Ventricular Unloading Using the Impella^{TM} Device in Cardiogenic Shock

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Cardiogenic shock (CS) remains a leading cause of hospital death. However, the use of mechanical circulatory support has fundamentally changed CS management over the last decade and is rapidly increasing. In contrast to extracorporeal membrane oxygenation as well as counterpulsation with an intraaortic balloon pump, ventricular unloading by the Impella^{TM} device actively reduces ventricular volume as well as pressure and augments systemic blood flow at the same time. By improving myocardial oxygen supply and enhancing systemic circulation, the Impella device potentially protects myocardium, facilitates ventricular recovery and may interrupt the shock spiral. So far, the evidence supporting the use of Impella^{TM} in CS patients derives mostly from observational studies, and there is a need for adequate randomized trials. However, the Impella^{TM} device appears a promising technology for management of CS patients. But a profound understanding of the device, its physiologic impact and clinical application are all important when evaluating CS patients for percutaneous circulatory support. This review provides a comprehensive overview of the percutaneous assist device Impella^{TM}. Moreover, it highlights in depth the rationale for ventricular unloading in CS and describes practical aspects to optimize care for patients requiring hemodynamic support.

Keywords: cardiogenic shock, ventricular unloading, mechanical circulatory support device, Impella, hemodynamics, expert group, review

INTRODUCTION

Ventricular dysfunction despite normal or elevated filling pressures associated with hypoperfusion of end organs and tissue hypoxia defines cardiogenic shock (1–3). Acute myocardial infarction (AMI) represents the most common trigger of CS. Other common causes include acute valvular heart disease, ventricular arrythmias, fulminant myocarditis, post-cardiotomy shock and acute or chronic heart failure (HF).

Despite multiple advances including early revascularisation strategies, mortality rates in CS patients remain high (up to 50%) (4, 5). The cornerstones of contemporary CS management include prompt diagnostic workup and initiation of directed therapy aiming to re-establish tissue perfusion and halt the shock spiral. Therapeutic options remained limited for decades, and generally only involved inotropes, vasopressors, ventilatory support and reperfusion therapies. However, the introduction of mechanical circulatory support (MCS) has fundamentally changed CS management over the last decade. This is also reflected by the current European Society of Cardiology (ESC) guidelines with a IIa recommendation for short-term MCS (6). Whereas, particularly in the early MCS era, counterpulsation with an intraaortic balloon pump (IABP) as well as extracorporeal

GRAPHICAL ABSTRACT | Central illustration. Design principles and hemodynamic effects of the Impella™ device. AOP, Aortic pressue; EDP, Enddiastolic pressure; EDV, Enddiastolic volume.
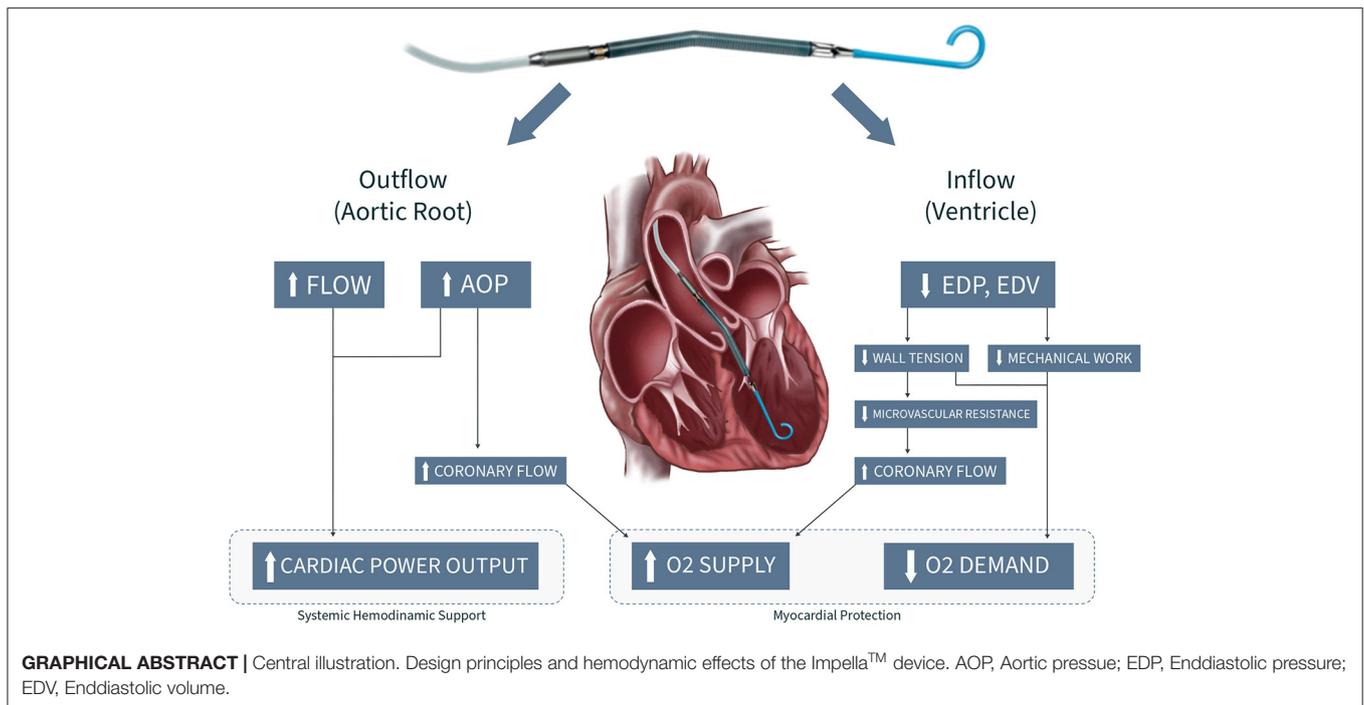
membrane oxygenation (ECMO) represented the preferred devices for refractory CS, the micro-axial Impella™ (Abiomed, Danvers, Massachusetts) is an emerging percutaneous ventricular assist device (pVAD), that has increasingly been used in Western countries (7). In fact, there is a paradigm shift in CS management, which not solely aims for enhancing coronary blood flow (IABP) and maintaining systemic perfusion (ECMO), but also incorporates ventricular unloading ultimately aiming for myocardial recovery.

