PART 4

PVAD PATIENT SELECTION AND OPTIMAL TIMING OF SUPPORT
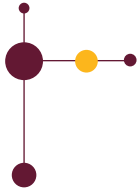
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Key messages

- MCS are expensive devices and have to be used economically.

- Most studies with general MCS application did not demonstrate superiority to conservative treatment, hence they should ideally be used in selected patient cohorts.

- Patients selected for MCS should be sick enough to allow pVAD to translate haemodynamic improvement into clinical outcome.

- If patients are candidates for pVAD, haemodynamic compromise should not yet have initiated end-organ failure which might limit survival irrespective of haemodynamic improvement.

- pVAD should be applied as rapidly as possible in refractory cardiogenic shock to limit the extent of ongoing end-organ damage.

- Previous resuscitation by itself is not an exclusion criterion for pVAD.

Executive summary

pVADs are expensive devices and have to be used economically. Most studies with general circulatory support did not demonstrate superiority to conservative treatment, hence they should ideally be used in selected patient cohorts. Patients selected for circulatory support should be sick enough to allow pVAD to translate haemodynamic improvement into clinical outcome. Haemodynamic alterations in the specific patient and haemodynamic profiles of the intended pVAD determine the choice of the most appropriate device.

When patients are candidates for pVAD, haemodynamic compromise should not yet have initiated end-organ failure which might limit survival irrespective of haemodynamic improvement. pVAD should be applied as rapidly as possible in refractory cardiogenic shock to limit the extent of ongoing end-organ damage and their implantation prior to PCI in AMI-CS has retrospectively been associated with better outcome.

It is pivotal to identify both key elements of cardiogenic shock prior to patient selection for potential benefit by pVAD: patients should have decreased cardiac output and organ hypoperfusion. Assessing cardiac output acutely requires invasive monitoring, which often is too time consuming when immediate revascularization is required in acute myocardial infarction. Combining clinical judgment, arterial lactate as a surrogate for systemic hypoperfusion and rapid trans-thoracic echocardiography focusing on left-ventricular function, mechanical complications and stroke volume rapidly identifies hemodynamically compromised patients suitable for pVAD.

Axial flow pumps such as the Impella® family of devices actively unload the LV. Therefore, an adequate right heart function is required to maintain LV preload. Hence, these devices are ideally suited for AMI-CS, when patients might rapidly deteriorate in the catheterisation laboratory due to large LV-infarction, as they can be placed within 10 minutes by percutaneous access. While it is appealing to perform coronary interventions on haemodynamic support, the issue of support-first as compared to PCI-first strategies has not been resolved yet. Nevertheless, registry data suggest a potential mortality benefit when axial flow pumps are implanted prior to PCI in infarct-related cardiogenic shock. On the contrary, if patients are in bi-ventricular failure or persistent cardiac arrest more complex settings such as V-A ECMO are required.

In non-ischaemic scenarios, speed to successful implantation is not as critical as durability of support and devices are preferred that allow for extended support over weeks, ideally allowing the patient to be mobilized.

Overall, there appears to be no single technique that suits all forms of haemodynamic impairment and in centers caring for hemodynamically compromised patients, both axial flow pumps and V-A ECMO should be available.
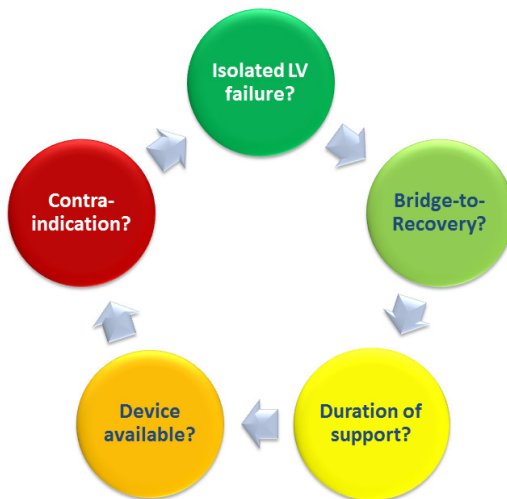
1 - PATIENT SELECTION, DEVICE SELECTION

Prior to device implantation, several key-issues have to be addressed: complexity of failure, potential for recovery, intended duration of support, device availability, and potential contraindications to the selected or desired support modality *(Figure 1)*.

