Determinants of prehospital lactate in trauma patients: a retrospective cohort study

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Abstract

Background: Point of care serum lactate measurement is emerging as an adjunct to prehospital clinical assessment and has the potential to guide triage and advanced treatment decision-making. In this study we aimed to assess which factors potentially affect prehospital lactate levels.

Methods: We performed a retrospective cohort study of all trauma patients attended by the Air Ambulance, Kent, Surrey & Sussex (AAKSS) between July 2017 and April 2018 in whom a pre-hospital lactate was measured. Lactate was measured before AAKSS treatments were commenced, but generally after prehospital treatment by ground ambulance crews was initiated. Primary endpoint of interest was the association of various patient- and treatment characteristics with prehospital lactate levels.

Results: During the study period, lactate was measured in 156 trauma patients. Median lactate was 3.0 [2.0–4.1] mmol/l. Patients with an elevated lactate more often had deranged indices of end organ perfusion- and oxygenation (shock index 0.80 [0.58–1.03] vs 0.61 [0.40–0.82], p < 0.001, SpO2 96 [89–100%] vs 98 [96–100%], p = 0.025). They more often suffered from head injuries (62% vs 41%, p = 0.008), and received less analgesia prior to arrival of the AAKSS team (51.6% vs 67.2%, p = 0.03). In multivariate analysis, indices of end organ perfusion- and oxygenation only explained 15% of the variation in lactate levels.

Conclusions: Prehospital lactate levels are not solely associated with indices of end organ perfusion- and oxygenation. Injury type, treatments given on scene and many other (unmeasured) factors likely play an important role as well. This should be taken into account when lactate is used in clinical algorithms to guide prehospital triage or treatment.

Keywords: Lactate, Prehospital, Helicopter emergency medical service (HEMS)

Background

Trauma triage guidelines are typically based on injury mechanism, injuries identified and vital signs reported. Reliance on vital signs and physical exam however, has been reported to miss patients with serious injury [1]. Point of care (POCT) serum lactate measurement is emerging as an adjunct to pre-hospital clinical assessment and has the potential to guide triage and advanced treatment decision-making: pre-hospital lactate levels have been shown to predict the need for resuscitative in-hospital care in trauma patients [2–5], and to predict outcome of trauma patients [6].

Historically, lactate formation in trauma patients was thought to originate from anaerobic glycolysis: hemorrhage and inadequate ventilation following a traumatic injury can lead to hypovolemia, hypoxaemia and end-organ hypoperfusion, resulting in anaerobic glycolysis and lactate formation.

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Over the past decade however, it has become clear that (beta adrenergic mediated) accelerated aerobic glycolysis is a major contributor to lactate formation under various conditions as well [7]. This is important to realize, as beta adrenergic stimulation in pre-hospital trauma patients is almost universally present as a result from pain and/or stress. Furthermore, many pharmacological and non-pharmacological treatments on scene have the potential to modulate beta adrenergic stimulation, and thereby influence lactate levels. Although this will not affect the prognostic ability of elevated prehospital lactate levels as such (several studies have shown that the prognostic ability of lactate exceeds the prognostic ability of markers of end organ hypoperfusion) [2–5], it might influence the use of lactate as a marker to guide advanced prehospital treatments such as blood product transfusion [8]. Therefore, this study aims to examine which patient- and treatment factors are related to POCT lactate levels in prehospital trauma patients.

Methods
Study design and subjects
We performed a retrospective study of all trauma patients attended by Air Ambulance Kent, Surrey Sussex (AAKSS) between July 2017 (when lactate measurements became available to the service) and April 2018 (when the study protocol was completed). All patients in whom a pre-hospital lactate levels was measured, irrespective of their age, injury type, injury severity or outcome were included. Consecutive patients with non-traumatic pathology in whom a lactate was measured were excluded.

Setting
AAKSS is a helicopter emergency medical service (HEMS) covering three counties in the southeast of England with a resident population of 4.5 million and transient population of up to 8 million. Two doctor/paramedic teams respond in helicopters or rapid response cars from one base and the service attends approximately 2000 patients per year. Most patients attended by the HEMS service are first seen by a ground ambulance crew and/or a critical care paramedic.

Lactate measurement
Prehospital lactate measurements became available to AAKSS HEMS teams as an adjunct to clinical assessment in July 2017 using the NOVA StatStrip® Biomedical Xpress™ Point of care (POCT) Lactate Meter system [9, 10]. Current AAKSS Standard Operating Procedures (SOP), recommend lactate measurement in all patients with suspected major hemorrhage. Lactate was measured from venous blood, drawn in a 2 ml syringe during venapuncture or after insertion of an intravenous canula. Lactate was drawn and analyzed in the prehospital setting before EMS treatments (including transfusion of any blood products) was commenced, but generally after prehospital treatment by ground ambulance crews (such as circulatory support, analgesia, and haemostatic interventions) was initiated.

