ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 3594–3602
Published online 23 August 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13546

ORIGINAL RESEARCH ARTICLE

Outcome of patients with non-ischaemic cardiogenic shock supported by percutaneous left ventricular assist device

Jean M. Haurand[1], Sandra Haberkorn[1], Jafer Haschemi[1], Daniel Oehler[1], Hug Aubin[2], Payam Akhyari[2], Udo Boeken[2], Malte Kelm[1,3], Ralf Westenfeld[1] and Patrick Horn[1]*

[1]*Division of Cardiology, Pulmonology, and Vascular Medicine, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany;* [2]*Division of Cardiovascular Surgery, Medical Faculty, University of Düsseldorf, Düsseldorf, Germany; and* [3]*Cardiovascular Research Institute, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany*

Abstract

Aims Percutaneous left ventricular assist devices (pVADs) are used to haemodynamically stabilize patients with cardiogenic shock (CS) caused by acute myocardial infarction (AMI). One out of every two patients has a non-ischaemic cause of CS, and these patients differ profoundly from patients with AMI-related CS. We assessed the usefulness of pVAD support for patients with non-ischaemic CS.

Methods and results We analysed 106 patients with CS and Impella® support between 2015 and 2018. CS was non-ischaemic in 36 patients and AMI-related in 70 patients. Compared with the AMI group, those in the non-ischaemic group were significantly younger [median age 62 (50.8, 70.8) years vs. 68 (58.0, 75.5) years, $P = 0.007$] and had more patients with severely reduced left ventricular function (94% vs. 79%, $P = 0.035$) and worse glomerular filtration rate [45 (27, 57) mL/min vs. 60 (44, 78) mL/min]. Propensity score matching yielded 31 patients with non-ischaemic CS and 31 patients with AMI-related CS, without a difference in baseline laboratory values or comorbidities. In both groups, pVAD support was performed along with haemodynamic stabilization, reduction of catecholamines and normalization of lactate levels. In 7 days, systolic blood pressure increased from 91 (80, 101) mmHg at baseline to 100 (100, 120) mmHg in the non-ischaemic CS group ($P = 0.001$) and 89 (80, 100) mmHg at baseline to 112 (100, 128) mmHg in the AMI-related CS group ($P = 0.001$). Moreover, in 7 days, the need of catecholamines (calculated as vasoactive-inotropic score) decreased from 32.0 (11.1, 47.0) at baseline to 5.3 (0, 16.1) in the non-ischaemic group ($P = 0.001$) and from 35.2 (18.11, 67.0) to zero (0, 0) in the AMI-related CS group ($P = 0.001$). Lactate level decreased from 3.8 (2.8, 5.9) mmol/L at baseline to 1.0 (0.8, 2.1) mmol/L ($P = 0.001$) in the non-ischaemic CS group and from 3.8 (2.6, 6.5) mmol/L to 1.2 (1.0, 2.0) mmol/L in the AMI-related group ($P = 0.001$).

In the non-ischaemic CS group, eight patients (25.8%) were upgraded to veno-arterial extracorporeal membrane oxygenation (VA-ECMO) or long-term mechanical circulatory support. Two of these upgraded patients received heart transplantation. In the AMI group, eight patients (25.8%) were upgraded to VA-ECMO or long-term mechanical circulatory support. Ninety-day survival did not significantly differ between the groups (non-ischaemic CS group 48.4%, AMI-related CS group 45.2%, $P = 0.799$).

Conclusions pVAD support is useful for haemodynamic stabilization of patients with non-ischaemic CS and is valuable as a bridge to patients' recovery or long-term left ventricular support and heart transplantation.

Keywords Impella; Heart failure; Mechanical circulatory support; Cardiogenic shock

Received: 26 March 2021; Revised: 1 July 2021; Accepted: 19 July 2021
**Correspondence to: Patrick Horn, Division of Cardiology, Pulmonology and Vascular Medicine, Medical Faculty, Heinrich-Heine University, Moorenstr. 5, 40,225 Düsseldorf. Phone: +00 49-211-81-18801; Fax: +0049-211-81-18812. Email: patrick.horn@med.uni-duesseldorf.de*
Jean M. Haurand and Sandra Haberkorn contributed equally.

Introduction

The mortality after cardiogenic shock (CS) is still tremendously high at approximately 50%.[1–3] The current guidelines recommend considering the use of mechanical circulatory support (MCS) systems in patients with CS in addition to medical therapy in order to stabilize patient haemodynamics and to maintain sufficient end-organ perfusion.[4,5] However, most studies focused on the role of MCS in patients in which CS was related to acute myocardial infarction (AMI). In this setting, percutaneous ventricular assist devices (pVADs) like the microaxial Impella pump can be used to stabilize the patient haemodynamically until early coronary revascularization has resolved coronary flow and the mismatch in oxygen supply and demand, and therefore, myocardial function has recovered.[6–8]

However, up to every second, CS patient has a non-ischaemic cause of CS that does not offer an immediate therapeutical approach such as percutaneous coronary intervention.[9–11] This includes patients with acute worsening of long-standing ventricular dysfunction that enter into CS or patients with acute fulminant myocarditis. Patients with non-ischaemic CS differ in terms of comorbidities and patient characteristic from patients with CS complicating AMI.[9,10] Based on the different underlying pathology, the only remaining therapy currently is to stabilize the patient with catecholamines until recovery of cardiac function, implantation of durable MCS or heart transplantation.[12] Patients with non-ischaemic CS were more likely to be treated with catecholamines, but less likely to be treated with pVAD when compared with patients with AMI-related CS.[10] However, catecholamines can be ineffective, increase oxygen consumption and impair tissue perfusion.[13] In fact, mortality in patients with non-ischaemic CS is higher compared with patients with AMI-related CS.[9,10] It remains unknown whether pVAD support in patients with non-ischaemic CS is useful for haemodynamic stabilization and bridging until recovery of previous cardiac function, implantation of durable MCS or heart transplantation.

