Deutsches Herzzentrum Berlin
Klinik für Herz-, Thorax- und Gefäßchirurgie

DISSERTATION

Mechanische Kreislaufunterstützung bei Patienten im akuten kardiogenen Shock

Mechanical circulatory support in patients with acute cardiogenic shock

zur Erlangung des akademischen Grades
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von

Gaik Nersesian

aus Ashtarak

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List of abbrevations

German abbrevations (german abstract):

DHZB – Deutsches Herzzentrum Berlin (German Heart Center Berlin)

HI – Herzinsuffizienz (heart failure)

KS – kardiogener Schock (cardiogenic shock)

KPR – kardiopulmonale Reanimation/ Herz-Lungen-Wiederbelebung (cardiopulmonary resuscitation)

MKU – mechanische Kreislaufunterstützung (mechanical circulatory support)

RVAD – rechtsventrikuläres Unterstützungssystem (right ventricular assist device)

SOP – standardisierte Operationsprozedur (standardized operating procedure)

v-a ECLS – veno-arterielle extrakorporale Kreislaufunterstützung (veno-arterial extracorporeal life support)

English:

AMI – acute myocardial infarction

AR – aortic (valve) regurgitation

AVR – aortic valve replacement

CABG – coronary artery bypass grafting

CAD – coronary artery disease

CI – cardiac index

CI – confidence intervals

CK – creatine kinase

CMP – cardiomyopathy

CPR – cardiopulmonary resuscitation

CS – cardiogenic shock

CVP – central venous pressure

DHZB – German Heart Center Berlin

ESC – European Society of Cardiology

GOT – glutamate oxalacetat transaminase

HF – heart failure

HTx – heart transplantation

IABP – intra-aortic balloon counterpulsation
INTERMACS – Interagency Registry for Mechanically Assisted Circulatory Support
IQR – interquartile range
LDH – lactate dehydrogenase
L/ R V – left/ right ventricle
LVEF – left ventricular ejection fraction
MAP – mean arterial pressure
MCS – mechanical circulatory support
NYHA – New York Heart Association
OR – odds ratio
PCWP – pulmonary capillary wedge pressure
RHF – right heart failure
ROC – receiver operating characteristic
ROSC – return of spontaneous circulation
rtPA – recombinant tissue plasminogen activator
SBP – systolic blood pressure
SCAI – Society of Cardiovascular Angiography and Interventions
SV – stroke volume
TAH – total artificial heart
TI – tricuspid valve insufficiency (regurgitation)
(L/ R / Bi) VAD – left/ right/ (bi-) ventricular assist device
v-a ECLS – veno-arterial extracorporeal life support
VIS – vasoactive inotropic support
VSD – ventricular septal defect
VT / VF – ventricular tachycardia/ fibrillation

Zusammenfassung

Ziele

Kardiogener Schock (KS) als Endstadium der Herzinsuffizienz (HI) tritt in ungefähr 25% der Fälle auf und ist mit einer hohen Sterblichkeit assoziiert. Temporäre mechanische Kreislaufunterstützung (MKU) wird in der Therapie des KS eigesetzt. In unseren Studien wurden verschiedene Konzepte für temporäre MKU auf der Basis der mikroaxialen intraaortalen Impellerpumpe untersucht und verglichen.

Methoden

Die Daten von allen im Deutschen Herzzentrum Berlin (DHZB) seit 01/2016 zur mechanischen Kreislaufunterstützung mit einem temporären linksventrikulären mikroaxialen Impellersystem versorgten Patienten*innen wurden retrospektiv in einer Datenbank gesammelt, analysiert und publiziert.

Diese Dissertation ist eine Zusammenfassung der Ergebnisse der drei wichtigsten Publikationen.

Ergebnisse

Die Ergebnisse der Pilotstudie zeigten ein Überleben von 43% bei 28 Patienten*innen unter isolierter mikroaxialer Impellerpumpentherapie, sowie 44% bei 9 Patienten*innen mit Kombination von v-a ECLS und Impella. Präoperative kardio-pulmonale Reanimation (KPR) sowie ein arterieller pH <7,2 oder >7,45 waren mit einem schlechteren Überleben assoziiert.

In der zweiten Studie wurden 70 Patienten*innen isoliert mit Impella 5.0/5.5® behandelt. Das 30-Tage-Überleben betrug 51%. Ein präoperativer Anstieg des arteriellen Laktatwertes (OR 1.217 pro 1 mmol/l; p=0.015) sowie KPR (OR 16.74; p=0.009) wurden als Prädiktoren für die 30-Tage-Mortalität identifiziert. Ein arterielles Laktat von 8 mmol/l wies hierbei eine Spezifität von 0.944 und eine Sensitivität von 0.294 (OR 7.083, CI 1.422–35.28; p=0.017). Auf der Basis dieser Daten wurde ein Algorithmus für die Behandlung des KS mittels temporärer MKU entwickelt und folglich im DHZB im Rahmen einer SOP festgelegt.

In meiner dritten Analyse haben wir die perkutan implantierbaren Impella CP und die größeren chirurgischen Impella 5.0/5.5® Systeme verglichen. Das nicht adjustierte 30-Tage-Überleben war signifikant höher in der Impella 5.0/5.5® Kohorte (58% vs. 36%, p=0.021). Nach der Propensity-Score-Adjustierung waren die Kohorten ähnlich (OR 1.23, 95% CI

[0.34-4.18], p=0.744). Ein präoperativer Laktatwert über 8 mmol/L sowie präoperative KPR gingen mit einer erhöhten Mortalität einher (OR 10.7, 95% CI [3.45-47.34], p<0.001; OR 13.2, 95% CI [4.28-57.89], p<0.001). Der Algorithmus aus der zweiten Studie wurde auf der Basis neuer Ergebnisse um die Anwendung der perkutan implantierbaren Impellerpumpen erweitert.

Schlussfolgerung

Insgesamt wurden von mir 203 Patienten*innen mit verschiedenen MKU-Systemen analysiert. Unsere Studien haben gezeigt, dass mikroaxiale Impellerpumpen eine effektive Therapie im KS darstellen.

Präoperative KPR sowie Laktatwerte ≥ 8 mmol/L sollten eine erweiterte Therapie bestehend aus einer Kombination von einer Impellerpumpe und v-a ECLS nach sich ziehen. Ein Algorithmus basierend auf diesen Erkenntnissen kann helfen eine optimale temporäre MKU-Therapie auszuwählen.

Abstract

Objectives

Cardiogenic shock (CS) as the final stage of Heart failure (HF) is present in approximately 25% of cases and is associated with high mortality. Temporary mechanical circulatory support (MCS) is widely used for CS therapy. In our research, we investigated and compared different temporary MCS concepts based on microaxial intra-aortic impeller pumps.

Methods

The data of all patients who received MCS with a temporary microaxial left ventricular impeller pump in the German Heart Center Berlin (DHZB) since 01/2016 were collected retrospectively and used for a database establishment. The obtained data were analyzed in regard to different clinical aspects and published.

This dissertation summarizes and describes the results of three major publications.

Results

The results of the pilot study demonstrated a 43% survival in 28 patients on isolated impeller pump support, as well as 44% in 9 CS patients on combination of v-a ECLS and Impella. Preoperative cardiopulmonary resuscitation (CPR) and an arterial pH <7.2 or >7.45 were associated with poor outcomes.

In the second study, 70 patients were supported with Impella 5.0/5.5®. The overall 30-day survival was 51%. An increase in arterial lactate (OR 1.217 per 1 mmol/L; p=0.015) and CPR before implantation (OR 16.74; p=0.009) were identified as predictors of 30-day mortality on Impella support. A cut-off of 8 mmol/L for preoperative lactate showed a specificity of 0.944 and a sensitivity of 0.294 (OR 7.083, CI 1.422-35.28; p=0.017) for 30-day mortality. Based on these data, an algorithm for optimal short-term MCS therapy was developed and thereafter applied as a standardized operational procedure at the DHZB.

In my third analysis we compared the percutaneously implanted Impella CP® and larger surgical Impella 5.0/5.5®. In unadjusted cohorts the 30-day survival was significantly higher in the Impella 5.0/5.5® group (58% vs. 36%, p=0.021). After propensity score adjustment for relevant preoperative demographic and hemodynamic parameters, the 30-day survival was similar between the groups (OR 1.23, 95% CI [0.34-4.18], p=0.744).

Preoperative lactate levels above 8 mmol/L and CPR before implantation were associated with poor outcomes in both cohorts (OR 10.7, 95% CI [3.45-47.34], p<0.001; OR 13.2, 95% CI [4.28-57.89], p<0.001). Based on these results the selection algorithm from the second study was amended to include the use of percutaneous impeller pumps.

Conclusions

A total of 203 patients treated with different MCS devices were analyzed. Our studies demonstrated that temporary MCS with microaxial impeller pumps is a feasible treatment in CS patients.

In cases with preoperative CPR or lactate levels ≥ 8 mmol/L an advanced treatment concept with a combination of Impella and v-a ECLS should be pursued. An algorithm based on these parameters may prove useful for optimal patient selection and to identify optimal temporary MCS in CS patients.

1 Objectives

1.1 Introduction

Cardiogenic shock (CS) is one of the main factors for in-hospital mortality in the industrialized world.[1] It occurs in 5-10% of patients suffering an acute myocardial infarction (AMI) and is associated with a substantial in-hospital mortality of 50-65%.[1,2]

1.2 Definition

The definition of CS varies between different studies and institutions. CS is characterized as a mismatch between cardiac output and body demand, resulting in end-organ hypoperfusion and ischemia. The definitions mostly include the following criteria:

- Systolic blood pressure (SBP) <90 mmHg or inotropic support to maintain that pressure[2-4]
- Dyspnea, cold extremities, mental confusion, dizziness[3]
- Cardiac index (CI) <2.2 L/min/m^2 and pulmonary capillary wedge pressure (PCWP) <15 mmHg[2]
- Oliguria with urine output <30 mL/h
- Metabolic acidosis and/or lactate >2 mmol/L[4]

1.3 Classification of cardiogenic shock

Several classification systems are available to describe the severity of CS and patients' condition and play an essential role in the decision-making process. Currently the most commonly used assessment tool is the SCAI (The Society of Cardiovascular Angiography and Interventions) classification, which was recently developed in cooperation with cardiologists, intensive care physicians, and cardiothoracic surgeons (Figure 1. SCAI classification).[5] The SCAI definitions are based on patients' clinical presentation and the response to the adequate therapy.

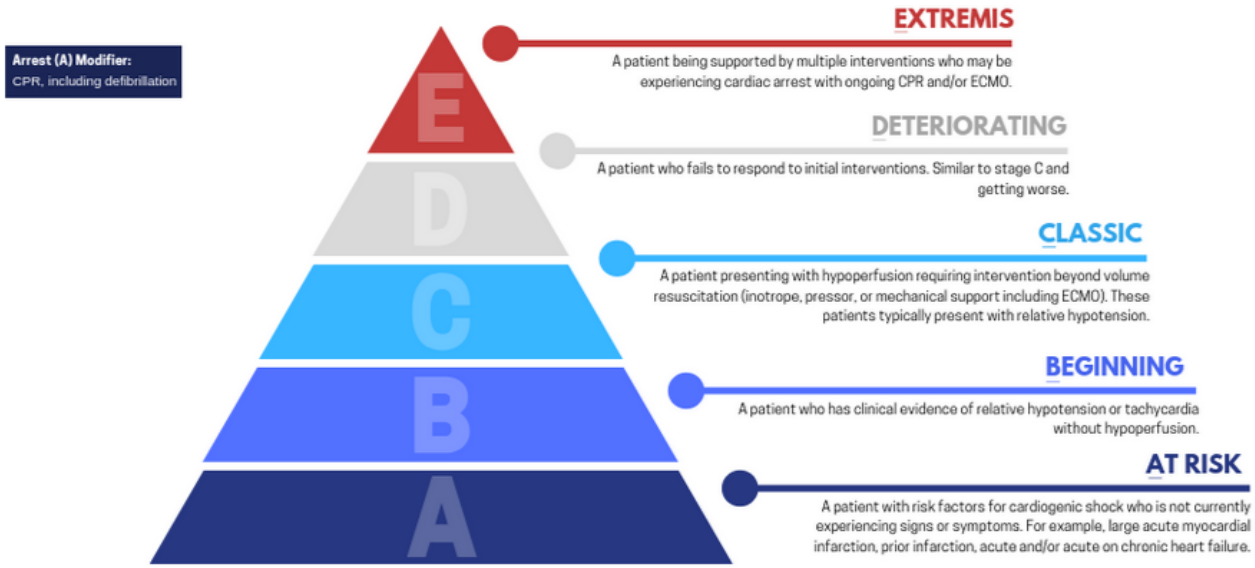

Figure 1. SCAI classification of cardiogenic shock.
From “SCAI clinical expert consensus statement on the classification of cardiogenic shock,” by Baran DA et al., Catheter Cardiovasc Interv., 94(1):29-37.

The INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) classification, which is mostly used within the MCS community, uses the number of administered inotropes to evaluate the severity of CS.

INTERMACS classification of cardiogenic shock		
Profile	Description	
1. Critical cardiogenic shock	"Crash and burn": life-threatening hemodynamic instability despite rapidly escalating inotropic support	**Manifested cardiogenic shock**
2. Progressive decline	"Sliding on inotropes": declining function despite intravenous inotropic support	
3. Stable but inotrope dependent	"Dependent stability": patients with stable blood pressure and organ function on continuous intravenous inotropic support	
4. Resting symptoms	Patient stabilized close to normal volume status, but experiencing symptoms of congestion at rest or during daily activities	
5. Exertion intolerant	Comfortable at rest and with daily activities, but unable to engage in any other activity	
6. Exertion limited	Patient experiencing fatigue after the first few minutes of any meaningful activity	
7. Advanced NYHA III	Patient living comfortably with meaningful activity limited to mild physical exertion	
NYHA – New York Heart Association		

Table 1. INTERMACS classification of cardiogenic shock.
Adapted from “INTERMACS profiles of advanced heart failure: the current picture,” by Stevenson LW and Pagani FD, et al., J Heart Lung Transplant., 28(6):535-41.

Patients’ outcomes correlate strongly with CS severity, and in case of SCAI D and E (equivalent to INTERMACS 2 and 1) an in-hospital mortality of 40 % and 67 %, respectively, is to be expected.[5,6]

1.4 Etiology of cardiogenic shock

CS develops as a sequelae of derangements in the entire cardiovascular system. A distinction can be made primarily between CS as a result of cardiac failure, vasoplegia, shunting, or a combination thereof. CS can be caused by a range of different cardiovascular diseases (Figure 2. Etiology of cardiogenic shock).[1,2,7-9]

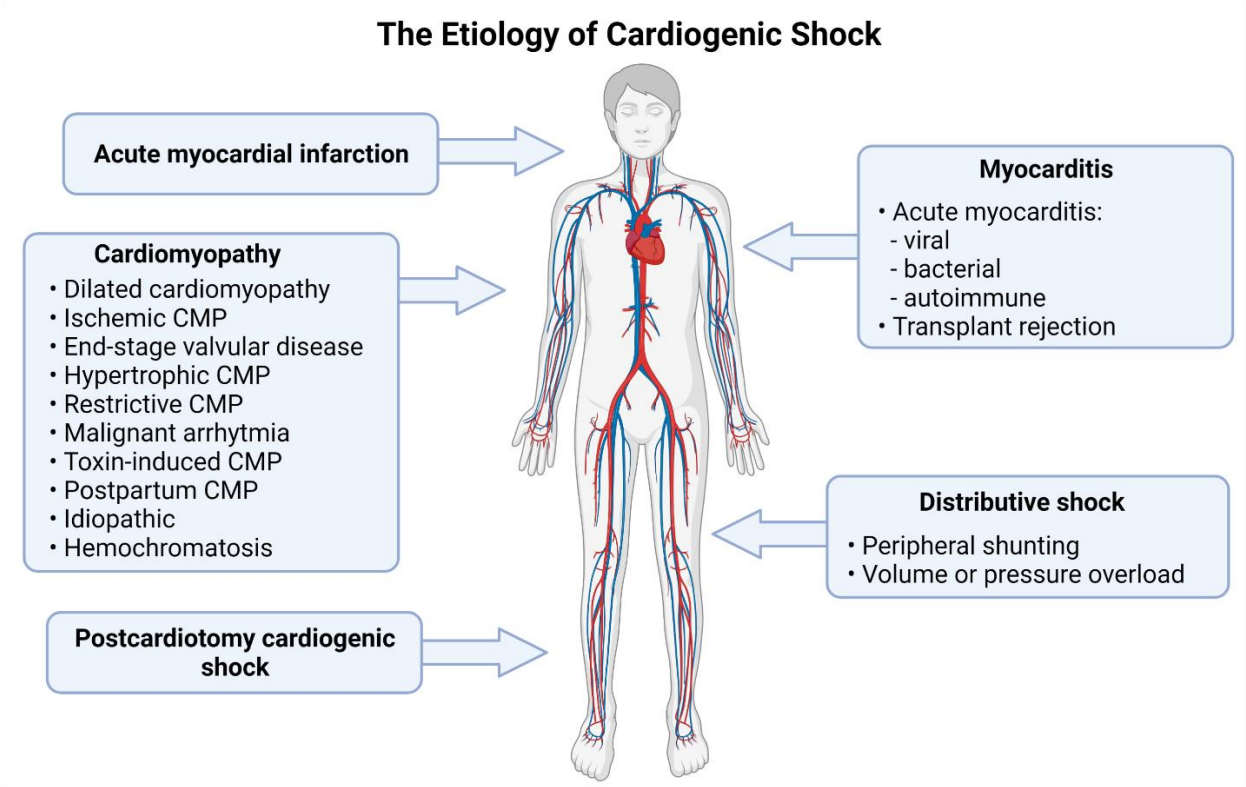

Figure 2. Etiology of cardiogenic shock.
Created by G. Nersesian.

