Adding lactate to the prime solution during hypothermic cardiopulmonary bypass: a quantitative acid–base analysis

D. Himpe1*, H. Neels2, S. De Hert3 and P. Van Cauwelaert4

1Department of Anaesthesia and Intensive Care, Middelheim General Hospital, Antwerp, Belgium. 2Clinical Laboratory, Stuyvenberg Hospital, Antwerp, Belgium. 3Department of Anaesthesia, University of Antwerp, Belgium. 4Department of Cardiovascular Surgery, Middelheim General Hospital, Antwerp, Belgium

*Corresponding author: Department of Anaesthesia and Intensive Care, Middelheim General Hospital, Lindendreef 1, B-2020 Antwerp, Belgium. E-mail: dirk.himpe@pi.be

Background. The effect of adding lactate to the cardiopulmonary bypass (CPB) prime was investigated using Stewart's quantitative acid–base approach. According to this quantitative model, serum pH and bicarbonate are determined by three independent factors: the partial pressure of carbon dioxide (PCO₂), the total concentration of weak acids (e.g. albumin), and the strong ion difference. The apparent strong ion difference is calculated as the sum of sodium, potassium, magnesium and calcium minus chloride concentrations. The pH decreases with a smaller strong ion difference and vice versa.

Methods. Twenty patients scheduled for coronary surgery were studied prospectively. All patients were treated identically, except for the prime, which either contained lactate or was lactate free. Just before bypass and before coming off bypass, haemoglobin, glucose, plasma osmolality and colloid osmotic pressure were determined; albumin, lactate, sodium, potassium, ionized calcium, magnesium, phosphate, arterial pH, PCO₂, bicarbonate, and base excess were measured for use in Stewart's analysis.

Results. Metabolic acidosis had resolved by the end of bypass with the lactated prime. Although the strong ion gap (apparent minus effective strong ion difference) increased significantly in both groups, its composition differed significantly between the groups. The Stewart technique detected polyanionic gelatin as a weak acid component contributing to the unidentified anion fraction. Colloid osmotic pressure was maintained in both groups.

Conclusion. Exogenous lactate attenuates acidosis related to CPB. The oncotic and weak acid deficits produced by hypoalbuminaemia may be compensated for temporarily during CPB by polyanionic synthetic colloids such as succinylated gelatin.

Keywords: acid–base equilibrium, metabolic acidosis; protein, albumin; metabolism, lactate; blood, replacement

Accepted for publication: November 19, 2002

Metabolic acidosis related to cardiopulmonary bypass (CPB) has been a problem for many years.1 It has been shown that the composition of the prime solution may influence acid–base balance.2 Recently, Liskaser and colleagues3 and Prough4 suggested that Stewart’s quantitative approach to acid–base chemistry is indispensable for understanding the mechanisms involved. Applying accepted physicochemical principles, this method separates the components of observed acid–base imbalances, and provides insight into the contribution of any unidentified anion.5–7 In Stewart’s model, water is considered the main source of protons. With acidosis, plasma water is more dissociated as a result of alterations in strong ions, carbon dioxide and weak acids (independent variables). Subsequently, secondary changes occur in pH and bicarbonate (dependent variables).

Liskaser and colleagues3 further concluded that CPB-related acid–base disorders are largely iatrogenic, and are derived from pump prime effects. However, metabolic acidosis during CPB is also inversely related to
the colloid osmotic pressure (COP)\(^8\) and the blood-buffering capacity, which may vary with the degree of haemodilution.\(^9\)\(^10\)

We hypothesized that during CPB using an iso-oncotic prime, acidosis is reduced by the addition of lactate, a bicarbonate precursor, to the prime. Applying Stewart’s biophysical approach,\(^5\) we tested this hypothesis by means of a randomized double-blind study comparing succinylated gelatin dispersed in either a lactated solution, or saline with sodium hydroxide (NaOH).

### Methods

After procedure approval by the institutional review board, 20 male patients consecutively undergoing elective coronary surgery gave informed consent and were studied prospectively. Patients with significant coagulopathy, anemia, chronic renal failure, respiratory insufficiency, diabetes mellitus or liver dysfunction were excluded. Treatment was identical for all patients except for the composition of the priming fluid.

