Original Article

The Buffering Ability of Commonly Employed Cardiopulmonary Bypass Solutions and Alkalizing Agents

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Keywords: acid-base balance; cardioplegia; perfusion;cardiopulmonary bypass; extracorporeal circulation

Presented at the 32nd AmSECT International Conference, April 8-12, 1994, Anaheim, California

ABSTRACT

This experiment evaluated the hydrogen ion (H^+) buffering capacity (BC) of solutions and alkalizing agents employed during cardiopulmonary bypass (CPB). A solution's BC can be determined when a known quantity of H^+ is titrated into the solution and the change ( ) in pH (-log of the hydrogen ion activity ($[H^+]_a$)) is measured ($[H^+]_a$/ mmole H^+). Eleven solutions were studied: Lactated Ringers (LR), 0.9% NaCl (NS), Plasma-Lyte A™, Hespan ™ (6% hetastarch), banked donor blood with citrate phosphate dextrose adenine (CPDA-1), fresh donor blood, THAM™, sodium bicarbonate ($NaHCO_3$; 1 mEq/ml), high potassium crystalloid cardioplegic solution (HKCCPS), oxygenated crystalloid cardioplegic solution (OCCPS), and adult crystalloid priming solution (AP) per institutional protocol. The solutions were studied at three temperatures: 37°C, 28°C, and 18°C. The null hypothesis stated there was no difference in the BC of the solutions studied. The solutions were first titrated to the same starting pH of 8.0. The solutions were then titrated with a predetermined concentration of hydrochloric acid (HCl) to a pH of 7.0. A higher quantity of H^+ added to a solution indicated a greater ability of that solution to buffer H^+ within pH limits of 8.0 to 7.0. The data was analyzed with a two way ANOVA and Bonferonni method. A p value <0.05 was considered to be statistically significant. The significant results of our study indicated that THAM™ demonstrated the best BC, followed in decreasing order by $NaHCO_3$, banked blood, fresh blood, HKCCPS, AP, OCCPS, Plasmalyte™, LR, Hespan™, and NS.

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INTRODUCTION

The perfusionist must have an understanding of acid-base chemistry in order to maintain the patient's normal acid-base status. The occurrence of metabolic acidosis while on cardiopulmonary bypass (CPB) is usually the result of hypoperfusion (1), though it may occur during cooling, rewarming, administration of intravenous solutions, and hypoxia (2-6). Metabolic acidosis is routinely palliated during cardiac surgery by the intravenous administration of sodium bicarbonate ($NaHCO_3$) (7-9). Various solutions are available to treat an acid-base abnormality. It is the perfusionist's responsibility to be cognizant of the buffering capacity (BC) of commonly used solutions and alkalizing agents employed during cardiopulmonary bypass (CPB).

One of the major therapeutic characteristics of a solution is its BC (10-14). The BC indicates the solution's ability to resist a change in pH (15). To quantify a solution's BC, a known quantity of hydrogen ions (H^+) can be titrated into the solution and the change (Δ) in pH measured (Δ pH / Δ mmole H^+) (11,14,16,17) (Figure 1).

A solution's best BC occurs at its pK. The pK of a solution is the pH at which 50% of the solution (acid or base) is in its pronated form and 50% is in its depronated form (i.e. HA<--> H^+ + A^-). Each solution has its own pK, and thus its own unique buffering curve which is graphically represented by plotting percentage dissociation on the Y-axis and pH on the X-axis.

In order for this study to be clinically relevant, we studied solutions over a pH range (7.0 to 8.0) that would encompass normal pH values. In addition, it is understood from basic biochemistry that a change in a solution's temperature will change the pK of that solution. A change in pK will result in a change in the BC of a solution at the same pH. Perfusionists manage patients on CPB at different temperatures. Therefore, we decided to study the BC of solutions at temperatures used clinically (37, 28, & 18°C).

