Validation of a point-of-care capillary lactate measuring device (Lactate Pro 2).

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Abstract

Background: The measurement of lactate in emergency medical services has the potential for earlier detection of shock and can be performed with a point-of-care handheld device. Validation of a point-of-care handheld device is required for prehospital implementation.
Aim: The primary aim was to validate the accuracy of Lactate Pro 2 in healthy volunteers and in haemodynamically compromised intensive care patients. The secondary aim was to evaluate which sample site, fingertip or earlobe, is most accurate compared to arterial lactate.
Methods: Arterial, venous and capillary blood samples from fingertips and earlobes were collected from intensive care patients and healthy volunteers. Arterial and venous blood lactate samples were analysed on a stationary hospital blood gas analyser (ABL800 Flex) as the reference device and compared to the Lactate Pro 2. We used the Bland-Altman method to calculate the limits of agreement and used mixed effect models to compare instruments and sample sites.
Results: A total of 49 intensive care patients with elevated lactate and 11 healthy volunteers who performed a maximal oxygen consumption test to obtain elevated blood lactate levels were included. There was no significant difference in measured lactate between Lactate Pro 2 and the reference method using arterial blood in either the healthy volunteers or the intensive care patients. Capillary lactate measurement in the fingertip and earlobe of intensive care patients was 47% (95% CI (29% to 68%), $p<0.001$) and 27% (95%CI (11% to45%), $p<0.001$) higher, respectively, than the corresponding arterial blood lactate.
Conclusion: Our results showed that the handheld Lactate Pro 2 had good agreement with the reference method using arterial blood in both intensive care patients and healthy volunteers. However, we found that the agreement was poorer using venous blood in both groups. Furthermore, the earlobe may be a better sample site than the fingertip in intensive care patients.

Key words: lactate, point-of-care, shock.

Background

Traumatic haemorrhage or sepsis may lead to shock when blood flow and oxygen delivery to vital organs and tissues is insufficient. When oxygen delivery is below a critical level, a state of shock may occur with the accumulation of oxygen debt (1, 2). Occult shock is the state of early hypoperfusion causing metabolic acidosis, that may occur in patients prior to detectable changes in vital signs (1). Due to insufficient oxygen delivery to the tissues, anaerobic metabolism leads to the production of lactate.

Prehospital monitoring of vital signs such as systolic blood pressure (SBP) and heart rate (HR) are the main indicators used to identify shock. However, such vital signs often do not change until a patient is near a critical stage, and therefore often fail to predict shock at an early stage (3-5). Identification of patients in early stages of shock in the field is difficult. Blood lactate monitoring is widely accepted in-hospital as an indirect marker of tissue hypoxia in critically ill patients. The Surviving Sepsis Campaign Guidelines use a cut-off value of greater than 4 mmol/L lactate for early resuscitation therapy to treat sepsis (6). Furthermore, lactate levels are commonly measured during resuscitation to predict mortality and to evaluate and guide treatment in both the emergency department (ED) and the intensive care unit (ICU). However, lactate levels are infrequently measured in the prehospital setting (7, 8).

Recent prehospital studies on lactate measurement suggest that lactate may be more sensitive than SBP and HR in identifying haemorrhagic shock patients who may benefit from early blood transfusion, and suggest that lactate may be independent of conventional vital signs in identifying these patients (8-12). Implementation of point of care lactate monitors in emergency medical services (EMS) may contribute to the evaluation of patients in the early stages of shock, thereby establishing a trigger for resuscitation (13, 14). However, there is little evidence on the prehospital use of point-of-care lactate monitors in the field.

The primary aim of this study was to validate the handheld device Lactate Pro 2 (LP2) in two different groups: healthy volunteers and critically ill patients. The secondary aims were to compare capillary blood lactate in the fingertip and earlobe with arterial blood lactate to investigate whether capillary lactate reflects the actual arterial levels.

Methods

Study design

This study was performed with two groups: haemodynamically compromised intensive care patients and healthy volunteers performing a maximal oxygen consumption test (VO2 max test).

Setting

The study took place in the Intensive Care Unit, Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway (Jonas Lies Vei 65, 5021 Bergen). The healthy volunteers were tested at the VO2 test laboratory at the Department of Paediatrics at Haukeland University Hospital. The study was conducted from September 2016 to November 2017.

Participants

Patients were enrolled from the ICU at Haukeland University Hospital. Inclusion criteria for intensive care patients were (i) adults at least 18 years of age, (ii) an arterial line and a central venous catheter, and (iii) informed consent from the next of kin or the patient him- or herself if awake and competent to give consent. Inclusion criteria for the healthy volunteers included were (i) adults at least 18 years of age and (ii) informed consent.

