Differential diagnosis of elevated blood lactate is the daily bread and butter of all clinicians looking after critically ill patients. In principle, hyperlactatemia can either be caused by increased production in tissues (type A) or impaired lactate uptake (type B) or by these two mechanisms combined [1, 2]. Correctly determining the cause(s) of hyperlactatemia is of utmost importance, indeed, because it determines the treatment, which can be life saving for a patient with one underlying cause, but harmful for another. A classical example of this concept is fluid resuscitation that can be helpful in correcting tissue hypoperfusion, but harmful for patients with other causes of elevated lactate. Nice as it sounds, recognizing patients that would benefit from fluid administration (or other ways of increasing cardiac output) is often very difficult at the bedside and often results in fluid abuse, particularly in patients with elevated lactate and on vasopressors [3]. It was recognized in sepsis that pCO2 gap (or its mathematical derivatives) outperformed other markers in detecting tissue hypoperfusion [4–7]. We hypothesize that the difference in carbon dioxide partial pressure between central venous and arterial blood (pCO2 gap) can be a useful aid in the differential diagnosis of elevated lactate also outside the context of sepsis. In this paper, we present the theoretical
rationale for this hypothesis and review published data and confront them with observations of pCO2 gaps in a case series of nonseptic patients with known cause of lactate elevation.

1.1. Physiological Background. During the process of cellular respiration, carbon dioxide is produced mostly by decarboxylation reactions in citric acid cycle and diffuses into the bloodstream through the extracellular fluid. Whilst approximately 10% of the carbon dioxide (CO2) in the blood remains dissolved in the plasma, the remaining CO2 diffuses rapidly into the red blood cells, where it is either bound to terminal NH2 groups (30%) forming carbaminohaemoglobin or reacts with water to form carbonic acid (60%) that dissociates to bicarbonate and a proton (H+): [8]:

\[
\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}^+ + \text{HCO}_3^- \quad (1)
\]

The production of HCO3\(^-\) occurs rapidly because of catalysis by carbonic anhydrase. The HCO3\(^-\) then leaves the red blood cells in exchange for Cl\(^-\) (the process known as chloride or Hamburger shift), thereby promoting the entry of more CO2 into the red blood cell. In the bloodstream, CO2 in all 3 forms is conveyed back to the respiratory surfaces at a rate, which is directly proportional to cardiac output.

Cardiac output (CO) calculated using the Fick principle applied to CO2 agrees well with cardiac output calculated from O2-derived parameters in normal subjects at rest and during exercise [9]. The Fick equation (for indirect CO calculation) applied to CO2 is

\[
\text{CO} = \frac{\text{VCO}_2}{\text{VctCO}_2 - \text{ActCO}_2} \quad (2)
\]

where VCO2 is the CO2 production, CO is the cardiac output, and VctCO2 − ActCO2 is the venous-to-arterial CO2 content difference. After substituting ctCO2 gap into the abovementioned equation, we obtain

\[
\text{ctCO}_2 (B)\text{gap} = \frac{\text{VCO}_2}{\text{CO}}, \quad (3)
\]

where the ctCO2 (B) gap is inversely related to CO and proportional to VCO2. The value for ctCO2 is not directly measured; instead, it is calculated from measured pH and pCO2, which is a mathematically complex and error-prone process, whereas pCO2 is a directly measured parameter that is readily available to clinicians. In this paper, we will determine the pCO2 gap by subtracting the peripheral arterial pCO2 from the central venous pCO2. This is because central venous pCO2 has been shown to be a reliable substitute for mixed-venous pCO2 [10], and pulmonary artery is rarely catheterized in contemporary ICU practice because of the invasiveness of the procedure [11].

