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Predictors of Mortality and Associated Lactate Trends in Cardiogenic Shock Patients Treated with Impella® Placement - A Single Center Experience

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Abstract

Background

The Impella® devices have increasingly become a desired treatment option for cardiogenic shock (CS) as demonstrated by studies analyzing real-world use of hemodynamic support devices. However, data regarding outcomes after Impella® device implant and optimal timing of device placement remains scarce. This study investigates prognostic factors including serial lactate levels in CS patients treated with Impella®.

Methods

This retrospective study reviewed 76 consecutive patients diagnosed with CS supported with Impella® at a large, tertiary-care university medical center. Clinical variables and outcomes examined include co-morbidities, pre- and post-procedural lactate levels, and mortality.

Results

Of the 76 patients requiring an Impella®, 70% of patients survived to hospital discharge. Those who died post-device implant had a higher prevalence of hyperlipidemia (HLD), chronic kidney disease (CKD), and were more likely to require multiple (>1) vasopressors. The mean pre-procedural lactate levels were significantly higher (5.86 +/- 5.11 vs 2.16 +/- 1.50, p = 0.01) in the population who died, along with the change in lactate levels (1.90 +/- 2.56 vs -0.40 +/- 1.73, p=0.04). Those who died within 24 hours of implant showed a trend toward higher mean pre-procedural lactate levels (8.46 +/- 6.00 vs 3.86 +/- 3.31, p = 0.12).

Conclusions

Higher pre-procedural lactate levels, HLD, CKD, and increased vasopressor requirement were predictive of increased mortality in CS patients post-Impella® placement, especially within 24 hours of implant. Through serial lactate measurements, we demonstrated favorable outcomes in patients with early stabilization or greater lowering of post-procedural lactate levels suggestive of improved end organ perfusion.

Keywords: cardiogenic shock; mechanical circulatory support; lactate; myocardial infarction, hypoperfusion

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Introduction

Cardiogenic shock (CS) is a serious and devastating complication of acute myocardial infarction (AMI). Mortality from cardiogenic shock can range anywhere from 70-80% [1,2] and is particularly high in patients who present with CS in the setting of AMI. In patients with shock, several variables have been studied to help determine mortality in the acute setting. Lactate production is one of these variables and is known to be the result of mismatched oxygen supply and demand resulting in anaerobic metabolism [3]. The stress response to shock includes an increased metabolic rate, increased adrenergic output, accelerated glycolysis and modified myocardial bioenergetics supply resulting in increased lactate levels [3]. Given the high mortality rates in CS, early risk stratification is helpful in guiding treatment therapies.

A sub-study of the IABP-SHOCK II (Intra-Aortic Balloon Pump in Cardiogenic Shock) trial demonstrated that six variables could independently predict 30-day mortality. These include age, hyperglycemia, prior stroke, Thrombolysis In Myocardial Infarction (TIMI) flow grade after percutaneous coronary intervention <3, elevated creatinine and arterial blood lactate >5mmol/L at admission [4,5].

Previous studies analyzing real-world use of hemodynamic support devices have demonstrated favorable outcomes with the Impella® left ventricular assist devices (2.5, CP and 5.0) and these have increasingly become a desired treatment option for CS [6]. An Impella® is a percutaneously inserted left ventricular assist device inserted through the femoral artery via a modified Seldinger technique and placed in a retrograde fashion across the aortic valve into the left ventricle. Data on outcomes after implant and optimal timing of placement; however, remains scarce. The Impella-EUROSHOCK-registry retrospectively studied 120 patients and reported that lactate levels decreased from admission after Impella® device implant, suggestive of improved organ perfusion although 30-day mortality remained high. In addition, admission lactate levels >3.8mmol/L predicted a higher 30-day mortality [6].

Our study sought to investigate the prognostic significance of pre-procedural lactate levels, and lactate clearance after device implant. We hypothesized that patients in CS requiring Impella® device with lower lactate levels at admission, as well as those with a greater decrease in lactate levels, had improved survival compared to those patients with higher admission lactate levels, and/or an increase or lesser decrease in lactate levels after Impella® placement.

