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Mechanical Circulatory Support in Refractory Cardiogenic Shock due to Influenza Virus-Related Myocarditis

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Abstract

Background:

In patients with influenza-related myocarditis complicated by refractory cardiogenic shock (rCS) there is scarce evidence for mechanical circulatory support (MCS). We

sought to investigate the impact of MCS using combined veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and micro-axial flow pumps in rCS complicating influenza-related myocarditis.

Methods:

This is a prospective and observational analysis from the single center Hannover Cardiac Unloading REgistry (HACURE) from two recent epidemic influenza seasons. We analyzed patients with verified influenza virus infection-associated myocarditis complicated by rCS admitted to our ICU on MCS. Subsequently, we performed a propensity score matched analysis to patients with acute myocardial infarction complicated by rCS and non-ischemic cardiomyopathy related rCS.

Results:

We describe a series of seven patients with rCS complicating influenza-related myocarditis (mean age: 56±10 years, 58% males, Influenza A/B n=2/5). No patient had been vaccinated prior to the influenza season. MCS was provided using combined VA-ECMO and Impella. In two patients with out-of-hospital cardiac arrest VA-ECMO had been implanted for extracorporeal-cardiopulmonary resuscitation. All patients died within 18 days after hospital admission. By propensity score-based comparison to patients with myocardial infarction- or non-ischemic cardiomyopathy related rCS with combined MCS, 30-day mortality was significantly higher in influenza-related rCS.

Conclusion:

Despite initial stabilization with combined MCS in patients with rCS complicating influenza-related myocarditis, the detrimental course of shock could not be stopped

and all patients died. Potentially, influenza virus infection critically affects other organs besides the heart leading to irreversible end-organ damage, which MCS cannot compensate and, therefore, resulted in a devastating outcome.

Keywords: Cardiogenic Shock, left ventricular unloading, extracorporeal membrane oxygenation, influenza, myocarditis

Introduction

Influenza virus commonly causes seasonal respiratory infections and periodically leads to epidemics and pandemics. Respiratory failure and pneumonia are common respiratory complications, which are associated with impaired survival.[1] The myocardium is affected in about 10% of cases starting usually between day 4 and 7 after symptom onset.[1,2] Myocardial manifestations are underdiagnosed due to variability, non-specificity and onset of symptoms.[3] Definite acute myocarditis was diagnosed in one-third of 33 cases with unexpected death without prior suspicion of myocardial involvement during the Asian influenza pandemic of 1957.[4] Influenza-related myocarditis presents in a variable manner from subclinical to fulminant myocarditis with or without overt cardiogenic shock (CS), which can ultimately result in cardiac failure leading to death.[1] CS complicating influenza-related myocarditis is scarce. In their systematic review of 184 cases of myocarditis complicating influenza infection, Hékimian and co-workers reported 48 CS cases treated with mechanical circulatory support (MCS).[5]

Catecholamines are recommended by guidelines to stabilize blood pressure in patients with CS, but contribute to secondary multi-organ failure due to systemic vasoconstriction.[6,7] In refractory CS (rCS), percutaneous MCS are considered as optional treatment for patients unresponsive to fluid load and vasopressors.[7] In this analysis we sought to investigate the efficacy of combined MCS with veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and Impella micro-axial flow pumps in rCS complicating influenza virus-related myocarditis.

Methods

Study design and participants

Our analysis was performed in accordance with the Declaration of Helsinki and has been approved by the local ethics committee (#3566-2017). In the analysis, all patients with rCS complicating influenza who were treated with MCS using VA-ECMO and Impella micro-axial flow-pumps admitted to the Department of Cardiology at Hannover Medical School during two recent influenza epidemic seasons (2013 and 2018) were analyzed. Of 400 consecutive patients treated with micro-axial flow-pumps included in a local database, the Hannover Cardiac Unloading REgistry (HACURE) [8], those who had received combined MCS support with VA-ECMO and Impella (also known as ECMELLA concept) from 01/2013 to 06/2018 for rCS due to myocardial infarction (AMI-rCS group) or non-ischemic cardiomyopathy (DCM-rCS group) were considered for propensity score (PS) matching as described in Figure 1. Shock severity score at admission (Survival After Veno-arterial ECMO score (SAVE) [9]) demographic data, laboratory data and complications during in-hospital stay were registered.

Patient treatment and definitions

Influenza infection was confirmed by PCR-analysis of pharyngeal swab tests. rCS was defined as persistence or deterioration of hypotension and/or end organ hypoperfusion (i.e., elevated lactate levels (≥ 2.5 mmol/l) plus ≥1 clinical sign of hypoperfusion (e.g. clammy skin, tachycardia, altered mental status, oliguria (<30mL/h), pulmonary edema) despite catecholamine administration (weight-adjusted maximal dosing of ≥2 catecholamines) and appropriate standard shock therapy, according to group D and E of the Society for Cardiovascular Angiography & Interventions (SCAI) clinical expert consensus statement.[10,11] Patients were

treated according to current guidelines [7] and a local treatment algorithm (HaCRA) for CS and cardiac arrest.[12] Detailed patient treatment is provided in Figure 2 and in the supplement.

Statistical analysis

Categorical parameters are given as n (%). Normally distributed metric variables are presented as mean values ± standard deviation (SD), non-normally as median and interquartile ranges (IQR). Comparison between time points was performed with ANOVA and Mann-Whitney U test as nonparametric test followed by correction for multiple comparison by Bonferroni test or Dunn`s test. Statistical analyses for comparison between PS-matched groups of metric parameters were performed using unpaired t-tests as parametric tests and Mann-Whitney tests as non-parametric tests. Chi-square test was applied to compare nominally scaled parameters. 30-day survival was calculated using Kaplan-Meier curves and performing Log-Rank comparison between the groups. Cox regressions analysis was performed to calculate hazard ratios (HR) with 95% confidence intervals (CI). Reported P values are two-sided, with $p<0.05$ considered statistically significant. Data were analyzed using GraphPad Prism 7.04 (GraphPad Software, San Diego, CA, USA), R program 3.3.3, and SPSS 25 (IBM SPSS Statistics 25). Detailed PS matching is presented in the supplement.

Results

Patient characteristics

A total of seven Caucasian patients without prior influenza vaccination and rCS complicating influenza infection treated with MCS were analyzed (mean age: 56±10 years). PCR analysis confirmed influenza B in five and influenza A in two patients (#4&7). In four patients (#1-4), left-ventricular endomyocardial biopsy had been performed. Histological examination revealed interstitial lymphocytic infiltration and focal myocyte necrosis (Figure 3). Myocarditis was clinically diagnosed based on symptoms, cardiac enzyme elevation, and echocardiographic findings [13] in the other 3 patients. A median SAVE-Score of -11 [-12;-8] indicated an estimated mortality of 82% even when supported on VA-ECMO. Between January 1st 2013 and June 30th 2018 87 patients with myocardial infarction (n=49)- or non-ischemic cardiomyopathy- (n=38) related rCS had been treated with ECMELLA at our institution. After 1:2 propensity score matching 14 patients from the myocardial infarction-related rCS (AMI-rCS group) and 14 patients from the non-ischemic cardiomyopathy (DCM-rCS group) were included for further comparison as described in Figure 1. Baseline characteristics between the groups did not differ in a statistically significant way. Patient characteristics are shown in Table 1 and supplemental Table 1.

Intensive care and MCS characteristics

During a median ICU stay of 3 [1-16] days all patients were mechanically ventilated. Transfer from a referral hospital had been performed on VA-ECMO in two patients (#3&4). Four patients suffered from cardiac arrest prior to hospital admission. All resuscitated patients had witnessed arrest and bystander resuscitation. VA-ECMO was implanted for extracorporeal CPR in two patients (#1&6). Respiratory failure due

to acute respiratory distress syndrome (ARDS) occurred in two patients (#3&4) resulting in escalation to veno-arterial-venous-ECMO.[14] Impella was inserted secondary to VA-ECMO based on LV-distension and pulmonary congestion in two patients (#1&6). Admission lactate levels, cardiac arrest as well as durations from shock onset to either first device, VA-ECMO, or Impella did not significantly differ between the matched groups. Clinical course on ICU and MCS characteristics are summarized in Table 2 and supplementary Table 2. MCS provided hemodynamic stabilization (Figure 4A/B) resulting in decreased infusion of inotropes and vasopressors (Figure 4C) in patients with influenza-related myocarditis-associated rCS. Lactate levels declined rapidly during MCS and increased in two patients after LV-recovery probably based on subsequent sepsis following pneumonia and ARDS (Figure 4D).