Over the physiologic range of pCO2, the relationship between pCO2 and the total blood CO2 content is close to linear, so pCO2 may be considered a reliable substitute for CO2 content [12, 13]. Factors that disturb the linearity between pCO2 and CTCO2 tend to offset each other for a given CtCO2, and pCO2 is higher in metabolic acidosis and lower for lower saturation of haemoglobin with oxygen (see Figure 1). During low flow states, organic acids (mainly lactate) are released from hypoperfused tissues, causing base excess of venous blood to be more negative as compared with the arterial blood. On the other hand, venous blood leaving the hypoperfused tissue tend to be more deoxygenated, causing pCO2 to be lower for a given CtCO2 (Haldane effect [14]). In turn, it can be hypothesized that A-V pCO2 gap is representative of CTCO2 gap under a wide range of clinical situations. In turn, when pCO2 replaces CtCO2 in equation (3), we get

\[
(PvCO_2 - PaCO_2) = pCO_2 (B)\text{gap} = \frac{\text{VCO}_2}{\text{CO}} * k, \quad (4)
\]

where \((PvCO_2 - PaCO_2)\) is the venous-to-arterial PCO2 difference and \(k\) is the PCO2 to CTCO2 correlation (assumed to be constant). In line, both CTCO2 and pCO2 gaps were found to increase with the decrease in CO, and the relationship follows a hyperbolic pattern (see Figure 2) [15, 16].

Moreover, elevated CO2 gap can be considered as the marker of the cardiac output in relation of peripheral metabolic requirements. Hypoxic hypoxia in the presence of adequate cardiac output cannot cause pCO2 gap elevation as demonstrated by elegant experiments of Vallet et al. [17]. On the other hand, if there is an inhomogeneity of distribution of perfusion as it is the case in sepsis, the pCO2 gap is more sensitive than ScvO2 drop in detecting patients who would benefit from measures aimed at increasing cardiac output [4–6, 18–20]. The cut-off value of pCO2 gap in a septic patient was found to be 0.8 kPa (6 mmHg) [20, 21]. The superiority of pCO2 gap over ScvO2 desaturation in detecting hypoperfusion likely reflects the fact that in the presence of microvascular shunting, central venous blood is a mixture of arterialized blood from shunts and desaturated blood from the hypoperfused regions. Because of 20 times higher diffusibility of CO2 as compared with O2 [22, 23] central venous blood can have normal or high ScvO2 (due to arterialized blood form shunts), whilst CO2 content is elevated proportionally to the degree of peripheral tissue hypoperfusion as shunting capillaries are still capable to drain CO2 from the hypoperfused tissues. It has been proposed (L. Gattinoni–personal communication) that local tissue acidosis caused by hypoperfusion releases free CO2 from bicarbonate, thereby increasing venous pCO2 even further, a phenomenon called “Coca Cola effect” in analogy to releasing bubbles by adding piece of lemon into a carbonated drink. In addition, some CO2 can be produced anaerobically [18].

Tissue metabolism also influences the respiratory exchange ratio (RER), i.e., the amount of CO2 produced per each mole of O2 consumed. Oxidation of lipids releases less CO2 (0.7 moles) than oxidation of amino acids (0.84 moles) or carbohydrates (1.0 mole) for 1 mole of consumed O2. After reaching anaerobic threshold, RER increases well above 1.0. In analogy, anaerobic metabolism in peripheral tissues can be detected by calculating a surrogate of tissue RER:
The value of $RER_{sur} > 1.4$ (when $pCO_2$ gap is in (mmHg) and $ctCO_2$ in (ml/dL)) was found to be associated with the presence of tissue hypoxia [24]. This is the analogy of the increase of whole-body respiratory quotient when a person exercising on a treadmill overcomes the aerobic threshold. Indeed, $RER$ can be elevated even with normal $pCO_2$ gap, if venoarterial difference of oxygen content is very low, as could be the case when significant left-to-right shunting (e.g., at microcirculation level) is accompanying tissue ischaemia.

To summarize, unlike oxygen in the opposite direction, $CO_2$ is able to reach the bloodstream regardless of the status of microcirculation. According to the Fick principle, mixed venous-to-arterial $ctCO_2$ gap is inversely related to cardiac output and central venous-to-arterial $pCO_2$ gap seems to be its acceptable surrogate. In the light of this, it can be hypothesized that even outside the context of sepsis, $pCO_2$ gap can be a useful aid in the differential diagnosis of lactic acidosis. In particular, elevated $pCO_2$ gap can identify patients who would benefit from fluids and/or other measures aimed at increasing cardiac output. In order to support this hypothesis, we present a series of patients in whom $pCO_2$ gap was measured, and the cause of lactic acidosis was conclusively known.