The aim of this study was to assess the use of pVAD in propensity score-matched groups of patients with non-ischaemic CS compared with patients with CS complicating AMI.

Methods

In this retrospective observational study, we assessed haemodynamic stabilization and outcome in patients with CS treated by pVAD. Between 2015 and 2018, 106 patients were included who were in CS and received an Impella device. Patients were classified in two groups: AMI-related CS group and non-ischaemic CS group. The definition of non-ischaemic CS included patients with CS related to acute decompensation of chronic heart failure and patients with CS of acute non-ischaemic origin.

CS was defined as a systolic blood pressure $<$90 mmHg or the need for continuous infusion of inotropes or vasopressors to maintain a systolic blood pressure $>$90 mmHg with clinical and laboratory evidence of end-organ damage (oliguria, altered mental state, cool extremities).[4] Only patients with elevated baseline lactate $>$2 mmol/L were included who were classified into shock stage C or worse according to the Society for Cardiovascular Angiography and Interventions (SCAI) shock classification.[14]

The duration of mechanical support was individual and was dependent on clinical, haemodynamic and biological parameters. All data were collected from patient charts and medical records until primary discharge including laboratory parameters, complications and therapy strategies. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and was approved by the University of Düsseldorf Committee on Human Research (study number 5467R). All participants who survived gave written informed consent for the use of their anonymous medical data relating to the defined hospitalization.

Haemodynamic stabilization was assessed by measurements of lactate levels, systemic blood pressures and the amount of applied catecholamines at admission to the intensive care unit (ICU), during and after Impella support. The amount of applied catecholamines was calculated by using the vasoactive-inotropic score [dobutamine (μg/kg/min) + 100 × epinephrine (μg/kg/min) + 100 × norepinephrine (μg/kg/min)].

Safety end points included severe or life-threatening bleeding and moderate bleeding during the hospital stay, as assessed according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) and peripheral ischaemic vascular complications requiring surgical or interventional therapy.[15]

Statistical analysis was performed using SPSS Statistics, Version 24 (IBM, Armonk, NY, USA) and GraphPad Prism® Version 7.0 (GraphPad Software, San Diego, CA, USA).

Propensity score matching was used to compare the groups in terms of survival and to reduce confounding factors due to imbalances in baseline characteristics. We used these variables as potential cofounders that might have impact on the outcome of CS: age, baseline left ventricular ejection fraction (LVEF), glomerular filtration rate (GFR), prior cardiac arrest, baseline lactate, the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Sequential Organ Failure Assessment (SOFA) score. We created 1:1 matched groups using the nearest neighbour matching without replacement with a calliper of 0.10.

Categorical variables are reported as absolute values and percentages, whereas continuous data are expressed as median with interquartile range. Categorical data were

compared by chi-square test or Fisher's exact test. Continuous variables were tested for normal distribution with the D'Agostino and Pearson omnibus normality test. In case of a normal distribution, Student's unpaired *t*-test was performed to compare the means between the two groups. Continuous variables not following a normal distribution were compared using the Mann–Whitney *U* test. We used pairwise deletion respectively listwise deletion methods to eliminate missing data. A one-way repeated measures analysis of variance was used to compare the multiple time points of blood pressure values, lactate level and used catecholamines.

Results

We screened 106 patients receiving Impella support for CS at our institution. In 36 patients, CS was related to acute decompensation of chronic heart failure or acute non-ischaemic origin (non-ischaemic CS); in 70 patients, CS was related to AMI (AMI group). In the non-ischaemic group, median age was lower compared with the AMI group [62 (50.8, 70.8) years vs. 68 (58.0, 75.5) years, $P = 0.007$], and the proportion of patients with severely reduced LVEF was higher (94% vs. 79%, $P = 0.035$) (*Table 1*). Atrial fibrillation was more frequent in

Table 1 Baseline characteristics of the full cohort and propensity score matched study population