Figure 1 - Key issues prior to pVAD selection
pVAD selection is guided by patient-, disease-, and health care system-dependent factors.

The first influencer in patient selection is the kind of underlying disease: bi-ventricular failure or additive hypo-oxygenation favour the use of VA-ECMO, urgent left-ventricular failure with distended and overloaded LVs favour the rapidly deployable axial flow pumps, and acute deterioration of pre-terminal chronic heart failure favours options allowing for longer bridging scenarios such as Impella 5.x or TandemHeart.

The second determinant obviously is local availability of certain systems.

Third, patients should have a potential to recover or to be bridged to a destination therapy. Furthermore, the location of implantation influences device selection, e.g., whether pVAD needs to be implanted while the patient is resuscitated or whether the patient requires pVAD implantation in the emergency room or the intensive care unit and whether the patient can be transferred to a catheterisation laboratory.

Another major contributor in the selection process is whether a certain device might not be helpful in a specific condition. The inherited limitation of IABP is the need for intrinsic contractility as the main effect is assumed to be due to improved coronary perfusion in diastole. Therefore, patients in scenarios, in which contractility is lost such as during prolonged PCI in AMI-CS, will not be adequately supported; a point that might have influenced the negative trial results in that entity. The major limitation of axial flow pumps is their dependence on adequate LV filling, which requires sufficient RV function to provide enough volume for LV unloading and indicates why these devices by themselves are not ideally suited to treat bi-ventricular failure or patients in persisting cardiac arrest.

1.1 - Device selection

If, in an ideal world, all pVADs were available for treatment, a step-wise approach to device selection is suggested *(Figure 2)*.
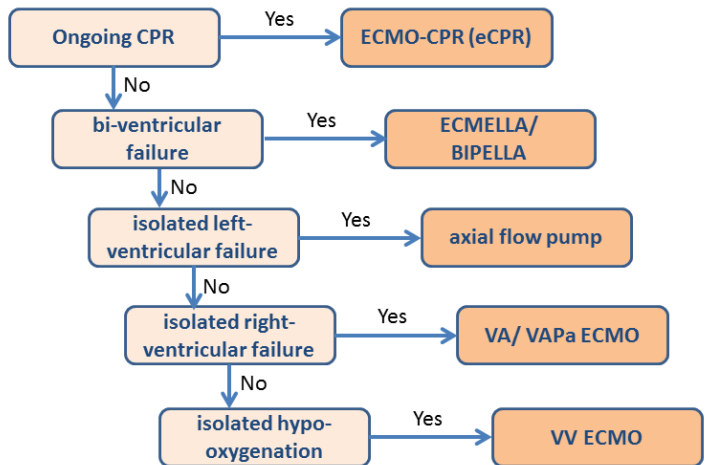
Figure 2 - pVAD selection

pVAD selection is primarily defined by the underlying disease condition, e.g. the presence of left-, right-, or bi-ventricular failure.

If the patient is under resuscitation in the emergency room, VA-ECMO bypassing both heart and lung and restoring circulation and oxygenation without need for fluoroscopy will be the primary choice.

Similarly, if there is evident bi-ventricular failure, bi-ventricular support is mandated. There are several possibilities for combined right- and left-ventricular support: VA-ECMO will bypass both ventricles and often further compromise and distend the LV mandating additional use of an axial flow pump (ECMELLA), direct surgical venting or a percutaneously placed pig-tail catheter connected to the venous ECMO circuit to actively unload the LV, or using one left-ventricular flow pump together with a dedicated RV flow pump (Impella RP) as BIPELLA. While the antegrade bi-ventricular flow pump concept is appealing, there are only a few centres having it available and being accommodated to it, therefore, most patients in such a situation will be treated rather by an ECMELLA approach. Importantly, bi-ventricular failure often is not evident from the beginning and might only unmask after unloading a distended LV with an axial flow pump. It is not too unusual to have about 3.4 L/min support on an axial flow pump in AMI-CS initially followed by a steady decline to only 0.5 L/min or less. This is highly suggestive of unmasking RV failure and should immediately prompt an echocardiography to verify or exclude RV failure. In general, any unforeseen change in haemodynamic support with any device should prompt an immediate re-evaluation of the patient and the support setting.