2. Methods

In a clinical information system (MetaVision ver. 6, IMD Soft, Israel) that contains data of 5251 patients admitted to 22 bed ICU of the Department of Anaesthesia and Intensive Care of FNKV University Hospital since 2012, we retrospectively searched for patients who had central venous and arterial blood gases measured simultaneously (within 2 min) and also had elevated lactate within 24 hours of paired blood gas measurement. From the list of patients fulfilling these criteria, we selected those where 2 clinicians independently agreed on lactic acidosis being either type A or B, and the diagnosis was either beyond all doubts (e.g., a young fit trauma victim with active bleeding and hemorrhagic shock) or supported by additional evidence (e.g., findings at autopsy). All the rest of the cases were labeled as undetermined.

In those cases, we calculated arterial and venous blood $CO_2$ content as

$$ctCO_2 (B) = 9.286 \times 10^{-3} \times pCO_2 \times ctHb \times \left[ 1 + 10^{\left(1+10^{(\frac{-pKery}{10} + \frac{-pHERY}{10})})\right) \right] + ctCO_2 (P) \times \left(\frac{ctHb}{21}\right).$$

where
ctCO₂ (P) = 0.23 * pCO₂ + CHCO₂⁻ (P)

\[ \text{pK}_p = 6.125 - \log \left( 1 + 10^{(\text{pH} - 8.7)} \right) \]

\[ \text{pH}_{\text{ERY}} = 7.19 + 0.77 \times (\text{pH} - 7.4) + 0.035 \times (1 - \text{sO}_2) \]

\[ \text{pK}_{\text{ERY}} = 6.125 - \log \left( 1 + 10^{(\text{pH}_{\text{ERY}} - 7.84 - 0.06 \times \text{sO}_2)} \right) \]

These equations were from the manual of ABL-800 blood gas machine (Radiometer, Denmark), and indices “ERY” indicate erythrocyte (red blood cell).

Oxygen content in arterial blood was calculated as

\[
\text{Act(O}_2\text{)}_{\text{dl}} = \left[ 1.34 \times \text{Hb} \left( \frac{\text{g}}{\text{dl}} \right) \times \text{SaO}_2 \times 0.01 \right] + \left[ 0.0225 \times \text{PaO}_2 \text{ (kPa)} \right]
\]

Oxygen content in venous blood was correspondingly calculated as

\[
\text{Vct(O}_2\text{)}_{\text{dl}} = \left[ 1.34 \times \text{Hb} \left( \frac{\text{g}}{\text{dl}} \right) \times \text{SVo}_2 \times 0.01 \right] + \left[ 0.0225 \times \text{PvO}_2 \text{ (kPa)} \right]
\]

The study was performed in accordance with the Declaration of Helsinki. Because of retrospective and epidemiological nature of the study, informed consent was not required.

3. Results

Out of all 5,251 patients in the database, we have found 23 cases with nonseptic patients with elevated lactate and both arterial and venous gases measured. Out of these, there were 6 cases where the diagnosis of either type A or B was beyond any reasonable doubt as independently agreed by 2 clinicians.

3.1. Case Series

3.1.1. Example Case 1: Type A Lactacidemia due to Global Hypoperfusion. A 40-year-old male attempted suicide by jumping out of 3rd floor window. He was intubated at scene, brought in, and diagnosed complex pelvic fracture and compressive fracture of L3. Parenchymatous organs were without signs of injury. After volume resuscitation and blood transfusions, he was haemodynamically stable and remained sedated with plan to operate fractures the next day. In very early hours of the next morning, he suddenly developed signs of haemorrhagic shock with tachycardia 150/min, haemoglobin drop from 129 to 92 g/L, and hypotension with an increase of noradrenaline dose from 0.4 to 1.1 µg.kg\(^{-1}\).min\(^{-1}\). Lactate at this stage was 1.4 mM (only 90 min later increasing to 3.4 mM), ScvO2 68%, pCO₂ gap was 1.02 kPa, and RER 1.86. CT scan was repeated and showed a haemoperitoneum and R-sided haemothorax due to right-sided diaphragmatic injury that included rupture and bleeding from the teres hepatitis ligament. He was classified as having type A lactic acidosis due to haemorrhagic shock.