With this background, this comprehensive review highlights the rationale for ventricular unloading in CS. Moreover, it summarizes important practical aspects, possible complications and current evidence one needs to be aware of, when managing patients requiring hemodynamic support with an Impella™ device.

PATHOPHYSIOLOGY OF CARDIOGENIC SHOCK

CS represents a complex interplay between the heart and all other organ systems. Rapidly deteriorating myocardial contractility results in a spiraling process of ventricular dysfunction, hypotension, reduced venous return and diminished coronary perfusion leading to pulmonary congestion, hypoxia, decreased

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Abbreviations: AMI, Acute myocardial infarction; HF, Heart failure; CS, Cardiogenic shock; ECMO, Extracorporeal membrane oxygenation; LVEF, Left ventricular ejection fraction; LVAD, Left ventricular assist device; MCS, Mechanical circulatory support; MODS, Multiorgan dysfunction syndrome; PCI, Percutaneous coronary intervention; pVADs, Percutaneous ventricular assist devices; RHF, Right heart failure; SIRS, Systemic inflammatory response syndrome; STEMI, ST-elevation myocardial infarction.

organ perfusion and worsening ischemia (3). Compensatory peripheral vasoconstriction initially improves coronary and peripheral perfusion. However, it contributes to increased cardiac afterload that overburdens damaged myocardium further diminishing circulating oxygenated blood flow (3, 8). Systemic hypoperfusion triggers endothelial dysfunction, systemic inflammatory response syndrome (SIRS) and coagulopathies, which all promote multiorgan dysfunction syndrome (MODS) (3). Activated systemic inflammatory mediators (e.g., interleukins, TNF-alpha) result in vasodilation and additional hypotension. Consequently, these mechanisms add up to the high mortality associated with cardiogenic shock (9).

ROLE OF pVADs IN CARDIOGENIC SHOCK

The management of CS should focus on preventing and reversing organ failure through hemodynamic resuscitation and simultaneously addressing treatable causes.

Vasoactive and inotropic drugs, especially those with adrenergic mechanisms, have the burden to increase afterload, aggravate myocardial ischemia and trigger arrhythmias, which all ultimately worsen the patient's prognosis. Therefore, they must be cautiously titrated in the setting of CS (10, 11). Consequently, in patients presenting with impeding or already established cardiogenic shock, immediate MCS may be the first choice to rapidly re-establish stable hemodynamics and potentially prevent related MODS.

To date, three basic concepts have commonly been used for percutaneous MCS in acute CS management: (1) counterpulsation using the IABP, (2) ventricular unloading

provided by Impella™ technology or by the pulsatile PulseCath iVAC2L device, and (3) veno-arterial extracorporeal membrane oxygenation (VA-ECMO) circulatory support. The mechanisms and hemodynamic effects of currently available MCS are highlighted in **Table 1**.

THE IMPELLA™ DEVICE

The Impella™ is a percutaneous, microaxial pump that continuously draws blood from its inlet inside the ventricle and expels it in the ascending aorta (*Central Illustration*) (12–15). Owing its properties, the Impella™ unloads the left ventricle (LV) while simultaneously augmenting cardiac output (CO). The power connections for the pump motor and sensors are contained inside the 9F guiding catheter. The end of the catheter is connected to an external console consisting of an integrated controller for the pump and purge system. Unlike IABP, the Impella™ does not require ECG or arterial waveform triggering, facilitating stability even in the setting of ongoing tachyarrhythmias or electromechanical disassociation.

TABLE 1 | Characteristic features of cardiogenic shock.

Clinical features of cardiogenic shock
Myocardial contractile dysfunction
• Low CO (CI <2.2L/min/m^2) despite normal or elevated pre-load (LVEDP ≤ 15mmHg)
Prolonged hypotension requiring support by catecholamine
• SBP <90mmHg for ≥ 30 minutes
Clinical signs of impaired end-organ perfusion*
• Cool extremities
• Altered mental status
• Oliguria (<30 ml/h)
• Rising lactate levels (>2.0 mmol/L)
Pulmonary congestion

Despite normovolemia or hypervolemia.
CO, Cardiac output; CI, Cardiac index; LVEDP, Left ventricular enddiastolic pressure; SBP, Systolic blood pressure.

Currently, four devices are available: Impella™ 2.5, Impella™ CP and Impella™ 5.0/5.5 and Impella™ RP (**Table 2**). While the Impella™ 2.5 and CP are inserted percutaneously, the Impella™ 5.0 requires a surgical cutdown for insertion. Thus, in many institutions, the Impella™ 2.5 or CP reflect the first choice for mechanical support. The Impella™ RP is a 22 French, three-dimensional catheter-based micro-axial pump approved for use in acute right heart failure (RHF). The inflow of the Impella™ RP is positioned in the inferior vena cava (IVC) and the outflow in the pulmonary artery (PA) expelling blood from the IVC into the PA at a rate of up to 4.6 L/min.

HEMODYNAMIC EFFECTS OF pVADs AND THE CONCEPT OF VENTRICULAR UNLOADING

From Ventricular Venting to Unloading

Ventricular "venting" has been used in cardiac surgery for decades and refers to strategies to treat ventricular distension and prevent pulmonary edema occurring during cardiopulmonary bypass support and VA-ECMO (16). Different techniques have been applied including trans-septal septostomy (17), and surgical placement of an LV vent. Counterpulsation using is an alternative percutaneous option, thought to decompress the LV.

