



Predictors of In-hospital Mortality in Cardiogenic Shock Patients on Vasoactive or Inotropic Support

Clinical Medicine Insights: Cardiology
Volume 15: 1–7
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/11795468211049449



Shuktika Nandkeolyar¹ , Tanya Doctorian¹, Gary Fraser², Rachel Ryu³, Colleen Fearon⁴, David Tryon⁴, Whitney Kagabo⁵, Dmitry Abramov¹, Christopher Hauschild³, Liset Stoletny¹ , Anthony Hilliard¹ and Antoine Sakr¹

¹Division of Cardiology, Department of Internal Medicine, Loma Linda University Medical Center, Loma Linda, CA, USA. ²School of Public Health, Loma Linda University, Loma Linda, CA, USA.

³Department of Pharmacy, Loma Linda University Medical Center, Loma Linda, CA, USA.

⁴Department of Internal Medicine, Loma Linda University Medical Center, Loma Linda, CA, USA.

⁵School of Medicine, Loma Linda University, Loma Linda, CA, USA.

ABSTRACT

BACKGROUND: Though controversial, the short-duration in-patient use of inotropes in cardiogenic shock (CS) remain an ACC/AHA Class IIa indication, and are frequently used in the initial treatment of CS. We evaluated in-patient mortality and effect on mortality risk of commonly used vasoactive inotropic medications for the medical management of SCAI stage B and C cardiogenic shock patients in a tertiary care cardiac care unit: dobutamine, dopamine, milrinone, and norepinephrine.

METHODS: We retrospectively evaluated 342 patients who received dobutamine, milrinone, dopamine, norepinephrine or a combination of these medications for SCAI stage B and C cardiogenic shock. Cox proportional hazards were used to form longitudinal mortality predictions.

RESULTS: Overall in-patient mortality was 18%. Each 1 µg/kg/minute increase in dobutamine independently corresponded to a 15% increase in risk of mortality. High dose dobutamine >3 µg/kg/minute is associated with 3-fold increased risk compared to ≤3 µg/kg/minute ($P < .001$). Use of milrinone, norepinephrine, and dopamine were not independently associated with mortality.

CONCLUSION: We demonstrate that the overall in-hospital mortality of SCAI stage B and C cardiogenic shock patients medically managed on inotropes was not in excess of prior studies. Dobutamine was independently associated with mortality, while other vasoactive inotropic medications were not. Inotropes remain a feasible method of managing SCAI stage B and C cardiogenic shock.

KEYWORDS: Cardiogenic shock, vasoactive inotropic score, in-hospital mortality

RECEIVED: March 28, 2021. **ACCEPTED:** September 1, 2021.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Antoine Sakr, Advanced Heart Failure and Transplant, Division of Cardiology, Department of Internal Medicine, 11234 Anderson Street, Schuman Pavilion, SP 1617, Loma Linda University Medical Center, Loma Linda, CA 92354, USA. Email: asakr@llu.edu

Key Points

1. SCAI stage B and C patients on dobutamine have a 15% increased risk of mortality per each 1 µg/kg/minute increase in dobutamine.
2. Higher doses of combined inotropes (measured by the VIS) and dobutamine >3 µg/kg/minute are associated with 3-fold increased risk of mortality in cardiogenic shock.
3. Milrinone, Norepinephrine, and Dopamine were not significantly associated with mortality in this population.

