Agreement between arterial and peripheral venous lactate levels in the ED: A systematic review

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ABSTRACT

Background: In the Emergency Department, lactate measurement is a useful tool to risk-stratify critically ill patients. However, it is unclear whether arterial or peripheral venous lactate levels can be used interchangeably for this purpose. In this systematic review, we provide an overview of studies investigating the agreement between arterial and peripheral venous lactate levels in the Emergency Department.

Methods: PubMed, Embase, the Cochrane Central Register of Controlled Trials/Wiley, Web of Science/Clarivate Analytics, and references of selected articles were assessed for all studies comparing arterial and peripheral venous lactate levels in adult patients in the emergency department. Two reviewers independently screened all potentially relevant titles and abstracts for eligibility using a standardized data-worksheet.

Results: Nine studies were included. Peripheral venous lactate levels tend to be higher than arterial lactate levels with mean differences ranging from 0.18 mmol/l to 1.06 mmol/l. Importantly, poorer agreement occurs in hyperlactatemia. At a cut-off level of 1.6 mmol/l, peripheral venous lactate can rule out arterial hyperlactatemia with a sensitivity between 94% and 100%. At a cut-off level of 2 mmol/l, sensitivities of 97% and 100% were found.

Conclusion: Agreement between arterial and peripheral venous lactate is poor in hyperlactatemia, making peripheral venous lactate an unreliable parameter to use interchangeably in the ED. In clinical practice, peripheral venous lactate can be used as a screening tool to rule out arterial hyperlactatemia at a cut-off value of 2 mmol/l. However, hyperlactatemia should be confirmed using arterial sampling in case of a peripheral venous lactate level > 2 mmol/l.

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1. Introduction

Lactate is the end-product of the glycolytic breakdown of glucose under anaerobic conditions [1]. In any condition where production exceeds metabolism, hyperlactatemia will develop. Traditionally, causes of hyperlactatemia are subdivided in hypoxic circumstances (type-A) associated with circulatory insufficiency, severe anemia, mitochondrial enzyme dysfunction and non hypoxic circumstances (type-B) which can be seen in association with malignancies, liver- or kidney failure, severe infections, thiamin deficiency and nART-inhibitors in HIV [2].

Shock, severe heart failure, severe trauma, and sepsis are the most common causes of lactic acidosis [1]. In these conditions, elevated lactate levels have been associated with increased morbidity and mortality [3]. For this reason, initial lactate measurement is a useful marker to risk-stratify critically ill patients in the Emergency Department (ED) [4-6].

Particularly in sepsis, hyperlactatemia has important prognostic value [7]. A recent study found that lactate levels of ≥2 mmol/l have a greater sensitivity (85.3%) predicting mortality in septic shock patients compared with lactate clearance [8]. Furthermore, lactate levels between 2 and 4 mmol/l have also been found predictive of adverse prognosis in the Emergency Department [9]. For this reason, lactate has been incorporated into definitions of sepsis and septic shock. The Third International Consensus Definitions for Sepsis and Septic Shock defines septic shock by a vasopressor requirement to maintain a mean arterial pressure of ≥65 mm Hg and serum lactate level > 2 mmol/l in the absence of hypovolemia [10]. The Surviving Sepsis Campaign defines a lactate level of ≥4 mmol/l as indicator of sepsis-induced tissue hypoperfusion [11] and advises that an initially elevated lactate level (>2 mmol/l) should be remeasured within 2 to 4 h to guide resuscitation [12].

However, these guidelines do not specify whether arterial lactate (AL) levels or peripheral venous (PVL) levels should be used. In the ED, where sepsis is frequently encountered, the use of PVL might be safer and easier then AL. Whereas correlation and agreement between conventional blood gas parameters have been extensively studied in ED patients [13,14], comparative data focusing on peripheral venous versus arterial lactate in the ED is limited.
In this systematic review, we provide an overview of studies investigating the agreement between AL and PVL.

2. Methods

2.1. Registration

In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on February 12th 2018.

