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ORIGINAL RESEARCH ARTICLE

Outcome differences in acute vs. acute on chronic heart failure and cardiogenic shock

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Abstract

Aims Despite advances in coronary reperfusion and percutaneous mechanical circulatory support, mortality among patients presenting with cardiogenic shock (CS) remains unacceptably high. Clinical trials and risk stratification tools have largely focused on acute CS, particularly secondary to acute coronary syndrome. Considerably less is understood about CS in the setting of acute decompensation in patients with chronic heart failure (HF). We sought to compare outcomes between patients with acute CS and patients with acute on chronic decompensated HF presenting with laboratory and haemodynamic features consistent with CS.

Methods and results Sequential patients admitted with CS at a single quaternary centre between January 2014 and August 2017 were identified. Acute on chronic CS was defined by having a prior diagnosis of HF. Initial haemodynamic and laboratory data were collected for analysis. The primary outcome was in-hospital mortality. Secondary outcomes were use of temporary mechanical circulatory support, durable ventricular assist device implantation, total artificial heart implantation, or heart transplantation. Comparison of continuous variables was performed using Student's *t*-test. For categorical variables, the χ^2 statistic was used. A total of 235 patients were identified: 51 patients (32.8%) had acute CS, and 184 patients (64.3%) had acute decompensation of chronic HF with no differences in age (52 ± 22 vs. 55 ± 14 years, $P = 0.28$) or gender (26% vs. 23%, $P = 0.75$) between the two groups. Patients with acute CS were more likely to suffer in-hospital death (31.4% vs. 9.8%, $P < 0.01$) despite higher usage of temporary mechanical circulatory support (52% vs. 25%, $P < 0.01$) compared with patients presenting with acute on chronic HF. The only clinically significant haemodynamic differences at admission were a higher heart rate (101 ± 29 vs. 82 ± 17 b.p.m., $P < 0.01$) and wider pulse pressure (34 ± 19 vs. 29 ± 10 mmHg, $P < 0.01$) in the acute CS group. There were no significant differences in degree of shock based on commonly used CS parameters including mean arterial pressure (72 ± 12 vs. 74 ± 10 mmHg, $P = 0.23$), cardiac output (3.9 ± 1.2 vs. 3.8 ± 1.2 L/min, $P = 0.70$), or cardiac power index (0.32 ± 0.09 vs. 0.30 ± 0.09 W/m^2, $P = 0.24$) between the two groups.

Conclusions Current definitions and risk stratification models for CS based on clinical trials performed in the setting of acute coronary syndrome may not accurately reflect CS in patients with acute on chronic HF. Further investigation into CS in patients with acute on chronic HF is warranted.

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

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Introduction

Despite advances in coronary reperfusion therapy, multidisciplinary shock team development, and percutaneous mechanical circulatory support (MCS) devices, mortality rates among patients presenting with cardiogenic shock (CS) range from 25% to 50%.[1–4] Significant energy has been dedicated to the development of management guidelines and treatment algorithms in an effort to improve survival from this highly morbid condition.[5–7] However, there remains a paucity of clinical trial

data. Although the exact pathophysiology of this multifactorial, hemodynamically diverse population remains poorly understood, early recognition and intervention to prevent the devastating 'cardiogenic shock spiral' is critical to survival.[8]

Cardiogenic shock is characterized as a state in which ineffective cardiac output (CO) due to a primary cardiac condition results in inadequate tissue and end-organ perfusion. This is conceptualized as an initial cardiac insult resulting in impaired CO with progressive myocardial dysfunction and maladaptive compensatory mechanisms leading to hypoperfusion and cardiovascular collapse.[5,9–11] Definitions for CS have varied in earlier clinical trials and guidelines, and current recommendations are largely based on data from patients with CS due to acute coronary syndrome (ACS).[1,2,12] Although ACS represents approximately 60–80% of CS presentations, at least 20% of admissions are due to CS from other causes.[12,13] Considerably less is understood regarding identification and outcomes in the non-ACS population who present in CS, particularly acute decompensation in patients with pre-existing chronic heart failure (HF). Extrapolation of current CS haemodynamic definitions to patients with chronic HF is therefore both unreliable and impractical. Many patients with stable HF have similar haemodynamic profiles to those in acute CS based on blood pressure and cardiac index, which makes recognizing true CS in patients with chronic HF challenging. Thus, early identification of shock and impending cardiovascular collapse in this very heterogeneous patient population remains problematic. While a recently developed classification system provides a schematic for rapid assessment and identification of patients at risk for CS, this has yet to be validated in either the acute or acute on chronic HF patient population.[6]