Outcome measures
The primary outcome measure in this study was defined as the association of various patient- and treatment characteristics with (elevated) prehospital lactate levels. In accordance with previous studies [11, 12], elevated lactate was defined as a blood concentration > 2.5 mmol/l.

Data acquisition
Patient demographics, mechanism- and nature of injuries, vital signs, POCT test results (including lactate), and treatments provided by the HEMS team and other EMS services are recorded by clinical crews in a dedicated electronic patient record (HEMSbase 2.0, Medic One Systems Ltd., UK). Data were retrieved from this electronic record for the purpose of this study, using a standardized proforma (See Supplementary file 1).

Ethics
This project met National Institute for Healthcare Research (NIHR, UK) criteria for service evaluation and ethical review was therefore not conducted by an external body (such as an NHS research Ethics Committee [13]. All the data used for this study were routinely collected as part of standard prehospital and hospital patient data collection. The project was approved by the AAKSS Research & Development Committee. The study has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Patient and public involvement
It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination of our research.

Statistical analysis
Shapiro Wilk tests were performed to assess normal distribution, and residual plots were drawn to assess linearity of data. Descriptive statistics are given as numbers [%] or median [interquartile range, IQR]. Comparisons across groups were made using Fisher’s exact test and Mann-Whitney U test where appropriate. Univariate correlation analysis with calculation of Spearman correlation coefficients was performed to evaluate the correlation of clinical- and treatment factors with the primary outcome (lactate). Stepwise multivariable regression analyses including factors with a significant correlation was performed to determine which factors were independently related to the primary outcome measure. Missing
values are reported in the results section of the manuscript according to the STROBE guideline [14]. A \( p \)-value \(< 0.05\) was regarded as statistically significant. All statistical analyses were conducted using IBM SPSS 23.0 for Apple statistical package (SPSS Inc., Chicago, Illinois, USA) and VassarStats online statistical software (Vassarstats.net).

### Results

#### Study population

During the study period, 1188 patients were seen by AAKSS. A prehospital lactate was obtained in 174 patients (14.6%). Eighteen patients were excluded as they were attended by HEMS for a medical (non-trauma) reason (supplementary file 1). Subsequent results refer to the remaining 156 trauma patients (13.1%). The majority of the patients were male (79.5%), and involved in road traffic collisions (blunt trauma mechanism, 89.7%). The average time from 999-call to drawing blood for a lactate sample was 66 [46–87] minutes. Injuries, vital signs upon arrival of HEMS, and treatments provided by the HEMS team or other emergency medical services before blood was drawn to determine lactate, are described in Table 1.

#### Correlation of patient- and treatment characteristics with lactate levels

Injury type was related to (elevated) lactate levels: Patients with head injury more often had elevated lactate levels (41% vs. 62%, \( p < 0.008\), Table 1), and head injury was correlated to lactate levels (\( r = 0.22, \ p = 0.006\), Table 2). As expected from previous studies, lactate levels were related to markers of end-organ perfusion- and oxygenation (radial pulse, heart rate [HR], systolic blood pressure [SBP], Shock index [SI], Oxygen saturation (SpO\textsubscript{2}) and end-tidal CO\textsubscript{2} (EtCO\textsubscript{2}) (Tables 1 and 2). SI demonstrated the highest correlation with lactate levels (\( r = 0.35, \ p < 0.001\)). Several treatment factors were related to lactate levels: iv fluid administration showed a (weak) positive correlation with lactate levels, whereas administration of IV analgesia, showed an inverse relation with both absolute- and elevated lactate levels (Table 2).

In multivariate analysis, SpO\textsubscript{2}, SI and IV analgetic administration prior to HEMS arrival remained independently associated with prehospital lactate, together explaining 17.7% of the variation in lactate levels (Table 3). Indices of end-organ perfusion and oxygenation (SpO\textsubscript{2} and SI) were responsible for 15% of the variation in lactate levels. Sensitivity analysis revealed that within the subgroup of patients with a head injury (\( n = 76\)) SpO\textsubscript{2} and SI predicted a similar percentage (17%) of the variation in lactate levels.

### Discussion

As expected, indices of end-organ perfusion- and oxygenation are associated with (elevated) lactate levels in prehospital trauma patients. However, these factors explained only 15% of the variation in prehospital lactate levels. Therefore, it is likely that other (independent) processes were responsible for lactate production- and clearance in these patients as well.