Since ventricular volume and pressure overload represents the hallmark of patients in CS, the concept of ventricular "venting" was adopted for CS patients. For many years, the IABP was the preferred and only support device for patients presenting with AMI and CS. However, efficacy of circulatory support by IABP is often insufficient considering the results of the randomized IABP-SHOCK II trial and a large meta-analysis with 2,123 patients showing no mortality reduction (18, 19).

In contrast to ventricular "venting", "unloading" is an active process reducing volume and pressure by pumping blood from the right or left ventricle to the pulmonary artery or aortic root, respectively. Historically, ventricular unloading in CS has been technically challenging, and a series of devices including the TandemHeart remained prototypes or never found widespread clinical use due to their complicated mode of implantation. The introduction of the catheter-based

TABLE 2 | Impella devices and pump characteristics.

	IMPELLA 2.5	IMPELLA CP	IMPELLA 5	IMPELLA RP
Access	Percutaneous	Percutaneous	Surgical	Percutaneous
Access site	Femoral; (axillary)	Femoral; (axillary)	Axillary; Femoral/ascending aorta	femoral vein
Guiding catheter size	9 F	9 F	9 F	11 F
Motor size	12 F	14 F	21 F	22 F
Introducer size RPM	13 F peel away	14 F peel away	23 F peel away*	23 F peel away
RPM (max.)	51,000	46,000	33,000	33,000
Duration of support (days)#	5	5	10	14

Surgical cutdown and insertion through a Dacron graft (8-10 mm) recommended.
#*European approval (CE Mark).*
F, French; RPM, Revolutions per minute.
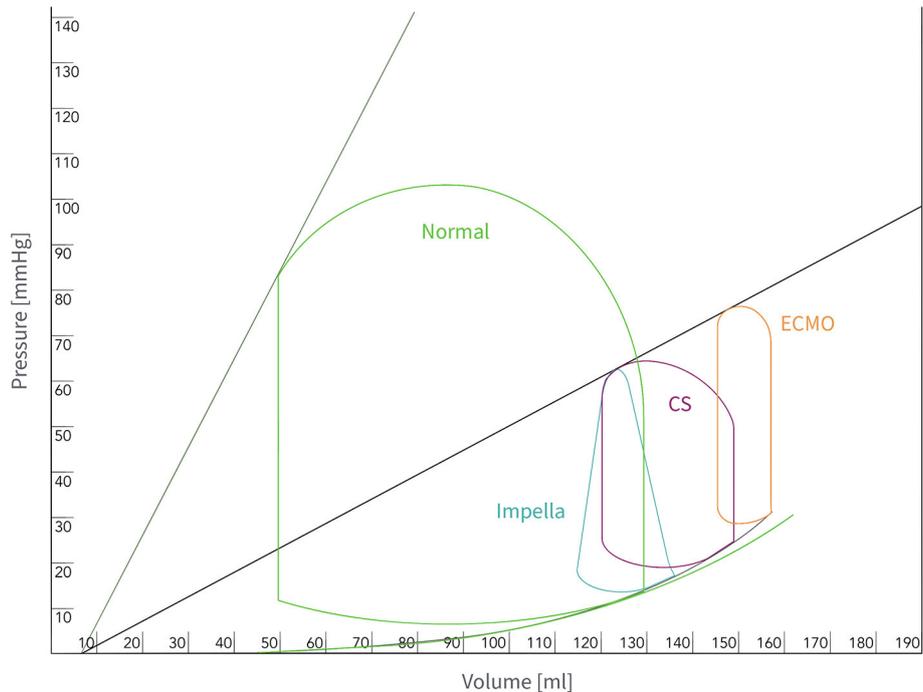
FIGURE 1 | Pressure-volume relationship: Normal conditions (CO 5l; green), CS (CO 3l, PAWP 27 mmHg; purple), CS on VA-ECMO support (3l flow, orange); CS on Impella™ CP support and "P" Level 9 (4 l flow; turquoise). The pressure-volume area represents an estimate of mechanical work performed by the ventricle. The pressure-volume area is only reduced with the Impella™, thus decreasing LV work. *CO, Cardiac output; CS, Cardiogenic shock; LV, Left ventricular; PAWP, Pulmonary artery wedge pressure; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.*

ventricular assist device Impella™ helped to overcome some of those hurdles.

Hemodynamic Effects of the Impella Device

There are four physiologic effects of left sided Impella support: (1) With the inflow of the device drawing blood directly from the ventricle (ventricular unloading), it reduces ventricular end-diastolic volume (EDV) and pressure (EDP) (20). Decreasing EDV and EDP leads to a reduction of myocardial wall tension and workload, both of which diminish myocardial oxygen demand (21–24). This is further highlighted by the progressive loss of isovolumic phases during increasing Impella support illustrated by the conversion of pressure-volume loop into a triangular shape (**Figure 1**). (2) The outflow of the Impella™ device in the aortic root provides active flow increasing mean arterial pressure (AOP), diastolic pressure, CO and thus cardiac power output (20, 25, 26). If properly placed, the outflow of the device resides just above the aortic valve plane and provides before mentioned systemic pressure augmentation in correlation to the level of Impella support ("P" level) (27). (3) The synergistic effect of increased mean AOP and decreased myocardial wall tension leads to augmented coronary flow, thus improving myocardial oxygen supply. Overall, the Impella device favorably alters the balance of myocardial oxygen demand and supply and

therefore improves the heart's ability to survive ischemic challenges (28, 29).