Full cohort	Non-ischaemic CS ($n = 36$)	AMI-related CS ($n = 70$)	P
Age (years)	62 (50.8, 70.8)	68 (58.0, 75.5)	0.007*
Male, *n* (%)	27 (75.0)	51 (72.9)	0.813
Prior cardiac arrest, *n* (%)	10 (27.8)	23 (32.9)	0.593
Severely reduced LV function, *n* (%)	34 (94.4)	55 (78.9)	0.035*
PAD, *n* (%)	4 (11.1)	17 (24.3)	0.107
Atrial fibrillation, *n* (%)	22 (61.1)	25 (35.7)	0.013*
Diabetes mellitus, *n* (%)	8 (22.2)	20 (28.6)	0.639
COPD, *n* (%)	4 (11.1)	12 (17.1)	0.411
Chronic renal failure, *n* (%)	18 (50.0)	25 (35.7)	0.156
sPAP (mmHg)	33 (27, 46)	38 (26.8, 54.0)	0.498
TAPSE (mm)	15 (14.0, 21.8)	17 (14.5, 20.5)	0.906
GFR (mg/dL)	45 (27, 57)	60 (44, 78)	0.022*
Lactate dehydrogenase (U/L)	401 (321, 938)	510 (348, 854)	0.772
Bilirubin (mg/dL)	1.0 (0.4, 1.4)	0.7 (0.3, 1.1)	0.071
Haemoglobin (g/dL)	13.0 (11.2, 14.7)	13.1 (10.5, 14.4)	0.432
Baseline lactate (mg/dL)	3.8 (2.6, 5.9)	3.1 (2.6, 5.5)	0.527
C-reactive protein (mg/dL)	2.8 (0.8, 6.6)	2.5 (0.4, 7.0)	0.735
SCAI shock classification C/D/E, *n*	8/28/0	10/60/0	0.303
SOFA score	6 (4, 9)	6 (4, 8)	0.467
APACHE II score	17.0 (13.8, 21.3)	21 (15.0, 25.0)	0.103
Baseline vasoactive-inotropic score	30.8 (6.6, 50.2)	38.4 (19.2, 65.5)	0.105
PS-matched cohort	Non-ischaemic CS($n = 31$)	AMI-related CS($n = 31$)	*P*
Age (years)	63 (53, 71)	65 (57, 73)	0.311
Male n, (%)	24 (77.4)	23 (74.2)	0.767
Prior cardiac arrest, *n* (%)	8 (25.8)	10 (32.3)	0.578
Severely reduced LV function, *n* (%)	29 (93.5)	27 (87.1)	0.390
PAD, *n* (%)	3 (9.7)	5 (16.1)	0.449
Atrial fibrillation, *n* (%)	18 (58.1)	11 (35.5)	0.075
Diabetes mellitus, *n* (%)	8 (25.8)	10 (32.3)	0.576
COPD, *n* (%)	4 (12.9)	3 (9.7)	0.688
Chronic renal failure, *n* (%)	14 (45.2)	12 (38.7)	0.607
sPAP (mmHg)	31 (28, 46)	32 (23, 47)	0.675
TAPSE (mm)	18.0 (14.0, 22.3)	17.0 (14.3, 19.0)	0.561
GFR (mg/dL)	46 (24, 57)	50 (34, 63)	0.709
Lactate dehydrogenase (U/L)	393 (302, 867)	422 (282, 919)	0.211
Bilirubin (mg/dL)	0.9 (0.4, 1.2)	0.4 (0.3, 0,9)	0.082
Haemoglobin (g/dL)	13.0 (10.7, 14.8)	12.4 (9.9, 15.6)	0.500
Baseline lactate (mg/dL)	3.8 (2.8, 5.9)	3.8 (2.6, 6.5)	0.848
C-reactive protein (mg/dL)	2.3 (0.5, 6.6)	2.7 (0.3, 9.7)	0.737
SCAI shock classification C/D/E, *n*	5/26/0	4/27/0	0.718
SOFA score	6 (4, 9)	6 (4, 9)	0.662
APACHE II score	17.0 (13.5, 21.0)	21.0 (14.0, 24.0)	0.375
Baseline vasoactive-inotropic score	32.0 (11.1, 47.0)	35.2 (18.1, 67.0)	0.427

Categorical variables are reported as absolute values and percentages, whereas continuous data are expressed as median with interquartile range. Values are *n* (%) or median (interquartile range).
APACHE II, Acute Physiology Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LV, left ventricular; PAD, peripheral arterial disease; SCAI, Society for Cardiovascular Angiography and Interventions; SOFA, Sequential Organ Failure Assessment; sPAP, systolic pulmonary artery pressure; TAPSE, Tricuspid Annular Plane Systolic Excursion.
*$P \leq 0.05$ between the groups.

DOI: 10.1002/ehf2.13546

the non-ischaemic group compared with the AMI group (61% vs. 36%, $P = 0.013$), and the patients had worse renal function (GFR) [45 (27, 57) mL/min vs. 60 (44, 78) mL/min] (*Table 1*).

Propensity score matching yielded 31 patients with non-ischaemic CS and 31 patients with AMI-related CS (*Supplemental Figure 1*). In this propensity score-matched cohort, there was no difference in baseline laboratory values or comorbidities between the two groups (*Table 1*). The median age in the non-ischaemic group was 63 (53, 71) years, which was similar to the AMI group, 65 (57, 73) year ($P = 0.311$). In the 31 patients with non-ischaemic origin, CS was based on decompensated dilated cardiomyopathy or acute myocarditis in 20 patients (64.5%) and ischaemic cardiomyopathy in 11 patients (35.5%). The overall resuscitation rate was 25.8% and 32.3% ($P = 0.578$). In both groups, patients were severely ill, as reflected in the APACHE II score [17.0 (13.5, 21.0) vs. 21.0 (14.0, 24.0), $P = 0.375$] and the SOFA score [6 (4, 9) vs. 6 (4, 9), $P = 0.662$]. In 28 out of 31 (90.3%) patients, the Impella CP device was used; in three out of 31 (9.7%) patients, the Impella 2.5 device (similar in both groups).

In both groups, implantation of Impella went along with haemodynamic stabilization, reduction of catecholamines and normalization of lactate levels (*Figure 1*).

Systolic blood pressure increased continuously from 91 (80, 101) mmHg at baseline to 100 (100, 120) mmHg at Day 7 in the non-ischaemic CS group ($P = 0.001$) and from 89 (80, 100) mmHg at baseline to 112 (100, 128) mmHg at Day 7 in the AMI-related CS group ($P = 0.001$) (*Figure 1A*).

Diastolic blood pressure increased in the non-ischaemic CS group during 24-h pVAD support from 45 (40, 60) mmHg at baseline to 70 (60, 80) mmHg ($P = 0.002$ vs. baseline) and then decreased again to 59 (50, 60) mmHg at Day 7 ($P = 0.005$ vs. 24 h). In the AMI-related group, diastolic blood pressure did not change with values of 50 (40, 60) mmHg at baseline, 65 (55, 75) mmHg during 24-h pVAD support ($P = 0.087$ vs. baseline) and 60 (50, 68) mmHg at Day 7 ($P = 0.5334$ vs. 24 h) (*Figure 1A*).