A volume of 1700 ml was necessary to prime the extracorporeal circuit. Patients were randomly allocated to receive one of two solutions (data on composition provided by the respective manufacturers): Group I, succinylated gelatin 30 g Geloplasma\(^\circledR\) (Fresenius) in 150 milliequivalents (mEq) Na\(^+\), 5 mEq K\(^+\), 100 mEq Cl\(^-\), 3 mEq Mg\(^2+\), 30 mEq lactate; Group II, succinylated gelatin 40 g Gelofusin\(^\circledR\) (B. Braun) in 154 mEq Na\(^+\), 120 mEq Cl\(^-\), 34 mEq OH\(^-\) per litre.

Just after CPB (T\(_1\)), haemoglobin, glucose, plasma osmolality, COP, albumin, lactate, sodium, potassium, ionized calcium, magnesium, phosphate and bicarbonate concentrations, arterial pH, \(P_{CO_2}\), and base excess were measured.

Use of cardioplegic solutions was avoided by using an intermittent technique of cross-clamping the aorta,\(^11\) as these solutions can interfere with the biochemical measurements. Total cross-clamp times for each patient were noted.

All measurements were repeated after rewarming to normothermia at the end of CPB just before separation (T\(_3\)). While the patient’s blood was cooled to 30°C, the \(\alpha\)-stat acid–base management strategy was followed.\(^12\)\(^13\) Arterial carbon dioxide tensions were kept rigorously in the ‘normal’ 37°C ranges using exhaust capnometry,\(^14\) with intermittent arterial blood sampling to control arterial partial pressures of carbon dioxide and oxygen.

Arterial lactate was also sampled immediately after going on bypass (Ts) to take account of the exogenous lactate levels (Ts) in the two groups. COP, and lactate and haemoglobin levels were measured again after 40 min of hypothermic CPB (T\(_2\)).

Quantitative analysis of the results at T\(_1\) and T\(_3\) was performed using Stewart’s biophysical approach as modified by Figge and colleagues.\(^15\) As described by Liskaser and colleagues,\(^3\) this method starts with calculation of the apparent strong ion difference (SIDa), which decreases with acidosis:

\[
\text{SIDa} = \text{Na}^+ + \text{K}^+ + \text{Mg}^{2+} + \text{Ca}^{2+} - \text{Cl}^- \quad (1)
\]

Then, applying the mathematical model of Figge and colleagues,\(^15\) the contribution to the electrical balance of measured weak acids such as carbon dioxide, phosphate and albumin can be expressed by calculating the effective strong ion difference (SIDe):

\[
\text{SIDe} = \left[1000 \times 2.46 \times 10^{-11} \times P_{CO_2}/(10^{pH})\right] + \left[\text{albumin} \times (0.309 \times p\text{H} - 0.469)\right] (2)
\]

With a positive value for SIG, unidentified anions in the blood contribute to the measured pH, and strong and weak ions preserve electroneutrality. Since electroneutrality implies an equal number of mEq of cations and anions in the blood, the variable mEq litre\(^{-1}\) is used throughout for clarity.

### Statistical analysis

With a power of 80%, a sample size of 10 subjects in each treatment group was estimated to be appropriate. This calculation was based on an estimated between-group difference of 40% in the number of subjects having changes in SIDa over time of more than 1.5 mEq, which can be considered clinically relevant.\(^3\)\(^4\) A Wilcoxon matched-pairs ranked sign test was used on each group to test whether changes over time from T\(_1\) to T\(_3\) were significant. Adjusting for multiple comparisons, changes with time in haemoglobin, COP and lactate values were measured at Ts (lactate only), T\(_2\) and T\(_3\), and compared with T\(_1\) (baseline). Once all these changes over time were calculated for each group, a Mann–Whitney U-test was performed to compare the two groups at the different time points, to test the hypothesis that the lactated prime affected acid–base variables differently over the time span of CPB. Sample size estimation and statistical analysis were performed using the Statistica package for Windows (StatSoft Inc., Tulsa, OK, USA). \(P\)-values <0.05 were considered significant.
Results

No significant differences between groups were found in the physical characteristics of the patients, their clinical data, CPB duration or total cross-clamp times (Table 1).

Figure 1 shows the mean haemoglobin concentrations and oncotic pressures throughout the study. As expected, a significant haemodilution occurred in both groups. No differences between groups were observed, ensuring homogeneous populations.