First, catecholamine release as a result of pain, stress or increased metabolic demand can result in lactate formation by activating intracellular cAMP, resulting in accelerated aerobic glycolysis [15, 16]. As trauma patients invariably have pain and/or stress, this is a likely contributor to pre-hospital lactate levels. We haven’t been able to quantify this directly in our study. However, it is well known that adequate analgesia blunts the physiological stress response and limits endogeneous catecholamine release, resulting in a decreased rate of glycolysis [17]. This is in agreement with the inverse relation between IV analgesic administration and lactate levels as found in this study.

Second, supportive treatments such as sodium chloride 0.9% or adrenaline administration, initiated before a blood sample for lactate measurement is drawn, may moderate HR, SBP, SI, and SpO\textsubscript{2}, and thereby influence tissue perfusion. The effect on lactate levels however, is more difficult to predict, as improved tissue perfusion may result in increased shuttling of lactate throughout the body [18]. This may have contributed to the (weak) positive association of fluid administration with elevated lactate levels as found in this study, although the effect of confounding by indication (sicker patients receiving more fluids) might have played a role as well.

Third, isolated injuries may result in elevated blood lactate levels, whereas their influence on indices of end organ perfusion- or oxygenation may be limited. Examples of these injuries are traumatic amputation [19] or isolated traumatic brain injury (TBI) [20]. Previous studies have shown that glia cells in the brain increase lactate production purposely in order to meet the increased metabolic demand of adjacent neurons during TBI [21]. This is in agreement with the association we found between head injured patients and (elevated) lactate levels in this study. As a significant interaction was also present between “head injury” and the administration of IV analgesics however, head injury did not contribute to the amount of explained variance in lactate levels in the multivariate model.

Furthermore, lactate levels measured at any point in time are not only the result of lactate production, but also of lactate clearance and utilization [15]. The liver takes up lactate from the blood, where it is reconverted to glucose in the Cori Cycle. Lactate can also be taken up by various tissues (brain, heart, muscle) and be
directly utilized. Clearance is affected by various factors, including alcohol consumption (dose dependent decrease [22]) and (liver) tissue patency. Many of these are unknown to the clinicians caring for the patient in the prehospital situation.

In our study we observed that pre-hospital lactate levels not only represent end-organ perfusion, but also other processes, as the adrenergic response of the body to injuries and the adequacy of the initiated treatment(s). Elevated prehospital lactate levels should therefore not

