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Role of Pump Prime in the Etiology and Pathogenesis of Cardiopulmonary Bypass–associated Acidosis

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Background: **The development of metabolic acidosis during cardiopulmonary bypass (CPB) is well recognized but poorly understood. The authors hypothesized that the delivery of pump prime fluids is primarily responsible for its development. Accordingly, acid–base changes induced by the establishment of CPB were studied using two types of priming fluid (Haemaccel, a polygeline solution, and Ringer's Injection *vs.* Plasmalyte 148) using quantitative biophysical methods.**

Methods: **A prospective, double-blind, randomized trial was conducted at a tertiary institution with 22 patients undergoing CPB for coronary artery bypass surgery. Sampling of arterial blood was performed at three time intervals: before CPB (t_1), 2 min after initiation of CPB at full flows (t_2), and at the end of the case (t_3). Measurements of Na^+, K^+, Mg^{2+}, Cl^-, HCO_3^-, phosphate, Ca^{2+}, albumin, lactate, and arterial blood gases at each collection point were performed. Results were analyzed in a quantitative manner.**

Results: **Immediately on delivery of pump prime fluids, all patients developed a metabolic acidosis (base excess: 0.95 mEq/l (t_1) to −3.65 mEq/l (t_2) ($P < 0.001$) for Haemaccel–Ringer's and 1.17 mEq/l (t_1) to −3.20 mEq/l (t_2). The decrease in base excess was the same for both primes (−4.60 *vs.* −4.37; not significant). However, the mechanism of metabolic acidosis was different. With the Haemaccel–Ringer's prime, the metabolic acidosis was hyperchloremic (ΔCl^-, +9.50 mEq/l; confidence interval, 7.00–11.50). With Plasmalyte 148, the acidosis was induced by an increase in unmeasured anions, most probably acetate and gluconate. The resolution of these two processes was different because the excretion of chloride was slower than that of the unmeasured anions (Δ base excess from t_1 to t_3 = −1.60 for Haemaccel–Ringer's *vs.* +1.15 for Plasmalyte 148; $P = 0.0062$).**

Conclusions: **Cardiopulmonary bypass–induced metabolic acidosis appears to be iatrogenic in nature and derived from the effect of pump prime fluid on acid–base balance. The extent of such acidosis and its duration varies according to the type of pump prime. (Key words: Acid–base physiology; anion gap; hypoalbuminemia; strong ion gap.)**

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CARDIOPULMONARY bypass (CPB) has long been recognized as being associated with a metabolic acidosis.[1] Several causes have been suggested to explain this phenomenon, including an increase in serum lactate and chloride levels,[2] yet the etiology and pathogenesis of such changes are not understood. On the other hand, metabolic acidosis after administration of intravenous fluids has been recognized since the 1920s.[3] Although such acidosis has also been the subject of controversy,[4] a recent controlled study[5] demonstrated that chloride-rich fluids (*e.g.*, saline) delivered in appropriate quantities over a short period of time can induce a non–anion-gap acidosis.

Another situation in which rapid delivery of fluids occurs is on initiation of CPB. Delivery of pump prime fluids can amount to almost 50% of plasma volume in most patients. It is therefore possible that such fluids could induce an immediate metabolic acidosis. Its pathogenesis and characteristics would depend on the type of pump prime fluids. However, demonstrating such phenomena requires a quantitative analysis of changes in acid–base physiology.[6] Thus, we hypothesized that pump prime fluids are responsible for the acidosis of CPB and that the characteristics of such acidosis would differ with different kinds of pump prime. We tested this hypothesis by means of a randomized double-blind study comparing two different types of pump priming fluids and their effect on acid–base balance. The results were then analyzed using quantitative methods.

Materials and Methods

After obtaining Human Research Ethics Committee (Melbourne, Australia) approval, all patients gave written informed consent. Twenty-two patients were prospectively studied. All patients were to undergo elective primary coronary revascularization. Predetermined exclusion criteria for the study included age greater than 75 yr, creatinine concentration greater than 0.15 mM, diabetes mellitus, anemia (hemoglobin level < 10 g/dl), preexisting acid–base abnormalities, and extremes in weight (body weight < 50 kg or > 100 kg).

