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Cardiac intensive care management of high-risk percutaneous coronary intervention using the venoarterial ECMO support

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Abstract

The emerging concept of high-risk percutaneous coronary intervention (HR-PCI) has required the adoption of a multidisciplinary team approach. Venoarterial ECMO (VA-ECMO) has been introduced as a temporary mechanical circulatory support (MCS) for HR-PCI patients in order to provide an adequate systemic perfusion during the procedure. Both patient's complexity and technological evolutions have catalyzed the development of critical care cardiology; however, ECMO therapy faces several challenges. Indeed, the management of patients on ECMO remains complex; moreover, the lack of specific recommendation for HR-PCI patients further complicates the management of these patients. In this narrative review, we give a reappraisal for the management of HR-PCI patients supported with VA-ECMO according to the available data published in current literature.

Keywords Mechanical circulatory support · Intensive care unit · Shock · Critical care · Hemodynamic monitoring · High-risk PCI · VA-ECMO

Abbreviations

AMI	Acute myocardial infarction
CAD	Coronary artery disease
CCU	Cardiac care unit
HR-PCI	High-risk percutaneous coronary intervention
IABP	Intra-aortic balloon pump
LV	Left ventricle
MCS	Mechanical circulatory support
PCI	Percutaneous coronary intervention
pVAD	Percutaneous ventricle assists devices
VA-ECMO	Venoarterial ECMO

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Introduction

Percutaneous treatments of acute coronary artery disease (CAD) have drastically changed over the last two decades [1]. In fact, a huge amount of efforts has been made in order to achieve "equivalent" outcomes compared to those expected from the traditional by-pass surgery [2]. As result, percutaneous coronary interventions (PCIs) have become more complex and most frequently performed in patients with multiple comorbidities. Furthermore, an increasing number of patients not candidates for surgery due the higher pre-operative risk has been more frequently referred to PCI [3]. The complex peri-operative management of these subjects has required to adopt a collaborative team-based model. In this scenario, the term "high-risk PCI" (HR-PCI) has been recently coined to indicate a PCI performed providing short-term mechanical circulatory support (MCS) [4, 5]. Among these procedures, a growing number of PCIs have been performed using the venoarterial extracorporeal membrane oxygenation (VA-ECMO), both during rescue intervention in acute myocardial infarction (AMI) or elective HR-PCI, to maintain an adequate organ perfusion and prevent further hemodynamic deteriorations [6]. Despite the widespread diffusion of cardiac care unit (CCU) and even more sophisticated anti-ischemic therapies, a small, but not neglectable proportion of

HR-PCI patients require VA-ECMO, hemodynamic and ventilatory support in cardiac care unit (CCU) [7]. In this narrative review, we give a reappraisal for the management of HR-PCI patients supported with VA-ECMO according to the available data published in medical literature.

Definition of HR-PCI

Nowadays, a clear definition of HR-PCI has not yet been provided since this clinical entity is constantly evolving. However, in 2015, Rihal et al. have identified some features able to predict a higher perioperative risk. These characteristics have been categorized into the following groups: (1) patient-specific, (2) lesion-specific, and (3) clinical presentation (Table 1; Fig. 1) [5].

Specifically, patient-specific factors include increased age (> 75 years old), diabetes mellitus (DM), relevant chronic kidney disease (CKD) or chronic obstructive pulmonary disease (COPD), severe heart valvular disease (HVD), heart failure (HF), previous myocardial infarction (MI), peripheral artery disease (PAD), and previous history of transient ischemic attack (TIA) or stroke.

The lesion-specific group includes ostial stenosis, last patent conduits, presence of a severe multivessel coronary artery disease (defined as a SYNTAX score > 33 [8, 9]), chronic total occlusions (CTOs), heavily calcified lesion, and significant stenosis involving the left main (LM) or its bifurcation.

Conversely, the group of items referred to clinical presentation refers to the hemodynamic status, left ventricular function, and presence or risk of electrical instability.

Rationale of mechanical circulatory support during HR-PCI

Physiologically, PCI systematically induces a transient myocardial ischemia, which is generally well tolerated in patients without significant comorbidities and/or impaired hemodynamic compensatory mechanisms. Conversely, those subjects with a basal poor left ventricular (LV) function, either for acute or chronic causes, multiple comorbidities, and/or severe CAD, cannot be able to face the transient PCI-related ischemia [10]. As consequence, a prophylactic cardiac assistance provides a more stable hemodynamic profile during both the procedure post-operative period.

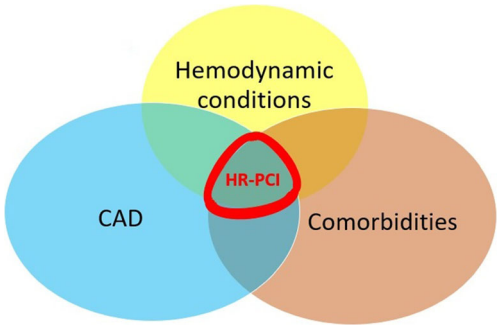


Fig. 1 Graphical representation of combined features related to the three main clinical areas currently defining high-risk PCI. CAD: coronary artery disease; HR-PCI: high-risk PCI

Interventional cardiologists and HR-PCI: when and why?

It is not possible to plot all the potential scenarios in which interventional cardiologists can be involved in the support of HR-PCI patients. Indeed, critical care can be required both in the pre- and/or post-operative period. A protective PCI can be performed in high-risk patients without any complications and/or the need of post-operative advanced monitoring/support. At the same manner, patients admitted with ST-segment elevation myocardial infarction (STEMI) having multiple organ failure can require either a pre-operative hemodynamical stabilization

Table 1 Characteristics related to a higher peri-operative risk in patients undergoing percutaneous coronary intervention

Patient-specific	Lesion-specific	Clinical presentation
Age > 75 years	Ostial stenosis	Hemodynamic status
Diabetes mellitus	Last patent conduits	Left ventricular function
Chronic kidney disease	Severe multivessel coronary artery disease (SYNTAX score > 33)	Arrhythmias or electrical instability
Chronic obstructive pulmonary disease	Chronic total occlusions	
Severe heart valvular disease	Heavily calcified lesion	
Heart failure	Significant stenosis involving the left main	
Previous myocardial infarction	Left main bifurcation stenosis	
Peripheral artery disease		
Previous transient ischaemic attack or stroke		

followed by advanced life support during the post-procedural period in CCU.

