Fencl–Stewart analysis of acid–base changes immediately after liver transplantation

David A Story, Rakesh Vaja,
Stephanie J Poustie and Larry McNicol

ABSTRACT

Objective: The Fencl–Stewart approach to acid–base physiology allows detailed, quantitative insights into acid–base disorders. We tested the hypothesis that this type of analysis would reveal complex acid–base changes in patients after liver transplantation that differed from those in a general intensive care unit population.

Methods: Data were collected retrospectively on patients on admission to the ICU after liver transplantation between 2001 and 2003 and prospectively on a convenience group of general ICU patients in 2001.

Results: Data were collected from 100 ICU patients and 83 liver transplant patients. Values for most clinical chemistry variables differed between the two groups, with considerable variation within the groups. All acid–base variables differed between the control and transplant groups ($P < 0.005$). Overall, the transplant group had metabolic acidosis (mean base excess ±SD, –4.5 ± 3.1 mmol/L) due to both a sodium chloride effect on base excess (–4.0 ± 4.1 mmol/L) and an other ion effect on base excess (–6.3 ± 4.2 mmol/L). The sodium chloride effect was mainly due to increased chloride concentration. All estimates of other anions (anion gap, corrected anion gap, strong ion gap, and the other ion effect on base excess) suggested that other anions play an important role in the acid–base status of patients after liver transplantation. These effects on base excess were partly offset by a greater metabolic alkalosis in the transplant group caused by a marked effect of decreased albumin on base excess (5.8 ± 1.5 mmol/L).

Conclusions: The Fencl–Stewart approach allowed us to quantitatively assess the factors contributing to patients' acid–base status. We found complex acid–base changes in patients immediately after liver transplantation.

Crit Care Resusc 2008; 10: 19–23

The acid–base changes associated with liver transplantation are complex.[1,2] This complexity has multiple causes, including the pathophysiology of preoperative liver disease and the intraoperative changes associated with the anhepatic and subsequent reperfusion phases, as well as large-volume fluid therapy.[1] The Stewart approach to acid–base physiology allows detailed, quantitative insights into acid–base disorders.[3,4] We have developed a simple clinical approach to acid–base disorders[5] using Stewart's principles (simplified Fencl–Stewart approach). To date, there has been only limited Stewart-style analysis of acid–base changes associated with liver transplantation, in a small number of patients.[6] There are no detailed, quantitative studies of patients after liver transplantation using this approach. We hypothesised that a Stewart-style analysis would reveal complex acid–base changes in patients after liver transplantation that would differ from those in a general intensive care unit population. We tested this hypothesis by comparing blood samples from patients on arrival in the ICU after liver transplantation with routine samples from other critically ill patients.

Methods

Data were collected from ICU records at the Austin Hospital, Melbourne, Victoria, a university-affiliated, tertiary referral hospital. All samples were taken from arterial lines in patients requiring ICU management. No additional sampling was required. The Austin Hospital Research Ethics Committee waived the need for informed consent.

Data were collected for two groups of patients. The first comprised patients who had undergone orthotopic liver transplantation (liver transplant); data were collected retrospectively for samples taken on their arrival in the ICU from patients who had undergone liver transplantation between 2001 and 2003. The second group comprised critically ill patients with a wide variety of clinical problems (general ICU patients); data for routine morning blood samples were collected prospectively from a convenience sample in 2001.

Arterial blood samples were analysed. We collected data on the plasma concentrations of sodium, chloride, potassium, calcium, magnesium, lactate, phosphate, and albumin; and the pH, partial pressure of carbon dioxide (P_{CO_2}), the bicarbonate, and the standard base excess.

Several variables were determined. Firstly, the anion gap was calculated:[7]

Anion gap (mmol/L) = $[Na^+] + [K^+] - [Cl^-] - [HCO_3^-]$.