Isolated LV-failure, however, is the most prevalent form in AMI-CS, myocarditis, tako-tsu-bo-syndrome, or other acutely deteriorating cardiomyopathies and is featured by impaired LV contractility, LV distension and increased LVEDP. In those scenarios, the patient often is already in the catheterisation laboratory or has to be moved there anyway. For such over-load scenarios, active unloading by an axial flow pump is intuitive *(Figure 6)*.

Figure 3 - The concept of LV unloading

Most primary LV failures result in distension of the left ventricle and raised LVEDP described as LV overload. LV unloading by axial flow pumps appears as an intuitive therapeutic option in such a scenario and contributes to rapid reduction of wall tension and improvement of myocardial perfusion.

LV distended
LVEDP ↑

LV unloaded
LVEDP ↓
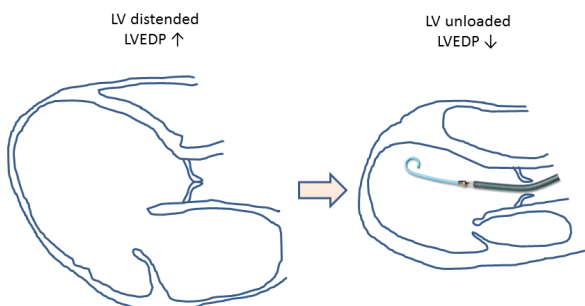
Treatment of isolated RV-failure
is described in the previous chapter by Bergmark & Morrow, and optimising ECMO cannula-tion to maintain blood flow and intrinsic LV function is sometimes challenging. LV overload often impairs recovery. Interventional strategies providing active LV unloading seem to be

intuitive, but study data are lacking. In small clinical observations and experimental studies, LV unloading by axial flow pumps has contributed to disease-modifying gene expression and cytokine release. The distinct pros and cons for the individual devices are listed in *Table 1*.

Table 1 - Pro's and con's for specific pVADs in LV failure

|	IABP	AFP	Tandem Heart	vaECMO	ECMELLA
Coronaries	Perfusion (↑)	Perfusion ↑↑	Perfusion (↑)	Perfusion (↑)	Perfusion ↑↑
LVEDP;LVEDV	(↓)	↓↓	↓↓	↑	↓↓
LV afterload	(↓)	≈	(↑)	↑↑	↑

1.2 - LV Unloading

In many scenarios, LV unloading using axial flow pumps may improve patient haemodynamics in parallel with rapid catecholamine weaning and limit vasopressor-facilitated end-organ ischemia, prevent haemo-metabolic shock and reduce morbidity and mortality in cardiogenic shock. However, when haemodynamics and lactate clearance do not improve properly, escalation to stronger than femoral placed pVADs might be necessary (switching to surgically placed Impella 5.x or escalation to ECMELLA).

The haemodynamic changes caused by different pVADs help to understand why a dedicated device should be selected in a specific situation *(Figure 4)*. The majority of low-output failures are primary LV failures. Those are haemodynamically characterized mostly by LV overload with increased LVEDP. Unloading by axial flow pumps counteracts the pathophysiological process, lowers LVEDP and improves systemic haemoperfusion. VA-ECMO, on the other side, increases LV afterload and further compromises the LV. Systolic pressures increase, but do so as a consequence of increased diastolic pressures and wall tension. Simplified, axial flow pumps have certain advantages in primary LV failure, while VA-ECMO has advantages in primary RV, biventricular and non-ejecting cardiac failures.