The need of catecholamines (calculated as vasoactive-inotropic score) decreased from 32.0 (11.1, 47.0) at baseline to 5.3 (0, 16.1) at Day 7 in the non-ischaemic group ($P = 0.001$) and from 35.2 (18.1, 67.0) to 0 (0, 0) at Day 7 in the AMI-related CS group ($P = 0.001$) (*Figure 1B*). The need of catecholamine support was longer in the non-ischaemic group compared with the AMI-related CS group: Vasoactive-inotropic score in the non-ischaemic group at 48 h was 24.2 (8.1, 112.3) vs. 8.4 (0, 22.3) in the AMI group ($P = 0.007$), 14.8 (3.6, 28.9) vs. 0 (0, 9.8) ($P = 0.002$) at 72-h pVAD support and 5.3 (0, 16.1) vs. 0 (0, 0) ($P = 0.037$) after 7d.

Lactate level decreased continuously from 3.8 (2.8, 5.9) mmol/L at baseline to 1.0 (0.8, 2.1) mmol/L at Day 7 ($P = 0.001$) in the non-ischaemic CS group and from 3.8 (2.6, 6.5) mmol/L to 1.2 (1.0, 2.0) mmol/L in the AMI-related group ($P = 0.001$) (*Figure 1C*).

Post-procedural outcome and survival of the propensity score-matched cohort did not differ among the groups (*Table 2* and *Figures 2* and *3*). In the non-ischaemic CS group, four patients died during Impella support, 19 patients were successfully weaned from device, and eight patients were upgraded to veno-arterial extracorporeal membrane oxygenation (VA-ECMO) or to long-term MCS (*Figure 2*). Two of these upgraded nine patients received heart transplantation. In the AMI group, eight patients died during Impella support; in 15 patients, the device could be successfully weaned, and eight patients were upgraded to VA-ECMO or long-term MCS ($P = 0.406$).

In the full cohort, 20 out of 36 patients survived (55.5%) the first 30 days in the non-ischaemic CS group, and 32 out of 70 patients (45.7%) in the AMI-related CS group ($P = 0.337$). Ninety-day survival was 44.4% (16 patients survived) in the non-ischaemic CS group, and 40% (28 patients survived) in the AMI-related CS group ($P = 0.660$). Kaplan–Meier curves and the log-rank (Mantel–Cox) test confirmed similar 90-day survival in both groups ($P = 0.190$) (*Figure 3A*).

In the propensity-matched cohort, 17 out of 31 patients survived (54.8%) after 30 days in the non-ischaemic CS group, and 16 out of 31 patients (51.5%) in the AMI-related CS group ($P = 0.799$). Ninety-day survival was 48.4% (15 patients survived) in the non-ischaemic CS group, and 45.2% (14 patients survived) in the AMI-related CS group ($P = 0.799$). Kaplan–Meier curves and the log-rank (Mantel–Cox) test confirmed similar 90-day survival in both groups ($P = 0.471$) (*Figure 3B*).

There were no differences between the non-ischaemic CS group and the AMI group regarding rates of moderate or life-threatening bleedings and ischaemic peripheral vascular complications (*Table 2*). The overall ICU length of stay [10 (4; 15) d vs. 7 (3; 12) d, $P = 0.115$] as well as the hospital length of stay [24 (12; 35) d vs. 12 (4; 29) d, $P = 0.415$] did not differ in the non-ischaemic CS group as compared with the AMI group (*Table 2*).

