Lactate- or bicarbonate-buffered solutions for CRRT?

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Once again we have a burning question concerning continuous renal replacement therapy (CRRT) i.e. which type of solution is most appropriate for this purpose, lactate or bicarbonate buffered? Our unit manager urges us to use the lactate replacement because it is cheaper. We are concerned whether its use is safe in the critically ill, especially when we observe a rise in plasma lactate.

Introduction
The kidney maintains blood pH by filtering metabolic acids and regenerating blood buffers such as bicarbonate. During CRRT, pH is regulated in a comparable way, metabolic acids are filtered or dialysed and buffer is replaced to correct metabolic acidosis and compensate for the bicarbonate lost by filtration or diffusion. Lactate, bicarbonate, acetate and citrate are the available buffers. Acetate is no longer generally used because of its lower buffer capacity, vasodilatory and negative inotropic effects [1]. Citrate is a potent buffer which is given in the setting of regional anticoagulation; its use has previously been extensively discussed [2]. When conventional anticoagulation is used, in daily practice the choice of buffer is either lactate or bicarbonate. The lactate or bicarbonate content of commercial replacement fluids ranges from 32-46 mmol/l.

Lactate as a buffer
Lactate has buffer potency, since it is administered as conjugated base. It acts as a buffer if and when it is converted to pyruvate. Under aerobic conditions pyruvate is converted to acetyl-CoA, which is subsequently oxidized in the citric acid cycle or pyruvate is metabolized to glucose by gluconeogenesis (Fig 1). According to the Stewart concept, metabolic conversion of lactate increases the strong ion difference explaining its alkalizing effect. To generate one mole of bicarbonate, each mole of lactate consumes three moles of oxygen (Fig 2). Thus oxygen is consumed for the generation of buffer from lactate.

Although lactate has been shown to provide adequate buffering in most clinical trials comparing lactate to bicarbonate solutions (Table 1), lactate solutions should be used with caution for several reasons. First, in two of the controlled trials lactate buffering was associated with a poorer control of acidosis despite a higher net gain of buffer substrate [3, 4]. Second, in both of these studies lactate replacement was associated with more hypotension [3, 4], more vasopressor support and a lower cardiac index [4]. In the larger study, there was a trend towards a higher mortality in patients with cardiac failure [3]. Third, in all controlled studies, lactate concentration in plasma significantly increased in the lactate buffered group, indicating that net lactate infusion surpassed metabolic capacity. Despite the increase in lactate, acid base control was adequate in most studies. Base excess normalizes due to a decrease in chloride and phosphate and the effective removal of strong anions, while lactate contributes to acidosis only by decreasing the strong ion difference [7, 8]. It should be noted that in most studies the concentration of buffer substrate in the lactate solutions was higher than in the bicarbonate-based fluids. Apparently, not all lactate is used as a buffer [4]. Finally, in a small randomized controlled cross-over study showing effective acid base control, nitrogen excretion was higher in patients starting with lactate buffering, possibly indicating a higher protein catabolism [5].

It could be argued that in these studies the dose of CRRT was lower than is currently recommended (35 ml/kg/h) [9, 10]. With the use of high-volume haemofiltration (2 l/h predilution and 4 l/h postdilution) and a replacement fluid containing 46 mmol lactate/l, plasma lactate increased from about 0.4-3.8 to 6.5-12 mmol/l. Base excess slightly decreased initially, but the range after 8 hours was not significantly different compared to baseline [11].

The hyperlactataemia occurring during CVVH is due to the decreased metabolic capacity for lactate in critically ill patients and the simultaneous supera-physiological infusion. The citric acid cycle operates only under aerobic conditions, because it is linked to oxygen consumption to regenerate nicotinamide adenine dinucleotide (NAD$^+$). If oxygen availability is limited, the citric acid cycle slows down (Fig 1). CRRT balance of lactate depends on ultrafiltrate (dialysate) flow and lactate concentration in the replacement (dialysis) fluid (Table 2). If, for example, 4 l/h are exchanged in postdilution CVVH using a lactate buffered replacement fluid, a positive lactate balance of 360 g/day is attained, while a metabolic capacity of lactate 0.6-0.9 mmol/kg/h (about 60 mmol/h, 130 g/day) is measured in patients with multiple organ failure [12-14]. If liver function and tissue perfusion fail, lactate conversion is limited further, leading to lactate accumulation and aggravating acidosis, because lactate is not converted and bicarbonate continues to be lost by filtration or dialysis.