Introduction/Background

The inpatient use of inotropes in acute decompensated heart failure (ADHF) and cardiogenic shock (CS) remains controversial. There is a paucity of randomized control trials for placebo versus dobutamine or milrinone in patients with cardiogenic shock. Studies examining the use of inpatient inotropes have yielded mixed results. Inpatient inotropic support has been associated with worsening arrhythmias and worse

mortality due to arrhythmias.¹ Milrinone was studied in a randomized, placebo-controlled trial and found to have an increase in hypotension and new atrial arrhythmias, but did not differ in in-patient or 60-day mortality.² However, inotropes have been shown to improve other important metrics for heart failure, including reducing length of stay and symptomatic improvement while awaiting left ventricular assist devices or heart transplant.^{3,4} Also, a small placebo-controlled study demonstrated survival benefit of dobutamine and amiodarone compared to those on amiodarone alone.^{5,6}

For patients who have contraindications to mechanical circulatory support (MCS) or present at a site without those resources, inotropes remain an accessible, noninvasive method of managing acute decompensated heart failure. Current class I indications for inotropes are as bridge therapy until definitive therapy such as coronary revascularization, MCS, or heart transplantation can occur to preserve end-organ performance. Inotropes also have a class IIa indication as longer-term therapy as bridge to transplant or left ventricular assist device and a



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

class IIb indication for short term use in hospitalization for those with severe systolic dysfunction and hypotension with depressed cardiac output to maintain systemic perfusion and preserve end-organ performance, or otherwise palliative care.⁷ These recommendations are largely based on trials which used a high dose of inotropes: most studies used a range of 0.375 to 0.85 $\mu\text{g}/\text{kg}/\text{minute}$ for milrinone, 2.5 to 20 $\mu\text{g}/\text{kg}/\text{minute}$ for dobutamine, 0.11 to 0.16 $\mu\text{g}/\text{kg}/\text{minute}$ for norepinephrine, 3 to 10 $\mu\text{g}/\text{kg}/\text{minute}$ for dopamine.^{1,2,5,8,9}

Hypothesis and Purpose

We sought to define in-patient mortality and predictors of mortality in a contemporary cohort of patients presenting with ADHF and CS requiring low dose inotropic medications at our center.

Methods

This observational study was a retrospective analysis of patients admitted to Loma Linda University Medical Center who were diagnosed with cardiogenic shock as coded by ICD-10 code R57.0 or ICD-9 code 785.51, and then evaluated for risk of in-hospital mortality using a retrospective longitudinal analysis. Data was collected for patients who satisfied inclusion criteria that consisted of all adults (≥ 18 years of age) who presented with cardiogenic shock and were admitted to the cardiac care unit and received inotropic and/or vasoactive pressor support between January 2015 and December 2018. Patients were excluded if they were on home inotropic support or received mechanical circulatory support. Key data collected were demographic baseline characteristics (age, gender, race, weight), reason for admission (ADHF, acute coronary syndrome [ACS], or other), length of stay, left ventricular ejection fraction (LVEF), comorbidities (hypertension, hyperlipidemia, diabetes, coronary artery disease [CAD], etiology of heart failure), blood pressure and heart rate at the time of inotropic or vasoactive drip initiation, time-averaged doses and duration of intravenous vasoactive or inotropic therapy, acute hypoxic respiratory failure (AHRF) (requiring 2L oxygen or more), acute liver injury (ALI) (elevation of ALT $> 10\times$ upper limit of normal, INR > 2.0 in patients not on warfarin), or bilirubin ($> 3 \text{ mg/mL}$) and acute kidney injury (AKI) ($> 0.3 \text{ mg/dL}$ increase in serum creatinine within the 3 months prior to admission, or lowest serum creatinine noted during hospitalization).¹⁰ The clinical endpoint evaluated was inpatient mortality.

Vasoactive and inotropic medication doses were time-averaged: duration of each dose was multiplied by the concentration for that time, so the $\mu\text{g}/\text{kg}$ per person was calculated for each dose duration, then summed and divided by the total administration duration. A vasoactive inotropic score (VIS) was calculated for each patient ($\text{dopamine dose}(\text{mg} / \text{kg} / \text{min}) + \text{dobutamine dose}(\text{mg} / \text{kg} / \text{min}) + 100 \times \text{epinephrine dose}(\text{mg} / \text{kg} / \text{min}) + 10 \times \text{milrinone dose}(\text{mg} / \text{kg} / \text{min}) + 10000 \times \text{vasopressin dose}(\text{mg} / \text{kg} / \text{min}) + 100 \times \text{norepinephrine dose}(\text{mg} / \text{kg} / \text{min})$).¹¹ The clinical endpoint