In contrast, VA-ECMO decreases preload, but at the same time substantially increases afterload, which adversely impacts myocardial oxygen consumption. While a healthy LV can cope with increased afterload by recruiting more contractility, the impaired LV in CS may further decompensate leading to a vicious cycle of mechanically driven injury with worsen pulmonary congestion, acute lung injury and pulmonary hemorrhage, thereby worsening cardio-pulmonary function (30, 31). (4) Left ventricular Impella™ support results in decreased pulmonary capillary wedge pressure (PCWP) and a secondary reduction in RV afterload (14). (**Table 3**, Central Illustration).

Systemic Hemodynamic Support

The Impella augments both flow and pressure in the aorta leading to improved cardiac power output and increased AOP. The actively generated forward flow depends on (1) the specific device (**Table 3**), (2) the performance ("P") level setting and (3) the pressure gradient across the aortic valve. Higher "P" level settings or lower pressure gradients result in higher flow augmentation (20, 25, 26, 29, 32). Importantly, the increase in systemic CO results from the net effect of native CO reduction after ventricular unloading and the forward flow contribution of the Impella™ pump. As a consequence, the mean AOP correlates with the Impella™ support and can be modified by changes in the "P" level setting, as highlighted in **Figure 2**.

TABLE 3 | Technical properties of percutaneous circulatory assist devices.

	IAPB	IMPELLA 2.5	IMPELLA CP	IMPELLA 5.0	VA-ECMO
Mechanism	Aorta	LV→ aorta	LV→ aorta	LV→ aorta	RA→ aorta
Cannula size (Fr)	7–8	13–14	13–14	22	14–16 arterial 18–21 venous
Flow (L/min)	0.3–0.5	1.0–2.5	3.7–4.0	5.0	3.0–7.0
Pumpmechanism	Pneumatic	Axial flow	Axial flow	Axial flow	Centrifugal
Stable rhythm	Yes	No	No	No	No
Implantation time	+	++	++	+ + + +	++
Risk of ischemia	+	++	++	++	+ + +
Anticoagulation	+	+	+	+	+ + +
Cardiac power	↑	↑↑	↑↑	↑↑	↑↑↑
Afterload	↓	↓	↓	↓	↑↑↑
MAP	↑	↑↑	↑↑	↑↑	↑↑
LVEDP	↓	↓↓	↓↓	↓↓	↔
PCWP	↓	↓↓	↓↓	↓↓	↔
LV preload	–	↓↓	↓↓	↓↓	↓
Coronary perfusion	↑	↑	↑	↑	–

IABP, intraaortic balloon pump; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; LV, Left ventricle, RA, Right atrium; MAP, Mean arterial pressure; LVEDP, Left ventricular end-diastolic pressure; PCWP, Pulmonary capillary wedge pressure.
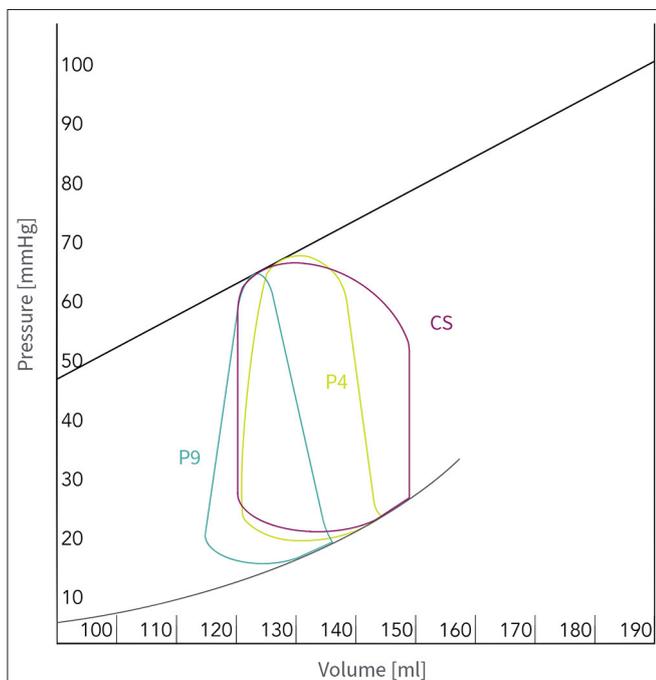
FIGURE 2 | Pressure-volume relationship on Impella™ CP support and different performance ("P") level settings: The evolution of the pressure-volume relationship before (CS: CO 3l, PAWP 27 mmHg; purple) and after support with "P" Level 4 (2.5 l flow; green) and "P" Level 9 (4 l flow; turquoise). *CO, Cardiac output; CS, Cardiogenic shock; PAWP, Pulmonary artery wedge pressure.*

Myocardial Protection: Augmenting Coronary Flow and Increasing O₂ Supply

Coronary artery flow is proportional to the ratio of AOP and microvascular resistance. By drawing blood directly from the ventricle, the Impella™ reduces maximum wall tension and microvascular resistance. Therefore, the synergistic effect of increased AOP and the reduction of microvascular resistance with increasing Impella support levels lead to a subsequent augmentation of the coronary flow (15, 28). Of note, the constant flow of the Impella device provides more sustained augmentation throughout the diastolic period. In contrast, the IABP deflates in late diastole, which leads to transient pressure increase only early in diastole but this augmentation reverses just before systole, lowering end-diastolic pressure. For instance, the positive effects of the Impella™ on coronary microcirculation has been illustrated in a case report from Agel et al. (33). On nuclear perfusion imaging, they demonstrated adequate myocardial perfusion through collaterals while on Impella™ support in a patient with severe three vessel disease, including complete occlusion of the right and left circumflex coronary artery (33).