Safety Outcome

In one patient (#7) Impella could not be re-positioned in the LV after dislocation to the ascending aorta. In two patients (#2&3), after active LV-unloading of 369 (#2) and 312 (#3) hours, Impella was explanted after primary LV-recovery. Pulmonary influenza infection was complicated by ARDS in three (#1, 3&4) and by secondary bacterial pneumonia in two (#2&5) patients with consecutive septic shock. Liver failure at admission was present in five patients (71%, #1, 4-7). No patient survived for 30 days after hospital admission (Figure 5). Withdrawal of further life support was decided by a consensus view due to multi-organ failure and protracted rCS (#2) and distinct anoxic brain damage following resuscitation (#6) (Figure 2). The remaining five patients (#1, #3-5, #7) died on maximal escalated intensive care. During MCS, no apparent thromboembolic events occurred.

Patients with influenza-related myocarditis-associated rCS suffered more frequently from secondary pneumonia and subsequent respiratory failure necessitating escalation to VAV-ECMO compared to the DCM-rCS group. Safety outcomes are summarized in Table 2, supplemental Figure 2 and supplemental Table 3.

30-day mortality in Propensity score matched groups

In propensity score-matched groups 57% of patients in the AMI-rCS group (n=8) and 50% in the DCM group (n=7) survived until day 30 after ICU admission, while their predicted mortality on VA-ECMO based on the SAVE score had been 82% for both groups. All patients with influenza-related myocarditis-associated rCS died within 18 days. Thus, 30-day survival was significantly different between the influenza-rCS group (n=7) and both matched AMI-rCS (n=14) (p=0.006; HR 3.56 (95%CI 1.07-12.83)) and DCM-rCS groups (n=14) (p=0.003; HR 3.39 (95%CI 1.30-13.86)). Kaplan-Meier curves are provided in Figure 5.

Review of the literature

Detailed literature review is provided in the supplement. We identified 10 cases, 70% were females (n=7) with a mean age of 39.5±13.2 years (influenza A n=2, influenza B n=8), who were supported with VA-ECMO (n=8) or (Impella n=2, ECMELLA n=0) with an in-hospital survival of 80% as provided in supplementary Table 4. Two patients (20%) full-filled the applied definitions of rCS.[10,11] A prior influenza vaccination was not reported in any case. Three patients were in need for renal replacement therapy and two patients (20%) had cardiac arrest. No patients suffered from secondary pneumonia or ARDS and escalation of ECMO cannulation strategies was not performed.

Discussion

Our present analysis includes seven patients with rCS complicating influenza-related myocarditis treated with combined Impella and VA-ECMO circulatory support (ECMELLA). Based on the extent of shock determined by SAVE-Score (SAVE-Score -11[-12;-8], these patients were at extreme risk of death. The ECMELLA-strategy [15,16] obviously improved hemodynamic compromise in these patients, reduced the need for inotropes and led to Impella weaning in two patients after left-ventriclular recovery. However, despite initial hemo-metabolic improvement by ECMELLA, none of our severely compromised patients with influenza-related, myocarditis-associated rCS survived. When applying PS matching to patient cohorts with myocardial infarction- or non-ischemic-cardiomyopathy-related rCS to account for hemodynamic compromise, patients with influenza-related, myocarditis-associated rCS showed a significantly higher 30-day mortality. Patients with rCS complicating influenza-related myocarditis suffered from irreversible end-organ failure complicated by cardiac arrest (n=4, 57%) and/or liver failure (n=5, 71.4%), which was not necessarily a consequence of rCS but rather a direct extra-cardial organ injury caused by influenza infection itself. Therefore, combined MCS with ECMELLA may had minor impact on prognosis in these patients in comparison to patients with either myocardial infarction or non-ischemic cardiomyopathies resulting in rCS. In those entities, symptoms of end-organ failure are most probably a consequence of hemodynamic deterioration. In contrast, influenza infection causes multiple extra-cardiac injuries that are independent from hemodynamic deterioration, and hemodynamic stabilization by MCS is unable to improve end-organ injury. MCS strategies had yielded a promising therapeutic concept to interrupt the fatal consequences of rCS. [17,18] Due to lacking evidence for many MCS devices in general and their application in rarer disease such

as rCS in myocarditis, decision making for MCS is an individual decision based on local experience.

In patients with rCS combined MCS with ECMELLA compared to singular VA-ECMO treatment has been associated with improved outcome. [19] Of note, that retrospective analysis also included patients with myocarditis associated rCS, but probably only infections restricted to the heart itself. To the best of our knowledge, the MCS approach of either VA-ECMO or Impella in CS complicating influenza-related myocarditis is limited to sporadic case reports. [5,20,21]

In our analysis, five patients (71%) were transferred from referral hospitals to our department after some delay (median duration from shock to first device 26 (IQR 18-40) hours). Early diagnosis of myocarditis in case of a concomitant influenza infection is challenging based on the length of the disease course prior to hospital admission, variability in clinical presentation, comorbidities, and challenges in influenza virus detection.[22,23] This might delay the transfer of severely compromised patients to tertiary hospitals. Furthermore, invasive hemodynamic monitoring is not commonly performed in all patients with borderline or compensated CS. An obvious contributor to counteract cardio-metabolic deterioration of CS is door to support time.[8,24] Therefore, we considered duration from shock to first device in addition to biventricular failure at admission and out-of hospital cardiac arrest in PS-matching. Both matched cohorts showed a significantly higher survival compared to the influenza cohort within 30 days after ICU-admission and as predicted by SAVE-score. Thus, the ECMELLA concept as well as the standardized care on our ICU clearly was able to benefit extremely compromised rCS patients. However, patients suffering from influenza-related, myocarditis-associated rCS did not profit from hemodynamic stabilization.

Cardiac end-organ damage owing to Influenza-related myocarditis complicated by rCS is presented in left-ventricular endomyocardial biopsies (Figure 3). Additionally, severity of myocardial damage in influenza-related myocarditis is enhanced owing to cytokines and overwhelming inflammatory response. [23,25-27] We conclude that in these patients the probability of myocardial recovery is less than expected in comparison to the PS matched non-ischemic cardiomyopathy cohort.

On first sight, our results seem to be in contrast to previous case reports, which indicated a low mortality rate in patients with influenza-related myocarditis complicated by CS who had been supported by VA-ECMO or Impella (suppl. Table 4). Overall, the distinction of in-hospital survival of patients with influenza-related myocarditis between our cohort and the historic patient examples may be explained by their younger age (55.6±9.5 vs. 39.5±13.2 years), absence of additional influenza-related complications, the severity of CS, and subsequent differences in end-organ damage.

Similarly, in the current pandemia of another challenging RNA-virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), older age, comorbidities as well as virus-related complications and end-organ damages are associated with impaired outcome.[28] The infection is presented by influenza-like symptoms (e.g. fever, cough, headache, fatigue, myalgia, shortness of breath, myalgia) and can ultimately result in multi-organ dysfunction involving ARDS, acute liver failure, acute kidney injury and acute heart failure.[28-30] Two recently published articles describe Coronavirus disease 2019 (COVID-19)-associated myocardial injury detected by elevated high-sensitivity troponin I and troponin T levels. [31,32] Of note, in both analyses myocardial injury was associated with a higher in-hospital mortality. Similar to influenza virus infection, the reported case by Inciardi et al. describe myocardial injury might be represented by acute myocarditis.[33] However, due to scarce

reported cases of MCS in rCS related to confirmed COVID-19, the effect of ECMELLA on mortality in these patients cannot be extrapolated from our analysis and, therefore, remains uncertain [28,34]. Nevertheless, the experience of futile causes in influenza-related, myocarditis-associated rCS patients due to the extra-cardiac end-organ damage by the virus might as well apply in case of COVID-19.