Patients were randomly assigned to one of two groups. Group I received 500 ml of a polygeline solution (Haemaccel, Hoechst, Sydney, Australia), which is a colloid solution, and 1,000 ml of Ringer's Injection (Baxter, Sydney, Australia) as the priming fluid in the CPB circuit (constituents can be seen in table 1). Ringer's Injection

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Table 1. Concentration of Ions in Primes

Strong Ion	Group 1* (mEq/l)	Group II (mEq/l)
Sodium (Na^+)	146	140
Chloride (Cl^-)	151	98
Potassium (K^+)	4.4	5
Calcium (Ca^{2+})	6.8	0
Magnesium (Mg^{2+})	0	3.0
Acetate	0	27
Gluconate	0	23

The composition of strong ions in the two types of pump primes. Group I prime solution calculated by averaging ion concentrations in the mixture of Haemaccel and Ringer's Injection.

* Approximately 11.7 g/l polygeline and traces of phosphoric acid and sulfuric acid.

differs from Ringer's lactate. This was the standard priming solution at our institution. In group II, the CPB priming fluid was 1,500 ml of Plasmalyte 148 (Baxter), which was selected because it a commonly used prime that differs considerably in its composition from our usual prime (table 1). CPB was performed using a membrane oxygenator (Sorin Monolyth; Biomedica, Mirandola, Italy). The pump rate was set at $2.4\ l \cdot m^{-2} \cdot min^{-1}$, and body temperature was 32–34°C. Blood sampling was performed at three time points: immediately before CPB (t_1), 2 min after initiation of CPB at full flows (t_2), and at the end of the case (t_3). Samples collected after initiation of CPB were taken before any cardioplegia was administered, limiting its effects only to the variables at t_3. Serum sodium, potassium, ionized calcium, ionized magnesium, chloride, phosphate, albumin, and lactate were measured at the three time points. Arterial blood gases were also measured (*p*H, carbon dioxide tension, oxygen tension, calculated standard bicarbonate, and calculated standard base excess). Analysis of blood gases and measurement of serum sodium, potassium, ionized calcium, and chloride and lactate was performed on an ABL 30 Blood Gas Analyzer (Radiometer, Copenhagen, Denmark). All other variables were measured on a Hitachi 747 Analyzer (Boehringer Manheim, Indianapolis, IN).

Conceptual Framework for the Interpretation of Data: Quantitative acid–Base Analysis

Quantitative physicochemical analysis of the results was performed using Stewart's[6] quantitative biophysical methods as modified by Figge[7] to take into account the effects of plasma proteins. This method involves first calculating the strong ion difference apparent (SIDa):

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

with all concentrations in milliequivalents per liter.

This equation, however, does not take into account the role of weak acids (carbon dioxide, albumin, phosphate) in the balance of electrical charges in plasma water. This is expressed through the calculation of the strong ion difference effective (SIDe). The formula for SIDe as determined by Figge[7] is as follows:

$$SIDe = 1{,}000 \times 2.46 \times 10^{-11} \times Pco_2/(10^{-pH}) + [Alb](0.123 \times pH - 0.631) + [Phos] \times (0.309 \times pH - 0.469) \quad (2)$$

with carbon dioxide partial pressure (Pco_2) in millimeters mercury, albumin in grams per liter, and phosphate in millimoles.

This formula quantitatively accounts for the contribution of weak acids to the electrical charge equilibrium in plasma. Once weak acids are quantitatively taken into account, and lactate (a strong acid that behaves like a strong anion in blood) is factored in, SIDa − SIDe must equal 0 (electrical charge neutrality). If this is not so, there must be unmeasured charges to explain this "ion gap," which is called the strong ion gap (SIG):

$$SIG = SIDa - SIDe - lactate \quad (3)$$

A positive value for SIG must represent unmeasured anions (ketoacids, sulfate, citrate, pyruvate, acetate, gluconate, etc.) that must be present in the blood to account for the measured *p*H, the measured levels of strong and weak ions, and the need to maintain isoelectricity.