Table 1. Clinical chemistry results for routine arterial blood samples from ICU patients (mean [SD])

Variable	General ICU ($n = 100$)	Liver transplant ($n = 83$)	P*
Sodium (mmol/L)	141 (5)	141 (5)	0.54
Potassium (mmol/L)	4.1 (0.5)	4.2 (0.7)	0.70
Chloride (mmol/L)	103 (5)	107 (4)	< 0.001
Lactate (mmol/L)	2.1 (1.5)	3.3 (1.8)	< 0.001
Albumin (g/L)	23 (6)	19 (6)	< 0.001
Phosphate (mmol/L)	1.2 (0.5)	1.2 (0.4)	0.22
pH	7.42 (0.08)	7.34 (0.06)	0.007
Pco_2 (mmHg)	42.3 (5.5)	39.3 (8.7)	< 0.001
Bicarbonate (mmol/L)	26.9 (5.6)	21.0 (2.8)	< 0.001
Base excess (mmol/L)	2.3 (5.7)	–4.5 (3.1)	< 0.001
Anion gap (mmol/L)	15.4 (3.9)	17.2 (3.9)	0.002
Corrected anion gap (mmol/L)	20.0 (4.2)	23.0 (4.1)	< 0.001
Strong ion gap (mEq/L)	8.7 (3.9)	10.0 (3.8)	0.03

* P for comparison of liver transplant and general ICU groups by t test.

The anion gap was corrected for decreased albumin using the approach of Figge et al:[8]

Corrected anion gap (mmol/L) = calculated anion gap + 0.25 × (42 – measured albumin [g/L]).

Another estimate of other anions is the strong ion gap.[9] This is the sum of commonly measured cations minus the sum of measured anions. Anions include the anions from albumin and phosphate.[9]

Strong ion gap (mEq/L) = $[Na^+] + [K^+] + [Mg^{++}] + [Ca^{++}] - [Cl^-]$ – [albumin anions] – [phosphate anions] – [bicarbonate] – [lactate].

Albumin and phosphate anions were calculated using the approach of Figge et al:[10]

Albumin anions (mEq/L) = albumin (g/L) × (0.123 × pH – 0.631)

Phosphate anions (mEq/L) = phosphate (mmol/L) × (0.309 × pH – 0.469).

We also used the simplified Fencl–Stewart approach to quantify effects on the base excess.[5] Sodium and chloride are the principal components of the strong ion difference.[11] Albumin is the principal weak acid in plasma.[11] The simplified Fencl–Stewart approach quantifies the sodium chloride and albumin effects on base excess. The residual effect is due to other strong ions and weak acids.[5,12]

Sodium chloride effect on base excess (mmol/L) = $[Na^+] - [Cl^-] - 38$

Albumin effect on base excess (mmol/L) = 0.25 × (42 – albumin [g/L])

Other ion effect = base excess – sodium chloride effect – albumin effect.

Statistical analysis

Data were expressed as means ± standard deviations. Student's t test was used to compare variables important to acid–base analysis: sodium, chloride, strong ion difference, albumin, phosphate, anion gap, strong ion gap, and the base-excess effects of sodium chloride, albumin, and other ions. Confidence intervals (95%) were calculated for the mean differences. A $P < 0.05$ was considered statistically significant. We used GraphPad Prism, version 4 software (GraphPad Software, San Diego, Calif, USA).

Results

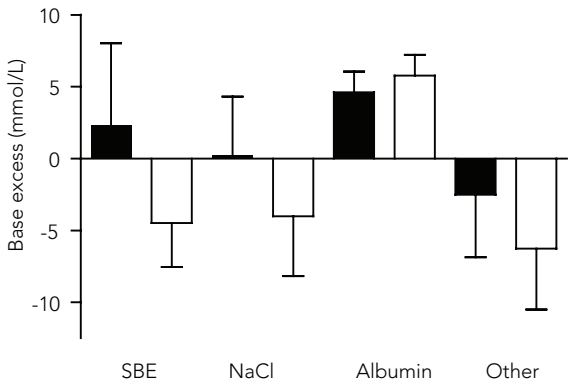
We collected data on 83 liver transplant patients on their arrival in the ICU and on 100 general ICU patients. Most clinical chemistry variables differed between the two groups, with considerable variation within the groups (Table 1).

Table 2. Acid–base differences, general ICU group versus liver transplant group

Variable	Difference (95% CI)*	P
pH	0.08 (0.06 to 0.10)	< 0.001
Pco_2 (mmHg)	2.9 (0.8 to 5.0)	0.005
Base excess (mmol/L)	6.8 (5.4 to 8.2)	< 0.001
NaCl effect† (mmol/L)	4.2 (3.1 to 5.4)	< 0.001
Albumin effect† (mmol/L)L	–1.2 (–1.6 to –0.7)	< 0.001
Other ion effect† (mmol/L)	3.7 (2.5 to 5.0)	< 0.001

* General ICU group – liver transplant group.
† Effect on base excess.