Between 2005 and 2017, 441,696 patients with CS were treated in German hospitals. Despite a relevant increase in the annual incidence of cardiogenic shock cases from 45/100,000 (30,808 cases) in 2010 to 51.7/100,000 (42,779 cases) in 2017, the general in-hospital mortality remained relatively constant over time (61% in 2005 and 59% in 2017).[10]

Before 2010 an AMI represented the main cause of CS, occurring in approx. 53% of cases; however, since 2011-2013 the proportion of CS patients changed in favor of acute on chronic HF. One possible explanation for this shift might be the general aging of the

German population and simultaneous improvements in modern therapy and medical care, with an increasing density in hospital distribution.[10]

In case of CS as a sequelae of acute on chronic HF, different forms of cardiomyopathy may be responsible for the deterioration in patients' health. In principle, one can distinguish between ischemic and non-ischemic forms of cardiomyopathy, whereby ischemic cardiomyopathy accounts for the vast majority of CS cases. Ischemic cardiomyopathy (iCM) usually occurs as a consequence of prolonged coronary artery disease (CAD) or after AMI.[11] The pathogenesis of iCM is based on ischemia-induced loss of cardiomyocytes, followed by myocardial remodeling and fibrosis, ultimately resulting in systolic dysfunction.[12,13] Myocardial fibrosis also impairs the electrophysiological signal transduction of the heart, increasing the risk for ventricular fibrillation.[7]

Dilated cardiomyopathy (dCM) includes most of the non-ischemic forms of advanced heart failure and is the result of a combination of environmental and genetic factors. Dilated cardiomyopathy is characterized mainly by left ventricular dilatation and myocardial dysfunction in the absence of CAD, hypertensive or valvular heart disease, or congenital malformations.[14] The pathophysiology of dCM is diverse and multifactorial, but is based on direct non-ischemic cardiomyocyte damage. Dozens of gene phenotypes are associated triggers of dCM and can be found in up to 35% of patients. However, the genetically driven forms of dCM remain relatively rare and symptoms frequently already manifest at a young age.[14] Most mutations associated with hereditary dCM occur in the genes responsible for structural proteins of the cytoskeleton, cell membrane channels, and sarcoplasmic reticulum of cardiomyocytes. Beside single-gene mutations affecting predominantly the myocardial cells (titin [TTN], lamin A/C [LMNA], troponin T [TNNT2]), syndromic diseases such as musculoskeletal (Duchenne muscular dystrophy, Becker muscular dystrophy) or metabolic disorders (hemochromatosis, mitochondrial diseases) can be responsible for the pathogenesis of dCM.[14]

One of the most common forms of dCM is toxic cardiomyopathy (tCM), which can occur as a result of exposure to different toxins, including alcohol, drugs, and anthracyclines.[11] In the industrialized world up to 36% of dCM cases are related to chronic alcohol abuse.[14] In contrast to alcohol-induced dCM, drug-related tCM demonstrates a fulminant clinical picture with a rapid deterioration of myocardial function. Besides direct cardiotoxicity,

sympathomimetic drugs (cocaine, amphetamines) have a thrombogenic effect and lead to severe vasospasms of the coronary arteries. Cardiotoxic processes are accompanied by an inflammatory reaction which leads to additional myocardial damage. In case of high-dose drug abuse, patients may rapidly develop severe CS requiring MCS.[14,15]

A cardiotoxic effect has been observed for a wide range of medications; however, anthracyclines (doxorubicin, daunorubicin), which are widely used in oncology, are among the leading contributors to tCM. Anthracyclines are used specifically as a treatment for breast cancer, acute lymphocytic leukemia and Kaposi sarcoma, all of which often require multiple high-dose chemotherapy cycles.[16] Anthracycline-related toxicity is dose-dependent and is based on oxidative stress through an excessive generation of reactive oxygen species and mitochondrial alteration, which primarily affect bone marrow and cardiomyocytes.[16] Surprisingly, in the setting of chemotherapy-induced tCM, no significant difference to dCM is observed despite cancer-related morbidity and mortality. Fornaro et al. confirmed that patients with anthracycline-induced cardiomyopathy treated with optimized heart failure therapy demonstrate a comparable survival as dCM patients at 5 (86% and 88%, respectively) and 10 years (61% and 75%, respectively).[16] However, patients with toxin-induced cardiomyopathy who develop CS demonstrate inferior survival.[17]

Acute or chronic myocarditis is a relatively rare complication of infections or severe inflammatory reactions, with a prevalence of 22 cases per 100,000 persons.[12] Nevertheless, myocarditis demonstrates variable clinical manifestations, ranging from mild symptoms of dyspnea to severe CS, and is responsible for up to 12% of sudden cardiac deaths.[7] Although myocarditis can be caused by various bacterial pathogens, parasites, autoimmune reactions and even fungus, currently common viral infections such as parvovirus B19, Coxsackievirus, influenza A, cytomegalovirus, Epstein-Barr virus, and SARS-CoV-2 represent the most common key causes of cardiac inflammation.[11] The standard therapy of myocarditis is complex and usually includes a combination of antiviral and immunosuppressant drugs. In recent years, temporary MCS has frequently been used to treat severe myocarditis. The study of Tschöpe et al. demonstrated a positive effect of LV unloading with temporary MCS in patients with fulminant myocarditis. Temporary MCS with Impella devices not only stabilizes patients' hemodynamics, but also reduces the extent of myocardial inflammation and consequently helps to preserve the

ventricular function. However, patients with persistent inflammation frequently develop myocardial fibrosis and non-ischemic dCM requiring durable MCS or HTx.[18]
Restricted (rCM) and hypertrophic cardiomyopathies (hCM) represent a very rare cause of heart failure and can be characterized by severely increased myocardial stiffness leading to impaired ventricular filling and diastolic dysfunction.[19] The effect of medical therapy in this setting is inferior due to the complex pathogenesis including genetic factors.[9] Both rCM and hCM are diagnosed in 3% of patients undergoing heart transplantation and in 1 % of patients on durable LVAD.[9,20] An analysis of the INTERMACS register demonstrated similar outcomes in rCM and hCM patients undergoing durable LVAD implantation compared to dCM with a 1-year survival of 74%, 80% and 81%, respectively.[21]
Compared to other forms of HF, the recovery potential in rCM and hCM patients is reduced; therefore, the feasibility of long-term solutions such as durable LVAD or HTx should already be evaluated in early stages of the disease.[19]

Postcardiotomy CS is a fatal complication of cardiac surgery, affecting 0.5-6% of patients. The risk for postcardiotomy CS is difficult to predict preoperatively and is extremely hard to treat, which results in poor outcomes.[22] A systematic review by Khorsandi et al. demonstrated a pooled survival to hospital discharge of 30.8 %.[23] Several pre- and intraoperative factors such as patients' comorbidities, the severity of myocardial dysfunction, active bleeding, and the success of the surgery are strongly related to the outcome.[24] And last but not least, the time between the onset of severe end-organ hypoperfusion and establishment of effective circulatory support represents the strongest mortality predictor for postcardiotomy CS; therefore, rapid establishment of circulatory support is crucial.[24]
Despite the fact that mortality among postcardiotomy patients remains high, ranging from 43% to 85%, without MCS the chances of survival would tend towards zero.[25]

1.5 Current guidelines on CS treatment

CS therapy represents a clinical challenge in each individual case and is often based on the experience of the attending physician. Currently the guidelines of the European Society of Cardiology (ESC) systemize and summarize the standard of care in CS patients.
Previous ESC guidelines suggested the use of intravenous inotropes and vasopressors, such as adrenaline, noradrenaline, dopamine, and vasopressin as first-line therapy in CS

patients. These substances help maintain organ perfusion when the systolic blood pressure drops significantly. However, at the same time vasoactive inotropic support (VIS) increases myocardial oxygen consumption and shows pro-arrhythmogenic effects. These side effects increase vascular resistance and impair coronary perfusion of the already damaged myocardium, leading to further ischemia and inflammation.[12] Therefore, it is recommended to administer VIS at the lowest dose and for the shortest time required. VIS can be administered indiscriminately only if low blood pressure is considered a reversible condition or if the patient is being bridged to MCS or HTx.[26]

Temporary MCS devices can be implanted in an uncomplicated manner and provide hemodynamic support for up to several weeks. Nevertheless, managing patients on circulatory support remains challenging especially in the setting of therapy determination and potential recovery progress. Despite the vast experience that has been made in this field to date, MCS support remains a prerogative of major cardiological or cardiac surgery departments.

In recent years the strategy of MCS use in CS patients has been transformed from a bail-out option to standard of care. According to the latest version of the ESC guidelines, temporary MCS implantation should be considered simultaneously with VIS administration, and it is given a higher class of recommendation than conventional inotropes and vasopressors (Figure 3). Additionally, for the first time MCS was recommended for refractory pulmonary congestion with a class IIa level of recommendation.[8]

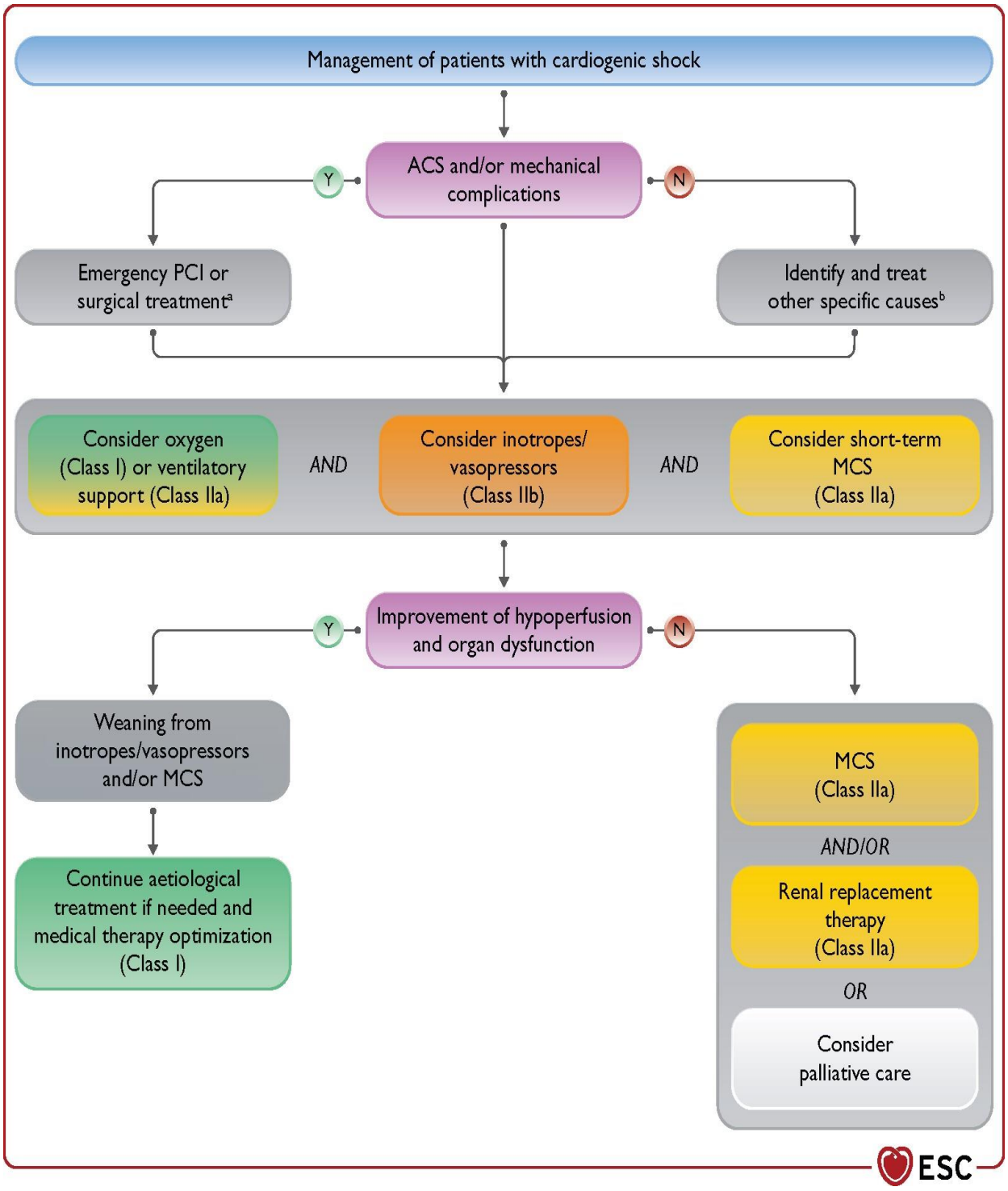

Figure 3. 2021 ESC guideline on treatment of cardiogenic shock.
From “2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure”, by McDonagh TA et al., Eur Heart J., 42(36):35-99.

1.6 Mechanical circulatory support classification

Modern MCS provides a wide range of interventional tools: from mechanical chest compression for patients undergoing cardiopulmonary resuscitation to durable ventricular assist devices (VAD) for bridging to heart transplantation.

Modern MCS devices can be classified according to four major criteria to describe their mechanism of action (Figure 4):

I. Support duration
II. Support configuration
III. Blood flow profile
IV. Placement

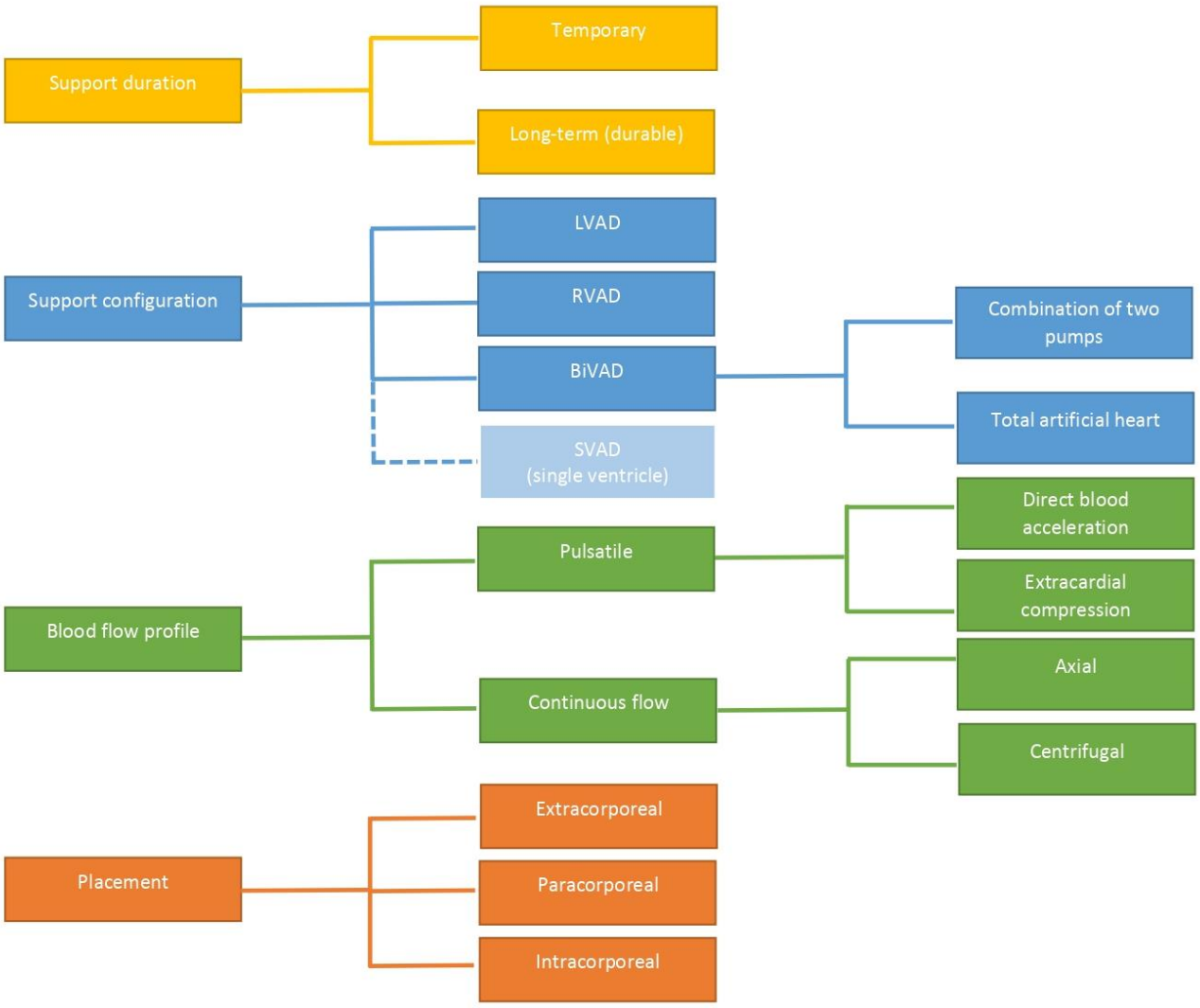

Figure 4. Mechanical circulatory support classification.
Created by G. Nersesian.