Methods

This study reviewed 76 consecutive patients with CS supported with Impella® placement at a large, tertiary-care university medical center between 2012 and 2017. Patients who developed CS were treated with either Impella® 2.5 or CP devices which were inserted via a standard catheterization procedure through the femoral artery. Only 1 patient had a surgically implanted Impella® 5.0 device. Cardiogenic shock was defined as having systolic blood pressure of 90 or less with or without signs of hypoperfusion, encompassing the beginning and later stages of cardiogenic shock. Variables examined include age, sex, comorbidities including HTN, DM, HLD, and CKD, and etiology of cardiogenic shock (STEMI vs no STEMI).

The dependent variables examined were pre- and post-procedural lactate levels, delta or change in lactate levels, and percentage delta lactate. Serial pre-procedural lactate levels were collected, but the level closest to the time of device implant was used. Patients who did not have either pre-device or post-device implant lactate levels were excluded from the smaller analytic dataset which consisted of 46 patients. Delta lactate level was calculated by subtracting the admission lactate level from the post-procedural lactate level (post-procedural lactate level – pre-procedural lactate level). Percentage delta lactate values were calculated by 100x(delta lactate level / pre-device lactate). These levels were examined in patients who survived and died post device placement. Patients who died were further categorized into patients who died within or after 24 hours of implant. Mortality was determined by review of medical charts. Patients who survived were not followed after discharge.

Statistical Methods

Our continuous data, pre- and post-procedural lactate levels, were expressed as means ± standard deviations. The differences in the continuous data between two study arms were assessed using a 2-sample t test. The significance of differences in proportions were tested using chi-squared tests. An alpha value of 0.05 was used to assign statistical significance. Multivariate logistic analyses were used to evaluate the odds ratios evaluating the odds ratios for mortality when proportionate delta lactate takes different values compared to a reference value of -50% (i.e. halving of levels post-implant). Given the modest study size, the number of independent variables in statistical models was restricted to four in order to avoid biased estimates [7]. We explored three different models, each being 4-variable combinations of covariates. As the outcome variable (mortality) was not a rare event, the logistic odds ratio (OR) is a poor estimate of the relative risk (RR). Log binomial models did not converge, so the RR was estimated directly from the logistic beta coefficients as

RRk = [1+exp(b1.(-0.5) +…+ bn.Xn)]/ [1+exp(b1.X1k +…+ bn.Xn), where X1 represents percentage delta lactate and b1 its coefficient; X2,…,Xn are the values of other covariates that for this calculation are fixed at their mean values; and X1k represents a particular value of X1 (the kth) that is being compared to the reference value of -50%. The 95 % confidence intervals are estimated from the 2.5th and 97.5th percentiles of 10,000 simulated values of the beta coefficients at each value of X1k between -50% and +100% (intervals of 10%). The simulation of the beta coefficients assumed multivariate normality, taking as parameters maximum likelihood estimates of betas as the means, and their estimated variance-covariance matrix.

Results

The study cohort initially consisted of 76 patients requiring an Impella® device placement. Of the 76 patients, 70% survived to hospital discharge. There were 23 inpatient deaths, 43% occurring within 24 hours of device implant, and 57% after 24 hours of implant. The average ages of those who survived to hospital discharge and those who died post-device implant were 58 ± 17 and 60 ± 17 years respectively (p=0.67) (Table 1). There was no significant difference between patients who survived to discharge or died inpatient with respect to gender (65% males vs 74% males, p=0.52) or STEMI as the presenting case (43% vs 48%, p=0.76). Among those who died post-device implant, there was a trend demonstrating a higher intubation rate (96% vs 81%, p=0.13) but this was not found to be statistically significant. However, a significantly higher percentage patients who died post-device implant required multiple vs single vasopressors (91% vs 55%, p=0.01). Of all the baseline co-morbidities encountered, some did not differ between outcome groups, including HTN (70% vs 87%, p=0.15) and DM (48% vs 35%, 0.37), but there was a higher prevalence of HLD (61% vs 24%, p=0.02) and CKD (35% vs 9%, p=0.03) in those who died post-device implant.