3.1.2. Example Case 2: Type A Lactacidaemia due to Local Ischaemia. A 53-year-old female, previously fit and well, underwent Whipple’s pancreateoduodenectomy due to pancreatic tumour. The operation and the immediate postoperative course were uneventful. She was extubated and haemodynamically stable, passing urine and not requiring vasopressors. Three hours after surgery, she developed severe abdominal pain despite functional epidural analgesia. Her lactate increased to 5.3 mM, ScvO2 was 71%, pCO₂ gap 1.06 kPa, and RER 1.58. She was diagnosed small bowel ischaemia due to occlusion of superior mesenteric artery on angio-CT and underwent relaparotomy and an aortomesenteric bypass operation. She was classified as type A lactic acidosis based on perioperative finding of ischaemic bowel.

3.1.3. Example Case 3: Type A Lactacidemia due to Combination of Global and Local Hypoperfusion. A 25-year-old man, previously fit and well, completely transected his brachial artery by a broken glass. He suffered massive blood loss and was found in profound shock by emergency services. He was brought in after having received 2 L of crystallloids and 1 g of tranexamic acid. This patient with evident tissue hypoperfusion due to acute blood loss, with lactate 7.2 mM and ScvO2 58%, had pCO₂ gap 1.38 kPa (10 mmHg), and RER of 2.5. In addition, CT scan performed at admission revealed a nonocclusive ischaemia and necrosis of the small bowel that required laparotomy and bowel resection. He was classified as type A lactacidosis based on perioperative finding of ischaemic bowel.

3.1.4. Example Case 4: Type B Lactacidemia due to Metformin Overdose. A 71-year-old female with type 2 diabetes was admitted after suicidal attempt committed due to metformin overdose. On admission, she was unconscious, intubated and ventilated, haemodynamically unstable (noradrenaline dose 0.53 µg.kg\(^{-1}\).min\(^{-1}\)), and in profound acidosis (pH 6.58), with lactate 17 mmol/L, ScvO2 was 78.7%, pCO₂ gap 0.37 kPa (2.8 mmHg), and RER 1.14. She was classified as type B lactic acidosis due to metformin overdose [25] by consensus of clinicians.

3.1.5. Example Case 5: Type B Lactacidemia due to High Dose Steroids and Betamimetics. A 66-year-old obese female with a history of asthma was hit by a car whilst crossing the road. At scene, she was confused and complaining of shortness of breath. She was intubated and air-lifted to the trauma centre. She was stable and found to have no injuries on the CT scan, and the decision was made to wake her up and extubate. Her pre-extubation lactate was 1.7 mM. Immediately after extubation, she developed severe bronchospasm, which did not respond to inhalatory betamimetics
3.1.6. Example Case 6: Type B Lactacidemia in Patient with Advanced Multiple Myeloma. A 75-year-old male with known advanced multiple myeloma was referred for sudden-onset paraplegia. He was found to have T8 fracture and underwent an urgent decompressive spinal surgery. Perioperatively, he also received spinal dose steroids. Blood loss was estimated to 1.6 L and he required perioperative transfusion of blood products, but remained haemodynamically stable. Perioperative blood gas showed lactate 12.8 mM, SvcO2 72%, pCO2 gap 0.3 kPa, and RER 0.71. He was referred to ICU after operation. Despite persistent elevation of lactate, he remained stable and was extubated. He was discharged to ward after 5 days, in much improved condition but with lactate still in range of 5–10 mM, a phenomenon that has been described in patients with multiple myeloma [28–30]. He was diagnosed by a posteriori consensus of clinicians as having type B lactic acidosis due to a combined effect of betamimetics [26] and steroids [27].