was inpatient mortality documented in the electronic health record. SCAI cardiogenic shock stages were assigned retrospectively using admission data based on presence of hypotension, tachycardia, elevated lactate, end-organ dysfunction and refractory shock, as there were very few cases in which invasive hemodynamics were performed. In this data, all therapeutic regimens, including choice of inotropic or vasoactive medication captured in this study, were based on clinician judgment rather than a study protocol. The Loma Linda University Institutional Review Board approved the data collection protocol used in this study.

We compared baseline characteristics stratified by survival in this analysis. Baseline characteristics are described as mean \pm SD for continuous variables and number (proportion) for categorical variables. These variables were compared using *F*-test, *t*-test, or fisher exact test, or chi-square test as appropriate. Cox proportional hazards were adjusted for age, gender, race, history of hypertension, presence of AKI, AHRF, or ALI on admission, admission lactate, and SCAI stage.^{12,13} The average doses of all inotropes or vasoactive medications were treated as continuous variables. Low-dose dobutamine was defined as $\leq 3 \mu\text{g}/\text{kg}/\text{minute}$, and high-dose dobutamine was defined as doses $\geq 3 \mu\text{g}/\text{kg}/\text{minute}$. Three Cox proportional hazards regressions were used. In the first, we analyzed the average dose of each inotrope or vasoactive medication in addition to the risk factors listed above to determine the contribution of each inotrope on mortality risk. In the second and third, we explored the significance of a high dose versus low dose of dobutamine in the setting of an overall vasoactive or inotropic medication load by using the VIS score. The second cox regression compares dobutamine doses ≤ 3 , 3 to 6, and $> 6 \mu\text{g}/\text{kg}/\text{minute}$ to those who were not on dobutamine (but were on other inotropes, as represented by VIS), which established the linearity of the mortality risk of dobutamine. The third compares those with an average dobutamine dose of $\leq 3 \mu\text{g}/\text{kg}/\text{minute}$ to those with an average dobutamine dose of $> 3 \mu\text{g}/\text{kg}/\text{minute}$ to compare low dose to high dose dobutamine. Missing data were omitted. R version 3.6.1 was used for all statistical analysis (The R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 342 patients meeting inclusion criteria were identified. The baseline characteristics of the cohort stratified by survival group are summarized in Table 1, with combinations of inotropes in Supplemental Figure 1. There were no statistically significant differences between the 2 groups, except for end-organ damage at presentation, reason for admission, lactate, and SCAI stage.

Vital signs, time-averaged vasoactive and inotropic medications, and admission lactate levels summarized according to survival group in Table 2. In univariate analysis, the cohort that survived had an average lower heart rate (84 vs 93 beats per

Table 1. Basic characteristics of the study population, stratified by survival status.