In summary, all cases of rCS related to influenza-infection were observed in non-vaccinated patients over two epidemic seasons. Therefore, physicians should strengthen the importance of influenza vaccination in both healthy people and in patients with pre-existing cardiac disease.[35] Furthermore, AMI and DCM related rCS affect primarily cardiomyocytes selectively while influenza infection secondarily affects the heart by a systemic inflammatory response while it hits other vital organs as well. Thus, influenza causes severe end-organ damage, which might not be salvageable by MCS in contrast to the beneficial effects observed in primary cardiac causes of rCS. Hence, in patients with influenza-related myocarditis-associated rCS MCS should be considered carefully, in particular related to the fatal outcome. However, without indicators for the irreversible stage of end-organ failures and diagnosis of influenza infection in these patients, MCS strategies seem to be the only option to treat acute hemodynamic deterioration and prevent early death. Further analyses of ECMELLA support in patients with influenza-associated, myocarditis-related rCS are warranted to verify our hypothesis.

Limitations

This observational registry reports a small series of patients with rCS complicating an influenza virus infection. Based on the retrospective and observational design, no randomized control group is available. While the results may be hypothesis

generating, registries provide relevant information for therapeutic approaches in rare diseases. Patients with influenza-associated, myocarditis-related rCS are scarce and represent a subset of severely compromised patients. Therefore, in this analysis we cannot extrapolate if an earlier implantation of MCS would have resulted in a beneficial effect and to what extent respiratory failure, ARDS, and secondary pneumonia contributed to mortality. The results of propensity score matching with small patient numbers can only be carefully extrapolated based on possible biases regarding potentially unknown covariates.[36]

Conclusion

We show that rCS in influenza-related myocarditis seems to have a fatal course even despite implantation of combined MCS. Our data do not support the concept of standardized aggressive MCS use in those patients. Nevertheless, the alternative of immediate fatal outcome without MCS will often trigger implantation, however, might not relevantly influence prognosis.

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Authorship Contributions

J-T.S. and M.A. contributed equally to the manuscript. J.-T.S., A.S. and J.B. designed the registry. J-T.S., M.A., S.S., C.R, U.F., T.J.P., V.H, J.D., M.M.H., and C.K. recruited patients and collected data. J-T.S., M.A. and S.S. analyzed and interpreted data. J-T. S., M.A., C.R., J.B. and A.S. wrote the manuscript. J-T.S., M.A., U.F., J.D. and A.S. performed literature review. D.J. rated and analyzed endomyocardial biopsies of patients supported by MCS with Influenza-rCS and DCM-rCS. All authors revised the manuscript critically. J.B. and A.S. accurately approved the manuscript.

Disclosure of Conflicts of Interest

J-T S received travel funds to congresses from Abiomed. AS and JB received honoraria and research funding from Abiomed. CR received travel funds from Abiomed. The Department of Cardiology and Angiology of Hannover Medical School is supported by a research grant from Abiomed. M.H. received honoraria for lectures and consultations from Actelion, Bayer, MSD and Pfizer, all outside the present work. M.A., S.S., U.F., T.J.P., V.H., C.K. and J.D. report no conflicts or disclosures.

Table1: Patient characteristics

		Patients with Influenza related myocarditis complicated by cardiogenic shock n= 7	Patients with myocardial infarction complicated by cardiogenic shock n= 14	P Influenza-rCS vs AMI-rCS	Patients with non-ischemic cardiomyopathy complicated cardiogenic shock n=14	P Influenza-rCS vs DCM-rCS
Age [years]		55.6±9.5	57.1±8.8	ns	54.9±11.3	ns
Female gender		3 (43%)	2 (14%)	ns	4 (29%)	ns
Card Shock Score		5 [4-6]	5 [5-6]	ns	6 [5-6]	ns
SAPS II Score		59.9±11.8	56.8±12.1	ns	55.3±13.1	ns
SAVE Score		-12 [-13- -8]	-10 [-13- -10]	ns	-10 [-11- -8]	ns
SOFA Score		15 [14-16]	14 [13-15]	ns	14 [12-16]	ns
Pre-existing conditions						
	Arterial hypertension	5 (71%)	10 (71%)	ns	4 (29%)	ns
	COLD	2 (29%)	1 (7%)	ns	3 (21%)	ns
	Smoking	3 (43%)	5 (36%)	ns	7 (50%)	ns
	Coronary artery disease	1 (14%)	7 (50%)	ns	1 (7%)	ns
Transferred from referral hospital		5 (71%)	8 (57%)	ns	11 (79%)	ns
Biventricular failure		4 (57%)	7 (50%)	ns	11 (79%)	ns

AMI-rCS- Patients with myocardial infarction related refractory cardiogenic shock, CAD- Coronary artery disease, COLD- Chronic obstructive lung disease, DCM-rCS- Patients with non-ischemic cardiomyopathy related refractory cardiogenic shock, Influenza-rCS-

Patients with influenza associated refractory cardiogenic shock, NSTEMI- Non ST-elevation myocardial infarction, PAD- Peripheral artery disease, STEMI- ST-elevation myocardial infarction

Table2: Intensive care and mechanical circulatory support

	Patients with Influenza related myocarditis complicated by cardiogenic shock n= 7	Patients with myocardial infarction complicated by cardiogenic shock n= 14	P Influenza-rCS vs AMI-rCS	Patients with non-ischemic cardiomyopathy complicated by cardiogenic shock n=14	P Influenza-rCS vs DCM-rCS
Resuscitation	4 (57%)	11 (79%)	ns	7 (50%)	ns
OHCA	2 (29%)	7 (50%)	ns	4 (29%)	ns
Initial rhythm (VT/VF)	2 (100%)	7 (100%)	ns	4 (100%)	ns
Witnessed arrest	4 (57%)	9 (64%)	ns	4 (29%)	ns
Bystander CPR	4 (57%)	8 (57%)	ns	4 (29%)	ns
ROSC [min]	53 [15-97]	30 [17-64]	ns	15 [5-23]	ns
eCPR	2 (29%)	2 (14%)	ns	1 (7.0%)	ns
MCS					
Escalation to VAV-ECMO	2 (29%)	2 (14%)	ns	0	***0.035***
Biventricular support with Impella and ECMO	7 (100%)	14 (100%)	ns	14 (100%)	ns
Duration shock to 1. device [min]	20 [2-32]	6 [4-22]	ns	17 [5-28]	ns
Bridge to			***0.019***		***0.019***
recovery	0	8 (57%)		2 (14%)	
LVAD	0	1 (7%)		7 (50%)	

transplant	0	0		0	
Secondary pneumonia	2 (29%)	0	***0.035***	0	***0.035***
Secondary ARDS	3 (43%)	2 (14%)	ns	0	***0.008***
AKI at admission	6 (86%)	12 (86%)	ns	12 (86%)	ns
Renal replacement therapy	6 (86%)	9 (64%)	ns	7 (50%)	ns
30-day mortality	7 (100%)	6 (43%)	***0.011***	7 (50%)	***0.035***

AKI- Acute kidney injury, AMI-rCS- Patients with myocardial infarction related refractory cardiogenic shock, ARDS- Acute respiratory distress syndrome, CPR- Cardio pulmonary resuscitation, DCM-rCS- Patients with non-ischemic cardiomyopathy related refractory cardiogenic shock, ECMO- Extracorporeal membrane oxygenation, eCPR- extracorporeal cardio pulmonary resuscitation, Influenza-rCS- Patients with influenza associated refractory cardiogenic shock, LVAD- Left ventricular assist device (durable), OHCA- Out of hospital cardiac arrest, ROSC- Return of spontaneous circulation, VA- veno-arterial, VAV- veno-arterial-venous ,

Figure legend:

Figure 1: Study enrollment

AMI-rCS- Patients with myocardial infarction related refractory cardiogenic shock, DCM-rCS- Patients with non-ischemic cardiomyopathy related refractory cardiogenic shock, ECMELLA- combined MCS with ECMO and Impella, ECMO- Extracorporeal membrane oxygenation, Influenza-rCS- Patients with influenza associated refractory cardiogenic shock, MCS- Mechanical circulatory support, OHCA- Out-of-hospital cardiac arrest, VA-Veno-arterial

Figure 2: Time course of treatment in patients with refractory cardiogenic shock complicating myocarditis induced by influenza virus infection

ABD- Anoxic brain damage, ARDS- Acute respiratory distress syndrome, CPR- Cardio pulmonary resuscitation, CAG- coronary angiography, CS-Cardiogenic shock, ECMO- Extracorporeal membrane oxygenation, ICU- Intensive care unit, MHH- Hannover Medical School, PCI- Percutaneous coronary intervention, PE- Pericardial effusion, VA- Veno-arterial, VAV- Veno-arterial venous

Figure 3: Endomyocardial biopsies of patients supported by percutaneous MCS with rCS complicating non-ischemic cardiomyopathy and influenza-related myocarditis

Controls (A – C)

Cardiac left ventricular biopsies of patients with rCS complicating non-ischemic cardiomyopathy with percutaneous MCS. In these endomyocardial biopsies cardiomyocytes show signs of irregular hypertrophy with varying hyperchromasia of the corresponding nuclei. Present are also unevenly dispersed, mildly eosinophilic contraction bands, as well as a mild intra- and extracellular edema. While there is

some sparse interstitial inflammatory infiltration, the criteria of an active myocarditis - according to the Dallas classification - are not met. By definition, the histological changes in dilated cardiomyopathy are nonspecific, rendering the histopathological diagnosis one of exclusion. Signs of specific disorders, such as granulomatous inflammation, myocardial inclusions or siderosis are absent.