In the setting of acute cardiogenic shock, temporary MCS devices are used to stabilize patients' hemodynamics before bridging them to recovery or to a durable VAD. Optional bridging to transplant from temporary MCS is possible; however, in Germany it is exceedingly rare due to the shortage of donor organs and the resulting potentially long wait.

CS shock can be the result of isolated right, left or combined biventricular heart dysfunction; however, the vast majority of patients predominantly presents with left heart failure. Therefore, most of the modern MCS devices were primarily designed for providing left heart support. The characteristics of the most common temporary MCS devices are presented in Table 2.

	IABP	Impella 2.5/ CP®	Impella 5.0/ 5.5®	v-a ECLS	CentriMag® (Levitronix)	Tandem Heart®
Insertion	Percutaneous	Percutaneous	Surgical vessel access	Percutaneous/ sternotomy	Percutaneous/ sternotomy	Percutaneous/ septal puncture
Placement	Intracorporeal	Intracorporeal	Intracorporeal	Extracorporeal	Extracorporeal	Extracorporeal
Cannulation	Peripheral	Peripheral	Peripheral	Peripheral/ central	Peripheral/ central	Peripheral
Max. flow (L/min)	No	3.5	5–5.5	7	9.9	4.5–5
Circulatory support (%)	15	70	30–100	75–100	75–100	30–60
Anticoagulation (ACT) sec.	120-140*	160-180	160-180	180-200	160-180	>200
Pump mechanism	Pulsatile **	Axial	Axial	Centrifugal	Centrifugal	Centrifugal
Recommended maximum duration of use	14 days	10 days	10 days	7 days	30 days	14 days
RVAD/BiVAD option	No	No	No	Yes	Yes	Yes
Oxygenation	No	No	No	Yes	Yes	Yes
LV unloading	No	Yes	Yes	No	No	Yes

*usage without anticoagulation is possible; **direct blood acceleration; IABP – intra-aortic balloon counterpulsation; vaECLS – veno-arterial extracorporeal life support; R/BiVAD – right/ biventricular assist device; LV – left ventricular

Table 2. Modern temporary mechanical circulatory support devices.
Created by G. Nersesian.

1.7 Temporary MCS: State of the art

Despite the increasing role of temporary MCS in the treatment of CS patients, none of the modern devices are considered a gold standard. According to the current ESC statement on CS therapy management, class IIa with a level C recommendation has been proposed for temporary MCS.[26]

1.7.1 Intra-aortic balloon pump (IABP)

IABP is a catheter-based MCS device that is placed percutaneously into the descending aorta via the femoral or the axillary artery.[27] Electrocardiographically-triggered balloon inflation during diastole and deflation during systole increases coronary perfusion and indirectly increases cardiac output by reducing the afterload. IABP used to be the most common temporary MCS device; however, it failed to provide a significant survival benefit in patients with post-AMI CS compared with the standard medical treatment.[4] Despite the limited scientific evidence, IABP is still being used in patients with ischemic heart disease or during high-risk coronary interventions.[27]

1.7.2 Impella®

Impella is a family of microaxial catheter-based LVADs that are placed directly into the left ventricle and can provide partial (Impella 2.5/CP®) or full (Impella 5.0/5.5®) hemodynamic support. The success of Impella 2.5® and CP® devices during high-risk percutaneous coronary interventions (PCI; Protected PCI concept) and the low mortality rates in this setting have made it an attractive therapy strategy in interventional cardiology.[28] However, percutaneous Impella devices did not achieve the desired outcomes in CS patients and were associated with a higher complication rate compared with IABP.[29,30]
Larger devices such as the Impella 5.0/5.5® generate a flow of up to 5.5 L/min and are widely used for treating refractory CS.[31,32] Impella 5.0/5.5® implantation requires a vascular cut-down, which is why these devices are used predominantly in cardiothoracic surgery departments.[33]

The versatility of the Impella device family enabled the development of several therapy concepts. The combination of v-a ECLS and Impella (ECMELLA approach) achieves biventricular unloading and decreases cardiac oxygen consumption by reducing myocardial wall tension. LV unloading prevents pulmonary venous congestion and lung edema.[34,35] Impella 5.0/5.5® implantation in patients with fulminant myocarditis prevents myocardial remodeling by reducing cardiac inflammation, thereby allowing the ejection fraction to regenerate.[18]

An important advantage of surgically implanted Impella LVADs is that it potentially provides for mobilizing the patients on support if the axillary artery is used. This feature is especially beneficial in patients requiring prolonged circulatory support (PROPELLA concept) and those with complications on v-a ECLS.[18,36]

The Impella RP is a catheter pump specially designed for isolated right heart support; it provides up to 4.2 L/min of circulatory support. The BiPELLA concept describes the combination of Impella RP and Impella LVAD (2.5®; CP®; 5.0®; 5.5®), allowing fully percutaneous biventricular MCS.[18]

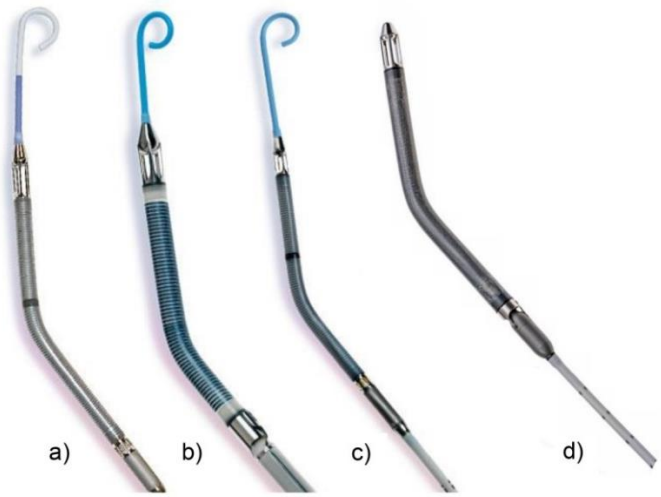

Figure 5. Impella left ventricular support devices.
Adapted from www.abiomed.de.

a) Impella CP®
b) Impella 5.0®
c) Impella 2.5®
d) Impella 5.5®

1.7.3 Extracorporeal life support

ECLS is one of the most commonly used temporary MCS devices worldwide. Due to its reasonable cost and diverse support features, it is used on a regular basis in cardiac surgery, but also in thoracic and in pediatric surgery.[24] Veno-venous cannulation is used only in cases of respiratory failure, while veno-arterial ECLS provides both blood oxygenation and circulatory support. Uncomplicated installation makes v-a ECLS suitable for use during cardiopulmonary resuscitation (eCPR concept).[17,37]
V-a ECLS is also the therapy of choice for postcardiotomy CS, when the patient cannot be weaned from cardiopulmonary bypass (CPB).[24] In this constellation, v-a ECLS implantation with cannulation of the aorta and the right atrium can be employed.[23] However, peripheral implantation is associated with better survival and lower complication rates compared with central vessel cannulation.[25]

Nevertheless, ECLS therapy is an invasive approach, and is associated with a high incidence of complications (Figure 6). The increased afterload on v-a ECLS presents a potential risk for LV ballooning and pulmonary venous congestion, especially if the myocardial contractility is severely restricted.[34,35] In order to prevent pulmonary edema on v-a ECLS therapy, left ventricular unloading should be achieved. This can be done with an IABP, a surgical vent, or with impeller pump implantation.[38]
A high risk of bleeding, vascular complications and limb ischemia present further limitations of v-a ECLS therapy and increase with support duration.[39] The timing of temporary MCS remains a topic of intense debate within the cardiothoracic community. Currently no limits for a maximum support time on v-a ECLS exist, so the support duration depends on patients' recovery potential and clinical scenario. Several scoring tools have been proposed for an outcome assessment on v-a ECLS: The SAVE (Survival After Veno-arterial ECMO) score uses physiological and laboratory parameters prior to ECLS implantation, so it can be used for preoperative risk evaluations.[24] Tsyganenko et al. designed a mortality assessment score for patients already on support; therefore, it is used for survival evaluations in patients undergoing durable LVAD implantation. In this score a v-a ECLS duration over 7 days was associated with poor outcomes, so the patients should be promptly evaluated for weaning, long-term support, or palliative care.[40]

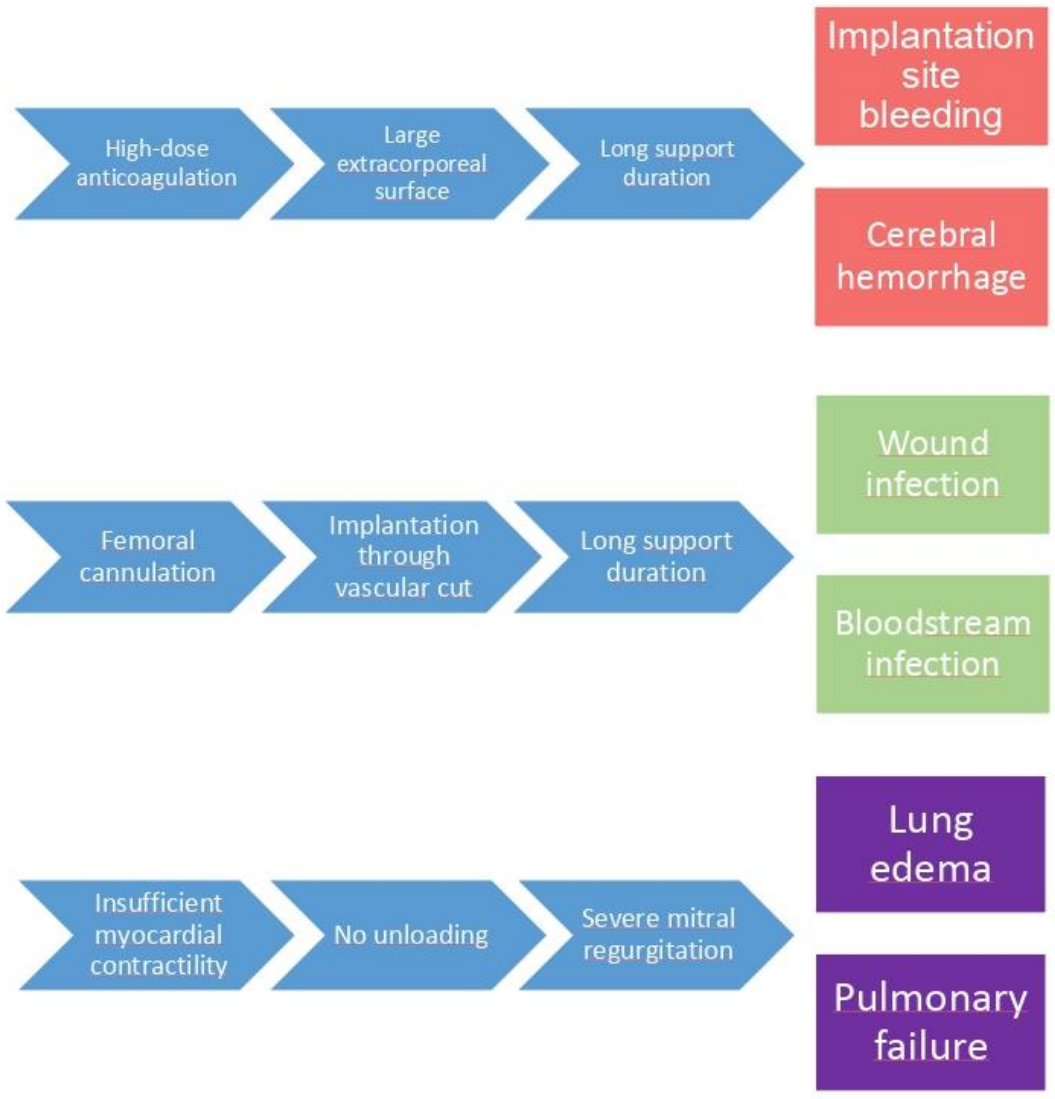

Figure 6. Sequel of complications on v-a ECLS support.
Created by G. Nersesian.

1.7.3.1 CentriMag® (Levitronix®)

The CentriMag® system is a modification of ECLS with the same work principle and configuration but with improved hemocompatibility. CentriMag® has a magnetically levitating impeller and bearingless design, allowing a longer support duration with a lower rate of hemolysis and thrombus formation compared with conventional ECLS.[2] The main limitation of CentriMag® is the need for central cannulation and sternotomy in the LVAD setting. As a result, CentriMag® is today mainly indicated for temporary right ventricular support in patients with post-LVAD right heart failure (RHF).[41]

1.7.3.2 TandemHeart®

TandemHeart® is a centrifugal continuous-flow temporary MCS device that has many similarities to v-a ECLS and CentriMag®; however, unlike them, TandemHeart® achieves direct LV unloading through a specially designed venous cannula that is placed directly into the left atrium through a septal puncture.[3] If right heart support is needed, a TandemHeart® kit includes a dual-lumen cannula, which allows single-access percutaneous cannulation via the jugular vein and patients' mobilization. It must be noted that this cannula can be also used on CentriMag®. Nevertheless, the high costs of TandemHeart® support in combination with relatively low blood flow generation and complicated implantation have precluded a widespread distribution of this device.

1.8 Durable circulatory support

1.8.1 Long-term left ventricular support

Although temporary MCS has been used successfully for severe CS therapy, a large proportion of patients cannot be weaned and require long-term circulatory support.[17] In such cases, durable LVAD implantation is usually performed. Within the scope of a bridge-to-assist concept, the decision whether to perform primary durable LVAD implantation or a two-stage approach is disputed. However, an analysis of international MCS datasets revealed significantly worse outcomes in patients with severe CS (INTERMACS profile 1 and 2) who underwent intracardiac assist device implantation.[42] INTERMACS profile 1 patients exhibit a one-year survival of 73.3%, compared to 81.7% and 84.5% in patients in INTERMACS profile 2 and 3, respectively.[6] Durable LVAD implantation in CS patients is associated with major surgical trauma, a high risk of complications, and is time-consuming. Therefore, preoperative conditioning of CS patients with temporary MCS is recommended.[42,43]

Durable LVAD therapy significantly improves the morbidity and mortality in patients with end-stage heart failure. Originally designed for bridging patients on the transplant waiting list, the indications for durable LVAD therapy have been expanded to include life-long support for patients ineligible for heart transplantation.[44]

Weaning from durable LVAD is also possible; however, is extremely rare and is feasible in only 1-2% of patients.[45] In these cases, multi-stage diagnostic procedures including right heart catheterization, interventional balloon occlusion of the outflow graft, and pump stop are usually performed for a rigid evaluation of myocardial functionality.[46] Weaning from durable LVAD includes surgical shortening and tunneling of the driveline. The device itself can be stopped and left in situ or surgically removed with concomitant left ventricular reconstruction or insertion of a titanium plug as described by Potapov et al.[47]

In the past, the vast majority of durable LVAD implantations worldwide were performed with third-generation continuous-flow centrifugal pumps: the HeartWare HVAD® (HW; Medtronic, Minneapolis, MN, USA) and the HeartMate 3® (HM3; Abbott, Chicago, IL, USA).[6,13] The advantages and disadvantages of one device over the other have been the subject of many debates. Several studies that compared the outcomes on HW and HM3 support suggested similar survival rates but a lower rate of hemocompatibility-related complications for HM3.[48] In the spring of 2021 a series of technical issues prompted the removal of the HW device from the market, so that the HW3 device currently remains the only commercially available centrifugal durable VAD.