Of the 76 patients, a smaller analytic dataset of 46 patients who had pre-device implant lactate levels available were studied. Several patients had their devices implanted in the earlier years, when there was no specific device implant order set nor have all

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Table 1. Baseline Characteristics and Co-morbidities (N=46)

	Total (N=46)	Survived (N=23)	Died (N=23)	P
Age (Yrs)	59 ± 16.9	58 ± 16.7	60 ± 17.4	0.67
Gender, Male (%)	32 (70%)	15 (65%)	17 (74%)	0.52
STEMI Cases	21 (46%)	10 (43%)	11 (48%)	0.76
HTN (%)	36 (78%)	16 (70%)	20 (87%)	0.15
HLD (%)	18 (43%)	5 (24%)	13 (61%)	0.02
DM (%)	19 (41%)	11 (48%)	8 (35%)	0.37
CKD (%)	10 (22%)	2 (9%)	8 (35%)	0.03
COPD (%)	2 (4%)	1 (4%)	1 (4%)	1.00
Intubated (%)	39 (89%)	17 (81%)	22 (96%)	0.13
Multiple (>1) Vasopressors (%)	32 (74%)	11 (55%)	21 (91%)	0.01

P values come from tests of hypotheses of no difference between survivors and those who died using two-sample t or chi-squared tests.

Table 2. Lactate and Change in Lactate Levels (N=46)

Outcome Comparison 1	Survived (N=23) Mean ±SD, Range	Died (N=23) Mean ±SD, Range	P
Pre-implant Lactate Level (mmol/L)	2.16 ± 1.50 (0.8 – 6.3)	5.86 ± 5.11 (1.3 – 16)	0.01
Delta Lactate (mmol/L)	- 0.4 ± 1.73 (-4.9 – 3.6)	1.9 ± 2.56 (-1.2 – 10)	0.04
% Delta Lactate	-7.4% ± 61% (-78% - 209%)	62% ± 112% (-33% - 500%)	0.02
Outcome Comparison 2	Died within 24 hrs of implant (N=23)	Died post 24 hrs (N=23)	P
Pre-implant Lactate Level (mmol/L)	8.46 ± 6.00 (2.8 – 16)	3.86 ± 3.31 (1.3 – 12)	0.12
Delta Lactate (mmol/L)	1.7 ± 1.44 (-0.3 – 4.4)	2.05 ± 3.20 (-1.2 – 10)	0.58
% Delta Lactate	32% ± 24% (-8.9% - 58%)	84% ± 145% (-33% - 500%)	0.27

Table 2: P values come from tests of the hypotheses of no difference between survivors and those who died using two-sample t tests.

their labs scanned into the electronic medical record system. In the subset analysis, the mean pre-procedural lactate level was significantly higher in the population who died in hospital post-implant compared to the population who survived to discharge (5.86 +/- 5.11 vs. 2.16 +/- 1.50, p=0.01) (Table 2). Those who died within 24 hours of implant showed a trend towards higher mean pre-procedural lactate levels than those who died after 24 hours of device implant (8.46 +/- 6.00 vs 3.86 +/- 3.31, p=0.12) (Table 2).

Of the 46 patients who had pre-procedural lactate levels available, 39 patients had serial lactate levels collected to calculate the change in lactate levels. The delta lactate level was significantly higher in the group who died in-hospital compared to the survivors to hospital discharge (1.90 +/- 2.56 vs -0.40 +/- 1.73, p=0.04), as was the percentage change (delta) in lactate (62 ± 112% vs -7.4 +/- 61%, p=0.02) (Table 2). Those who died within 24 hours of implant had a greater positive change, on average, in delta lactate levels than those who died after 24 hours of implant (2.05 +/- 3.20 vs 1.70 +/- 1.44, p=0.58) (Table 2), but this was not found to be statistically significant.

The pre-device lactate and percentage delta lactate levels (100xdelta lactate/pre-device lactate) both remained statistically significant in a multivariate logistic regression analysis in 2 of the 3 models (Table 4), and nearly so in model 1 where only the percentage delta lactate remained statistically significant. Prevalence of HLD was significantly higher in the univariate analysis but drops off in significance once adjusting for other variables in the multivariate study, possibly serving as a marker for patients with higher pre-device lactate levels.

