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JCS/JSCVS/JCC/CVIT 2023 Guideline Focused Update on Indication and Operation of PCPS/ECMO/IMPELLA

Takashi Nishimura; Yasutaka Hirata; Takayuki Ise; Hiroyuki Iwano; Hironori Izutani; Koichiro Kinugawa; Takeshi Kitai; Takayuki Ohno; Tomohito Ohtani; Takahiro Okumura; Minoru Ono; Kazuhiro Satomi; Akira Shiose; Koichi Toda; Yasumasa Tsukamoto; Osamu Yamaguchi; Takeo Fujino; Toru Hashimoto; Haruhiko Higashi; Akihiro Higashino; Toru Kondo; Hirotsugu Kurobe; Toru Miyoshi; Kei Nakamoto; Makiko Nakamura; Tetsuya Saito; Keita Saku; Shogo Shimada; Hiromichi Sonoda; Shinya Unai; Tomoki Ushijima; Takuya Watanabe; Kazuyuki Yahagi; Norihide Fukushima; Takayuki Inomata; Shunei Kyo; Tohru Minamino; Kenji Minatoya; Yasushi Sakata; Yoshiki Sawa on behalf of the Japanese Circulation Society, the Japanese Society for Cardiovascular Surgery, Japanese College of Cardiology, Japanese Association of Cardiovascular Intervention and Therapeutics Joint Working Group

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Refer to **Appendix 3** for the details of members.

Joint Working Groups: The Japanese Circulation Society; the Japanese Society for Cardiovascular Surgery; Japanese College of Cardiology; Japanese Association of Cardiovascular Intervention and Therapeutics; the Japanese Association for Thoracic Surgery; the Japanese Heart Failure Society; Japanese Society for Artificial Organs; Japanese Heart Rhythm Society; Japanese Society of Echocardiography; Japanese Society of Pediatric Cardiology and Cardiac Surgery; the Japanese Association of Cardiac Rehabilitation

Mailing address: Guideline Committee of the Japanese Circulation Society, 6th Floor, Uchikanda Central Building, 1-18-13 Uchikanda, Chiyoda-ku, Tokyo 101-0047, Japan. email: jcsGL@j-circ.or.jp

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Abbreviations

ACP	advance care planning
ACS	acute coronary syndrome
ACT	activated coagulation time
ADL	activities of daily living
AI	aortic insufficiency
ALT	alanine aminotransferase
AMI	acute myocardial infarction
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AVWS	acquired von Willebrand syndrome
BiVAD	biventricular assist device
BNP	B-type natriuretic peptide
BTB	bridge to bridge
BTC	bridge to candidacy
BTD	bridge to decision
BTR	bridge to recovery
BTT	bridge to transplantation
CK	creatine kinase
CPO	cardiac power output
CVP	central venous pressure
DIC	disseminated intravascular coagulation
DT	destination therapy
ECMO	extracorporeal membrane oxygenation
FAC	fractional area change
γGTP	gamma-glutamyltranspeptidase
GRV	gastric residual volume
IABP	intra-aortic balloon pumping
LDH	lactate dehydrogenase
LGE	late gadolinium enhancement
LVAD	left ventricular assist device
LVDd	left ventricular end-diastolic diameter
LVEDP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
MCS	mechanical circulatory support
NO	nitric oxide
NPPV	non-invasive positive pressure ventilation
NYHA	New York Heart Association
PAPi	pulmonary artery pulsatility index
PAWP	pulmonary artery wedge pressure
PCI	percutaneous coronary intervention
PCPS	percutaneous cardiopulmonary support
PVAD	percutaneous left ventricular assist device
RAP	right atrial pressure
RASS	Richmond agitation-sedation score
RCT	randomized controlled trial
ROSC	return of spontaneous circulation
RVAD	right ventricular assist device
RVSWI	right ventricular stroke work index
SCAI	Society for Cardiovascular Angiography and Interventions
SV	stroke volume
TAPSE	tricuspid annular plane systolic excursion
VAD	mechanical circulatory support

Introduction

Mechanical circulatory support (MCS) plays a significant role as a therapeutic option for severe heart failure, and its outcomes have been improving due to advancements in devices and management techniques. In particular, percutaneous cardiopulmonary support (PCPS) and extracorporeal membrane oxygenation (ECMO) have contributed to both expanding the range of conditions that can be treated and improving survival rates through the accumulation of knowledge on the clinical introduction, indications, and management of these novel devices in recent years. Additionally, the intracardiac implantable pump catheter for circulatory support, known as IMPELLA (the only such device available in Japan as of 2022), which was introduced for clinical use in Japan from October 2017, is a minimally invasive and rapidly deployable device that has demonstrated significant therapeutic effects, bringing about a paradigm shift in the management strategy for severe heart failure. MCS devices have been introduced at many institutions and are now used for many patients in daily practice. However, the evidence for the indications, management methods, and device selection is still insufficient, and each physician and facility is still accumulating experience in the treatment of patients. In Japan, continuous efforts are being made to overcome this situation, and new insights, such as those gained via the analysis of treatment outcomes using registry data for IMPELLA, are being compiled.[1]

In order to establish appropriate use and standardization of implantable ventricular assist device (VAD) therapy for severe heart failure patients in Japan, the Guidelines for device therapy: implantable left ventricular assist device for patients with severe heart failure were published in 2013 with the aim of achieving benefits from VAD therapy equivalent to or greater than those in Europe and the USA.[2] The role of MCS in the overall management of heart failure is also mentioned in the Guidelines for diagnosis and treatment of acute and chronic heart failure (revised in 2017) published in 2018.[3] Furthermore, the Revised 2021 Guideline on implantable left ventricular assist device for patients with advanced heart failure was published in 2021, and incorporates the latest evidence, including expanded indications for new devices and long-term destination therapy (DT).[4] The main purpose of this Focus Update is to provide guidelines for the appropriate use and safe management of MCS, especially PCPS, ECMO, and IMPELLA, in the treatment of severe heart failure. Currently, much of the knowledge in this field in Japan is based on analysis of a few relatively small case series in

individual facilities. Therefore, in this Focus Update, specific classes or levels of evidence are not strictly mandatory, but rather they are presented as expert consensus. However, we strongly hope that this Focus Update will (1) serve as a guideline for the standardization of PCPS, ECMO, and IMPELLA therapy within Japan, (2) be widely used by various healthcare professionals including physicians, nurses, clinical engineers, and other professionals involved in this treatment, and (3) be continuously revised in the future.

I. Indications for PCPS, ECMO, and IMPELLA

1. Indicated Diseases and Conditions

IMPELLA and veno-arterial extracorporeal membrane oxygenation (V-A ECMO) have different support mechanisms and approaches to their application, and their use alone or in combination should be considered according to the patient's condition. For device selection, please refer to Section 8 (Device Selection for Temporary MCS) later in this chapter.

Regarding the clinical results of V-A ECMO in Japan, an analysis of diagnosis–procedure combination (DPC) data of 5,263 patients, showed that 64.4% were weaned, but the subsequent in-hospital mortality rate was as high as 37.9%.[5] J-PVAD (Japanese registry for Percutaneous Ventricular Assist Device), a registry of IMPELLA in Japan, reported the initial results of 823 patients: 30-day survival rates for patients treated with IMPELLA alone and ECPELLA (V-A ECMO plus IMPELLA) were 81.1% and 49.6%, respectively.[1]

1.1 Cardiogenic Shock Due to Acute Myocardial Infarction

Intra-aortic balloon pumping (IABP) has been widely used as a recommended Class I indication. Although it is less effective than other circulatory support systems in terms of both myocardial protection and systemic circulatory support, it is superior because it is relatively easy and rapid to introduce and can be used at many institutions. IABP-SHOCK II, a randomized controlled trial (RCT) on the prognostic value of IABP, showed a 30-day mortality rate of 39.7% in the IABP group and 41.3% in the control group,[6] and that IABP did not reduce myocardial infarct size.[7] The routine use of IABP is no longer recommended by either Western[8,9] or Japanese guidelines.[10] Its frequency of use in Europe and the USA is also declining, while the use of V-A ECMO and IMPELLA is on the rise.[11] However, in European guidelines there is currently no individual recommendation for V-A ECMO/IMPELLA, and the use of MCS is to be considered (recommendation Class IIb), taking into account the patient's background and condition.[12]

In the treatment of ischemic heart disease, the use of V-A ECMO may have a negative effect on recovery of cardiac function due to its potential to increase left ventricular (LV) afterload. Based on data from the Japanese Society of Percutaneous Cardio-Pulmonary Support/Extracorporeal Membrane Oxygenation, of 7,697 patients treated with V-A ECMO between 2013 and 2015 in Japan, in 321 cases it was used for supported percutaneous coronary intervention (PCI), and in 3,298 for acute heart failure.[13] Due to the use of V-A ECMO for treating cardiac arrest caused by fatal arrhythmias and other complications of acute myocardial infarction (AMI), conducting a rigorous RCT is challenging. Moreover, there is limited data on the global management of cardiogenic shock associated with MI, as the utilization of V-A ECMO is not high in Europe or North America.

Although the number of patients is limited and evaluation is restricted, a meta-analysis comparing 58 cases of V-A ECMO use and 37 cases of IABP use in patients with acute coronary syndrome (ACS) complicated by cardiogenic shock reported a superior 30-day mortality rate of 33% (95% confidence interval [CI] 14–52%) in the V-A ECMO group.[14]

On the other hand, a later meta-analysis reported better short-term outcomes in patients who underwent IABP or IMPELLA or surgical vent insertion than in those who underwent V-A ECMO for the management of cardiogenic shock.[15]

IMPELLA is expected to be effective in the management of cardiogenic shock due to AMI by increasing the coronary blood flow and improving myocardial circulation. The use of IMPELLA in Japan is guided by the IMPELLA proper use guidelines[16] established by the IMPELLA Committee of the Japan VAD Council. According to the J-PVAD registry, IMPELLA has been used in 823 cases between 2017 and 2020, with 44.8% being associated with cardiogenic shock due to MI, which is the most common indication for this device.[1] Furthermore, from the same registry, in a report of 593 cases of cardiogenic shock associated with MI treated with IMPELLA, the 30-day survival rate was 80.9% for patients treated with IMPELLA alone and 45.7% for those treated with ECMO.[17]

However, although data have been obtained that show improvement in hemodynamic parameters (e.g., increase in mean arterial pressure and a decrease in lactate levels) with the use of IMPELLA, the superiority of IMPELLA over IABP in terms of survival has not been demonstrated and instead, bleeding complications are reported to be more common.[18] However, all of these data are from clinical trials with small sample sizes, there is a lack of high-quality RCTs, and interestingly, to date there are no specific recommendations in guidelines from Europe and North America, where IMPELLA is more widely used than in Japan.

Due to the difficulty in conducting RCTs on MCS, attempts have been made to develop protocols for cardiogenic shock and to evaluate outcomes with treatment according to these protocols. By following a protocol that includes early introduction of IMPELLA prior to revascularization, in-hospital mortality rates from cardiogenic shock associated with AMI have significantly decreased from >50% as reported previously[19] to 28%.[20]

IMPELLA is being increasingly utilized in various situations related to coronary artery disease, and IMPELLA-

assisted coronary bypass surgery[21] is being performed, albeit on a case report basis. Furthermore, IMPELLA has been utilized in Europe and the USA for high-risk PCI as a therapeutic indication (IMPELLA-assisted PCI) and there are to show improved outcomes with more complete revascularization in patients with low cardiac function or complex lesions.[22]

Based on the finding in animal experiments that reduction in the size of the myocardial infarct is achieved through unloading,[23] a clinical study (STEMI-DTU trial) is underway in the USA to evaluate the efficacy of pre-reperfusion IMPELLA assistance in STEMI (ST-elevation MI) without cardiogenic shock.[24,25] Depending on results, it is possible that the gold standard for the treatment of STEMI may change in the future.

Shock due to AMI includes not only pump dysfunction caused by ischemia but also mechanical complications such as acute mitral regurgitation due to papillary muscle rupture and ventricular septal perforation. The incidence of mechanical complications has decreased due to the widespread adoption of prompt revascularization with PCI, and it is reported to be approximately 0.25% of AMI,[26] but shock requiring assisted circulation is not uncommon. The use of IABP in patients with cardiogenic shock due to mechanical complications is recommended Class I. The use of V-A ECMO to maintain circulation until surgery for progressive circulatory failure due to mechanical complications is recommended Class IIb. Surgical treatment is the primary approach for ventricular septal defect, although in-hospital mortality rates remain high, and a consensus on the optimal timing for surgery has not been established.[9] However, a strategy of bridge to surgery, in which MCS with V-A ECMO/IMPELLA or other assist devices is used to maintain hemodynamic stability while awaiting surgery, has been attempted.[27] Considering the current situation as described, when hemodynamic instability cannot be managed with IABP, it is important to first consider the use of V-A ECMO/IMPELLA to achieve circulatory stabilization.

1.2 Fulminant Myocarditis

Fulminant myocarditis can progress rapidly, and prompt response to pump failure and fatal arrhythmias (including cardiac arrest) with V-A ECMO or IMPELLA can improve survival. According to the 2021 annual report of J-PVAD, IMPELLA had been used in a total of 265 cases, among which 108 required IMPELLA alone and 157 required adjuvant ECPELLA; the reported survival-to-discharge rates were 78.7% and 64.1%, respectively.[28] Although recovery of myocardial function and a favorable prognosis have traditionally been expected after surviving the acute phase of myocarditis,[29] recent reports from Japan indicate that a certain number of patients do not regain cardiac function.[30,31] Therefore, long-term management with consideration of transitioning to more durable MCS should be kept in mind.

1.3 Acute Exacerbation of Chronic Severe Heart Failure

In acute deterioration of chronic severe heart failure, V-A ECMO and IMPELLA may be used as circulatory support for nonpharmacologic therapy (PCI/coronary artery bypass grafting, valvular intervention, ablation, MitraClip, etc.) to recover cardiac function.[32,33] In patients with chronic heart failure who have indications for heart transplantation or DT, or are undergoing evaluation for these indications, V-A ECMO or IMPELLA may be used to prevent organ dysfunction during the evaluation of right heart function, respiratory function, etc., and may be followed by transition to VAD implantation surgery.[34] For patients who have not yet been evaluated for heart transplantation or DT, extracorporeal VADs that can provide mid- to long-term support are often used. However, with the introduction of IMPELLA 5.5, which is less invasive and allows for mid- to long-term support, more cases will be evaluated with consideration of assistance with IMPELLA 5.5. Thus, in the future, an increase in cases of IMPELLA 5.5 use for determination of candidacy is expected.[35,36]

1.4 Cardiogenic Shock After Open Heart Surgery

If a patient cannot be weaned from cardiopulmonary bypass after open heart surgery due to poor cardiac function, or is able to be weaned but the postoperative low cardiac output does not improve with medical therapy, the result is shock. The causes include preoperative low cardiac function, inadequate intraoperative myocardial protection, and prolonged cardiac arrest. The presence of left heart failure, right heart failure, and respiratory failure should be evaluated, and V-A ECMO or IMPELLA should be considered according to the patient's condition. Although there are limited reports, even when V-A ECMO (±IABP) is used, the survival rate remains around 30%.[37] One issue with V-A ECMO alone is the inability to decompress the left ventricle, and the addition of IMPELLA may potentially improve treatment outcomes.[38] For patients at high risk of postoperative low cardiac output based on preoperative evaluation, the use of IMPELLA for weaning from cardiopulmonary bypass and subsequent postoperative management has been reported, and evaluation of its effectiveness is awaited.[39]

1.5 Intractable Arrhythmia

Cases of out-of-hospital cardiac arrest, ventricular tachycardia (VT) and ventricular fibrillation (VF) without return of spontaneous circulation have a poor prognosis in terms of life and neurological outcome. Tachyarrhythmias, whether supraventricular or ventricular, trigger acute deterioration and are prognostic factors in patients with low cardiac function or heart failure. The main indications for MCS related to arrhythmias are as follows.

1.5.1 Non-Stop or Recurrent VT/VF

In cases of out-of-hospital cardiac arrest with initial VT/VF waveform, if the VT/VF does not terminate with standard cardiopulmonary resuscitation (CPR), the prognosis is poor. It has been shown that the combination of V-A ECMO with standard CPR in cases of refractory VF results in improved survival rates and neurological outcomes.[40–42]

Electrical storm (ES) refers to cases where VT/VF occurs ≥3 times within 24 h. The underlying causes of ES include myocardial ischemia, heart failure (evidenced by increased left ventricular end-diastolic pressure [LVEDP]), and electrolyte abnormalities. When these triggers have been corrected to the best possible correction and when antiarrhythmic drugs, including amiodarone, are not effective, MCS is indicated. The effectiveness of catheter ablation with

backup MCS for withdrawal of ES has been reported.[43]

1.5.2 Prophylactic Use for Catheter Ablation of VT/VF

In cases of VT/VF, hemodynamic instability often occurs, and it can be challenging to identify the mechanism and origin. Mapping during tachycardia with MCS backup may improve treatment outcomes if the optimal ablation site can be identified. There is also a risk of hemodynamic compromise during ablation, requiring MCS.

In a study of 21 patients with hemodynamic failure due to VT, in whom MCS was introduced but difficult to withdraw, ablation was performed under MCS insertion and 81% of the patients were successfully withdrawn from the MCS, although 29% died during the procedure.[44] Additionally, some reports suggest that although the acute success rate of ablation is favorable with the use of MCS (IMPELLA/Tandem heart/ECMO), the long-term recurrence rate of VT may not differ from cases in which MCS was not used.[45]

1.5.3 Management of Complications During Arrhythmia Treatment Procedures (Catheter Ablation or Implantable Cardiac Electrical Devices [CIEDs])

Cardiac tamponade occurs in 1% of atrial fibrillation ablations, and MCS may be required to maintain safe hemodynamics until surgery.