This study evaluated the H^+ BC of solutions and alkalizing agents commonly employed during CPB. Knowledge of the BC of these solutions enables the perfusionist to choose a solution which will minimize patient drug administration and work effectively in treating the acid-base disorder, once the cause of the acidosis has been determined (9, 18-20).

The null hypothesis stated there was no difference in the BC of the solutions studied.

METHODS AND MATERIALS

This experiment was designed to determine the BC of eleven solutions at normal physiologic pH and at three temperatures: 37°C, 28°C, and 18°C. The following eleven solutions were studied: lactated Ringers (LR)[a]; Hespan™[b]; Plasma-Lyte A™[c]; 0.9% NaCl (NS)[d]; oxygenated crystalloid cardioplegic solution (OCCPS), which consisted of 98.5 ml Ringers[a], 0.5 meq $NaHCO_3$, and 1 meq KCl; fresh blood with 3.5 units heparin/ml; banked blood with citrate phosphate dextrose adenine (CPDA-1)[e]; $NaHCO_3$; THAM™[f]; high potassium crystalloid cardioplegic solution (HKCCPS), which consisted of 60 meq KCl, 34 ml ACPD[g], and 29 ml THAM™ in 500 ml D5W.2NS[h]; and lastly, adult crystalloid prime (AP) which consisted of 69 ml LR, 28.7 ml Hespan™, and 2.3 meq $NaHCO_3$.

One hundred ml of each solution was placed in a 200 ml beaker. Each solution was maintained at the desired temperature using an ice bath or a heater/stir plate[i]. Five trials were performed for each solution at each of three temperatures: 37°C, 28°C, and 18°C. The solutions were initially titrated to a pH of 8.0 using a solution of sodium hydroxide (NaOH) or in the case of THAM™, a 12 Normal (N) solution of hydrochloric acid (HCl). The solutions were then titrated with a predetermined concentration of HCl to achieve approximately ten data points between a pH of 8.0 and 7.0. After each addition of HCl the new pH was recorded using a pH meter.

The hydrogen ion activity ($[H^+]_a$ (moles/l) = antilog -pH) for each solution was plotted against the number of H^+ (mmole) titrated into the solution ($[H^+]_a$ (moles/l) / mmole H^+). Five trials, of ten observations each, were used to derive five titration curves. The five titration curves were averaged to obtain one BC curve for each solution at each of the three temperatures. The observed BC were analyzed by two-way ANOVA using statistical software[j] to compare solutions at the three temperatures. A Bonferonni procedure was performed to determine which solutions were different when the ANOVA resulted in the failure to accept the null hypothesis.

RESULTS

Table 1 shows the BC ($\Delta[H^+]_a$ (moles/l) / mmole H^+). The three BC for each solution were then averaged and an overall ranking determined using these averages. The overall ranking was the same as the ranking at 37°C for each solution studied. The seven solutions with the highest BC had the same rank regardless

a Baxter Lactated Ringer's Injection USP, Baxter Healthcare Corporation, Deerfield, IL 60015
b Hespan 6% hetastarch in 0.9% Sodium Chloride Injection, DuPont Pharmaceuticals, Wilmington, DE 19880
c Baxter Plasma-Lyte A Injection pH 7.4, Baxter Healthcare Corporation, Deerfield, IL 60015
d Baxter 0.9% Sodium Chloride Injection USP, Baxter Healthcare Corporation, Deerfield, IL 60015
e Anticoagulant Sodium Citrate Solution USP, Miles, Inc. Cutter Biological, Elkhart, IN 46515
f THAM Solution, Tromethamine Injection, Abbott Laboratories, North Chicago, IL 60064
g Anticoagulant Citrate Phosphate Dextrose Solution USP, Abbott Laboratories, North Chicago, IL 60064
h Baxter 5% Dextrose and 0.2% Sodium Chloride Injection USP, Baxter Healthcare Corporation, Deerfield, IL 60015
i Fisher Thermix Stirring Hot Plate Model 210T, Fisher Scientific, Norcross, GA 30091
j Minitab v.7.2, 1989. Minitab, Inc. State College, PA 16801-2756

of temperature. There was a difference in the ranking of the last four solutions at 28°C and 18°C. The solutions or alkalizing agents with the highest BC included: THAM™, $NaHCO_3$, banked blood, fresh blood, HKCCPS, and AP.