Percutaneous devices for high-risk PCI: a brief overview

The aim of short-term MCS in HR-PCI is to reduce both myocardial work and oxygen demand while maintaining adequate systemic and coronary perfusion [5]. From a theoretical point of view, the optimal device should be able to increase the mean arterial pressure (MAP), cardiac output (CO), and coronary artery perfusion while unloading the left ventricle (LV) and reducing the cardiac work (CW). In daily clinical practice, MCS has been provided using different temporary percutaneous devices, as the "traditional" intra-aortic balloon pump (IABP), the Impella (ABIOMED Inc, Danvers, Massachusetts, US) or the TandemHeart (Cardiac Assist Inc, Pittsburgh, Pennsylvania, US) platforms, which are frequently named percutaneous ventricle assist devices (pVAD), or the VA-ECMO. These devices can provide different types of MCS, for different periods of time and clinical scenarios. Furthermore, the VA-ECMO, due to its properties, is generally used in combination with other MCS devices. Despite the description of their properties is out of the aim of the present review, a brief comparison of these devices is given in Table 2.

In everyday practice, the real challenge remains to choose which device offers the most adequate support in each patient. Generally, in patients with pre-shock (defined as a systemic hypoperfusion with a systolic blood pressure < 100 mmHg), hemodynamic support is generally provided using intra-aortic balloon counterpulsation (IABC) [11]. Conversely, patients with severe CS should receive a pVAD as first-line treatment, while, in case of further clinical deterioration such as refractory CS shock or cardiac arrest supported with cardiopulmonary resuscitation after an acute myocardial infarction (AMI), the MCS is further escalated to VA-ECMO (Fig. 2) [12].

VA-ECMO properties

VA-ECMO provides excellent circulatory support and blood oxygenation also in HR-PCI patients. Most of the available data on the use of VA-ECMO in these groups of patients have been obtained by single-center, observational, or single-series studies [13]. Unfortunately, VA-ECMO is unable to effectively unload the left ventricle (LV) since it increases both the afterload and thereby the myocardial oxygen consumption and myocardial work [14]. Furthermore, a higher afterload progressively leads to LV distension, intracardiac thrombosis, pulmonary edema, and hemorrhage, which represents some of the potential adverse events related to the VA-ECMO use. To prevent these hemodynamic unfavorable effects, VA-ECMO is generally used in combination with other devices for MCS such as Impella or IABC.

Different cannulation strategies can be adopted for VA-ECMO patients. Among these, the central cannulation remains the method of choice for patients with shock post-cardiotomy. Conversely, the peripheral cannulation currently represents the most commonly applied approach. Generally, the right femoral vein is used as venous cannulation with its tip lying in the right atrium (RA). Instead, for the arterial cannulation, the contralateral side is adopted. Moreover, in recent years, also, an upper extremity cannulation has been also adopted using an internal jugular venous and axillary artery arterial cannulas [15].

VA-ECMO implantation

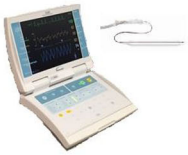
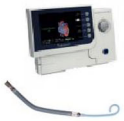
VA-ECMO can provide full hemodynamic support, independently from the underlying heart rhythm, simultaneously reducing carbon dioxide (CO_2) and adding oxygen (O_2) to venous blood before returning to the arterial circulation, bypassing pulmonary circulation. VA-ECMO insertion can be performed using central or peripheral cannulation. In the setting of HR-PCI, the peripheral approach is generally preferred since it allows an easier cannulation and decannulation. Specifically, venous cannulation can be performed using both an infrahepatic inferior vena cava cannula or a large 21–25 French cannula inserted in the femoral vein with its tip in the RA. Conversely, oxygenated blood is returned via the arterial cannula (17–21 French) inserted in the femoral artery. The tip of the venous and arterial cannula end into the right atrium (RA) and in the iliac artery, respectively [6].

Use and potential complications of VA-ECMO

Peripheral cannulation for the use of VA-ECMO can be also performed at bedside without the need of fluoroscopy or echocardiography. However, the larger part of VA-ECMO implantation is performed in cath-lab because these patients frequently had arterial and/or venous occlusive disease. Despite that the platform is completely transportable, cannula misplacement and/or dislodgments can be carefully avoided, especially during the patients' mobilization.

Among the device-related complications, vascular injuries, due to the large cannula size, bleeding events,

Table 2 Comparison of different mechanical circulatory support devices (MCS) used in high-risk percutaneous coronary intervention

	IABP	IMPELLA			TANDEMHEART	VA-ECMO
						
		2.5	CP	5.0		
General features						
Cardiac flow (L/min)	0.3-05	1.5			2.5-5	3-7
Mechanism	Aorta	Left ventricle→ Aorta			Left atrium→Aorta	Right atrium→Aorta
Cardiac Synchrony or stable rhythm	Yes	No			No	No
Implant days	Weeks	7 days			14 days	Weeks
Hemodynamic properties						
MAP	↑	↑↑			↑↑	↑↑
Afterload	↓	↓			↑	↑↑↑
LVEDP	↓	↓↓			↓↓	↔
PCWP	↓	↓↓			↓↓	↔
LV Preload	-	↓↓			↓↓	↔
Coronary artery perfusion	↑	↑			-	-
Myocardial oxygen demand	↓	↓↓			↓	↔
Contraindications						
Valve disease	Moderate to severe AR	Moderate to severe AR			Moderate to severe AR	Moderate to severe AR
Aortic disease	Aortic disease	• Aortic Stenosis (AVA <0.6) • Mechanical aortic valve				
PAD	Severe PAD	Severe PAD			Severe PAD	
Anticoagulation		Contraindications to AC			Contraindications to AC	Contraindications to AC
Intracardiac thrombosis		LV thrombus			LA Thrombus	
Coagulation disorders					HIT	
					DIC	
Septal defects					VSD	
Complications						
Stroke	X	X			X	
Limb Ischemia	X	X			X	X
Vascular trauma	X	X			X	X
Infection	X	X			X	X
Haemolysis/ bleeding (risk)	X (+)	X (++)			X (++)	X (++)
Device dislodgment/migration	X	X			X	
AKI	X					X
Thromboembolism					X	X
Neurological injury						X
Device Thrombosis		X				
Compartment syndrome						X
Balloon rupture	X					