1.5.4 Cardiogenic Shock Due to Antiarrhythmic Drug Use

Class I antiarrhythmic drugs may cause negative inotropic effects through sodium channel blockade, which can potentially lead to congestive heart failure and bradycardia when overdosed. In cases of heart failure and cardiogenic shock due to overdose of flecainide[46] or cibenzoline,[47] hemodynamic support with MCS until the drug effects are diminished has been reported as effective. In Brugada syndrome, Class I antiarrhythmic drugs are sometimes administered for diagnostic purposes, but in some cases VF can occur, requiring MCS intervention.[48]

1.6 Acute Extensive Pulmonary Thromboembolism

Acute extensive pulmonary thromboembolism occurs when a thrombus that forms mainly in a vein in the lower extremities or pelvis extensively occludes a pulmonary artery as an embolus, resulting in cardiac arrest or shock in the most severe cases. If hypoxemia and hypotension progress with medical therapy, and respiratory and circulatory failure do not stabilize, V-A ECMO may be used as an adjunct to thrombolytic therapy and surgical or catheter-based thrombectomy.[49] Although mortality rates reported from Europe and the USA are as high as 25–65% even with V-A ECMO assistance,[50,51] there are many reports stating that V-A ECMO is safe and effective at improving outcomes.[52,53]

1.7 Other (Drug Intoxication, Accidental Hypothermia, Sepsis)

In cases of refractory shock or cardiac arrest due to drug overdose resistant to medical treatment, V-A ECMO may be indicated. As many such cases involve reversible impairment, the possibility of saving lives increases with prompt initiation of V-A ECMO.[54] In cardiopulmonary arrest due to accidental hypothermia, restoration of temperature with V-A ECMO has been effective.[55] Although the indication for V-A ECMO in septic shock has not yet been fully established,[56] its use is reported to improve survival in cardiogenic shock due to sepsis-induced myocardial damage.[57]

2. Hemodynamic Evaluation

The indications for V-A ECMO and IMPELLA are cardiogenic shock; therefore, it is essential to evaluate whether the patient's hemodynamic status is consistent with, or prior to, cardiogenic shock. Cardiogenic shock is characterized by abnormal hemodynamics, metabolic abnormalities such as elevated lactate, and findings of tissue hypoperfusion despite appropriate inotropic, vasoactive, and other circulatory support.[58–61] Although there is no detailed universal definition, in clinical trials abnormal hemodynamics are commonly defined as a decline ≥30 mmHg from the basal value and a cardiac index <2.2 L/min/m^2 (<1.8 L/min/m^2 in the absence of circulatory support).[62,63] However, these values should not be interpreted as absolute and should be evaluated in the context of signs of organ hypoperfusion.[58,61,64] Blood pressure is sometimes maintained by the vasoconstrictor reflex,[64] and the cardiac index that causes tissue hypoperfusion varies depending on the etiology (i.e., AMI or exacerbation of chronic heart failure), and by modifying factors such as infection.[61] Furthermore, lactate and hemodynamics are not always concordant in chronic heart failure.[65] There have been no RCTs assessing the routine use, optimal timing, and treatment strategies of right heart catheterization in cardiogenic shock.[60] However, cardiogenic shock has various phenotypes, worsens easily, and has a poor prognosis as it becomes more severe, even under MCS.[65–67] Therefore, in cases of suspected cardiogenic shock or cases of predicted progressive heart failure, such as fulminant myocarditis, early evaluation of hemodynamics, including right heart catheterization, should be performed, and indications for MCS should be considered. Hemodynamic indices, such as LVEDP, cardiac index, peripheral vascular resistance, and right atrial pressure (RAP) are useful in differentiating noncardiogenic shock such as vasodilatory shock[61] and in selecting treatment (IMPELLA or LV venting) to reduce LV load.[68] It has been reported that the use of a Swan-Ganz catheter for management in AMI presenting with cardiogenic shock is associated with a good prognosis.[69] Therefore, hemodynamic assessments are performed over time from MCS induction to its management.

Echocardiography can be used to estimate stroke volume (SV), the presence of elevated left atrial pressure, and central venous pressure (CVP); SV is calculated using the time–velocity integral of the LV outflow tract (LVOT) blood velocity waveform by pulsed Doppler and the LVOT diameter.[70] In patients with severe systolic dysfunction who may be indicated for MCS, a diagnosis of highly elevated left atrial pressure due to restrictive diastolic dysfunction is made when the E/A ratio of transmitral flow is >2.0, and conversely, when the E waveform is <50 cm/s and the E/A ratio is <0.8, the diagnosis of no elevation of left atrial pressure is made.[71] If not applicable, E/e', peak velocity of tricuspid regurgitation, and the left atrial volume index are used to diagnose the presence or absence of left atrial pressure elevation.[71] However, when considering the indication for MCS, assessment of cardiac output, such as SV, has priority over that of detailed diastolic function. CVP is estimated from the diameter of the inferior vena

cava and respiratory change. Elevated CVP (15 mmHg) is diagnosed when the diameter of the inferior vena cava is >21 mm and the reduction in diameter when the patient sniffs is <50%.[72] However, it should be noted that an enlarged diameter of the inferior vena cava does not accurately predict elevated CVP in patients on positive pressure ventilation with ventilatory management.

3. Left Heart Function Assessment

Hemodynamic indices such as LVEDP, pulmonary artery wedge pressure (PAWP), cardiac power output (CPO), calculated from cardiac output, and mean blood pressure,[61,72] and LV ejection fraction (LVEF) are used to evaluate left heart function. The normal value of LVEDP in the supine position at rest is 5–13 mmHg,[58] and an increase ≥15 mmHg is often considered a significant elevation.[58,59,72] LVEF (<30% or <35%) is often used as an inclusion criterion in clinical trials of AMI with MCS.[70] Although lower values are associated with worse prognosis,[71] there is no clear cutoff value to determine the indication for MCS. In cases of temporal changes in systolic function such as fulminant myocarditis, serial evaluations, including preshock and the early stages of shock, are required.

LVEF is commonly used as an index of LV systolic function in echocardiographic assessment. LVEF in candidate cases for MCS is very low due to severe systolic dysfunction. However, in conditions with myocardial edema such as fulminant myocarditis, SV is sometimes highly reduced even if the LVEF is not very low, because the left ventricle is not dilated. In acute mitral regurgitation due to ruptured chordae tendineae, cardiac output decreases but LVEF does not, because of LV hypercontractility. Although the LVEF does not always accurately reflect cardiac output, it is widely used because of its simplicity and reproducibility. LVEF is also used when considering withdrawal from MCS.

Simpson's method, the disk addition method, which is done by tracing the endocardial surface from 2 planes of the apical 4- and 2-chamber views to obtain the volume, is recommended for measuring LVEF. However, when considering the indication for MCS, the Teichholz method, which uses the parasternal long-axis view, is also acceptable for convenient LVEF measurement. The disk addition method is not applicable when the LV shape is not the assumed prolate ellipsoid, such as in those with LV aneurysm; in that case, LVEF measurement using 3-dimensional data is recommended.[73]

Aortic insufficiency (AI) should be evaluated by color Doppler imaging, and if moderate or higher AI is suspected, its severity should be assessed by qualitative, semi-quantitative, and quantitative evaluation. Detailed assessment of severity was reported in the Guideline on the management of valvular heart disease, revised 2020.[74] In cases of moderate or severe AI, IABP, V-A ECMO, or IMPELLA is not suitable. In severe aortic stenosis, IMPELLA cannot be used, because the device passes through the aortic valve. Therefore, assessment of aortic stenosis must be required when considering IMPELLA. In addition, the conditions that may interfere with the insertion of IMPELLA into the left ventricle, such as LV thrombus, narrowing of the LV lumen, or abnormal tissue in the lower mitral valve, also should be evaluated. It is necessary to perform an echocardiographic assessment to detect reversible conditions, such as cardiac tamponade, which do not require MCS treatment.

Imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), and nuclear medicine, can be difficult to perform if the patient is hemodynamically unstable, given the risks and time required for patient transport. However, when considering the indication for MCS and subsequent treatments, it is important to distinguish between acute conditions, such as acute myocarditis, and exacerbation of chronic heart failure due to dilated or ischemic cardiomyopathy, and to determine whether recovery of cardiac function can be expected with temporary MCS. Myocardial viability can be evaluated by myocardial SPECT (single photon emission computed tomography) or PET (positron emission tomography) as nuclear medicine imaging techniques.[75,76] In cardiac MRI, late gadolinium enhancement is used to evaluate viability.[77] In cardiac CT, a mechanism similar to gadolinium delayed contrast in MRI has been reported to evaluate myocardial contrast effects in the late iodine contrast phase and contrast failure in the early contrast phase. However, the contrast resolution is limited compared with cardiac MRI, and its use in myocarditis is limited.[78,79]

4. Right Heart Function Evaluation

Evaluation of right heart dysfunction is required when considering both the indication for MCS and device selection, because right heart failure causes organ damage through congestion and low cardiac output derived from decreased return to the left ventricle. The following indices of right heart dysfunction in shock are used: increased CVP,[59,60,72] decreased pulmonary artery pulsatility index (PAPi),[59,60,72] and increased CVP:PAWP ratio.[59–61] However, these indices vary according to pathophysiology and the particular report; to date, clear cutoff values have not been established. Therefore, a composite evaluation should be performed.[59]

In echocardiography, measuring the volume of the right ventricle is challenging due to its complex morphology. Therefore, it is recommended to measure the inner diameter of the right ventricle at multiple sites using tomography.[73] Typical indices used to assess right ventricular systolic function include the tricuspid annular plane systolic excursion (TAPSE), tricuspid annulus peak systolic velocity (RV s′), and fractional area change (FAC). Values <17 mm for TAPSE, <9.5 cm/s for RV s′, and <35% for FAC are considered abnormal.[70]

5. Coronary Artery Evaluation

The most common cardiogenic shock requiring the use of V-A ECMO or IMPELLA is ACS. Coronary artery disease must be ruled out, even in cases of myocarditis, cardiomyopathy, or arrhythmias. When ACS is present, immediate revascularization is one of the important prognostic factors, and thus coronary artery evaluation should be performed. If immediate MCS is required, coronary angiography is performed in the catheterization laboratory. When IMPELLA 5.5 is placed in the subclavian artery, information on the diameter of the subclavian artery is useful, and may be obtained via cardiac CT imaging. Assisted circulation is introduced before and after coronary

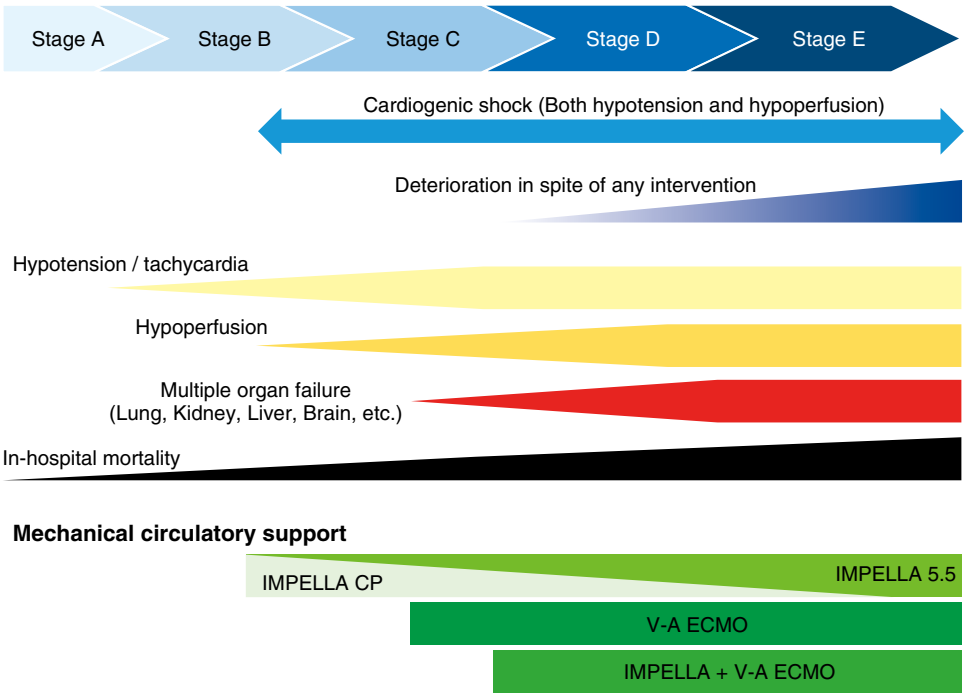

Figure 1. Society for Cardiovascular Angiography and Intervention classification of the stages of shock and their relationship to systemic condition. ECMO, extracorporeal membrane oxygenation. (Source: based on Baran et al, 2019;[81] Chioncel et al, 2020.[82])

artery evaluation, depending on hemodynamics.

6. Evaluation of Systemic Status

When MCS such as V-A ECMO and IMPELLA is being considered, the patient has unstable or collapsed hemodynamics, and systemic management must be performed simultaneously with circulatory management. Specifically, it is necessary to manage renal, hepatic, respiratory, and cerebral dysfunction due to circulatory failure. It is not uncommon for multiple organ failure to be the cause of death in patients with cardiogenic shock.[61,80] The mortality rate based on the severity classification of cardiogenic shock by the Society for Cardiovascular Angiography and Intervention (**Figure 1**)[81,82] is reported to be extremely high in situations where the condition worsens over time (stages D and E) (in-hospital death: stage D 40.4%, stage E 67.0%).[81,83] The mortality rate for cardiogenic shock is significantly higher in cases of hypoperfusion than in patients with hypotension.[84] Therefore, it is important not only to maintain blood pressure but also to evaluate tissue perfusion and intervene accordingly. In severe cases, the condition can deteriorate within hours or even minutes, so it is extremely important to promptly introduce catecholamines and MCS, as well as to evaluate hemodynamics with right heart catheterization in addition to arterial pressure monitoring. Blood tests should be performed to assess kidney function, liver function, lactate level, and coagulation, and any reversible conditions should be corrected as appropriate. Specifically, the lactate level is a sensitive indicator of circulatory failure and is useful for predicting prognosis and determining the efficacy of treatment.[83,84]

6.1 Kidney

In cardiogenic shock, renal function may deteriorate rapidly with hemodynamic collapse.[85,86] Renal dysfunction in cardiogenic shock is mainly caused by hypoperfusion or renal congestion and may transition from transient and reversible to irreversible. When renal dysfunction is observed, it should be evaluated to determine whether the cause is prerenal, renal, or postrenal; if the cause is not dependent on hemodynamics, appropriate management should be undertaken in accordance with the pathophysiology of the condition. Renal echocardiography (including renal artery echocardiography) is useful for the differential diagnosis. When renal dysfunction in the acute phase is observed, it is necessary to determine whether the patient has preexisting chronic kidney disease or whether the renal function was worsened due to this event. The causes of renal function deterioration should be differentiated, including the effects of iodine contrast media (contrast-induced nephropathy), cholesterol embolization, newly introduced drugs, and MCS device-related hemolysis.[87]

When right heart failure becomes prominent, CVP increases, leading to renal congestion and oliguria or anuria. If hemodynamics do not improve with diuretics or inotropic drugs (dopamine, dobutamine), or LV support with IMPELLA does not improve hemodynamics in cases of right heart failure (CVP >15 mmHg), mechanical right heart support may be required, and V-A ECMO (PCPS) should be introduced. If adequate diuresis cannot be achieved

even after hemodynamic improvement by MCS, renal replacement therapy should be introduced.

6.2 Liver

Hepatic dysfunction in cardiogenic shock occurs due to hepatic ischemia and hepatic congestion caused by hypoperfusion resulting from circulatory failure. Severe circulatory failure can cause significant hepatic dysfunction (also called shock liver, hypoxic hepatitis, or ischemic hepatitis),[88] and coagulation abnormalities have been reported to occur simultaneously. Acute liver failure due to circulatory failure is pathologically characterized by centrilobular necrosis and hemorrhage and is thought to progress to fibrosis in the chronic phase.[89] Blood tests show elevated aspartate aminotransferase (AST), elevated lactate dehydrogenase (LDH), and prolonged prothrombin time in the acute phase. Indirect bilirubin levels increase after a few days and remain elevated throughout prolonged cardiac failure. A subanalysis of the IABP-SHOCK II trial reported a higher 30-day mortality rate in patients with hypoxic hepatitis than in patients without hypoxic hepatitis (68% vs. 34%; P<0.001).[90] AST, serum lactate, and serum creatinine levels were independent factors for 30-day death. Hepatic congestion occurred in patients with right heart failure who had high CVP; also serologically elevated bilirubin, gamma-glutamyltranspeptidase (γ-GTP), and alkaline phosphatase were observed.[82]

In AMI, significant increases in AST and LDH occur, in addition to creatine kinase (CK-MB) as a cardiac enzyme, but when ALT levels also increase simultaneously, the possibility of concurrent acute liver dysfunction should be considered. In the initial treatment of AMI, new drugs, including antiplatelet agents, are often introduced, and drug-related hepatic dysfunction should always be considered as a differential diagnosis.