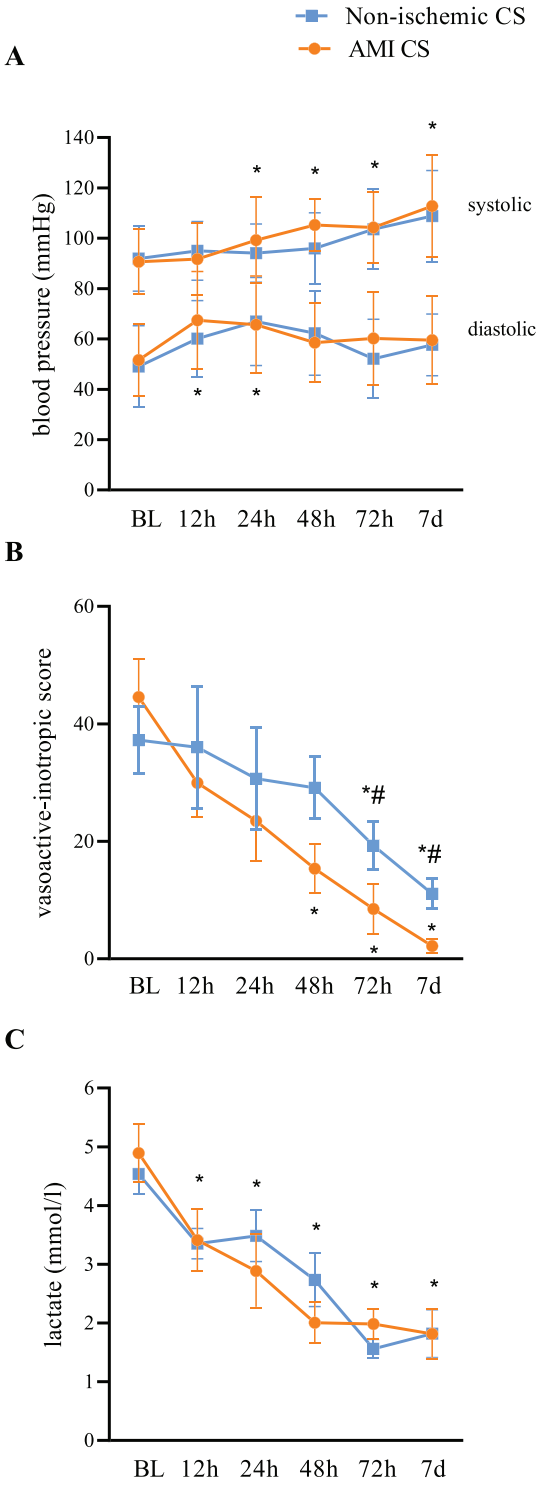
Discussion

We here demonstrate using a propensity-adjusted analysis that pVAD support can be used for haemodynamic stabilization in both groups, patients with non-ischaemic CS and patients with AMI-related CS. Patients with failed myocardial recovery could be bridged to long-term mechanical support or even heart transplantation. Altogether, survival of patients supported by pVAD did not differ between non-ischaemic CS and AMI-related CS patients.

Patient characteristics in non-ischaemic CS

Patients with non-ischaemic CS differ profoundly from patients with AMI-related CS. Many patients suffer from acute

Figure 1 Haemodynamic stabilization of patients with non-ischaemic CS on pVAD support compared with patients with AMI-related CS on pVAD supportComparison of propensity score-matched groups (each n = 31). (A) Stabilization of systolic and diastolic blood pressure values. (B) Decreased need of catecholamines assessed by vasoactive-inotropic score. (C) Normalization of lactate levels during pVAD support. *$P < 0.05$ compared to baseline, **$P < 0.05$ between the adjusted groups.AMI, acute myocardial infarction; CS, cardiogenic shock, pVAD, percutaneous ventricular assist device.



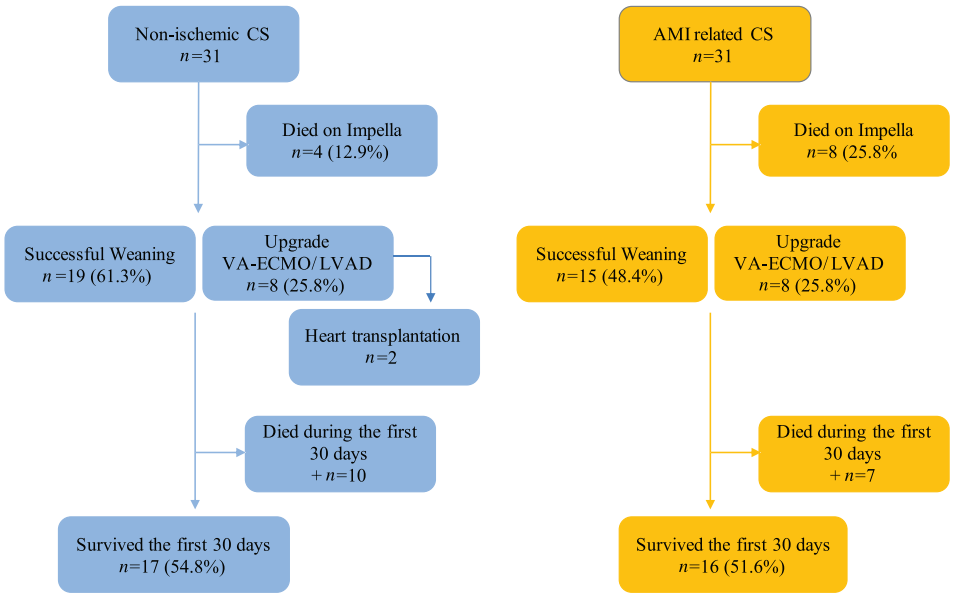
DOI: 10.1002/ehf2.13546

Table 2 Clinical outcome of the propensity score matched study population

	Non-ischaemic CS(n = 31)	AMI-related CS(n = 31)	p
Length of support (d)	3 (2, 5)	2 (1, 4)	0.075
Mechanical ventilated, *n* (%)	23 (74.1)	25 (80.6)	0.544
Peripheral ischaemic complications requiring intervention in hospital, *n* (%)	1 (3.3)	2 (6.5)	0.554
Moderate bleeding in hospital, *n* (%)	3 (9.7)	4 (12.9)	0.688
Life-threatening or severe bleeding in hospital, *n* (%)	2 (6.5)	1 (3.2)	0.554
Length of mechanical ventilation (h)	175 (15, 355)	195 (43, 456)	0.370
Renal replacement therapy, *n* (%)	17 (54.8)	13 (41.9)	0.309
Hospitalization (d)	24 (12, 35)	12 (4, 29)	0.415
ICU length of stay (d)	10 (4, 15)	7 (3, 12)	0.115

Categorical variables are reported as absolute values and percentages, whereas continuous data are expressed as median with interquartile range. Values are *n* (%) or median (interquartile range).
ICU, intensive care unit.

Figure 2 Outcome of patients with non-ischaemic CS supported by Impella compared with patients with AMI-related CS and Impella support.Comparison of propensity score-matched groups (each *n* = 31).AMI, acute myocardial infarction; CS, cardiogenic shock; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; LVAD, left ventricular assist device.