We sought to compare outcomes of patients with laboratory and haemodynamic findings of CS based on established criteria between patients with acute CS and patients with acute on chronic decompensated HF.[1,2,12]

Methods

This was a single-centre, retrospective, observational study conducted at the University of Washington Medical Center. Data were collected retrospectively by electronic medical record review. The study was conducted with the approval of the local institutional review board.

Patient population

Patients were identified via query of the Mac-Lab (GE Healthcare, Chicago, IL, USA) cardiac catherization laboratory monitoring system. We included all adults ≥18 years old whom were hospitalized at the University of Washington Medical Center between 1 January 2015 and 17 October 2017 with CS, defined as cardiac index ≤2.2 L/min/m^2 and systolic blood pressure ≤100 mmHg or on inotropic or vasopressor support at time of the initial right heart catheterization. Acute on chronic HF presentations were defined by a prior diagnosis of HF on admission, and acute HF admissions were characterized as new diagnosis of HF on admission. Prior diagnosis of HF was determined by review of medical records from our institution as well as any referring institution.

Patients requiring veno-arterial extracorporeal membrane oxygenation (VA-ECMO) support were also identified by review of current procedural terminology codes in the instance that right heart catheterization was not performed at our institution prior to initiation of VA-ECMO support. For patients with multiple hospitalizations meeting our criteria for CS, each hospital encounter was captured with a unique identifier, and only the initial hospitalization was included in our analysis to avoid survival bias. We excluded those patients with post-cardiotomy shock, post-transplant cardiac graft dysfunction, or presence of a durable left ventricular assist device (LVAD) at time of admission.

The primary outcome was all-cause in-hospital mortality. Secondary outcomes were use of temporary MCS, durable ventricular assist device implantation, total artificial heart implantation, or heart transplantation during the index hospitalization and hospital length of stay or length of hospitalization to death.

Data collection

Several variables including past medical history and haemodynamic and laboratory values were collected to evaluate for baseline presenting differences in our patient population. Past medical history was defined as a diagnosis present prior to admission based on electronic medical record review from our institution or from the referring facility. Right heart catheterization values recorded were that of initial invasive haemodynamic values obtained during the index hospitalization. Baseline laboratory markers of end-organ dysfunction including creatinine, sodium, total bilirubin, and serum lactate were also recorded upon hospital admission. Echocardiographic parameters collected for our analysis were from the first echocardiographic assessment after hospitalization, or the most recent echocardiogram prior to admission if an echocardiogram was not performed during the hospitalization.

Study data were collected and managed using REDCap electronic data capture tools hosted at the Institute of Translational Health Sciences.

Statistical analysis

Analysis was carried out using STATA Version 15 (StataCorp, College Station, TX) statistical analysis software. Continuous

variables are expressed as a mean ± standard deviation. Categorical variables are summarized by reporting absolute frequency and percentage. Comparison of continuous variables between patient groups was performed using Student's *t*-test. For categorical variables, the χ^2 statistic was used to compare differences between acute and acute on chronic HF study groups. A *P*-value of less than 0.05 was considered significant. Patients with missing outcomes data were excluded in the outcomes analysis, however not excluded from the overall data description.