6.3 Lung

In cardiogenic shock, pulmonary congestion, caused by elevated pulmonary capillary pressure resulting from elevated left atrial pressure due to left heart failure, occurs.[91] When oxygenation cannot be maintained, oxygen is administered; inadequate oxygenation requires noninvasive positive pressure ventilation (NPPV) or intubation for ventilator management.[92] In addition to cases in which oxygenation cannot be sufficiently maintained even with NPPV, intubation for ventilator management is appropriate in cases of decreased consciousness or inability to clear secretions. The JCS 2017/JHFS 2017 Guidelines for diagnosis and treatment of acute and chronic heart failure has detailed descriptions and should be referred to for more information.[3]

6.4 Brain

Acute circulatory failure may cause impaired consciousness, most often due to cerebral circulatory failure, and inotropic agents or MCS should be administered promptly.[80] In addition, imaging diagnosis by cerebral CT is necessary when findings that suggest cerebrovascular disease, such as headache, vomiting, motor paralysis, and decreased level of consciousness, are observed during the acute phase. If cerebral circulation does not improve and oxygen supply is inadequate, irreversible hypoxic encephalopathy may occur. In cases of cerebral infarction or hemorrhage identified before initiating MCS, careful consideration of the indication for MCS is necessary. Anticoagulants (e.g., heparin) are used in addition to antiplatelet agents during PCI for AMI, and antithrombotic therapy is necessary during MCS device management. For the management of stroke, please refer to **Chapter III.3.4**: Patient Management for Stroke and Gastrointestinal Hemorrhage.

6.5 Coagulation System

Organ dysfunction during circulatory failure often affects multiple organs. Abnormalities in the coagulation system, such as platelet reduction, elevation of fibrin degradation product and D-dimer, decreased fibrinogen, and prolonged prothrombin time may be observed, and prompt therapeutic intervention is necessary.[93,94] As mentioned earlier, coagulation abnormalities may occur in patients with severe hepatic dysfunction, and comprehensive systemic management is necessary. Without improvement in the systemic condition, disseminated intravascular coagulation may develop, which is characterized by significant systemic coagulation activation under various conditions, including shock, multiple microthrombi in small vessels, causing organ dysfunction, and bleeding symptoms. Patients with MCS may have abnormal coagulation due to thrombocytopenia and loss of coagulation factors (including destruction of von Willebrand factor multimers). Patients with abnormal coagulation are at high risk of bleeding from the sites of device insertion, and management of coagulation abnormalities is extremely important. Unfortunately, the pathogenesis of coagulation abnormalities in patients with circulatory failure associated with cardiogenic shock has not been fully elucidated, and further research is needed in this field.

6.6 Vascular Assessment

V-A ECMO basically drains from the right atrium through femoral vein cannulation and is returned via femoral artery cannulation. As the flow rate of V-A ECMO depends on cannula size, it is important to select the appropriate size; evaluation of vascular characteristics in addition to vessel diameter is crucial. The pump diameters of IMPELLA CP and IMPELLA 5.5 are 14Fr (5.05 mm) and 21Fr (6.74 mm), respectively; the evaluation of arterial vessel diameter is equally important for these approaches as for V-A ECMO.

Echocardiography, CT, magnetic resonance angiography, and angiography are the most commonly used imaging methods to evaluate the artery, but in cases where urgent femoral artery access is required, evaluation using echocardiography should be performed whenever possible. If significant stenosis is observed by echocardiography, changing the puncture site should be considered. For IMPELLA implantation, consideration of angiography with a pigtail catheter prior to IMPELLA implantation is recommended because the device may be difficult to insert due to severe stenosis or tortuosity of the access vessel. If the vessel is highly tortuous, insertion of an IMPELLA with a long sheath may also be considered. There is a risk of lower limb ischemia with V-A ECMO or IMPELLA placement, so it is recommended to maintain lower limb perfusion as needed.

7. Social Evaluation and Advance Care Planning

This section draws on the guidelines outlined in the Statement on palliative care in cardiovascular disease, revised 2021[95] to emphasize the importance of balancing life-saving interventions in patients with cardiogenic shock while respecting the autonomy and preferences of both the patient and the family. Specifically, it explores the utilization of advance care planning (ACP) and advance directives in patients with preexisting cardiac conditions, such as stage D heart failure (e.g., dilated cardiomyopathy or ischemic cardiomyopathy), who have had recurrent hospitalizations. The process of ACP involves proactive discussions regarding treatment preferences and decisions, with advance directives serving as written expressions of the patient's will. These directives are typically shared among the patient, family, and the primary care physician while the patient retains decision-making capacity. Notably, the contents of advance directives may vary across healthcare facilities, encompassing preferences regarding the use of mechanical ventilation, hemodialysis, assisted circulation, and the identification of a surrogate decision-maker. In the urgent context of introducing assisted circulation, timely assessment of the patient's and family's wishes is crucial. However, it is important to acknowledge that ACP is an ongoing process, and previous declarations should be reconsidered as the patient's condition deteriorates. Some patients who initially express reluctance for assisted circulation may have a change in perspective as their health deteriorates and end of life approaches. To ensure comprehensive understanding and facilitate informed decision making, multidisciplinary conferences, at which healthcare professionals from diverse specialties attend, should be conducted to provide thorough explanations to the patient and family members.

8. Device Selection for Temporary MCS

The device selection for patients with cardiogenic shock depends on the severity of end-organ damage, the degree of left and right heart impairment, the time from shock onset to initiation of mechanical support, the approach for device insertion or implantation (i.e., percutaneous or open chest), and the supposed duration of MCS.[59,96] An algorithm for initiating IMPELLA support has been proposed by several institutes.[97]

Classical signs and laboratory findings of cardiogenic shock have been reported: hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <60 mmHg,

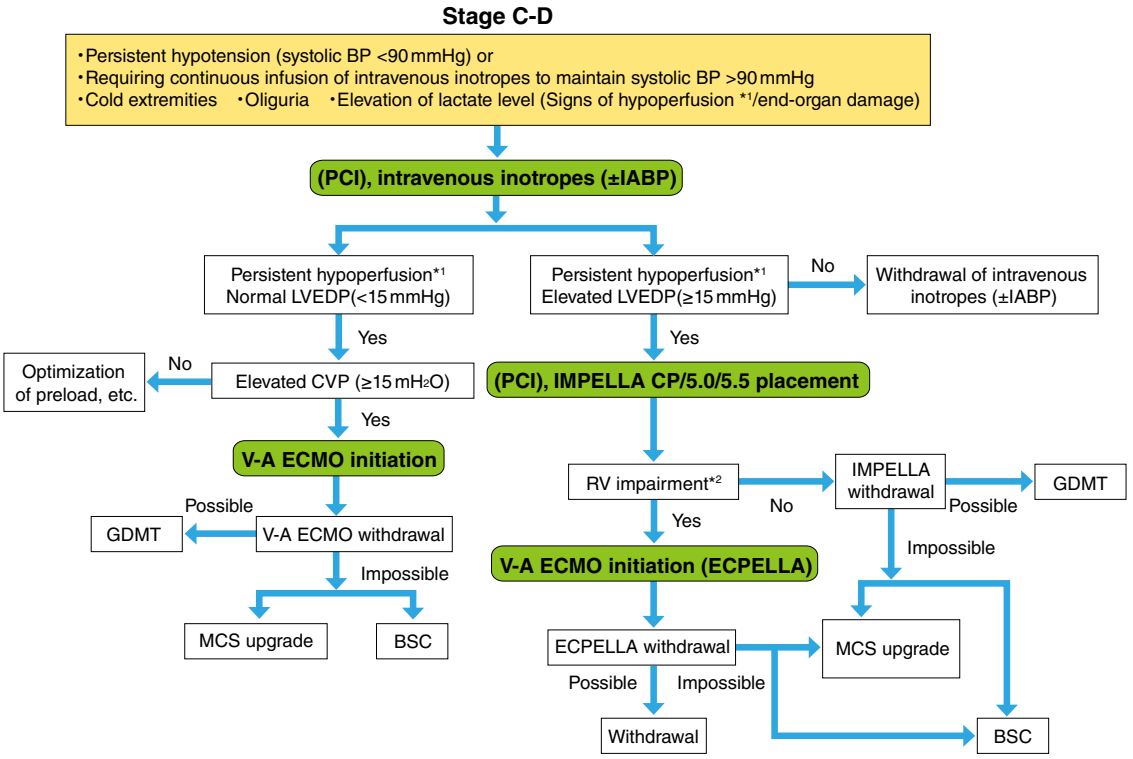

Figure 2. Algorithm for escalation of temporary MCS in Society for Cardiovascular Angiography and Intervention shock stages C and D. *1SvO_2 <60%, MAP <60 mmHg, Lac ≥2.0 mmol/L, CI <2.2 L/min/m^2, cardiac power output <0.6. *2Low right ventricular stroke work index (<5 g/m), low right atrial pressure/pulmonary capillary wedge pressure (<0.6), low pulmonary artery pulsatility index (<0.9). BSC, best supportive care; CI, cardiac index; CVP, central venous pressure; GDMT, guideline-directed medical therapy; IABP, intra-aortic balloon pumping; LVEDP, left ventricular end-diastolic pressure; MAP, mean arterial pressure; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; SvO_2, mixed venous oxygen saturation.

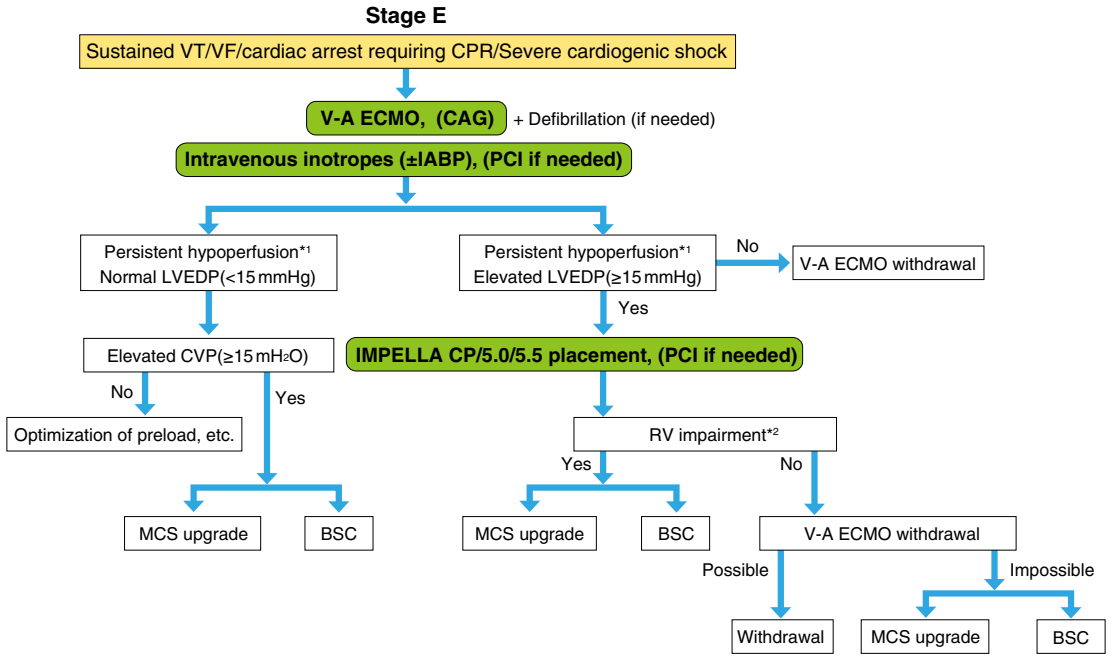

Figure 3. Algorithm for escalation of temporary MCS in Society for Cardiovascular Angiography and Intervention shock stage E. *1SvO_2 <60%, MAP <60 mmHg, Lac ≥2.0 mmol/L, CI <2.2 L/min/m^2, cardiac power output <0.6. *2Low right ventricular stroke work index (<5 g/m), low right atrial pressure/pulmonary capillary wedge pressure (<0.6), low pulmonary artery pulsatility index (<0.9). BSC, best supportive care; CAG, coronary angiography; CI, cardiac index; CVP, central venous pressure; IABP, intra-aortic balloon pumping; LVEDP, left ventricular end-diastolic pressure; MAP, mean arterial pressure; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; SvO_2, mixed venous oxygen saturation; VF, ventricular fibrillation;VT, ventricular tachycardia.

blood pressure drop >30 mmHg from baseline, requiring intravenous inotropes to maintain blood pressure), and findings of hypoperfusion (cold extremities, reduced urine output <30 mL/h, lactate ≥2 mmol/L, serum Cr doubling, liver dysfunction, elevated plasma B-type natriuretic peptide level, cardiac index <2.2 L/min/m^2, PAWP >15 mmHg, CPO <0.6, etc.).[81,83] As shock progresses, either incremental doses of intravenous inotropes or initiating MCS therapy is required (**Figures 2**,**3**).

According to the JCS/JHFS 2021 Guideline focused update on diagnosis and treatment of acute and chronic heart failure, the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support)/J-MACS (Japanese Registry for Mechanically Assisted Circulatory Support) profile 2 is a condition in which renal function, nutritional status and signs of congestion worsen despite the use of intravenous inotropic drugs, and as a result, incremental doses are required. J-MACS/INTERMACS profile 1 is a condition with hemodynamic collapse and end-organ dysfunction, despite the use of incremental dosage of inotropic drugs and initiating MCS. The IMPELLA device is indicated for patients with INTERMACS/J-MACS profile 1 or 2.[98] ECMO is also indicated in patients with INTERMACS/J-MACS profile 1 or 2.[98] The INTERMACS/J-MACS profile for patients who receive temporary MCS is defined in Japan; the VAD Council has announced the definition (shown in **Table 1**).[99]

The Society for Cardiovascular Angiography and Intervention shock classification, which describes the stages of cardiogenic shock from "at risk" (stage A) to "extremis" (stage E), is shown in **Figure 1**.[81,82] Stage C is "classic" cardiogenic shock. Stage D is the "deteriorating" stage in which hemodynamics have not been restored by initial treatment and are worsening. Stage E is severe cardiogenic shock requiring CPR or ECMO support (i.e., pH <7.2, lactate ≥5 mmol/L, refractory VT/VF, and pulseless electrical activity [PEA]). Stage E typically corresponds to INTERMACS/J-MACS profile 1.

For patients with shock stages C and D, intravenous inotropic drugs (±IABP) should be administered first (**Figure 2**). Coronary revascularization, such as PCI, should be performed if necessary, and IMPELLA is indicated if hypoperfusion persists accompanied by elevated LVEDP (≥15 mmHg). LVEDP can be substituted with PAWP, in the absence of mitral valve stenosis. The patient can be weaned off IMPELLA if hypoperfusion/elevated LVEDP improve after the initiation of IMPELLA support. If the symptoms of end-organ hypoperfusion or pulmonary congestion (high PAWP) persist even after IMPELLA support, the patient may be upgraded to IMPELLA 5.5 or an extracorporeal LV assist device (LVAD). If the patient has complications of severe hypoxemia, frequent and persistent ventricular arrhythmias, right heart failure that disturbs sufficient blood supply even after increasing the IMPELLA pump speed, or uncontrolled hemolysis when IMPELLA pump speed is increased to ensure sufficient blood flow, V-A ECMO is added (i.e., ECPELLA). If pulmonary congestion and end-organ hypoperfusion persist, MCS may be upgraded by adding V-V ECMO or converting to central ECMO. Right ventricular function is

Table 1. Consensus of NYHA Classification and INTERMACS/J-MACS Profile for Patients With Temporary Mechanical Circulatory Support

Medical treatment	NYHA classification*1	INTERMACS/ J-MACS profile	
Intravenous inotropic drugs	IV	3	Generally dependent on low-dose intravenous dobutamine (≤3γ) without progression of end-organ damage*2 and/or nutritional disorder*3
	IV	2	Progression or possible progression of end-organ damage, nutritional disorders, etc., and requiring escalation of types and doses of intravenous inotropic drugs
IABP alone	IV	2	End-organ damage and nutritional disorders are not evident
IABP alone	IV	1	Progressive end-organ damage and nutritional disorders are present, and not anticipated, as usually used in combination with ECMO
IABP + V-A ECMO	IV	1	In non-IMPELLA-certificated facilities or in cases of non-IMPELLA-eligible cases
IMPELLA alone	IV	2	End-organ damage and nutritional disorders are not evident
IMPELLA alone	IV	1	Progressive end-organ damage and nutritional disorders are present, and often requiring concomitant use of ECMO (ECPELLA)
ECPELLA	IV	1	Regardless of the evidence of end-organ damage or nutritional status
Peripheral V-A ECMO alone	IV	2	Patient has no apparent end-organ damage or nutritional impairment and can perform rehabilitation without the need for a ventilator
Peripheral V-A ECMO alone	IV	1	Progressive end-organ damage and nutritional disorders are present
Central ECMO (± left ventricular vent)	IV	2	Patient does not require a ventilator and can perform rehabilitation without obvious end-organ or nutritional impairment
Central ECMO (± left ventricular vent)	IV	1	Progressive end-organ damage and nutritional disorders are present
Extracorporeal LVAD	IV	3	Right heart failure*4 signs of end-organ failure and nutritional damage are not evident without inotropic drugs, and rehabilitation can be performed
Extracorporeal LVAD	IV	2	Patient requires concomitant use of inotropic drugs to compensate for right heart failure, end-organ damage, or nutritional disorders, and cannot perform rehabilitation
BiVAD	IV	2	Patient has no apparent end-organ or nutritional damage, and does not require inotropic drugs, and can perform rehabilitation
BiVAD	IV	1	Patient requires concomitant use of inotropic drugs to compensate for end-organ damage, nutritional disorders, etc., or and cannot perform rehabilitation
Implantable LVAD	IV	Not applicable*5	

*1If the patient requires MCS, classification is NYHA class IV.
*2End-organ damage mainly refers to pulmonary, renal, and hepatic dysfunction due to hypoperfusion and congestion.
*3Although it is difficult to strictly define nutritional disorders, muscle mass, grip strength, and albumin levels are used as references.
*4Right heart failure is determined by echocardiography (right ventricular size, TAPSE) and right heart catheter (PAPi, RVSWI).
*5The INTERMACS/J-MACS profile classification is not applicable after implantable LVAD implantation because it is used for preoperative evaluation of the implantable LVAD.
BiVAD, biventricular assist device; IABP, intra-aortic balloon pumping; LVAD, left ventricular assist device; NYHA, New York Heart Association; PAPi, pulmonary arterial pulsatility index; RVSWI, right ventricular stroke work index; TAPSE, tricuspid annular plane systolic excursion; V-A ECMO, veno-arterial extracorporeal membrane oxygenation.
(Adapted from Council for Clinical Use of Ventricular Assist Device-Related Academic Societies, 2022.[99])

evaluated using the right ventricular stroke work index (RVSWI), RAP/PAWP, and PAPi. In cases of cardiogenic shock with right-sided heart failure, in which there are signs of end-organ hypoperfusion and right ventricular impairment with normal LVEDP, the initiation of V-A ECMO support should be considered.