	TOTAL (N=342)	SURVIVED (N=279)	DIED (N=63)	P VALUE
	MEAN ± SD OR # (%)	MEAN ± SD OR # (%)	MEAN ± SD OR # (%)	
Gender				.8
Men	226 (66)	183 (65.6)	43 (68.2)	
Women	116 (34)	96 (33.4)	20 (31.7)	
Race				.39
Caucasian	139 (40.6)	112 (40.1)	27 (42.9)	
Hispanic	127 (37.1)	100 (35.8)	27 (42.9)	
Black	40 (11.7)	35 (12.5)	5 (7.9)	
Other	36 (10.5)	32 (11.5)	4 (6.3)	
Age (years)		63.4 ± 15.2	67 ± 14.8	.54
Reason for admission				<.001
ADHF	225 (65.8)	200 (71.7)	25 (39.7)	
ACS	77 (22.5)	45 (16.1)	32 (50.8)	
Other	40 (11.7)	34 (12.2)	6 (9.5)	
LVEF (%)	23.2 ± 15.4	23 ± 15.4	23.7 ± 15.3	.79
Heart failure etiology†				.31
Ischemic	175 (51.8)	137 (50)	38 (60.3)	
Non-ischemic	130 (38.5)	112 (40.1)	18 (28.6)	
Combined	32 (9.5)	25 (9.1)	7 (11.1)	
Comorbidities				
HTN	229 (67)	194 (69.5)	35 (55.5)	.05
HLD	158 (46.2)	125 (44.8)	33 (52.4)	.34
DM	152 (44.4)	120 (43)	32 (50.8)	.32
CAD	188 (55)	147 (52.7)	41 (65.1)	.10
Valvular disease	87 (25.4)	79 (28.3)	8 (12.7)	.015
ESRD	16 (4.7)	11 (3.9)	5 (7.9)	.3
COPD	42 (12.3)	34 (12.2)	8 (12.7)	1
OSA	19 (5.6)	18 (6.5)	1 (1.6)	.22
Methamphetamine abuse	41 (12)	36 (12.9)	5 (7.9)	.48
Afib/flutter	131 (38.3)	109 (39.1)	22 (34.9)	.64
ICD	77 (22.5)	66 (23.7)	11 (17.5)	.37
CRT	32 (9.4)	28 (10.3)	4 (6.3)	.50
SCAI stage				<.001
B	96 (28.7)	95 (34.1)	3 (4.8)	
C	241 (70.5)	181 (64.9)	60 (95.2)	

(Continued)

Table 1. (Continued)

	TOTAL (N=342)	SURVIVED (N=279)	DIED (N=63)	P VALUE
	MEAN ± SD OR # (%)	MEAN ± SD OR # (%)	MEAN ± SD OR # (%)	
D	3 (0.9)	3 (1.1)	0 (0)	
End-organ damage				
AKI	223 (65)	171 (61)	52 (82.5)	.002
ALI	96 (28)	62 (22)	34 (54)	<.001
AHRF	175 (51)	127 (45)	48 (76)	<.001
Length of stay (days)	8.5 ± 15.4	8.8 ± 6.6	7 ± 8.8	.12

Abbreviations: ADHF, acute decompensated heart failure; ACS, acute coronary syndrome; Afib/flutter, atrial fibrillation or atrial flutter; AHRF, acute hypoxic respiratory failure; AKI, acute kidney injury; ALI, acute liver injury; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; ESRD, end stage renal disease; HLD, hyperlipidemia; HTN, hypertension; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnea.

†Data available for 274 in the survived group, 337 in the total cohort.

Table 2. Inotrope and pressor dosing, and associated vitals, stratified by survival status.