Figure 1. Fencl–Stewart analysis of base excess



Mean (standard deviation) of the standard base excess (SBE), and the sodium chloride (NaCl), albumin and other ion (other) effects on base excess. The differences between the 100 general intensive care unit patients (black columns) and 84 liver transplant patients (white columns) were all statistically significant (Table 2).

Overall, the transplant group had metabolic acidosis (mean base excess ± SD, –4.5 ± 5.7 mmol/L) due to both a sodium chloride effect on base excess (–4.0 ± 4.1 mmol/L) and an other ion effect on base excess (–6.3 ± 4.2 mmol/L). Compared with the general ICU group, the transplant group had greater metabolic acidosis due to increased sodium chloride effect and other ion effect on base excess (Table 2 and Figure 1). The sodium chloride effect was mainly due to increased chloride (Table 1). All estimates of other anions (anion gap, corrected anion gap, strong ion gap, and the other ion effect on base excess) suggested that other ions play an important role in the acid–base status of patients after liver transplantation. These effects on base excess were partly offset by a greater metabolic alkalosis in the transplant group caused by profound hypoalbuminaemia.

Discussion

We analysed the acid–base status of patients on arrival in the ICU after liver transplantation. We used a simplified Fencl–Stewart approach[5] to acid–base status. This allowed us to assess quantitatively the components contributing to patients' acid–base status. Consistent with our hypothesis, we found complex acid–base changes in patients after liver transplantation that differed from those in routine samples from a general ICU population.

The simplified Fencl–Stewart approach[5] was derived from the work of Fencl et al[11] to apply clinically the mathematically complex approach of Stewart.[4] Analysis of acid–base status using Stewart's method is becoming increasingly popular in anaesthesia and critical care medicine.[3,13,14] Stewart concluded[4] that the acid–base status of body fluids is controlled by three independent factors: the strong ion difference; the total concentration of weak acids; and the partial pressure of carbon dioxide. The hydrogen ion concentration (and therefore pH) and bicarbonate concentration depend on these three factors. Using Stewart's approach, carbon dioxide remains the principal respiratory source of acid. The non-respiratory component is quantitatively divided into the effects of strong ions and weak acids. In plasma, the principal strong ions (completely dissociated) are sodium and chloride.[4] Importantly, acidosis increases as the strong ion difference decreases.[4] The principal weak acid is albumin,[10] with a secondary role for phosphate.[12]

In this study, most clinical chemistry variables in the transplant group differed from those in the general ICU group. Analysis of the differences using three approaches — the bicarbonate "rules of thumb",[7] the standard base excess[15] and the simplified Fencl–Stewart[5] approaches — highlights the differences between them. Using the rules of thumb, we conclude (from Table 1) that in the general ICU group there is metabolic alkalosis with possible respiratory alkalosis. In the transplant group, we conclude that there is a metabolic acidosis with respiratory compensation. We can only identify these qualitative differences, and the underlying pathophysiology is unclear. If we add the (uncorrected) anion gap,[7] the liver transplant group had an increased anion gap, whereas the general ICU group did not. Therefore, the transplant group had an anion gap acidosis. Lactate may be part of this effect. If we use the standard base excess approach, we reach similar conclusions but can quantify the overall difference; the base excess was almost 7 mmol/L more negative in the transplant group. However, we cannot further determine the underlying causes.

If we then apply the Fencl–Stewart approach, we can determine and quantify the underlying mechanisms. The difference in base excess between the transplant and general ICU groups was due to several effects. First, the sodium-to-chloride difference was decreased, leading to hyperchloraemic metabolic acidosis.[16] In the presence of hyponatraemia, hyperchloraemic metabolic acidosis can occur even when the chloride concentration is in the reference range.[16] This accounted for about 4 mmol/L of the decrease in base excess. The other ion effect on base excess was a decrease of about 3.5 mmol/L. About 1 mmol/L of that was due to lactate. The differences between the groups were minimal for calcium, magnesium and phosphate; these ions are included in the strong ion gap calculation but not the other ion effect on base excess. The other 2.5 mmol/L difference was caused mainly by ions that are not measured in routine clinical chemistry tests, as shown by the albumin-corrected anion gap[8] and strong ion gap[9] (Table 1). These anions include strong ions such as sulfate, acetate and gluconate,[17,18] and weak acids such as polygeline.[18,19] Some of the unmeasured ions, particularly acetate,[18] gluconate[18] and polygeline,[20] are associated with the large volumes of intravenous fluids used during liver transplantation.[2] Individual anaesthetists used their own strategies to manage plasma chemistry, acid–base status and intravenous fluid therapy. The frequent use of fluids containing chloride and weak acids, such as albumin or polygeline, will have a twofold effect: first, hyperchloraemic acidosis and, second, an albumin or other ion acidosis. Both albumin and polygeline are weak acids, but albumin is routinely measured while polygeline is not.[18,20] However, the alkalinising effect of solutions such as Hartmann's solution and Plasmalyte[17,21] (Baxter, Sydney, NSW) will depend on hepatic and renal mechanisms to remove these strong ions from plasma.