If end-organ hypoperfusion improves with MCS support, it is common to wean the patient off V-A ECMO first, followed by IMPELLA weaning. For patients with biventricular heart failure who cannot be weaned from V-A ECMO due to unrecovered heart function, consider upgrading MCS to provide long-term support, such as central ECMO with LV vent or extracorporeal biventricular assist device (BiVAD). If right heart function improves and the patient can be weaned off ECMO or right ventricular assist device, conversion to an extracorporeal LVAD/ implantable LVAD may be considered as a bridge to transplantation (BTT), or bridge to candidacy (BTC), or DT.

For patients who have a difficulty in weaning from IMPELLA, an implantable LVAD, (implantable by thoracotomy) which can provide long-term hemodynamic support, may be considered as BTT (bridge to transplantation) or DT (including BTC) indication.

In shock stage E, such as refractory VT/VF, cardiac arrest requiring CPR, and severe cardiogenic shock, V-A ECMO is introduced first (**Figure 3**). Coronary angiography is performed to evaluate the cause of shock, and coronary revascularization is performed if necessary. If the pulmonary congestion worsens or aortic valve closure occurs, even after cessation of the ventricular arrhythmias or achievement of sinus rhythm, the concomitant use of IABP or IMPELLA should be considered. If end-organ hypoperfusion does not improve even after initiation of ECPELLA

support, the sized-up or added cannulation of V-A ECMO, or IMPELLA upgrade may be considered depending on whether LVEDP is elevated (≥15 mmHg) or not. If end-organ hypoperfusion improves with ECPELLA support, the patient is generally weaned from V-A ECMO first, followed by weaning from IMPELLA. If the patient is unable to wean from V-A ECMO, the same management is followed as described earlier; MCS upgrade may be considered (i.e., conversion to central ECMO with LV vent or extracorporeal BiVAD). In cases of cardiac arrest or hemodynamic collapse due to massive pulmonary embolization, patients are also classified as stage E, and V-A ECMO is inserted. If LV function is preserved and the LVEDP is not elevated, neither IABP nor IMPELLA is necessary, and if end-organ damage, as well as hemodynamics, has improved, V-A ECMO is withdrawn.

Because the shock stage may change even over a short period depending on the cause of shock, repeated hemodynamic evaluation should be performed over time and appropriate device selection should be considered each time. Lastly, the indication of MCS upgrade and device selection should also be determined by the patient's general condition, body size, vascular diameter, and vascular characteristics.

II. Installation and Management of PCPS, ECMO, and IMPELLA

1. IABP

Intra-aortic balloon pumping (IABP) augments coronary blood flow even under conditions of highly reduced microvascular circulatory reserve, such as cardiogenic shock, by dilating a balloon placed in the descending aorta during diastole. Conversely, rapid balloon deflation during systole reduces afterload and increases cardiac output.[100,101] Because these mechanisms increase oxygen supply to the myocardium and reduce oxygen demand, IABP has been used for acute coronary syndrome as circulatory support for many years. However, IABP might be difficult to use in cases of aortic regurgitation, aortic aneurysm, aortic dissection, severe atherosclerosis of the aorta, and severe stenosis or tortuosity of the iliac artery. The effectiveness of circulatory support with IABP may be less in cases of arrhythmia or severe tachycardia, and may be ineffective in cases of marked hypotension. IABP use is contraindicated for patients with cardiac arrest. In addition, complications related to the artery into which the balloon is inserted, especially ischemia of the lower extremities, should be carefully monitored.

Next, the manner of placement and management of IABP will be discussed.

1.1 Balloon Selection and Placement

The balloon size of the 7 or 8Fr catheter should be selected based on the patient's body size and vessel diameter. Also available are 6Fr catheters, which may be an option if lower extremity ischemia is a concern, but the effectiveness of circulatory support may be diminished. It is important to place the balloon in the correct position under fluoroscopic guidance, and to be aware of the risk of ischemia of the abdominal aortic branch if the balloon is placed below the celiac artery. Appropriate balloon length should be selected for each case.

1.2 Device Driving

Optimal driving is important to obtain the maximum circulatory support of IABP. The timing of balloon dilation coincides with aortic valve closure, and the timing of deflation is adjusted to minimize end-diastolic arterial pressure. The device console has a built-in drive algorithm based on ECG and blood pressure synchronization, and can be used with automatic drive. Appropriate anticoagulation therapy is required during the IABP drive to prevent thromboembolism and bleeding complications.

1.3 Device Weaning and Withdrawal

Hemodynamic monitoring by right heart catheterization is generally used as a weaning and withdrawal criterion. Although individual adjustment is necessary depending on the patient's background and condition, an increase in the cardiac index or a decrease in pulmonary artery wedge pressure (PAWP) is a guideline for weaning. It is safe to try weaning with catecholamine support. Arrhythmias may interfere with weaning and withdrawal; therefore, the cardiac rhythm should be noted during device weaning. Weaning is generally performed by decreasing the assist ratio in steps of 1 : 1 to 1 : 2 and then 1 : 3. Another method is to gradually decrease the driving gas volume of the balloon. After device removal, check for hemostasis of the femoral artery at the puncture site and ischemia of the lower extremity.

2. V-A ECMO

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) provides more powerful circulatory and respiratory support than IABP, and also reduces preload of the right and left ventricles by draining the right heart system. It is an excellent device that can be rapidly introduced in any hemodynamic situation to ensure circulation. V-A ECMO is considered for patients with INTERMACS/J-MACS profile 1 or 2, along with IABP. Especially in INTERMACS/J-MACS profile 1, IABP alone is insufficient for circulatory support, and V-A ECMO is indicated.

2.1 Installation

The access route and cannula size must be determined when placing V-A ECMO, but because ECMO installation is often urgent, the femoral artery and femoral vein are the first choices of access. Care should be taken when inserting a venous cannula through the left femoral vein because of the risk of injury. If femoral artery access is difficult, the right subclavian artery is the second choice in terms of

perfusion of oxygenated blood to the coronary and carotid arteries. The cannula size depends on the patient's physique, generally 15–17Fr for the arterial cannula and 21–23Fr for the venous cannula. In a patient with severely impaired cardiac function in whom no forward blood flow can be expected, a larger cannula size, such as 19Fr for the arterial cannula or 25Fr for the venous cannula, should be selected to ensure effective supplemental circulatory flow. Additional supplementary circulation, such as an intracardiac pump catheter (IMPELLA), should be considered if necessary. The cannula tip position should be confirmed by fluoroscopy, or if fluoroscopy is not available, transesophageal echocardiography or radiography should be used to confirm the tip position. The activated coagulation time (ACT) should be 180–200 s, the activated partial thromboplastin time (APTT) should be 50–60 s, and continuous heparin administration should be started.

2.2 Distal Limb Perfusion for Limb Ischemia

It has been reported that during V-A ECMO establishment femoral artery access resulted in distal limb ischemia in 17% of patients and required leg amputation in 5%.[102] The use of large cannulas (>20Fr) and younger age are reported to be risks for distal limb ischemia.[103]

To make an early diagnosis, it is necessary to confirm a color change of the lower limb, cold sensation, contracture of the lower leg muscles, elevation of creatine kinase and other muscle dehydratase enzymes, tissue oxygen saturation by near-infrared spectroscopy, and peripheral arterial blood flow by Doppler echocardiography. With regard to the risk of distal limb ischemia, it is recommended that a 4–7Fr sheath be inserted prophylactically into the peripheral femoral artery to maintain distal limb perfusion.

2.3 Management

Management of the patient requires hemodynamic monitoring, V-A ECMO rotation and flow rate, artificial lung function, alveolar gas exchange, cardiac function (left ventricular [LV] function, right ventricular function, intracardiac and aortic cusp thrombus, LV decompression), the presence of cannula entry site bleeding or infection, organ damage due to insufficient systemic organ perfusion, coagulation function, and daily neurological evaluation.

2.4 Establishment of Systemic Organ Perfusion With ECMO

The primary objective of V-A ECMO is to maintain systemic organ perfusion and to improve organ damage caused by heart failure. The right heart catheter is continuously monitored for the presence of pulmonary congestion and LV pressure load by PAWP, and right heart function according to pulmonary artery pressure. After systemic perfusion by V-A ECMO is established, the presence of aortic valve opening is confirmed by arterial pressure waveforms and echocardiography. Autologous pulmonary oxygenation capacity is assessed by blood gas and SpO_2 in the right upper extremity. Patients should be followed regularly by blood tests for systemic organ damage and circulatory failure with reference tolactate levels. Anticoagulation therapy is based on an ACT of 180–200 s and an APTT of 50–60 s with heparin.

2.5 Insufficient V-A ECMO Flow

The patient should be carefully monitored for poor systemic organ perfusion, including renal and liver dysfunction. If poor systemic perfusion is present, poor venous drainage due to insufficient intravascular volume should be suspected. If sufficient intravascular volume can be confirmed, other causes should be investigated. If it is determined that sufficient flow cannot be obtained due to the diameter of the arterial and venous cannulas, the size of the cannulas should be increased, or an additional venous cannula should be inserted.

2.6 Developing LV Distension and Pulmonary Edema

In patients with severely impaired cardiac function without aortic valve opening, the risk of pulmonary congestion is high due to increased LV afterload and elevated LV end-diastolic pressure caused by ECMO. LV decompression should be considered in patients with progressive pulmonary congestion. The absence of aortic valve opening as assessed by arterial pressure waveforms or echocardiography, and progression of pulmonary congestion on chest radiography can indirectly diagnose elevated LV intraventricular pressure. PAWP and pulmonary artery diastolic pressure by Swan-Ganz catheter can most directly detect elevated LV pressure. It has been reported that LV decompression improves the prognosis in patients on V-A ECMO due to cardiogenic shock.[104,105] IABP, IMPELLA, and left ventricular or left atrial vent insertion for LV decompression should be considered depending on the situation. In recent years, there have been reports of improved outcomes with IMPELLA in patients on ECMO,[38,106] and many are upgrading to ECPELLA for LV decompression.

2.7 North–South Syndrome

If the patient's cardiac function has recovered, but there is still poor alveolar oxygenation, North–South syndrome occurs when insufficiently oxygenated blood is pumped from the left ventricle to perfuse the coronary artery and partial carotid artery. Blood gas measurements and SpO_2 monitoring of the right upper extremity are necessary. If the patient has North–South syndrome, switching to V-AV ECMO with an additional venous cannula should be considered to allow oxygenated blood to flow to the lungs, or to V-V ECMO from V-A ECMO if cardiac function has improved. For oxygenated blood delivery to the aortic root and cervical branch, the blood delivery site should be changed to the right subclavian artery, and in patients with severe pulmonary congestion and impaired the patient's lung function, surgical insertion of a LV vent or conversion to central ECMO with a vent should be considered.

2.8 Assessment of Self-Cardiac Function

Because of the risk of complications such as bleeding, infection, and embolism with V-A ECMO, the possibility of withdrawal should always be considered after device placement. Patients should be evaluated for cardiac function at least daily, using arterial pressure waveforms to determine aortic valve opening, pulmonary artery pressure waveforms to assess right ventricular contractility, and echocardiography to evaluate LV systolic function and aortic valve patency time.[107]

2.9 ECMO Withdrawal

There are no established criteria for weaning patients from V-A ECMO, and each institution decides on a case-by-case basis. If mean arterial pressure >60 mmHg, mixed venous blood oxygen saturation (SvO_2) >60–65%, and blood lactate (Lac) <2 mmol/L can be confirmed, the patient should be weaned from V-A ECMO. The pulmonary artery pulsatility index (PAPi) is frequently used to evaluate right heart function, but interpretation should be done with caution under V-A ECMO management with low preload of the right heart.

If possible, patients should be weaned 48–72 h after V-A ECMO application, as the survival rate is reported to decrease after that time.[108] If a patient requires V-A ECMO circulatory support for >7 days, weaning due to improvement in cardiac function is unlikely, and the patient should be considered for a heart transplant or LV assist device (LVAD).

3. Central ECMO

Central ECMO is a form of temporary circulatory support that consists of an oxygenator, centrifugal pump, and cannulas. The same ECMO equipment is used for both central and peripheral ECMO, and both the V-A and V-V configuration is possible for centrally cannulated ECMO. Central V-A ECMO (hereinafter referred to as "central ECMO") for the purpose of cardiopulmonary support is described here.

Central ECMO is an effective cardiopulmonary support system for refractory cardiac or cardiopulmonary dysfunction in any combination of left heart failure, right heart failure, and respiratory failure. Central ECMO generally refers to a V-A ECMO configuration with ascending aortic perfusion and right atrial drainage, but in practice, it is often used combined with LV drainage (broadly defined as central ECMO, or central ECMO with LV venting). The combination with LV drainage is often considered when pulmonary congestion develops due to severe left heart dysfunction or when the aortic valve closes and thrombus formation in the left ventricle is a concern.[109]

Some patients are considered for conversion to central ECMO when peripheral V-A ECMO becomes difficult to manage for some reason. In younger patients, central ECMO may be initially selected due to small access vessels and physique issues. The primary indications for central ECMO are shown in **Table 2**. It is also effective as a solution for North–South syndrome, which is often a problem with peripheral V-A ECMO.[109]

Table 2. Major Indications for Central ECMO

1. Unsuitable access vessel conditions for peripheral cannulation for V-A ECMO
2. Progressive organ dysfunction due to insufficient peripheral ECMO flow
3. Progressive lower limb ischemia
4. Uncontrollable bleeding from the cannulation site
5. Prolonged ECMO treatment
6. Possible transition to VAD
7. Difficulty to manage with peripheral V-A ECMO for some reason

V-A ECMO, veno-arterial extracorporeal membrane oxygenation; VAD, ventricular assist device. (Source: based on Rao et al, 2018.[109])

Central ECMO and peripheral V-A ECMO have their own advantages and disadvantages; the most significant hemodynamic difference is that central ECMO generates anterograde blood flow while peripheral V-A ECMO generates retrograde blood flow. Peripheral V-A ECMO is less invasive than central ECMO and has a lower risk of bleeding and infection than central ECMO.[109,110] However, central ECMO generates more blood flow, leading to higher circulatory support, than peripheral ECMO. Therefore, it is important to select the appropriate device based on a thorough assessment of the patient's general condition, presence of multiple organ dysfunction, hemodynamics, and the severity of the underlying disease.

3.1 Surgical Procedure

The standard approach is a median sternotomy. The pericardium is incised to expose the heart. Each access cannula and circuit is exited through the skin. The cannulas used for ascending aortic perfusion, right atrial and LV drainage vary from institution to institution. For ascending aortic perfusion, the cannula used with ECMO or cardiopulmonary bypass is inserted directly into the ascending aorta or an artificial graft is anastomosed to the ascending aorta to provide a blood supply to the systemic circulation. For right atrial drainage, a large-diameter cannula for cardiopulmonary bypass is commonly used. The size of cannulas used for LV drainage varies among institutions, depending on the role. When LV drainage is intended to serve as short-term LV decompensation under ECMO support, a small-diameter cannula is generally selected. If central ECMO is considered to be a preliminary step before later extracorporeal ventricular assist device (VAD), a large-diameter cannula is usually selected. In any case, peripheral V-A ECMO and central ECMO are not differentiated in terms of insurance coverage, and cannulas and circuits used are diverted from the ones used with cardiopulmonary bypass and extracorporeal VADs.

3.2 Central ECMO Management

Hemodynamic management and anticoagulation in central ECMO are similar to peripheral V-A ECMO. In general, in high-flow-assisted central ECMO, pulmonary arterial blood flow is markedly reduced, and blood flow to the systemic circulation through the oxygenator is increased. Therefore, it may be difficult to assess native pulmonary function while on central ECMO, and care must be taken to predict native pulmonary function after weaning from ECMO. Because central ECMO requires open chest manipulation for its placement and withdrawal, more careful management is necessary for bleeding complications such as cardiac tamponade.[110] Peripheral V-A ECMO with femoral access often makes rehabilitation difficult, but central ECMO, with no cannula inserted in the groin, makes rehabilitation possible. The possibility of respiratory and circulatory support in parallel with respiratory and cardiac rehabilitation is an advantage of central ECMO.