Influenza-associated myocarditis (D – F)

Endomyocardial biopsies of patients with rCS complicating Influenza-related active myocarditis: there is a pronounced, if unevenly distributed, interstitial inflammatory infiltrate, for the most part made up by activated T-lymphocytes. All biopsies show evidence of myocyte damage, which ranges from prominent contraction bands to hypereosinophilic - early - stages of necrosis. Adjacent capillaries are dilated, packed with erythrocytes and their endothelial nuclei are activated. Cardiomyocytes, as well as the cardiac interstitium, show accompanying edematous changes. As in A – C, signs of specific disorders, such as granulomatous inflammation, myocardial inclusions or siderosis are absent.

Scale bar= 50µm

Figure 4: Hemodynamic effects of MCS in patients with rCS complicating myocarditis induced by influenza virus infection

A= Systolic blood pressure, B= heart rate, C= Inotropic equivalent, D= Lactate

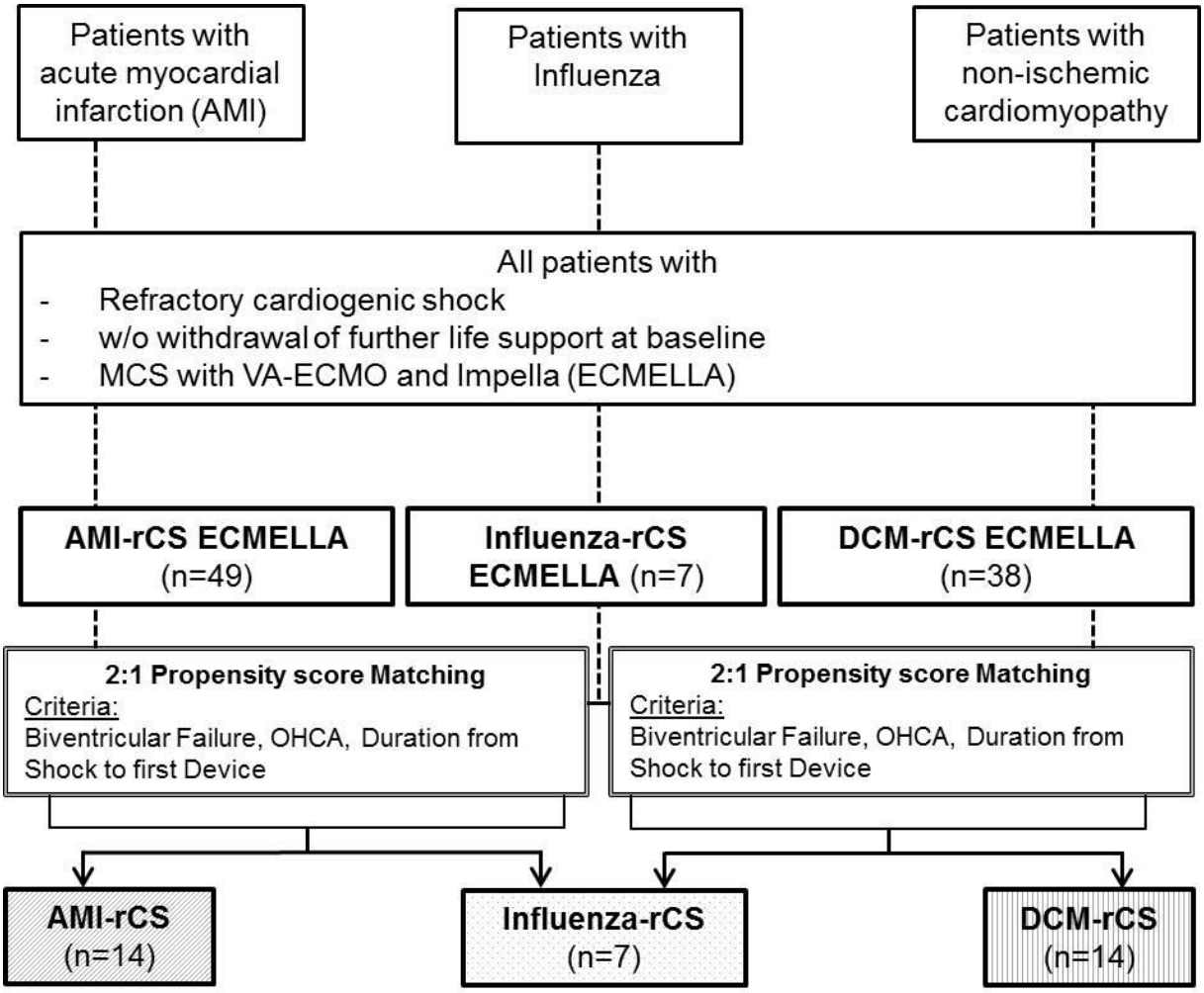
Despite of stabilization of hemodynamic parameters (A & B) with decrease of the inotropic equivalent (C) and counteracting rCS status with the consequence of declined lactate levels (D) based on percutaneous mechanical circulatory support patients died within 18 days after admission to the ICU and cardiac arrest center of Hannover Medical School. Catecholamine dose was evaluated by the inotrope

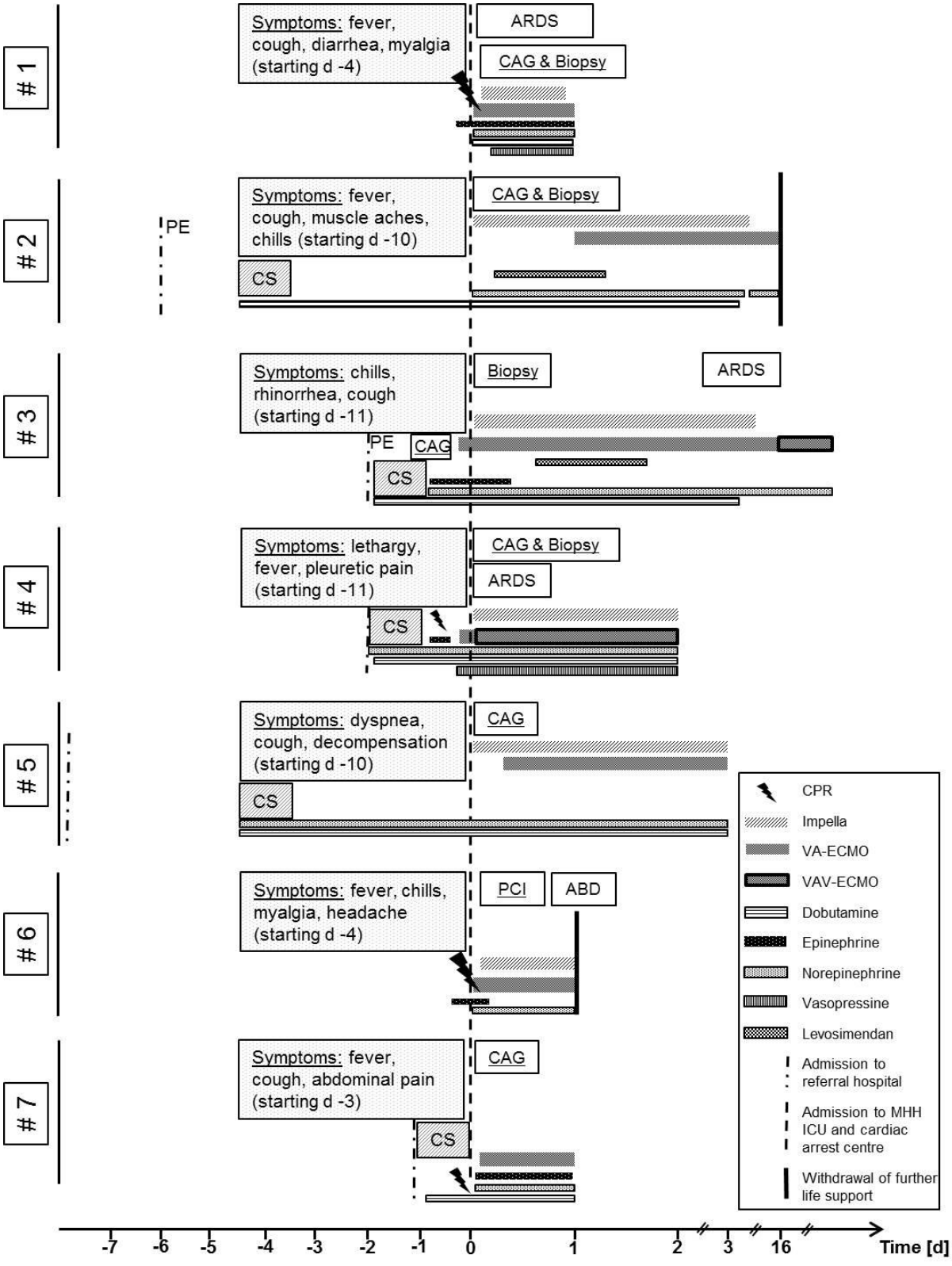
equivalent method ([ug/kg/min] = dopamine + dobutamine + 100*epinephrine + 100*norepinephrine + 100*isoproterenol + 15*milrinone).[37]

