformité Européenne-marked in Europe and is currently available in 28 countries (blue). In other five countries, it awaits approval (yellow).

The PULSE trial (ClinicalTrials.gov: NCT03200990) is an international multi-center mechanistic study currently enrolling patients who undergo high-risk PCI with iVAC2L MCS simultaneously with invasive pressure volume analysis. The aim of the trial is to identify a particular pattern of unloading with iVAC2L and evaluate how this compares with the unloading pattern of the axial flow Impella CP.

Technique

Like all large bore MCS, iVAC2L requires meticulous access site management. The current 17F design demands a 19F sheath, but a 16F device is on the way. We recommend proper preprocedural access planning by means of multi-slice CT scanning if time and kidney function permits. Ultrasound guided access technique further secures arteriotomy in the common femoral artery avoiding inappropriate arterial entry too high in the external iliac artery (at risk for retroperitoneal bleeding) or too low in the superficial femoral artery. Real time vessel entry also allows visualizing and avoiding calcified and diseased segments (Figure 6). LV access is obtained after aortic valve crossing with a pigtail catheter. We recommend measuring the LV end diastolic pressure (LVEDP) to avoid hypovolemia/underfilling and aim for a minimum LVEDP of 12 mmHg. If needed we would administer fluid to obtain proper filling before iVAC2L insertion. A long preshaped or manually shaped stiff 0.035′ guidewire (e.g., Safari, Amplatz Superstiff wire) is then seated in the LV apex to help advance the iVAC2L. Eventually the iVAC2L tip should be located at the mid-ventricular level beyond the LV outflow tract and avoiding the LV free wall or apex. After air free connection of the catheter with the two-chamber pump on one end and with the IABP console on the other, the IABP console is put on a 1:1 support mode. Weaning before removal of iVAC2L implies turning down assist mode to 1:3 and eventually switching off the IABP console. Upon removal of the iVAC2L we rely on either suture or plug based arteriotomy closure [31].

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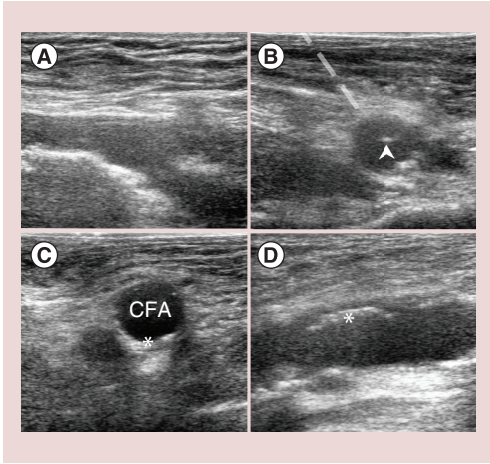

Figure 6. Ultrasound guided large bore access. (A) Bifurcation of the common femoral artery into the superficial and deep femoral artery. **(B)** Needle insertion. Dashed line: needle pathway. Arrow: tip of the needle inside the vessel. **(C)** Sagittal view of the common femoral artery and common femoral vein. The asterisk marks calcification of the posterior arterial wall. **(D)** Longitudinal view of the common femoral artery. Asterisk marks calcification of the arterial wall.
CFA: Common femoral artery.

Box 1. Major contra-indications to iVAC2L.

- Mural thrombus in the left ventricle
- Presence of a mechanical aortic valve
- Aortic valve stenosis/calcification (equivalent to an orifice area of 0.6 cm^2 or less)
- Moderate-to-severe aortic insufficiency (echocardiographic assessment graded as $\geq +2$)
- Severe peripheral arterial disease precluding placement of the iVAC2L
- Femoral artery diameter <6.0 mm
- Significant biventricular or right heart failure
- Combined cardiorespiratory failure
- Presence of an atrial or ventricular septal defect (including postinfarct VSD)
- Left ventricular rupture
- Cardiac tamponade
- Recent major bleeding event
- Recent stroke

VSD: Ventricular septal defect.

Safety & performance

The iVAC2L can generate an output of up to 2.0 l/min, with a displaced volume per beat of up to 26 ml [9]. The optimal heart rate for iVAC2L support is 70–90 bpm. Frank bradycardia (<60 bpm) or tachycardia (>120 bpm) and manifest rhythm irregularities (ectopic beats and uncontrolled irregular atrial fibrillation) may compromise proper blood displacement. Internal mode operations with the IABP console at a rate of 80 bpm may (partially) overcome heart rate related issues. Suction phenomena can hamper proper blood displacement and may result from relative underfilling (LVEDP < 12 mmHg) or device malpositioning (e.g., contact between device tip and endomyocardium) [9]. Target activated clotting time is >200 s. Clot formation may partially or totally obstruct flow thus impede device performance or provoke cerebro–embolic events. Therefore, the blood chamber and the flexible membrane should be inspected regularly.

In the presence of severe RV dysfunction, LV unloading may precipitate RV failure [32]. Hemolysis is rare with iVAC2L. A full list of contra-indications can be seen in Box 1.

Future perspective

A new version of the iVAC system will feature an improved 16F profile to accommodate smaller ilio-femoral anatomies for its insertion and reduce access related complications. This new version would not require a separate (larger) sheath but follows a 'sheathless' insertion.

Conclusion

The iVAC2L is a completely percutaneous mechanical circulatory device that offers pulsatile unloading and improved myocardial mechanics. Growing experience and continued device iterations should further establish its use in contemporary clinical practice.

Executive summary

Background

- Presence of high-risk percutaneous coronary intervention is increasing in clinical practice. Percutaneous mechanical circulatory support may be useful to reduce rates of complications in this subset.

Principles of action

- PulseCath iVAC2L is a percutaneous mechanical circulatory support that is driven by a conventional intra-aortic balloon pump console and combines forward flow with diastolic augmentation.
- The iVAC2L consists of a 17F 100 cm length bidirectional flow catheter that is connected to an extracorporeal dual chamber pump containing a flexible membrane.
- Left ventricle blood is aspirated to the blood chamber during systole and ejected in the ascending aorta during diastole producing an output of 1.5–2.0 l/min.

Clinical efficacy

- When activated, iVAC2L augments mean arterial pressure, enhances cardiac output and oxygen delivery and reduces pulmonary vascular pressures. Current findings suggest that iVAC2L unloads the left ventricle, reduces the afterload and improves myocardial oxygen consumption.

Technique

- Introduced percutaneously through the common femoral artery. Positioned across the aortic valve with its inlet (tip) in the left ventricle and its outlet (two-way valve) in the ascending aorta.

Author contributions

MB Bastos contributed to Figures 1–5, manuscript elaboration and review, and article submission. MP van Wiechen contributed to Figure 6 and manuscript review. NM Van Mieghem contributed to the manuscript supervision and review.

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Financial & competing interests disclosure

MB Bastos works for PulseCath BV and is Research Fellow at the ThoraxCentrum. MP Van Wiechen has nothing to disclose. NM Van Mieghem is clinical advisor for PulseCath BV. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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