3.3 Standpoint of Central ECMO

Central ECMO is generally indicated for severe cardiogenic

shock corresponding to INTERMACS/J-MACS profile 1 or profile 2.[92] According to the Japanese consensus, the New York Heart Association (NYHA) functional classification IV/INTERMACS/J-MACS profile 1 is defined when progressive organ dysfunction or nutritional disorders are present during central ECMO support; NYHA functional classification IV/INTERMACS/J-MACS profile 2 is defined when there is no obvious organ dysfunction or nutritional impairment and the patient can undergo rehabilitation without the need for a ventilator during central ECMO support.[99]

Both peripheral V-A ECMO and central ECMO are suitable for short-term use.[92] In other words, they are mainly used as a bridge to recovery (BTR), which aims at recovery from the underlying disease. Another feature of central ECMO is that it can play a variety of roles, such as a bridge to decision (BTD) and bridge to candidacy (BTC), and furthermore, central ECMO can also play a role in bridge to bridge (BTB), which leads to conversion to an implantable VAD for long-term support to heart transplantation.[92,111] If right atrial drainage is removed from central ECMO with a LV venting system and the oxygenator is removed from the ECMO circuit, mechanical circulatory support (MCS) can be converted to an extracorporeal VAD. If pulmonary arterial perfusion is added to central ECMO with a left venrticular venting system, the MCS can be converted to a biventricular assist device (BiVAD). Thus, central ECMO is the MCS that can be converted to other types of support.

4. IMPELLA

4.1 Operating Principle

IMPELLA is a percutaneous LVAD and the most widely used in the world. A small axial flow pump is mounted within a catheter and provides LV assistance by withdrawing blood from the tip of the catheter positioned within the left ventricle and ejecting it into the ascending aorta.[112] Several catheter types have been developed according to the specific conditions of use. In Japan, the indication of IMPELLA is "Acute heart failure resistant to drug therapy, such as cardiogenic shock" (**Table 3**). IMPELLA 2.5 and 5.0 were approved in 2016, IMPELLA CP in 2019, IMPELLA CP SmartAssist in 2020, and IMPELLA 5.5 SmartAssist in 2022. In 2022, IMPELLA 2.5 and 5.0 were replaced by IMPELLA CP SmartAssist and IMPELLA 5.5 SmartAssist, which use optical sensors to acquire aortic position waveforms for pump position monitoring.

The decrease in LV mechanical work (LV unloading) with IMPELLA is directly related to a decrease in LV oxygen consumption.[113] In most cases of IMPELLA use the aim is for early weaning within a short period of time (hours to days), which differs from extracorporeal and implantable VADs. Therefore, it is important to understand the hemodynamics of the partial support condition in the presence of residual native cardiac output, as well as to maintain a total support condition that is a completely IMPELLA-dependent circulation with high flow rates for management and weaning.

4.2 Insertion Technique

IMPELLA can be inserted by either the traditional catheter puncture method or through surgical exposure of the vessel at the puncture site and subsequent insertion via an artificial vessel. However, prior to inserting an IMPELLA device, a comprehensive assessment of the presence and severity of aortic stenosis and regurgitation is crucial. Additionally, the use of IMPELLA following mechanical aortic valve replacement requires caution.

4.3 Insertion by Puncture

IMPELLA CP is primarily utilized through the transfemoral approach due to its relatively small diameter. A thorough

Table 3. Differences in IMPELLA Catheters

IMPELLA device	2.5*1	CP CP SmartAssist	5.0*1	5.5 SmartAssist
Support ventricle	Left ventricle			
Access	Percutaneous approach		Surgical cutdown technique	
Access vessel	Femoral artery*2		Axillary, subclavian, or femoral arteries	Axillary or subclavian arteries
Maximum average flow (L/min)	2.5	3.7	5.0	5.5
Catheter size (Motor)	12Fr	14Fr	21Fr	21Fr
Maximum rotational speed (rpm)	51,000	46,000	33,000	33,000
Indication in the USA	High risk PCI*3		Cardiogenic shock refractory to existing therapy*4	Cardiogenic shock refractory to existing therapy*4
	Cardiogenic shock refractory to existing therapy*4			
Indication in Japan	Acute heart failure resistant to drug therapy, such as cardiogenic shock			

*1As of 2022, IMPELLA 2.5 and 5.0 were replaced by IMPELLA CP SmartAssist and IMPELLA 5.5 SmartAssist, which use optical sensors to acquire aortic position waveforms for pump position monitoring with SmartAssist.
*2Axillary and subclavian approaches are also approved.
*3Temporary support for high-risk PCI when the heart team has determined high-risk PCI is the appropriate therapeutic option.
*4Ongoing cardiogenic shock as a result of isolated left ventricular failure that is not responsive to optimal medical management and conventional treatment measures (including volume loading and use of pressors and inotropes, with or without intra-aortic balloon pump).
PCI, percutaneous coronary intervention.

assessment of the optimal puncture site, delivery vessel, and risk of lower extremity hemorrhage should be conducted before insertion. Following femoral artery puncture and wire advancement, a sheath introducer is inserted using a dilator, and a pig-tail catheter is inserted in the left ventricle via a 0.035-inch wire from the sheath. The IMPELLA catheter is then inserted into the left ventricle with the monorail method using a 0.018-inch wire and the following protocol: (1) ensure that the catheter does not cause any interference with the mitral valve or chordae, (2) verify that the inlet does not come into contact with any LV structures, and (3) confirm that the outlet does not come into contact with the aortic valve. Initiate driving at the desired support level and assess the pressure value and motor waveforms on the control device monitor.

4.4 Insertion by Surgical Approach

The IMPELLA catheter is typically inserted via the subclavian and axillary arteries as the primary surgical approach, with the femoral artery or the ascending aorta reserved as alternative routes for patients with poor vascularity or those undergoing open chest surgery, respectively. During the catheter insertion procedure, the use of an artificial vessel is recommended. Following anastomosis of the artificial vessel, a sheath introducer is inserted, after which a pig-tail catheter is carefully threaded through the left ventricle using a 0.035-inch wire. Subsequently, the IMPELLA catheter is advanced through the pig-tail catheter using a 0.018-inch wire. It is essential to (1) ensure that the catheter does not cause any interference with the mitral valve or chordae, (2) verify that the inlet does not come into contact with any LV structures, and (3) confirm that the outlet does not come into contact with the aortic valve. Subsequently, remove the introducer sheath, perform trimming of the artificial blood vessel, insert the retention positioning unit sheath into the artificial blood vessel, secure it to the skin, and perform closure. Subcutaneous tunneling may also be performed as necessary. Initiate driving at the desired support level and assess the pressure level and motor waveforms on the control device monitor.

4.5 Management Precautions

4.5.1 Thrombosis Prevention

Thrombus formation within the IMPELLA pump and shaft should be prevented and strictly controlled because it can cause embolism and severe hemolysis. After IMPELLA insertion, anticoagulation therapy with unfractionated heparin is administered to achieve a target ACT of 160–180 s.[114] The IMPELLA is equipped with a purge system that creates a pressure barrier using a purge fluid composed of heparin glucose solution to prevent blood from entering the motor housing. The recommended heparin concentration in the purge fluid is 50 units/mL; however, in certain cases appropriate dosage reduction should be considered if there are concerns of bleeding. Because the purge fluid flow rate is automatically adjusted between 2 and 30 mL/h to maintain a pressure between 300 and 1,100 mmHg, many patients may require additional systemic heparin administration depending on the purge flow rate.[115] In April 2022, the US Food and Drug Administration approved the use of a heparin-free purge solution with a solution of sodium bicarbonate and glucose for patients with heparin-induced thrombocytopenia or bleeding.

4.5.2 Complications

Bleeding complications are the most important concern in the management of IMPELLA.[116–118] Many bleeding complications are related to access site bleeding, with modifying factors such as the use of large sheaths, decreased von Willebrand factor due to shear stress, and sustained anticoagulation caused by heparin. Attention must also be paid to hemolysis caused by increases in pump rotation speed or suction. In addition, IMPELLA is reported to induce valvular diseases such as aortic insufficiency caused by catheter placement in the aortic valve and mitral regurgitation due to chordal rupture during catheter insertion into the ventricle.[119] In managing these complications, appropriate anticoagulation therapy, repeated echocardiography, and regular confirmation of the pump position using pressure waveforms and motor current waveforms on the console are essential.

4.5.3 Escalation

The recommended duration for percutaneous placement of IMPELLA CP is several days. Therefore, if IMPELLA support needs to be extended, consideration should be given to escalating to IMPELLA 5.5, an externally placed VAD, or an implanted VAD due to concerns such as device degradation, infection, and hemolysis. Additionally, in cases of severe right heart failure or during cardiac arrest, LV suction by IMPELLA may occur due to poor blood return to LV, consequently preventing sufficient support flow. Although IMPELLA RP, a right heart assist device, is available in Europe and the USA, in Japan V-A ECMO or the combination of V-A ECMO and IMPELLA (ECPELLA) is available.[120]

4.6 Withdrawal

The 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure[121] recommend consideration of discontinuing MCS when there is improvement in organ dysfunction or hemodynamics within the treatment chart for cardiogenic shock. However, there is no specific description of withdrawal protocols or methods for IMPELLA. Various reports describe withdrawal protocols, but it is recommended to consider multiple factors such as hemodynamic parameters, cardiac function indicators, lactate levels, peripheral organ dysfunction, respiratory status, and the dosage of inotropic and vasoconstrictor agents. The insertion of a pulmonary artery catheter (PAC) is crucial for the assessment of hemodynamics.[20,69,122] Cardiac power output (CPO), which is calculated based on the measured cardiac output and mean blood pressure from the PAC, has been shown to be a predictor of death in patients with cardiogenic shock treated with MCS.[20,123] PAPi, which is calculated from the pulmonary artery pulsation pressure and right atrial pressure, is used as an indicator of right heart function in patients with cardiogenic shock.[124,125] Combining CPO and PAPi in the hemodynamic evaluation facilitates assessment of the risk of withdrawal.[59,126]

The withdrawal method involves gradually lowering the P level by 1–2 increments, confirming hemodynamic stability at P2, and removing the IMPELLA from the left ventricle. The rate of P level decrease varies according to the cause of shock and the degree of LV function.[59] Monitoring via a PAC should continue after removal to confirm the absence of deterioration in shock status. If withdrawal is

ultimately impossible, various options should be considered for the patient, such as prolonged placement or replacement of IMPELLA, escalation to IMPELLA 5.5 or ECPELLA, transition to an externally or implanted VAD, or transfer to a cardiac transplantation facility.[59]

5. ECPELLA

5.1 Management and Complications

Urine output, organ dysfunction, and lactate levels should be monitored to confirm whether V-A ECMO and IMPELLA are providing sufficient blood flow. At the same time, the following should be checked as indicators: reduction in LV load via PAWP on right heart catheterization, the transition of LV diameter on echocardiography, and pulmonary congestion on chest X-ray. In situations where the left ventricle is collapsed and IMPELLA low-flow alarms occur frequently, lowering the IMPELLA flow, concomitant use of inotropic drugs, vasodilators or inhalation of nitric oxide (NO),[127] and lowering the V-A ECMO flow should be considered.

Until pulmonary function improves, circulatory assistance by ECPELLA is primarily provided by V-A ECMO while setting the IMPELLA flow to a low level; this is done because increasing the IMPELLA flow can lead to North–South syndrome, and coronary and cerebral hypoxemia due to low oxygenated blood flow. Once pulmonary congestion is relieved by reducing the LV load with IMPELLA, the IMPELLA flow can be gradually increased. Because oxygenation during V-A ECMO is mainly provided by the artificial lungs in the ECMO circuit, the ventilator should be set according to the lung protection strategy for acute respiratory distress syndrome. However, ECPELLA support requires a certain level of oxygenation by autologous lungs to prevent North–South syndrome; therefore, ventilator settings should be made with particular attention to avert ventilator-induced lung injury. If the use of IMPELLA at low flow to preclude North–South syndrome does not improve pulmonary congestion due to inadequate reduction in LV load, the addition of a V-V ECMO system to ECPELLA should be considered.[128,129] Perfusion of hypoxic blood in the coronary circulation could impede myocardial recovery and consequently affect withdrawal from MCS. Because oxygenation of the coronary circulation cannot be assessed noninvasively,[130] the settings of ECMO, IMPELLA, and the ventilator are adjusted based on the oxygenation saturation of the right upper extremity, which is used as a surrogate measure of oxygenation of the cerebral circulation. To prevent thrombus formation in the artificial lung, V-A ECMO requires stronger anticoagulation than IMPELLA; therefore, ECPELLA is anticoagulated with unfractionated heparin similar to V-A ECMO. ECPELLA is reported to be associated with more hemolysis and hemorrhagic events than V-A ECMO alone, but there is no difference in the incidence of stroke.[38,106,131]

Once hemodynamic stability and organ function improve with ECPELLA, the level of circulatory support is gradually reduced and weaning from ECPELLA can be considered. The decision on whether to wean off IMPELLA or V-A ECMO depends on the duration of MCS and the patient's condition, but weaning from V-A ECMO is often attempted first. If the patient is to be converted to an implantable LVAD, the first step is to wean the patient from V-A ECMO in order to evaluate whether circulation can be established with LV assistance alone. During the process of gradually decreasing V-A ECMO flow, right heart catheterization and echocardiography should be evaluated and IMPELLA support should be increased, if necessary. If IMPELLA can maintain sufficient flow without causing suction, V-A ECMO should be discontinued, and withdrawal of IMPELLA support can be considered based on the patient's hemodynamics.

6. Extracorporeal VAD (Centrifugal Pump)

6.1 Synopsis

Extracorporeal VAD plays an important role in determining the treatment strategy for patients with cardiogenic shock who cannot immediately undergo implantion of a durable VAD.[132–136] Although extracorporeal VAD requires an invasive surgical procedure, it has the advantages of greater durability and provision of stable blood flow to organs in the short–medium-term compared with temporary-use percutaneous MCS devices such as IABP, V-A ECMO, and low-flow pump catheters (IMPELLA 2.5, CP). The current clinical role of the extracorporeal VAD is to provide a BTR or BTB, bridging to durable VAD implantation for patients with advanced heart failure or cardiogenic shock whose status makes it difficult to wean from temporary MCS, including those with worsening organ damage even with temporary MCS support.[137–139] Despite recent innovations in temporary-use MCS devices and concomitant improvements in therapeutic management, the prognosis for severe cases of bilateral heart failure, respiratory failure, and severe organ dysfunction remains poor.[1] In anticipation of the next treatment strategy, stabilizing hemodynamics using an extracorporeal VAD may lead to an improved long-term prognosis for patients with unstable heart failure despite temporary MCS support.

6.2 Indication for Extracorporeal VAD

In Japan, patients with cardiogenic shock (INTEMACS/J-MACS profile 1) are not currently eligible for bridge to transplantation (BTT) or destination therapy (DT) VAD implantation.[111,140] If short-term treatment does not improve cardiac function, it is necessary to stabilize hemodynamics and the patient's general condition with MCS, and to consider the indications for subsequent treatment for advanced heart failure, including durable VAD implantation. The assessment of reversibility of cardiac dysfunction in the short-term is very difficult and remains a clinical challenge.[141] Depending on comorbidities and the social background of the patient, it can take time to evaluate the indication of heart transplantation or DT. Bridge therapy using MCS, which enables stable hemodynamic support in short- to medium-term care, is a particularly necessary therapeutic strategy in Japan.[137]

Thanks to the relatively minimally invasive insertion of the IMPELLA 5.5 pump catheter, it is expected to be used as a bridging therapy with short- to medium-term hemodynamic support.[35,142] However, it is challenging to insert IMPELLA when the subclavian arteries or axillary arteries of the patient are too small. It is difficult to continue hemodynamic support with IMPELLA when complications such as hemolysis occur. If the need for long-term MCS is assumed due to severe organ damage, support with an extracorporeal VAD is more highly

Figure 4. Biofloat. (Adapted from Nipro Corporation website, attached document.)

recommended. In cases of severe right heart failure or pulmonary edema, a right VAD or central ECMO may also be considered.[30] Because the outcomes of BTB are not favorable in terms of survival and cerebrovascular event rates compared with primary LVAD implantation, careful consideration is necessary when evaluating its indications.[143,144] In contrast, it is important to consider upgrading the MCS, including extracorporeal VADs, without hesitation when multiple organ damage due to unstable hemodynamics is progressing, despite temporary MCS.

6.3 Centrifugal Pumps for Extracorporeal VAD

CentriMag, a magnetic levitation continuous-flow pump, is in clinical use as an extracorporeal VAD in other countries,[145–148] as it has not been approved in Japan. There are reports of the use of steady flow pumps such as Rotaflow, Gyro pump, and Mera centrifugal pump as extracorporeal VADs in Japan.[149–151] Although these continuous-flow pumps provide acceptable outcomes when used as extracorporeal VADs in patients with advanced heart failure, they have not been approved for such use or for extended use beyond a period of a few days.

In 2021, an extracorporeal VAD system (Biofloat, **Figure 4**) using a hydrodynamically levitated continuous-flow centrifugal pump was approved for reimbursement by health insurance, based on the results of an investigator-initiated clinical trial in Japan.[135,152] As a result of that trial, the Biofloat VAD has been approved for right ventricular support in addition to LV support.

6.4 Management After Biofloat Placement

Within 24 h of Biofloat placement surgery, the patient should be supported with the device set at high rotation and high flow rate to prevent thrombus formation; once bleeding is controlled, unfractionated heparin should be started as soon as possible.[153] At 24 h postoperatively, unfractionated heparin is administered by continuous infusion with an anticoagulation time of 150–170 s (APTT 50–70 s); the dosage is adjusted during monitoring for bleeding and thrombus formation. Once postoperative bleeding, hemodynamics, and the patient's general condition have stabilized, antiplatelet agents (aspirin 100 mg/day) and warfarin should be initiated. The dose of warfarin is adjusted with a target prothrombin time-to-international normalized ratio (PT-INR) of 2.5–3.5 and subsequently it is adjusted according to thrombus formation and bleeding complications. A thrombus is likely to form at the connection part of the circuit, and if a large and mobile thrombus is observed, pump/circuit replacement should be considered.