MAP mean arterial pressure, *LVEDP* left ventricular end-diastolic pressure, *PCWP* pulmonary capillary wedge pressure, *AR* aortic regurgitation, *PAD* peripheral artery disease, *AC* anticoagulation, *LV* left ventricle, *LA* left atrium, *HIT* heparin-induced thrombocytopenia, *DIC* disseminated intravascular coagulation, *VSD* ventricular septal defect, *AKI* acute kidney injury

hemolysis, infections, stroke, neurological or acute kidney injuries (AKIs), and pulmonary edema, are the most frequently observed. While the management of systemic complications can be managed by the interventional

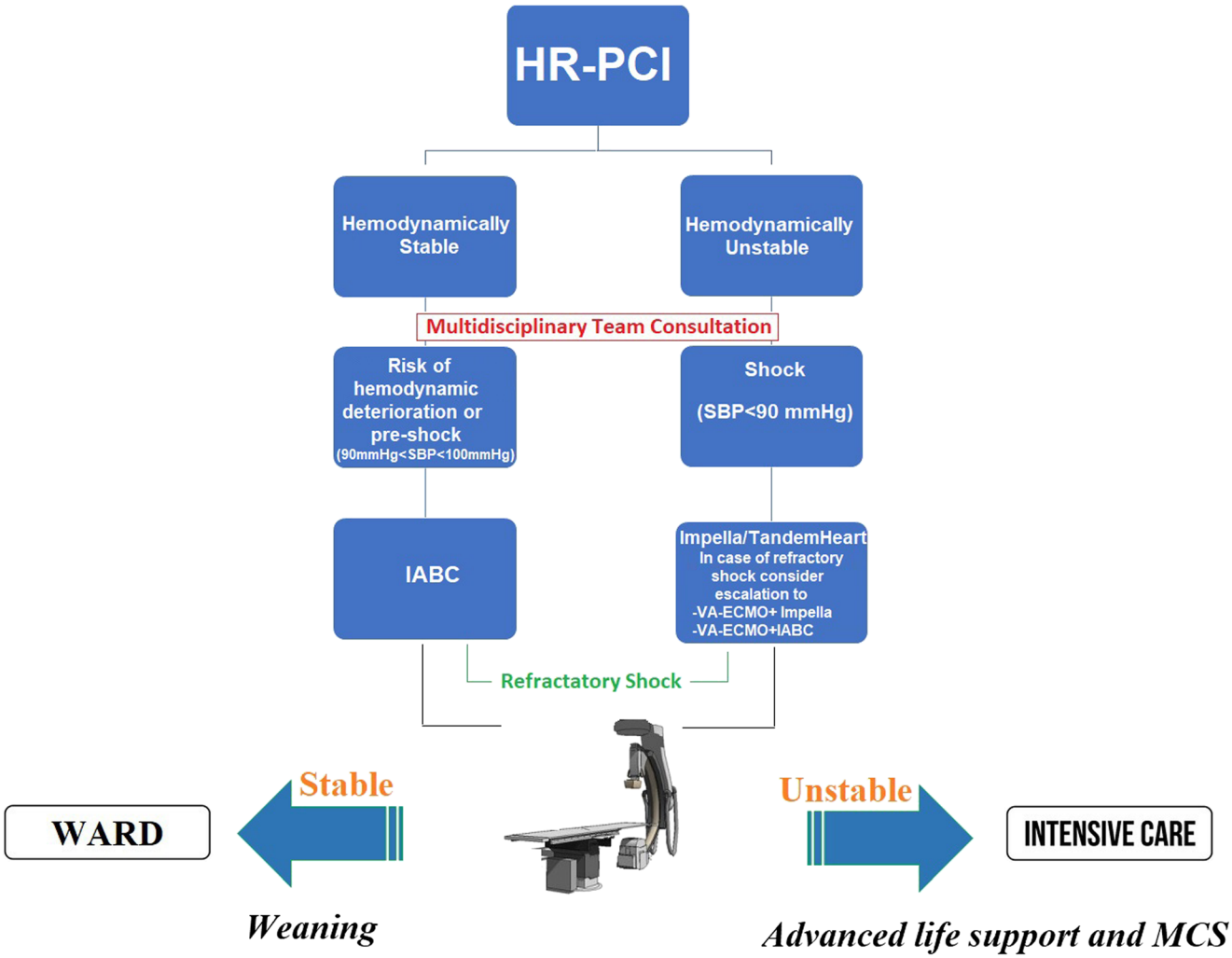


Fig. 2 Types of mechanical circulatory support provided accordingly to the baseline patient's hemodynamic status. SBP: systolic blood pressure; IABP: intra-aortic balloon-pump

cardiologists and/or intensivists, issues related to the cannulation require the coordination with the interventional cardiologist.

Current evidences supporting the use of VA-ECMO in high-risk PCI

General aspects

Shaukat et al. described the use of VA-ECMO in five patients treated with elective high-risk PCI with ECMO support. In all cases, MCS was successfully weaned within 24 h without any post-procedural complication or major adverse cardiovascular events (MACE) within 1 year [16]. Similarly, the reduced incidence of MACE and cerebral events as well as the more favorable short-term outcome in HR-PCI patients supported by VA-ECMO has been reported by Tommasello et al. [13]. Huang et al. successfully demonstrated that prophylactic ECMO implantation in STEMI patients with refractory CS significantly improved both short- and long-term outcomes [17].