2.2. Population of interest

All studies comparing PVL and AL in adult patients in the ED were included. Studies including children, animals or ICU-patients were excluded. Studies investigating capillary, central venous or mixed venous blood samples were also excluded. The primary outcome parameter was the mean venous-arterial difference (VA-MD) with 95% limits of agreement (LOA) as described by Bland and Altman [15]. Secondary outcomes included the predictive value of PVL to rule out arterial hyperlactatemia, the classification error rate and the rate of discrepant measurements between PVL and AL.

2.3. Literature search

A systematic literature review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-statement [16]. The search was conducted on December 21th 2017 and updated on October 1th 2018. Studies were identified by searching PubMed, Embase.com, Cochrane Central Register of Controlled Trials/Wiley, Web of Science/Clarivate Analytics as well as references of the selected articles. The following terms, including synonyms and closely related words, were used as index terms or free-text words: ‘emergency department’ and ‘lactate’. Full search strategies for all the databases are available in the appendix.

2.4. Selection of studies

Two authors (AT and CB) independently screened all potentially relevant titles and abstracts for eligibility using Rayyan [17]. The full text articles were checked for the eligibility criteria. Differences in judgments were resolved by discussion.

2.5. Assessment of methodological quality

The full texts of the selected articles were obtained for further review. A data-worksheet was used for data extraction which included the following variables: type of study, patient characteristics, study outcomes (mean AL, mean PVL, VA-MD and 95% LOA), main conclusion and limitations.

3. Results

The literature search generated 4090 references. One study was added after checking the references of all relevant studies [18]. After removal of duplicates 2250 references remained. By screening titles and abstracts, AT included 10 articles and CB included 14 articles, generating a Cohen’s kappa of 0.83 (SPSS 22.0 for windows [IBM SPSS Inc., Chicago, IL, USA]). Full texts of 10 selected articles were obtained for further review, after which one article was excluded because it did not report our primary or secondary outcomes. Nine studies met our inclusion criteria. The flow chart of the search and selection process is presented in Fig. 1.

Four studies focused on a heterogeneous ED population [18-21]. Three studies compared AL and PVL in septic ED patients [22-24]. The study of Browning [23] was a pilot study of the later published study of Datta et al. [24]. One study focused on a trauma population [25] and one study exclusively focused on ED patients with hyperlactatemia [26]. A meta-analysis was not performed due to the heterogeneity of the data. Five studies [18,20,23,24,26] used a blood gas analyzer in the ED as point-of-care test whereas one study used a handheld point-of-care device for the analysis of both arterial and peripheral venous samples [22]. Three studies [19,21,25] used blood gas analyzers in central laboratories. Importantly, within these studies the same method of measurement was used for both arterial and peripheral venous samples. The primary outcome is presented in Table 1 and the secondary outcomes are presented in Table 2. Overall, PVL was higher compared with AL with VA-MD ranging from 0.18 mmol/l to 1.06 mmol/l.

3.1. Agreement between AL and PVL in consecutive ED patients

Younger et al. [18] performed a prospective study using 48 samples reporting a VA-MD of 0.18 mmol/l. 95% LOA were not reported but calculated by Bloom et al. [14] between −1.18 and 1.54 mmol/l. Samples were taken with a mean time interval 6 ± 5 min. The mean AL and PVL were not reported. Gallagher et al. [19] investigated 69 paired samples obtained within 5 min and found a VA-MD of 0.22 mmol/l (95% LOA −1.3 to 1.7 mmol/l). The mean AL and PVL were 2.8 and 3.0 mmol/l respectively. Mikami et al. [20] reported a VA-MD of 0.268 mmol/l in 72 paired samples with a mean AL and PVL of 2.15 and 2.42 mmol/l respectively. Hypoxic patients were excluded and 95% LOA were not expressed. Finally, Paquet et al. [21] reported a VA-MD of 0.66 mmol/l (95% LOA of −1.7 to 0.6) in 132 simultaneously withdrawn paired samples. The median AL and PVL were 1.4 and 2.0 mmol/l respectively.