Sampling

Blood gases from the arterial and central venous lines of the ICU patients were sampled in heparinized syringes by the ICU nurses. They were analysed on both the LP2 and the ABL800Flex (ABL) immediately. Capillary blood was drawn from the fingertip and earlobe and analysed on the LP2. Two LP2 instruments, denoted LP2.1 and LP2.2, were used for quality assessment: the first drop of blood was measured on the LP2.1 and the second on LP2.2. All capillary samples were measured by the same researcher (A.R).
The healthy volunteers underwent a VO2-max test on treadmill (Modified Bruce Protocol) with an arterial line and a peripheral venous catheter during the test (15). Anaesthesiologists conducted the arterial cannulation. Repeated measurements of arterial, venous and capillary blood lactate in this group were recorded at rest, directly after the VO2-max test and at 3, 5, 10 and 20 min after the test was completed. Capillary blood samples were drawn from the

fingertip and earlobe. The arterial and venous blood samples were drawn in heparin tubes, stored on ice and analysed on the ABL within 30 min.

Materials

Lactate Pro 2 (AKRAY Europe B.V. Prof J.H Bavincklaan 5 1183 AT, Amstelveen, the Netherlands) is a handheld point-of care analyser that operates by enzymatic amperometric detection. Blood lactate reacts with the reagent on the test strip, which produces a small electrical current proportional to the concentration of blood lactate. The meter measures this current and calculates the blood lactate level. It requires 0.3 microliters of a whole-blood sample and 15 seconds to measure the lactate value. LP2 can measure lactate values in the range between 0.5-25.0 mmol/L. If "Hi" or "Lo" appears on the display it means that the blood lactate level is above 25.0 mmol/L or below 0.5 mmol/L respectively. In this study only values between 0.5 and 25 were used.

ABL Flex 800 (Radiometer Medical ApS, Åkandevej 21, DK-2700 Brønshøj, Denmark) is the standard blood gas machine used in the ICU at Haukeland University Hospital. It uses an amperometric method to measure the lactate value. The electrode consists of a silver cathode and a platinum anode and is protected by an electrode jacket filled with electrolyte solution and a multilayer membrane mounted at the tip. A polarization voltage of 675 mV is applied to the electrode chain and the current through the chain is measured by an amperemeter. The enzyme lactate oxidase immobilized between the inner and outer membrane layers converts lactate according to the following reaction: lactate + O_2 → pyruvate + H_2O_2. A potential is applied to the electrical chain, and the oxidation of H_2O_2 produces an electrical current that is directly related to the amount of lactate. The analyser thereby automatically calculates the concentration in the sample.

Statistical methods

Logarithmic transformation was performed for lactate and the inverse transformation was used to obtain interpretable estimated differences. Due to the repeated measurements in each individual in the healthy volunteer group, a mixed effects model including instrument and time as variables was used. First, we estimated a model with the same difference between instruments at all time points and then a model when this was not assumed. For ICU patients, mixed effects models were used for the measurements at different sites and with different instruments, and Bland-Altman analysis was used to compare different instruments and

different sites (16). Calculations were performed with R (R Foundation for Statistical Computing, Vienna, Austria) (17), using the R package nlme for mixed effects analysis.

Results

Forty-nine ICU patients and 11 healthy volunteers were included. In the ICU patients there were 41missing values, including 34 values above the detection limit. In the healthy volunteers, there were 10 missing values, including 4 values above the detection limit.

Instrument comparisons

In the ICU group (n=49), we found no significant difference in measured lactate between the LP2 and the ABL using arterial blood (Table 1, Figure 1). We found significantly higher values with LP2 than ABL using central venous blood (Table 1, Figure 2).

In the healthy volunteer group (n=11), we also found no significant difference between LP2 and ABL using arterial blood but significantly higher values for LP2 when using peripheral venous blood (Table 1). We found only a small and insignificant difference between LP2.2 and LP2.1 in both arterial and venous blood. In a mixed effects model where the instrument discrepancy could vary during follow-up, LP2 measured lower values in arterial blood compared to ABL at "rest" (data not shown), but we found no significant difference between LP2 and ABL at the other time points.

Table 1: Results of instrument comparisons in ICU patients and healthy volunteers.