Concurrent implantation of VA-ECMO and Impella: "EC-PELLA"

Patients supported with VA-ECMO need to be unloaded to prevent a failing static LV. In this regard, different investigations have demonstrated that the concomitant implantation of the Impella system in these patients (so-called "EC-PELLA") is a viable solution. Patel et al. analyzed the largest US-based dataset on the use of VA-ECMO, with and without simultaneous Impella support, in patients with refractory CS. They demonstrated that the addition of the Impella system was significantly associated with a lower 30-day all-cause mortality as well as lower need for inotropic support and a comparable safety profile as compared with VA-ECMO alone [18]. Similar findings were reported by Pappalardo et al. in a 2:1

propensity-matching analysis based on the comparison between patients treated with and without the combination of VA-ECMO and Impella®. They demonstrated that patients in the VA-ECMO and Impella group had a significantly lower hospital mortality (47% vs. 80%, $P < 0.001$), higher rate of successful bridging to either recovery or further therapy (68% vs. 28%, $P < 0.001$) compared with VA-ECMO patients. No significant differences in the occurrence of major bleeding events were observed among the two groups ($p = 0.6$) [19]. Akanni et al. recently reported in a retrospective analysis comparing patients treated with pLAVD or only VA-ECMO therapy that despite a higher rate of hemolysis in the former (44.83% vs 17.35% $p = 0.002$), the combined use of VA-ECMO and pLVADP may improve or circumvent LV distension in refractory CS [20].

Concurrent implantation of VA-ECMO and intra-aortic balloon pump

Despite used less frequently, the combination of a VA-ECMO plus IABP has demonstrated to effectively unload the LV by different clinical investigations (Fig. 3) [21]. Li et al. compared the effect of VA-ECMO plus IABP with that of VA-ECMO alone in a meta-analysis based on 29 studies. These authors reported that VA-ECMO plus IABP was associated with decreased in-hospital deaths [risk ratio (RR) 0.90; 95% confidence interval (CI) 0.85–0.95; $P < 0.0001$]. Furthermore, IABC was associated to decreased in-hospital mortality of patients with extracorporeal cardiopulmonary resuscitation, post-cardiotomy CS, and ischemic heart disease. Intriguingly, gastrointestinal, neurological, and limb-related were comparable between the two groups [22].

Tandem heart, Maquet Cardiohelp, and VA-ECMO

The TandemHeart® device (CardiacAssist Inc.) is an external centrifugal pump that can be used in HR-PCI patients. This MCS device consists in a 21-Fr inflow cannula placed transeptally into the LA and an outflow cannula placed into the femoral artery. Cannulation requires to be done in the Cath lab using fluoroscopy and echo guidance. However, the need for transeptal puncture has and still represents the major limitation for operators [23]. Other investigations have reported that an adequate hemodynamic support in HR-PCI patients can be rapidly achieved with excellent procedural success [24]. Negi et al. have compared the TandemHeart and VA-ECMO in patients with AMI and refractory CS demonstrating a no significant differences in survival rate as well as in the incidence of complications such as limb ischemia, significant hemolysis, need for renal replacement therapy (RCT), stroke or recurrent myocardial infarction between the two groups. However, a higher incidence of ventricular arrhythmic events was registered in VA-ECMO patients (16% vs. 50%, $p = 0.02$) [25]. Similarly, Chamogeorgakis et al. demonstrated no differences in the short-term mortality in CS patients supported with VA-ECMO and TandemHeart or Impella [26]. Moreover, Bernhardt et al. have demonstrated that the use of TandemHeart in an ECMO represents a feasible and sage prevention strategy for pulmonary edema and an adjunctive treatment able to facilitate the weaning from VA-ECMO in patients with CS and LV thrombus [27]. As for the Impella, limb ischemia, hemolysis, vascular trauma, thromboembolism, and cardiac tamponade are potential life-threating complications related to the use of this MCS device.

Some interesting data has been presented also using the Maquet Cardiohelp (MAQUET Cardiopulmonary AG; Germany). This device is currently the world's smallest portable heart-lung support system, available mostly for ECMO patients who need transportation. The Maquet Cardiohelp is able to provide several clinical information such as system pressures, mixed venous oxygen saturation, and hematocrit utilizing the incorporated sensors. Its use in the setting of HR-PCI has been successfully presented by different investigations [28–30].

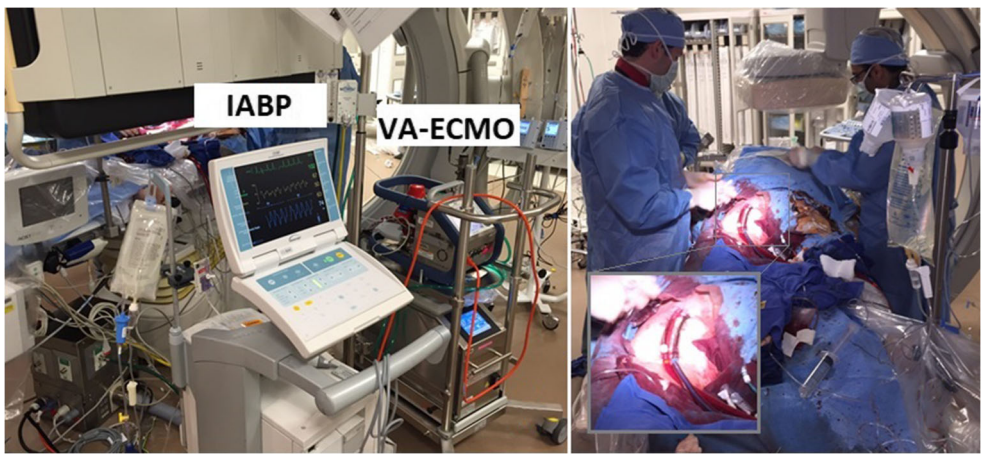


Fig. 3 **a** An example of patient with complex PCI and high-risk features assisted by IABP + Impella. **b** Mechanical circulatory support provided by IABP plus VA-ECMO. The position of ECMO's venoarterial cannulas, inserted percutaneously, is highlighted into the magnification

