Lactate levels as a marker of tissue hypoperfusion in acute heart failure patients seen in the emergency department: a pilot study

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Abstract

Acute heart failure (AHF) may lead to subclinical tissue ischemia due to hypoperfusion from inadequate forward flow or congestion. The aim of the present study is to test whether lactate levels are elevated in emergency department (ED) patients with AHF. A prospective pilot study of ED AHF patients was conducted. Venous lactate level was measured at baseline and 6-12 hours after initial draw. Of the 50 patients enrolled, mean age was 65.3 years, 68% were male. Only 7 (14%) had an elevated lactate on either draw, with no differences in baseline characteristics between patients with and without elevated lactate. Patients with an elevated lactate had a higher mean heart rate (99 *vs* 81, P=0.03) and trended toward an increased rate of abnormal initial temperature (57 *vs* 23%, P=0.06). In this pilot study, only a minority of acute HF patients had an elevated lactate on presentation.

Introduction

Heart failure occurs with any impairment in the heart's ability to fill with or eject blood.[1] During acute heart failure (AHF), further deleterious hemodynamic and neurohormonal changes occur, which may lead to tissue hypoperfusion.[1,2] As myocardial, renal, and liver injury has been observed in AHF, significant tissue injury and organ hypoperfusion may result in elevated lactate levels.[2] As a marker of poor perfusion, lactate rises with tissue hypoxia. Elevated lactate is used clinically, and serves as a prognostic marker in trauma and sepsis.[3] In a small study of AHF patients with reduced ejection fraction (<30%), 22 of 29 patients had elevated lactate levels ≥2 mmol/L; this suggests AHF patients may suffer from occult tissue hypoperfusion despite no overt clinical shock.[4] However, this study was conducted prior to the era of natriuretic peptide testing, only included patients with reduced ejection fraction (EF), and did not perform a detailed characterization of patients at baseline, though central venous catheterization was performed.[4]

In this small pilot study, our primary objective was to evaluate whether AHF is associated with subclinical organ hypoperfusion, as demonstrated by elevations in serum lactate, and if so, the magnitude and duration of the elevation.

Materials and Methods

Study design

This was a prospective cohort study of a convenience sample of patients presenting with AHF to a single urban emergency department (ED) during the study period of August 2010 through April 2012. The study was funded through an Investigator Initiated Grant from Abbott Point of Care and approved by the Institutional Review Board. The study design, database, data analysis, and final manuscript were independent of the sponsor.

Study population

Acute heart failure patients were identified within 8 hours of ED presentation. In order to qualify, patients had to have signs and symptom of HF resulting in a primary diagnosis of AHF, were >18 years of age, and had an initial B-type natriuretic peptide (BNP)>200 pg/mL. Patients with ongoing acute coronary syndrome or troponin elevation greater than three times the upper limit of normal, dialysis dependent, new devices or surgery within the last 30 days, enrolled in an investigational agent or therapy in the last 30 days, unable to provide informed consent, and currently pregnant or up to 60 days *post-partum*, were excluded.

Study protocol

After providing written informed consent, a venous blood draw and serum lactate level were determined using whole blood by i-STAT (Abbott Point-of-Care, Inc., Abbott Park, IL, USA) lactate analyzer. The reportable range is 0.30-20.00 mmol/L, reference range of 0.36-1.25 mmol/L arterial and 0.90-1.70 mmol/L venous. Per the package insert, lactate is measured amperometrically. The enzyme lactate oxidase, immobilized in the lactate biosensor, selectively converts lactate to pyruvate and hydrogen peroxide (H_2O_2). The liberated hydrogen peroxide is oxidized at a platinum electrode to produce a current which is proportional to the sample lactate concentration. While venous or arterial blood may be sampled, for our study, capillary whole blood was used. Initial lactate level was determined within 8 hours of ED presentation, and a follow-up level was measured at 6-12 hours from first measurement. Demographic, clinical, and physical exam characteristics were also collected either primarily or through review of the medical record.

Objectives

Our primary outcome was lactate elevation at time of initial assessment. Lactate level <2 mmol/L was defined as normal a priori, based on literature where lactate level of 2 or higher was associated with worse outcomes.[5] Our secondary objective was to examine lactate clearance in the subset of patients with an initial elevated lactate.