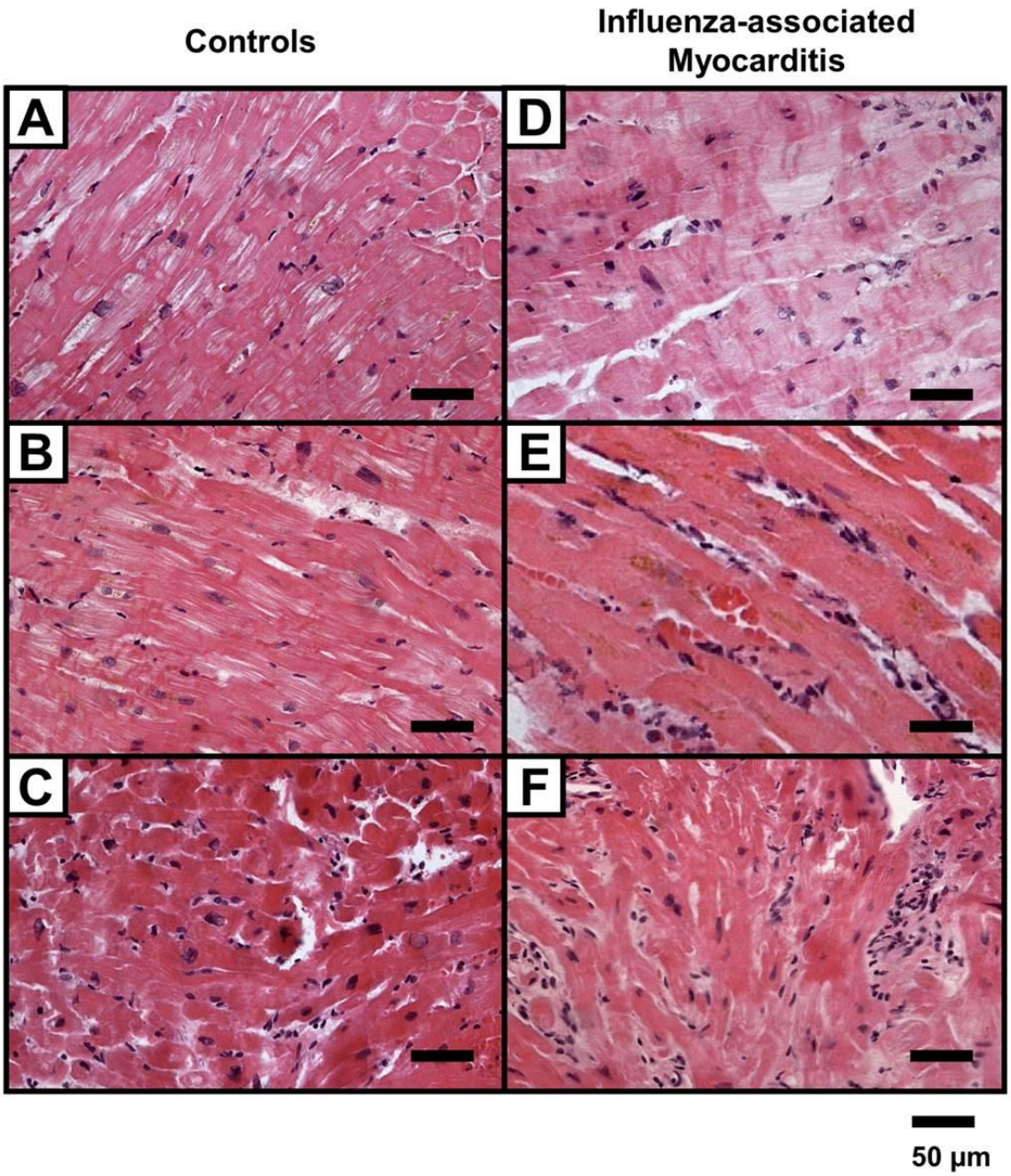
*p<0.05 vs. BL

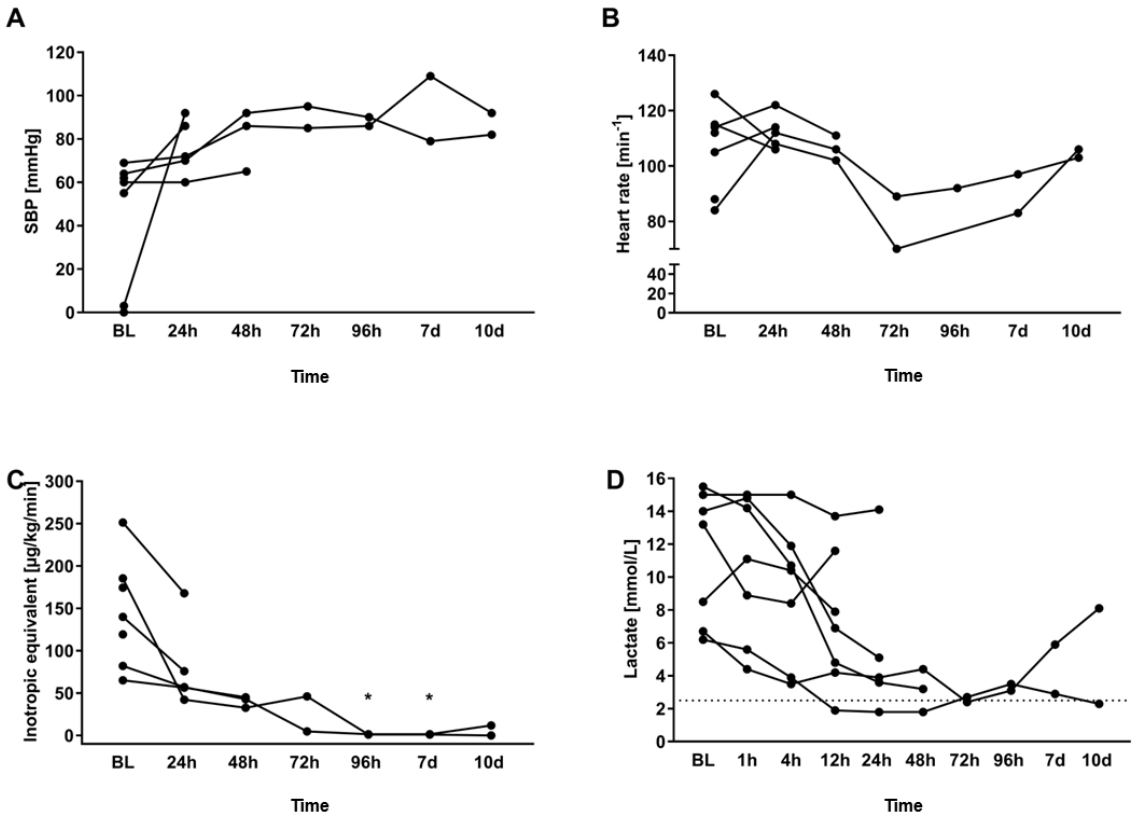
Figure 5: 30-day survival of propensity score matched cohorts