Intensive care monitoring and weaning from VA-ECMO

Hemodynamic monitoring is central in the management of ICU patients, especially in those receiving MCS. Adequate monitoring plays a pivotal role in assessing the course of the underlying life-threatening cardiac and/or respiratory diseases. Moreover, its appropriate use remains fundamental to plan the timing of weaning from the MCS. The weaning planification must carefully outweigh the risk of mortality or adverse events towards the myocardial recovery. Two different groups of issues should be considered: patient- and device-related monitoring (Table 3) [31]. Volume status, degree of LV pressure unloading, mean arterial pressure (MAP), central venal pressure, and PCWP are essential to maintain or add additional LV unload. Most of HR-PCI patients require additional vasopressor support which must be tailored only after considering the patient's volume status (Fig. 4). As evidenced in Table 3, bedside transthoracic echocardiography (TTE) plays a fundamental role not only for monitoring the clinical course of the underline ischemic cardiomyopathy but also to detect complications and support the decision making. Conversely, different investigations have demonstrated that cardiac biomarkers are not useful for identifying those who will recover [32].

To date, only few investigations have analyzed potential strategies for weaning from VA ECMO [33–35]. To over-complicate this matter, the percentage of patients successfully weaned from ECMO varies from 31 to 76%, depending on the underlying cause of CS and the definition of successful weaning [36]. Moreover, weaning does not mean survival, because up to 65% of patients weaned from VA ECMO support do not survive to hospital discharge [37, 38]. Current recommendations and TTE criteria for the weaning from VA-ECMO are resumed in Fig. 5a, b, respectively. It is useless to attempt weaning within the first 72 h after VA ECMO implantation, because damaged organs need time to recover. Previous investigations have reported that patients could be considered for VA ECMO weaning when the following hemodynamic parameters are maintained with the pump off: cardiac index > 2.4 L/min/m^2, MAP > 60 mmHg, pulmonary capillary wedge pressure < 18 mm Hg, and central venous pressure < 18 mmHg [38, 39].

Previous efforts, made to identify potential predictors of successful weaning from VA-ECMO, have demonstrated that only the pulse pressure appeared to be unquestioned clinical factor associated with weaning success [33, 40, 41]. Further studies are needed to recognize potential markers of successful weaning from VA-ECMO, especially in those requiring a relative short MCS, such as HR-PCI patients.

VA-ECMO and the right ventricle

As known, the RV is a thin-walled and compliant chamber which has received less attention over the years when compared to LV. As a matter of fact, nowadays, no clinical trials have investigated the effect of VA-ECMO alone in the treatment of acute RV failure despite several investigations have reported the efficacy and feasibility of this MCS in these patients [42]. However, despite VA-ECMO results not able to intrinsically unload the LV, especially when the LV function is severely compromised, it is able to efficiently unload, when used alone, both the right atrium (RA) and ventricle (RV) by decreasing the right ventricular preload [43]. Unfortunately, the assessment of the RV function during full VA-ECMO support remains difficult because the ECMO circuit creates negative pressure and drains venous blood from the RA [37].

Determination of the left ventricular (LV) and right ventricular (RV) function before ECMO weaning remains essential to predict biventricular or univentricular recovery. Indeed, lack of recognition of significant coexisting RV dysfunction may significantly increase the post-procedural morbidity and mortality as well as requiring prolonged inotropic agents, biventricular device support, or prolonged extracorporeal support [34]. Moreover, animal models have demonstrated that the unloaded RV during VA-ECMO support has a lower metabolic flexibility contributing to the inability to increase high-energy phosphate reserve during MCS [44]. In this setting, adjuvant RV support during weaning can be required. Surely, further translational and clinical studies are needed to further optimize the management of the RV in patients requiring VA-ECMO support, especially after HR-PCI.

Post PCI management

From a theoretical point of view, VA-ECMO and other types of MCS should be removed at the end of the HR-PCI in cath-lab unless the weaning cannot be performed. In this regard, no specific criteria still exists, and in most of the case, a patient-tailored approach is generally performed. However, some generic criteria, based in part on those used for the standard weaning from VA-ECMO, should be used to determine in which patients the MCS can be stopped at the end of coronary artery procedure. During the weaning trial, if the patient maintains a MAP ≥ 65 mmHg, a CVP < 15 mmHg, a LVEF ≥ 25%, in the absence of LV or RV dysfunction and preserved respiratory function (evaluated in terms of FiO2 and PaO2 10 min after having decrease the ECMO and sweep gas flows), absence of intra-procedural complication and a successful revascularization defined and a TIMI 3 flow in all treated lesions, physicians can consider to stop the MCS directly in the cath-lab. However, in the presence of significant comorbidities (either cardiac, respiratory, or metabolic) as well as in patients which had a higher probability of early clinical

Table 3 Patient- and device-related issues requiring monitoring in high-risk percutaneous coronary intervention patients supported with VA-ECMO

Patient-related issues	Parameters	Useful to plan and evaluate the weaning phase	TTE
Hemodynamic issues			
LV load	LVEDD		*
	Grade of MR		*
	PCWP		
LV inotropic-afterload relation	Pulsatility of arterial blood pressure		
	Opening of the aortic valve		*
RV preload	Size of the RA	*	*
Volume status	CVP		
LV-inotropy	LVEF	*	*
RV-inotropy	RVEF; TAPSE	*	*
LV-preload	PCWP	*	*
LV-afterload	MAP	*	
Heart rate:	Continuous ECG		
Microcirculation	Serum lactate	*	
Cardiac output	Central venous O2-saturation	*	
Perfusion			
Leg ischemia	Clinical signs	*	
Peripheral ischemia	Serum lactate	*	
Cardiac ischemia	cTn	*	
Ventilation and gas exchange			
Adequate gas exchange and prevention of VILI	ABG; pulse oximetry; lung imaging (either x-ray or US)	*	
Anticoagulation status and prevention of haemolysis	ACT, fibrinogen, platelets, LDH, haptoglobin, indirect bilirubin, reticulocytes		
Monitoring of underling disease or patient's general assessment	Routine laboratory tests		
Device-related issues			
Bleeding, infections at the cannula site insertion	Inspection		
Cannula dislodgment at the insertion site	Inspection		
Pump function	Pump driving speed, pump minute volume, Temperature, FiO2, arterial pressure, venous suck pressure	*	