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Conflict of interest: KS, LA, and LP declare no potential conflict of interest; PSP reports that in the last 12 months, he is or has been or received consultant for Intersection Medical, INSYS, Janssen, Medtronic, Novartis, Trevena, scPharmaceuticals, Cardioxyl, Roche Diagnostics.

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Table 1. Baseline patient characteristics.

Demographics		All patients (n=50)	Elevated lactate (n=7)	Normal lactate (n=43)	P
Mean age, years (SD)		65.3 (15.7)	65.6 (10.0)	65.2 (16.6)	0.96
Male gender, % (n)		68 (34)	71 (5)	67 (29)	0.83
Race, % (n)	White	58 (29)	43 (3)	60 (26)	0.85
aT	Asian	0	0	0	
	Hispanic	2 (1)	0	2 (1)	
	Other	2 (1)	0	2 (1)	
Cardiovascular history	Coronary artery disease, % (n)	38 (19)	14 (1)	42 (18)	0.16
	Valvular disease, % (n)	17 (8)	14 (1)	18 (7)	0.84
	Prior myocardial infarction, % (n)	19 (8)	0	22 (8)	0.17
	History of cardiomyopathy, % (n)	46 (21)	57 (4)	44 (17)	0.51
	Prior PCI, % (n)	23 (11)	0	28 (11)	0.11
	Prior CABG, % (n)	14 (6)	0	16 (6)	0.29
	Prior CVA, % (n)	16 (7)	0	18 (7)	0.22
	Ejection fraction mean, % (%range, n)	45 (10-76, 38)	38 (15-70, 4)	46 (10-76, 34)	0.38
Non-cardiovascular history, % (n)	Obesity	38 (17)	0	44% (17)	0.04
	Peripheral vascular disease	4 (2)	0	5 (2)	0.54
	Asthma/COPD	33 (16)	43 (3)	32 (13)	0.57
	Diabetes, insulin-dependent	13 (6)	0	15 (6)	0.28
	Diabetes, non-insulin dependent	10 (5)	14 (1)	10 (4)	0.70
	Renal insufficiency	54 (25)	67 (4)	53 (21)	0.52
	Liver disease	2 (1)	17 (1)	0	0.008
	Anemia (hgb<12)	34 (16)	14 (1)	38 (15)	0.23
	Cancer history	20 (10)	0	24 (10)	0.15
	Hypertension	83 (40)	67 (4)	86 (36)	0.24
Baseline medications	Beta blocker	68 (34)	57 (4)	70 (30)	0.51
	ACE inhibitor	48 (24)	57 (4)	47 (20)	0.60
	ARB	10 (5)	14 (1)	9 (4)	0.68
	Aldosterone antagonist	10 (5)	0	12 (5)	0.34
	Diuretic	66 (33)	71 (5)	65 (28)	0.74
	Cardiac glycoside	4 (2)	14 (1)	2 (1)	0.13
	Pacemaker	14 (7)	0	16 (7)	0.25
	ICD	10 (5)	0	12 (5)	0.34
Presentation	Abnormal temperature (>38°C, or <36°C), % (n)	28 (14)	57 (4)	23 (10)	0.06
	Systolic BP ,% (n)				
	>140	48 (24)	43 (3)	49 (21)	0.61
	100-140	44 (22)	43 (3)	44 (19)	
	<100	8 (4)	14 (1)	7 (3)	
	Heart rate, mean, % (%range, SD)	84 (37-138, 21)	99 (75-138, 22)	81 (37-118, 20)	0.03
	Respiratory rate mean, % (%range, SD)	19 (16-28, 2)	20 (16-24, 3)	19 (16-28, 2)	0.88
	SpO_2 mean, % (%range, SD)	97 (90-100, 2)	96% (90-100, 4)	98 (91-100, 2)	0.06
	Supplemental O_2 source % (n)				
	None	56 (28)	43 (3)	58 (25)	0.45
	Nasal cannula	44 (22)	57 (4)	42 (18)	
	Facemask	0	0	0	
	Non-rebreather	0	0	0	
	Positive pressure ventilation	0	0	0	
Physical exam findings, % (n)	JVD	54 (27)	71 (5)	51 (22)	0.382
	Rales	44 (22)	29 (2)	47 (20)	0.553
	Peripheral edema	78 (39)	71 (5)	79 (34)	0.155
Lab values, median (IQR)	Creatinine, mg/dL	1.21 (1.04-1.57)	1.35 (1.00-1.55)	1.19 (1.04-1.64)	0.675
	BUN, mg/dL	21 (15-26)	24 (22-30)	20 (13-26)	0.218
	BNP, pg/mL	1103 (647-1936)	2213 (1225-4941)	991 (564-1586)	0.009
CXR findings, % (n)	Interstitial edema	50 (25)	43 (3)	51 (22)	0.684
	Pulmonary edema	42 (21)	57 (4)	40 (17)	0.381
	Pleural effusion	44 (22)	43 (3)	44 (19)	0.948