AMI-rCS- Patients with myocardial infarction related refractory cardiogenic shock, CI- Confidence interval, DCM-rCS- Patients with non-ischemic cardiomyopathy related refractory cardiogenic shock, Influenza-rCS- Patients with influenza associated refractory cardiogenic shock

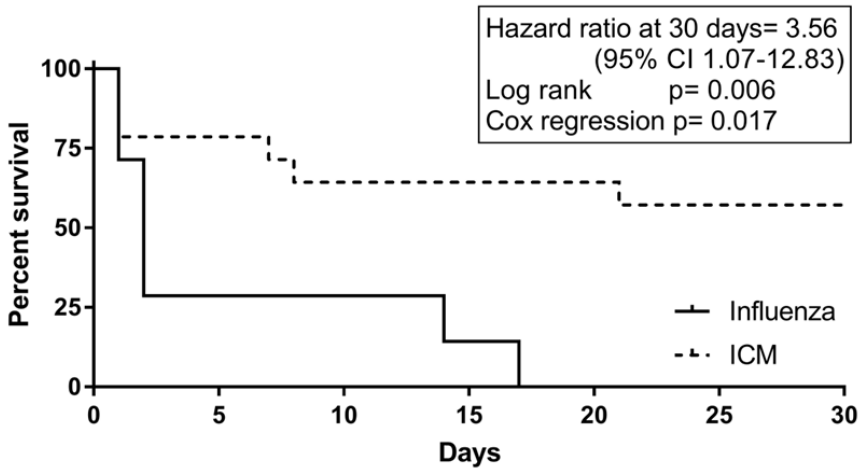

Patients with acute myocardial infarction (AMI)
Patients with Influenza
Patients with non-ischemic cardiomyopathy
All patients with
- Refractory cardiogenic shock
- w/o withdrawal of further life support at baseline
- MCS with VA-ECMO and Impella (ECMELLA)
AMI-rCS ECMELLA (n=49)
Influenza-rCS ECMELLA (n=7)
DCM-rCS ECMELLA (n=38)
2:1 Propensity score Matching
Criteria:
Biventricular Failure, OHCA, Duration from Shock to first Device
2:1 Propensity score Matching
Criteria:
Biventricular Failure, OHCA, Duration from Shock to first Device
AMI-rCS (n=14)
Influenza-rCS (n=7)
DCM-rCS (n=14)


1
Symptoms: fever, cough, diarrhea, myalgia (starting d -4)
ARDS
CAG & Biopsy
2
PE
Symptoms: fever, cough, muscle aches, chills (starting d -10)
CAG & Biopsy
CS
3
Symptoms: chills, rhinorrhea, cough (starting d -11)
Biopsy
ARDS
PE
CAG
CS
4
Symptoms: lethargy, fever, pleuretic pain (starting d -11)
CAG & Biopsy
ARDS
CS
5
Symptoms: dyspnea, cough, decompensation (starting d -10)
CAG
CS
6
Symptoms: fever, chills, myalgia, headache (starting d -4)
PCI
ABD
7
Symptoms: fever, cough, abdominal pain (starting d -3)
CAG
CS
CPR
Impella
VA-ECMO
VAV-ECMO
Dobutamine
Epinephrine
Norepinephrine
Vasopressine
Levosimendan
Admission to referral hospital
Admission to MHH ICU and cardiac arrest centre
Withdrawal of further life support
-7
-6
-5
-4
-3
-2
-1
0
1
2
3
16
Time [d]


Controls
Influenza-associated Myocarditis
A
B
C
D
E
F
50 µm

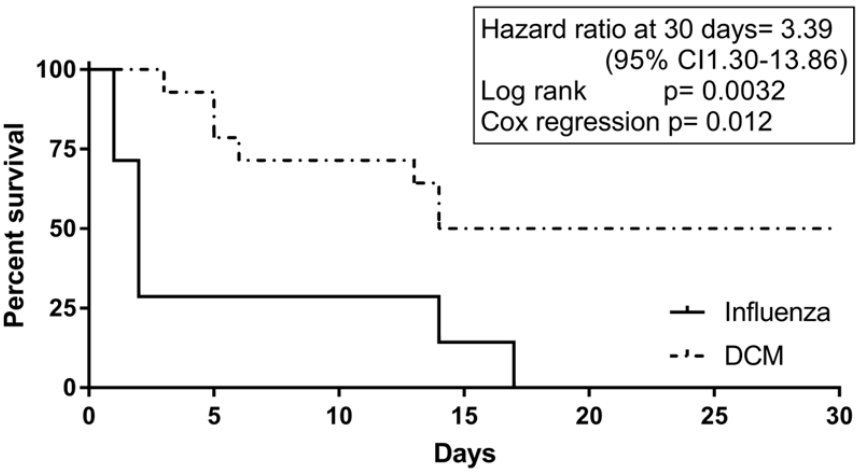

A
SBP [mmHg]
120
100
80
60
40
20
0
BL
24h
48h
72h
96h
7d
10d
Time
B
Heart rate [min-1]
140
120
100
80
40
20
0
BL
24h
48h
72h
96h
7d
10d
Time
C
Inotropic equivalent [µg/kg/min]
300
250
200
150
100
50
0
*
*
BL
24h
48h
72h
96h
7d
10d
Time
D
Lactate [mmol/L]
16
14
12
10
8
6
4
2
0
BL
1h
4h
12h
24h
48h
72h
96h
7d
10d
Time

A



No. at risk							
Influenza-rCS [n]	7	2	2	1	0	0	0
AMI-rCS [n]	14	11	9	9	9	8	8

B



No. at risk							
Influenza-rCS [n]	7	2	2	1	0	0	0
DCM-rCS [n]	14	11	10	7	7	7	7

Supplemental Material

Methods

Patient treatment

VA-ECMO was utilized to stabilize hemodynamics, enable transfer from a referral hospital, perform extracorporeal-cardiopulmonary resuscitation, or to treat biventricular failure. Implantation of an Impella was performed in patients with CS with left-ventricular (LV) failure or LV distension on VA-ECMO. Impella implantation, positioning and anticoagulation were performed as previously described.[1] Management of sympathomimetic inotropic and vasopressor agent was performed at the estimation of the clinician in charge targeting decrease of drugs account, dosis and duration to minimize the risk of mediated end-organ failure. Target blood pressure was defined as MAP ≥65 mmHg and SBP ≥80 mmHg or individualized determined by the treating clinician. However, despite our institutional standards, we thus cannot exclude bias. Appropriateness of end-organ perfusion was verified by considering markers of systemic perfusion: arterial lactate, central or mixed venous oxygen saturation, urine output, and if a pulmonary artery catheter was considered: cardiac output, pulmonary capillary wedge pressure, and peripheral vascular resistance.

A left ventricular endomyocardial biopsy (EMB) was obtained if the procedure was considered safe by the interventional cardiologist at the time of Impella implantation.

Clinical parameters, complications, and demographic characteristics were continuously documented in a standard patient file and data monitoring system. Patients were followed-up until 30 days. Records were extracted from the electronic hospital patient data management system. In case of discharge before 30 days after admission consecutive outpatient visits and/or chart review were performed. No patient was lost to follow-up.,

Propensity score matching

To minimize confounding bias due to the non-randomized nature of the investigation, to yield a balanced distribution of baseline characteristics and to estimate effects of dual circulatory support with Impella and VA-ECMO in patients with Influenza-related myocarditis and rCS a propensity score matching was performed to patients with rCS due to acute myocardial infarction (AMI-rCS group) and to patients with non-ischemic cardiomyopathy complicated by rCS (DCM-rCS group). Propensity scores were estimated using multivariable logistic regression modelling accounting for variables related to the outcome [2]: biventricular failure at baseline, out-of-hospital cardiac arrest with initial shockable rhythm and duration from shock to first device [hours]. Cases of influenza related myocarditis and control groups were matched stepwise on the logit of the estimated propensity score (1:2 propensity score matching) using a nearest neighbor model using calipers width equal to 0.15. In our study a lower caliper width was used in order to maximize correct matching and to reduce bias.