Ventricular Unloading: Decreasing O₂ Demand

Myocardial oxygen demand is determined by the amount of mechanical work the muscle produces and the amount of myocardial potential energy, which is related to wall tension (21–24, 28). By drawing blood from the ventricle, the Impella™ reduces total filling volume and pressure, which leads to a reduction in stroke volume according to the Frank-Starling mechanism: "If the heart fills less, it expands less and reduces its subsequent stroke output, which corresponds to a reduction in mechanical work" (Central Illustration).

Oxygen Demand-Supply Ratio

The reduction in EDP, EDV and wall stress lead to reduced microvascular resistance and increased myocardial perfusion (increasing myocardial oxygen supply). In addition to this perfusion effect, ventricular unloading results in reduced

mechanical work and potential energy (reduced myocardial oxygen demand). This impact is expressed in the pressure-volume (PV) loop by a leftward shift in its position and an overall reduction in its area (**Figure 1**). Of note, while significant reduction of ventricular work as well as end-diastolic pressure and volume was shown with the Impella, changes in the same parameters with the IABP were not significant (28).

ACUTE RIGHT HEART FAILURE AND RIGHT VENTRICULAR UNLOADING

RHF is a characterized by the inability of the right ventricle (RV) to sustain pulmonary flow caused by increased RV afterload (e.g., acute pulmonary embolus, severe hypoxia, acidemia, or increased intrathoracic pressures) or decreased RV contractility (e.g., RV ischemia, myocarditis, post-cardiotomy CS, or LVAD support) (34–36). RHF is associated with high morbidity, mortality, and longer hospital length of stay (37). The thin walled RV differs markedly from the LV in architecture, mechanics, metabolism, and recovery from injury (38). The RV is exquisitely susceptible to failure under conditions of ischemia and pressure overload. However, the RV is remarkably resilient and tends to recover once hemodynamics improve and the underlying insulting cause is eliminated. But in some patients RHF persists and, similar to LV related shock, outcome in patients requiring multiple and prolonged inotropic and vasopressor support is poor (10, 11). Moreover, 10–40% of patients undergoing isolated left ventricular assist device (LVAD) implantation experience some degree of RHF (39). While RHF associated with LVAD insertion may be partially caused by the underlying cardiomyopathy, the pathophysiology of RHF after LVAD implantation is complex.

In this context, the Impella^{TM} RP provides an opportunity for mechanical support in the downward spiral of refractory RHF and may serve as a bridge to recovery or heart transplant. Since survival after impella^{TM} RP insertion strongly depends on timing and patient selection (37, 40, 41), early identification of RHF and careful consideration of patient's clinical status and comorbidities is key to obtain the best clinical outcomes. Device implantation requires some expertise and, in contrast to LV pumps, can only be performed under fluoroscopy guidance. Frequent monitoring of RV function using echocardiography and pulmonary artery catheter measurements is crucial to guide Impella^{TM} RP therapy. Based on the inclusion and exclusion criteria of the RECOVER RIGHT trial (37) and a series of smaller clinical studies and case series (42–45), a dedicated checklist for patient selection has been proposed, see **Table 4**.

CURRENT EVIDENCE

The only two randomized clinical trials comparing the Impella^{TM} vs. IABP have both been neutral with respect to survival. However, both were underpowered, the ISAR-SHOCK trial mainly targeted hemodynamic improvements (46). The small IMPRESS trial also showed similar outcomes with both Impella CP and IABP in patients with ST-elevation myocardial infarction (STEMI) and CS undergoing primary percutaneous coronary

TABLE 4 | Impella RP heart pump patient selection recommendations.

Clinical conditions in which the Impella RP is not recommended
Active infection with positive blood cultures
RA, RV or PA thrombus
Mechanical valves in the right heart*
Unrepaired ASD, PFO, or aortic dissection
PA conduit
Anatomic abnormalities precluding insertion
Moderate to severe pulmonary valve stenosis or insufficiency
Severe pulmonary hypertension (PAPs > 60mmHg)
Documented DVT and/or presence of IVC filter
Patients on right-sided support or ECMO
Allergy or intolerance to contrast
HIT or sickle cell disease

Definition of RHF

CI <2.2 l/min/m^2 despite continuous infusion of high dose inotropes$^{\#}$ and any of the following:
• CVP > 15 mmHg or
• CVP/PCWP > 0.63 or
• Moderate to severe global RV dysfunction on echocardiography defined as one of the following criteria:
  ○ Global RV hypokinesis
  ○ TAPSE score of ≤14 mm
  ○ RV diameter at basis >42 mm
  ○ RV short axis (or mid-cavity) diameter >35 mm

Table adapted from Abiomed® recommendations for Impella RP patient selection.
*Presence of a tricuspid ring or bio-prosthesis is not a contra-indication, but it may result in a difficult implantation depending on the valve strut orientation within the RVOT.
$^{\#}$Dobutamine of ≥ 10 μg/kg/min or equivalent for more than 15 min (120 min for milrinone) and/or administration of more than one inotrope/vasopressor.
ASD, Atrial septal defect; CVP, Central venous pressure; PCWP, Pulmonary capillary wedge pressure; DVT, Deep vein thrombosis; HIT, Heparin induced thrombocytopenia; PA, Pulmonary artery; PAPs, Pulmonary artery systolic pressure; PFO, Persistent foramen ovale; RA, Right atrium; RV, Right ventricle.

intervention (PCI) (47). One must take in account that this trial included critically ill patients and the major cause of death was anoxic brain injury, suggesting that mechanical hemodynamic support may be of limited utility in this patient cohort. Also, the trial was underpowered (47). Although, some centers have reported better survival rates in CS after implementation of a comprehensive shock protocol using pVADs (48, 49), the use of Impella^{TM} has been associated with higher risks of bleeding, stroke, and death, as well as higher costs compared to IABP in propensity-matched analyzes from registry data (7, 50, 51). However, confounding due to the use of pVADs in sicker patients cannot be ruled out (51). Despite neutral results in randomized clinical trials and the remaining high mortality rates in this severely ill population there is some evidence that the use of larger Impella^{TM} pumps (e.g., Impella^{TM} CP), the initiation of Impella^{TM} prior to PCI and its use in patients without cardiac arrest may be correlated with outcome improvements (52).