Biochemical data and the results from the quantitative acid–base analysis are summarized in Table 2. A moderate respiratory alkalosis with a slightly elevated pH was present in the two groups just before bypass (T1) because of prepump hypocapnia. The median pH was 7.39 at the end of CPB (T3) in Group I and 7.33 in Group II but the difference was not statistically significant.

Although the lactate levels were lower in Group I than in Group II before bypass (T1), but not significantly so, lactate increased significantly in Group I after the initiation of hypothermic CPB (Ts) as a result of the exogenous load of lactate by the prime (Fig. 2). Lactate levels were increased in both groups after 40 min of CPB (T2) to the same range and remained significantly elevated at the end of bypass (T3) compared with baseline values in both groups (Fig. 2).

As shown in Table 2, a hyperchloraemic metabolic acidosis occurred at the end of CPB in Group II, as evidenced by the negative base excess (median −2.90 mEq litre⁻¹) and slightly increased chloride levels (median 108 mEq litre⁻¹). Both primes also caused a significant decrease in plasma albumin with a decrease in SIDe.³

Even though unbuffered hyperchloraemic solutions generally decrease SIDa, it remained unchanged in Group II. This is related to the effects of the 34 mEq per litre OH⁻ in the buffer, which also reduced the chloride content from the start of CPB. In contrast, in Group I, SIDa increased, reflecting the alkalization.

The initial peak of lactate in Group I was overcome by its conversion to bicarbonate, with significantly higher concentrations of the latter at the end of CPB compared with Group II. Lactate concentrations in both groups were comparable by the end of CPB at T3 (Fig. 2).

A similar SIG occurred in both groups. Lactate could not be the cause of this increase since the SIG remained almost unchanged once lactate was removed from the calculation (SIG minus lactate). This suggests the presence of a massive amount of unmeasured and unidentified weak anions, equal in both groups. The importance of these findings is presented in Gamble diagrams (Fig. 3), demonstrating the sums of the relative serum concentrations of, respectively, cations and anions by the use of two proportional bars, both of equal height, to demonstrate electroneutrality.

The small but significant changes in potassium and phosphate are common during CPB, and the significant differences in magnesium are caused by the different contents of the primes. Significant hyperglycaemia and elevated plasma osmotic pressures were observed in both groups at the end of CPB (Table 2).

Discussion

Routine acid–base variables such as bicarbonate concentration and base excess demonstrate the benefits of a lactated prime in this study. Although regulation of albumin concentration is not considered a part of classic acid–base homeostasis, the similar decrease in SIDe in both groups can be explained by the hypoalbuminaemia producing an alkalinizing effect per se.¹⁵ The SIG increased dramatically
at the end of bypass in both groups, however, but failed to
differentiate between a resolving metabolic acidosis in
Group I, in contrast to a sustained metabolic acidosis in
Group II.
Even though SIDa was expected to decline in Group II as
a result of the high chloride content of the prime, 16 it
remained virtually unchanged and the acidosis was reduced
by the presence of NaOH. By contrast, in Group I, the SIDa
increased, confirming how exogenous proton-free lactate
vitiated the acidosis without causing a higher plasma lactate
at the end of CPB. Lactate contributed to the reduction in
acidosis both by its conversion to bicarbonate and by
reducing consistently the initial chloride load. 17
On theoretical grounds, bicarbonate precursors such as
acetate and gluconate (Plasmalyte®, Baxter) could also be
used. With these substances in the prime, and performing
Stewart’s acid–base analysis immediately after the start of
CPB, Liskaser and colleagues 3 and Prough 4 highlighted
unique information on the initial effects of prime delivery.

### Table 2
Biochemical and quantitative acid–base variables in Groups I (lactate-containing prime) and II (lactate-free prime). Normal ranges of variables were provided by the laboratory. 