### Table 1 Study population characteristics

|                    | All (n = 156) | Lactate < 2.5 mmol/L (n = 61) | Lactate > 2.5 mmol/L (n = 95) | p   | missing |
|--------------------|---------------|------------------------------|------------------------------|-----|---------|
| **Biometric data** |               |                              |                              |     |         |
| Age (y)            | 44 [24–64]    | 44 [23–66]                   | 45 [27–63]                   | .642|         |
| Male Gender (n,%)  | 124 [79.5]    | 48 [78.7]                    | 76 [80]                      | .842|         |
| **Injury characteristics** |           |                              |                              |     |         |
| Mechanism          |               |                              |                              |     |         |
| Blunt trauma (n,%) | 140 [89.7]    | 56 [91.8]                    | 84 [88.4]                    | .595|         |
| Sharp trauma (n,%) | 16 [10.3]     | 5 [8.2]                      | 11 [11.6]                    | .595|         |
| Body regions affected |            |                              |                              |     |         |
| Head (n,%)         | 84 [53.8]     | 25 [41.0]                    | 59 [62.1]                    | .008| 2       |
| Chest (n,%)        | 73 [46.8]     | 31 [50.8]                    | 42 [45.2]                    | .513| 2       |
| Abdomen (n,%)      | 72 [46.2]     | 29 [47.5]                    | 43 [45.3]                    | .870|         |
| Limb (n,%)         | 75 [48.1]     | 29 [47.5]                    | 46 [48.4]                    | .990|         |
| Nr of regions affected (n) | 2 [0–4] | 2 [0–4]                      | 2 [0–4]                      | .373|         |
| **Lactate**        |               |                              |                              |     |         |
| 999-lactate sample (min) | 66 [46–87] | 62 [45–80]                   | 67 [46–88]                   | .420| 33      |
| Lactate (mmol/l)   | 3.0 [2.0–4.1] | 1.8 [0.5–2.2]                | 3.8 [2.7–4.9]                | <.001|         |
| **Indices of end organ perfusion and oxygenation** | |                              |                              |     |         |
| Palpable radial pulse [y] | 138 [88.5] | 58 [95.1]                    | 80 [84.2]                    | .042|         |
| SBP (mmHg)         | 129 [109–149] | 134 [117–152]                | 123 [102–144]                | .001| 10      |
| HR (bpm)           | 88 [66–110]   | 85 [64–106]                  | 96 [75–117]                  | .023| 14      |
| Shock index        | .72 [51–93]   | .61 [40–82]                  | .80 [58–103]                 | <.001| 14      |
| EtCO2 (kPa)        | 4.1 [3.5–5.4] | 4.1 [2.0–6.0]                | 4.0 [3.2–4.8]                | .390| 44      |
| SpO2 (%)           | 97 [93–100]   | 98 [96–100]                  | 96 [89–100]                  | .025| 16      |
| **Treatments before HEMS** |        |                              |                              |     |         |
| Circ and resp. support |           |                              |                              |     |         |
| Adrenaline         | 6 [3.8]       | 1 [1.6]                      | 5 [5.3]                      | .405|         |
| IV fluids          | 14 [9.0]      | 2 [3.3]                      | 12 [12.6]                    | .050|         |
| Pain relieving interventions |       |                              |                              |     |         |
| IVP and/or morphine| 87 [55.8]    | 41 [67.2]                    | 49 [51.6]                    | .031|         |
| IVP                | 61 [39.1]     | 30 [49.2]                    | 31 [32.6]                    | .045|         |
| morphine           | 51 [32.7]     | 23 [37.7]                    | 28 [29.5]                    | .299|         |
| Reduction or splinting a | 29 [18.6] | 8 [13.1]                     | 21 [22.1]                    | .207|         |
| Haemostatic interventions |        |                              |                              |     |         |
| Pelvic splint      | 76 [48.7]     | 28 [45.9]                    | 48 [50.5]                    | .624|         |
| Compression Bandage or tourniquet | 14 [9.0] | 7 [11.5]                     | 7 [7.4]                      | .402|         |
| TXA                | 75 [48.1]     | 26 [42.6]                    | 49 [51.6]                    | .325|         |

Footnote: Continuous data represented as n [%], nominal data as median [IQR]. a manual reduction of fracture or dislocation and/or Kendrick and/or vacuum splint application. SBP Systolic blood pressure, HR Heart rate, EtCO2 End tidal CO2, SpO2 Percentage oxygen saturation, IV Intravenous, IVP Intravenous paracetamol, TXA Tranexamic acid.
simply be considered as a marker of end organ hypoperfusion- or oxygenation. Although lactate levels were related to HR, SBP and SI in this study, correlation coefficients were low, especially compared to previously published in-hospital studies [23, 24]. The difference with in-hospital studies may be explained by the likelihood of the presence of a time lag between deterioration of vital signs and increased lactate formation and/or decreased lactate clearance. For in-hospital patients this argument may be less important, as sufficient time since the injury will have passed to ensure both lactate and vital signs are deranged.

Our study has some limitations, most of them inherent to the retrospective design. Firstly, the reported associations do not necessarily represent causality (as selection by indication might have been present for treatment factors such as analgesics administration). This study should therefore mainly be regarded as hypothesis generating. Prospective studies are warranted to confirm our findings, especially regarding the effect of treatment factors

### Table 2

Univariate correlation coefficients of patient characteristics with pre-hospital lactate levels in trauma patients attended by HEMS (n = 156)