In comparison to VA-ECMO, the incidence of major complications, such as bleedings, might be lower with Impella^{TM} use (53). The data supporting the use of RV pVADs, namely the Impella^{TM} RP, is even more limited and randomized data is not yet available. The RECOVER RIGHT study was the first to

suggest feasibility and safety of the Impella™ RP in patients with severe RHF (13). A series of recent studies indicated possible clinical benefit with the Impella™ RP demonstrating 30-day survival rates of of 64–72% (37, 40, 41). However, the survival rate was much lower among patients in whom Impella™ RP was implanted as salvage support (41). This caused the U.S. Food and Drug Administration to issue a warning advice. This controversy highlights the need for proper patient selection and early initiation of hemodynamic support.

CASE SELECTION

Left Ventricular Impella™ Devices

Contraindications to the placement of the LV Impella™ include mechanical aortic valve, LV thrombus, moderate to severe aortic regurgitation, and severe obstructive peripheral arterial disease.

Visualization of the ventricle before implantation excluding the presence of a thrombus is recommended if time permits using a bed-side echocardiogram. Thrombus may be sucked up by the impeller and interrupts its proper functioning. As with any other catheter placed in the LV, the Impella™ catheter may furthermore dislodge thrombus, potentially causing systemic embolization. Moderate to severe aortic regurgitation (AR) is a relative contraindication. Only a competent aortic valve separating the LV and aorta allows optimal antegrade Impella™ flow. In patients with relevant AR, AOP augmentation by the Impella™ may worsen AR and LV dilation. Given concerns regarding compromise of the remaining valvular orifice and worsening hemodynamics with the introduction of the Impella™ catheter, aortic stenosis (AS) has been considered an exclusion criterion in clinical trials. Also, crossing of a severely stenotic aortic valve with the impella device might be very challenging. Despite these concerns, feasibility of Impella™ insertion in severe AS before high-risk PCI, during balloon valvuloplasty or transcatheter aortic valve replacement (TAVR) and bail-out use as a bridge to TAVR in CS has been demonstrated in several reports (54–60). Peripheral artery disease (PAD) may not be an absolute contraindication for the Impella™ insertion, nevertheless its presence and extent need to be considered prior to device implantation. Femoral angiography in an ipsilateral projection prior to Impella™ insertion to assess puncture height and anatomical suitability of the iliac and femoral arteries allows to identify prohibiting PAD and may prevent access site complications and limb ischemia. Additionally, ultrasound guidance helps to find the ideal puncture site and avoid impeding calcifications. In afflicted patients, alternative access routes (trans-subclavian or -axillary) may be evaluated. However, to avoid complications prudent access site management is crucial. Several strategies for closure of the arteriotomy after removal of the device are utilized dependent on availability and local experience. Manual compression is a cost-effective, although time intensive means to achieve hemostasis. Femoral compression systems (e.g., using FemoStop, Abbott Vascular) can be applied to avoid bleeding after device removal. Latest generation of the Impella™ sheaths allow advancement of a wire for sheath exchange or placement of closure devices, such as the MANTA® 14 F device

(Teleflex Inc., Morrisville, North Carolina) or the Perclose ProGlide™ suture-mediated closure System (Abbott Vascular Inc., Santa Clara CA, U.S.A.). In selected cases at high risk for bleeding or ischemic complications surgical removal might be safest.

Impella™ RP

As for the left ventricular devices, only a competent pulmonary valve allows optimal forward flow. However, a certain degree of pulmonary valve regurgitation is often present in the setting of acute RHF and elevated pulmonary artery pressures. Albeit significant tricuspid valve regurgitation (TR) often accompanies RHF, hemodynamic effects of the Impella™ RP are usually not affected if the pulmonary valve is competent. So far, TR represents a relative contraindication for Impella™ RP implantation according to the manufacturer. However, TR might improve after RV unloading, particularly if TR is secondary to annular dilatation in the setting of acute RHF. Therefore, TR should rather be seen as a warning sign than as an absolute contraindication.

INDICATIONS FOR VENTRICULAR UNLOADING

In addition to its application in high-risk PCI and cardiogenic shock complicating AMI, the Impella™ technology has been successfully introduced in a broad variety of clinical scenarios requiring left or right ventricular support. Indication for ventricular unloading and issues to be considered when selecting patients for pVAD support are depicted in **Table 5**.

Timely implantation is often key. Considering the rapidly progressing shock spiral, early identification and treatment are crucial to increase chances of survival. This seems underlined by observational data suggesting that Impella™ implantation before revascularization maximizes the potential benefit (61) and that survival decreases by about 10% for every 60 min of delay (49).

Mechanical Support in Coronary Bypass Surgery and Post-cardiotomy Cardiogenic Shock

Nowadays most patients presenting with CS secondary to myocardial infarction (MI) are revascularized percutaneously. However, there is a subset of patients who need to be referred for urgent or emergent coronary artery bypass grafting (CABG). In a US registry, 129 (2.3%) patients with MI and CS undergoing CABG had MCS inserted (62). Most of these patients were bridged to surgery with an Impella™ device. Although, operative mortality in this emergency setting was very high (37.2%), the data suggests that there may be some benefit to instituting MCS prior to CABG in this very high-risk group of patients. Also, there are reports of prophylactic pVAD utilization in high-risk patients undergoing off-pump CABG to minimize cardiovascular instability following heart positioning for proper suturing of coronary anastomoses (63–65).