Inflow and outflow cannulas should be fixed at the exit sites. Furthermore, to prevent deterioration of the wound at the exit site, the patient should be instructed to be careful not to put tension on the cannulas during body movement.

6.5 Weaning From Extracorporeal VAD

The decision to remove the extracorporeal VAD should be made according to the cardiac function of the patient and clinical indications such as VAD complications that make it difficult to continue VAD support (e.g., device infection and cerebrovascular complications). As there is little evidence on the evaluation of the feasibility of weaning from a continuous-flow extracorporeal VAD, the weaning criteria for pulsatile-flow VADs or implantable continuous-flow VADs should be referenced. The "Berlin" criteria (off-pump echocardiographic LVEF ≥45% and LV end-diastolic diameter [LVDd] ≤55 mm) are considered as the standard for weaning off the LVAD.[154] The so-called "water (saline) load test", which involves loading 10 mL/kg of saline in 15 min under minimal auxiliary flow, can be useful as an evaluation tool in cases of implantable continuous-flow VADs as well as pulsatile-flow VADs.[155] Evaluation of both hemodynamics and LV wall motion response to dobutamine loading under minimal assist flow have also been reported as valuable for VAD weaning.[156,157] These weaning criteria and tests may also be useful in determining withdrawal from centrifugal pump extracorporeal VADs.

III. Considerations in MCS Management

1. Arrhythmia Management

1.1 Treatment of Arrhythmia

Tachyarrhythmias, both supraventricular and ventricular, can cause hemodynamic compromise even in patients with mechanical circulatory support (MCS). When tachycardias cause hemodynamic deterioration, electrical cardioversion should be considered. Modifying factors, such as electrolyte abnormalities, myocardial ischemia, and blood gas abnormalities, are potential causes of arrhythmias and should be evaluated and treated. Serum K >4.0 mEq/L and serum Mg >2.0 mg/dL should be targeted: hypo potassium often does not improve in the case of hypomagnesemia. The

efficacy of prophylactic electrolyte administration in patients without hypokalemia or hypomagnesemia has not been reported.[158] In cases of IMPELLA support, mechanical stimulation of the catheter can trigger ventricular tachyarrhythmias (ventricular tachycardia/ventricular fibrillation: VT/VF). Subsequent anti-arrhythmia treatments, such as intravenous amiodarone, nifekalant, and β-blockers, are generally indicated to prevent the recurrence of VT/VF. Amiodarone can be the first antiarrhythmic drug in patients with low cardiac function and renal dysfunction.[159]

Nifekalant is a pure potassium-blocking intravenous agent and is only available in Japan. It is effective for hemodynamically stable monomorphic VT, and especially useful in intensive care because of its fast-acting, ultra-short-acting, and negative inotropic effects. In patients with reduced renal function, careful monitoring of QT prolongation is necessary to reduce the risk of torsade de pointes. The additional effect of landiolol, a very short-acting β-blocker, has been demonstrated with class III antiarrhythmic drugs to prevent VT/VF in those with structural heart disease.[160] Left stellate ganglion block may be effective in refractory VT/VF that is difficult to control even with drugs.[161]

1.2 Pharmacokinetic Changes by MCS Circuitry

Amiodarone is also noted to decrease the blood concentration in patients on ECMO compared with controls due to adhesion to the ECMO circuits.[162] In patients on ECMO, blood levels should be monitored and appropriate doses should be used.

2. Concomitant Heart Failure Drugs

Continuous hemodynamic monitoring using right heart catheterization is recommended for hemodynamic management with drugs during MCS use.[163–165] Intravenous fluids or diuretics are used to maintain an adequate preload.[163,164] MCS is usually indicated in cardiogenic shock refractory to inotropes,[61,82,92] though it is noteworthy that inotropes should be reduced or discontinued if possible during MCS because they increase myocardial oxygen demand, resulting in arrhythmias, myocardial ischemia, and myocardial damage. However, in many cases, inotropes are often necessary, even during MCS. Inotropes and vasodilators, etc. are recommended to be indicated and used with particular attention to the points described below.

2.1 Afterload Management for Patients Using V-A ECMO

The use of V-A ECMO causes increased left ventricular (LV) afterload and decreased stroke volume from the left ventricle due to retrograde aortic blood flow.[109,166] In severe cases, opening of the aortic valve is inhibited, leading to increased LV pressure, exacerbation of pulmonary congestion, and thrombus formation in the cardiac cavity or the aortic root, with potentially fatal outcomes. There are several invasive and also noninvasive means of LV unloading to prevent these incidents (**Table 4**).[109,166] Decreasing the V-A ECMO flow reduces the LV afterload but may result in tissue hypoperfusion if cardiac output is severely impaired.[167] Intra-aortic balloon pumping (IABP) is most commonly used for this purpose, but if IABP is not feasible or cannot function sufficiently for LV unloading, inotropes (catecholamines, PDE III inhibitors, etc.) may be effective by increasing myocardial contraction or vasodilation.[109,166,168] Vasodilators (e.g., nitrates) may also be indicated if blood pressure is maintained.[109,166,168] It is recommended that drug doses are optimized in consideration of hemodynamic indices such as mean blood pressure and pulmonary artery wedge pressure, as well as echocardiographic indices including aortic valve opening (see **Section 3.6** Echocardiography During MCS Management). When these approaches fail or are insufficient, the use of IMPELLA or LV vent is an option.[169–171]

Table 4. Procedures for Left Ventricular Unloading During V-A ECMO Support

	Feature
Non-invasive	
Reduce V-A ECMO flow	Easy, but may lead to inadequate tissue hypoperfusion
Inotropes	Easy, but limited effect, elevation of myocardial oxygen demand and induction of arrhythmias
Vasodilators	Easy, but limited effect and inappropriate for patients with low blood pressure
Invasive	
IABP	Relatively easy
IMPELLA	Somewhat invasive
Left ventricular vent	Invasive, requiring surgical insertion

(Compiled from Rao et al, 2018[109] & Lorusso et al, 2021.[166])

2.2 Drug Therapy for Right Heart Failure

When hemodynamics cannot be adequately maintained due to right heart failure, despite optimal treatment for the underlying cardiac disease and preload control, augmentation of right ventricular contractility with inotropic agents or reduction of right ventricular afterload with pulmonary vasodilators (e.g., NO inhalation) can be effective.[163,172,173] Inadequate right ventricular preload reduces right ventricular ejection; on the other hand, excessive intravenous fluids can also be harmful because right ventricular enlargement with a septal shift to the LV side inversely reduces LV filling.[173] Control of right heart failure is especially important for patients on IMPELLA because the IMPELLA flow is highly dependent on LV preload.[163] In cases of the patient's hemodynamics being difficult to control with drug therapy, it is necessary to consider adding or changing the MCS device such as V-A ECMO.

2.3 Drug Treatment During MCS Weaning

Vasodilators, intravenous fluids, and diuretics need to be adjusted to maintain an appropriate preload and afterload in reference to the setting of the MCS and the hemodynamic indices. Inotropes can be used to facilitate withdrawal from MCS,[59,122,166] but in such cases these drugs should be used only in low doses: dobutamine $<3\,\mu$g/kg/min, dopamine $<3\,\mu$g/kg/min, and milrinone $<0.3\,\mu$g/kg/min.[166] If vasopressors are required, the dose of noradrenaline should be limited to $<0.06\,\mu$g/kg/min.[166]

The use of vasopressors (e.g., noradrenaline) may increase LV afterload, causing microvascular congestion and decreased cardiac output, resulting in worsening hemodynamic and tissue metabolism.[59,164] When vasopressors are used to improve hypotension, they are cautiously indicated based on assessment of achievement of appropriate preload control and adequate blood flow by cardiac output and MCS.[164,174]

Although some observational studies have shown that continuing heart failure medications, such as RAS inhibitors and β-blockers, during heart failure exacerbations are associated with a better outcome, the evidence of whether these drugs should be continued is not yet confirmed because data on patients receiving MCS are lacking and there have been no randomized controlled trials.[175] In clinical practice, the continuation or introduction of these drugs is sometimes considered with the hope of improving cardiac function and weaning the MCS.

3. Nutrition, Sedation, Infection, etc.

3.1 Nutrition

3.1.1 Route of Feeding

Several guidelines, including the Japanese Guidelines for the nutrition support therapy of critically ill patients in 2016,[176] recommend enteral rather than parenteral nutrition for the route of feeding in critically ill patients. Enteral nutrition is reportedly feasible even in patients on MCS. Gastroprokinetic agents should be used when necessary.[177–179]

Enteral nutrition can be administered either intermittently or continuously. In a report on critically ill patients, diarrhea was reported to be less frequent with continuous enteral feeding than with intermittent feeding. Because the digestive and absorptive functions of the intestinal tract are thought to be impaired in patients with heart failure, continuous administration is preferable in the early phase of enteral nutrition.[180]

3.1.2 Timing of Starting Nutrition

The Japanese Guidelines for the nutrition support therapy of critically ill patients recommend that enteral nutrition be initiated within 24 h, or at least within 48 h after starting the treatment of the critical illness.[176] However, enteral nutrition is thought to increase oxygen consumption in the gastrointestinal tract; it is difficult to increase intestinal blood flow to meet demand under conditions of low cardiac output, resulting in the risk of hypotension, intestinal ischemia, and intestinal necrosis. Importantly, enteral nutrition should not be initiated, especially under high-dose catecholamine or in the presence of low blood pressure. After initiation of enteral nutrition, careful monitoring of hemodynamic changes and gastrointestinal symptoms such as vomiting and diarrhea.[176,180]

The ELSO (Extracorporeal Life Support Organization) guidelines recommend that intravenous nutrition be initiated if enteral nutrition is difficult to administer for 5–7 days.[177] Peripheral and central IV nutrition can be used, but peripheral IV nutrition is insufficient because products with high osmolality are difficult to administer. The central route is necessary to deliver sufficient energy.

3.1.3 Type and Dosage of Enteral Feeding

There are 2 types of enteral nutrients, oligomeric formula and polymeric formula, and there is no significant difference in length of hospital stay, incidence of infection, or mortality rate between them. There is also no difference in the incidence of diarrhea. Most of the nutrients available in Japan are 1 kcal/mL, but when fluid intake is limited, higher concentrations of 1.5 kcal or 2 kcal/mL should be considered. The concentrations of protein or lipid differ between products and thus should be carefully selected based on each patient's condition.

Simple formulas for calculating the target energy dose of 25–30 kcal/day per body weight or the Harris-Benedict formula are widely used. It has been reported that excessive energy administration in the acute phase increases the risk of death; therefore, it is better to administer nutrient energy of less than the target energy dose in the early phase of administration.[181,182]

3.1.4 Patient Management During Enteral Nutrition Therapy

When enteral nutrition therapy is administered, care must be taken in positioning the patient to prevent aspiration. Regarding positioning for intubated patients during enteral nutrition, a semi-Fowler's position has been reported to decrease the incidence of pneumonia.

The amount of nutrients and digestive fluid stored in the stomach during enteral nutrition, termed gastric residual volume (GRV), is considered to be an indicator of gastric motility. In the intensive care unit (ICU), GRV is generally measured every 4–6 h, and if it increases, a reduction or interruption of enteral feedings should be considered.

3.2 Sedation

3.2.1 Analgesics and Sedatives

Adequate sedation management requires adequate analgesia (analgesia-first sedation). It is important to remember that analgesia is different from sedation. Pain management with analgesics is essential. Special attention should be paid to analgesia in patients on MCS who often require surgical or invasive procedures; it is recommended to use intravenous opioids (fentanyl, morphine) as the first-line analgesic.[183]

Benzodiazepine sedatives (midazolam), propofol, and dexmedetomidine are currently the most common sedatives used in the ICU. For sedation of adult patients under ventilatory management, use of benzodiazepines has been reported to prolong the duration of ventilation and ICU stay compared with the use of nonbenzodiazepines; thus, nonbenzodiazepines are recommended.[184,185] In contrast, midazolam, which has less of a hypotensive effect than propofol and dexmedetomidine, may be easier to use in patients with hemodynamic instability. In a comparison of propofol and dexmedetomidine, dexmedetomidine was reported to be associated with less agitation and delirium and better communication, but dexmedetomidine alone sometimes has insufficient sedative effects.[186]

3.2.2 Depth of Sedation and Assessment

Appropriate sedation has the advantages of (1) ensuring patient comfort and safety (prevention of anxiety and agitation), (2) decreasing oxygen consumption and basal metabolism, and (3) improving ventilation and reducing pressure trauma. However, unnecessarily deep sedation leads to prolonged ventilation, prolonged ICU stay, and an increased risk of complications such as muscle weakness, pneumonia, decubitus and delirium. The appropriate depth of sedation allows communication with the patient,

pain assessment, and early recognition of cerebrovascular events. It is important to objectively monitor the depth of sedation to assess the patient's sedation status and prevent unnecessary deep sedation. The Richmond agitation-sedation scale (RASS) is often used to evaluate the depth of sedation: a RASS score of −2 to 0 is generally the target in critically ill patients. Patients on MCS often require several cannulas, and problems associated with cannulation can be fatal. Thus, adequate depth of sedation is critically important.[187]

Agitation is defined as aimless and excessive movements, and it is important to address the reasons for it in ICU patients; for example, pain, delirium, hypoperfusion, hypoxemia, and infection. Delirium is the most common cause of ICU patient discomfort and it can worsen prognosis, requiring specialized care, sometimes including psychiatric specialists. Although there are some reports on the efficacy and safety of early movement and exercise while on MCS, the scientific evidence is not sufficient, and further validation is needed.

3.3 Infection Management During MCS

Patients on ECMO are at high risk for nosocomial infections because in addition to ECMO cannulas they also have various medical devices including IABP, IMPELLA, central venous catheters, endotracheal tubes, and indwelling urinary catheters. More than 60% of patients on ECMO for ≥48 h have complications of infection. The most common infection is ventilator-associated pneumonia, followed by bacteremia and cannula infection. The risk of infection increases with ventilator management, ECMO management, and length of hospital stay.[188] The most common organisms causing infection are *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus*, *Pseudomonas aeruginosa*, Enterobacteriaceae including *Escherichia coli* and *Klebsiella*, *Stenotrophomonas maltophilia*, and *Candida* species.[188–190] Severe sepsis and septic shock are independent risk factors for death in patients on ECMO.[188] Although a multicenter surveillance reported 74% of centers administering prophylactic antibiotics during ECMO management,[191] there are no recommended protocols. Selection of prophylactic antibiotics should be determined based on the trends in healthcare-associated infection at each institution.

For IABP-related infections, a prospective analysis of 60 patients with IABP reported that 52% had systemic inflammatory response syndrome and 22% had positive blood cultures.[192] The most common pathogen was coagulase-negative staphylococci in that report, followed by *S. aureus* and *Enterobacter* species. Considering the high risk of infection during ECMO management, prophylactic antibiotic therapy may be advisable, but there is no evidence-based recommendation.

Although there are no comprehensive reports on IMPELLA-associated infections, patients on IMPELLA should be managed in accordance with recommendations for patients with ECMO and IABP.

3.4 Patient Management for Stroke and Gastrointestinal Hemorrhage

3.4.1 Cerebral Hemorrhage

The incidence of bleeding complications during ECMO is 30–60%,[193–195] but the frequency of cerebral hemorrhage has been reported to vary from 1.8% to 21.3%.[193–201] Most patients undergoing ECMO treatment are managed under mechanical ventilation, sedation, and sometimes muscle relaxants, making it difficult to immediately detect central nervous system (CNS) abnormalities due to cerebral hemorrhage. This is thought to be the reason for the high variation in the frequency of cerebral hemorrhage. The detection rate of cerebral hemorrhage tends to be higher in reports from facilities that can frequently perform cerebral CT scans, which is the most useful diagnostic imaging tool for cerebral hemorrhage.[196] Clinical findings at the onset of a cerebral hemorrhage, such as a sudden increase in mean arterial blood pressure, a sudden decrease in platelet count, and the appearance of anisocoria, render it essential to detect initial changes in the clinical course of cerebral hemorrhage, and it is important to suspect that a CNS abnormalities may be occurring.[202] Intraparenchymal hemorrhage is the most common (59–88%), followed by subarachnoid hemorrhage (22–56%) and subdural hemorrhage (2%).[202–204]

The cause of bleeding is often unclear: a high anticoagulant state due to heparin administration with ECMO induction, or a deviation from physiologic antegrade blood flow due to ECMO blood flow.In addition, the activity of von Willebrand factor in the blood decreases due to the strong shear stress of the artificial lungs, ECMO, and IMPELLA pumps, leading to acquired von Willebrand syndrome (AVWS) and various hemorrhagic complications.[205] Risk factors that promote bleeding include female sex, thrombocytopenia, heparin use, dialysis, serum Cr >2.6 mg/dL, long-term ECMO treatment,prolongationof activated coagulation time (ACT), and rapid decline in $PaCO_2$.[200,206,207] Also, patients who have been already anticoagulated before ECMO introduction, higher SOFA (Sepsis-related Organ Failure Assessment) coagulation score, thrombocytopenia, and spontaneous non-intracranial bleeding have been reported as risk factors.[202]

A cerebral CT scan is the most helpful modality for diagnosing of cerebral hemorrhage. It is difficult for patients to be moved to the laboratory for routine scans when their condition is unstable during ECMO treatment. Therefore, regular bedside neurologic checks by physicians and nurses (e.g., response to verbal command and pain, tendon reflexes, pupil checks) should be performed, and a cerebral CT scan is recommended in the presence of unexpected events (convulsion, delirium, failure to awaken after sedation discontinuation, etc.).[207]

For the treatment of cerebral hemorrhage, if the hemorrhage is small enough not to cause neurologic abnormalities, conservative treatment is performed by temporarily stopping or neutralizing anticoagulation therapy and/or administering blood products, such as platelet transfusion. However, cases of severe cerebral hemorrhage that require drainage, such as when complicated by a cerebral hernia, even when anticoagulation therapy is urgently neutralized, the blood coagulation function is often already impaired, thus, treatment indications must be carefully determined due to the very-high risk operation status.