Figure 4 - Haemodynamic consequences of LV unloading

ESPVR and EDPVR define the shape of pressure-volume loops of the LV during a physiological cardiac cycle (green). If contractility declines in shock, ESPVR is lowered and the pressure-volume loop moves rightwards indicating higher end-diastolic filling (red). Axial flow pumps (right top, blue) unload the LV by direct aspiration of arterial blood from the LV, which is ejected by the pump several centimeters above the aortic valve into systemic circulation. This is accompanied by reduced LVEDP and increased contractility. VA-ECMO (right bottom, black) unload the RV but increase afterload to the LV, thereby raising LVEDP and reducing LV stroke volume.
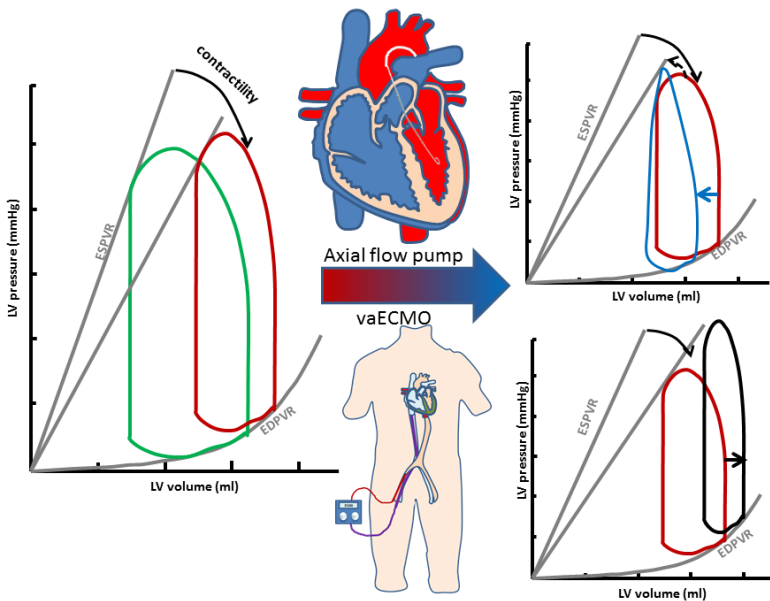

1.2 - LV Unloading

Cardiogenic shock is common after resuscitation from out-of-hospital cardiac arrest, but severity is extremely variable depending on duration and etiology of arrest. Lactate, which is a good surrogate for the extent of systemic hypoperfusion in non-resuscitated shock patients, is commonly increased due to systemic hypoperfusion post-arrest, but is not specific for low-output failure *(Figure 5)*. Post-arrest cardiogenic shock may be severe and refractory to conventional treatment and pVAD can restore hemodynamic stability. Echocardiography should be performed at first contact; quick pVAD implantation using VA-ECMO is preferred

if the patient is profoundly unstable. pVAD implantation in refractory post-arrest cardiogenic shock can improve patient survival with good neurological outcome when used as part of a dedicated protocol. Although neurologic prognosis at presentation is unknown, rapid treatment including pVAD may be warranted in patients with post-arrest cardiogenic shock. A standardized treatment protocol ensuring high-quality post-resuscitation care is recommended. In general, there should be a fair chance that the detected systemic hypoperfusion can be counteracted by restoring haemodynamics using a pVAD. If there is an underlying non-cardiac disease that limits survival, implantation of pVADs will not alter the overall fate of the patient.