SD, standard deviation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; hgb, hemoglobin; ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; ICD, implantable cardioverter defibrillator; BP, blood pressure; JVD, jugular venous pressure; IQR, interquartile range; BUN, blood urea nitrogen; BNP, B-type natriuretic peptide; CXR, chest x-ray.

Table 2. Characteristics of patients with elevated lactate levels.

Patients	Characteristics					
	Age (years)	Gender	Brief history	Exam	Lactate levels	Hospital course
1	69	M	History of HF, afib, s/p MVR, presented with fatigue and dyspnea on exertion, EF=30%	T=97.6 F, BP=124/95, HR=91 in afib, 98%, signs of congestion (JVD)	2.05, 2.46	In the ED, diuresed with lasix 40 mg IV. Admitted to the general medicine floor for heart failure exacerbation, no additional HF therapies initiated aside from resumption of patient's home meds, discharged on HD #2
2	73	M	History of COPD, alcoholic cirrhosis, hypothyroidism (no history of HF), presented with SOB and dyspnea on exertion	T=95.1 F, BP=93/68, 98%, HR=138, signs of congestion (crackles, LEE)	2.49, 1.84	In the ED, diuresed with bumex 1 mg IV, also empirically treated for community acquired pneumonia with antibiotics, and given a therapeutic dose of LMWH for suspected PE. Admitted to the CCU after developing hypotension in the ED. Echography performed on HD#2 demonstrated EF 20% and Grade II-III diastolic dysfunction. Underwent LHC given new HF, no obstructive CAD. Determined to have likely alcohol induced vs tachycardia induced ca diomyopathy. Patient had a hospital course complicated by hypotension, atrial fibrillation with RVR, delirium, thrombocytopenia, and urinary retention. Discharged on HD#20
3	70	M	History of DM2, HTN (no history of HF), presented with cough and leg swelling	T=96.6 F, BP=127/79, HR=114 in afib, 95%,x signs of congestion (LEE)	1.79, 2.08	In ED, diuresed with lasix 20 mg IV, hypokinesia with EF<25%, Grade III diastolic dysfunction. Admitted to general medicine floor for evaluation and management of new heart failure and afib with RVR. Started on lasix gtt for diuresis, and bridged with heparin to oral anticoagulant for new afib. Underwent RHC and LHC demonstrating significant CAD w 75% lesion in left main coronary artery, CABG recommended. Underwent extensive pre-operational evaluation as an inpatient, discharged home with LifeVest on HD# 12. Readmitted for planned CABG and Maze procedure 9 days later
4	60	F	History of HTN, COPD (no history of HF), presented with SOB, cough and leg swelling	T=97.1 F, BP=186/108, HR=121, 99%, signs of congestion (crackles, LEE)	1.08, 2.20	In ED, diuresed with lasix 20 mg IV, had been given sublingual nitro 400 mcg by EMS prior to arrival. Also received 1 duoneb for cough/SOB. Echography performed in ED demonstrated dilated cardiomyopathy with EF=10-15%. Admitted to cardiology initiated on lasix 40 mg IV BID. Hospital course complicated by DVT, stayed inpatient to titrate oral anticoagulant dose, threatened to leave AMA on multiple occasions. Discharged on HD#14, stated to her team upon dicharge that she planned to be non-compliant with her medications