Regarding the prognosis after cerebral hemorrhage, the mortality rate at 1 month is reported to be 81–89% in patients with cerebral hemorrhage (28–57% in non-bleeding patients), and a severe cerebral hemorrhage has a negative effect on prognosis in patients on ECMO treatment.[197,202]

The J-PVAD (Japanese registry for Percutaneous Ventricular Assist Device) registry reported a bleeding complication rate of 6.1% during IMPELLA operation,[1]

but this information was based on a limited number of patients and further accumulation of data is desirable.

3.4.2 Cerebral Embolism

Cerebral embolism, as with cerebral hemorrhage, is a known complication that can occur during ECMO treatment, with an incidence of 3.4–6.8%.[197] There are various causes of cerebral ischemia, including cerebral infarction due to hypoperfusion during shock, release of intra-aortic plaque, mural thrombus, or thrombus formation in the ECMO circuit, and dispersal into cerebral vessels by retrograde blood flow from peripheral V-A ECMO. However, the cause of cerebral ischemia is unclear, because it has been reported that cerebral infarction occurs in approximately 2% of patients with V-V ECMO.[207] Most patients undergoing ECMO treatment are managed under mechanical ventilation with sedation, and it is difficult to immediately detect the onset and severity of cerebral embolism unless obvious neurologic abnormalities (anisocoria, convulsion, etc.) are present in the acute phase of the disease.[207] Cerebral angiography with contrast-enhanced CT is likely the simplest and most accurate method for detecting cerebral embolism. The treatment depends on the cause, but mechanical embolus retrieval by catheter may be indicated for acute embolism showing extensive cerebral ischemia in the main cerebral artery. If a thrombus in the ECMO circuit is suspected to be the cause of cerebral embolism, circuit exchange is critical to prevent further thromboembolism.

As for IMPELLA, the incidence of cerebral infarction during support is reported to be 1.7–3.5%.[208–211] The J-PVAD registry reported a rate of 1.6%,[1] but detailed data accumulation in the future will be crucial. The cause of IMPELLA-induced embolism is unclear, but assumed to be the release of thrombus in the left ventricle due to IMPELLA insertion or thrombus formation around the device.

Table 5. Situations in Which Early Release From Bed or Active Exercise From the Bedside in the Intensive Care Unit Should Not Be Performed in Principle

1. Without the permission of the physician in charge
2. Patient is overexcited and unable to obtain the necessary rest or compliant behavior (RASS ≥2)
3. Severe arousal disorder (RASS ≤–3) with uncooperative exercise
4. Unstable circulatory dynamics requiring assisted circulation such as intra-aortic balloon pumping
5. Low blood pressure, despite administration of high doses of inotropic or hypertensive drugs
6. Blood pressure fluctuates greatly when the patient changes position
7. Untreated aneurysms at risk of imminent rupture
8. Uncontrolled pain
9. Poorly controlled intracranial hypertension (≥20 mmHg)
10. Unstable phase of head or neck injuries
11. Presence of a fracture with poor fixation
12. Presence of active bleeding
13. Inadequate length or inadequately secured catheters or IV lines that are prone to be accidentally removed due to early bed release or aggressive movement from the bedside
14. No staff available to ensure the safety of the patient when leaving the bed
15. Consent of the person or from the family cannot be obtained

RASS, Richmond Unrest (Excited)-Sedation Scale. (Adapted from Japanese Society of Intensive Care Medicine Early Rehabilitation Review Committee, 2017.[214])

3.4.3 Patient Management for Gastrointestinal Bleeding

Bleeding complications due to ECMO are said to have an incidence of 30–60%;[193–195] bleeding from cannula insertion sites is the most common (17.1%), followed by pulmonary bleeding (8.1%), gastrointestinal bleeding (5.1%), and intracranial bleeding (3.8%).[212] Bleeding is most frequently caused by anticoagulation therapy during ECMO, which is known to induce bleeding in V-A ECMO when the ACT is prolonged to ≈200 s with heparin; platelet consumption also contributes to bleeding. In addition, it has been reported that strong shear stress inside the artificial lungs and ECMO pumps reduces the activity of von Willebrand factor in the blood, which can complicate AVWS and cause various bleeding complications.[205]

Gastrointestinal bleeding occurs in 5.1% of patients on ECMO treatment, mainly due to hemorrhagic gastritis or peptic ulcer caused by severe systemic stress due to circulatory failure;[195] such bleeding is also from gastrointestinal mucosal damage as part of multi-organ damage. Small intestinal hemorrhage is particularly difficult to diagnose and requires special attention. Long-term ECMO management may, in principle, cause angiodysplasia (vascular dysplasia) of the gastrointestinal tract due to AVWS, as is the case during LVAD treatment, but this has not been reported, probably because ECMO management is generally completed within a short period of time.

Endoscopic hemostasis is commonly used for gastrointestinal bleeding, with clipping of the bleeding site and/or fibrin application, but there are no clear guidelines for treatment. Cryoprecipitate or fresh-frozen plasma as transfusion therapy for consumed von Willebrand factor is effective for AVWS in terms of bleeding, but it should be used with caution because there is a risk of thrombus formation.[195]

The J-PVAD registry reported a 6.1% incidence of bleeding complications during IMPELLA operation,[1] but detailed data on gastrointestinal bleeding alone are lacking. It has been suggested that because IMPELLA is a small-diameter, high-rotation axial flow pump it can cause AVWS during its operation, which may result in gastrointestinal bleeding by a similar mechanism.[213]

3.5 Rehabilitation During MCS Management

When patients are unstable and undergo MCS, sedation, ventilator management, or bed rest, then ICU-acquired weakness (ICU-AW), which is acute diffuse muscle weakness, arises; respiratory complications such as deconditioning, joint contractures, atelectasis, and dysphagia, may also occur. The goal of rehabilitation for patients undergoing MCS is to prevent ICU-AW, deconditioning, joint contractures, and respiratory complications, which is difficult when patients are often under sedation.

In order to start rehabilitation as early and effectively as possible, it is extremely important to stabilize the hemodynamics and pathophysiology and to wean the patient from MCS as soon as possible. If the patient's condition is unstable and life-threatening, active exercise should be avoided. The Japanese Society of Intensive Care Medicine's "Early Rehabilitation in Intensive Care: An Evidence-Based

Table 6. Eligibility for Rehabilitation During MCS Implementation

Indicators for rehab eligibility assessment	Level of consciousness, vital signs (blood pressure, pulse, oxygen saturation), ECG (arrhythmia, ST-T changes) Subjective symptoms (e.g., shortness of breath, fatigue, decreased appetite, and pain) Other findings (e.g., cyanosis, pale face, cold sweat, edema, and pulmonary rales), muscle strength, joint range of motion Weight, urine volume and color, cardiac function, respiratory function, swallowing function, presence of cerebral complications Hemostasis, thrombus, hemorrhage, infection, pulmonary stasis, deep vein thrombosis, embolism, paralysis Position and fixation of catheters and devices Medication and nutritional status Blood test findings (including Hb, CK, BNP, and CRP) Imaging findings (including simple chest X-ray, echocardiography, CT scan, and cardiac catheterization) Hemodynamic indices (including intracardiac pressure data and cardiac output) Safe environment (ventilators, oxygen tubes, IV lines, multiple medical staff) Driving condition of mechanical support and timing of replacement
Indicators for monitoring safety during rehabilitation	Level of consciousness, vital signs, ECG, subjective symptoms, other findings No catheter or device misalignment and bleeding Driving condition of mechanical support Hemodynamic index
Indicators for monitoring safety after rehabilitation	Level of consciousness, vital signs, ECG, subjective symptoms, other findings, weight, urine volume and color Hemostasis, hemorrhage, pulmonary congestion Position and fixation of catheters and devices Blood test findings, imaging findings, and hemodynamic indices

BNP, B-type natriuretic peptide; CK, creatine kinase; CRP, C-reactive protein; Hb, hemoglobin.

Expert Consensus"[214] lists contraindications to rehabilitation in the ICU (**Table 5**).

If early weaning from MCS is not expected and the patient is confined to a bed for a long period of time, rehabilitation should be considered after confirming that there are no contraindications to deconditioning or preventing the progression of joint contractures.

The condition for "early bed release and early active exercise" is that the various organ functions are improving and the patient is no longer in a life-threatening situation.[214] In such cases, "early bed release and early active exercise" is intended to be active in-bed exercise during bed rest and expansion of activities of daily living (ADL).[214] It is advised to avoid prolonged bed rest as much as possible, because 10 days of bed rest in healthy elderly patients reduces exercise tolerance and skeletal muscle strength by 12–13%,[215] and the decrease in muscle layer thickness and circumference of the thigh in ICU negatively correlates with the number of days of hospital stay.[216]

The effectiveness of cardiac rehabilitation for patients undergoing MCS has been reported in a small number of case reports.[112,217] When rehabilitation is provided to patients undergoing MCS, a team consisting of attending physicians, ICU physicians, physical therapists, clinical engineers, and nurses should thoroughly evaluate the eligibility of the patient before developing a program, which is then implemented while monitoring safety (**Table 6**). The team should share information on the patient's condition, such as the presence or absence of complications, MCS status, echocardiography, CT, and blood sampling data and carefully perform rehabilitation in the presence of several staff members who are familiar with the operation and management of the VAD in case of unexpected mechanical problems.

During rehabilitation, extreme care should be taken to avoid complications such as bleeding or hemorrhage from the MCS insertion site, catheter misalignment, kinking, and device misalignment. When the MCS is inserted through the groin, there is a high risk of bleeding or catheter migration due to flexion of the insertion leg, and only limited motion exercises should be performed to prevent joint contractures. If the catheter insertion site cannot be kept straight, a restraint band or deep sedation should be used to avoid complications on the insertion side. If the lower limb is immobilized in the externally rotated position, the peroneal nerve is easily compressed by bed rails or cushions, which may cause peroneal nerve palsy.

The dorsal foot and posterior tibial artery should be palpated for pulsation, and the presence of elevated blood creatine kinase levels and myoglobinuria should be checked to see if lower extremity hemorrhage has occurred during the rehabilitation process. Because sedation and bed elevation are often difficult during the period when an MCS is inserted through the groin, when replacing the MCS, switching to IMPELLA for subclavian artery access, central ECMO, or VAD implantation should be considered, a process that facilitates rehabilitation. In the case of IMPELLA with subclavian artery access, central ECMO or VAD implantation, patients should begin with positioning, joint mobilization exercises, and breathing exercises that are possible in bed and then gradually increase ADL to sitting and standing positions. When the patient is sitting, standing, or gait training during rehabilitation, the condition and vitals are monitored under the supervision of multiple medical staff members, while checking for problems with the mechanical device insertion site and the driving status.

If any problems occur during the rehabilitation process, rehabilitation should be stopped immediately, and the cause should be evaluated. During weaning from MCS,

vitals and hemodynamics are often unstable, and active rehabilitation should be avoided.[112,217] When the patient is successfully weaned from MCS, rehabilitation for weaning should be performed after checking for the presence of contraindicated conditions, wound problems, and hemodynamic stability.

Although early rehabilitation is desirable after withdrawal from MCS,[112,217] especially in the early post-withdrawal period, cardiac output support is often lost, and catecholamine is often administered at high doses; therefore, bed rest and ADL training should be carefully conducted in stages. In particular, sitting and standing postures and the ability to maintain posture are important for improving ADLs. Although complications such as brain complications, infections, and residual cardiac function may delay the progress of rehabilitation, each patient's program should be reviewed in the short term, and any rehabilitation that can be performed should be actively carried out to support the patient's return home.

In the early stages of exercise, anaerobic metabolism becomes predominant in the disused muscles, and acidification within the muscle is renewed due to a lack of high-energy phosphate, and fatigue is likely to occur.[218] With this in mind, the Borg scale is initially set at 11–13 so that the anaerobic metabolic threshold is not exceeded, and the program is managed so that fatigue does not remain the following day. During the check for changes in the patient's condition, the program should be adapted in the following order according to the patient's motor abilities: passive, assisted, automatic, and resistance exercises. Initially, the exercise should be performed in small and frequent doses and gradually increased as the patient's exercise capacity improves. As long as the patient's cardiovascular status is stable, motor function improves gradually, requiring frequent modifications of the program. Even after the patient recovers well and gains ambulatory independence, physiotherapy intervention should be targeted to meet the patient's social needs.

3.6 Echocardiography During MCS Management

During the placement and management of MCS, echocardiography is used not only to monitor changes in cardiac function, but also to evaluate hemodynamics specific to MCS, detect complications, and evaluate candidacy for weaning from MCS.

3.6.1 V-A ECMO

a. Blood Stagnation in the Left Ventricle

With V-A ECMO, the LV wall motion is lower than without support due to decreased return flow from the right heart system and increased afterload.[219] In the presence of severe LV systolic dysfunction, the aortic valve does not open, and blood may stagnate in the left ventricle and sinus of Valsalva. If there is no opening of the aortic valve and a high degree of spontaneous echo contrast is observed in the left ventricle, the risk of thrombus formation is high. Therefore, the presence of thrombus in the left ventricle and aortic root should be thoroughly evaluated in this situation.[219]

b. Aortic Insufficiency (AI)

Advanced AI is difficult to treat with V-A ECMO, and in cases where V-A ECMO was introduced in an emergency situation and without adequate preoperative evaluation, the severity of AI should be evaluated after placement of the V-A ECMO.

c. Pericardial Effusion

Although pericardial effusion is a rare complication of percutaneous V-A ECMO, it should be included as a daily observation item because hemodynamic changes by cardiac tamponade are difficult to detect and such effusion may be first detected on echocardiography.

d. Evaluation for Withdrawal

Although there is no established protocol using echocardiography for V-A ECMO weaning, factors include LV ejection fraction (LVEF) >35%, time–velocity integral (TVI) of the LVOT waveform >10 cm, no LV enlargement, and no cardiac tamponade.[219] On weaning, TVI >10 cm of the LV outflow tract (LVOT) waveform after decreasing pump flow, LVEF >20–25%, systolic motion velocity (s′) of the mitral annulus on the lateral side[220] and increase in early diastolic mitral annular velocity on the lateral side >10%, and increase in s′ of tricuspid annulus >10%[221] have been reported as the conditions for the device withdrawal.

3.6.2 IMPELLA

a. Confirmation of Catheter Position

Because insertion of the catheter in an inappropriate position in the left ventricle can cause complications, its position should be confirmed using echocardiography as well as fluoroscopy during placement. Parasternal or apical LV long-axis images are suitable for simultaneous observation of the aortic valve, LVOT and mitral valve. The catheter should be positioned so that the blood inlet is 3.5 cm from the aortic valve and the tip of the catheter is directed toward the apex. (For IMPELLA 5.5, the tip should be approximately 5 cm from the inlet.) If hemolysis occurs during administration, the inhaler may be in contact with the subvalvular mitral tissue or LV wall, or the outlet portion may be in contact with the aortic valve or aortic wall, and these findings should be confirmed.[97,222]

b. Changes in Valve Regurgitation

Because the left ventricle shrinks during IMPELLA placement due to unloading and the relationship between the catheter and LV changes, new interference of the catheter with the mitral valve should be monitored during the management of IMPELLA. Color Doppler images around the catheter are difficult to observe because of artifacts caused by the axial flow pump implanted at the base of the catheter. Transesophageal echocardiography may be useful in detecting the appearance of AI after IMPELLA placement.[223] Because AI increase after weaning has been observed in some cases,[224] changes in AI before and after weaning should also be evaluated.

3.7 Palliative and End-of-Life Care

Palliative care refers to an approach aimed at enhancing the quality of life (QOL) of patients and their families facing life-threatening illnesses, through the prevention and relief of suffering by identifying, assessing, and responding to pain and other physical, psychosocial, and spiritual problems at an early stage.[225,226] Appropriate management of heart failure, the underlying pathology, often leads to an improvement in symptoms such as dyspnea and general malaise, as well as QOL. Palliative care in cardiovascular disease is

extensively detailed in the Statement on palliative care in cardiovascular disease, a joint guideline of the Japanese Circulation Society/Japanese Heart Failure Society.[95] Palliative care is also crucial in heart failure requiring MCS and can be achieved through treatment of heart failure with catecholamines and diuretics in addition to MCS. Patients undergoing MCS treatment may require medical narcotics, non-narcotic analgesics, and anti-anxiety medications as needed to alleviate physical and psychological distress. Furthermore, because patients receiving MCS treatment are often anxious about their social life, a palliative care team consisting of multiple professionals, including a clinical psychologist and social worker, should intervene.

In cases of chronic heart failure, it is desirable to provide appropriate pharmacological and non-pharmacological treatment for heart failure in accordance with guidelines before the patient reaches stage D, which is treatment-resistant heart failure, and to conduct sufficient advanced care planning with the patient, family, and medical team to reflect the patient's own wishes as much as possible.[227,228] The medical team should explain medical information, such as treatment options and prognosis, in an easy-to-understand manner, and share information, including the patient's wishes, values, and outlook on life, with all involved. Both the medical team and the family should contribute to the decision-making process (shared decision making).[95] However, because MCS is often introduced urgently at the first onset of acute heart failure to save a patient's life, it may be initiated in a situation where it is impossible to confirm the patient's decision. Although it is not easy to share information and support decision-making with patients and their families in a limited time, we should endeavor to support optimal decision-making for patients by holding multiple meetings whenever possible.