	TOTAL (N=342)	SURVIVED (N=279)	DIED (N=63)	P VALUE
	MEAN ± SD OR # (%)	MEAN ± SD OR # (%)	MEAN ± SD OR # (%)	
HR inotrope started (BPM)	86 ± 19	84 ± 19	93 ± 21	.002
SBP inotrope started (mmHg)	100.4 ± 20.7	102 ± 20	93 ± 20	.002
DBP inotrope started (mmHg)	65.4 ± 15.6	66 ± 16	62 ± 15	.04
HR max inotrope (BPM)	90.6 ± 20.5	88.5 ± 19	99.9 ± 24.1	<.001
SBP max inotrope (mmHg)	105.5 ± 22.1	108.4 ± 20	92.4 ± 25.9	<.001
DBP max inotrope (mmHg)	65.1 ± 17.2	67 ± 16	56 ± 17.9	<.001
Dobutamine (yes/no)	256 (74.9)	201 (72)	55 (87)	.02
Milrinone (yes/no)	70 (20.5)	62 (22)	8 (12.7)	.14
Norepinephrine (yes/no)	61 (17.8)	36 (12.9)	25 (39.6)	<.001
Dopamine (yes/no)	109 (31.9)	86 (31)	23 (36.5)	.4
Dobutamine dose (µg/kg/min)	3.7 ± 2.4	3.2 ± 1.8	5.4 ± 3.3	<.001
Milrinone dose (µg/kg/min)	0.27 ± 0.1	0.26 ± 0.08	0.35 ± 0.19	.21
Norepinephrine dose (µg/kg/min)	0.15 ± 0.16	0.11 ± 0.13	0.22 ± 0.16	.008
Dopamine dose (µg/kg/min)	4.6 ± 3.8	3.7 ± 2.7	8 ± 5	<.001
VIS	7.5 ± 11.1	5.4 ± 7.4	16.8 ± 18	<.001†
Number of patients on 1 VI med	220 (64.3)	188 (67.4)	22 (34.9)	
Number of patients on 2 VI meds	112 (32.7)	78 (28)	34 (54)	
Number of patients on 3 VI meds	18 (5.3)	11 (3.9)	7 (11)	
Number of patients on 4 VI meds	2 (0.6)	2 (0.7)	0 (0)	
Admission lactate (mmol/L)*	4.1 ± 3.6	3.4 ± 2.8	6.7 ± 5.1	<.001

Abbreviations: BPM, beats per minute; HR, heart rate; mmHg, millimeters of mercury; SBP, systolic blood pressure; VI, vasoactive or inotropic; VIS, vasoactive inotropic score.

*Lactate data available for 291 patients.

†Fisher-exact test used, and groups 3 and 4 collapsed into 1 in analysis.

Table 3. Results of multivariate analyses.

	HAZARD RATIO	LOWER 95% CI	UPPER 95% CI	P-VALUE
Milrinone dose*	1.12	0.08	14.9	.93
Dobutamine dose*	1.15	1.05	1.3	.002
Norepinephrine dose*	2.0	0.26	16.3	.50
Dopamine dose*	0.97	0.90	1.06	.54
Dobutamine <3 µg/kg/min [‡]	0.68	0.29	1.63	.38
Dobutamine 3-6 µg/kg/min [‡]	1.77	0.78	4.0	.17
Dobutamine >6 µg/kg/min [‡]	4.83	1.77	13.2	.002
High dose dobutamine (>3 µg/kg/min) [†]	2.85	1.58	5.14	<.001

*Corrected for age, gender, race, lactate, hypertension, SCAI score, acute kidney injury, acute liver injury, acute hypoxic respiratory failure, dobutamine, dopamine, milrinone, dopamine.

[‡]Corrected for age, gender, race, lactate, hypertension, SCAI score, acute kidney injury, acute liver injury, acute hypoxic respiratory failure, VIS. Compared to those not on dobutamine.

[†]Corrected for age, gender, race, lactate, hypertension, SCAI score, acute kidney injury, acute liver injury, acute hypoxic respiratory failure, vasoactive inotropic score, and compared to low-dose dobutamine (≤ 3 µg/kg/minute).

minute), and a higher initial systolic (102 vs 93 mmHg), higher diastolic blood pressure (66 vs 62 mmHg), and lower lactate (3.4 vs 6.7 mmol/L) as compared to those who died. These differences were more pronounced at peak doses of vasoactive and inotropic drips (Supplemental Table 2, Supplemental Figure 2). Time-averaged doses were lower in the survivors as compared to those who died: average dobutamine was 3.2 µg/kg/minute versus 5.4 µg/kg/minute, average milrinone dose was 0.26 µg/kg/minute versus 0.35 µg/kg/minute, average norepinephrine dose was 0.11 µg/kg/minute versus 0.22 µg/kg/minute, and the average dopamine dose was 3.7 µg/kg/minute versus 8 µg/kg/minute. Overall, the cohort was predominantly SCAI stage C (70%), though amongst those who died, there were 95% SCAI stage C. A summary of combinations of inotropes used in the study can be found in Supplemental Figure 1. The mortality rate with dobutamine alone was 15% (n = 137), milrinone alone was 3% (n = 35), dopamine alone was 4% (n = 24), and norepinephrine alone 18% (n = 13).