Some of the other ions in the transplant samples were probably a result of pre-existing liver and kidney disease,[1,2,22] but their exact nature remains elusive.[22] These acidifying effects were offset by a greater decrease in albumin (a weak acid) in the transplant group that

increased base excess by about 1 mmol/L. While hypoalbuminaemia is common in critically ill patients,[16] the lower albumin in the transplant group probably reflects the hypoalbuminaemia of end-stage liver disease[2] combined with intraoperative dilution.[2] A factor in the differences between the groups may be that the samples for the general group were routine morning samples from a mixed surgical and medical ICU population. The general samples might have been more similar to the liver transplant samples if they had been ICU admission samples, particularly from surgical patients.

The effects of acid–base management strategies are easier to quantify and understand using the Stewart approach than using older approaches. Importantly, while bicarbonate maintains a role in assessing overall acid–base status, it has no role in explaining mechanisms.[14] Sodium bicarbonate therapy is alkalinising[1] because of the direct effect of increased plasma sodium leading to an increased strong ion difference. Tromethamine (THAM) acts by increasing the total plasma concentration of weak base,[1] which is directly alkalinising.[4] Dichloracetate acts to reduce lactate.[1] Lactate anions are directly acidifying because they are strong ions in plasma and decrease the strong ion difference.[11] If other strong ions remain constant, base excess decreases in a one-to-one mmol/L ratio with the increase in lactate.[11] The most common acidifying technique, often inadvertently applied, is to administer 0.9% (normal) saline, rather than solutions with less chloride, such as Hartmann's solution[23] or Plasmalyte.[18]

Acid–base changes have long been associated with liver transplantation, with an initial phase of metabolic acidosis in the perioperative period often followed by metabolic alkalosis within the next few days.[1] However, there has been little quantitative research on this pattern. While we have studied the early acidotic phase, most published studies that include patients during the later alkalotic phase do not provide enough biochemical data to perform a Fencl–Stewart-style analysis.[5] An exception is a study by Shangraw and Jahoor[6] which included 11 patients on the second day after liver transplantation (during the alkalotic phase). Their average results showed an overall base excess of 7.0 mmol/L. The sodium chloride effect on base excess[5] was 2 mmol/L. The albumin effect on base excess[5] was 2.5 mmol/L. Therefore, much of the alkalosis could be explained by these two effects. However, a detailed prospective study would further clarify this phenomenon.

In summary, using a mathematically simple method to quantify the acid–base effects of various components of plasma, we found a complex picture in the early post-transplant period that differed from the situation in a general ICU population. Further, little of this would have been revealed if a more traditional bicarbonate-based approach[7] had been used. Given the importance of managing plasma chemistry, including acid–base status, during the perioperative period of liver transplantation, we conclude that the approaches derived from Stewart's work[4] are more useful than bicarbonate-based approaches[7] and will provide important tools for further clinical studies.

Acknowledgements

This study was presented as a poster at the Annual Scientific Meeting of the Australian and New Zealand College of Anaesthetists, 1–5 May 2004, Perth, Western Australia.

Author details

David A Story, Joint Director of Research and Principal Fellow[1,2]
Rakesh Vaja, Fellow[1]
Stephanie J Poustie, Research Governance Coordinator[1,3]
Larry McNicol, Director[1,2]

1 Department of Anaesthesia, Austin Health, Melbourne, VIC.
2 Department of Surgery, University of Melbourne, Melbourne, VIC.
3 Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC.

Correspondence: David.Story@austin.org.au

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