The term "terminal stage" in cardiovascular intensive care is defined as "a situation in which a patient is in a terminal stage of illness despite the best efforts of life-saving medical treatment" or "a situation that results in dependence on inotropic drugs or mechanical therapy, even when treatment is effective."[95] The determination of whether a patient is in the terminal phase should be made objectively by a medical team consisting of physicians, nurses, and clinical engineers from multiple departments, including cardiology, cardiovascular surgery, intensive care, and palliative care, in a situation where appropriate intensive cardiovascular care has been exhausted. In addition, consideration should also be given to the clinical ethics committee and medical safety management department of the facility concerned, as necessary. However, it should be noted that some patients can be saved with the option of heart transplantation, even if they were once judged to be in the terminal stage. Therefore, intensive cardiac care should be conducted with the patient's indication for heart transplantation in mind.

When a patient undergoing treatment with MCS has been determined to be in the terminal stage, the patient's wishes should be respected in principle, provided there is the capacity to make decisions.[229,230] Medical personnel should furnish the necessary information to enable the patient to make informed decisions, taking into account the patient's condition. If the patient lacks decision-making capacity, the decision should be made based on medical appropriateness while respecting the patient's advance directives. Should the patient be unable to make decisions or provide advance instructions, family members should respect the presumption of the patient's will, provided they can do so. If the patient's will cannot be determined, the medical team should confer with the family members who will act as surrogate decision makers to decide the best course of action for the patient. The medical team should facilitate the decision-making process by providing supportive communication and sharing information with the family members repeatedly. Due to the sudden onset of the need for MCS, patients and family members often struggle to comprehend the situation and make calm decisions. Depending on the progression of the disease, it may be necessary to convey bad news, but the medical staff should endeavor to establish a relationship of trust with the patient and their family members by repeatedly explaining the situation in simple terms.

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Appendix 1. Pediatric MCS

There are 3 major types of mechanical circulatory support (MCS) for severe heart failure in children: (1) extracorporeal membrane oxygenation (ECMO), (2) extracorporeal mechanical circulatory support (VAD), and (3) implantable VAD. ECMO is generally limited to a few weeks to 1 month of support, whereas VADs can provide longer-term support.

The EXCOR Pediatric VAD can be used in neonates weighing as little as 3 kg and is primarily used as a bridge to heart transplantation.

Implantable VADs are sometimes indicated for children of relatively large size, because they can be discharged from the hospital and go to school.

1.1 ECMO

When ECMO is used after cardiac surgery, it is often established through a median sternotomy in the same manner as for normal cardiac surgery. However, in cases of acute heart failure due to fulminant myocarditis or cardiomyopathy, the cannula insertion site is selected according to body size to ensure rapid and reliable cannulation. Generally, in patients weighing <20 kg, cannulation is performed in the neck, where larger blood vessels can be secured, because the femoral vessels are not well developed.

1.1.1 Perioperative Management

a. Bleeding and Thrombosis

Bleeding is one of the most difficult complications to manage with ECMO. Especially with postoperative cardiac ECMO, continued transfusion of blood due to hemorrhage leads to edema of organs and multiple organ failure. Therefore, it is recommended to control bleeding with an activated coagulation time (ACT) of 180–200 s, but in some cases, priority may be given to controlling bleeding by lowering the ACT to ≈150 s. It is also important to monitor for thrombi in the circuit and the oxygenator. If a floating thrombus in the circuit or a thrombus in the oxygenator that increases the pressure in the circuit or decreases gas exchange is detected, the circuit should be replaced.

b. Renal Failure

When ECMO is used, renal failure often occurs at the same time. In adults, continuous hemodiafiltration (CHDF) on a separate circuit from ECMO is recommended, but in children, it may be difficult to secure blood vessels, so sometimes CHDF is integrated into the ECMO circuit. In such cases, great care should be taken to prevent air retraction and possible air emboli.

c. Pulmonary Congestion

When ECMO is used in patients with fulminant myocarditis or cardiomyopathy, left ventricular failure may cause pulmonary congestion due to the inability to eject blood from the left ventricle, resulting in elevated left ventricular diastolic pressure and left atrial pressure. Pulmonary hemorrhage may occur, requiring immediate decompression of the left heart by venting the left atrium or the left ventricle. There have been reports of decompression by catheterization to create an atrial septal defect (ASD), but residual ASD can be a problem.[231]

1.2 Pediatric Extracorporeal VAD (EXCOR Pediatric)

The EXCOR Pediatric, which is a pediatric, pneumatically driven/pulsatile, extracorporeally placed VAD is the only such device currently available for use in children with a body surface area <0.7 m^2. As of 2022, >2,000 implantations have been performed worldwide. The EXCOR Pediatric consists of a pump, cannula, and Ikus drive unit. The pump is pneumatically driven by Ikus to control pulsation and output, thereby assisting cardiac function. The pump is available in 6 sizes (10, 15, 25, 30, 50 and 60 mL) depending on the volume of the blood chambers. The 10 mL, 15 mL, 25 mL, and 30 mL pumps for children are indicated for use with body weights of 3–9 kg, 7–14 kg, 10–25 kg, and 20–30 kg, respectively.

1.2.1 EXCOR Implantation Procedure

In general, a LVAD with left ventricular apex cannulation and ascending aortic perfusion is used. If right heart failure is also present, a RVAD with right atrial cannulation and pulmonary artery perfusion may be necessary. Left atrial cannulation may also be performed when left ventricular apex cannulation is difficult due to restrictive cardiomyopathy or other conditions, but this is less common.

1.2.2 Attachment of the Apex Cannula

The left ventricle is lifted, and gauze is placed dorsally to lift the apex. The left anterior descending artery is identified, and the planned incision site is marked. In children, the apical cannula is inserted slightly anterior to the apex, ≈2 cm from the left anterior descending artery. The apex cannula is inserted with the long side toward the lateral wall (the opening faces the septum).

1.2.3 Attachment of the Blood Cannula

The anastomosis of the arterial cannula should be placed as close to the aortic root as possible, in consideration of the subsequent transplantation procedure. The cannula position should be slightly to the right of the ascending aorta to prevent pressure from the sternum and pressure on the right ventricle. Many centers use an artificial vessel to avoid compression of the right ventricle by the cannula.[232]

1.2.4 Connection to the Pump and Weaning From Cardiopulmonary Bypass

The blood chamber and the connector are thoroughly de-aired and connected to the pump. When weaning the patient from cardiopulmonary bypass, the pump membrane should be closely observed to ensure that the pump is completely filling and emptying, and the device settings and patient volume should be adjusted. Signs of right heart failure, such as elevated central venous pressure and poor filling, should also be noted. It is important to use transesophageal echocardiography to confirm left ventricular volume and septal position.

1.2.5 Postoperative Management

a. Anticoagulation and Antithrombotic Therapy

If hemostasis is confirmed 24–48 h after surgery, continuous heparin administration should be started at 100 U/kg/day and gradually increased to 200 U/kg/day, with the target activated partial thromboplastin time of ≈50 s. However, it

should be noted that heparin overdose may exacerbate bleeding tendency. If oral or tube feeding can be started, warfarin should be started, with a target INR of ≈3. Aspirin 1 mg/kg/day and dipyridamole 4 mg/kg/day should also be started.

b. Check for Pump Thrombus

The most common sites of thrombus formation are the attachment points of polyurethane valves, the connection points of cannulas and pumps, and other areas where the flow of blood changes. Small, white, stable thrombi do not require pump replacement, but pump replacement should be considered with red or floating thrombi.

c. Right Heart Failure

Carefully monitor for perioperative right heart failure. If the pump is not filling properly, right heart failure as well as volume deficiency should be considered, and right heart support with administration of nitric oxide or catecholamine should be considered. In addition, right heart failure may gradually become apparent over a long period of time after surgery, and periodic echocardiography and chest X-ray should be performed to evaluate cardiac function.

d. Infection

Infection around the cannula has been reported in about two-thirds of cases in Europe and the USA.[233] As the patient becomes more active, granulation tissue forms between the cannula and the skin, which often becomes infected. Although local disinfection can sometimes control the infection, antibiotics should be administered if the infection extends to the surrounding skin.

e. Body Growth

In Japan, the waiting period after EXCOR implantation is particularly long, with the average waiting period before implantation exceeding 1 year. Therefore, the size of the extracorporeal pump may need to be increased as the body grows.

1.3 Implantable VAD

Implantable VADs for neonates and infants are not yet common, but may be indicated for relatively large children. In particular, the HeartMate 3 has been increasingly used in children worldwide.[234]

Appendix 2. IMPELLA RP

The IMPELLA RP (Abiomed, Danvers, MA) is a 22Fr axial-flow pump right heart assist catheter device mounted on the tip of an 11Fr catheter. The catheter is inserted by puncturing the femoral vein, and the tip blood outlet is placed in the pulmonary artery beyond the tricuspid and pulmonary valves. The proximal blood inlet is positioned in the inferior vena cava.[235] The RECOVER RIGHT study was conducted to evaluate the safety and efficacy of the IMPELLA RP; 30 patients over the age of 18 years were randomized to Cohort A (18 patients with a LVAD) and Cohort B (12 patients after open heart surgery, heart transplant, or myocardial infarction). Patients with right heart failure who were eligible for the device had a cardiac index <2.2 L/min/m^2 under the use of high-dose inotropic drugs (dobutamine ≥10 μg/kg/min or other inotropic drugs of equivalent dose, or multiple inotropic or pressor drugs) and met 1 of the following criteria: (1) CVP ≥15 mmHg, (2) central venous pressure (CVP)/PCWP >0.63, or (3) extensive right heart failure on echocardiography (TAPSE ≤14 mm, right ventricular base diameter >42 mm or right ventricular short-axis diameter >35 mm). Patients with extremely high risk conditions, such as INTERMACS profile 1 or very low cardiac index (<1.3 L/min/m^2) were excluded. The mean age of the study patients was 59 years. Patients received an average of 3.2 inotropic or pressor drugs. The cardiac index increased from 1.8±0.2 to 3.3±0.23 L/min/m^2 and CVP decreased significantly from 19.2±4 to 12.6±1 mmHg after device insertion. The duration of device assistance was 3.0±1.5 days (0.5–7.8 days), with a 30-day survival rate of 73.3%, survival at discharge of 70.0%, and 180-day survival rate of 70.0%.

A pooled analysis of 60 patients (Cohort A: 31, Cohort B: 29), 30 from the RECOVER RIGHT study plus 4 continuing clinical trials following the same protocol and 26 patients from the post-approval registry, was published in 2018.[236] The post-approval enrollment patients included several patients with profile 1 and more patients in a worse condition before device insertion than in the RECOVER RIGHT study. Significant increases in the cardiac index and decreases in CVP were similarly observed after 4.0±1.5 days (0.5–14 days) of assistance. The survival rate at 30 days or until discharge, whichever was the latest, was 72%, with no significant difference in survival between the cohorts.

In November 2022, the US Food and Drug Administration granted premarket approval for IMPELLA RP Flex, which can be punctured and implanted through the internal jugular vein. The approved conditions for use are as follows: the device can be used for up to 14 days in patients with a body surface area ≥1.5 m^2 and acute right heart failure or decompensated heart failure after left ventricular assist device, myocardial infarction, heart transplant, or open heart surgery.[237] An application is being prepared for approval in Japan (as of November 2022).

Appendix 3. Details of Members

Chair
- Takashi Nishimura, Department of Cardiovascular and Thoracic Surgery, Ehime University Graduate School of Medicine

Members
- Yasutaka Hirata, Department of Cardiovascular Surgery, Graduate School of Medicine, The University of Tokyo
- Takayuki Ise, Department of Cardiovascular Medicine, Tokushima University Hospital
- Hiroyuki Iwano, Division of Cardiology, Teine Keijinkai Hospital
- Hironori Izutani, Department of Cardiovascular and Thoracic Surgery, Ehime University Graduate School of Medicine
- Koichiro Kinugawa, Second Department of Internal Medicine, University of Toyama
- Takeshi Kitai, Department of Heart Failure and Transplantation, National Cerebral and Cardiovascular Center
- Takayuki Ohno, Division of Cardiovascular Surgery, Mitsui Memorial Hospital
- Tomohito Ohtani, Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine
- Takahiro Okumura, Department of Cardiology, Nagoya University Graduate School of Medicine
- Minoru Ono, Department of Cardiovascular Surgery, Graduate School of Medicine, The University of Tokyo
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- Koichi Toda, Department of Thoracic and Cardiovascular Surgery, Dokkyo Medical University Saitama Medical Center
- Yasumasa Tsukamoto, Department of Transplant Medicine, National Cerebral and Cardiovascular Center
- Osamu Yamaguchi, Department of Cardiology, Pulmonology, Hypertension and Nephrology, Ehime University Graduate School of Medicine

Collaborators
- Takeo Fujino, Department of Advanced Cardiopulmonary Failure, Faculty of Medical Sciences, Kyushu University
- Toru Hashimoto, Department of Cardiovascular Medicine, Faculty of Medical Sciences, Kyushu University
- Haruhiko Higashi, Department of Cardiology, Pulmonology, Hypertension and Nephrology, Ehime University Graduate School of Medicine
- Akihiro Higashino, Division of Cardiovascular Surgery, Mitsui Memorial Hospital
- Toru Kondo, Department of Cardiology, Nagoya University Graduate School of Medicine
- Hirotsugu Kurobe, Department of Cardiovascular and Thoracic Surgery, Ehime University Graduate School of Medicine
- Toru Miyoshi, Department of Cardiology, Pulmonology, Hypertension and Nephrology, Ehime University Graduate School of Medicine
- Kei Nakamoto, Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine
- Makiko Nakamura, Second Department of Internal Medicine, University of Toyama
- Tetsuya Saito, Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine
- Keita Saku, Department of Cardiovascular Dynamics, National Cerebral and Cardiovascular Center
- Shogo Shimada, Department of Cardiac Surgery, The University of Tokyo Hospital
- Hiromichi Sonoda, Department of Cardiovascular Surgery, Kyushu University Hospital
- Shinya Unai, Department of Thoracic & Cardiovascular Surgery, Cleveland Clinic
- Tomoki Ushijima, Department of Cardiovascular Surgery, Kyushu University Hospital
- Takuya Watanabe, Department of Transplant Medicine, National Cerebral and Cardiovascular Center
- Kazuyuki Yahagi, Division of Cardiology, Mitsui Memorial Hospital

Independent Assessment Committee
- Norihide Fukushima, Graduate School of Nursing, Senri Kinran University
- Takayuki Inomata, Department of Cardiovascular Medicine, Niigata University Graduate School of Medical and Dental Sciences
- Shunei Kyo, Tokyo Metropolitan Institute for Geriatrics and Gerontology
- Tohru Minamino, Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine
- Kenji Minatoya, Department of Cardiovascular Surgery, Graduate School of Medicine, Kyoto University
- Yasushi Sakata, Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine
- Yoshiki Sawa, Osaka Police Hospital

(Members are listed in alphabetical order, and affiliations are as of September 2023)

Appendix 4. Disclosure of Potential Conflicts of Interest (COI): JCS/JSCVS/JCC/CVIT 2023 Guideline Focused Update on Indication and Operation of PCPS/ECMO/IMPELLA (2020/1/1–2022/12/31)

Author	Member's own declaration items									COI of the marital partner, first-degree family members, or those who share income and property			COI of the head of the organization/department to which the member belongs (if the member is in a position to collaborate with the head of the organization/department)	
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Collaborators: Toru Hashimoto				Bayer Yakuhin, Ltd.				Abbott Medical Japan LLC. Medtronic Japan Co., Ltd. Nipro Corporation						
Collaborators: Haruhiko Higashi														Takeda Pharmaceutical Company Limited
Collaborators: Toru Miyoshi														Takeda Pharmaceutical Company Limited
Collaborators: Keita Saku				Ono Pharmaceutical Co., Ltd. Abiomed Japan K.K. Mallinckrodt Pharma K.K.		JT Central Pharmaceutical Research Institute NTT Research, Inc. OMRON HEALTHCARE Co., Ltd. Asahi Kasei ZOLL Medical Corporation. Otsuka Medical Devices Co., Ltd Abiomed Japan K.K. Zeon Corporation								

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Independent Assessment Committee: Kenji Minatoya				TERUMO CORPORATION Japan Lifeline Co.,Ltd.		Sumitomo Bakelite Co., Ltd. Akita Sumitomo Bakelite Co., Ltd.	Edwards Lifesciences Corporation							
Independent Assessment Committee: Yasushi Sakata				AstraZeneca K.K. Novartis Pharma K.K. Bayer Yakuhin, Ltd. Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited. Nippon Boehringer Ingelheim Co., Ltd. Medtronic Japan Co., Ltd.		Biosense Webster, Inc. Bristol-Myers Squibb Abbott Medical Japan LLC. Sony Corporation TOA EIYO LTD. Nipro Corporation Roche Diagnostics K.K. Nippon Boehringer Ingelheim Co., Ltd. FUJIFILM Toyama Chemical Co., Ltd.	Abbott Medical Japan LLC. Eisai Co., Ltd. Johnson & Johnson K.K. Bayer Yakuhin, Ltd. BIOTRONIK Japan, Inc. Boston Scientific Japan K.K. Kowa Company, Ltd. Ono Pharmaceutical Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Mitsubishi Tanabe Pharma Corporation Nippon Boehringer Ingelheim Co., Ltd. Nihon Medi-Physics Co., Ltd. Medtronic Japan Co., Ltd. Takeda Pharmaceutical Company Limited							

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*The following persons have no conflict of interest to declare:
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Members: Koichi Toda
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