1.8.2 Right ventricular and biventricular support

Five to ten percent of patients undergoing LVAD implantation develop acute right heart failure (RHF) requiring mechanical circulatory support. Temporary MCS with CentriMag® represents a common procedure in this constellation. If right ventricular functionality cannot be restored on temporary MCS, long-term support has to be established.[49] Modern durable continuous-flow ventricular assist devices such as HW and HM3 were originally designed for left ventricular support; however, with some modifications they can be adjusted for the right heart.[44] Primary biventricular support with two continuous-flow devices can be performed; however, a two-stage approach with a switch from temporary to durable RVAD is more common.[44] The right ventricle has a higher recovery potential compared with the left heart, but requires prolonged circulatory support.[17] The study by Eulert-Grehn et al. demonstrated that patients with post-LVAD RHF exhibit a similar survival irrespective of whether they receive a durable RVAD right away or undergo a two-stage implantation procedure after temporary support on a CentriMag® device.[49] Thus, in patients with post-LVAD RHF the right ventricular function has the chance to regenerate on

temporary RVAD support by avoiding intracardiac BiVAD implantation without adverse effects on survival.[17]

As an alternative to durable BiVAD, a total artificial heart (TAH) can be implanted. Today, the SynCardia 50cc® TAH (SynCardia Systems, Tucson, AZ, USA) is the only FDA-approved device in its class. The pneumatically driven pulsatile pump replaces the right and the left ventricle, which have to be surgically excised for implantation. The current indications for TAH therapy remain limited and include salvage therapy for patients with biventricular heart failure who are not eligible for an assist device implantation and patients with severe biventricular thrombosis or cardiac tumors.[50]

The Berlin Heart Excor® (Berlin Heart GmbH, Berlin, Germany) is a paracorporeal pulsatile pump that can be configured for an isolated left or right heart or for biventricular support. Additional versatility is achieved through the use of different artificial ventricle volumes, allowing individually adjusted support based on the patient's weight. Currently the Berlin Heart Excor® is predominantly used in pediatric patients as bridge-to-transplant therapy. Excor® implantation in adult patients is extremely rare and is usually performed in patients in whom assist therapy is contraindicated, e.g. those with restrictive cardiomyopathy with a severely reduced ventricular volume.[51]

Biventricular failure is an advanced stage of heart failure and is associated with inferior outcomes. The data from the EUROMACS register demonstrated a one-year survival of 55% for patients with a continuous-flow BiVAD, 52% for LVAD plus temporary RVAD, 37% for pulsatile BiVADs (e.g. Berlin Heart Excor), and 36% for patients with a TAH.[52]

1.9 Heart transplantation

The indications for durable MCS and heart transplantation (HTx) generally overlap. However, HTx remains the therapy of choice due to the mortality-determining complications on durable VAD support, such as driveline infections, bleeding, and thromboembolic events.[42,53,54] The current donor organ shortage in Europe calls for a strict selection system for advanced heart failure patients. According to the French Biomedicine Agency the median 1-year waiting list mortality is estimated as 11 %, with at least two listed candidates per available donor organ, while the median post-transplant survival does not exceed 12 years. Active cancer, advanced kidney disease, or pulmonary hypertension are contraindications for HTx. Patients with alcohol or drug abuse are required to demonstrate

at least a 6-month abstinence period in combination with psychological counseling in order to be listed for a donor organ. In these cases, durable MCS implantation can bridge patients to potential HTx or can be performed as a destination therapy. The age limit represents an additional restriction for HTx listing, excluding a large proportion of advanced heart failure patients. Long-term LVAD significantly reduces the mortality on the transplant waiting list and achieves a 1-year survival of >80%.[21]

Primary heart transplantation (HTx) after temporary MCS is also possible but is rarely performed in Europe and strongly depends on donor organ availability. Cheng et al. reported about 21 highly selected patients who were bridged to HTx directly from Impella® support; all patients were alive at the 30-day and 60-day follow-up.[55] It must be noted that this study was conducted in the USA, where the donor allocation system and the amount of donor organs allow patients to be directly bridged to HTx from temporary MCS.[55]

2 Methods

2.1 Research summary

Patients in CS require rapid and advanced treatment for hemodynamic stabilization. Modern temporary MCS devices provide versatile support concepts and can be individually adjusted depending on patients' needs. Nevertheless, currently no guidelines on the specific use of MCS systems exist. Therefore, in our research we evaluated different temporary MCS devices, aiming to improve and standardize the treatment of CS patients.
In the first study we evaluated the DHZB's experience with three different temporary MCS systems and combinations thereof for left or right ventricular support. Outcomes and complication profiles for the various devices were analyzed.
In the following step, we shifted our focus to surgically implanted impeller pumps as an effective and uncomplicated approach for left heart support. Based on the results of the second study we identified preoperative mortality predictors and used them to develop a selection protocol for optimal temporary MCS for CS patients.
Our research trilogy was completed with a propensity score-based comparison of percutaneous and surgically implanted impeller pumps, which confirmed the findings of the second study, following which the selection protocol was modified.

2.2 Statistical analysis

The data collected for the analysis included patients' demographics, relevant co-morbidities as well as last available hemodynamic and laboratory values prior to
Impella® implantation. The patients' follow-up data from at least 30 postoperative days were collected.[56]
Continuous variables were tested for a normal distribution using the Kolmogorov-Smirnov test and were presented as median (interquartile range) or mean (± standard deviation), respectively. Categorical variables were presented as n (%). Categorical variables were compared using the Chi-squared test, the t-test for independent samples, and the Mann–Whitney U test to compare continuous variables.
Univariable logistic regression analysis was performed to predict risk factors for 30-day mortality. For this analysis, several parameters were logarithmically transformed (natural

logarithm). The odds ratios (OR) with their 95% confidence intervals (CI) were calculated for relevant risk factors. Parameters with two-sided p-values <0.05 in the univariable logistic regression were included in the multivariable logistic regression analysis.[56]
A receiver operating characteristic (ROC) curve was plotted for preoperative lactate. The area under the ROC curve was calculated as a measure for discrimination ability. The Youden index (sensitivity + specificity -1) was used to define the cut-off for preoperative lactate. Overall survival and survival in different patient groups was analyzed using Kaplan-Meier estimates with 95% confidence intervals (CIs). Log-rank testing was used to compare patient groups.[56]
All tests were performed using IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY: IBM Corp.[56]

2.3 Impella 5.0/5.5® implantation technique

Impella 5.0/5.5® implantations are performed in the catheter lab or hybrid operating room under fluoroscopic and echocardiographic guidance. The surgery is regularly performed on intubated patients under general anesthesia. While implantation in an awake patient is possible under local anesthesia, it might be challenging for hemodynamics management and traumatizing for the patient.[56]
The device size precludes transcutaneous placement, therefore surgical access via an axillary artery is considered optimal for Impella 5.0/5.5® implantation.[44] The incision is usually performed in the infraclavicular fossa, after which the axillary artery is surgically exposed; in this regard, great care has to be taken not to damage the branches of the brachial plexus. The artery is partially clamped and a 10-mm Hemashield® graft (MAQUET Ltd., Rastatt, Germany) is anastomosed end-to-side and tunneled under the skin to allow primary wound closure. After that, the pump is inserted through the graft using the introducer and guidewires from the implantation kit. Optimal imaging for the pump insertion and positioning requires a combination of fluoroscopic and echocardiographic guidance.[56] The device is advanced through the aortic valve and the device inlet is positioned 5 cm below the level of the valve annulus. At this point the device has to be activated and set to support level P2 (17,000 revolutions/min [rpm]) in order to prevent retrograde blood flow into the left ventricle. The tip of the pump should be positioned at a safe

distance from the chordae of the mitral valve in order to prevent iatrogenic mitral regurgitation. After optimal positioning, the pump speed can be increased up to level P9 (34,000 rpm) with a stepwise reduction of inotropic support. A target mean arterial pressure (MAP) of at least 60 mmHg should be maintained.[56]

Small or calcified axillary arteries can represent a challenge during Impella 5.0/5.5® implantation. If the device size does not fit, an alternative access site or Impella CP® or 2.5® implantation should be considered. Extensive mechanical pressure during the pump insertion should be avoided in order to prevent vessel rupture or dissection. In young patients without calcifications, small axillary arteries can be dilated with a flexible mandrel from a 21-23 Fr venous cannula; however, extreme care should be taken.[56]

Arteria lusoria is an uncommon anatomical feature of the right subclavian artery and precludes implantation through this vessel. In this case, a contralateral access should be performed instead.[56]

2.4 Temporary mechanical circulatory support for refractory heart failure

Thirty-seven patients, who underwent Impella 2.5/CP/5.0® implantation for left ventricular support (01/2016 to 07/2018) and 69 patients who received a CentriMag® for short-term right ventricular support (01/2015 to 07/2018) (Figure 7. Flow chart) were included in the study. Different temporary MCS concepts, including a combination of v-a ECLS and Impella® for LV unloading and CentriMag® for patients suffering from acute RHF after durable LVAD implantation were analyzed.

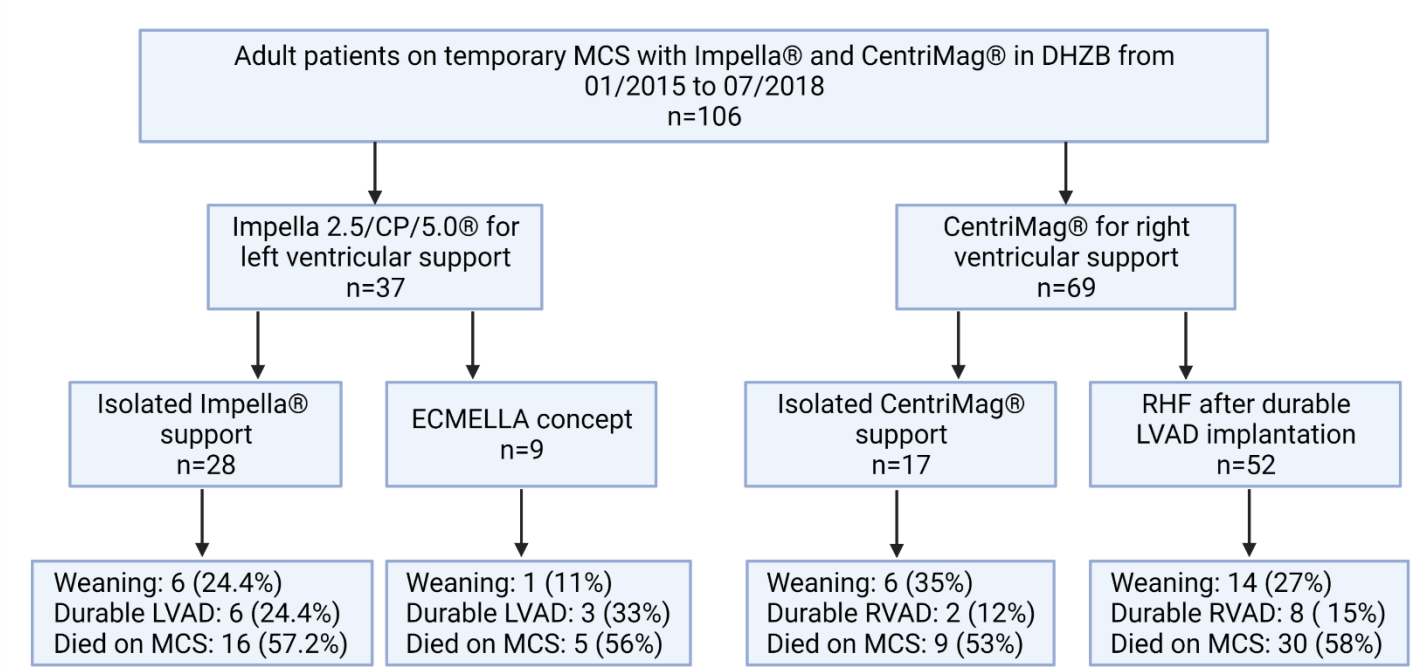

Figure 7. Flow chart, study population of the pilot study.
Adapted from “Temporary mechanical circulatory support for refractory heart failure: the German Heart Center Berlin experience,” by Nersesian G. et al., Ann Cardiothorac Surg., 8(1):76-83.

2.5 Prediction of survival in CS patients treated with Impella 5.0 or 5.5®

Ninety-one adult patients who underwent Impella 5.0/5.5® implantation between 10/2016 and 10/2019 at the DHZB were identified (Figure 8. Flow chart). The indication for Impella implantation was cardiogenic shock (INTERMACS profile 1, 2 or 3). Patients, who were already on v-a ECLS before Impella implantation (n=21), were excluded from the analysis. The remaining patients were retrospectively divided into two groups in regard to 30-day survival.[56]

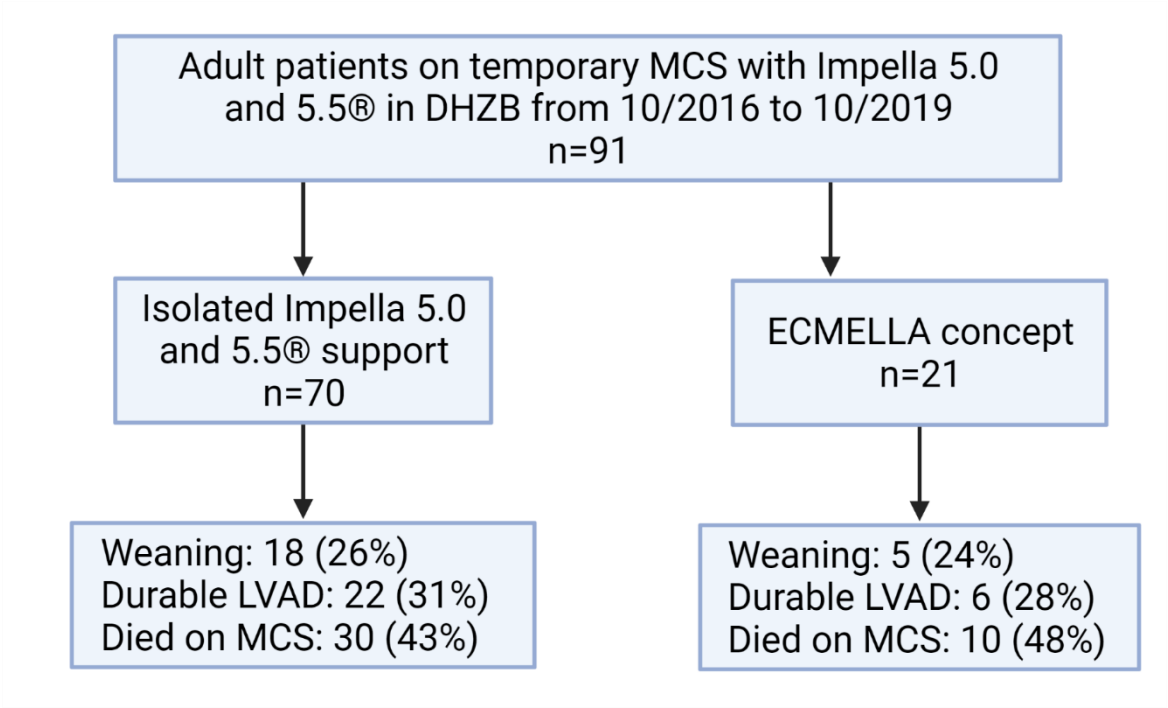

Figure 8. Flow chart, study population of the second study.
Adapted from “Prediction of survival of patients in cardiogenic shock treated by surgically implanted Impella 5+ short-term left ventricular assist device”, by Nersesian G. et al., Interact Cardiovasc Thorac Surg., 31(4):475-482.

2.6 Propensity score-based comparison of Impella CP and Impella 5.0/5.5®

In our third study we retrospectively analyzed 126 consecutive patients supported with the percutaneously implanted Impella CP® or surgical Impella 5.0/5.5® devices at two tertiary care centers between January 2014 and December 2019 (Figure 9). Patients were divided into two study cohorts according to the device type: an Impella CP® group (n=64) and an Impella 5.0/5.5® group (n=62).[33]

To account for imbalances in preoperative data in the Impella CP® and 5.0/5.5® groups, a propensity score was calculated with sex, age, etiology of cardiogenic shock, INTER-MACS profile, CPR, coronary artery disease, IABP, arterial hypertension, diabetes mellitus, renal insufficiency, COPD (chronic obstructive pulmonary disease), liver insufficiency, lactate, WBC (white blood cells), creatinine and INR (international normalized ratio). The influence of a specific Impella pump model on 30-day survival was calculated using logistic regression adjusting for the propensity score. Due to the small patient number no propensity score matching was performed.