In this cohort of predominantly SCAI Stage B and C cardiogenic shock patients on inotropic or vasoactive medications who did not undergo mechanical support, the overall mortality rate was 18%. In patients on low-dose dobutamine, and in the lowest quintile of the VIS, the mortality was 9% (Supplemental Tables 2 and 3). A summary of the multivariable cox proportional hazards results are presented in Table 3. When adjusting for the doses of other inotropes, SCAI stage, presence of end-organ dysfunction, lactate, and other common risk factors, only dobutamine was significantly associated with a 15% increased risk in mortality with each 1 µg/kg/minute increase in dose. Milrinone, norepinephrine, and dopamine were not significantly associated with mortality in the same multivariable cox regression. When high-dose dobutamine (>3 µg/kg/minute) was compared to low-dose dobutamine (≤ 3 µg/kg/min), adjusting for use of other inotropes using the VIS, those on

high-dose dobutamine are at nearly 3-fold increased risk of mortality ($P < .001$) (Table 3). The risk of mortality of dobutamine was found to be non-linear, with no increased risk at low doses (Table 3). Moreover, the statistical model, given the adjustment for total inotrope dose, actually tested the predictive ability of dobutamine in comparison to “equivalent” doses of other inotropes, holding the total inotrope load constant.

Discussion

In this retrospective analysis of real world SCAI stage B and C cardiogenic shock patients at a single tertiary care academic center, we demonstrate that low doses of inotropes can be used in the initial medical management cardiogenic shock without excess mortality.¹⁴ We also report lower doses of inotropes than used in previous studies where the vasoactive/inotrope dosing data is available, and provide in detail the combinations of vasoactive or inotropic medications used.¹⁵

Our data would also suggest that for patients with cardiogenic shock stage B or C, the mortality of low-dose inotropes is approximately 9%. However, the mortality rate significantly increases as the dose of inotropes increases. This would suggest that for patients with SCAI stage B and C cardiogenic shock, low-dose inotropes may not be as deleterious as previously thought as an initial strategy. However, if higher doses are required to maintain hemodynamic and perfusion parameters, then more invasive strategies should be considered in those who are candidates for mechanical circulatory support.

The inpatient mortality of cardiogenic shock has been reported to be between about 12% to 37% recent major studies.^{13,15,16} Similar to these groups, our cohort is a heterogeneous group, with a 66% with ADHF complicated by cardiogenic shock, while 22.5% had ACS complicated by cardiogenic shock. The ADHERE registry had patients with ADHF of whom 8% were on inotropic support, though no data was

published on use of dopamine or norepinephrine within this registry.¹⁵ Mortality associated with patients only on milrinone or only on dobutamine were 12% to 14% respectively.¹⁵ Our cohort demonstrated a 3% mortality rate on milrinone alone, and 13% mortality rate on dobutamine alone (Supplemental Figure 1). However, there are 2 crucial differences to be noted between our cohort and the ADHERE HF patients who were on inotropic support, these being average systolic blood pressure and use of multiple vasoactive or inotropic medications. Only 2% of the patients in the ADHERE registry were hypotensive, but 8% received inotropic or vasoactive medications.¹⁷ In our cohort of SCAI stage B and C cardiogenic shock patients, the average systolic blood pressure when dobutamine or milrinone was initiated was 99 and 108 mmHg respectively, lower than that of the patients in the ADHERE registry (about 120 mmHg).^{15,16}