LV left ventricle, *RV* right ventricle, *LVEDD* left ventricular end diastolic diameter, *MR* mitral regurgitation, *PCWP* pulmonary capillary wedge pressure, *RA* right atrium, *CVP* central venous pressure, *LVEF* left ventricular ejection fraction, *RVEF* right ventricular ejection fraction, *TAPSE* tricuspid annular plane systolic excursion, *MAP* mean arterial pressure, *cTn* cardiac troponin, *ABG* arterial blood gas analysis, *LDH* lactate dehydrogenases, *TTE* transthoracic echocardiography

decompensation due to the type of the lesion treated (last conduit, left main, or left main bifurcation) or have experienced significant arrhythmic event during the PCI, the weaning from the MCS should be delayed [39, 40].

After the PCI, a more intensive and medical and nursing cares are required for these patients. Several problems can be encountered during VA-ECMO support (Table 4). In this regard, vascular access and limb perfusion must be carefully monitored. Cannula dressings may be performed by nursing staff following consultation with the interventional cardiologist or the ICU physician. A standard invasive line dressing procedure should be used without using alcohol-based solutions but applying betadine and subsequently covering with an occlusive and transparent dressing. During the procedure, the sterility of the operator must be guaranteed.

Prevention of limb ischemia represents another fundamental aspect of the post-operative management. A recent meta-analysis has reported that this complication occurs in about 17% of VA-ECMO patients while among these, 10% progress to compartment syndrome and 4.7% to amputation [45]. To avoid these events, some techniques can be adopted to improve the distal arterial flow in the limbs. A distal perfusion

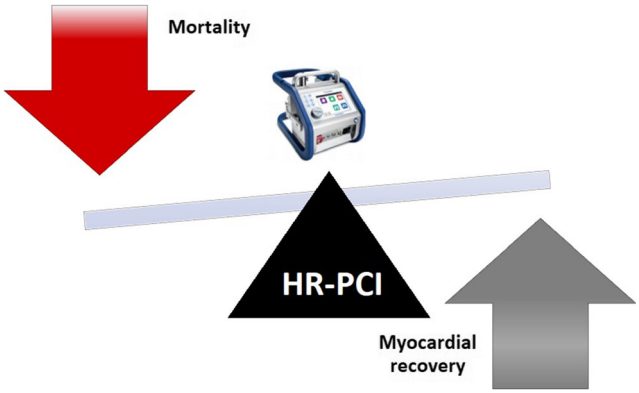


Fig. 4 VA-ECMO weaning planification must carefully outweigh the risk of mortality or adverse events towards the myocardial recovery

cannula (DPC) could be inserted distally to the arterial return cannula or a T-graft can be performed in place of a direct arterial cannulation, but this last one approach required a surgical approach which can lead to the hyperemia of the limb [46, 47].

A major disadvantage of peripheral cannulation is represented by the risk of the so-called Harlequin or North-South syndrome. This event is observed as a consequence of upper body hypoxemia which can be due to the concomitant lung failure or wrong ventilator settings. From a pathophysiological point of view, this event occurs when well-oxygenated retrograde blood from the femoral arterial cannula meets poorly oxygenated blood from the LV. In these patients, the blood perfusing the brain, the heart, and the upper extremities may have a saturation below the 90%. After a prompt recognition, ventilator setting must be adjusted to improve the oxygenation of pulmonary venous return or by decreasing the LVEF. Alternatively, a V-VA ECMO should be considered [15].

Always to prevent bleeding and thrombotic events, an adequate anticoagulation must be maintained. Nowadays, anticoagulation therapy in HR-PCI patients is adjusted accordingly to the activated clotting time (ACT). Unfractionated heparin (UFH) currently remains the main anticoagulant in VA-ECMO patients after a HR-PCI due to its rapid onset and potential neutralization with protamine sulfate. Indeed, these patients are generally treated also with antiplatelet drugs due to the recent PCI. It is easy to imagine that the bleeding risk and the occurrence of bleeding events often happen. In some patients, the administration of UFH may cause a heparin-induced thrombocytopenia (HIT) which must be promptly recognized and managed modifying the anticoagulation strategies. In this scenario, thrombin inhibitors (e.g., Bivalirudin or Argatroban) must be administered; these drugs are independent from the antithrombin levels , have no antagonists and a lower coagulative inhibition in area of stasis [48, 49].

Different alarms can be set on the ECMO console. In this regard, it is important to consider that when an alarm is set on, the VA-ECMO stop working and an immediate must be set to resolve the problem. The continuous presence of a bedside or ICU perfusionist should be highly due to the profound impact on the patient's care. However, the perfusion services must be contacted regarding all circuit issues related to VA-ECMO and the contact information for the perfusionist-on-call must be provided at the bedside [50].

A real emergency is represented by the membrane oxygenator rupture. Small defects in the integrity of the blood/gas barrier with little bleeding can be tolerated because the small tear will usually clot off. However, major bleeding events require an emergent oxygenator change. Despite that it is a rare event, a massive air embolus and death can occur in this scenario.

A close collaboration between physicians, registered nurses (RNs), and perfusionists plays a pivotal role in the management of these complex patients. In this regard, an adequate and interdisciplinary training as well as shared operative protocols are required.