Statistical Analysis

The data were collected and analyzed in the following manner. First, the median value with 95% confidence interval was calculated for each variable at the three time points: t_1, t_2, and t_3. The data were then tested for normality using skewness measurements. As the data were not normally distributed, Friedman's statistic for multiple comparisons of nonparametric data was used on each group to test if there was any significant change over the time $t_1 \rightarrow t_2 \rightarrow t_3$. For measured variables that showed significant change over this time frame, a Wilcoxon ranked sign test, adjusted for multiple comparisons, was performed to obtain an estimated median change (with 97.5% confidence interval) over the following time periods: $t_1 \rightarrow t_2$, $t_2 \rightarrow t_3$, and $t_1 \rightarrow t_3$. Once these changes were calculated for each pump prime group, a Mann–Whitney U test was performed to compare the median changes seen at these points in time with each prime, to test the hypothesis that each prime affected acid–base variables differently.

Results

There was no difference with respect to age, sex, weight, pump time, number of grafts, and surgical time between the two groups. Twenty-two patients were recruited, but one had surgery postponed (group I, n = 11; group II, n = 10). The patients were randomized to either group by the hospital pharmacy staff who were

Table 2. Median Concentration of Measured Variables over the Three Time Points

Measured Variable	Group	Median Value of Measured Variable t1	t2	t3
Sodium (mM)	I	136.00	136.50	136.00
	II	135.00	133.00*	133.50‡
Potassium (mM)	I	4.10	4.25	4.35
	II	4.15	4.30*	4.05†
Chloride (mM)	I	103.50	113.00*	108.50†‡
	II	104.00	101.50	103.00
Calcium (mM)	II	1.26	0.92*	1.02†‡
Magnesium (mM)	I	0.76	0.59*	1.05†‡
	II	0.72	0.87*	1.32†‡
Phosphate (mM)	I	1.00	0.80*	1.00
	II	0.92	0.71*	0.83
Albumin (g/l)	I	31.50	18.00*	22.00‡
	II	28.50	17.00*	23.50†‡
Lactate (mM)	I	1.10	0.95*	1.70†
	II	1.55	1.10*	2.12
pH	I	7.40	7.36*	7.40
	II	7.40	7.39	7.44†
P_{CO_2} (mmHg)	I	40.20	35.15*	39.65†
	II	41.400	34.60*	39.47†
Bicarbonate (mM)	I	25.20	20.35*	23.65†
	II	25.38	20.77*	25.88†
Base excess (mM)	I	0.95	−3.65*	−0.65†
	II	1.17	−3.20*	2.32†‡
Anion gap (mEq/l)	I	11.40	7.40	8.20
	II	9.80	15.00*	8.70†‡
SIDa (mEq/l)	I	40.42	32.53*	36.86†‡
	II	39.43	39.61	39.21
SIDe (mEq/l)	I	35.94	27.09*	32.16†‡
	II	35.55	27.39*	34.40†
SIG (mEq/l)	I	4.35	5.74	5.10
	II	4.02	12.85*	4.64
SIG-lactate (mEq/l)	I	3.36	4.79	3.17
	II	2.33	11.36*	2.29†

* Significant change ($P < 0.025$) from t_1 to t_2. † Significant change ($P < 0.025$) from t_2 to t_3. ‡ Significant change ($P < 0.025$) from t_1 to t_3.

P_{CO_2} = partial pressure of carbon dioxide; SIDa = strong ion difference apparent; SIDe = strong ion difference effective; SIG = strong ion gap.

independent of the investigators. The results are summarized in table 2.

Effects of Pump Prime I (Haemaccel and Ringer's Solution)

The administration of polygeline and Ringer's solution (group I) induced marked hyperchloremia, as well as hypercalcemia and hypoalbuminemia. These alterations induced a non–anion gap hyperchloremic acidosis (significant decrease in SIDa), which was only partially compensated for by the onset of hypoalbuminemic alkalosis (decreased SIDe). This partial compensation was manifested by a significant decrease in base excess.