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Table 2. Continued from previous page

Patients	Age (years)	Gender	Brief history	Characteristics Exam	Lactate levels	Hospital course
5	78	F	History of CHF, HTN, presented with SOB. EF=30-35%	T=94.6 F, BP=152/122, HR=105, 100%, signs of congestion (hepatomegaly, LEE)	1.84, 2.83	In ED, diuresed with lasix 40 mg IV and given home dose of PO antihypertensives, but persistently hypertensive so given nitropaste. Admitted to general medicine floor, underwent diuresis with bumex IV BID and bumex gtt. Had HF and HTN meds titrated as an inpatient. Discharged on HD# 7
6	61	F	History of CHF, sarcoidosis, pulmonary HTN, presented with leg swelling and cough. EF>70%	T=97.2 F, BP=131/74, HR=83, 87%, signs of congestion (JVD, LEE)	1.06, 3.13	In ED, diuresed with lasix 80 mg IV, placed on 40% FiO2 via face mask for low O2 saturations. CTA in ED negative for PE. MICU consulted given supplemental O2 requirement, determined patient stable for admission to general medicine floor. Admitted to general medicine floor for lasix gtt and titration of HF and pulmonary HTN medications, with pulmonary service following. Echography obtained as inpatient demonstrated severe, worsened pulmonary HTN. On HD#4, transferred to the MICU for tachypnea, increasing O2 requirement, increased WOB and fever. Upon transfer to MICU was placed on BiPAP, treated for HCAP with antibiotics, and continued on treatment for HF and pulmonary HTN. Respiratory status failed to improve in the MICU, but patient decided she did not want to be on BiPAP at home. Transitioned back to 5L nasal cannula and seen by palliative care. Patient elected to go home from the MICU and at the time of discharge on HD#10 was considering hospice care
7	48	M	History of nonischemic cardiomyopathy, CHF, atrial flutter, presented to EP clinic with vomiting and epigastric pain, sent to ED by EP medical doctor due to concern for digoxin toxicity. EF=15%	T=95.8 F, BP=150/107, HR=121 in afib, 98%, signs of congestion (LEE)	1.87, 2.83	In the ED, given diltiazem 10 mg IV for afib with RVR, no diuretics or nitrates administered. Digoxin level obtained and was within normal limits (1.9). Patient admitted to the inpatient cardiology service for management of heart failure exacerbation and afib w RVR. Daily diuresis with IV lasix, bumex; initially on IV anticoagulant therapy for afib while cardiology service considered cardioversion, but TTE demonstrated thrombus, so patient bridged to oral anticoagulant as an inpatient and discharged on HD#5 with plan to return to EP clinic for scheduled outpatient cardioversion

HF, heart failure; afib, atrial fibrillation; MVR, mitral valve replacement; EF, ejection fraction; T, temperature; BP, blood pressure; HR, heart rate; ED, emergency department; JVD, jugular venous pressure; IV, intravenous; HD, hospital day; COPD, chronic obstructive pulmonary disease; SOB, shortness of breath; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; CCU, coronary care unit; LHC, left heart catheterization; CAD, coronary artery disease; RVR, rapid ventricular rate or response; DM2, type 2 diabetes; HTN, hypertension; RHC, right heart catheterization; CABG, coronary artery bypass graft surgery; EMS, emergency medical system; BID, twice a day; DVT, deep vein thrombosis; AMA, against medical advice; CHF, chronic heart failure; CTA, computed tomography angiography; MICU, medical intensive care unit; WOB, work of breathing; BiPAP, bi-level positive airways pressure; HCAP, healthcare-associated pneumonia; EP, electrophysiology; TTE, transthoracic echocardiogram.

Data analysis

Our sample size of 50 patients was determined based on logistical and budgetary constraints. Using a one-tailed estimate, 80% power, and an alpha of 0.05, this sample size was powered to show an effect size of 33% comparing the proportion of patients with and without elevated lactate. Patients were divided into elevated (≥2 mmol/L) or normal lactate groups. Due to small number of patients with elevated lactate levels, patients were included in the elevated group if they had an elevated lactate on either of the two blood draws. Comparisons between groups were done with student's t-test, chi-square test, and ANOVA as appropriate. Given the small number of patients with elevated lactate levels, repeated measures analysis was not performed.

