Increased blood lactate is prevalent and identifies poor prognosis in patients with acute heart failure without overt peripheral hypoperfusion.

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Abstract

Aims. Lactate is produced by anaerobic metabolism and may reflect inadequate tissue perfusion in conditions such as acute heart failure (AHF). We evaluated the prevalence and clinical significance of elevated blood lactate on admission in patients with AHF.

Methods and Results. We enrolled 237 patients with AHF (mean age 67±12 years; 70% men) presenting without overt clinical evidence of peripheral hypoperfusion ("warm hemodynamic profile"). Median blood lactate on admission was 1.8 [1.5, 2.4] mmol/L; 103 (43%) patients had an elevated blood lactate (≥2 mmol/l). Patients with an elevated lactate had higher blood high-sensitivity troponin I (15.4 [8.5; 26.1] vs 9.9 [4.3; 19.6] pg/mL, aspartate aminotransferase (28 [20; 44] vs 24 [19; 36] IU/L) and endothelin-1 (12.1±6.2 vs 9.3±3.9 pg/mL), (all $p<0.05$). In this group plasma concentration of neutrophil gelatinase-associated lipocalin increased during the first 48 hours, whereas values fell for those with normal baseline lactate: 1.9 [-3.2; 9.7] vs -1.3 [-13.9; 5.6] µg/dL ($p<0.05$). One-year mortality was higher amongst patients with an elevated blood lactate (36% versus 21%; $p<0.05$). After adjustment for other well-established prognostic variables, blood lactate on admission predicted poor outcome: hazard ratio (95% confidence interval): 1.24 (1.08-1.4) ($p<0.05$).

Conclusions. An elevated blood lactate on admission is common in AHF patients without overt clinical evidence of peripheral hypoperfusion and is associated with markers of organ dysfunction/damage and a worse prognosis.

Introduction

Traditionally, lactate is considered an end-product of anaerobic cell metabolism, signalling tissue hypoxia, most often due to impaired peripheral perfusion [1]. However, an interpretation of systemic lactate level is far more complex and reflects tuned balance between lactate production and elimination[1]. Under normal conditions, the former occurs in most tissues, mainly in the skeletal muscle, whereas lactate is rapidly cleared predominantly in the liver and the kidneys[1–3]. Both processes – lactate production and elimination – can be affected by numerous factors, like tissue energy requirement, peripheral perfusion, adrenergic activity, hormones, use of concomitant medications and liver blood flow/function [1–3].

In critical care medicine, increased blood lactate is a marker of tissue hypoperfusion, being a powerful prognostic marker, and is often used in the therapeutic decision-making algorithms [4–6]. Interestingly, only few studies have reported on blood lactate in heart failure, either chronic or acute [7,8]. In the settings of acute heart failure (AHF) there are several mechanisms which can potentially alter a production/clearance balance, promoting lactate accumulation, namely: peripheral hypoperfusion (due to low cardiac output, high central venous pressure or vasoconstriction), activation of sympathetic drive, hypoxaemia, anaemia, liver or renal dysfunction[3]. Some of these mechanisms may conspire to impair oxygen delivery to peripheral organs and accelerate disease progression and worsen prognosis. Therefore, an early (baseline) assessment of lactate in AHF patients may be important to identify imperilled patients and for implementation of more adequate treatment strategies to improve the outcome in AHF.

Accordingly, we aimed to describe the prevalence, clinical characteristics and consequences of an elevated blood lactate amongst patients with AHF without overt clinical evidence of hypoperfusion.

Methods

Study population

The study population consists of patients who were hospitalized at the Centre of Heart Diseases, 4th Military Hospital, Wroclaw, Poland, and prospectively included into two AHF registries that run in our institution between either 2009-2010 or 2010-2012 [9,10]. The detailed flowchart of the study population has been presented in the supplementary section (Figure S1). Inclusion criteria for this analysis were: age ≥18 years; AHF as the primary cause of hospitalization AHF (diagnosis was based on the European Society of Cardiology [ESC] guidelines criteria [11,12]; patient's written agreement to participate. Exclusion criteria included cardiogenic shock or clinically obvious hypoperfusion (clinical assessment was either performed or supervised by a cardiologist experienced in heart failure management); a clinical diagnosis of concurrent acute coronary syndrome or infection; known severe liver disease or renal disease requiring or with planned renal replacement therapy. After inclusion, information on demographics, clinical history, comorbidities, previous therapies and physical findings was recorded. The present analysis is retrospective and includes only patients in whom lactates were measured on admission as a part of standard blood test to assess capillary blood oxygen saturation and acid-base balance. For the purposes of this analysis, an elevated blood lactate was defined as ≥ 2 mmol/l [13–15].