3.2. Agreement between AL and PVL in septic ED patients

Contenti et al. defined sepsis as the presence of at least two SIRS criteria combined with a suspected infection [22]. Prospectively comparing arterial, venous and capillary lactate, 103 patients were enrolled, of which 63 had severe sepsis. With a mean time interval of 8 ± 2 min, mean AL and PVL levels were 2.03 and 2.51 mmol/l respectively. The VA-MD was not reported. In a pilot study, Browning et al. [23] prospectively studied 37 patients with sepsis, using the same definition for sepsis as Contenti et al. [22]. Eight patients met the criteria for severe sepsis. All paired samples were withdrawn within 15 min. The VA-MD was 0.54 mmol/l (95% LOA of −0.11 to 1.18 mmol/l). As a result of the pilot study from Browning et al., Datta et al. [24] carried out a prospective cohort study in 304 patients with presumed sepsis, as judged by the treating physician. Blood samples were obtained within 20 min of each other. The VA-MD was 0.4 mmol/l (95% LOA of −0.11 to 1.18). Mean PVL and AL levels were not reported.

3.3. Agreement between AL and PVL in trauma patients

Lavery et al. [25] investigated 221 paired samples in a trauma patient population. Fifty-eight paired samples were withdrawn from a femoral vein. No difference was seen in lactate levels between central venous and peripheral venous samples. Mean AL was 3.11 mmol/l and mean PVL was 3.43 mmol/l. Not reported by the authors, a VA-MD of 0.32 mmol/l with 95% LOA of −1.95 to 2.31 mmol/l was calculated by Bloom et al. [14].

3.4. Agreement between AL and PVL in patients with hyperlactatemia

One study exclusively studied the agreement between AL and PVL in ED patients with hyperlactatemia, defined as a PVL ≥ 2 mmol/l. In a retrospective chart review a VA-MD of 1.06 mmol/l (95% LOA of −1.53 to 3.66 mmol/l) was found with a median AL and PVL of 2.45 and 3.50 mmol/l respectively [26].
3.5. Predictive value of PVL to predict arterial hyperlactatemia

Five studies investigated the value of PVL to predict arterial lactate levels (Table 2) [18,19,21,24,26]. Non-elevated PVL were almost always associated with normal AL with a negative predictive value for normal AL of 97% (95% CI: 92–100%) [21]. The rate of discrepant measurements in this study was 8% (95% CI 3–12%). At a cut-off value for hyperlactatemia of 1.6 mmol/l, PVL has a sensitivity of 94 to 100%, and a specificity of 57 to 86% for ruling out arterial hyperlactatemia [18,19].

Using a cut-off value of 2 mmol/l, PVL of ≥2 mmol/l predicts AL of ≥2 mmol/l with 100% sensitivity (95% CI: 89–100%) and 83% specificity (95% CI 77–87%) with a negative predictive value of 100% [24]. At a cut-off value of ≥3.3 mmol/l, PVL had a sensitivity of 43% (95% CI 29–58%) and specificity of 100% (95% CI 98–100%) to predict AL ≥ 2 mmol/l. At the cut-off value of 2 mmol/l, a classification error rate of 36.2% was seen in which AL was not elevated but PVL was elevated. In case of a cut-off value of 4 mmol/l, this classification error rate was 17.9% [26].

Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Study population</th>
<th>Time interval between sampling (min)</th>
<th>Number of paired samples</th>
<th>Mean arterial lactate (mmol/l)</th>
<th>Mean peripheral venous lactate (mmol/l)</th>
<th>Mean venous-arterial difference (mmol/l)</th>
<th>95% limits of agreement (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger et al. [18]</td>
<td>Prospective</td>
<td>ED patients</td>
<td>6 ± 5</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>0.18</td>
<td>-1.18 to 1.54</td>
</tr>
<tr>
<td>Gallagher et al. [19]</td>
<td>Prospective</td>
<td>ED patients</td>
<td>≤5</td>
<td>69</td>
<td>2.80</td>
<td>3.00</td>
<td>0.22</td>
<td>-1.30 to 1.70</td>
</tr>
<tr>
<td>Mikami et al. [20]</td>
<td>Prospective</td>
<td>ED patients</td>
<td>≤5</td>
<td>72</td>
<td>2.15</td>
<td>2.42</td>
<td>0.268</td>
<td>-</td>
</tr>
<tr>
<td>Paquet et al. [21]</td>
<td>Prospective</td>
<td>ED patients</td>
<td>Simultaneous</td>
<td>132</td>
<td>1.04</td>
<td>2.00</td>
<td>0.6</td>
<td>-0.6 to 1.7</td>
</tr>
<tr>
<td>Contenti et al. [22]</td>
<td>Prospective</td>
<td>ED patients with sepsis</td>
<td>8 ± 2</td>
<td>103</td>
<td>2.03</td>
<td>2.51</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Browning et al. [23]</td>
<td>Prospective</td>
<td>ED patients with sepsis</td>
<td>≤15</td>
<td>37</td>
<td>1.40</td>
<td>1.90</td>
<td>0.54</td>
<td>-0.11 to 1.18</td>
</tr>
<tr>
<td>Datta et al. [24]</td>
<td>Prospective</td>
<td>ED patients with sepsis</td>
<td>5b</td>
<td>304</td>
<td>-</td>
<td>-</td>
<td>0.40</td>
<td>-0.4 to 1.2</td>
</tr>
<tr>
<td>Lavery et al. [25]</td>
<td>Prospective</td>
<td>ED trauma patients</td>
<td>≤2</td>
<td>221</td>
<td>3.11</td>
<td>3.43</td>
<td>0.32b</td>
<td>-1.95 to 2.31</td>
</tr>
<tr>
<td>Bloom et al. [26]</td>
<td>Retrospective</td>
<td>ED patients with PVL ≥ 2.0 mmol/l</td>
<td>22b</td>
<td>232</td>
<td>2.45b</td>
<td>3.50b</td>
<td>1.06</td>
<td>-1.53 to 3.66</td>
</tr>
</tbody>
</table>

a As previously calculated by Bloom et al. [13].

b Median levels (not mean) as reported by the authors.
4. Discussion

In this systematic review, we investigated the agreement between PVL and AL in ED patients. Overall, PVL is higher compared with AL with mean differences ranging between 0.18 mmol/l [18] and 1.06 mmol/l [26]. Higher mean differences with broader limits of agreement were found in patients with hyperlactatemia [26] and mean PVL levels ranged between 1.90 mmol/l [23] and 3.50 mmol/l [26] (Table 1). Several authors proposed that PVL can be used instead of AL in the ED [18,20,22-25]. However, as the mean AL and PVL levels are fairly low in all studies, the reported agreement is largely influenced by the amount of patients with normal lactate levels.

Agreement between PVL and AL in hyperlactatemia is of clinical importance since current guidelines do not specify whether PVL or AL should be used in the definition of sepsis and septic shock [10-12]. The Surviving Sepsis Campaign uses a lactate level of ≥ 4 mmol/l as indicator of sepsis-induced tissue hypoperfusion and recommends that initial elevated lactate levels (≥ 2 mmol/l) should be remeasured within 2 to 4 h to guide resuscitation [11,12]. The Sepsis 3.0 criteria identifies septic shock patients by the need of vasopressor agents and serum lactate level ≥ 2 mmol/L in the absence of hypovolemia [10]. In order to use PVL and AL interchangeably there must be excellent agreement between both measurement methods.

From a statistical perspective, two measurement methods can be used interchangeably if the differences within mean ± 1.96 SD are not clinically important [15]. From a clinical perspective however, little is known about what would be acceptable limits for decision making. For other blood gas parameters, discrepancies between statistical limits of agreement and clinical acceptable limits have been reported [27]. Similar questions now also come up in the case of PVL. Namely, is agreement between AL and PVL in the predefined higher lactate levels reliable enough for a clinician to feel comfortable using both parameters interchangeably?