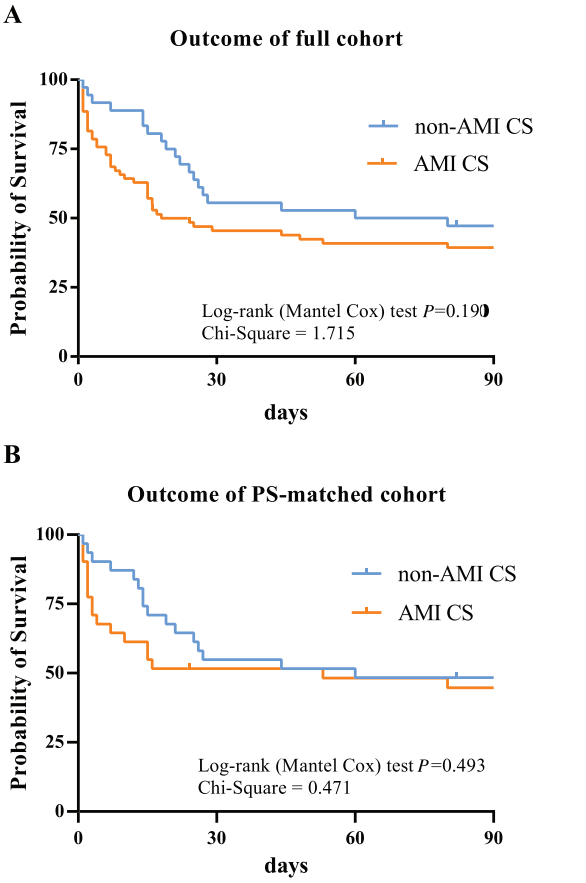
worsening of long-standing ventricular dysfunction that enters into CS or from acute fulminant myocarditis. Thus, baseline LVEF is usually worse than in patients with AMI-related CS. In general, these patients were younger and have less cardiovascular risk factors.[9,10] Propensity score matching allowed us to reduce these confounding factors in the present study and to reliably compare the use of pVAD in patients with a non-ischaemic and an AMI-related CS form.

Haemodynamic stabilization of patients with non-ischaemic CS

Despite different underlying pathology between patients with non-ischaemic CS and AMI-related CS, the haemodynamic effects leading to shock cycle did not differ. Impaired cardiac output and progressive diastolic dysfunction raise ventricular end-diastolic pressures, which reduce coronary perfusion pressure, myocardial contractility and stroke volume.[16] The tissue ischaemia triggers the release of inflammatory mediators that further impair tissue metabolism, cause systemic vasodilation and aggravate the haemodynamic and myocardial collapse.[16,17] This maladaptive cycle may be developed acute, as occurs in AMI-CS or in patients with fulminant myocarditis, or superimposed on chronic neurohormonal activations that accompany patients with long-standing ventricular dysfunction.

Catecholamines are commonly used in the treatment of CS, as they have a positive inotropic effect that provides support for the failing myocardium. Patients with non-ischaemic

Figure 3 Survival of non-ischaemic CS patients supported by Impella compared with AMI CS patients and Impella support(A) Comparison of full cohort and (B) propensity score-matched groups (each n = 31). Kaplan–Meier survival curves stratified by non-ischaemic or AMI-related CS for 90-day survival. 90-day survival did not differ among the groups (P = 0.593).AMI, acute myocardial infarction; CS, cardiogenic shock.



CS are less likely to improve with conventional medical interventions alone because their limited cardiac reserve makes them less responsive to inotropes compared with the AMI patient population.[18] In addition, inotropes increase oxygen demand and may thereby negatively impact mortality in this setting.[13]

Previous studies described the use of intra-aortic balloon pump (IABP) for haemodynamic stabilization of patients with non-ischaemic CS.[19,20] In an analysis of the National Inpatient Sample database from 2010 to 2014, the use of IABP was associated with lower mortality when compared with pVAD use.[21] This observation has to be interpreted with caution given the superior haemodynamic effects of pVADs over IABP and the inability of IABP to improve patient cardiac output.[6,22] In fact, the observational study was limited by heterogeneity in the patient populations with sicker patients being present in the pVAD group.

The use of pVAD as the Impella axial flow pump provides direct unloading of the left ventricular and augmentation of cardiac output and mean arterial pressure, which improve end-organ perfusion.[6–8] Directly unloading of the left ventricle decreases ventricular wall stress, external work and myocardial oxygen consumption while enhancing myocardial recovery.[6,22] Therefore, irrespective of the setting of CS, and even without the possibility of quick intervention that could promote recovery as in patients with AMI, left ventricular unloading using a pVAD could support the failing myocardium and therefore enhance its chances to recover and stabilize.[6,23] In our study, pVAD could successfully weaned after recovery of myocardial function in 59% of the patients with non-ischaemic CS. When recovery fails, the use of pVAD provides the circulatory support that enables the care team to make decisions as to the patient's candidacy for durable support devices or transplantation,[24] as this was performed in 18.8% of the patients with non-ischaemic CS in the present study. In case of a bridge to transplant concept, it might be preferable to upgrade to axillary pVAD because they enable patient mobility and a more stable and durable device position for prolonged haemodynamic support.[25,26]

Prognosis of patients with non-ischaemic CS

In general, mortality is higher in patients with non-ischaemic CS compared with patients with AMI-related shock.[10] The reasons for this observation might be multifactorial as patients with non-ischaemic CS were more likely to present in a worse clinical condition (unfavourable haemodynamics and more mechanical ventilation)[10] and the lack of evidence-based treatments for this group.[4] For AMI-related CS, the use of an Impella device in a retrospective analysis was not associated with lower mortality compared with matched patients treated with an IABP or medical therapy.[27,28] The prospective randomized DanGer shock trial is ongoing and compares the outcome of patients treated by Impella vs. medical therapy.[29] Up to now, no randomized study exists that investigates the outcome of patients with non-ischaemic CS treated by Impella vs. medical therapy.