Patients were treated in accordance with the attending physicians' recommendations of the ESC guidelines [11,12] rather than by a protocol. The research was approved by the local ethics committee, and all subjects gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Laboratory measurements

On admission (blood samples were drawn at the Emergency Department as a part of a standard AHF patient care), the following laboratory measurements were recorded using standard methods:

- capillary blood for oxygen saturation, carbon dioxide concentration, pH, bicarbonate and lactate (direct method, ABL 800 Flex analyzer, Radiometer Copenhagen)
- hematology: hemoglobin (HGB), leukocytes (WBC), platelets
- serum electrolytes: sodium (Na^+), potassium (K^+)
- renal and liver function tests: creatinine; estimated glomerular filtration rate [eGFR] [16], blood urea nitrogen (BUN), AST (Aspartate aminotransferase), ALT (Alanine Aminotransferase), bilirubin and albumin.
- plasma NT-proBNP (N-Terminal Pro-B-Type Natriuretic Peptide) (method: immunoenzymatic, Siemens, Marburg, Germany)

For patients who were enrolled between 2010-2012, we also measured additional biomarkers from venous blood samples taken at admission and 24 and 48 hours afterwards:

- NGAL (Neutrophil gelatinase-associated lipocalin), and high-sensitive troponin I (hs-TnI) reflecting renal and myocardial damage;
- Endothelin-1 – as highly potent endogenous vasoconstrictor

After centrifugation, supernatant plasma was immediately frozen at -70°C until assayed. The analysis of these biomarkers was based on a diagnostic platform (Singulex, Inc. (Alameda, CA, USA with the Erenna immunoassay system, which uses a microparticle immunoassay and single molecule counting technique in a capillary flow system [17].

Definitions

Consistent with established definitions of myocardial injury, hs-TnI concentration was defined as elevated when its value exceeded the 99th percentile of the upper reference limit for the assay i.e. 10.19 ng/L [17]. A significant increase in hs-TnI was defined as at least one hs-TnI value (at 24 or 48 hours) >20% above baseline [18]. Worsening renal function was defined as an increase in plasma creatinine ≥ 0.3 mg/l above baseline [19]. For creatinine, NGAL and hsTnI, peak levels were defined as the maximum value at any time within the first 48 hours. Peak change was the largest difference in log2-transferred values between baseline and 48 hours.

Clinical follow-up

Surviving patients were followed at the heart failure clinic for at least twelve months. Information was obtained directly from patients or their relatives (telephone contact), from the heart failure clinic database or from the hospital system. No patient was lost to follow-up. The primary end-point of interest was all-cause mortality at one year.

Statistical Analysis

Continuous variables with a normal distribution were described using means ± standard deviation, variables with skewed distribution were described by medians with upper and lower quartiles, categorized variables were given as numbers and percentages. The statistical significance of differences between the groups were assessed using: t-test, Mann-Whitney U-test or Chi^2 test, where appropriate. The associations between clinical/laboratory variables and lactate level on admission were assessed by Spearman correlation test, then the multivariable regression models were built. The Cox proportional hazards model was used to calculate the hazard ratio (HR) with corresponding 95% confidence interval (95% CI) for all-cause mortality. Proportional hazards assumption was verified by visual analisis of Martingale

residuals. Kaplan-Meier survival curves were constructed to demonstrate the survival. The p <0.05 was considered statistically significant. Statistical analyses were performed using the STATISTICA 12 (StatSoft, Inc, Tulsa, OK. 74104, USA).

Results

Characteristics of the population (Tables 1 and 2)

Of 237 patients enrolled, most had decompensated chronic heart failure (78%), were men 167 [70%] with ischemic heart disease (55%), and mean age of 67±12 years. Mean systolic blood pressure, haemoglobin and serum creatinine on admission were: 134±32 mmHg, 13±1.9 g/dl and 1.3±0.6 mg/dl, respectively. The median (upper and lower quartiles) plasma concentration of NTproBNP was grossly elevated at 5773 [2984, 10382] pg/ml.