3.2. Differences between Patients with Type A and B Lactacidemia. As summarised in Table 1, all patients with typical type A lactic acidosis had pCO2 gap well above 0.8 kPa (6 mmHg) including patients who had normal SvcO2. On the contrary, all patients with type B lactic acidosis had pCO2 gap around 0.4 kPa (3 mmHg). Similar or even better discrimination is obtained when RER is used (Table 1). We found a close correlation between ctCO2 gap and pCO2 gap ($R^2 = 0.71$ data not shown), but not so close correlation between ctCO2 gap and ctO2 gap ($R^2 = 0.54$, data not shown). Venoarterial lactate difference [31, 32] was in range of −0.3 to +0.2 mM and we have not found any difference between patients with type A and B lactacidemia.

### Table 1: Case series of patients with different causes of elevated lactate.

<table>
<thead>
<tr>
<th>Case</th>
<th>Lac (a) (mmol/L)</th>
<th>SaO2 (%)</th>
<th>SvcO2 (%)</th>
<th>pCO2 gap (kPa)</th>
<th>RER</th>
<th>Type of lactic acidosis and timing of diagnosis</th>
<th>Evidence for classifying hyperlactataemia as either A or B</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>3.4</td>
<td>99</td>
<td>68</td>
<td>1.02</td>
<td>1.86</td>
<td>A—a posteriori</td>
<td>Peroperative finding</td>
</tr>
<tr>
<td>#2</td>
<td>5.3</td>
<td>99</td>
<td>71</td>
<td>1.06</td>
<td>1.58</td>
<td>A—a posteriori</td>
<td>Peroperative finding</td>
</tr>
<tr>
<td>#3</td>
<td>7.2</td>
<td>100</td>
<td>58</td>
<td>1.38</td>
<td>2.5</td>
<td>A—a priori</td>
<td>Consensus of clinicians</td>
</tr>
<tr>
<td>#4</td>
<td>17.0</td>
<td>99</td>
<td>79</td>
<td>0.37</td>
<td>1.14</td>
<td>B—a priori</td>
<td>Consensus of clinicians</td>
</tr>
<tr>
<td>#5</td>
<td>7.4</td>
<td>94</td>
<td>76</td>
<td>0.30</td>
<td>0.78</td>
<td>B—a posteriori</td>
<td>Consensus of clinicians</td>
</tr>
<tr>
<td>#6</td>
<td>12.8</td>
<td>99</td>
<td>72</td>
<td>0.30</td>
<td>0.71</td>
<td>B—a posteriori</td>
<td>Consensus of clinicians</td>
</tr>
</tbody>
</table>

Note: Lac a = lactate (arterial); RER = respiratory exchange ratio calculated as per equation (5).

### Figure 3: Main physiological features of type A and B hyperlactaemias.

**Type A**
- Anaerobic
- ↑ Lactate/Pyruvate ratio
- ↑ pCO2 gap
- ↑ pCO2 gap/CA-VO2 gap
- norm. Lactate/Pyruvate ratio
- norm. pCO2 gap
- norm. pCO2 gap/CA-VO2 gap

**Type B**
- Aerobic
- Decreased lactate clearance
- norm. Lactate/Pyruvate ratio
- norm. pCO2 gap
- norm. pCO2 gap/CA-VO2 gap

### 4. Discussion

The presented review of physiology and the small case series generate the hypothesis that the use of venous-arterial pCO2 gap can be a useful aid in the differential diagnosis of hyperlactataemia. Type A lactic acidosis caused by global or local tissue hypoperfusion with a switch to anaerobic metabolism, whilst type B lactic acidosis is mostly characterized by the absence of tissue hypoxia, and the cause of elevated lactate is either aerobic production or decreased lactate clearance (Figure 3).