In the ALARM-HF trial, the mortality of those receiving IV inotropes was 25.9%, with a 1.5-fold increase in mortality for patients on dopamine or dobutamine, and a >2.5-fold increase in mortality for those on norepinephrine or epinephrine.^{16,18} Notably, the average dose of dobutamine was 10 µg/kg/minute, the average dose of norepinephrine used was 0.8 µg/kg/minute, and the average dose of dopamine was 3 µg/kg/minute. While our study used significantly lower doses of dobutamine and norepinephrine than ALARM-HF reported, we did use higher doses of dopamine (Table 2). Our study does demonstrate that patients on dobutamine doses >3 µg/kg/minute, as well as higher scores on the VIS were associated with increased risk of mortality, when corrected for measures of disease severity such as presence of end-organ dysfunction, lactate, and SCAI stage. However, contrary to the results of ALARM-HF and ADHERE, milrinone, dopamine, and norepinephrine did not have a statistically significant increase in mortality risk.

The CardShock trial had a significantly lower overall systolic blood pressure (78 mmHg) reported than the ALARM-HF or ADHERE trials, or than our cohort, and had an overall mortality rate of 37%.¹³ Similarly, a small, randomized control trial evaluating the use of IABP versus inotropes in cardiogenic shock (n = 32) demonstrated a significant improvement in the blood pressure, and pulmonary capillary wedge pressure in the IABP group compared with the inotrope group, however no significant difference in in-hospital mortality.¹⁹ Den Uil et al used relatively low doses of inotropes, similar to our cohort (though they used enoximone whereas we used milrinone as a phosphodiesterase 3 inhibitor). Unfortunately, CardShock did not report the doses of inotropes or vasoactive medications used in order to compare to our cohort.

We addressed combinations of inotropes by using the vasoactive inotropic score, which has been validated in pediatric and adult populations.¹¹ The VIS was developed originally in pediatric cardiogenic shock and post-surgical patients as a way

of measuring the cumulative effect of multiple vasoactive or inotropic medications on 1 patient, though originally developed in pediatric patients, has recently been validated in an adult cardiogenic shock patient population.¹¹ This prior analysis by Na et al grouped the VIS scores to demonstrate higher mortality rate by VIS both when grouped and as a continuous variable. Interestingly, the VIS was not significantly associated with mortality when dobutamine doses greater than 3 µg/kg/minute were administered. Confounding factors for using dobutamine including AKI on admission or hypotension were corrected for both indirectly with SCAI staging and directly with a categorical variable.

This study had several limitations. It is a single-center study, so prescribing biases in dosing and choice of inotropic or vasoactive medication may not represent that of other trials. It is difficult to elucidate clear differences between vasoactive inotropic medication groups as there were a significant portion of patients who were on multiple medications, though correction with VIS attempted to account for this. We also had limited data from right heart catheterizations, so SCAI classifications, which were proposed after this study was completed, were based on non-invasive measures such as end organ dysfunction, lactate, systolic blood pressure rather than invasive hemodynamics.¹² Additionally, we measured in-patient mortality rather than 30 or 60 day mortality, which may attribute to the overall lower rate of mortality. As this was an observational study, the conclusions drawn here are hypothesis generating and need evaluation in prospective randomized trials. However, such a trial would be difficult to design, as the development of a true control group of patients not treated with vasoactive or inotropic medications for cardiogenic shock would not be ethical.

Conclusion

This paper demonstrates that low-dose inotropes remain a high-risk but acceptable method of initially managing cardiogenic shock. The use of dobutamine at higher doses is independently associated with mortality in a contemporary patient population of SCAI stage C and B cardiogenic shock when correcting for the presence of other inotropes in 2 separate models. Treating the CS population remains a significant challenge, requiring further prospective randomized trials which may specify optimal doses and combinations of vasoactive inotropic medications. Given the broad spectrum of patients presenting with cardiogenic shock, practitioners need further clarification on the least harmful initial medical management of cardiogenic shock, and when a patient should be supported with MCS rather than vasoactive inotropic medications alone. Further areas of inquiry include management of CS with vasoactive inotropic support and invasive hemodynamics to better assess at what doses or combined vasoactive inotropic escalation to MCS should be considered to improve overall mortality in CS.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Dr. Gary Fraser and Dr. Shuktika Nandkeolyar. The first draft of the manuscript was written by Dr. Shuktika Nandkeolyar and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of Data and Material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Loma Linda University Medical Center approved this study.