In Figure 1, results transformed to directly show relative risk (RR) rather than the biased odds ratio (OR) estimator, confirm the strong association between proportionate change in lactate levels and risk of dying. Although the confidence intervals are wide, they do not include the null, and the estimated slope of the lactate effect is large.

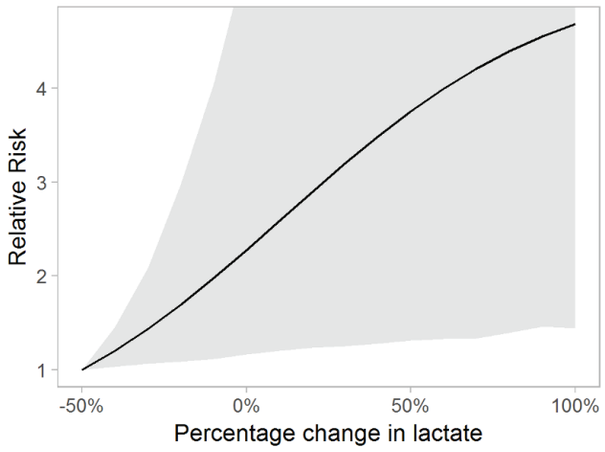

Figure 1. Percentage Lactate Change and Relative Risk of Death.

Reference value of percentage delta lactate is -50%; Shaded area is a 95% confidence band for the relative risk.

Discussion

Although only 7-10% of AMI patients present with CS, the mortality attributable to CS in these cases can be as high as 70-80% [8]. The randomized SHOCK trial [8] showed that with emergency revascularization, and hemodynamic support, including use of intra-aortic balloon pump (IABP), patients with CS had a mortality of 50% at six months. There was no difference in mortality at 30 days between the Impella® and IABP groups. The ISAR-SHOCK Trial demonstrated that using an Impella® device resulted in greater improvement in cardiac index compared to IABP [9]. While the Impella® device has demonstrated improved hemodynamic parameters compared with IABP, data on outcomes and guidance of timing remains scarce.

Table 3: Lactate levels as Predictors of pre-Discharge Death in Multivariate Logistic Regression (N=46)

Multivariate variable logistic regression			
	OR	95%CI	P1
Model 1			
Pre-device Lactate mmol/L	1.65	0.95 – 2.86	0.08
% Delta Lactate (per 50% change)	3.25	1.33 – 7.94	0.01
HLD (Yes=1, No=0)	5.75	0.82 – 40.28	0.08
Model 2			
Pre-device Lactate mmol/L	2.76	1.19 – 6.41	0.02
% Delta Lactate (per 50% change)	3.48	1.29– 9.37	0.01
Age (per 10 years)	1.32	0.71 – 2.46	0.38
HTN (Yes=1, No=0)	9.06	0.57 – 144.32	0.12
Model 3			
Pre-device Lactate mmol/L	1.87	1.03 – 3.42	0.04
% Delta Lactate (per 50% change)	3.260	1.21 – 8.74	0.02
DM (Yes=1, No=0)	0.65	0.11 – 3.69	0.62
CKD (Yes=1, No=0)	0.62	0.06 – 6.75	0.70

Table 3: P values come from tests of the null hypothesis that the OR=1.0.

There have been several studies that have investigated the utility of lactate levels as a prognostic tool in patients with CS or in determining the severity of circulatory compromise. Admission hyperlactatemia has been demonstrated as a predictor of in-hospital mortality. A study by Valente et al. demonstrated that admission lactate level >6.5 mmol/L was an independent predictor of in-hospital death in patients with CS [3]. Our study evaluates the clinical significance of pre-procedure lactate levels and the change in lactate levels over the course of hospital stay in patients with CS treated with percutaneous mechanical circulatory support. With the increasing use of Impella® devices in patients who present with AMI and hemodynamic instability, studies have looked at the utility of various clinical markers which may help predict outcomes in this group of patients. In our analysis, as previously mentioned, patients who did not survive to hospital discharge had a significantly higher pre-device lactate level. In addition, although not statistically significant, our analysis showed a trend towards increased 24 hour mortality after device placement for patients with higher pre-procedural lactate levels.