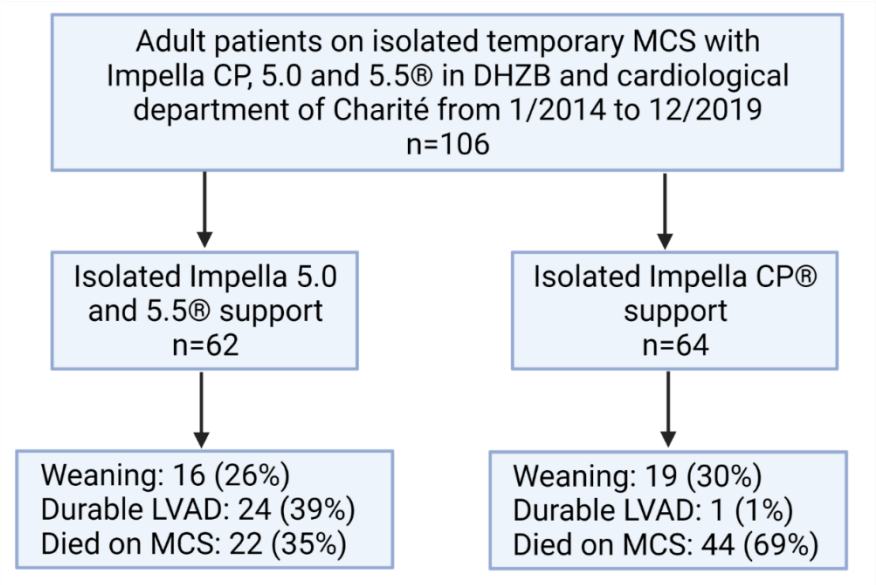

Figure 9. Flow chart, patient population of the third study.
Adapted from “Propensity score-based analysis of 30-day survival in cardiogenic shock patients supported with different microaxial left ventricular assist devices,” by Nersesian G and Potapov EV et al., J Card Surg., 36(11): 4141-4152.

3 Results

3.1 Temporary mechanical circulatory support for refractory heart failure

A 43% survival in 28 patients on isolated Impella support, as well as 44% in 9 patients on combination of Impella and v-a ECLS was demonstrated. Preoperative cardiopulmonary resuscitation (CPR) and an arterial pH <7.2 or >7.45 were associated with poor outcomes in patients on impeller pump therapy. Patients on CentriMag® demonstrated a 46% survival on support.[17]

Among Impella® patients, severe bleeding and infections occurred in 4 cases (11%), while hemolysis/pump thrombosis was observed in 8 cases (22%). The CentriMag® patient cohort was more likely to suffer from bleeding and infections (24 [35%] and 28 patients [41%], respectively), but less hemolysis/pump thrombosis (8 patients [12%]) was present.

3.2 Prediction of survival in CS patients treated with Impella 5.0 or 5.5®

The survival rate at 30 days was 51%; survival on device was 57%. A 6-month and 1-year survival rates of 43% and 39% were achieved, respectively.[56]

The odds ratio (OR) calculations for preoperative 30-day mortality risk factors after Impella implantation identified eight predictors:

- Bilirubin (OR 1.372; 95% CI: 1.025-1.836; p=0.033), GOT (OR 1.377; 95% CI: 1.043-1.818; p=0.024), and LDH (OR 1.649, 95% CI: 1.016-2.678; p=0.043)
- CK (OR 1.445; 95% CI: 1.05-1.99; p=0.024) and CK-MB (OR 1.806; 95% CI: 1.152-2.832; p=0.010)
- Lactate (OR 1.217; 95% CI: 1.039-1.426; p=0.015). The ROC curve and Youden index calculations revealed a cut-off value for lactate of 8 mmol/L (72 mg/dL), a specificity of 0.944, and a sensitivity of 0.294. No patient with lactate above 11 mmol/L survived the 30-day benchmark.[56]
- Patients who underwent preoperative cardiopulmonary resuscitation (OR 16.74; 95% CI: 2.022-138.57; p=0.009) demonstrated especially poor results: the 30-day mortality with and without CPR was 92% and 41%, respectively (p=0.001).[56]

Based on our data and existing guidelines we adopted our institutional algorithm for optimal short-term MCS selection for patients in severe cardiogenic shock (Figure 10). We

propose that patients with lactate ≥8 mmol/L and/or a status post CPR should be primarily supported with v-a ECLS and undergo Impella LVAD implantation if LV unloading is suboptimal.[56]

Complications on support included major access site bleeding in ten (14%) patients, and one (1.5%) case of reversible brachial plexus injury. In eight cases of pump thrombosis and three cases of severe hemolysis, device exchange or explantation was necessary. Pump dislodgement called for repositioning in ten cases; in two patients (Impella 5.5®) a new pump had to be implanted after unsuccessful repositioning attempts.[56]

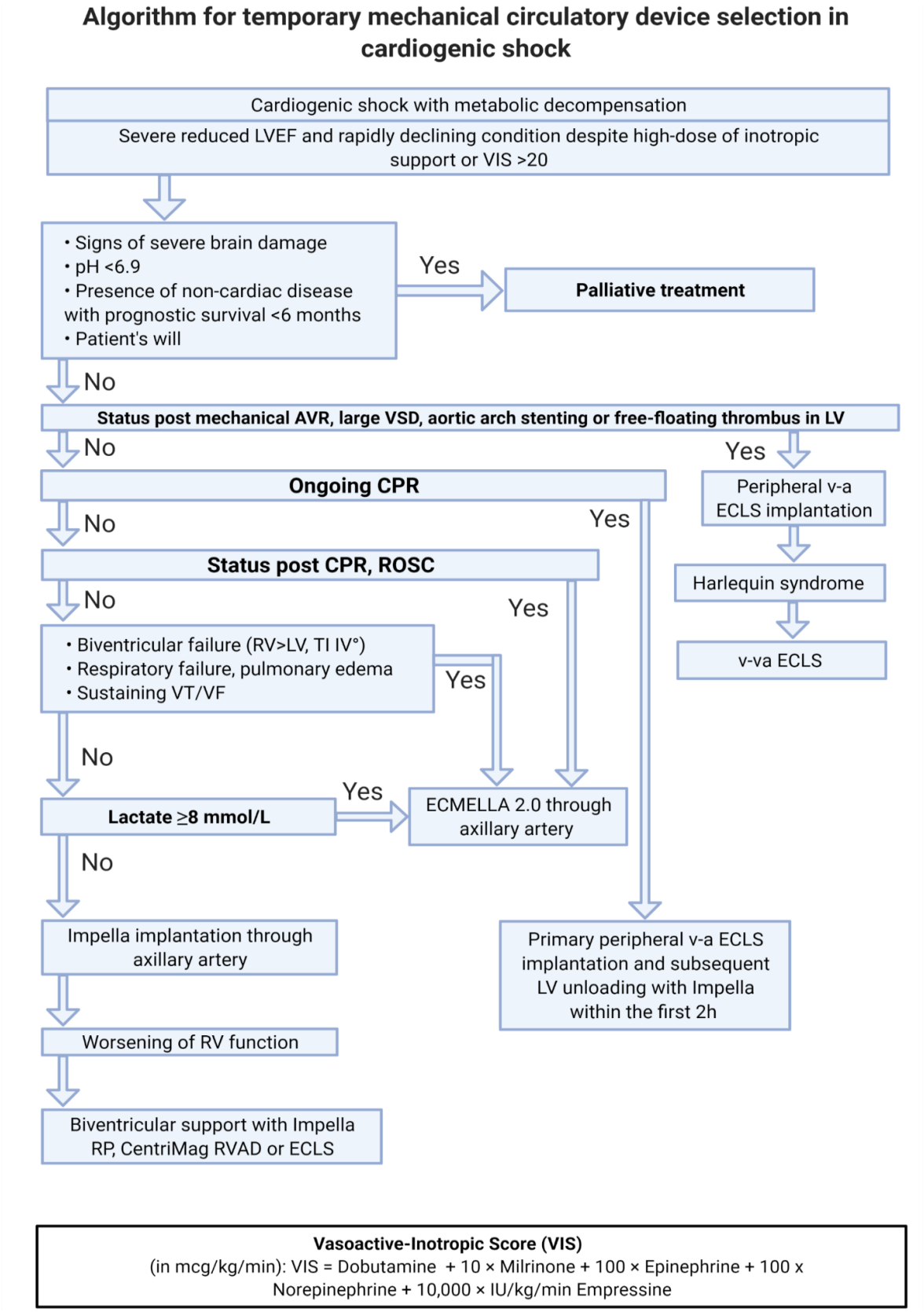

Figure 10. Current version of the temporary MCS selection algorithm used at the DHZB. Adapted from “Propensity score-based analysis of 30-day survival in cardiogenic shock patients supported with different microaxial left ventricular assist devices,” by Nersesian G and Potapov EV et al., J Card Surg, 36(11): 4141-4152.

3.3 Propensity score-based comparison of Impella CP and Impella 5.0/5.5®

Descriptive statistics revealed significant differences between the study groups:
Impella CP® patients were older (69.6±10.7 vs. 58.7±11.9 years; p=0.001), were more frequently in INTERMACS profile 1 (76.6% vs. 50%, p=0.003), and had previously undergone resuscitation (36% vs 13 %, p=0.006).[33]

The comparison of Impella CP® and 5.0/5.5® patients in statistically adjusted cohorts revealed no difference in 30-day survival (OR=1.23, 95% CI [0.34-4.18], p=0.74). The median lactate level in patients surviving 24 h after implantation was similar between the groups: 1.67 mmol/L [1.11, 3.83] for Impella CP® and 1.72 mmol/L [1.16, 3.16] for Impella 5.0/5.5® (adjusted p-value=0.91).[33]

Major bleeding and hematoma occurred in 6 (9%) Impella CP® and in 8 (13%) Impella 5.0/5.5® patients, while hemolysis/pump thrombosis was reported in 4 (6%) and in 7 (11%) patients, respectively. Vascular complications such as limb ischemia, plexus injury, vascular thromboembolism, arteriovenous fistula, and vessel dissection were observed in 7 (11%) Impella CP® patients and in one Impella 5.5® patient. At the same time, 5 (8%) Impella 5.0/5.5® patients developed an access site infection, compared with no cases in the Impella CP® group.[33]

4 Discussion

4.1 Interpretation of the results

The results of our studies demonstrate that CS treatment with Impella 5.0/5.5® LVADs is a feasible concept with acceptable outcomes and low complication rates. Our results are in the line with previous studies investigating Impella support for which a 30-day survival of 45-65% was reported. However, these studies analyzed different Impella devices (Impella 2.5, CP, 5.0/5.5®, and even RP® models) together and the main etiology of CS was predominantly AMI.[30,57-59] In contrast, our study focuses on Impella 5.0/5.5®, both of which achieve full hemodynamic support and are implanted surgically. Furthermore, our study cohort includes mainly patients with acute decompensated chronic HF (59%).[56] Nevertheless, these publications also showed preoperative lactate to be a strong outcome predictor for Impella support. Interestingly, all publications share one striking finding: the mean lactate level inversely correlates with 30-day survival (Table 3). High lactate is indicative of more prolonged and severe cardiogenic shock, so that the association with high mortality is to be expected. The lactate level mirrors the perfusion in the patients' body in real time and exhibits a sharp increase and decrease dynamic, making it a suitable parameter not only for a preoperative assessment, but also for monitoring the circulatory support. The effectiveness of temporary MCS with Impella devices can be evaluated on the basis of the postoperative arterial lactate level as well as the need for inotropes and vasopressors.[31,60]

Study	Number of patients	Devices analyzed	Mean lactate (mmol/L)	30-day survival (%)
Nersesian et al.[32]	70	Impella 5.0/ 5.5®	3.86	51
Guadard et al.[31]	40	Impella 5.0®	3.5	65*
Ouweneel et al.[30]	112	Impella 2.5/CP/5.0®	6.2	44.8
Jensen et al.[57]	79	Impella RP/CP/5.0®	7.6	46
Karatolios et al.[58]	27	Impella 2.5/CP®	4.75	55.5
Schrage et al.[29]	237	Impella 2.5/CP®	4.1	51.5
Mastroianni et al.[60]	14	Impella 5.0®	4.7	64.3

*28-day survival is presented; **AMI patients only

Table 3. Impeller pump study comparison.
Created by G. Nersesian.

Our study allowed us to set clear limitations for Impella 5.0/5.5® support: namely CPR during the index event and preoperative blood lactate level above 8 mmol/L (72 mg/dL) and to develop a selection algorithm for temporary MCS (Figure 9). This algorithm has been used consistently at the DHZB since 11/2019. After one year the 30-day survival of the historical cohort (10/2016-10/2019, n=74 patients) was compared to 65 isolated Impella 5.0/5.5® implantations performed between 11/2019 and 10/2020. An 18% increase in 30-day survival was achieved (53 % vs. 71%, p=0.037), (Figure 11).

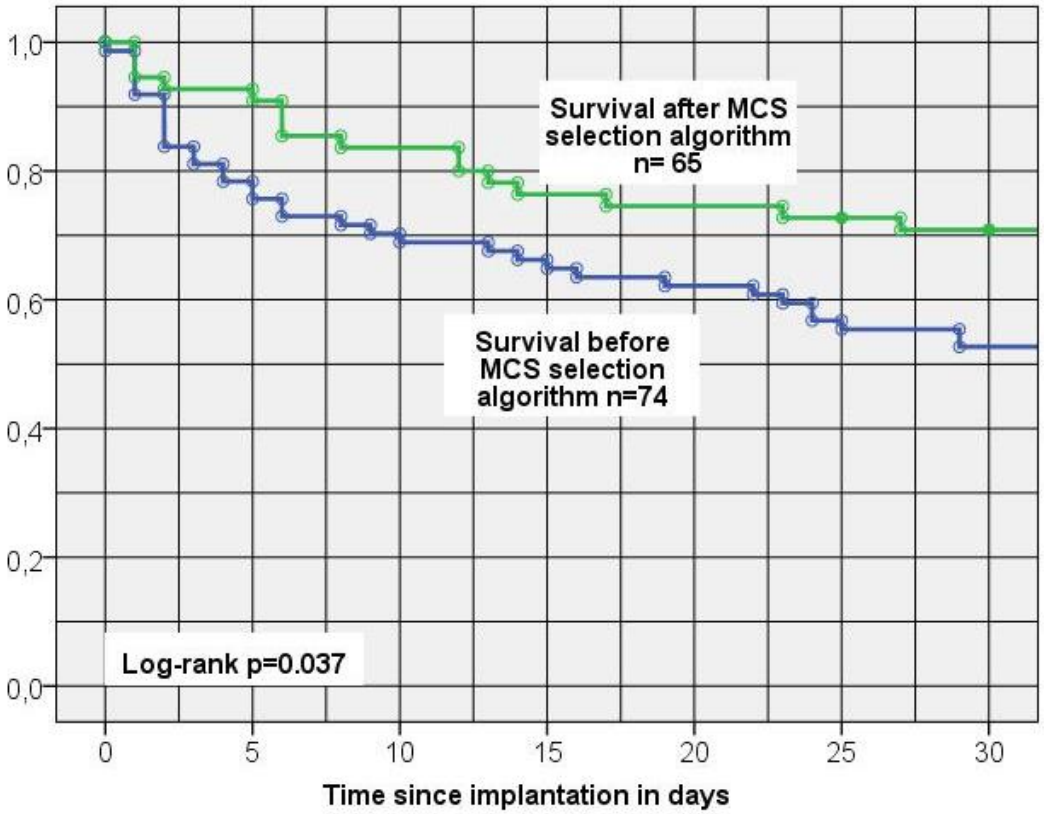

Figure 11. 30-day survival in isolated Impella 5.0/5.5® patients before and after MCS device selection algorithm implementation in DHZB
Created by G. Nersesian.

However, it is important to underline that this survival benefit was achieved by excluding extremely sick patients from isolated Impella 5.0/5.5® support. In our opinion, severe cases of CS call for more advanced support.