Results

Between January 2014 and August 2017, 235 patients met criteria for CS: 51 patients (32.8%) had acute CS, and 184 patients (64.3%) had acute decompensation of chronic HF. Baseline demographics, medical history, and admission laboratory and haemodynamic data are reported in *Tables 1* and *2*, respectively. Mean age was 54 ± 16 years with no difference between acute and acute on chronic HF groups ($P = 0.28$). The group with chronic HF was more likely to have a history of atrial fibrillation, chronic kidney disease, and cerebrovascular disease and were more likely to have an implantable cardiac defibrillator in place. The only clinically significant haemodynamic differences at admission were a higher heart rate (101 ± 29 vs. 82 ± 17 b.p.m., $P < 0.01$) and wider pulse pressure (34 ± 19 vs. 29 ± 10 mmHg, $P < 0.01$) in the acute HF group. The acute on chronic HF group was noted to have a lower left ventricular ejection fraction (24% ± 12% vs. 34% ± 16%, $P < 0.01$) and larger left ventricular end-diastolic dimension (6.6 ± 1.1 vs. 5.2 ± 1.2 cm, $P < 0.01$) by transthoracic echocardiography.

The in-hospital mortality rate of the study cohort was 14.5%. Patients with acute CS were more likely to suffer in-hospital death as compared with patients admitted with acute on chronic decompensated HF (31.4% vs. 9.8%, $P < 0.01$) despite higher utilization of temporary MCS devices (59% vs. 26%, $P < 0.01$) and full support with VA-ECMO (28% vs. 4%, $P < 0.01$) (*Table 3* and *Figure 1*).

Secondary outcomes of durable LVAD and total artificial heart implantation also differed significantly between the two groups (*Table 4* and *Figure 2*). Patients presenting with acute on chronic HF were more likely to receive a durable LVAD during the index hospitalization (28% vs. 2%, $P < 0.01$). Patients with acute HF were more likely to undergo total artificial heart implantation, although overall numbers were small. Rates of cardiac transplantation were similar between the two groups. There was no significant difference in hospital length of stay (28.1 ± 26.7 vs. 23.4 ± 21.5, $P = 0.26$) or length of hospitalization to death (32.6 ± 61.1 vs. 12.4 ± 9.3, $P = 0.17$) between the two groups though there were large numerical differences.

Discussion

In this study, we evaluated outcomes in a large cohort of patients at a single quaternary care centre meeting haemodynamic criteria for CS and evaluated the in-hospital outcomes by clinical presentation classified as acute vs. acute on chronic HF.[1–3] The primary finding of this analysis is that the acute and acute on chronic populations appear to be

Table 1 Baseline demographic and medical history variables according to heart failure status

Characteristic	All ($n = 235$)	Acute heart failure ($n = 51$)	Acute on chronic heart failure ($n = 184$)	*P*
Demographics				
Age (years)	54 ± 16	52 ± 22	55 ± 14	0.28
Female gender	56 (24%)	13 (26%)	43 (23%)	0.75
Non-White ethnicity	61 (26%)	12 (24%)	49 (27%)	0.73
Weight (kg)	88 ± 23	80 ± 17	90 ± 23	<0.01
Medical history				
Acute myocardial infarction	50 (21%)	7 (14%)	43 (24%)	0.13
Out-of-hospital cardiac arrest	6 (2.6%)	3 (5.9%)	3 (1.6%)	0.09
Any valve disease	67 (29%)	10 (20%)	57 (31%)	0.11
Hypertension diagnosis	69 (29%)	17 (33%)	52 (28%)	0.48
Diabetes mellitus	60 (26%)	12 (24%)	48 (26%)	0.71
Atrial fibrillation		9 (18%)	81 (44%)	<0.01
Chronic kidney disease	66 (28%)	3 (5.9%)	63 (34%)	<0.01
Peripheral vascular disease	8 (3.4%)	2 (3.9%)	6 (3.3%)	0.82
Chronic obstructive pulmonary disease	26 (11%)	3 (5.9%)	23 (12.5%)	0.18
Cerebrovascular disease	37 (16%)	2 (4.0%)	35 (19%)	0.01
Percutaneous coronary intervention	53 (23%)	11 (22%)	42 (23%)	0.91
Coronary artery bypass grafting	21 (8.9%)	5 (9.8%)	16 (8.7%)	0.84
ICD	112 (48%)	1 (2.0%)	111 (60%)	<0.01

ICD, implantable cardioverter defibrillator.