ICU patients	**Estimate (Ratio)**	**95 % CI**	**p-value**
Arterial			
LP2.1 vs ABL	1.03	0.99 to 1.08	0.140
LP2.2 vs ABL	1.04	0.99 to 1.09	0.102
LP2.2 vs LP2.1	1.004	0.96 to 1.05	0.871
Venous			
LP2.1 vs ABL	1.29	1.24 to 1.35	<0.001
LP2.2 vs ABL	1.29	1.23 to 1.35	<0.001
LP2.2 vs LP2.1	0.998	0.96 to 1.04	0.938
Healthy volunteers	**Estimate (Ratio)**	**95 % CI**	**p-value**
Arterial, LP2 vs ABL	0.96	0.93 to 1.002	0.063
Venous, LP2 vs ABL	1.07	1.03 to 1.11	0.001

Sample site comparisons

In the ICU group, we found significant differences in both fingertip and earlobe compared to arterial blood using the LP2.1. Capillary blood lactate in the fingertip and earlobe was 47% (95% CI 29% to 68%, p<0.001) and 27% (95% CI 11% to 45%, p<0.001) higher than in arterial blood, respectively (Table 2). When comparing fingertip to earlobe we found that capillary blood lactate in the fingertip was 16% higher than in the earlobe (95% CI 2% to 32%, p=0.029). Bland Altman plots for comparison between capillary blood lactate in fingertip with arterial blood lactate on both handheld instruments (LP2.1 and LP2.2) in the ICU group are presented in Figure 3.

In the healthy volunteer group (n=11), we found that capillary blood lactate in the fingertip was 14% higher than arterial blood lactate (95% CI 4% to 24%, p=0.003) (Table 2). We found no significant difference between capillary blood lactate in the earlobe and arterial blood lactate (Table 2).

Table 2: Results of sample site comparisons in ICU patients and healthy volunteers.

ICU patients	**Estimate (Ratio)**	**95 % CI**	**p-value**
Finger LP2.1 vs Arterial LP2.1	1.47	1.29 to 1.68	<0.001
Earlobe LP2.1 vs Arterial LP2.1	1.27	1.11 to 1.45	<0.001
Finger LP2.2 vs Arterial LP2.2	1.85	1.55 to 2.21	<0.001
Earlobe LP2.2 vs Arterial LP2.2	1.22	1.03 to 1.46	0.024
Finger LP2.1 vs Venous LP2.1	1.14	1.01 to 1.30	0.040
Earlobe LP2.1 vs Venous LP2.1	0.99	0.87 to 1.12	0.871
Finger LP2.2 vs Venous LP2.2	1.43	1.20 to 1.69	<0.001
Earlobe LP2.2 vs Venous LP2.2	0.95	0.80 to 1.13	0.569
Healthy volunteers	**Estimate (Ratio)**	**95 % CI**	**p-value**
Finger vs arterial	1.14	1.04 to 1.24	0.003
Earlobe vs arterial	0.98	0.90 to 1.06	0.568

Discussion

We evaluated the agreement between two analysers of blood lactate, the handheld Lactate Pro 2 (LP2) and the stationary instrument ABL800 Flex (ABL) and compared two different sample sites of capillary blood lactate with arterial and venous blood. The LP2 and ABL agreed well in arterial blood taken from both healthy volunteers and intensive care patients.

However, the LP2 overestimated the venous blood lactate value in both groups. Capillary blood lactate values in the fingertip were significantly higher than the corresponding arterial values in both ICU patients and healthy volunteers. Capillary blood lactate values in the earlobe were significantly higher than arterial blood lactate values in the ICU group but not in the healthy volunteer group. The earlobe seems to be a better sample site than the fingertip, possibly because it is more central than the fingertip. However, more importantly, it is less sensitive to the variation between two measurements taken consecutively. We observed a rise in the lactate values in the fingertip from the first blood drop measured on LP2.1 to the second blood drop measured on LP2.2. We did not observe the same effect in the earlobe. Contenti et al. used the earlobe as a sample site for capillary blood and found that capillary blood lactate was higher than both venous and arterial lactate in patients in an ED, while in our study, ICU patients had capillary blood lactate higher than arterial blood lactate but almost the same as venous blood lactate (18).

Studies performed with other handheld devices in ICU populations also report good agreement between capillary and arterial lactate, but the devices were validated in lower lactate ranges (20-22).

Collange et al. is the only other study that compared both capillary and arterial blood samples on a handheld device instead of comparing capillary blood measured on a handheld device with arterial blood measured on a reference method. Like us, they found that capillary lactate was higher than arterial blood lactate. However, in contrast to our findings, they reported that the handheld instrument measured slightly lower lactate values than the reference instrument using arterial blood (21).