V-a ECLS achieves a higher flow compared to Impella and is equipped with an oxygenator; therefore, in theory, it should be more beneficial in patients with severe CS. However, in their recent study comparing CS patients supported with Impella CP® or 5.0® with those on v-a ECLS, Karami et al. were unable to substantiate this thesis. Propensity score-adjusted results demonstrated no significant difference between the investigated cohorts; a 30-day survival of 47% vs. 51% (p=0.30), and a 1-year survival of 32% vs. 31.5% (p=0.62) were reported.[61] At the same time, v-a ECLS support was associated with a significantly higher rate of device-related vascular complications (17% vs. 40%, p<0.01). The need for blood products also differed significantly between the groups: 63% of patients in the Impella group received blood transfusions, compared with 97% of v-a ECLS patients (p<0.01).[61] These findings represent strong arguments against using

v-a ECLS indiscriminately in every CS patient, and call for re-evaluating the current indications. In the case of ongoing CPR or cardiac surgery with failed weaning from CPB, the importance of rapid hemodynamic stabilization provided by v-a ECLS cannot be overstated. Nevertheless, v-a ECLS is an aggressive approach with high complication rates, so that further therapy options have to be taken into consideration in patients on prolonged support.[33]

In this setting the ECMELLA concept represents a feasible alternative to isolated v-a ECLS and Impella support. ECMELLA achieves biventricular unloading with a simultaneous reduction in pre- and afterload, giving the damaged myocardium the opportunity to regain its functionality.[34] Several studies suggested a significant outcome benefit for the ECMELLA approach compared with v-a ECLS alone. Pappalardo et al., for instance, reported a lower in-hospital mortality (47% vs. 80%, $p< 0.001$).[34] The study by Schrage et al. confirmed this statement with a large-scale 1:1 propensity score-matched analysis with 255 patients in each group. The timing of LV support plays a crucial role: if Impella implantation is performed >2h after v-a ECLS, the survival benefit in the ECMELLA cohort disappears.[35] Based on these findings, we improved our institutional operational protocols, following which all patients who undergo v-a ECLS implantation have to be promptly upgraded to ECMELLA.

Patients on ECMELLA support have a higher risk for bleeding complications compared with v-a ECLS alone.[35] The recently developed ECMELLA 2.0 approach provides an elegant solution for advanced CS treatment and may significantly reduce the rate of vascular complications associated with ECMELLA support. The ECMELLA 2.0 technique uses a Y-shaped vascular graft prosthesis anastomosed end-to-side to the axillary artery in order to establish a single arterial access. One distal branch of the prosthesis is used for Impella insertion, while the arterial cannula of the v-a ECLS is inserted through another branch. This technique allows circumventing the typical ECLS complications associated with femoral cannulation: leg ischemia, thrombus formation between arterial and venous cannulas, and a high incidence of groin infections.[39] A completely groin-free approach, enabling patients' mobilization on support, is also possible (Figure 12). With the ECMELLA 2.1 technique the venous cannula is inserted through the jugular vein into the right atrium to drain the blood from the patient.

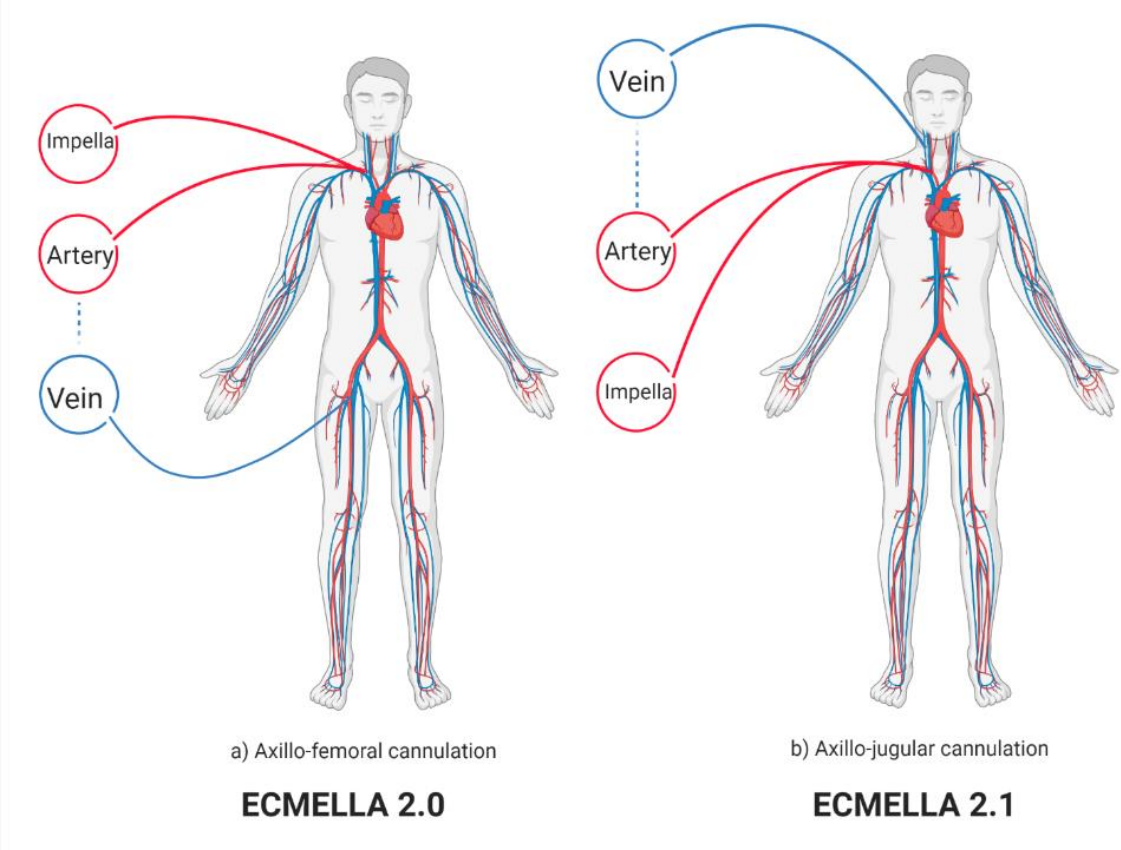

Figure 12. Single-arterial access ECMELLA approach.
Created by G. Nersesian.

ECMELLA 2.0/2.1 enables a biventricular unloading and provides a combined circulatory support of approx. 10 L/min.[62] Arm hyperperfusion, which can potentially occur on ECMELLA 2.0/2.1 support, can be treated with distal narrowing of the axillary artery using vessel loops.[62] De-escalation from ECMELLA 2.0/2.1 support can be easily performed by removing the arterial cannula of the v-a ECLS and ligating the side branch; this method does not require any surgical intervention.[62]

4.2 Complications on Impella 5.0/5.5® support

Despite the milder complication profile compared to v-a ECLS, some device- and access-related complications requiring intervention may occur on Impella 5.0/5.5® support.

- The pump rotor can reach a maximum speed of 34,000 rpm, generating a flow of 5.5 L/min. However, the enormous speed in combination with the narrow inflow cannula creates high shear forces, which precipitate hemolysis. Hemolysis occurs in 10-12% of Impella® patients.[31,57] In severe cases with impaired organ function, which occurred in 4% of our cases, pump explantation or exchange must be performed promptly.[32]
- Device thrombosis is a life-treating emergency in Impella patients. The signs of pump thrombosis include a rapid decrease in flow and high pressure in the purge solution system; additionally, hemolysis can occur. In some cases the thrombus formation is echocardiographically visualized on the Impella, so that the device has to be explanted or exchanged. Alternatively, thrombolytic therapy with recombinant tissue Plasminogen Activator (rtPA) can be administered.[63]
- The direct placement of the Impella into the LV may represent a potential pro-arrhythmogenic factor. Sustained ventricular tachycardia or fibrillation may require a flow reduction and cardioversion in 8-10% of patients on Impella support.[32,57] As the pigtail catheter on the tip of the Impella 5.0® was considered a potential cause of arrhythmia and thrombus formation on support, it was removed in the Impella 5.5® model.[64]
- Correct Impella 5.0/5.5® functionality requires precise placement: the pump inlet should rest approx. 5 cm below the level of the aortic valve and the tip of the catheter should point to the apex of the heart without compromising the mitral valve apparatus. Pump misplacement or dislodgement is the most commonly described complication on Impella and occurs in 20-60% of patients.[31,32,57] Repositioning can be performed bedside with echocardiographic control; however, corresponding expertise is required. If repositioning is not possible, the pump has to be explanted or exchanged. The first generation of the Impella 5.5® devices had a shorter body design compared the to Impella 5.0®; however, this feature was associated with a high prevalence of pump dislodgement. This fault was corrected with the improved Impella 5.5® design, which has the same length as the Impella 5.0®.[64]
- The access-related complications depend on the surgical implantation technique used. Impella 5.0/5.5® require a vascular cut-down due to their size. In this setting, implantation through a vascular prosthesis anastomosed to the axillary artery is considered a safe and feasible approach.[65] However, we observed four cases of pectoral hematoma, which in one case led to injury of the brachial plexus.[32] Percutaneous placement via the femoral artery, which is usually performed for Impella 2.5® and CP®, poses a high risk of access site bleeding and limb ischemia. In severe cases, limb amputation might be inevitable.[57,61]
- Early device-related infections relate to the rare complications on Impella.[61] However, the part of the vascular prosthesis that is anastomosed to the access vessel remains in situ after the device explantation and may represent a potential

risk for late-onset infections.[17] Implantation site infections are observed in approx. 8% of our patients.[33] Whether to further perform prosthesis shortening or surgically remove the graft during Impella explantation remains a topic of intense debate. Currently our study group is conducting a research project about surgical complications on Impella 5.0/5.5® support.

- Intracardial placement of impeller pumps through the aortic valve might represent a potential risk for valve injury. Aortic regurgitation (AR) after Impella support is extremely rare and has been described only in case reports. However, it remains unclear whether the aortic valve was damaged during the implantation or on support by the Impella pump itself.[66] Despite the low incidence of AR in Impella patients, this topic might have a special impact in patients bridged with an Impella from temporary MCS to durable LVAD, which is a well-known risk factor for developing AR. Our future project will address this issue.[67]

In summary, the complications on Impella support represent important therapy limitations. Their incidence and severity are significantly lower than on v-a ECLS and can be adequately managed. Importantly, none of the Impella-related complications were associated with a high mortality risk.[31,32,57,61]

4.3 Concomitant procedures on Impella

In addition to the retrospective analysis of the DHZB's experience with temporary MCS in the past five years, I presented a case report about percutaneous mitral valve repair on circulatory support with an Impella LVAD in a heart transplant patient.

In recent years, minimally invasive and endovascular approaches have become more and more popular. The protected PCI concept is a well-known approach for coronary interventions in high-risk patients, using catheter-based IABP, Impella 2.5® or CP® to provide short-term circulatory support during the procedure. Today, temporary MCS is more commonly used for beating-heart coronary bypass and mitral valve surgery. The MitraClip® implantation can be performed successfully on Impella support. In our recent publication we described the case of a post-HTx patient treated with Impella 5.5® due to acute CS.[68] The patient showed signs of myocardial recovery; however, in his case, severe mitral regurgitation precluded circulatory weaning. Mitral valve surgery with cardioplegic arrest as well as LVAD implantation was associated with an extremely high mortality risk. Ultimately, the patient underwent a MitraClip® implantation on Impella 5.5® support and was successfully weaned days after the procedure.[68]

4.4 Temporary MCS weaning and explantation

Temporary MCS devices may provide hemodynamic stabilization in cardiogenic shock; however, further therapeutic options should be discussed early on. In order to improve postoperative patient management at the German Heart Center Berlin we developed a standardized operational procedure for stepwise weaning from temporary MCS. Patients on support are regularly evaluated for signs of myocardial recovery. Based on this it can be decided whether weaning is possible or whether alternative options such as durable LVAD implantation, heart transplantation, or palliative care have to be ruled out due to a limited recovery potential.[42]

Patients on Impella support who achieve an inotrope- and vasopressor-free status should be considered for circulatory weaning and undergo echocardiographic evaluation of myocardial function.[32] After that, Impella® support should be gradually reduced to the P2 level over the course of 2 days under constant hemodynamic and echocardiographic monitoring (Figure 13).

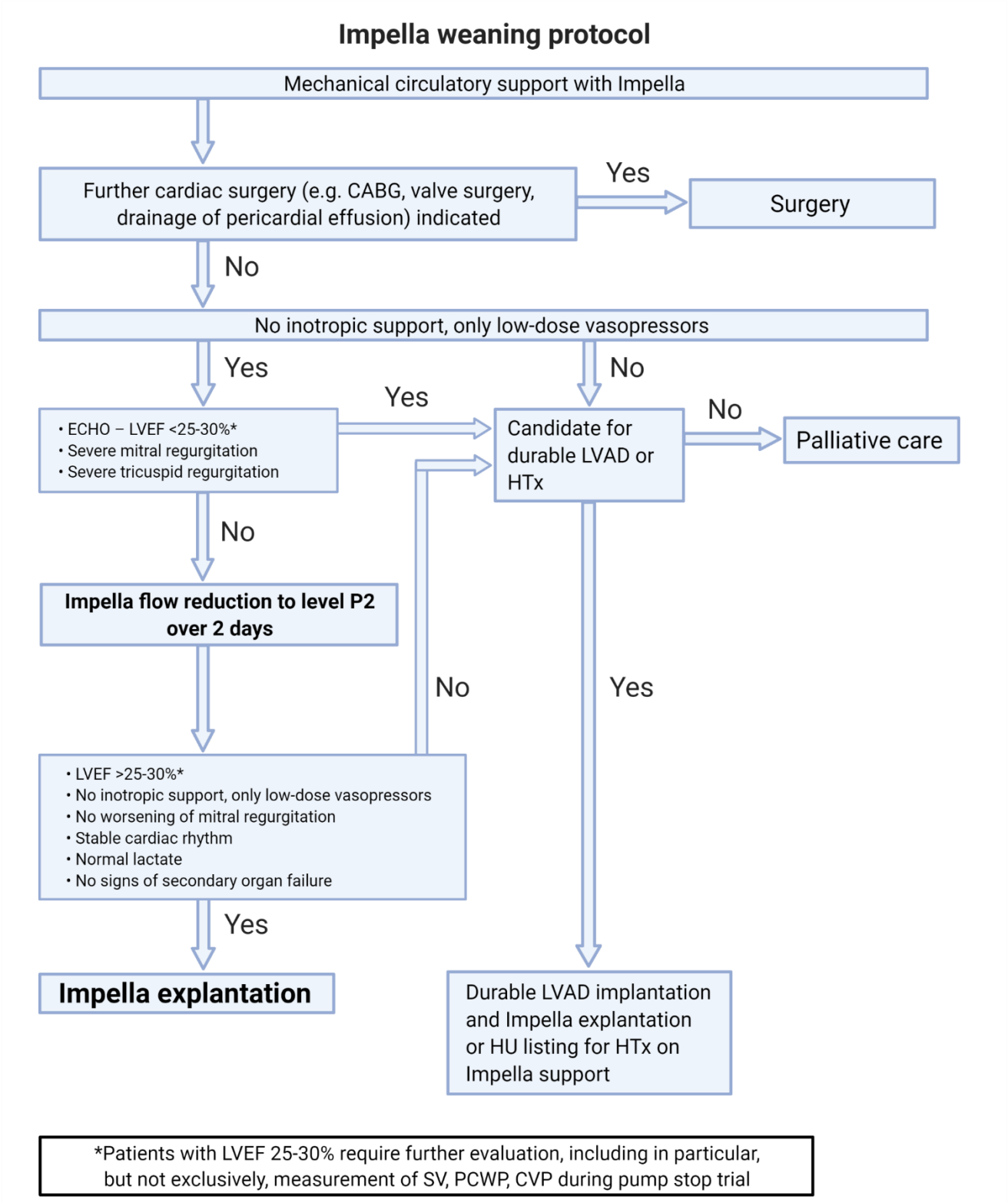

Figure 13. Impella weaning protocol.
Created by G. Nersesian.

Impella 5.0/5.5® explantation is usually performed bedside under sterile conditions and local anesthesia. The Impella is stopped completely and removed. The vascular prosthesis is shortened, ligated and buried under the pectoral muscle. Alternatively, the wound may be re-opened and the prosthesis completely removed and the axillary artery reconstructed with a pericardial patch. Skin closure is then performed.[17]

Similar protocols were developed for v-a ECLS (Figure 14) and ECMELLA weaning (Figure 15).