Table 2 Admission laboratory and haemodynamic variables according to heart failure status

Characteristic	All (n = 235)	Acute heart failure (n = 51)	Acute on chronic heart failure (n = 184)	P
Laboratory				
Blood urea nitrogen (mg/dL)	34.6 ± 21.1	30.0 ± 18.1	35.9 ± 21.7	0.08
Creatinine (mg/dL)	1.57 ± 1.0	1.4 ± 0.8	1.6 ± 1.1	0.32
GFR (mL/min)	48.5 ± 14.6	49.6 ± 15.1	48.2 ± 14.5	0.54
Haemoglobin (g/dL)	12.9 ± 6	12.5 ± 2.5	13.0 ± 6.6	0.54
Haematocrit (%)	38.5 ± 6.5	37.9 ± 7.2	38.7 ± 6.3	0.42
Lactate (mmol/L)	3.8 ± 4	3.4 ± 3.4	4.2 ± 4.6	0.55
Sodium (mmol/L)	134.8 ± 5.1	135.7 ± 5.2	134.6 ± 5.0	0.18
Bilirubin (mg/dL)	1.6 ± 1.5	1.3 ± 1.1	1.6 ± 1.6	0.23
Haemodynamic				
Systolic blood pressure (mmHg)	92 ± 14	94 ± 20	92 ± 12	0.47
Systolic blood pressure <90 mmHg	92 (39%)	22 (43%)	70 (38%)	0.44
Diastolic blood pressure (mmHg)	62 ± 10	59 ± 12	63 ± 9	<0.01
Pulse pressure (mmHg)	30 ± 13	34 ± 19	29 ± 10	0.02
Mean arterial pressure (mmHg)	73 ± 10	72 ± 12	74 ± 10	0.23
Heart rate (b.p.m.)	86 ± 21	101 ± 29	82 ± 17	<0.01
Right atrial pressure (mmHg)	11.4 ± 0.4	11.3 ± 0.5	11.9 ± 0.7	0.55
Mean pulmonary artery pressure (mmHg)	30.7 ± 0.6	31.0 ± 0.7	29.8 ± 1.4	0.44
Pulmonary capillary wedge pressure (mmHg)	21.8 ± 0.6	21.7 ± 0.6	22.2 ± 1.4	0.75
Cardiac index (L/min/m^2)	1.9 ± 0.5	2.0 ± 0.5	1.9 ± 0.5	0.04
Cardiac index (<2.2 L/min/m^2)	200 (85%)	37 (72%)	163 (89%)	0.02
Cardiac output (L/min)	3.8 ± 1.2	3.9 ± 1.2	3.8 ± 1.2	0.70
Cardiac power output (W)	0.61 ± 0.21	0.61 ± 0.21	0.62 ± 0.21	0.89
Cardiac power index (W/m^2)	0.31 ± 0.09	0.32 ± 0.09	0.30 ± 0.09	0.24
Ejection fraction (%)	27 ± 14 (n = 228)	34 ± 16 (n = 51)	24 ± 12 (n = 177)	<0.01
Left ventricular end-diastolic dimension (cm)	6.3 ± 1.3	5.2 ± 1.2	6.6 ± 1.1	<0.01

GFR, glomerular filtration rate.