|                                      | Lactate (mmol/l) | Lactate > 2.5 mmol/l |
|--------------------------------------|------------------|----------------------|
|                                      | r [95%CI]        | p                    | r [95%CI]     | p |
| **Biometric data**                   |                  |                      |               |   |
| Age (y)                              | .01 [-15-16]     | .974                 | -.04 [-24-17] | .643 |
| Gender (n,%male)                     | -.03 [-18-13]    | .758                 | -.02 [-17-14] | .844 |
| **Injury/disease characteristics**   |                  |                      |               |   |
| Mechanism                            | .09 [-07-25]     | .255                 | .05 [-10-21]  | .500 |
| Nr Body regions affected              | .22 [07-37]      | .006                 | .22 [07-37]  | .066 |
| Head (n,%)                           | .950             | .06 [-21-10]         | .495         |    |
| Abdomen (n,%)                        | -.03 [-19-13]    | .718                 | -.02 [-18-14] | .782 |
| Limb (n,%)                           | -.03 [-19-13]    | .688                 | .01 [-15-17]  | .915 |
| 999-lactate sample (min)             | .12 [-04-27]     | .197                 | .07 [-09-23]  | .422 |
| **Indices of end-organ perfusion and oxygenation** |                  |                      |               |   |
| Palpable radial pulse [y]            | -.29 [-42-14]    | <.001                | -.17 [-31-01] | .038 |
| SBP (mmHg)                           | -.31 [-44-16]    | <.001                | -.28 [-42-13] | .001 |
| HR (bpm)                             | .21 [06-36]      | .011                 | .19 [-34-03]  | .023 |
| Shock index                          | .35 [20-48]      | <.001                | .34 [19-47]   | <.001 |
| First EtCO2 (kPa)                    | -.16 [-31-01]    | .101                 | -.08 [-24-08] | .392 |
| SpO2                                 | -.24 [-38-08]    | .005                 | -.19 [-34-03] | .024 |
| **Treatments before HEMS**           |                  |                      |               |   |
| Circ and resp. support                |                  |                      |               |   |
| Adrenalin                             | .11 [-04-27]     | .155                 | .09 [-06-25]  | .254 |
| IV fluids                             | .17 [01-31]      | .040                 | .16 [01-31]  | .046 |
| Pain relieving interventions          |                  |                      |               |   |
| IVP and/or morphine                   | -.24 [-38-09]    | .003                 | -.19 [-33-03] | .021 |
| Morphine                              | -.18 [-32-02]    | .027                 | -.17 [-31-01] | .039 |
| Reduction or splinting*               | -.16 [-31-01]    | .040                 | -.09 [-24-07] | .288 |
| Haemostatic interventions             |                  |                      |               |   |
| Pelvic splint                         | .05 [-10-21]     | .502                 | .05 [-11-20]  | .576 |
| Compression bandage or tourniquet     | -.12 [-27-01]    | .126                 | -.07 [-22-09] | .384 |
| TXA                                   | .12 [-04-27]     | .147                 | .09 [-07-24]  | .278 |

Footnote: *Manual reduction of fracture or dislocation and/or Kendrick and/or vacuum splint application. SBP Systolic blood pressure, HR Heart rate, EtCO2 End tidal CO2, SpO2 Percentage oxygen saturation, IV Intravenous, IVP Intravenous paracetamol, TXA Tranexamic acid
on lactate, as there is an inherent risk of confounding by indication when considering the relation between lactate and treatment factors. Second, this study was done in a convenience sample of trauma patients in whom a lactate was measured, and cannot be extrapolated to the wider population of all prehospital trauma patients. Furthermore, although overall data completeness was good due to the use of our electronic patient record, there were missing data for some variables. Furthermore, as lactate samples were drawn before HEMS treatments (such as transfusion of blood products or RSI) were commenced, it is unclear how these advanced treatments would be related to lactate levels.

Finally, only single lactate measurements were available. Previous studies in other populations have shown that serial measurements improve not only prognostication, but might be helpful to guide treatment as well [25].

**Conclusion**

Prehospital lactate levels are not solely associated with indices of end organ perfusion- and oxygenation. Injury type, treatments given on scene and many other (unmeasured) factors likely play an important role as well. This should be taken into account when lactate is used in clinical algorithms to guide prehospital triage or treatment.

**Supplementary information**

**Supplementary information** accompanies this paper at https://doi.org/10.1186/s12873-020-00314-1.

**Additional file 1: Supplementary Table 1.** Standardised data collection proforma. **Supplementary Table 2.** Patients excluded.

**Abbreviations**

AAKSS: Air Ambulance Kent, Surrey and Sussex; HEMS: Helicopter Emergency Medical service; POCT: Point-of-care testing; SOP: Standard operating procedure

**Acknowledgements**

Not Applicable

**Authors’ contributions**

EtA and RL conceived the study. JG, JW and MQR made a substantial contribution to the acquisition of the data and/or analysis and interpretation of the data. EtA drafted the manuscript, and all authors revised it critically and approved the final manuscript before submission. The authors want to thank the AAKSS HEMS teams for collecting the data.

**Funding**

The Authors have not declared a specific grant for this research from any funding agency in the public, commercial or non-profit sectors.

**Availability of data and materials**

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

**Ethics approval and consent to participate**

This project met National Institute for Healthcare Research (NIHR, UK) criteria for service evaluation and formal ethical approval was therefore waived. All the data used for this study were routinely collected as part of standard prehospital and hospital patient data collection. The project was approved by the AAKSS Research & Development Committee. The study has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

**Consent for publication**

Not Applicable

**Competing interests**

All authors are employees of Air Ambulance Kent, Surrey and Sussex.

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Received: 10 November 2019 Accepted: 4 March 2020

**Published online: 11 March 2020**

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