At a cut-off value of 2 mmol/l, peripheral venous hyperlactatemia is present in 8 to 36.2% of cases in which arterial hyperlactatemia is absent [21,26]. At a cut-off value of 4 mmol/l this classification error rate is 17.9% [26]. In patients with a peripheral venous lactate of ≥ 2 mmol/l the agreement between PVL and AL declines resulting in a higher mean difference with broader limits of agreement [26]. Declining agreement in higher lactate levels or critically ill patients was also described by Younger [18], Gallagher [19] and Datta [24] and is further supported by several comparative studies performed in the Intensive Care in patients with sepsis and septic shock [28,29]. The high misclassification error rate as well as augmenting differences occurring in hyperlactatemia make PVL an unreliable substitute for AL in ED patients with hyperlactatemia. With regard to the cut-off values defined by the SSC, the use of PVL and AL interchangeably might result in different diagnosing of sepsis eventually leading to different therapeutic measurements.

The question now rises what role PVL could fulfill in the ED. In an environment where rapid triaging of patients is of major importance and arterial or central lines are generally not present, peripheral venous blood withdrawal is faster, safer and easier to perform than arterial or central venous blood sampling [14]. For this reason, PVL has previously been proposed as a screening tool for arterial hyperlactatemia [26]. The determination up to which cut-off level PVL can be used as a reliable tool to rule out arterial hyperlactatemia is thereby of clinical importance. Using a cut-off level of 1.6 mmol/l, PVL can rule out arterial hyperlactatemia with sensitivities between 94% [19] and 100% [18] with a negative likelihood ratio of 0.1 [19]. In case of a cut-off value of 2 mmol/l, sensitivities of 97% [20] and 100% were found [24]. In higher cut-off values for PVL, sensitivity to predict an AL of ≥ 2 mmol/l declines whereas specificity rises up to 100% [24]. These high sensitivity rates implicate that at a cut-off level of PVL of 2 mmol/l, elevated arterial lactate levels can be ruled out with sufficient security.

Even though a cut-off value of 2 mmol/l seems fairly low, there is growing evidence that this cut-off value is of clinical importance [4-9]. Using this cut-off value, PVL can fulfill a reliable role in ruling out arterial hyperlactatemia in the ED. In higher values, caution should be put in the interpretation and we recommend that true hyperlactatemia should be confirmed taking an arterial sample.

5. Conclusion

There is evidence that PVL can rule out arterial hyperlactatemia in ED patients at a cut-off value of 2 mmol/l. Although data concerning agreement between AL and PVL in patients with hyperlactatemia is limited, there is a trend towards declining agreement in higher lactate levels. This trend makes PVL an unreliable parameter to use interchangeably in the ED in patients with hyperlactatemia. We therefore recommend that guidelines should define whether peripheral venous or arterial samples should be used in the definition of sepsis and septic shock. For clinical use in the ED, we recommend the use of PVL as a screening tool to rule out arterial hyperlactatemia with a cut-off value of 2 mmol/l. Depending on the clinical context, hyperlactatemia should be confirmed using arterial sampling in case of a PVL > 2 mmol/l.

Key learning points

• In Emergency Department patients, peripheral venous lactate is generally higher compared with arterial lactate with mean differences ranging from 0.18 mmol/l to 1.06 mmol/l.
• In higher lactate levels, agreement between arterial and peripheral venous lactate levels declines.
• A peripheral venous lactate level of ≤ 2 mmol/l is highly predictive of an arterial lactate level of ≤ 2 mmol/l with sensitivities between 97% and 100%.
• A peripheral venous lactate level of ≤ 2 mmol/l can be used as a screening tool to rule out arterial hyperlactatemia.
• In peripheral venous hyperlactatemia > 2 mmol/l arterial sampling should be considered to rule out arterial hyperlactatemia.
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