The following time period was characterized by a corrective physiological response, with a decrease in serum chloride toward baseline and an increase in serum albumin also toward baseline. Accordingly, there was a significant improvement in the degree of metabolic acidosis with an increase in base excess. However, this improvement failed to restore homeostasis by the end of the case, resulting in admission of the patient to the cardiothoracic intensive care unit with a residual metabolic acidosis. Several small changes in other variables (phosphate, potassium, and magnesium) were of minimal impact.

Effects of Pump Prime II (Plasmalyte)

The effect of the administration of pump prime II (Plasmalyte 148) was manifested by the immediate changes in acid–base balance associated with its delivery (t_1 *vs.* t_2).

The major effect of Plasmalyte was to lower serum albumin and to induce an anion gap acidosis (decrease in base excess). This change is confirmed by an increase in SIG (the albumin, phosphate, and carbon dioxide–corrected anion gap). This anion gap acidosis was not caused by lactate, however, because it remained unchanged once lactate was removed from the SIG calculation. The subsequent time period (t_2–t_3) was characterized by a return to homeostasis. The serum albumin increased together with the SIDe. There was also a prompt resolution of the anion gap metabolic acidosis (SIG and SIG–lactate decreased back to baseline). Accordingly, at the end of the case, there was a complete resolution of the metabolic acidosis.

Comparison of the Two Pump Primes

Both primes induced a metabolic alkalosis by causing hypoalbuminemia, although this was slightly less for Plasmalyte. However, although polygeline–Ringer's induced a hyperchloremic non–(strong)anion gap acidosis, Plasmalyte did not.

Plasmalyte, on the other hand, induced a non–lactic (strong)anion gap acidosis, which resolved by the end of the case. The hyperchloremic acidosis induced by pump prime I cleared more slowly than the Plasmalyte-induced anion gap acidosis. Therefore, at the end of the case, Plasmalyte-induced acidosis had fully resolved, but polygeline-Ringer's-induced acidosis had not completely resolved.

Discussion

Metabolic acidosis is associated with CPB.[1] However its pathogenesis is poorly understood because the traditional methods of examining acid–base changes (anion gap analysis) are lacking in this setting.[2] The effect of the composition of pump priming solution on serum lactate concentration has been studied. It has been demonstrated that using a solution with no lactate significantly limits the increase in serum lactate concentrations during the postoperative period.[8] Priming fluids in both our groups contained no lactate. As expected, we found no clinically significant increase in lactate concentration from t_1 to t_3, yet both groups developed an acidosis within 2 min of pump prime delivery. In our opinion, such acidosis can only be reasonably attributed to the delivery of pump prime fluids.

Because traditional methods cannot accurately quanti-

tate the impact of hypoalbuminemia (ubiquitous after CPB) on acid–base balance, we applied a quantitative biophysical approach to the problem, based on the work of Stewart.[6] It centers around three independent factors affecting *p*H and bicarbonate: the partial pressure of carbon dioxide, the strong ion difference, and the total concentration of weak acids. Stewart proposed that, as the strong ion difference becomes smaller, the plasma *p*H would decrease. The increased dissociation of plasma water is proposed as the main source of hydrogen ions. Changes in bicarbonate are seen as secondary changes in the three independent factors.

The two pump primes differ in the types and concentrations of strong ions they contain (table 1), and their bolus administration also provided a "natural experiment" to test the practical usefulness of Stewart's approach in interpreting and quantifying changes in acid–base physiology. The difference in content between the two primes is shown in table 1.

Using Stewart's framework, we expected the following immediate major effects of the bolus administration of the pump primes:

1. Prime I (Haemaccel–Ringer's) should induce hyperchloremia.
2. Assuming a volume of distribution for chloride at 2 min of 5–7 l, the increase in chloride should be 10 mEq/l.
3. Dilutional hypoalbuminemia should occur for both primes (decrease of 10–14 g/l).
4. Minor changes should occur in in Ca^{2+}, K^+, and phosphate (< 1 mEq/l).
5. Because the anionic milliequivalent value of the increase in chloride concentration would be greater than the anionic loss because of decreased albumin concentration, a mild to moderate hyperchloremic acidosis should develop.
6. Prime II (Plasmalyte) should have no effect on chloride.
7. Because of hypothermia,[9] liver uptake of gluconate and acetate should not be immediate. The two anions would therefore remain in plasma at a concentration equal to the total administered dose divided by their expected volume of distribution (similar to chloride), thus increasing the number of anions by approximately 10 mEq/l.
8. Similarly to Prime I, the acidifying effect of extra anions would overcome the alkalinizing effect of hypoalbuminemia and induce a moderate metabolic acidosis. However, and this is fundamental, the nature of this acidosis would be different with an increase in SIG caused by unmeasured anions.