The distribution of lactate levels is presented in Figure 1. Median (upper and lower quartiles) blood lactate on admission was 1.8 [1.5, 2.4] mmol/L and 103 (43%) patients had elevated lactate concentrations (≥ 2mmol/L). The characteristics of patients with lactate above or below 2mmol/L were broadly similar (Table 1). Patients with lactates ≥ 2 mmol/L had faster heart rate and higher diastolic blood pressure (94±26 vs 89±24 beats/min and 80±20 vs 73±21 mmHg, respectively, p<0.01 in both comparisons). Patients with elevated lactate levels also had higher baseline values of WBC (9.8±3.8 vs 8.6±3.4 $x10^3/\mu L$), platelets (236±106 vs 209±76 $x10^3/\mu L$), and lower pH (7.41 vs 7.43) and HCO_3^- (22 vs 25 mmol/l) vs those with normal lactates (all p< 0.05).

Table 2 summarizes the results of the analyses to identifying predictors of lactate level on admission. In the multivariable models heart rate, WBC, AST, ALT and ET-1 were independent predictors of lactate level.

Elevated lactates level and biomarkers of organ dysfunction/injury (Table 3)

Liver

Patients with elevated lactate levels on admission had higher values of AST (28 [20; 44] vs 24 [19; 36] IU/L, p=0.02) and a trend towards higher values of ALT (26 [18; 47] vs 24 [17; 35] IU/L; p=0.07) (medians with upper and lower quartiles, respectively). Values for bilirubin and albumin on admission were similar between groups.

Kidney

Patients with blood lactate above or below 2.0 mmol/L had similar serum creatinine concentrations at baseline and 48h: (1.3±0.6 vs 1.4±0.6 and 1.2±0.6 vs 1.3±0.6 mg/dL, respectively) and similar rates of worsening renal function during the first 48 hours (4% vs 8%) (all p>0.05). Plasma concentrations of NGAL on admission were lower amongst those with elevated lactate (29.3±16.2 vs 42.7±30.5 µg/dl, p<0.01), but increased during the first 48 hours, whereas values fell for those with normal baseline lactate: 1.9 [-3.2; 9.7] vs -1.3 [-13.9; 5.6] µg/dl (p<0.05).

Myocardium

Patients with and without an elevated lactate on admission had similar baseline plasma concentrations of hs-TnI. Peak hs-TnI and hs-TnI measured at 48h were higher in patients with elevated lactate: 19.8 [10.4; 49.4] vs 14.5 [6.9; 28.2] and 15.4 [8.5; 26.1] vs 9.9 [4.3; 19.6] pg/ml, respectively (both p<0.05).

Vasoconstriction

Patients with elevated lactate had higher concentration of endothelin-1 on admission (12.1±6.2 vs 9.3±3.9 pg/mL, $p<0.01$), with subsequent significant decrease within 48h (-1.9 [-4.8;-0.6] vs -0.2 [-1.3;0.7], $p<0.001$).

Peripheral blood lactates and mortality

Sixty five patients (27%) died in the first year; 36% of those with a blood lactate ≥2mmol/l and 21% with lower values ($p<0.05$) (Figure 2). On univariate analysis elevated blood lactate on admission predicted all-cause mortality HR (95% CI): 1.2 (1.02-1.4) ($p<0.05$). After adjusting for well-established prognostic markers (age, systolic blood pressure, hemoglobin, creatinine, serum sodium, NTproBNP levels), the association between elevated blood lactate on admission and one-year, all-cause mortality was strengthened HR(95% CI): 2.7 (1.6-4.5) ($p<0.001$) (Table 4). Additional mortality analyses are resented in supplementary materials.

Discussion

We found that blood lactate was commonly elevated at admission amongst patients with AHF, even if clinical evidence of hypoperfusion was not obvious, and was associated with increases in biomarkers reflecting dysfunction or damage to the liver, myocardium, the kidney, vasoconstriction, and, ultimately, a higher mortality rate.

Several reports have confirmed the prognostic utility of blood lactate concentrations in critical care populations, including patients with septic shock, after cardiac arrest or multiple trauma [4–6,14]. However, there are few data available for patients with heart failure [7,8,20]. A previous study of just 27 patients with decompensated chronic heart failure found that >80% had an elevated blood lactate and that this was associated with low mixed venous oxygen saturations without marked arterial oxygen desaturation suggesting hypoperfusion as the main contributor to raised lactate [7]. These authors noted the poor relationship between raised lactate and vital signs but did not investigate the relationship with prognosis. Additionally, these patients were clinically far different from our population, and represented advanced, late stage of the disease, with lower blood pressure, severely compromised left ventricular ejection fraction, more than 80% receiving inotropic support. Adamo et al [8], reported prevalence of elevated lactate lower than our study, but they studied stable patients, who despite having an advanced disease may have already adapted mechanisms for a higher lactate clearance. In patients with cardiogenic shock elevated lactate (>2mmol/l) predicted poor outcome [20], being also the variable used in the CardShock risk Score to stratify risk of short-term mortality in this population [20].