Mechanical ventilation

Patients with a low CO are generally predisposed to decrease pulmonary compliance, to V/Q mismatch and premature airway closure. Similarly, HR-PCI patients, especially those with

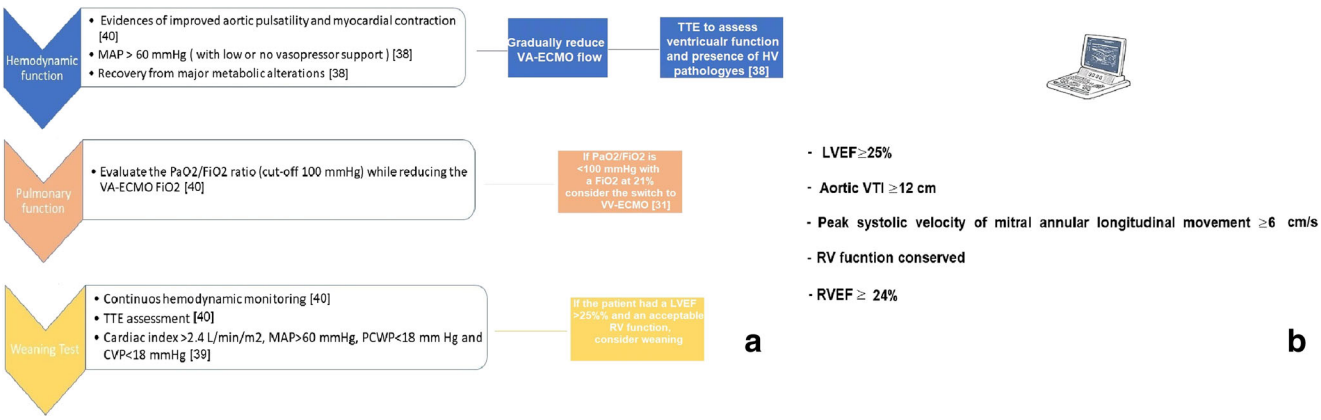


Fig. 5 **a** Current recommendations for the weaning from VA-ECMO obtained by reviewing the current literature. **b** Current echocardiographic criteria for VA-ECMO weaning

Table 4 Common and life-threatening problems related to the use of VA-ECMO

Problems and potential causes	Clinical presentation	Actions
Common problems		
Bleeding cannula site	Bleeding from the vascular access	-Confirm that the cannula is properly positioned. -Thrombotic dressings -Direct manual pressure (or with a sandbag) -Decrease the ACT target -Local injections of adrenaline (1:200,000) or adrenaline-soaked gauze -Re-cannulation
Limb ischemia -Arterial embolism -Haematoma compression -Large femoral arterial cannula (not allows retrograde perfusion)	Range from pain of different severity to pallor, poikilothermia, motor or sensory deficit and gangrene.	-Perform a Doppler US of lower extremities Consult the vascular surgical team
Flow-fluctuation -Problem with the venous access line -Low venous pressure.	Values on VA-ECMO control panel	-Assess the venous access line and correct the venous pressure if low
Circuit thrombosis	Related to the thrombotic burden	-Small clots in the oxygenator don't tend to modify the VA-ECMO function and can be monitored. -Provide adequate anticoagulation -Arrange staff and exchange the thrombosed circuit element.
Decreased venous pressure - Low intravascular volume - Increased intrathoracic pressure - Increased intraabdominal pressure	Values on VA-ECMO control panel	-Correct the intravascular volume and/or modify the ventilation settings
Severe problems		
Motor failure	Resembles cardiac arrest. Specific alarm can be present on the VA-ECMO console	-Hand-cranking the pump while getting a new motor console.
AC power failure	Resembles cardiac arrest.	-Hand-cranking the pump while trying to re-establish AC power.
Pump head disengagement	Resembles cardiac arrest. an unusual grinding noise and vibration of the pump head should be perceived	-Clamp the venous line -Re-engage the pump head -Turn the pump to a slow RPM setting (about 1000 RPM) and unclamp the line -Gradually increase the RPM to the previous setting -If the grinding sound persist the circuit needs to be changed urgently
Pump flow sensor failure	Specific alarm on the VA-ECMO console	-In the absence of clinical modification or sudden cardiac arrest the problem is due to the ultrasonic flow sensor. Contact the perfusionist
Accidental venous access decannulation	Bleeding loss from the cannulation site (in patient with central cannulation means blood loss from the RA.	-Start CPR -Control bleeding -Re-establish the vascular access -Obtain another circuit
Accidental arterial access decannulation	Cardiac arrest	-Clamp immediately the line -Stop the pump -Start CPR. -Control bleeding: (in case of peripheral cannulation attempt to control the bleeding by manual pressure while in patients centrally cannulated contact the cardiac surgeon for urgent thoracotomy -Replace the blood loss as fast as possible -Re-establish the vascular access -Obtain another circuit
Air embolism	Cardiac arrest	-Clamp the circuit -Start CPR -Carefully evaluate the patient for systemic embolism and consider neuroprotective measures as hypothermia

ACT activated clotting time, *US* ultrasound, *RPM* revolutions per minutes, *RA* right atrium, *CPR* cardio-pulmonary resuscitation

concomitant respiratory comorbidities, often need mechanical respiratory support in both peri- and post-operative period. Obviously, the duration and type of mechanical ventilation depend on the basal lung functions and underlying disease. The lung protective principles are useful among the different ventilation strategies adopted during VA-ECMO support. The addition of positive-end-expiratory pressure (PEEP) could be helpful in treating those patients with an afterload-dependent LV failure since its application decreases peripheral vascular residences (PVR). On the contrary, lower levels of PEEP are suggested for those subjects experiencing a preload-dependent myocardial failure [51–54]. As well known, weaning from MV and subsequent shift to spontaneous breathing can be difficult and associated with adverse hemodynamic events. Indeed, spontaneous breathing causes both hemodynamic and neuroendocrine effects: the former encompasses a decrease in intrathoracic pressure which leads to an increase in LV afterload and venous return, resulting in increased RVEDV and LVEDV, while the latter leads to an increase in the myocardial oxygen consumption due to a significant sympathetic activation. This last neuroendocrine activation is generally more pronounced in COPD patients which had a significant higher risk of complications during the weaning process [55, 56]. Importantly, HR-PCI patients supported with ECMO represent a subgroup of patients at higher risk of ventilatory-induced lung injury (VILI). Several mechanisms have been recognized such as the alveolar strain, the occurrence of an atelectrauma, or reabsorption atelectasis. However, as generally recommended, an appropriate ventilator setting can limit the risk of alveolar overdistension or strain.