To validate the method and perform a sensitivity analysis of the propensity score matching, the primary outcome (30-day mortality) was reanalyzed using the entire (unmatched) cohort (Supplemental Fig 1)

Review of the literature

Literature review between 2013 and 2019 was performed using PubMed search engine and the following criteria: infuenza, myocarditis, mechanical circulatory support. Original research articles, Case reports, and case series handling with adult patients with verified influenza virus infection, proven or suspected myocarditis, cardiogenic shock and MCS using VA-ECMO and/or Impella were eligible. Manuscripts with limited clinical information were excluded. Parameters were selected as follows: Influenza virus type, patients` characteristics (i.a. pre-existing conditions, vaccination status, occurence of cardiac arrest), use of inotropes/vasopressors, mechanical ventilation, lactate levels, complications (i.a. renal replacement therapy, pericardial effusion, pneumonia), type of MCS, intention to treat, outcome data.

Supplemental Table 1: Patient characteristics

	Patients with Influenza related myocarditis complicated by cardiogenic shock n= 7	Patients with myocardial infarction complicated by cardiogenic shock n= 14	P Influenza-rCS vs AMI-rCS	Patients with non-ischemic cardiomyopathy complicated by cardiogenic shock n=14	P Influenza-rCS vs DCM-rCS
height [cm]	175±6	172±12	ns	176±9	ns
weight [kg]	81±14	86±12	ns	87±18	ns
pre-existing disease					
stroke	0	1 (7%)	ns	1 (7%)	ns
PAD	0	1 (7%)	ns	1 (7%)	ns
myocardial infarction	0	14 (100%)		0	
STEMI	0	11 (79%)		0	
NSTEMI	0	3 (21%)		0	
cardiomyopathy					
myocarditis	7 (100%)	0		0	
dilative		0		14 (100%)	
extrahospital thrombolysis	0	4 (29%)	ns	2 (14%)	ns

AMI-rCS- Patients with myocardial infarction related refractory cardiogenic shock, DCM-rCS- Patients with non-ischemic cardiomyopathy related refractory cardiogenic shock, NSTEMI- Non-ST-elevation myocardial infarction, PAD- Peripheral artery disease, STEMI- ST-elevation myocardial infarction

Supplemental Table 2: Intensive care and mechanical circulatory support

	Patients with Influenza related myocarditis complicated by cardiogenic shock n= 7	Patients with myocardial infarction complicated by cardiogenic shock n= 14	P Influenza-rCS vs AMI-rCS	Patients with non-ischemic cardiomyopathy complicated by cardiogenic shock n=14	P Influenza-rCS vs DCM-rCS
in-hospital stay [days]	3 [1-16]	18 [1-25]	ns	14 [5-36]	***0.025***
mechanical ventilation	7 (100%)	14 (100%)	ns	14 (100%)	ns
coronary angiography	7 (100%)	14 (100%)	ns	14 (100%)	ns
PCI performed	1 (14%)	14 (100%)	***0.005***	0	ns
type of Impella			ns		ns
2.5	1 (14%)	2 (14%)		2 (14%)	
CP	6 (86%)	12 (86%)		12 (86%)	
shock to Impella-insertion-time			ns		ns
<6 hours	2 (29%)	9 (64%)		4 (29%)	
6-12 hours	1 (14%)	0		1 (7%)	
12-24 hours	1 (14%)	1 (7%)		0)	
>24 hours	2 (29%)	4 (29%)		9 (64%)	
duration of Impella-support [hours]	28 [11- 326]	129 [28-203]	ns	80 [64-147]	ns
ECMO support	7 (100%)	14 (100%)	ns	14 (100%)	ns
duration of ECMO support [hours]	43 [14-312]	196 [23-331]	ns	114 [94-166]	ns
duration shock to	20 [2-32]	10 [4-23]	ns	20 [3-30]	ns

	ECMO [hours]					

AMI-rCS- Patients with myocardial infarction related refractory cardiogenic shock, DCM-rCS- Patients with non-ischemic cardiomyopathy related refractory cardiogenic shock, ECMO- Extracorporeal membrane oxygenation, Influenza-rCS- Patients with influenza associated refractory cardiogenic shock, PCI- Percutaneous coronary intervention, VA- Veno-arterial

Supplemental Table 3: Outcome

		Patients with Influenza related myocarditis complicating cardiogenic shock n= 7	Patients with myocardial infarction complicated by cardiogenic shock n= 14	P Influenza-rCS vs AMI-rCS	Patients with non-ischemic cardiomyopathy complicated by cardiogenic shock n=14	P Influenza-rCS vs DCM-rCS
hemolysis		1 (14%)	4 (29%)	ns	10 (71%)	***0.013***
anoxic brain damage		1 (14%)	2 (14%)	ns	1 (7%)	ns
TIMI bleeding				ns		ns
	none	2 (29%)	6 (43%)		8 (57%)	
	minimal	3 (43%)	1 (7%)		4 (29%)	
	minor	2 (29%)	7 (50%)		2 (14%)	
	major	0	0		0	

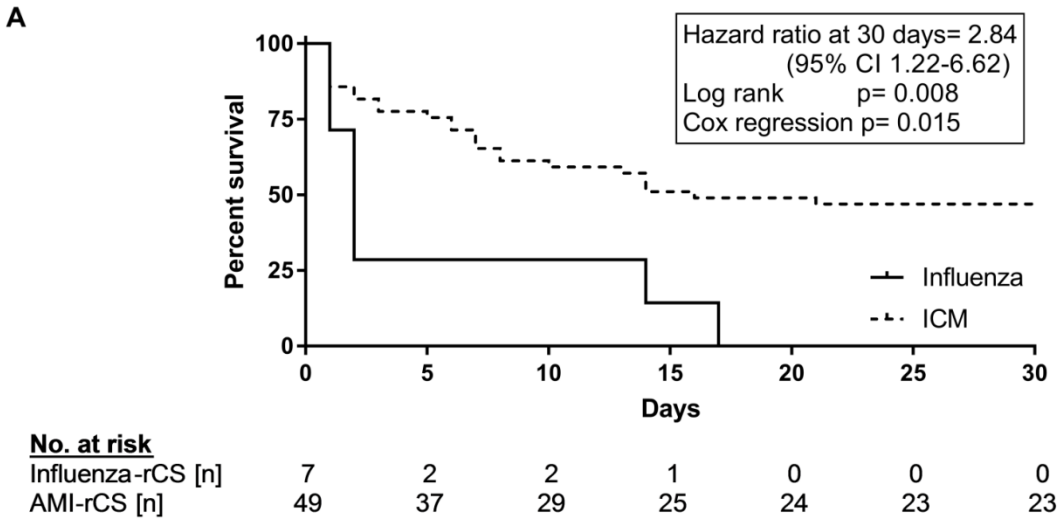
AMI-rCS- Patients with myocardial infarction related refractory cardiogenic shock, DCM-rCS- Patients with non-ischemic cardiomyopathy related refractory cardiogenic shock, Influenza-rCS- Patients with influenza associated refractory cardiogenic shock

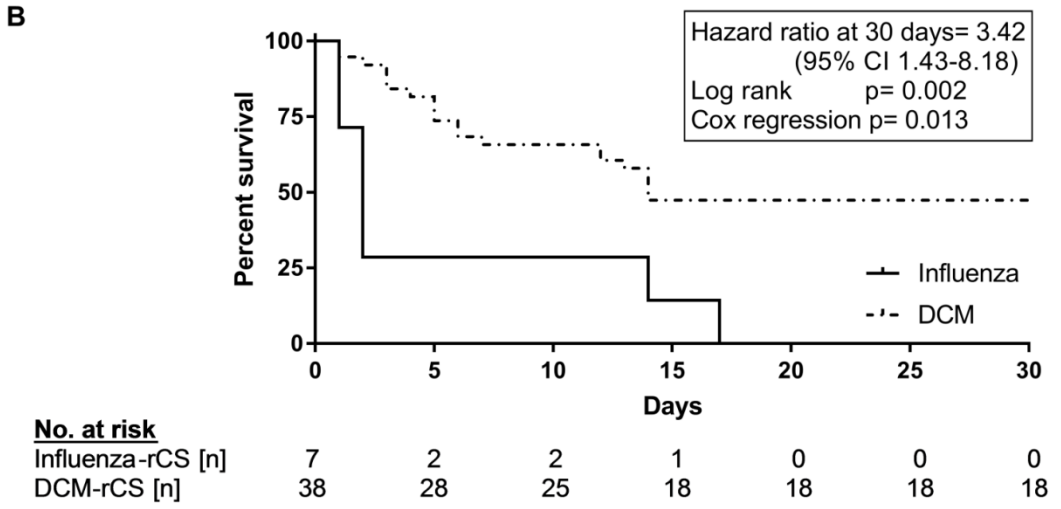
Supplemental Table 4: Summary of case reports (2013-2019) targeting adult patients with influenza-related cardiogenic shock requiring mechanical circulatory support (VA-ECMO and/or Impella) and additional administration of inotropes/vasopressors.