In our study, adjusted survival rate of CS patients treated by pVAD did not differ between the groups. Our findings are in line with a previous unadjusted study that also demonstrated similar survival rates between patients with pVAD support for non-ischaemic vs. AMI-related CS.[30]

The present study is limited by the retrospective study design and the inherent limitations of such an approach. Including all patients who are alive at a respective time point in the longitudinal analysis of blood pressure, catecholamines and lactate levels might have generated a relevant survivor-ship bias. In addition, we did not capture complete haemodynamic data in this patient population that could underline the mechanism of the observed effects. The form of

non-ischaemic CS is more likely to require a biventricular haemodynamic support compared with AMI-CS.[31] Thus, early identification of right ventricular failure using pulmonary artery catheter (PAC)-derived haemodynamic monitoring might be particularly important in this form of CS to individualize catecholamine und volume therapy and to identify early the need of MCS upgrade.[32,33]

Conclusions

We here demonstrate that in patients with non-ischaemic CS, pVAD support can be used for haemodynamic stabilization and bridging to recovery or for bridging to long-term mechanical support and heart transplantation.

Acknowledgement

Open Access funding enabled and organized by Projekt DEAL.

Conflicts of interest

There are no known conflicts of interest associated with this publication.

Author contributions

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. We screened 106 patients receiving Impella support for CS. In 36 patients, CS was related to acute decompensation of chronic heart failure or acute non-ischemic origin (non-ischemic CS), in 70 patients CS was related to AMI (AMI CS group). Propensity score matching was used to compare the groups in terms of survival and to reduce confounding factors due to imbalances in baseline characteristics (age, baseline left ventricular ejection fraction (LVEF), glomerular filtration rate (GFR) and presence of atrial fibrillation). Propensity score matching yielded 31 patients with non-ischemic CS and 31 patients with AMI-related CS.

References

1. Schumann J, Henrich EC, Strobl H, Prondzinsky R, Weiche S, Thiele H, Werdan K, Frantz S, Unverzagt S. Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome. *Cochrane Database Syst Rev* 2018; **1**: CD009669.
2. Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, Kociol RD, Lewis EF, Mehra MR, Pagani FD, Raval AN, Ward C, American Heart Association Council on Clinical C, Council on Cardiovascular Disease in the Y, Council on Cardiovascular S, Anesthesia. Evaluation and management of right-sided heart failure: a scientific statement from the American Heart Association. *Circulation* 2018; **137**: e578–e622.
3. Thiele H, Zeymer U, Thelemann N, Neumann FJ, Hausleiter J, Abdel-Wahab M, Meyer-Saraei R, Fuernau G, Eitel I, Hambrecht R, Bohm M, Werdan K, Felix SB, Hennersdorf M, Schneider S, Ouarrak T, Desch S, de Waha-Thiele S, Investigators IIT. Intraaortic balloon pump in cardiogenic shock complicating acute myocardial infarction: long-term 6-year outcome of the randomized IABP-SHOCK II Trial. *Circulation* 2019; **139**: 395–403.
4. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med* 1999; **341**: 625–634.
5. Tehrani BN, Truesdell AG, Sherwood MW, Desai S, Tran HA, Epps KC, Singh R, Psotka M, Shah P, Cooper LB, Rosner C, Raja A, Barnett SD, Saulino P, deFilippi CR, Gurbel PA, Murphy CE, O'Connor CM. Standardized team-based care for cardiogenic shock. *J Am Coll Cardiol* 2019; **73**: 1659–1669.
6. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESCSD. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
7. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017; **70**: 776–803.
8. Burkhoff D, Sayer G, Doshi D, Uriel N. Hemodynamics of mechanical circulatory support. *J Am Coll Cardiol* 2015; **66**: 2663–2674.
9. Ouweneel DM, Henriques JP. Percutaneous cardiac support devices for