Lactate and glucose
The use of lactate as a buffer has other metabolic effects as well. Normally, gluconeogenesis accounts for 20% of the lactate conversion and the majority of pyruvate is converted to Acetyl-CoA which enters the citric acid cycle. If, however, the exogenous supply of lactate surpasses the capacity of the Krebs (citric acid) cycle, a higher proportion is used for gluconeogenesis. The consequence of this metabolic pathway in the critically ill is shown in a controlled study comparing lactate to bicarbonate buffered CVVH (30 ml/kg/h). Compared to bicarbonate, lactate replacement was associated with a higher glucose turnover and plasma glucose, despite higher insulin levels [14]. Thus lactate buffering may increase glucose intolerance.

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Table 1. Controlled studies published as full paper comparing lactate- to bicarbonate-buffered solutions for CRRT in critically ill patients with acute renal failure

<table>
<thead>
<tr>
<th>Study design</th>
<th>Study period</th>
<th>Number of patients</th>
<th>Buffer</th>
<th>CRRT dose rate</th>
<th>Acid base control</th>
<th>Plasma lactate</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kierdorf</td>
<td>1995</td>
<td>Cross-over 2 x 4 days</td>
<td>B: 37.5</td>
<td>1.2 l/h CVVH</td>
<td>Both good</td>
<td>B: 2.54 ± 0.76 mmol/l</td>
<td>Higher N-excretion in patients starting with lactate</td>
</tr>
<tr>
<td>Heering</td>
<td>1999</td>
<td>Prospective cohort ICU</td>
<td>B: 35.5</td>
<td>1 l/h CVVH</td>
<td>A: Poor</td>
<td>B: 3.8 ± 3.2 mmol/l</td>
<td>A: More hypotension and lower CI no difference in mortality</td>
</tr>
<tr>
<td>Thomas</td>
<td>1997</td>
<td>24 h</td>
<td>B: 43.5</td>
<td>1.7 l/h CVVH</td>
<td>Equal correction of acidosis</td>
<td>B: 2.2 ± 2.5 mmol/l</td>
<td>L: 2.3 ± 4.3 mmol/l</td>
</tr>
<tr>
<td>Barenbrock</td>
<td>2000</td>
<td>RCT 5 days</td>
<td>B: 35</td>
<td>1 l/h CVVH</td>
<td>B: bic</td>
<td>B: 2.9 ± 1.9 mmol/l</td>
<td>L: More hypotension (p&lt;0.05) mortality: B: 33%, L: 43% subgroup of cardiac failure (n=45) mortality B: 29 vs. 57%</td>
</tr>
<tr>
<td>McLean</td>
<td>2000</td>
<td>Non-randomized cross-over 72 h</td>
<td>B: 24.4</td>
<td>1.5 l/h pumped CAVHD</td>
<td>B: bic 18–23 mmol/l</td>
<td>B: 2.2 ± 1.7 mmol/l</td>
<td>B: MAP ↑, vasopressors ↑ L: MAP ↓, vasopressors ↑ NB: patients with and without liver dysfunction: idem</td>
</tr>
<tr>
<td>Tan</td>
<td>2003</td>
<td>RCT Cross-over 2 x 2 h</td>
<td>B: 35</td>
<td>2 l/h pre-dilution CVVH</td>
<td>B: bic 28.3–28.2 mmol/l</td>
<td>B: 2.8 ± 2.5 mmol/l</td>
<td>B: Hyperlactatemia with a slight non-progressive acidifying effect despite positive buffer balance</td>
</tr>
<tr>
<td>Bollmann</td>
<td>2004</td>
<td>RCT Cross-over 2 x 24 h</td>
<td>B: 35</td>
<td>20 ml/kg/h CVVHDF</td>
<td>B: bic 26.6 mmol/l</td>
<td>B: 1.7 mmol/l</td>
<td>B: higher glucose (23%), higher glucose turnover (20%)</td>
</tr>
</tbody>
</table>

Abbreviations: RCT: randomised controlled trial, B: bicarbonate-buffered solution, L: lactate-buffered solution, A: acetate-buffered solution, CVVH continuous venovenous haemofiltration, CAVHD continuous arteriovenous haemodiafiltration, CVVHD continuous venovenous haemodiafiltration, i.v. intravenous, MAP mean arterial pressure, CI cardiac index.

Table 2. Calculated lactate infusion rates and lactate balance in patients on different doses and modes of CVVH, assuming a plasma lactate concentration of 2, 3 and 4 at a CVVH doses of 2, 3 and 4 l/h respectively and a sieving coefficient ([lactate]plasma/[lactate]filter) of lactate of about one. Lactate removal (lactate out) is calculated as filtrate flow x [lactate]filter.