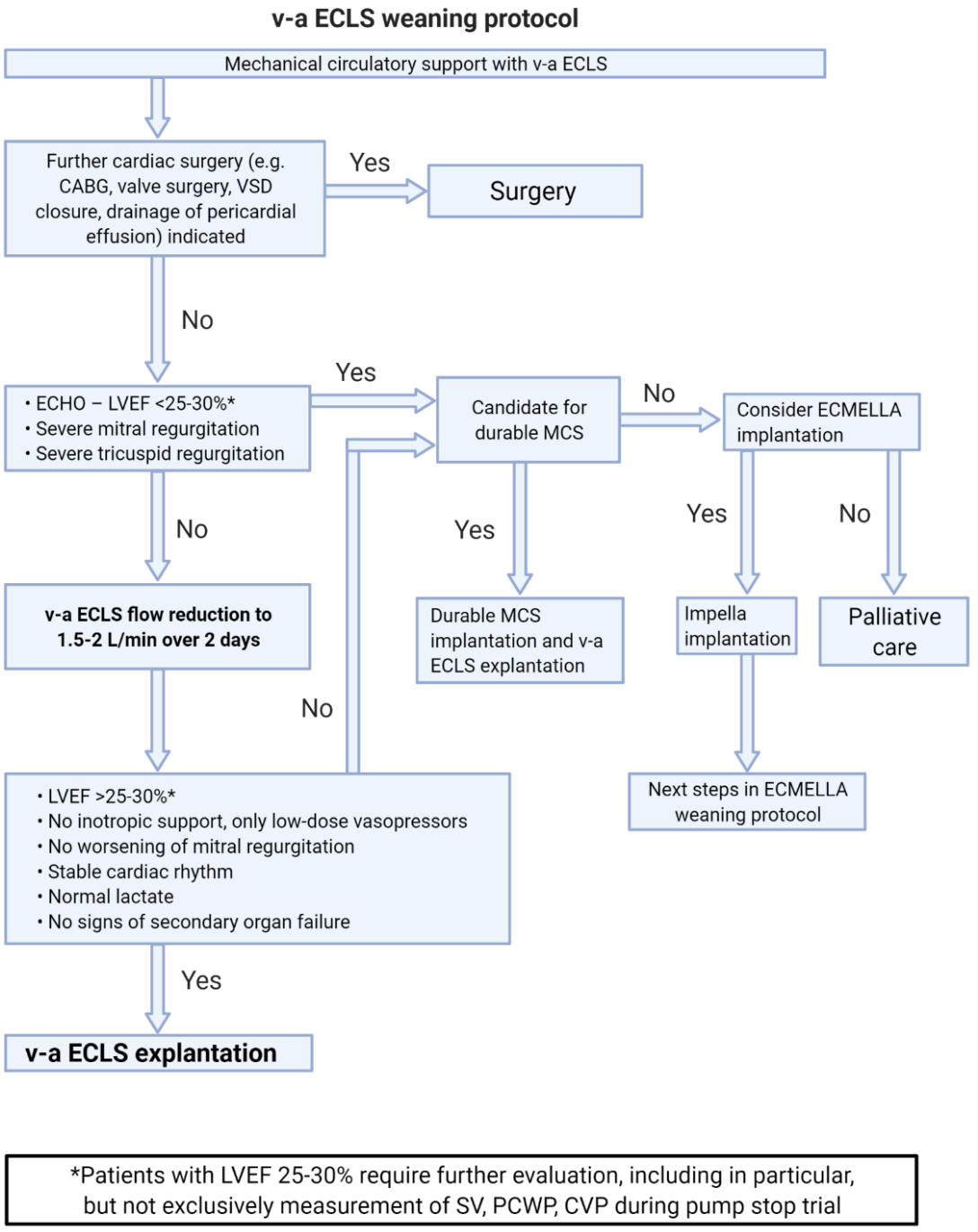

Figure 14. v-a ECLS weaning protocol.
Created by G. Nersesian.

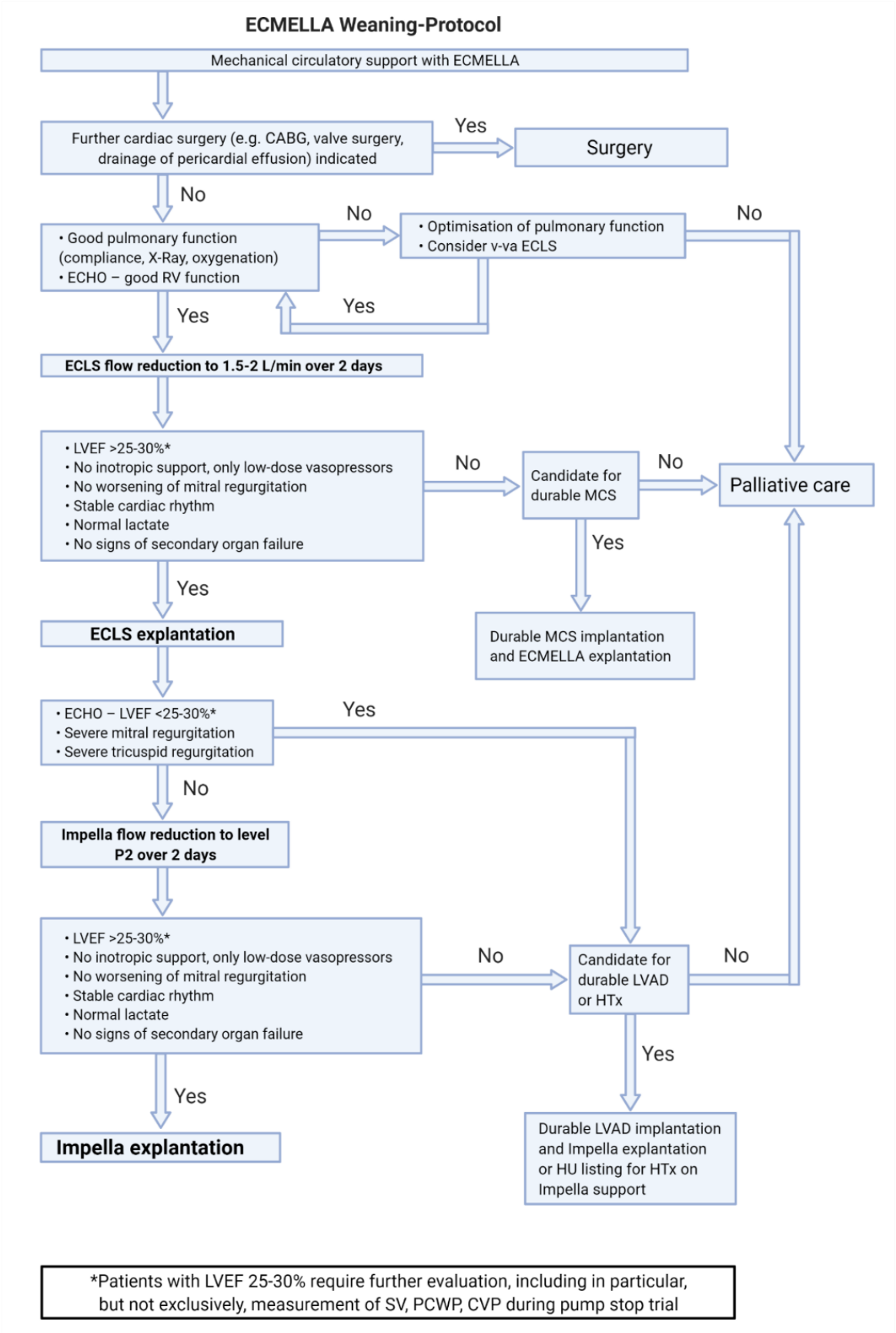

Figure 15. ECMELLA weaning protocol.
Created by G. Nersesian.

Since the introduction of the MCS selection algorithm (Figure 7), the number of patients on isolated v-a ECLS support in our institution has dropped and mainly includes patients in whom Impella is contraindicated. In these patients, we aim to achieve a short support duration with an early evaluation for durable LVAD in order to prevent ECLS-related complications.[40]

In case of ECMELLA weaning, stepwise de-escalation with primary v-a ECLS explantation and further patient mobilization on Impella support was preferred.

Patients with a borderline LVEF of 25-30% require further evaluation including, in particular, but not exclusively, measurement of SV (stroke volume), PCWP (pulmonary capillary wedge pressure), CVP (central venous pressure) during a pump-stop trial. Circulatory weaning in these patients can potentially be achieved but does not restore the previous quality of life. Therefore, durable LVAD or HTx should also be considered in these borderline cases.

4.5 Future perspectives of algorithm application

The standardized operational protocols suggested in this dissertation represent the results of my three years of work in the field of MCS and the DHZB's experience with impeller pumps in the past 5 years. First, we identified potential predictors for poor outcomes on Impella support: pathological arterial blood pH and preoperative CPR. In the second analysis on surgically implanted impeller pumps, arterial lactate and CPR were found to be significant mortality predictors and the temporary MCS selection protocol was developed. These findings were confirmed in the third study and translated to Impella CP® support. The consistent application of the temporary MCS protocols in combination with the extensive expertise gained in recent years allowed us to develop a standardized therapy concept that can be individually adjusted to specific CS patients. Our experience with the suggested protocols will be evaluated in future analyses and, depending on the results, might potentially be used for a multicenter investigation.

Another aspect of our future research is the analysis of long-term complications on MCS including an evaluation of histological cardiac samples and postoperative dynamics with the aim to predict and conceptualize a standardized management approach for MCS complications.

4.6 Limitations

Limitations of our research include the retrospective nature of the study and the relatively small number of patients. This might give rise to criticism, especially if we suggest therapy decisions based on our research. In order to circumvent potential overfitting with significant statistical parameters, which is typical for studies with a small dataset, we focused on variables selected from previous literature and clinical acumen.

Nevertheless, a prospective, randomized study comparing different treatment options in CS patients (e.g., percutaneous Impella CP®, surgical Impella 5.0/5.5®, and ECLS) would facilitate the search for an optimal treatment strategy.

5 Conclusion

Temporary MCS with Impella represents a feasible therapeutic approach in CS patients and has a low complication profile. In our research we demonstrated that the severity of preoperative organ dysfunction as well as the level and duration of shock predict early mortality on Impella support. Preoperative arterial lactate levels ≥8 mmol/L as well as CPR are valuable predictors of 30-day mortality in CS patients undergoing Impella 5.0/5.5® and CP® implantation. Based on these findings we developed an algorithm for preoperative MCS device selection and demonstrated its effectiveness in a 1-year study follow-up. However, studies should evaluate the effectiveness of more aggressive MCS strategies in critically ill patients excluded from Impella 5.0/5.5® support based on our protocol.

Additionally, we developed weaning protocols for different tempMCS devices with the aim of standardizing and improving outcomes of CS patients.

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7 Affidavit (Eidesstattliche Versicherung)

„Ich, Gaik Nersesian versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Mechanische Kreislaufunterstützung bei Patienten im akuten kardiogenen Shock“ (Englisch: „Mechanical circulatory support in patients with acute cardiogenic shock“) selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Berlin, 21.02.2023

Datum Unterschrift

8 Author contributions for listed publications

Gaik Nersesian contributed to the following publications:

Publication Nr. 1 (chronologically the second publication after the pilot study)

Nersesian G, Tschöpe C, Spillmann F, Gromann T, Roehrich L, Mueller M, Mulzer J, Starck C, Falk V, Schoenrath F, Potapov E. **Prediction of survival of patients in cardiogenic shock treated by surgically implanted Impella 5+ short-term left ventricular assist device.**
Interactive Cardiovascular Thoracic Surgery. 2020 Oct 1;31(4):475-482. PMID: 32879947.

Authors own contributions:
- Conceptualization
- Data curation
- Data analysis
- Statistic analysis
- Writing: original draft
- Writing: review and editing

Contributions in detail

Together with my first supervisor Prof. Dr. med. Felix Schoenrath and my second supervisor Prof. Dr. med. Evgenij Potapov we developed the concept of the study “Prediction of survival of patients in cardiogenic shock treated by surgically implanted Impella 5+ short-term left ventricular assist device.“ My supervisors and I identified clinically relevant parameters. Afterwards, data to all patients, who received Impella device in German Heart Centre Berlin (at that time n=91) was collected by me and used for a databank establishment. This databank is currently still active and is used to support further projects.
All patient-related data was collected respecting data protection regulations of the German Heart Centre Berlin and confirm to the German law. All patient-related data was stored in the internal servers of the German Heart Centre Berlin.
First, I summarized the collected information in Tables 1 and 2, which display relevant

demographics and preoperative laboratory parameters of the patient population.
Afterwards, I performed the statistical analysis of the data under supervision of our institutional statistician Ms. Julia Stein. The analysis is summarized in Table 3, which demonstrates the odds-ratios for clinically relevant parameters as well as a multivariate model for preoperative arterial lactate and MELD-XI score.
The cut-off value for preoperative arterial lactate was identified using receiver operating characteristic curve and a Youden-Index, the value of 8mmol/L (72mg/dL) was determined.
The Kaplan-Meier estimates with corresponding confidence intervals were created for a total survival (Figure 2), as well as for relevant subgroups (Figure 3 and 4). The Log-Rank test was used to calculate the significance.
Finally, based on collected data and previous publications an algorithm for a preoperative mechanical circulatory support selection in cardiogenic shock patients was developed (Figure 5).
The draft of the manuscript was written by me and edited by my supervisors. After the final approval of the manuscript by my supervisors and other co-authors, I was enabled to submit the manuscript to the journal.
Initially the manuscript was submitted by the European Journal of Cardio-Thoracic Surgery (EJCTS, IF=4.191). The manuscript was not accepted by the EJCTS but proposed for a transfer to the Interactive Cardiovascular and Thoracic Surgery (ICVTS, IF=1.905), which is the partner journal of the EJCTS and is also supervised by the European Association of Cardiothoracic Surgery.
During the peer-reviewing process, which included three rounds, I optimized the manuscript regarding the criticism and comments of the reviewers. The peer-reviewing process was also leaded by my supervisors. Finally, our manuscript was accepted by the ICTVS journal.

Publication Nr. 2 (pilot study)

Nersesian G, Hennig F, Müller M, Mulzer J, Tsyganenko D, Starck C, Gromann T, Falk V, Potapov E, Schoenrath F. **Temporary mechanical circulatory support for refractory heart failure: the German Heart Center Berlin experience.**
Annals of Cardiothoracic Surgery. 2019 Jan;8(1):76-83. PMID: 30854315;
The concept of the study was developed under supervision of Prof. Dr. med. Felix

Schoenrath Prof Dr. med. Evgenij Potapov. Relevant clinical parameters for the study cohort were discussed, chosen and collected by me for a databank establishment. Writing of the first version of the manuscript was done by me in close cooperation with my supervisors. All listed co-authors took part in editing of the manuscript. After the approval by the clinic direction, the manuscript could be submitted for a special issue of the Annals of Cardiothroracic Surgery (2018, IF= 2.895) about mechanical circulatory support. After peer-reviewing process, the manuscript was published by above mentioned journal.

Authors own contributions:

- Conceptualization
- Data curation
- Data analysis
- Statistic analysis
- Writing: original draft
- Writing: review and editing

Publication Nr. 3

Nersesian G, Potapov EV, Nelki V, Stein J, Christoph Starck C, Falk V, Schoenrath F, Krackhardt F, Tschöpe C, Spillmann F **Propensity score-based analysis of 30-day survival in cardiogenic shock patients supported with different microaxial left ventricular assist devices**
Journal of Cardiac Surgery. 2021 Jul 14. Epub ahead of print.

The concept of the study **"Propensity score-based analysis of 30-day survival in cardiogenic shock patients supported with different microaxial left ventricular assist devices"** was developed by myself in cooperation with my supervisor Prof. Dr. med. E. Potapov.
The surgically implanted Impella 5.0/5.5® deices from the German Heart Centre Berlin were compared with percutaneously implanted Impella CP® devices from the cardiological department of the Charité university hospital. Study was conducted in close cooperation with colleagues from the Charité: Dr. Spillmann, Prof. Dr. med. Tschöpe und Dr. Krackhardt. The statistical analysis of the data was done under supervision of the DHZB

statistician Ms. Julia Stein. Writing of the first version of the manuscript was done by me in close cooperation with my supervisors. All listed co-authors took part in editing of the manuscript. For this publication Prof. Dr. med. Potapov and me contributed equally as first authors.