The findings of our study are entirely consistent with the aforementioned hypotheses and explanations. The significant difference in the behavior of calcium and magnesium in the two groups is simply caused by their different content in the primes. Although albumin decreased by the same extent in both groups, there was a significantly better recovery in the patients of group II. In our opinion, this phenomenon is best explained by the dilutional effect of the polygeline, which may have been longer lasting in its effect on plasma volume.

Thus, both acidoses were caused by the sudden addition of excess strong anions with a decrease in the SIDa for group I. As expected, the SIDa did not change for group II, but the SIG did, signifying the importance of unmeasured anions (gluconate and acetate) in the genesis of metabolic acidosis in group II. Thus, increased serum chloride was responsible for the acidosis in group I, whereas plasma acetate and gluconate were responsible in group II. These events become more apparent during the resolution phase. From the initiation of CPB (t_2) to the end of the case (t_3), the SIDa for group I increased significantly as compared with that of group II (partial normalization of chloride). For group II, however, the main change seen from t_2 to t_3 was a rapid decrease in the SIG of almost exactly the same magnitude as the initial increase (rapid liver uptake of gluconate and acetate). Thus, the disposal of acetate and gluconate was more complete and rapid than it was for chloride, as seen when comparing changes in values between the two groups overall (*i.e.*, from t_1 to t_3). With group I, bicarbonate decreased a median of -1.4 mM but increased 0.3 mM in group II ($P = 0.0265$), and standard base excess decreased a median value of -1.5 mEq/l in group I but increased a median value of 1.1 mEq/l in group II ($P = 0.0062$). That such effects could be so clearly seen in a small group of patients attests to their consistent and quantitatively powerful nature.

In conclusion, this study strongly suggests that the metabolic acidosis of CPB is iatrogenic in nature and that its extent and duration varies according to the pump prime fluid. Quantitative acid–base chemistry according to Stewart's paradigm provides a logical and physiologically robust explanation that is entirely consistent with empirical observations and that explains a phenomenon that had previously been poorly understood.

References

1. Harris EA, Seelye ER, Barratt-Boyes BG: Respiratory and metabolic acid-base changes during cardiopulmonary bypass in man. Br J Anaesth 1970; 42:912–21
2. Ernest D, Herkes RG, Raper RF: Alterations in anion gap following cardiopulmonary bypass. Crit Care Med 1992; 20:52–6
3. Odeira T: Influence of some neutral salt solutions, intravenously administered, on the alkalai reserve of the blood. Tohoku J Exp Med 1923; 4:523–8
4. Garella S, Chang B, Kahn S: Dilution acidosis and contraction alkalosis: Review of a concept. Kidney Int 1975; 8:279–83
5. Scheingraber S, Rehm M, Sehmisch C, Finsterer U: Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynaecologic surgery. ANESTHESIOLOGY 1999; 90:1265–70
6. Stewart PA: Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 1983; 61:1444–61
7. Figge JT, Mydosh T, Fencel V: Serum proteins and acid base equilibria: A follow-up. J Lab Clin Med 1992; 120:713–9
8. McKnight CK, Elliot MJ, Pearson DT, Holden MP, Alberti KGMM: The effects of four different crystalloid bypass pump-priming fluids upon the metabolic response to cardiac operation. J Thorac Cardiovasc Surg 1985; 90:97–111
9. Koizumi M, Matsumoto N, Ueda K: Influences of cardiopulmonary bypass and fentanyl anesthesia on hepatic circulation and oxygen metabolism in beagles. Anesth Analg 1998; 86:1177–82