TABLE 5 | Indication for ventricular unloading.

Clinical scenarios requiring left or right ventricular support	
Emergency interventions	*Planned interventions*
AMI complicated by CS	High-risk PCI
Post-cardiac surgical (bi)ventricular failure	Catheter ablations of VT
Fulminant myocarditis	High-risk bypass surgery
Advanced heart failure Valvular heart disease (e.g. AS) with severe LV dysfunction	
Hemodynamic deterioration after TAVR	

Clinical conditions to be considered in patient selection with CS		
Coronary artery disease and treatment considerations	*Clinical considerations*	*Hemodynamic considerations*
Large LAD or RCx related STEMI Adequate peripheral access	Comorbidities (e.g. expected neurological outcome, diabetes, renal failure, PAD)	SBP <90mmHg and/or inotropic pressure-dependance Tachycardia (HR >100/min)
Preferably initiate Impella support before PCI	Bleeding risk (ACT 160–180 s)	LVEDP >30–35 mmHg

ACT, Activated clotting time; AMI, Acute myocardial infarction; AS, Aortic stenosis; CS, Cardiogenic shock; HR, Heart rate; PCI, Percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TAVR, Transcatheter aortic valve replacement; VT, Ventricular tachycardia.

Overall, 0.2–9% of the patients undergoing cardiac surgery experience post-cardiotomy CS, which is associated with a high mortality (66, 67). Early data from 24 patients, who could not be weaned from cardiopulmonary bypass or were hemodynamically unstable and therefore needed support with the Impella™ Recover device (providing 3–4 L/min flow), showed improved outcome compared to IABP alone, if the heart was able to pump >1l/min (68). Thomas et al. (69) reported the first successful use of an Impella™ 5.0 L/min for post-cardiotomy CS after coronary artery bypass grafting and bioprosthetic aortic valve replacement. Support was maintained for 7 days. Noteworthy, no damage to the bioprosthetic aortic valve was seen. Despite these promising reports, VA-ECMO is still much more commonly employed in patients with post-cardiotomy CS and further studies are necessary to support the use of the Impella™ device in the setting of cardiac surgery.

COMPLICATIONS ASSOCIATED WITH IMPELLA™

Overall, the type of complications related to the use of the Impella™ device are similar to those encountered with the IABP. The most common complications include limb ischemia, vascular injury and bleeding requiring blood transfusion (15). The reported incidence of limb ischemia ranges from 0.07–10% and for significant bleeding from 0.05 to 54% (70). The risk of bleeding is also related to the administration of antithrombotics (e.g., unfractionated heparin),

thrombocytopenia or consumption of coagulation factors (e.g., von-Willebrand factor) related to shear-stress with the impeller. Moreover, shear stress from the impeller (especially at very high "P" levels) can lead to clinically relevant hemolysis, which in worst case scenario can cause renal failure. This phenomenon has been observed in 5–10% of patients during the first 24 h on Impella™ support. The risk of hemolysis and aortic valve injury may be diminished by proper positioning of the inlet cannula, and thus limited flow turbulences.

Ischemic or hemorrhagic cerebrovascular accidents following Impella™ insertion have also been reported (2.4–6.3%) (70, 71). As with any percutaneous device, there is a risk of access site infection and sepsis, which increases with the duration of support. In the early experience, device migration and malfunction rarely led to injury of the aortic valve or ventricle causing tamponade due to LV perforation. Also, mitral regurgitation secondary to injury of the papillary muscles or chordae have been reported (32). Finally, the pigtail end of the Impella™ within the LV can provoke ventricular arrhythmias potentially further impairing CO and deteriorating CS.

ESCALATION OF SUPPORT AND COMBINATION OF IMPELLA™ WITH OTHER DEVICES

MCS is a key element of most modern cardiogenic shock care pathways (3). It is recommended to define triggers for initiation of MCS, choice of MCS modality, and escalation steps in CS patients. Such pathways should certainly be tailored to local MCS availability and experience. Irrespective of MCS modality, the adequacy of hemodynamic support and ventricular unloading needs to be closely monitored.

Adequate monitoring including a pulmonary artery catheter (measurement of central venous pressure (CVP), PCWP, CO) in combination with standard clinical measures such as blood pressure, lactate and urine output is mandatory. Frequent echocardiographic assessments of LV/RV size, function, and aortic valve opening can help to optimize pharmacologic treatment and guide escalation of mechanical circulatory support.

According to the anticipated degree of support required, the Impella™ 2.5, Impella™ CP, or the surgically implanted Impella™ 5.0/5.5 may be considered. The support requirements depend on body size as well as the degree of hemodynamic compromise. It is crucial to be aware, that due to the Anrep effect the intended Impella™ flow cannot be simply added to the pre-insertion native CO. Reduced contractility of the ventricle after pump insertion will result in a smaller total CO than expected. Among patients with profound LV dysfunction an Impella™ pump might unload the LV to the point of continuous aortic valve closure resulting in a non-pulsatile arterial curve on the monitor.

The Impella™ 2.5 and CP, which can rapidly be inserted percutaneously, are usually the first choice in the setting of CS. However, in patients with severe LV failure, low CO might persist for several days, sometimes even weeks or months. In such cases, upgrading to a larger device (e.g., Impella™ 5.0 or 5.5)

TABLE 6 | Combination of Impella[TM] with other devices.