Type B lactic acidosis is seen in the heterogeneous group of diseases that are of common occurrence in a typical general ICU [33]. Aerobic lactate production can occur as a paraneoplastic phenomenon (by Warburg effect [34, 35]) or more often as the result of β-adrenergic receptor stimulation either during a sympathetic surge (e.g., acute severe asthma, subarachnoidal haemorrhage, and pheochromocytoma) or after administration of β-receptor agonists (typically β2-mimetics or adrenaline). Decreased lactate clearance is seen in metformin or ethanol poisoning or in liver failure. Steroids cause hyperlactaemia [36] by a combination of increased aerobic lactate production and decreased lactate clearance [27]. Indeed, many patients would have a combination of type A and B causes of lactic acidosis (e.g., those with septic shock [37, 38], but also many others [39]) (Table 2).

Because the principal difference of type A and B of hyperlactataemia is the presence or absence of tissue hypoxia, the ratio of lactate/pyruvate has been proposed to aid...
Due to the ubiquitous presence of cytosolic lactate dehydrogenase, lactate/pyruvate ratio reflects the redox situation of cells, i.e., $\left[\text{NADH}\right]/\left[\text{NAD}^+\right]$ ratio, tissue hypoxia would lead to a block of reoxidation of NADH back to NAD$^+$. Accumulated NADH would cause a leftward shift of equilibrium shown in the following equation:

$$\text{pyruvate} + \text{NAD}^+ \leftrightarrow \text{actate} + \text{NADH}. \quad (10)$$

Hence, in the presence of any cessation of electron transfer chain (of which by far the most common cause is hypoxia), the lactate/pyruvate ratio increases above normal value of 10:1, which is considered a hallmark of type A lactic acidosis [33, 39]. In line, type B lactic acidosis would have both lactate and pyruvate increased, with the ratio 1:10 remaining constant. Nonetheless, the lactate/pyruvate ratio remains of very limited clinical use because currently it is impossible to measure pyruvate concentration by point-of-care techniques, and its laboratory assay is complex and prone to preanalytical errors [39]. Despite technical complexity, the study of lactate/pyruvrate ration in critically ill patients with elevated lactate demonstrated that a large proportion of them do not have the biochemical signs of tissue hypoxia and have in general a better prognosis. Indeed, those patients are unlikely to benefit from measures aimed to increase systemic oxygen delivery and more fluids or inotropes may actually cause harm. Unnecessary fluid loading is performed very often in the critically ill (as

<table>
<thead>
<tr>
<th>Group</th>
<th>Mechanism</th>
<th>Condition/disease</th>
<th>Expected finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (increased lactate production)</td>
<td>Severe hypoxia</td>
<td>Any cause (pO$_2$ &lt; 4 kPa)</td>
<td>High pCO$_2$ gap fluids and ↓ cardiac output are likely to help</td>
</tr>
<tr>
<td></td>
<td>Low O$_2$ transport capacity</td>
<td>CO poisoning</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low global oxygen delivery leading to excessive anaerobic glycolysis</td>
<td>Severe anaemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low cardiac output = hypodynamic shock</td>
<td>Low preload (hypovolaemia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal or high cardiac output, but demand even higher</td>
<td>Low contractility (cardiogenic)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inflow occlusion</td>
<td>High afterload (obstructive)</td>
<td></td>
</tr>
<tr>
<td>A (increased lactate production)</td>
<td>Local ischaemia leading to excessive anaerobic glycolysis</td>
<td>Stimulation of muscle and liver glycogenolysis</td>
<td>Fluids and ↑ cardiac output may or may not help</td>
</tr>
<tr>
<td></td>
<td>Increased glycolysis in the presence of enough oxygen</td>
<td>Decreased perfusion pressure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Local ischaemia (Wartburg effect)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stimulation of muscle and liver glycogenolysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blocked oxidative phosphorylation (cytopathic hypoxia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Production of L- and D-lactate by colon bacteria</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Failed conversion of pyruvate to AcCoA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Failed conversion of lactate to pyruvate</td>
<td></td>
</tr>
<tr>
<td>B (decreased lactate uptake)</td>
<td>Decreased lactate uptake</td>
<td>Failed conversion of pyruvate to AcCoA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Failed conversion of lactate to pyruvate</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>Sepsis</td>
<td>Element of hypoxia, aerobic glycolysis, and splanchnic ischaemia</td>
<td>Complex condition</td>
</tr>
<tr>
<td></td>
<td>Propylen glycol poisoning</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mix of D- and L-lactate overproduction and element of oxidative phosphorylation block</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Overview of causes of elevated lactate.
evidenced in FENICE study [3]), and we can only speculate how often this is triggered by elevated lactate being mis-interpreted as a marker of tissue hypoperfusion. Anecdotally, ordering of fluid boluses as automatic response to elevated lactate has been termed "fluid reflex". We suggest that the role of pCO2 gap in detecting tissue hypoperfusion is further studied as a possible marker of tissue hypoperfusion in situations of elevated lactate outside the context of sepsis. We demonstrate in our series of case reports that, in pCO2 gap reflected ctCO2 gap and was elevated (>1 kPa) in patients with global or local hypoxia, but remained low (<0.5 kPa) in patients with type B lactic acidosis, perhaps due in part to the hyperkinetic circulation that often accompanies diseases associated with type B hyperlactataemia. The pCO2 gap cut-off of 0.8 kPa, used in studies on early-goal-directed therapy in septic shock [18, 19] seems to be applicable to our nonseptic cases, too, but indeed, the cut-off with best sensitivity and specificity remains to be determined. Unlike ScvO2, the use of pCO2 gap is less distorted by the presence of microcirculatory shunts, and hence it should have higher sensitivity to detect tissue hypoperfusion.