ORCID iDs

Shuktika Nandkeolyar  <https://orcid.org/0000-0003-3163-3698>

Liset Stoletniy  <https://orcid.org/0000-0001-6113-2240>

Supplemental Material

Supplemental material for this article is available online.

REFERENCES

- De Santis V, Nencini C, Tritapepe L. Comparison of dopamine and norepinephrine in shock. *N Engl J Med*. 2010;362:2329; author reply 2330-2329; author reply 2331.
- Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287:1541-1547.
- Felker GM, Benza RL, Chandler AB, et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. *J Am Coll Cardiol*. 2003;41:997-1003.
- Verma S, Bassily E, Leighton S, et al. Renal function and outcomes with use of left ventricular assist device implantation and inotropes in end-stage heart failure: a retrospective single center study. *J Clin Med Res*. 2017;9:596-604.
- Nanas JN, Tsagalou EP, Kanakakis J, et al. Long-term intermittent dobutamine infusion, combined with oral amiodarone for end-stage heart failure: a randomized double-blind study. *Chest*. 2004;125:1198-1204.
- O'Connor CM, Gattis WA, Uretsky BF, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International randomized survival trial (FIRST). *Am Heart J*. 1999;138:78-86.
- Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:e240-e327.
- Elis A, Bental T, Kimchi O, Ravid M, Lishner M. Intermittent dobutamine treatment in patients with chronic refractory congestive heart failure: a randomized, double-blind, placebo-controlled study. *Clin Pharmacol Ther*. 1998;63:682-685.
- Elkayam U, Tasissa G, Binanay C, et al. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. *Am Heart J*. 2007;153:98-104.
- van den Akker JPC, Bakker J, Groeneveld ABJ, den Uil CA. Risk indicators for acute kidney injury in cardiogenic shock. *J Crit Care*. 2019;50:11-16.
- Na SJ, Chung CR, Cho YH, et al. Vasoactive inotropic score as a predictor of mortality in adult patients with cardiogenic shock: medical therapy versus ECMO. *Rev Esp Cardiol*. 2019;72:40-47.
- Baran DA, Grines CL, Bailey S, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock. *Catheter Cardiovasc Interv*. 2019;94:29-37.
- Harjola V-P, Lassus J, Sionis A, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur J Heart Fail*. 2015;17:501-509.
- Jentzer JC, van Diepen S, Barsness GW, et al. Cardiogenic shock classification to predict mortality in the cardiac intensive care unit. *J Am Coll Cardiol*. 2019;74:2117-2128.
- Abraham WT, Adams KF, Fonarow CG. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the acute decompensated heart failure national registry (ADHERE). *ACC Curr J Rev*. 2005;14:26-64.
- Follath F, Yilmaz MB, Delgado JF, et al. Clinical presentation, management and outcomes in the acute heart failure global survey of standard treatment (ALARM-HF). *Intensive Care Med*. 2011;37:619-626.
- Fonarow GC, Corday E; ADHERE Scientific Advisory Committee. Overview of acutely decompensated congestive heart failure (ADHF): a report from the ADHERE registry. *Heart Fail Rev*. 2004;9:179-185.
- Mebazaa A, Parissis J, Porcher R, et al. Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods. *Intensive Care Med*. 2011;37:290-301.
- Den Uil CA, Van Mieghem NM, B Bastos M, et al. Primary intra-aortic balloon support versus inotropes for decompensated heart failure and low output: a randomised trial. *EuroIntervention*. 2019;15:586-593.