Parameter	**Larsen TR et al.[3]**	**Taremi M et al. [4]**	**Hamoudi A et al. [5]**	**Ciabatti M et al. [6]**	**Marchetti L et al.[7]**	**Siskin M et al. [8]**	**Hekimian G et al. [9]**	**Hekimian G et al. [9]**	**Hekimian G et al. [9]**	**Hekimian G et al. [9]**
virus (RT-PCR)	A (H1N1)	B	A (H1N1)	B	B	B	B	B	B	B
age [y]	41	52	25	66	44	22	28	35	43	39
sex	F	F	F	M	M	F	F	F	F	M
pre-existing conditions	N	N	Nicotine	N	Nicotine, Non-Hodgkin lymphoma	N	Ectopic pregnancy	N	Multiple sclerosis	N
vaccination	NN	NN	NN	NN	N	NN	NN	NN	NN	NN
transferred in CS	N	Y	Y	N	Y	N	N	N	Y	N
beginning of flu-like symptoms	-4d	-6d	-7d	-2d	-2d	-14d	-3d	-3d	-5d	-5d
Mechanical ventilation	Y	Y	NN	NN	Y	NN	NN	NN	NN	NN
peak lactate [mmol/L]	8.8	8.2	NN	11	NN	4	9.8	10	3.7	14.4
inotropes/vasopressors	Y (n=1, NE)	Y (n=1, NE)	Y (n=2, NE, D)	Y (n=2, NE, D)	Y (n=2, NE, D)	Y (n=1, D)	Y (n=1, D)	Y (n=2, E, D)	Y (n=1, D)	Y (n=1, D)
LVEF [%]	30	10	35	10	15	10	20	10	10	10
PE	Y	N	N	Y	Y	Y	Y	Y	Y	Y
MCS	IABP/ Impella 2.5	VA-ECMO	VA-ECMO	IABP + VA-ECMO	VA-ECMO/ IABP	Impella	VA-ECMO	IABP + VA-ECMO	VA-ECMO	VA-ECMO
cardiac arrest	Y	N	N	Y	N	N	N	N	N	N
biventricular failure	NN	N	N	N	Y	N	NN	Y	NN	Y
ARDS	N	N	N	N	N	N	N	N	N	N
secondary pneumonia	N	N	N	N	N	N	N	N	N	N
RRT	Y	N	N	Y	N	N	N	Y	N	Y
bridge to	Destination	Recovery	Destination	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery
in-hospital survival	N	Y	N	Y	Y	Y	Y	Y	Y	Y

ARDS- acute respiratory distress syndrome, CS- cardiogenic shock, D- dobutamine, E-epinephrine, F- female, IABP- intra-aortic balloon pump, LVEF- left ventricular ejection fraction, M- male, MCS- mechanical circulatory support, N- no, NE- norepinephrine NN- not reported, PE- pericardial effusion, RRT- renal replacement therapy, VA-ECMO- venou-arterial extracorporeal membrane oxygenation, Y- yes

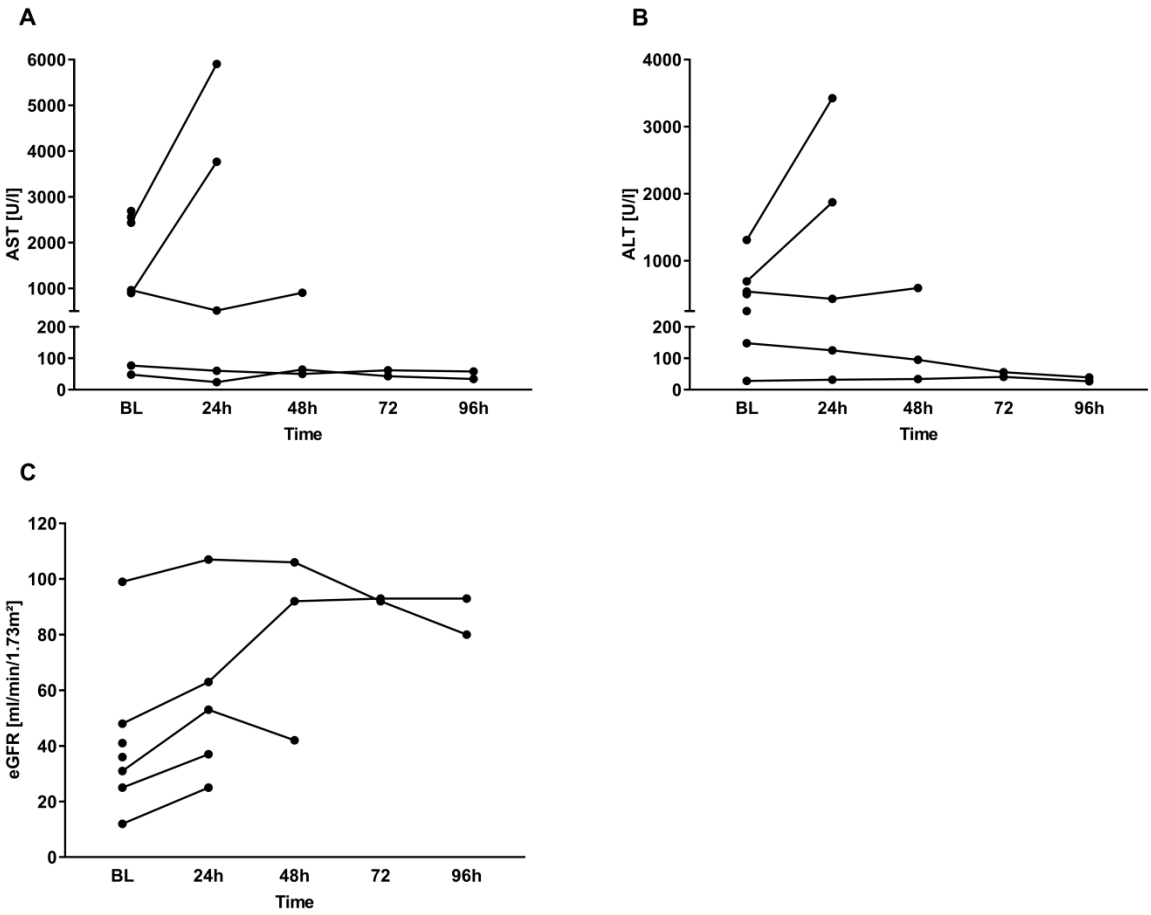
<u>Supplemental Figure 1:</u> Kaplan-Meier curves comparing 30 day survival between the Influenza group and the unmatched groups of patients with AMI related rCS (A) and patients with DCM related rCS (B)





AMI-rCS- Patients with myocardial infarction related refractory cardiogenic shock, CI- Confidence interval, DCM-rCS- Patients with non-ischemic cardiomyopathy related refractory cardiogenic shock, Influenza-rCS- Patients with influenza associated refractory cardiogenic shock

<u>Supplemental Figure 2:</u> Course of AST, ALT and eGFR in patients with influenza associated myocarditis related refractory cardiogenic shock



A: AST over time, **B:** ALT over time, **C:** eGFR over time

ALT- Alanine aminotransferase, AST- Aspartate aminotransferase, BL- Baseline, eGFR- estimated glomerular filtration rate

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