Nonetheless, our small observational case series is by no means the proof of the hypothesis outlined above. The next step would be a prospective trial looking at lactate dynamics after a fluid bolus in relation to pCO2 gap at baseline in patients with elevated lactate and with cardiac output continuously monitored. Also, much larger series of patients is needed to determine what is the proportion of hyperlactatemic patients in which pCO2 gap might be helpful as compared with those with mixed type A+B hyperlactatemia. Lastly, it remains unclear how specific and sensitive pCO2 gap is in detecting organ hypoperfusion in patients with mixed etiologies of lactic acidosis.

In conclusion, in this paper, we present a hypothesis that venous-arterial pCO2 gap may be a useful aid in the differential diagnosis of elevated lactate in critically ill patients and that it has potential to avoid administration of unnecessary fluids and ionotropics in patients, who have lactate elevated in the absence of tissue hypoperfusion. We demonstrate, for the first time in the literature, that pCO2 gap is elevated in nonseptic patients with type A lactic acidosis and normal in type B lactic acidosis.

**Abbreviations**

- Act(B)O2: Content of oxygen in whole arterial blood
- CaCO2: Total carbon dioxide content in whole arterial blood
- Central venous blood: Sampled from a central venous catheter (inserted into vena cava superior)
- CO: Cardiac output
- ct(B)CO2 gap: Arterial-to-venous carbon dioxide content difference
- ct(B)O2 gap: Arterial-to-venous oxygen content difference
- CvCO2: Total carbon dioxide content in whole venous blood
- DO2: Oxygen delivery
- EGDT: Early goal-directed therapy
- Hb: Haemoglobin
- MALA: Metformin-associated lactic acidosis
- Mixed venous blood: Sampled from a pulmonary artery catheter
- pCO2 gap: Central venous-to-arterial carbon dioxide partial pressure difference (in the literature ΔpCO2 is also used)
- RQ: Respiratory quotient
- S,O₂: Central venous oxygen saturation
- Vct(B)O2: Content of oxygen in whole venous blood

**Data Availability**

The deidentified patient’s data used to support the findings of this study are in extenso provided in the manuscript.

**Conflicts of Interest**

The authors declare no conflicts of interest.

**Authors’ Contributions**

PW and KJ performed the literature review and PW and FD collected and analysed the patients’ data. All authors contributed to writing the paper and read and approved its final version.

**Acknowledgments**

The work was supported by Charles University grant Q37 and by Institutional support of FNKV University Hospital.

**References**