Results

Of the 50 patients enrolled, 68% were male, 58% white, with a mean age of 65.3 years (standard deviation=15.7 years) (Table 1). Mean ejection fraction was 45% (range 10-76%), and the majority of patients were on a beta-blocker or a diuretic (68 and 66% respectively).

Seven patients had an elevated lactate level on either blood draw. Two patients had elevated lactate on the first blood draw, within 8 hours of ED presentation. One of those patients had a persistently elevated lactate on second blood draw 6-12 hours later, and 5 other patients had a newly elevated lactate on second draw. Patients were similar in cardiovascular and non-cardiovascular medical history, and in historical heart failure medications.

Characteristics of patients in the elevated lactate group are presented in Table 2, with brief summaries of history and hospital course. Of the 7 patients with elevated lactate, 4 were male, and ages ranged from 48-78 years. Three of the 7 patients had no previously documented diagnosis of heart failure. None of the patients had systolic blood pressure less than 90mmHg on ED arrival. Patients with an elevated lactate had a higher mean heart rate (99 *vs* 81, P=0.03) and trended toward an increased rate of hypothermia (57 *vs* 23% with either hyper or hypothermia, P=0.06). Six patients were admitted to the floor, and one to the coronary care unit; one patient was admitted to the floor and later transferred to the medical intensive care unit for respiratory distress. With the exception of one patient who developed pneumonia on hospital day four (Table 2), no patients were diagnosed with infection during the course of hospitalization. Hospital length of stay ranged 2-20 days (median 10 days). All patients survived hospitalization.

Discussion

The burden of acute heart failure has been well described.[1,6] Hospitalization consumes the largest portion of financial resources spent on heart failure every year, and are independently associated with a worse outcome.[6] EDs are the primary gateway for these admissions, yet the role of the ED in the management of AHF and its impact on downstream care or outcomes has not been well studied.[7] Small studies or retrospective analyses highlight the importance of timely intervention, suggesting a time-dependent pathogenic mechanism. As such, we sought to better understand the early pathophysiology of AHF through a pilot study of lactate levels over time to explore whether hypoperfusion might inform our understanding of AHF in the ED. Only a minority of patients presenting to the ED with AHF had elevated lactate levels. Although the study is limited by small sample size, overall our results suggest that the hemodynamic and neurohormonal derangements present in acute heart failure do not consistently lead to hypoperfusion sufficient to elevate lactate levels. This is in marked contrast to Ander and colleagues' study where the majority of patients enrolled, although also a convenience sample, had elevated lactate levels.[4] This may be due to differences in the patient populations. Most of our patients had an EF>40%, whereas in the Ander and colleagues' study, the mean EF was 16%.

Elevated lactate levels are most commonly associated with shock states, given their rise due to ischemia from hypoperfusion. However, we focused on a more general AHF population to determine whether sub-clinical hypoperfusion might be a pathologic finding. This hypothesis was informed by data suggesting that organ injury or dysfunction occurs in AHF outside of cardiogenic shock or clear hypoperfusion states.[2] Although great caution is warranted regarding conclusions from a limited sample, the fact that 5 patients had elevated lactate levels despite normal levels at baseline suggests that either patients worsened, required more aggressive management initially or during hospitalization, or reflects a unique pathophysiology of worsening perfusion despite appropriate treatment.

The small number of enrolled patients and utilization of a convenience sample from a single center are major limitations with a strong risk for Type II error. Also, samples were drawn within 8 hours of presentation. Thus, treatment may have impacted lactate levels.

Conclusions

In this pilot study, elevated lactate levels were rarely seen at baseline or soon after hospitalization. In those patients with elevated lactate, the elevation was more likely to occur after initial treatment. While this may be a chance finding, it was unexpected given that AHF patients presumably would be at greatest risk at the time of presentation. Given the small sample size, any conclusion should be interpreted with caution; still, this may represent an avenue for further investigation.

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