<table>
<thead>
<tr>
<th>Measured variable (normal range)</th>
<th>Group</th>
<th>T₁ (before CPB)</th>
<th>T₃ (end of CPB)</th>
<th>P&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq litre⁻¹) (135–145)</td>
<td>I</td>
<td>140.00 (0.75)</td>
<td>143.00 (2.25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>140.00 (1.75)</td>
<td>142.00 (2.50)</td>
<td></td>
</tr>
<tr>
<td>Potassium (mEq litre⁻¹) (3.5–5.1)</td>
<td>I</td>
<td>3.75 (0.40)</td>
<td>3.20 (0.43)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>3.85 (0.18)</td>
<td>4.10 (0.30)</td>
<td></td>
</tr>
<tr>
<td>Chloride (mEq litre⁻¹) (98–107)</td>
<td>I</td>
<td>105.00 (1.75)</td>
<td>106.00 (1.75)</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>105.50 (1.75)</td>
<td>108.00 (1.75)</td>
<td></td>
</tr>
<tr>
<td>Ionized calcium (mEq litre⁻¹) (2.4–2.6)</td>
<td>I</td>
<td>2.39 (0.14)</td>
<td>2.13 (0.07)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>2.38 (0.12)</td>
<td>2.22 (0.12)</td>
<td></td>
</tr>
<tr>
<td>Magnesium (mEq litre⁻¹) (1.3–2.1)</td>
<td>I</td>
<td>1.70 (0.18)</td>
<td>1.80 (0.15)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>1.65 (0.10)</td>
<td>1.40 (0.10)</td>
<td></td>
</tr>
<tr>
<td>Phosphate (mEq litre⁻¹) (1.6–2.8)</td>
<td>I</td>
<td>2.25 (0.58)</td>
<td>2.00 (0.43)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>2.10 (0.28)</td>
<td>1.75 (0.70)</td>
<td></td>
</tr>
<tr>
<td>Albumin (g l⁻¹) (35–50)</td>
<td>I</td>
<td>39.50 (5.00)</td>
<td>25.00 (3.00)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>40.50 (4.50)</td>
<td>23.50 (4.75)</td>
<td></td>
</tr>
<tr>
<td>Lactate (mEq litre⁻¹) (0.6–2.4)</td>
<td>I</td>
<td>1.10 (0.15)</td>
<td>2.10 (0.53)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>1.35 (0.58)</td>
<td>1.80 (0.95)</td>
<td></td>
</tr>
<tr>
<td>pH (7.35–7.45)</td>
<td>I</td>
<td>7.44 (0.08)</td>
<td>7.33 (0.04)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>7.44 (0.08)</td>
<td>7.33 (0.04)</td>
<td></td>
</tr>
<tr>
<td>PCO₂ (mm Hg) (32–45)</td>
<td>I</td>
<td>35.25 (3.20)</td>
<td>40.50 (2.95)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>32.25 (6.58)</td>
<td>38.20 (2.50)</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate (mEq litre⁻¹) (22–30)</td>
<td>I</td>
<td>23.00 (2.25)</td>
<td>23.05 (1.93)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>23.00 (1.00)</td>
<td>21.65 (0.93)</td>
<td></td>
</tr>
<tr>
<td>Base excess (mEq litre⁻¹) (–2.0 to +3.0)</td>
<td>I</td>
<td>-0.35 (1.28)</td>
<td>-0.95 (2.18)</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>-0.20 (3.13)</td>
<td>-2.90 (0.78)</td>
<td></td>
</tr>
<tr>
<td>Anion gap (mEq litre⁻¹) (10–18)</td>
<td>I</td>
<td>14.50 (3.65)</td>
<td>17.20 (2.25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>13.73 (2.58)</td>
<td>16.61 (2.54)</td>
<td></td>
</tr>
<tr>
<td>SIDa (mEq litre⁻¹) (38–44)</td>
<td>I</td>
<td>42.23 (2.45)</td>
<td>44.34 (4.05)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>41.73 (1.69)</td>
<td>41.66 (2.26)</td>
<td></td>
</tr>
<tr>
<td>SIDe (mEq litre⁻¹) (33–39)</td>
<td>I</td>
<td>36.09 (3.65)</td>
<td>31.80 (1.31)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>34.88 (2.66)</td>
<td>29.56 (2.15)</td>
<td></td>
</tr>
<tr>
<td>SIG (mEq litre⁻¹) (3–10)</td>
<td>I</td>
<td>6.59 (4.14)</td>
<td>13.14 (2.22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>5.63 (1.44)</td>
<td>12.36 (2.42)</td>
<td></td>
</tr>
<tr>
<td>SIG minus lactate (mEq litre⁻¹) (2.00–8.00)</td>
<td>I</td>
<td>5.39 (4.21)</td>
<td>10.56 (1.98)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>4.54 (1.48)</td>
<td>10.84 (3.56)</td>
<td></td>
</tr>
<tr>
<td>Glucose (mg dl⁻¹) (76–110)</td>
<td>I</td>
<td>131.50 (12.25)</td>
<td>200.30 (36.50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>141.50 (17.00)</td>
<td>179.00 (46.00)</td>
<td></td>
</tr>
<tr>
<td>Osmolality (mosm kg⁻¹) (278–305)</td>
<td>I</td>
<td>287.00 (6.00)</td>
<td>294.00 (3.50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>286.50 (6.00)</td>
<td>294.00 (8.25)</td>
<td></td>
</tr>
</tbody>
</table>