Patients with or without an elevated blood lactate were similar in terms of demographic, clinical or laboratory variables and, although prognosis was markedly different, they had very

similar indices of disease severity, suggesting that lactate is a biomarker independent from most other clinical variables. Lactate level in the blood reflects a balance between production and clearance, which in the settings of AHF can be impaired, favouring lactate accumulation[3]. Although our study was not designed to elucidate such underlying mechanisms, it is worthy to note that the multivariable analysis revealed HR, WBC, AST, ALT and ET-1 as independent predictors of elevated lactate level. Both elevated HR and WBC may be indirect markers of sympathetic overactivity in these patients, but an increase in leukocytes may be also a physiological response to metabolic acidosis. As C-reactive protein was similar whether or not lactate was elevated, we believe higher WBC counts did not appear linked to infection. Additionally, although we excluded patients with known severe renal and kidney dysfunction, a relationship with higher AST/ALT levels may indicate that impaired liver function (and hepatic lactates clearance) potentially also contributes. In our study, patients with elevated blood lactate demonstrated higher levels of endothelin-1, providing an indirect evidence of more pronounced endothelin-mediated vasoconstriction at the periphery[21]. High systemic vascular resistance, regulated by microvascular tone, may maintain blood pressure when cardiac output is low and therefore a normal or even raised blood pressure cannot be equated with adequate tissue perfusion. Therefore, even in AHF patients with "warm profile" on clinical examination, peripheral hypoperfusion may be another factor responsible for elevated lactates.

We have found biomarker evidence of organ (liver, cardiac and perhaps renal) injury within the first 48h of hospitalization in patients with a high blood lactate. This could reflect hypoxia, congestion or a combination of the two, all of which may lead to organ dysfunction in AHF [9,18,22,23]. Organ perfusion depends on the net difference between arterial and venous

pressure and arteriolar tone. High venous tone will not only cause organ congestion but also a fall in net perfusion pressure and therefore exacerbate hypoxia [24]. Congestion and hypoperfusion may often co-exist and improvement in one may improve the other. On the other hand, endothelin-mediated peripheral vasoconstriction, present in patients with a high blood lactate, may also indicate inadequate perfusion leading to organ injury, as discussed above. Interestingly, similarly to intensive care populations, we have shown that elevated blood lactate on admission is associated with high mortality also in AHF patients without overt clinical evidence of peripheral hypoperfusion (who are not considered as candidates for an intensive care). Poor outcome in these patients may be a result of organ damage/dysfunction due to inadequate peripheral perfusion (otherwise clinically concealed) and may reflect more profound hemodynamic/neurohormonal abnormalities. This goes together with an observation of elevated endothelin-1 in these patients. It has been recently reported that elevated endothelin-1 on admission is an independent predictor of short-term in-hospital outcomes and 180-day mortality in patients with AHF [21].

There are several limitations to this report. Patient numbers, especially for the biomarker analysis, were small and the analyses were retrospective. As the study comprised AHF patients without severe haemodynamic compromise, and the lactate levels were lower than in intensive care populations, the results can't be extrapolated to a broader range of lactate levels. In our study lactates were measured from capillary blood samples. Although recently published data show good correlation between lactate level measured from capillary and arterial probes, capillary blood tends to reveal higher values [25,26]. However, these studies recruited mainly patients in shock with severe microperfusion alterations which we believe was not a case in our population.We lack information on dynamic changes in blood lactate

during hospitalization, which could be a useful marker of the response to therapeutic interventions.

In summary, elevated blood lactate, an indicator of anaerobic metabolism which is most likely driven by hypoperfusion of essential organs is common in AHF and carries independent prognostic information. Blood lactate concentration may be useful for risk stratification, but whether this would be incremental to the already validated models is not known. Further research is required to demonstrate whether it is useful for monitoring the response to intervention or whether it should inform therapeutic decisions. Many clinicians may feel instinctively that they should intervene with inotropic or vasodilator agents or even mechanical support when blood lactate is elevated but opinions on what to do will vary and should be supported by evidence.

Figure 1.

The distribution of lactates in the AHF population (n=237).

Figure 2.

Comparison of one-year mortality in 237 AHF patients with peripheral blood lactate on admission < 2mmol/l (red line) and ≥ 2mmol/l (blue line).

log rank p= 0.02

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