Interpretations of capillary blood lactate levels in shock patients may be challenging due to discrepancies between capillary and arterial blood due to changes in peripheral perfusion. We did not adjust for vasopressor as a confounder in the ICU group, which may cause a discrepancy between capillary, venous and arterial blood lactate. Vasopressors may increase lactate production via stimulation of skeletal muscle beta-2 adrenergic receptors, and reduce lactate clearance in peripheral tissues, but we do not know exactly what effect these phenomena have on capillary blood lactate distribution (23). Vasopressors may also influence the difference in capillary blood lactate between the fingertip and earlobe. Pattharanitima et al. found no evidence of a relationship between capillary or arterial lactate and norepinephrine use (22).

Lactate monitoring in EMS has potential for the earlier detection of shock and may be used as an early trigger for blood transfusion in haemorrhaging patients or for fluid therapy in septic patients (12). In general, arterial blood is preferred and capillary lactate should be measured only when rapid measurement is necessary or when arterial blood is not available. Since patients in the prehospital setting in most cases do not receive an arterial line, a handheld capillary blood lactate measuring device may be well suited for EMS services. Measuring lactate values in the field is quick and should not delay other treatments or interventions on-scene. Our results show that LP2 also has the potential to overestimate the lactate values, which may lead to overtreatment or overtriage of patients. This may, however, be of less importance than the potential consequences of under-triage in situations where EMS providers fail to detect the early stages of shock.

Despite overestimation of the actual values, multiple readings may provide a trend that can be of value in clinical decision making in guiding treatment. When interpreting the lactate values, one must consider both the instrumental bias of the LP2 and the physiological discrepancy between arterial and capillary blood lactate values in different sample sites and different haemodynamical states.

Strengths and limitations

The strength of this study lies in the standardized procedure for collecting blood and analysing lactate. In contrast to other studies comparing capillary and arterial blood lactate we measured both capillary and arterial/venous blood on the same instrument. Most other studies compare the capillary lactate value measured on the handheld device with the arterial value measured by the reference method. We believe our method is more correct because it separates the instrument agreement from the difference in the different blood samples. Another strength is that we validated LP2 in a wide range of lactate values (from 1-25 mmol/l) in both healthy volunteers and intensive care patients, which shows the differences in lactate distribution in capillary and arterial/venous blood in these two haemodynamically different groups. This study has some limitations of note. We have previously observed that cold LP2 strips may influence the measured value randomly; therefore, we made sure that the LP2 and the strips were stored at room temperature. This limitation in the instrument may have caused a bias in patients with low body temperature. We are considering further research on this issue. Regarding capillary measurements, the disinfecting agent can cause haemolysis, which may increase the lactate concentration. This is a single-centre study including few

study subjects, which limits the generalizability of the study findings. The number of healthy volunteers included is low due to the ethical aspect of arterial cannulation and the associated risk of complication.

Conclusion

We found that Lactate Pro 2 had good agreement with the reference method using arterial blood but poorer agreement using venous blood. Our results show the potential for overestimation of the lactate value in haemodynamically compromised patients. The levels of lactate in capillary blood from the fingertip and earlobe were 47% and 27% higher, respectively, than in arterial lactate in intensive care patients. The earlobe may be a better sample site than the fingertip in haemodynamically compromised patients.

List of abbreviations

SBP: Systolic blood pressure
HR: Heart rate
ICU: Intensive Care Unit
EMS: Emergency medical services
LP2: Lactate Pro 2
ABL: ABL800Flex

Declarations

Ethics approval and consent to participate

All patients' next of kin and all volunteers involved signed an informed consent form. This study was approved by the Regional Ethics Committee (REK-Vest number 2016/815) and (2017/162).

Consent for publication

Not applicable.

Avaliability of data and materials

Data are available upon reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

A.R. was the lead investigator and contributed to all aspects of the study. J-K.H. contributed to all aspects of the study. G.S. contributed to the development of the study design, data interpretation and critical revision. B.B. contributed to the development of the study design, data analysis, data interpretation and critical revision. C.B., R.K. and H.S.E. contributed to the development of the study design and data collection. T.W-L. participated in planning and performing the statistical analyses and preparation of the data for statistical analysis together with the first author. All authors participated in critical revision.

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Figure legends:

Figure 1: Bland-Altman plot for instrument comparison of LP2 and ABL in arterial blood from ICU patients.

Figure 2: Bland-Altman plot for instrument comparison of LP2 and ABL in venous blood from ICU patients.

Figure 3: Bland-Altman plots for comparison between lactate in fingertip with arterial lactate in ICU patients.