	Indication	Effect	Limitations
Impella[TM] + VA-ECMO (ECMELLA)	- Gas exchange failure - Refractory CS/inadequate support - Concomitant RHF* following LV Impella[TM] insertion - RHF and severely elevated PVR - Recurrent tachyarrhythmias - Pulmonary hemorrhage	Hemodynamic support ↑ Oxygenation ↑ and CO_2 elimination RV unloading	- Access site complications - Increased LV afterload - Bleeding diathesis - Post-implantation management complexity - Cost-intensive
VA-ECMO + Impella[TM] (ECMELLA)	- LV stasis with thrombus formation - Pulmonary failure due to high PAP - LV distension - Myocardial ischemia	LV/RV unloading Myocardial perfusion ↑	- Reduction of VA-ECMO flow required - Post-implantation management complexity - Cost-intensive
Impella[TM] + Impella[TM] RP (BiPella)	- Biventricular failure - Concomitant RHF* following LV Impella[TM] insertion	RV output ↑ LV suction alarms ↓ (at maximal LV pump speed) CO ↑	- Implantation of Impella[TM] RP requires expertise and fluoroscopy guidance - Limited efficacy in severely elevated PVR - Cost-intensive
Impella[TM] + IABP	Refractory CS	Myocardial perfusion ↑ Oxygen demand–supply ratio ↓	- Limited hemodynamic support - Possible overall reduction in the Impella flow

*Which is not volume responsive.

CS, Cardiogenic shock; CO, Cardiac output; IABP, intraaortic balloon pump; VA-ECMO, Veno-arterial extracorporeal membrane oxygenation; LV, Left ventricle, RV, Right ventricle; PAP, Pulmonary artery pressure; PVR, Pulmonary vascular resistance.

might be a wise strategy (72). With these devices the patient can even be ambulated while awaiting recovery, cardiac transplant or LVAD implantation.

Simultaneous RHF results in reduced LV preload and therefore limits the flow of the LV Impella by recurrent suction events, which necessitates down-titration of the Impella[TM] pump power level. In case of inadequate hemodynamic response after LV unloading and recurrent suction alarms irresponsive to volume challenge, the insertion of an VA-ECMO or Impella[TM] RP may be considered. The latter augments RV output and therefore increases LV preload (BiPella approach), which in turn improves CO. Although, there are only small case series available (45, 73–78), the BiPella approach seems to be feasible and safe und might be used as a salvage treatment modality for refractory biventricular failure. VA-ECMO might be primarily considered in the setting of inappropriate oxygenation due to acute lung congestion or MODS. Also, VA-ECMO implantation might be evaluated in case of refractory shock and inadequate support from the Impella[TM].

Conversely, some patients on VA-ECMO support may benefit from additional LV unloading by an Impella[TM] device. Although potentially lifesaving in patients with CS, VA-ECMO burdens the already impaired LV by increasing afterload. This may further compromise the LV contractile function due to ventricular distension and impaired myocardial blood flow (79, 80). When deployed in combination with VA-ECMO, the Impella[TM] (ECMELLA approach) reduces filling pressures, ventricular distension, and maintains flow from the LV to the aorta even in the absence of LV ejection and a closed aortic valve (81–83). There is data proposing the combined use of VA-ECMO with an Impella[TM] device in severe CS cases to unload the LV, facilitate myocardial recovery and improve clinical outcomes. Yet, the evidence supporting the ECMELLA approach derives only from observational studies and has accordingly some limitation (81–84). Also, the increased risks of hemorrhagic and vascular complications due to the additional large bore vascular access required need to be considered.

Finally, there are small case series endorsing the combination of an Impella[TM] device and IABP as a bail out strategy in refractory CS (28, 85). However, further clinical investigations will be needed to assess if the combination of LV unloading and counterpulsation using the IABP brings any incremental physiological and clinical benefit. Possible combinations of different MCS devices, their indications, clinical effect and possible pitfalls are depicted in **Table 6**.

FUTURE PERSPECTIVES

With respect to the limited evidence supporting the use of the Impella[TM], especially in patients with AMI and/or CS, there are several trials in progress. For instance, the DanGer Shock trial (ClinicalTrials.gov Identifier: NCT01633502) is a prospective, multicenter, open-label trial randomizing AMI patients with CS 1:1 to Impella[TM] CP support or current guideline-driven therapy with a planned enrollment of 360 patients (86).

Also, following encouraging pre-clinical studies (87, 88), which suggest a reduction in infarct size by applying early ventricular unloading in patients with AMI, the STEMI-DTU trial (ClinicalTrials.gov Identifier: NCT03947619) will study the impact of ventricular unloading by the Impella[TM] device during 30 min before primary PCI on infarct size in patients with acute anterior MI.

Besides new treatment concepts, also new devices are currently under investigation or development. Since the actual versions of percutaneously implanted LV Impella[TM] devices

bear the risks of bleeding and vascular injury, there have been efforts to downsize the catheter size. There is now a nine french device – the Impella™ ECP – under clinical investigation (ClinicalTrials.gov Identifier: NCT04477603). Also, new devices allowing LV unloading with integrated batteries are under development, ensuring long-term hemodynamic support for several months and enabling patients to leave the hospital while awaiting heart transplant or as a destination therapy.

CONCLUSION

Albeit randomized evidence supporting its clinical use remains scarce, the Impella™ device is an emerging MCS device for treatment of CS. The Impella™ actively unloads the impaired left or right ventricle and maintains systemic pressure. If immediately applied, these devices not only unload the ventricle but also improve myocardial and peripheral oxygen supply and therefore have the potential to halt the shock spiral and reverse MODS. Owing to its design, the Impella™ relieves the battered ventricle, which appears to improve myocardial recovery. Profound understanding of the device, its physiologic impact, but also its limitations are important when considering a CS patient for percutaneous circulatory support.

AUTHOR CONTRIBUTIONS

AA-T has drafted and corrected the manuscript. MB, GC, GT, MM, AB, RK, and FC revised the manuscript critically for important intellectual content. All authors contributed to the article and approved the submitted version.

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