In our study, when compared to a reference of a decrease in lactate levels to half of the admission levels, others with lesser falls or rises in lactate levels post device placement had substantially worse outcomes, suggesting that the adverse lactate trends resulted from further hemodynamic impairment. A proportionate change in lactate levels even with a lower starting level was also still predictive. Despite several studies looking at various markers as prognostic indicators, it has been a difficult task to come up with a single clinical marker (i.e lactate levels) and a cut-off value to use as a guide for early intervention or resuscitation. Therefore, examining the marker's trend rather than an absolute endpoint may be a more reliable tool for early goal directed therapy for patients with CS. Our study helps identify a subset of patients who may need more aggressive resuscitation (patients with a higher lactate level at admission) and may also indicate insufficient hemodynamic resuscitation in patients who do not show a substantial decrease in lactate level after Impella® device placement. A study by Attana et al. showed a significantly lower survival rate in CS patient following STEMI with 12-hour lactate clearance < 10% [10]. A study in the Netherlands looking at patients with post-cardiotomy CS found that an increase in lactate of >10%, 12 hours after Impella® LP 5.0 implantation was associated with an increase in 30-day mortality [11]. In our analysis, based on serial lactate measurement, we concluded that early stabilization of circulatory shock with the Impella® 2.5 device was associated with improved hospital outcome.

Results from the multicenter Impella-EUROSHOCK registry in 2013 demonstrated a reduction in lactate levels in CS patient treated with Impella® 2.5; however their 30-day mortality remained high at 64.2% and admission lactate level >3.8 was shown to be an independent predictor for 30-day mortality [5]. In this study, despite a practice pattern of reserving Impella® placement for the sickest of patients with CS, we observed better survival when compared to that seen in many randomized clinical trials. We also showed that in addition to higher pre-procedural lactate levels, serial lactate measurements were useful prognostic indicators for hospital outcome.

Our study also demonstrated a higher prevalence of HLD in those who died post-device implant; however, the significance dropped going from univariate to multivariate analysis after adjusting for other variables. This may be explained by some collinearity as there may be a relationship between HLD and the acute phase variables, possibly serving as a marker for patients with higher pre-device lactate levels. HLD may indicate more advanced and diffuse coronary disease and hence less resilience to the effects of cardiogenic shock.

Limitations

This was a single center retrospective study with its inherent limitations. This study involved a relatively small number of subjects. Several patients were excluded for the smaller analytic database looking at lactate trends as these patients had Impella implantation during the earlier years where there was no clearly defined order set post-implant including serial lactate labs nor were all the lab values scanned into the electronic medical records at that time. The exact timing of the lactate levels and device implantation was not standardized. The closest lactate level prior to time of Impella® device implantation and 12-24 hours post implantation were used for the analysis. Lastly, patients who presented with CS were not categorized or differentiated into sub-categories delineating the various etiologies of shock (i.e. STEMI, myocarditis, stress induced cardiomyopathy). These variables were not accounted for and this study is not a completely comprehensive study investigating all factors that could potentially contribute to our outcomes. The study has a low power; however it does not preclude providing useful information as the effect is strong. One should perhaps acknowledge that our tentative conclusions need to be confirmed in larger datasets.

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Conclusions

We observed higher pre-procedural lactate levels in non-survivors of CS post-Impella® device placement. Through serial lactate measurements, we demonstrated favorable outcome in patients with early stabilization or lower post-procedural lactate levels suggestive of improved end organ perfusion. Conversely continued rise or lack of fall in lactate levels post-device placement was associated with worse outcomes. This data will aid clinicians in identifying patients who will best benefit from Impella® device placement.

Declarations of Interest

The authors declare no conflicts of interest.

Acknowledgements

The authors state that they abide by the "Requirements for Ethical Publishing in Biomedical Journals".[12]

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