cardiogenic shock: current indications and recommendations. *Heart* 2012; **98**: 1246–1254.
10. Seyfarth M, Sibbing D, Bauer I, Frohlich G, Bott-Flugel L, Byrne R, Dirschinger J, Kastrati A, Schomig A. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J Am Coll Cardiol* 2008; **52**: 1584–1588.
11. Shah M, Patnaik S, Patel B, Ram P, Garg L, Agarwal M, Agrawal S, Arora S, Patel N, Wald J, Jorde UP. Trends in mechanical circulatory support use and hospital mortality among patients with acute myocardial infarction and non-infarction related cardiogenic shock in the United States. *Clin Res Cardiol* 2018; **107**: 287–303.
12. Schrage B, Weimann J, Dabboura S, Yan I, Hilal R, Becher PM, Seiffert M, Bernhardt AM, Kluge S, Reichenspurner H, Blankenberg S, Westermann D. Patient Characteristics, Treatment and Outcome in Non-Ischemic vs. Ischemic Cardiogenic Shock. *J Clin Med* 2020; **9**: 931.
13. Jentzer JC, van Diepen S, Barsness GW, Henry TD, Menon V, Rihal CS, Naidu SS, Baran DA. Cardiogenic shock classification to predict mortality in the cardiac intensive care unit. *J Am Coll Cardiol* 2019; **74**: 2117–2128.
14. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Rev Esp Cardiol (Engl Ed)* 2016; **69**: 1167.
15. Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, Hollenberg SM, Kapur NK, O'Neill W, Ornato JP, Stelling K, Thiele H, van Diepen S, Naidu SS. SCAI clinical expert consensus statement on the classification of cardiogenic shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. *Catheter Cardiovasc Interv* 2019; **94**: 29–37.
16. Investigators G. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993; **329**: 673–682.
17. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK, Thiele H, Washam JB, Cohen MG. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation* 2017; **136**: e232–e268.
18. Kohsaka S, Menon V, Lowe AM, Lange M, Dzavik V, Sleeper LA, Hochman JS, Investigators S. Systemic inflammatory response syndrome after acute myocardial infarction complicated by cardiogenic shock. *Arch Intern Med* 2005; **165**: 1643–1650.
19. Samuels LE, Kaufman MS, Thomas MP, Holmes EC, Brockman SK, Wechsler AS. Pharmacological criteria for ventricular assist device insertion following postcardiotomy shock: experience with the Abiomed BVS system. *J Card Surg* 1999; **14**: 288–293.
20. den Uil CA, Galli G, Jewbali LS, Caliskan K, Manintveld OC, Brugts JJ, van Mieghem NM, Lenzen MJ, Boersma E, Constantinescu AA. First-line support by intra-aortic balloon pump in non-ischaemic cardiogenic shock in the era of modern ventricular assist devices. *Cardiology* 2017; **138**: 1–8.
21. Lauten P, Rademacher W, Goebel B, Kretzschmar D, Figulla HR, Lauten A, Ferrari M. Intra-aortic counterpulsation for hemodynamic support in patients with acute ischemic versus non-ischemic heart failure. *J Invasive Cardiol* 2012; **24**: 583–588.
22. Ogunbayo GO, Ha LD, Ahmad Q, Misumida N, Elbadawi A, Olorunfemi O, Kolodziej A, Messerli AW, Abdel-Latif A, Elayi CS, Guglin M. In-hospital outcomes of percutaneous ventricular assist devices versus intra-aortic balloon pumps in non-ischemia related cardiogenic shock. *Heart Lung* 2018; **47**: 392–397.
23. Burkhoff D, Naidu SS. The science behind percutaneous hemodynamic support: a review and comparison of support strategies. *Catheter Cardiovasc Interv* 2012; **80**: 816–829.
24. de Souza CF, de Souza BF, De Lima VC, De Camargo Carvalho AC. Percutaneous mechanical assistance for the failing heart. *J Interv Cardiol* 2010; **23**: 195–202.
25. Briceno N, Kapur NK, Perera D. Percutaneous mechanical circulatory support: current concepts and future directions. *Heart* 2016; **102**: 1494–1507.
26. Hall SA, Uriel N, Carey SA, Edens M, Gong G, Esposito M, O'Kelly R, Annamalai S, Aghili N, Adatya S, Kapur NK. Use of a percutaneous temporary circulatory support device as a bridge to decision during acute decompensation of advanced heart failure. *J Heart Lung Transplant* 2018; **37**: 100–106.
27. Esposito ML, Jablonski J, Kras A, Krasney S, Kapur NK. Maximum level of mobility with axillary deployment of the Impella 5.0 is associated with improved survival. *Int J Artif Organs* 2018; **41**: 236–239.
28. Schrage B, Ibrahim K, Loehn T, Werner N, Sinning JM, Pappalardo F, Pieri M, Skurk C, Lauten A, Landmesser U, Westenfeld R, Horn P, Pauschinger M, Eckner D, Twerenbold R, Nordbeck P, Salinger T, Abel P, Empen K, Busch MC, Felix SB, Sieweke JT, Moller JE, Pareek N, Hill J, MacCarthy P, Bergmann MW, Henriques JPS, Mobius-Winkler S, Schulze PC, Ouarrak T, Zeymer U, Schneider S, Blankenberg S, Thiele H, Schafer A, Westermann D. Impella support for acute myocardial infarction complicated by Cardiogenic Shock. *Circulation* 2019; **139**: 1249–1258.
29. Thiele H, Jobs A, Ouweneel DM, Henriques JPS, Seyfarth M, Desch S, Eitel I, Poss J, Fuernau G, de Waha S. Percutaneous short-term active mechanical support devices in cardiogenic shock: a systematic review and collaborative meta-analysis of randomized trials. *Eur Heart J* 2017; **38**: 3523–3531.
30. Udesen NJ, Moller JE, Lindholm MG, Eiskjaer H, Schafer A, Werner N, Holmvang L, Terkelsen CJ, Jensen LO, Junker A, Schmidt H, Wachtell K, Thiele H, Engstrom T, Hassager C, DanGer Shock Investigators. Rationale and design of DanGer shock: Danish-German cardiogenic shock trial. *Am Heart J* 2019; **214**: 60–68.
31. Maniuc O, Salinger T, Anders F, Muntze J, Liu D, Hu K, Ertl G, Frantz S, Nordbeck P. Impella CP use in patients with non-ischaemic cardiogenic shock. *ESC Heart Fail* 2019; **6**: 863–866.
32. Lim HS, Howell N. Cardiogenic shock due to end-stage heart failure and acute myocardial infarction: characteristics and outcome of temporary mechanical circulatory support. *Shock* 2018; **50**: 167–172.
33. Garan AR, Kanwar M, Thayer KL, Whitehead E, Zweck E, Hernandez-Montfort J, Mahr C, Haywood JL, Harwani NM, Wencker D, Sinha SS, Vorovich E, Abraham J, O'Neill W, Burkhoff D, Kapur NK. Complete hemodynamic profiling with pulmonary artery catheters in cardiogenic shock is associated with lower in-hospital mortality. *JACC Heart Fail* 2020; **8**: 903–913.