Figure 5 - Influence of resuscitation on lactate in AMI-CS

High admission lactate is a potential marker for higher mortality in patients with AMI-CS on circulatory support, but even levels >10 mmol/L do not have to be considered as futile in non-resuscitated AMI-CS patients.
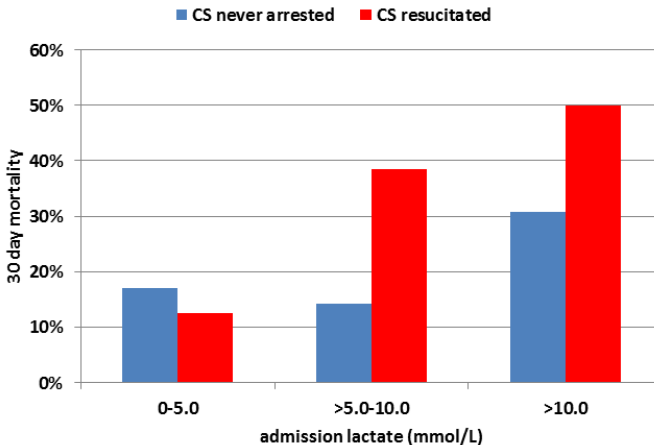
If patients are still in refractory cardiac arrest, ECPR by VA-ECMO is the preferred pVAD strategy. Implantation can be performed almost everywhere in the hospital; several emergency medical services provide specialized ECPR teams for out-of-hospital ECPR implementation. However, this procedure should only be performed in patients with reasonable prognosis, e.g., patients should be young, have observed arrest with a potentially reversible cause, received bystander CPR, have shockable initial rhythm, and high-quality CPR should have been performed for <60 minutes prior to establishing an ECPR circuit. Markers of systemic hypoperfusion should not be extreme (e.g., pH<6.8, lactate >20 mmol/L).

2 - OPTIMAL TIMING OF SUPPORT

As there are yet no conclusive trials on superiority of pVADs, it is even harder to determine the optimal timing of support. In general, mechanical circulatory support is recommended when initial treatment with vasopressors/inotropes and volume does not improve haemo-dynamics *(CPO & PAPI, Figure 6)* and lactate clearance

Figure 6 - Haemodynamic guidance

By using invasive haemodynamic measurement CPO and PAPI can be easily determined and be used to guide selection of LV and RV support.

Cardiac Power Output (CPO)

CPO = MAP x CO / 451

CPO < 0.6

PAPI

< 0.9   >0.9

RV Failure ?   RV normal

Consider RV Support   Consider ↑ LV Support
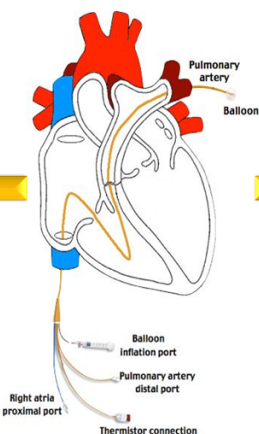
Pulmonary artery pulsatility index (PAPI)

PAPI = (sPA-dPA) / RA

CPO ≥ 0.6 and PAPI > 0.9

Continue to ↓ titrate Pressors/ Inotropes

Rapid calculation of CPO by MAP and CO:

CO (l/min)		MAP (mmHg)				
		90	80	70	60	50
	4,0	0,8	0,71	0,62	0,53	0,44
	3,5	0,70	0,62	0,54	0,47	0,39
	3,0	0,60	0,53	0,47	0,40	0,33
	2,5	0,50	0,44	0,39	0,33	0,28

For non-ischaemic causes of cardiogenic shock pVADs are predominantly used in a "bridge-to-LVAD" or "bridge-to-transplant" approach and to proceed to implantation once the clinical decision has been made to support the patient.

In ischaemic causes of cardiogenic shock, most patients present with AMI-CS and timing of support can be either prior to reperfusion or after successful revascularization.The advantage of the latter concept is that time to reperfusion is not prolonged by pVAD implantation, however, it inherits the risk of haemodynamic deterioration during PCI eventually leading to cardiac arrest.The advantage of a support-first strategy with pVADs other than IABP is that haemodynamic support will also be provided during prolonged or repeated PCIs even in last vessel interventions which would normally lead to deterioration in haemodynamics. Active support by axial flow pumps or VA-ECMO will ensure systemic perfusion irrespective of intrinsic contractility. Also, stabilized haemodynamics might enable the operator to perform more complete revascularization, which was previously recommended but is now discouraged in AMI-CS patients. After training, most pVADs can be rapidly inserted by experienced interventional teams and may delay reperfusion by only 10-15 minutes.

At least for the transfemoral Impella approaches using the 2.5 and CP devices in AMI-CS, there are registry data associated with a potential mortality benefit when Impella was implanted prior to PCI. In the future, data from sufficiently sized randomized controlled trials in AMI-CS will be available for Impella (DanGer-Shock) and VA-ECMO (ECLS-SHOCK, EURO SHOCK).