General considerations for high-risk PCI patients in CCU

Analgesia and sedation

Analgesic protocols and data for acute pain management and sedation of HR-PCI patients are scant. HR-PCI patients generally experience somatic pain at the drain and vascular cannulation sites. However, also endotracheal suctioning and mobilization are non-neglectable causes of pain during ICU stay. The administration of both analgesics and sedatives is necessary in MCS patients to provide optimal and safe care. A deeper sedation with muscle relaxants has different beneficial effects as the optimization of blood flows and gas exchange [39]. Furthermore, it is fundamental to avoid any cannula movement which may lead to dislodgements and complications as hemolysis. Pain management and sedation must begin before PCI and then must be continued after the procedure, tailored based on validated scales. Both overdoses and underdoses of medications for pain controls should be avoided. However, choosing the most adequate analgesic agent in these patients is often a challenge among the available drug armamentarium. The selection must take into account the pharmacodynamic and pharmacokinetic properties as well as the ongoing organ dysfunctions. Among the opioids, fentanyl and morphine have been reported as the most frequently administered while among sedatives, midazolam and propofol have been suggested [57]. For ECMO patients requiring high dose of opioids and sedatives during ECMO support, ketamine has been suggested as a viable alternative [58].

Electrolytes and metabolic alterations

Maintenance of electrolyte concentrations as well as fluid balance and acid-base homeostasis is vital to ensure body function. The prompt recognition of these disorders, which are frequently observed in HR-PCI patients hospitalized in ICU, is crucial to prevent further cardiac impairment or neurological complications. At the same manner, both hypovolemia and fluid overload must be avoided. In this regard, diuretic agents are doubtless helpful to assist fluid balance; however, it is important to underline that adverse events related to diuretic administration are dose dependent. Since no specific studies have yet been performed on these issues in HR-PCI patients' traditional therapeutic strategies, based on fluid administration, electrolyte substitution and in some cases to extracorporeal filtration must be adopted also in this subgroup of patients. Reviewing the available literature, Schmidt et al. have demonstrated that a positive fluid balance over the first 3 days in HR-PCI patients supported with VA-ECMO was an independent predictor of 90-day mortality [59].

Drug administration

In VA-ECMO patients, the drug dose should be optimized. Indeed, the interaction between the ECMO circuit and the physicochemical properties of several drugs may lead to significant changes in the pharmacokinetic and pharmacodynamic properties modifying the dosing requirements. Moreover, the ECMO alters the apparent volume distribution (Vd) through the hemodilution from priming solution, drug sequestration, and ECMO-related physiological changes. These aspects must be carefully considered when antibiotics, vasoactive drugs, and diuretic agents are administered [60, 61].

Acute kidney injury

Acute kidney injury (AKI) represents a frequent and serious complication in patients admitted to CCU with severe HF. Different degrees of renal impairment can be observed in patients requiring HR-PCI. In the same manner, different underlying processes, such as nephrotoxicity, hemodynamic, neurohormonal, or inflammatory abnormalities, can be encountered in daily clinical practice [62]. Considering that traditionally monitoring of renal function, based on serum creatinine or urea, has a limited use in critically ill patients, a daily

evaluation based on the urinary creatinine clearance or on the estimated glomerular filtration rate (eGFR) must be performed. In elective procedure, baseline renal function, evaluation of comorbidities influencing the renal filtration, as arterial hypertension, diabetes, anemia, or high dose of diuretics must be carefully evaluated to minimize AKI. A fundamental aspect is represented by a careful pre-operative assessment of renal function in those patients with pre-existing renal impairment that may be aggravated by intravenous contrast media. Contrast-induced acute kidney injury (CI-AKI) represents another critical aspect in HR-PCI patients. Ideally, adequate pre-operative IV volume expansion is recommended 24 h before the procedure, as well as the discontinuation of drugs with some potential nephrotoxic or metabolic effects as metformin [63]. Low-contrast protocols and prophylaxis for contrast allergy must be encouraged and adopted whenever possible. Renal replacement therapy (RRT) must be adopted in life-threatening modifications. Ostermann et al. have reviewed the most common indications for RRT during and continuous renal replacement therapy (CRRT) during ECMO. Their results suggest that the optimal timing for initiation of CRRT must be individualized, considering the degree of fluid overload and severity of AKI-related metabolic derangements. CRRT can be provided using two different approaches: using an in-line hemofilter or a fully integrated CRRT device or through a parallel system with separate ECMO and RRT circuits [64].

Limitations

The term HR-PCI as well as the therapeutic strategies adopted to treat these patients represent a relatively new field of cardiovascular medicine. A larger part of data that support the use of VA-ECMO in combination with other MCS have been obtained from studies performed on patients with CS with or without AMI. Conversely, few studies have been performed specifically in HR-PCI patients. As a result, areas of uncertainty associated with the MCS in HR-PCI still exist also in the treatment of ECMO patients after HR-PCI. Further studies performed on these patients will help to further improve the MCS during PCI. Moreover, the aim of the review was not to perform a systematic analysis on the use of VA-ECMO in HR-PCI patients or a device-based review but to help physicians in the management of these complex patients which will become more frequent in the future.

Conclusions

As emerged by our review, the management of HR-PCI patients requires a holistic approach. Interventional cardiologists, clinical cardiologists, and cardiac surgeons must share their knowledge and expertise to treat these patients. Some important aspects, which are faced every day in CCU, have been poorly investigated in HR-PCI patients. In the field of HR-PCI, the role of interventional cardiologists ranges from the defining goals of care and preprocedural patient's optimization, managing concomitant severe comorbidities and provides an adequate postprocedural care. In this clinical setting, a synergic cooperation between intensivists and cardiologists may be useful to deliver a patient-individual tailored therapy to impact patients' outcomes. Hub and spoke models for HR-PCI must be clearly delineated such that community cardiology centers should be able to establish efficient transfer mechanisms for those patients requiring VA-ECMO support.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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