SIDa=apparent strong ion difference; SIDe=effective strong ion difference; SIG=strong ion gap.

**Fig 2** Changes in lactate levels over time expressed as mean ± 2 SEM. At the start of hypothermic CPB (Ts), lactate was significantly more elevated in Group I (lactate-containing prime) (*P<0.05). Lactate levels also increased in Group II. After 40 min (T2) and at the end of CPB (T3), lactate levels in the two groups were in the same range and remained significantly elevated compared with baseline values (T1) (T<0.05).
known synthetic colloidal weak acid component could not be added into the equation appropriately. It contributes to a more positive SIG, together with unmeasured endogenous metabolites like ketoacids, citrate and pyruvate, all known to be present at the end of CPB.²³ Explanations, based on Stewart’s analysis, of the effects of using large amounts of anionic colloids in CPB therefore require further experimental confirmation.

In conclusion, exogenous lactate attenuates CPB-related acidosis. Other bicarbonate precursors may also have such an effect. Hypoalbuminaemia, with its oncotic and weak acid deficits, may temporarily be compensated for during CPB by polyanionic synthetic colloids such as succinylated gelatin.

Fig 3 Gamble diagrams illustrating the composition in mEq litre⁻¹ of positive and negative charges of serum ions before (T₁) and by the end of bypass (T₃). The total mEq are slightly greater in both groups at T₃ corresponding to the larger observed osmotic pressures. Significant within-group differences (†P<0.05) over time in ionic composition are noted for both groups at T₁ compared with T₃. Significant differences in the global ionic composition between groups at T₁ are also shown (*P<0.05). Details on individual ion levels are shown in Table 2.

However, only the values obtained at the completion of surgery were given; no data relating to the effects just before separation from CPB were given.¹³ In contrast, our study design allowed comparison of the interaction between patient, prime and pump during the strictly defined period of CPB. Although we found lower end-pump glucose concentrations with the non-lactated prime, this difference was not statistically significant. Whether the greater increase in post-pump hyperglycaemia caused by the lactate could be avoided by using gluconate and/or acetate needs further study.¹⁷

In experimental animal sepsis, the combination of lactate and hetastarch as a colloid (Hextend) was associated with less metabolic acidosis and longer survival compared with normal saline.¹⁸ According to Kellum,¹⁸ Stewart’s calculations in his study were not influenced by the starch, which is uncharged. In contrast, polyanionic colloids such as gelatin are likely to have complex effects on these calculations.¹⁹

With similar amounts of gelatin in both primes used in the present study, it can be assumed that these molecules are the unidentified weak acids²⁰ responsible for the similar and pronounced increases in the SIG observed in each group.

Loss of weak acid (e.g. decreased albumin concentration) reduces the anion gap and masks acidosis.²¹ Such changes suggest another (false) argument for the use of albumin in CPB besides increasing oncotic pressure, drug-carrying capacity and free-radical scavenging.²²

As well as its oncotic properties, gelatin as a polyanion has been shown to compensate for the weak acid loss secondary to hypoalbuminaemia in the present study. However, a mathematical correction of the Stewart equations, similar to the approach used by Figge and colleagues¹⁵ for albumin, is not available.²² For this reason, the

References

4 Prough DS. Acidosis associated with perioperative saline administration. Anesthesiology 2000; 93: 1167–9
7 Constable PD. Total weak acid concentration and effective dissociation constant of nonvolatile buffers in human plasma. J Appl Physiol 2001; 91: 1364–71