Table 3 Temporary mechanical circulatory support device utilization according to heart failure status

Device	All (n = 235)	Acute heart failure (n = 51)	Acute on chronic heart failure (n = 184)	P
IABP	48 (20%)	16 (31%)	32 (17%)	0.03
ECMO	21 (9%)	14 (28%)	7 (4%)	<0.01
Impella	30 (13%)	13 (25%)	17 (9%)	<0.01
Tandem heart	1 (0.4%)	0 (0%)	1 (0.5%)	0.60
Any percutaneous MCS	73 (31%)	27 (53%)	46 (25%)	<0.01
Any temporary MCS	77 (33%)	30 (59%)	47 (26%)	<0.01

ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; percutaneous MCS, any mechanical circulatory support device except full support with extracorporeal membrane oxygenation.

quite disparate from one another in both presentation and outcomes and thus may need to be considered as such in future analyses and trial design. Importantly, we have demonstrated a higher in-hospital mortality rate among patients presenting with acute HF and CS despite similar haemodynamic profiles and admission laboratory data, which raises the possibility that decisions regarding treatment escalation between the two populations may require very different criteria. Interestingly, there were also significantly higher rates of temporary MCS use in the acute CS population, which may corroborate that this patient population has a very different clinical phenotype even while measurable parameters are similar.

In our cohort, the 31.4% in-hospital mortality of patients presenting with acute CS is consistent with in-hospital mortality rates described in previous studies.[1–3] The mortality rate among patients presenting with CS in the setting of chronic HF was much lower at 9.8%. A recent study evaluating phenotypic differences between patients with CS due to end-stage HF and patients with CS due to ACS showed that patients with end-stage HF were characterized by higher filling pressures, lower oxygen delivery, greater anaerobic metabolism, and less severe metabolic acidosis.[14] While our study did not evaluate all of these parameters, the significant difference in mortality supports the theory that extrapolation of CS defining criteria from clinical trials in CS secondary to ACS may not appropriately risk stratify the very diverse chronic HF population.[1,2,5] Haemodynamic parameters commonly used to guide escalation of haemodynamic support in clinical trials may therefore be less reliable in titration of support in the chronic HF population.[1,7]

Physiological differences between acute CS and acute on chronic HF should also be considered. While no single unifying process has been implicated in chronic HF, several neurohormonal and haemodynamic compensatory feedback mechanisms lead to ventricular remodelling and

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Figure 1 Temporary mechanical circulatory support device use according to heart failure status. ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

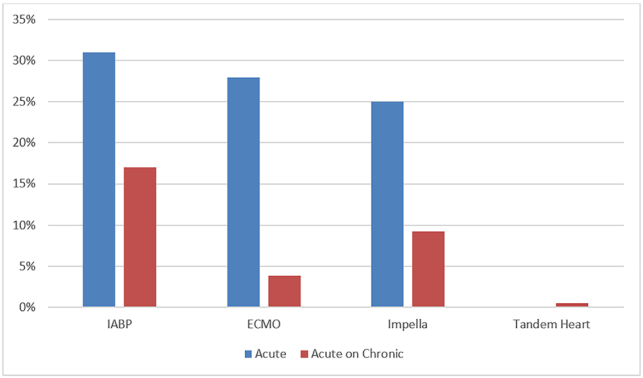
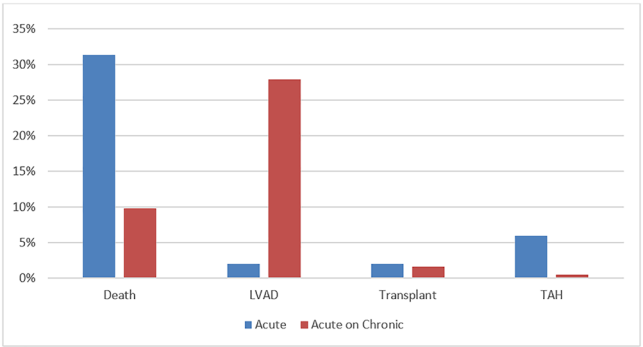