Authors own contributions:

- Conceptualization
- Data curation
- Data analysis
- Statistic analysis
- Writing: original draft
- Writing: review and editing

Berlin 21.02.2023

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Unterschrift, Datum und Stempel des erstbetreuenden Hochschullehrers

Berlin 21.02.2023

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Unterschrift des Doktoranden/der Doktorandin

9 Journal Summary List

9.1 Journal summary list 2018

Journal Data Filtered By: Selected JCR Year: 2018 Selected Editions: SCIE,SSCI Selected Categories: “CARDIAC and CARDIOVASCULAR SYSTEMS” Selected Category Scheme: WoS
Total: 136 journals

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	EUROPEAN HEART JOURNAL	57,358	23.239	0.125920
2	CIRCULATION	166,484	23.054	0.211290
3	JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY	100,986	18.639	0.193290
4	Nature Reviews Cardiology	6,301	17.420	0.018820
5	CIRCULATION RESEARCH	52,988	15.862	0.072290
6	EUROPEAN JOURNAL OF HEART FAILURE	13,107	13.965	0.027620
7	JAMA Cardiology	3,280	11.866	0.019320
8	JACC-Cardiovascular Imaging	8,801	10.975	0.026160
9	JACC-Cardiovascular Interventions	11,555	9.544	0.033640
10	JACC-Heart Failure	3,537	8.910	0.016830
11	JOURNAL OF HEART AND LUNG TRANSPLANTATION	12,436	8.578	0.027310
12	CARDIOVASCULAR RESEARCH	21,828	7.014	0.021500
13	European Heart Journal-Cardiovascular Pharmacotherapy	442	6.723	0.001430
14	Circulation-Heart Failure	6,900	6.526	0.022830
15	BASIC RESEARCH IN CARDIOLOGY	4,137	6.470	0.005590
16	PROGRESS IN CARDIOVASCULAR DISEASES	4,055	6.162	0.008860
17	JOURNAL OF THE AMERICAN SOCIETY OF ECHOCARDIOGRAPHY	10,478	6.111	0.016060
18	EUROPACE	10,908	6.100	0.025320
19	Circulation-Cardiovascular Interventions	5,289	6.060	0.016640

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
20	Cardiovascular Diabetology	5,392	5.948	0.011550
21	Circulation-Cardiovascular Imaging	5,456	5.813	0.018480
22	European Journal of Preventive Cardiology	4,782	5.640	0.013370
23	CANADIAN JOURNAL OF CARDIOLOGY	6,710	5.592	0.018500
24	JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY	29,599	5.261	0.036950
25	European Heart Journal-Cardiovascular Imaging	5,498	5.260	0.021650
26	HEART RHYTHM	12,344	5.225	0.029030
27	REVISTA ESPANOLA DE CARDIOLOGIA	3,566	5.126	0.004640
28	HEART	18,063	5.082	0.030620
29	JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE	5,113	5.070	0.014020
30	JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY	14,143	5.055	0.020450
31	Circulation-Arrhythmia and Electrophysiology	6,432	4.968	0.017840
32	Clinical Research in Cardiology	3,022	4.907	0.006760
33	Circulation-Cardiovascular Genetics	3,441	4.864	0.010500
34	Journal of the American Heart Association	13,230	4.660	0.060340
35	TRENDS IN CARDIOVASCULAR MEDICINE	2,667	4.462	0.003930
36	Circulation-Cardiovascular Quality and Outcomes	4,531	4.378	0.014350
37	ATHEROSCLEROSIS	23,442	4.255	0.033500
38	CARDIOVASCULAR DRUGS AND THERAPY	2,109	4.181	0.003140
39	JOURNAL OF NUCLEAR CARDIOLOGY	3,711	4.112	0.004480

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
40	AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY	27,828	4.048	0.022820
41	AMERICAN HEART JOURNAL	20,811	4.023	0.026780
42	EuroIntervention	6,097	4.018	0.016840
43	HEART FAILURE REVIEWS	2,598	4.015	0.005300
44	ANNALS OF THORACIC SURGERY	36,145	3.919	0.040630
45	JOURNAL OF CARDIAC FAILURE	5,339	3.857	0.009350
46	EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY	17,156	3.847	0.026410
47	European Heart Journal-Acute Cardiovascular Care	1,466	3.734	0.005330
48	INTERNATIONAL JOURNAL OF CARDIOLOGY	30,479	3.471	0.080570
49	ESC Heart Failure	680	3.407	0.002020
50	NUTRITION METABOLISM AND CARDIOVASCULAR DISEASES	5,821	3.340	0.010180
51	CURRENT PROBLEMS IN CARDIOLOGY	574	3.333	0.000700
52	Journal of Cardiovascular Computed Tomography	1,711	3.316	0.004430
53	Global Heart	881	3.238	0.003800
54	RESPIRATORY MEDICINE	11,846	3.237	0.015840
55	CIRCULATION JOURNAL	9,904	3.025	0.016510
56	JOURNAL OF THROMBOSIS AND THROMBOLYSIS	2,789	2.941	0.005860
57	JOURNAL OF CARDIOVASCULAR ELECTROPHYSIOLOGY	7,508	2.910	0.010700
58	Annals of Cardiothoracic Surgery	1,528	2.895	0.004950
59	AMERICAN JOURNAL OF CARDIOLOGY	37,275	2.843	0.044530

9.2 Journal summary list 2019

Selected JCR Year: 2019; Selected Categories: “CARDIAC and CARDIOVASCULAR SYSTEMS”

Journal Data Filtered By: Selected JCR Year: 2019 Selected Editions: SCIE,SSCI Selected Categories: “CARDIAC and CARDIOVASCULAR SYSTEMS” Selected Category Scheme: WoS

Total: 138 journals

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	CIRCULATION	158,218	23.603	0.205020
2	EUROPEAN HEART JOURNAL	59,968	22.673	0.140620
3	JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY	101,927	20.589	0.190280
4	Nature Reviews Cardiology	7,100	20.260	0.021130
5	CIRCULATION RESEARCH	51,539	14.467	0.071470
6	JAMA Cardiology	4,740	12.794	0.030110
7	JACC-Cardiovascular Imaging	10,110	12.740	0.027550
8	BASIC RESEARCH IN CARDIOLOGY	4,704	11.981	0.006380
9	EUROPEAN JOURNAL OF HEART FAILURE	12,784	11.627	0.028700
10	JACC-Heart Failure	4,117	8.750	0.019180
11	JACC-Cardiovascular Interventions	11,371	8.432	0.037330
12	CARDIOVASCULAR RESEARCH	21,526	8.168	0.019950
13	JOURNAL OF HEART AND LUNG TRANSPLANTATION	12,465	7.865	0.028140
14	Cardiovascular Diabetology	6,179	7.332	0.011390
15	PROGRESS IN CARDIOVASCULAR DISEASES	4,193	6.763	0.008340
16	European Heart Journal-Cardiovascular Pharmacotherapy	521	6.696	0.001640
17	Circulation-Heart Failure	6,773	6.033	0.018490
18	European Journal of Preventive Cardiology	5,589	5.864	0.015370
19	HEART RHYTHM	12,246	5.731	0.028620
20	Circulation-Cardiovascular Imaging	5,574	5.691	0.016320

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	JOURNAL OF THE AMERICAN SOCIETY OF ECHOCARDIOGRAPHY	11,347	5.508	0.018230
22	Circulation-Cardiovascular Interventions	5,012	5.493	0.018140
23	JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE	5,205	5.361	0.011120
24	Clinical Research in Cardiology	3,321	5.268	0.007280
25	HEART	18,108	5.213	0.030140
26	Circulation-Cardiovascular Quality and Outcomes	4,728	5.071	0.014350
27	CANADIAN JOURNAL OF CARDIOLOGY	6,980	5.000	0.017630
28	European Heart Journal-Cardiovascular Imaging	6,359	4.841	0.023110
29	TRENDS IN CARDIOVASCULAR MEDICINE	2,695	4.755	0.003920
30	REVISTA ESPANOLA DE CARDIOLOGIA	3,672	4.642	0.004610
31	Journal of the American Heart Association	17,149	4.605	0.070620
32	Circulation-Cardiovascular Genetics	3,090	4.534	0.008600
33	JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY	28,491	4.451	0.034300
34	Circulation-Arrhythmia and Electrophysiology	6,344	4.393	0.016630
35	AMERICAN HEART JOURNAL	19,814	4.153	0.026810
36	JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY	14,031	4.133	0.017960
37	CARDIOVASCULAR DRUGS AND THERAPY	2,114	4.069	0.003340
38	Circulation-Genomic and Precision Medicine	375	4.063	0.002220
39	Hellenic Journal of Cardiology	987	4.047	0.001000
40	EUROPACE	9,973	4.045	0.024750

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
41	EuroIntervention	5,542	3.993	0.016590
42	ATHEROSCLEROSIS	24,587	3.919	0.036590
43	Frontiers in Cardiovascular Medicine	1,303	3.915	0.004020
44	ESC Heart Failure	1,276	3.902	0.004120
45	AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY	26,114	3.864	0.020400
46	Global Heart	1,074	3.862	0.003180
47	European Heart Journal-Acute Cardiovascular Care	1,555	3.813	0.005430
48	NUTRITION METABOLISM AND CARDIOVASCULAR DISEASES	6,026	3.700	0.008820
49	ANNALS OF THORACIC SURGERY	35,221	3.639	0.040380
50	HEART FAILURE REVIEWS	2,697	3.538	0.005130
51	EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY	16,682	3.486	0.025820
52	JOURNAL OF CARDIAC FAILURE	4,983	3.435	0.008730
53	JOURNAL OF NUCLEAR CARDIOLOGY	3,600	3.366	0.004570
54	Journal of Cardiovascular Translational Research	1,656	3.312	0.003140
55	INTERNATIONAL JOURNAL OF CARDIOLOGY	31,193	3.229	0.068160
56	RESPIRATORY MEDICINE	11,934	3.095	0.013490
57	Annals of Cardiothoracic Surgery	1,828	3.058	0.005060
58	CURRENT PROBLEMS IN CARDIOLOGY	567	2.966	0.000740
59	Journal of Cardiovascular Computed Tomography	1,809	2.892	0.004850
60	American Journal of Cardiovascular Drugs	1,063	2.674	0.001580

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
61	Cardiovascular Diagnosis and Therapy	1,081	2.615	0.003050
62	JOURNAL OF CARDIOVASCULAR PHARMACOLOGY	5,340	2.598	0.003810
63	AMERICAN JOURNAL OF CARDIOLOGY	35,187	2.570	0.039490
64	CIRCULATION JOURNAL	9,860	2.540	0.014780
65	Cardiovascular Therapeutics	1,351	2.538	0.002120
66	Journal of Geriatric Cardiology	1,231	2.491	0.003270
67	Archives of Cardiovascular Diseases	1,628	2.434	0.003570
67	Current Cardiology Reports	2,127	2.434	0.005990
69	JOURNAL OF CARDIOVASCULAR ELECTROPHYSIOLOGY	6,886	2.424	0.010110
70	Heart Failure Clinics	1,020	2.327	0.002330
71	JOURNAL OF CARDIOVASCULAR PHARMACOLOGY AND THERAPEUTICS	1,358	2.322	0.002140
71	Korean Circulation Journal	1,335	2.322	0.002430
73	European Journal of Cardiovascular Nursing	1,723	2.296	0.002700
74	Cardiovascular Toxicology	1,272	2.284	0.001730
75	JOURNAL OF CARDIOTHORACIC AND VASCULAR ANESTHESIA	5,371	2.258	0.007310
76	CLINICAL CARDIOLOGY	4,233	2.248	0.008620
77	Journal of Cardiology	3,243	2.246	0.006090
78	Pulmonary Circulation	1,651	2.205	0.004290
79	Heart Lung and Circulation	2,889	2.194	0.006490
80	CURRENT OPINION IN CARDIOLOGY	2,051	2.149	0.003530
81	Seminars in Thoracic and Cardiovascular Surgery	1,320	2.133	0.002210

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
82	BMC Cardiovascular Disorders	3,684	2.078	0.008950
83	JOURNAL OF THROMBOSIS AND THROMBOLYSIS	2,794	2.054	0.005740
84	Cardiovascular Ultrasound	1,112	2.051	0.001490
85	CATHETERIZATION AND CARDIOVASCULAR INTERVENTIONS	8,295	2.044	0.015230
86	CARDIOVASCULAR AND INTERVENTIONAL RADIOLOGY	5,675	2.034	0.007340
87	INTERNATIONAL JOURNAL OF CARDIOVASCULAR IMAGING	3,176	1.969	0.006730
88	Netherlands Heart Journal	1,233	1.933	0.001950
89	International Heart Journal	1,942	1.906	0.002670
90	Kardiologia Polska	1,665	1.874	0.002570
91	Cardiology in Review	1,080	1.816	0.001510
92	CARDIOLOGY CLINICS	1,086	1.811	0.002030
93	CARDIOLOGY	2,359	1.791	0.002520
94	Cardiovascular Engineering and Technology	504	1.771	0.001090
95	JOURNAL OF INTERVENTIONAL CARDIOLOGY	1,309	1.758	0.002400
96	CARDIOVASCULAR PATHOLOGY	1,998	1.756	0.002360
97	CardioRenal Medicine	485	1.754	0.001100
98	Interactive Cardiovascular and Thoracic Surgery	5,684	1.675	0.009110
98	Journal of Cardiovascular Nursing	1,795	1.675	0.002220
100	Cardiology Journal	1,164	1.669	0.001950
101	Congenital Heart Disease	1,648	1.663	0.004000

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
102	EUROPEAN HEART JOURNAL SUPPLEMENTS	551	1.655	0.000810
103	HEART & LUNG	2,351	1.630	0.003020
104	HEART AND VESSELS	2,176	1.618	0.003670
105	Annals of Thoracic and Cardiovascular Surgery	1,087	1.584	0.001370
106	PEDIATRIC CARDIOLOGY	4,344	1.564	0.006710
107	Journal of Cardiothoracic Surgery	2,089	1.506	0.004210
108	JOURNAL OF CARDIAC SURGERY	2,054	1.490	0.003000
109	Annals of Thoracic Medicine	735	1.456	0.000990
110	JOURNAL OF INVASIVE CARDIOLOGY	1,593	1.453	0.002420
111	Arquivos Brasileiros de Cardiologia	3,065	1.450	0.002850
112	JOURNAL OF CARDIOVASCULAR SURGERY	1,825	1.415	0.002130
113	ECHOCARDIOGRAPHY-A JOURNAL OF CARDIOVASCULAR ULTRASOUND AND ALLIED TECHNIQUES	3,173	1.393	0.005780
114	Journal of Cardiopulmonary Rehabilitation and Prevention	1,706	1.383	0.001840
115	Postepy w Kardiologii Interwencyjnej	311	1.347	0.000620
116	CORONARY ARTERY DISEASE	1,637	1.335	0.002200
117	PACE-PACING AND CLINICAL ELECTROPHYSIOLOGY	5,012	1.303	0.005720
118	Cardiology Research and Practice	833	1.292	0.001360
119	JOURNAL OF INTERVENTIONAL CARDIAC ELECTROPHYSIOLOGY	1,507	1.277	0.003230
120	PERFUSION-UK	1,271	1.234	0.001760
121	Journal of Cardiovascular Medicine	1,667	1.225	0.002970

10 Texts of publications

10.1 Temporary mechanical circulatory support for refractory heart failure: the German Heart Center Berlin experience

https://doi.org/10.21037/acs.2018.12.01

10.2 Prediction of survival of patients in cardiogenic shock treated by surgically implanted Impella 5+ short-term left ventricular assist device

https://doi.org/10.1093/icvts/ivaa150

10.3 Propensity score-based analysis of 30-day survival in cardiogenic shock patients supported with different microaxial left ventricular assist devices

https://doi.org/10.1111/jocs.15932

11 Curriculum vitae Gaik Nersesian

Mein Lebenslauf wird aus Datenschutzgründen in der öffentlichen Version der Dissertation nicht veröffentlich.

12 List of publications

List of own publications as first author

11.1 Nersesian G, Hennig F, Müller M, Mulzer J, Tsyganenko D, Starck C, Gromann T, Falk V, Potapov E, Schoenrath F. Temporary mechanical circulatory support for refractory heart failure: the German Heart Center Berlin experience. Ann Cardiothorac Surg. 2019 Jan;8(1):76-83. PMID: 30854315; IF=3.06

11.2 Nersesian G, Tschöpe C, Spillmann F, Gromann T, Roehrich L, Mueller M, Mulzer J, Starck C, Falk V, Schoenrath F, Potapov E. Prediction of survival of patients in cardiogenic shock treated by surgically implanted Impella 5+ short-term left ventricular assist device. Interact Cardiovasc Thorac Surg. 2020 Oct 1;31(4):475-482. PMID: 32879947; IF=1.91

11.3 Nersesian G, Solowjowa N, Falk V, Potapov E, Buz S. Endovascular treatment of an anastomotic outflow graft pseudoaneurysm of the descending aorta after implantation of a left ventricular assist device. J Card Surg. 2020 Aug 2. Epub ahead of print. PMID: 32741036; IF=1.62

11.4 Nersesian G, Van Praet KM, van Kampen A, Solowjowa N, Falk V, Potapov E. Surgical treatment of outflow graft kinking complicated by external obstruction with a fibrin mass in a patient with LVAD. J Card Surg. 2020 Oct;35(10):2853-2856. Epub 2020 Jul 19. PMID: 32683721; IF=1.62

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11.6 Nersesian G, Lewin D, Schoenrath F, Solowjowa N, Kukucka M, Falk V, Klein C, Potapov E, Unbehaun A. Percutaneous mitral valve repair assisted by a catheter-based circulatory support device in a heart transplant patient. J Card Surg. 2021 Jul 11. Epub ahead of print. PMID: 34250624; IF=1.62

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