<table>
<thead>
<tr>
<th>Site of replacement</th>
<th>QR (ml/min)</th>
<th>QK (l/h)</th>
<th>[lactate]pl (mmol/l)</th>
<th>[lactate]filter (mmol/l)</th>
<th>[lactate]in (mmol/l)</th>
<th>[lactate]out (mmol/h)</th>
<th>Lactate balance (mmol/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predilution</td>
<td>150</td>
<td>2</td>
<td>46</td>
<td>2</td>
<td>11.2</td>
<td>92</td>
<td>37</td>
</tr>
<tr>
<td>Postdilution</td>
<td>200</td>
<td>3</td>
<td>46</td>
<td>2</td>
<td>12.2</td>
<td>138</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>4</td>
<td>46</td>
<td>4</td>
<td>13.2</td>
<td>184</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>3</td>
<td>46</td>
<td>3</td>
<td>3</td>
<td>138</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>350</td>
<td>4</td>
<td>46</td>
<td>4</td>
<td>4</td>
<td>184</td>
<td>16</td>
</tr>
</tbody>
</table>

Abbreviations: QR blood flow, QK replacement flow, [lactate] lactate concentration; pl plasma

Experimental studies suggest that this may additionally be due to an induction of insulin resistance [15].

It should further be noted that the glucose content of several commercial lactate replacement fluids (up to 14.5 mmol/l) is twice to three times as high as the glucose content of the bicarbonate buffered fluids (about 5.6 mmol/l). As a result, the use of lactate as a buffer contributes to caloric intake, both by the higher glucose concentration of the commercial fluids and the increased gluconeogenesis.

**Bicarbonate as a buffer**

Bicarbonate-buffered solutions have the advantage that the buffer is available without prior metabolic conversion and thus without the consumption of oxygen. Since the buffer has no caloric value, switching from lactate to bicarbonate replacement decreases caloric intake and may induce hypoglycaemia if insulin dose is not timely adjusted [16]. Bicarbonate solutions are however more expensive, and have limited tenability after the calcium and bicarbonate compartments have been mixed. Continuous venovenous haemofiltration (CVVH) may be a way to achieve better control of acidosis than lactate buffering. The difference between studies likely depends on the type of patient and the lactate content of the fluid. Second, all controlled studies evaluating lactate buffering, report increased lactate concentrations. Particularly if CVVH is administered a higher dose, the use of lactate based solutions is associated with supra-physiological infusions of lactate, surpassing...
Metabolic capacity. This may already be the case with a CRRT dose as low as 2L in predilution, but more pronounced if higher CRRT rates are delivered. We should question whether it is reasonable to give our patients more lactate than metabolism can cope with. Third, lactate buffering consumes oxygen. The fact that lactate needs to be metabolized and consumes oxygen for the titration of protons while bicarbonate is directly available, makes lactate a less desirable buffer in patients with marginal oxygen reserve. Fourth, lactate buffering may cause hyperglycaemia. Finally, if liver function and tissue perfusion fail, lactate conversion is limited leading to further lactate accumulation. While bicarbonate loss with filtration or dialysis continues, acidosis is aggravated. Limitations of the bicarbonate solution are that it is more expensive, that the solution has limited tenability after mixing and that its use requires effective venting.

**Recommendation**

Lactate buffered fluids should be used with caution in patients with impaired liver function, marginal tissue perfusion, poor myocardial function, glucose intolerance and if the CRRT dose is more than 2 L/h, because lactate infusion likely exceeds oxidative capacity. In these conditions, bicarbonate-buffered solutions are recommended. The level of evidence for this recommendation from clinical studies is low. Large randomized trials in well-defined patient groups using CRRT at optimal dose will be necessary to provide robust evidence. However, the physiological rationale for this recommendation is evident. Monitoring of plasma lactate and acid base balance can detect inadequate buffering, but not the oxygen consuming and gluconeogenic effects of lactate.

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**Figure 1.** Schematic presentation of the metabolic conversion of lactate. Lactate is primarily converted to pyruvate. Under aerobic conditions pyruvate is converted to acetyl-CoA, which is subsequently oxidized in the citric acid cycle or pyruvate is metabolized to glucose by gluconeogenesis. The citric acid cycle slows down if oxygen availability is limited, because oxygen is required for regeneration of NAD+. If exogenous supply of lactate surpasses the capacity of the citric acid cycle, a higher proportion of lactate is used for gluconeogenesis.

**Figure 2.** For the generation of 1 mol of bicarbonate, 1 mol of lactate consumes 3 moles of oxygen.

\[
\begin{align*}
3 \text{ mol } O_2 & \\
\text{CH}_2 - \text{CHOH} - \text{COONa} + 3 \text{ O}_2 & \rightarrow 2 \text{ CO}_2 + 2 \text{ H}_2\text{O} + \text{NaHCO}_3
\end{align*}
\]

1 mol lactate 1 mol bicarbonate

VO₂↑
References