Table 4 Outcomes according to heart failure status

Outcome	All (n = 235)	Acute heart failure (n = 51)	Acute on chronic heart failure (n = 184)	P
In-hospital death at discharge	34 (14.5%)	16 (31.4%)	18 (9.8%)	<0.01
Bridge to LVAD	52 (22%)	1 (2.0%)	51 (28%)	<0.01
Bridge to transplant	4 (1.7%)	1 (2.0%)	3 (1.63%)	0.87
Bridge to total artificial heart	4 (1.7%)	3 (5.9%)	1 (0.5%)	<0.01
Time to hospital discharge (days)	24.2 ± 22.4	28.1 ± 26.7	23.4 ± 21.5	0.26
Time to death (days)	21.9 ± 43	32.6 ± 61.1	12.4 ± 9.3	0.17

LVAD, left ventricular assist device.

Figure 2 Outcomes according to heart failure status. LVAD, left ventricular assist device; TAH, total artificial heart.



normalization of tissue perfusion.[15,16] Inhibition of these feedback mechanisms is often a pharmacological target for chronic HF therapies. In contrast, patients presenting with acute HF are more likely to suffer from acute onset of maladaptive and self-perpetuating compensatory mechanisms and are unlikely to have been exposed to HF pharmacological therapies chronically.[5,9–11] Although the exact pathophysiology of these multifactorial, hemodynamically diverse HF processes remains poorly understood, consideration should be given to differences between the two conditions.[8]

Many patient and hospital protocol factors could contribute to our observations. Clearly, there were significantly higher rates of durable LVAD implantation in the chronic HF patients, which may suggest a different set of expectations for patients who had 'failed' HF therapies and presented with acute decompensation vs. those presenting with a new acute insult, where temporary MCS device use suggests a hope that native heart recovery may be possible. Additionally, recent data suggest that despite restoration of more normal haemodynamic profiles in patients with temporary MCS, post-operative morbidity and mortality after durable LVAD implantation in patients with CS are similar to INTERMACS profile 1 patients without temporary MCS.[17] Recent data also suggest that while some temporary MCS devices do not

improve mortality, they are associated with significantly higher rates of life-threatening bleeding and vascular complications.[18] This further muddies the water in terms of deciding which patients may benefit from a temporary MCS bridge to a more durable solution. This, in addition to the aforementioned considerations, supports the need for separate risk stratification models particularly when considering temporary MCS in acute on chronic decompensated HF.

This study needs to be considered in light of several limitations. Foremost, it was a single-centre, retrospective analysis and may not be generalizable to all centres. Additionally, as with all observational analysis, unmeasured confounding is possible and causality cannot be inferred. Furthermore, patients who presented with CS that was misdiagnosed or who did not undergo right heart catheterization or initiation of VA-ECMO were not captured in our study population given our screening methods. Furthermore, based on the retrospective nature of our data collection, we were not able to comprehensively identify all aetiologies of CS but were able to stratify cohorts based on acute or acute on chronic decompensation and by acute myocardial infarction and out-of-hospital cardiac arrest. Finally, the follow-up period was limited to in-hospital outcomes, and long-term follow-up after hospital discharge was not included.

Conclusions

Early recognition, definition, and management of CS remains clinically challenging. In our cohort of 235 patients presenting with haemodynamic criteria for CS, patients with acute HF were more likely to suffer in-hospital death (31.4% vs. 9.8%, $P < 0.01$) despite similar haemodynamic parameters (mean arterial pressure, CO, and cardiac power index) between the two groups, and there was a higher usage of temporary MCS (59% vs. 26%, $P < 0.01$) among those with acute CS. Current definitions and risk stratification models for CS based on clinical trials performed in the setting of ACS may not accurately identify CS in patients with acute on chronic HF, as evidenced by the significantly lower in-hospital mortality rates in our study. This supports the pathophysiological differences between the two groups and suggests that further investigation into parameters for appropriate identification of CS in patients with acute on chronic HF is warranted.

Conflict of interest

C.M. has served as a consultant investigator for Abbott, Medtronic, Abiomed, and SynCardia. J.M.M. has received research and consultation funding from Abiomed. No other relevant disclosures.

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