The relative overall BC values (Table 2) were obtained by assigning an arbitrary number of 1 to NS. Thus the BC of each solution was compared relative to NS. For example, THAM™ was shown to have ≈12,000 times the BC of NS.

Blood had the highest BC of the solutions, excluding THAM™ and $NaHCO_3$. The next three solutions (HKCCPS, AP, and OCCPS) contained THAM™ or $NaHCO_3$. The alkalizing agent in these three solutions contributed to the observed BC.

Figure 1 is a graphic representation showing the relationship of the BC of THAM™, $NaHCO_3$, and fresh blood for all three temperatures. There was a significant difference in the BC between each of these three solutions ($p<0.05$).

The BC of $NaHCO_3$ was not the same at each of the three temperatures studied. Figure 2 illustrates the direct relationship between BC and temperature of $NaHCO_3$. As the temperature of the solution decreased the BC of $NaHCO_3$ also decreased. There was a significant difference between the BC at 37°C versus 18°C ($p<0.05$).

We were not able to titrate $NaHCO_3$ to a pH of 7.0 due to the increase of CO_2 as the $NaHCO_3$ was titrated down to a lower pH. At a pH of ≈7.0, CO_2 began to bubble out of the solution. Therefore, the $NaHCO_3$ solution was only titrated to a pH of ≈7.2.

Table 1: Buffering capacity of solutions at all three temperatures.

Solution	Overall BC 1=high	Avg. BC of all 3 temps ($\Delta[H^+]_a$ (moles/l)/ mmole H^+)	BC at 37°C ($\Delta[H^+]_a$ (moles/l)/ mmole H^+)	Vol. used to titrate to ($\Delta[H^+]_a$ (moles/l)/ mmole H^+)	Hosp. cost of solution ($\Delta[H^+]_a$ (moles/l)/ mmole H^+)
THAM™	1	4.3 x 10-9	4.7 x 10-9	4.0 x 10-9	4.2 x 10-9
$NaHCO_3$	2	1.1 x 10-8	7.5 x 10-9	1.1 x 10-8	1.4 x 10-8
Bk. Blood	3	8.8 x 10-8	*9.2 x 10-8	9.8 x 10-8	7.5 x 10-8
Fr. Blood	4	9.8 x 10-8	†9.5 x 10-8	1.0 x 10-7	9.9 x 10-8
HKCCPS	5	1.1 x 10-7	9.9 x 10-8	1.1 x 10-7	1.3 x 10-7
AP	6	2.7 x 10-7	3.1 x 10-7	2.5 x 10-7	2.5 x 10-7
OCCPS	7	1.1 x 10-6	1.5 x 10-6	9.0 x 10-7	8.6 x 10-7
Plasma-Lyte™	8	7.0 x 10-6	7.5 x 10-6	6.5 x 10-6	6.9 x 10-6
LR	9	1.2 x 10-5	1.1 x 10-5	2.4 x 10-5	2.2 x 10-6
Hespan™	10	1.3 x 10-5	2.0 x 10-5	1.1 x 10-5	6.8 x 10-6
NS	11	5.1 x 10-5	7.7 x 10-5	3.7 x 10-5	3.9 x 10-5

* - 2 trials
† - 1 trial

Overall ranking of the BC of the alkalizing agents and solutions researched from the average of their BC at each of the three temperatures studied (1=highest). The smaller the value ($\Delta[H^+]_a$ (moles/l) / mmole H^+), the greater the BC of that solution. AP= adult prime; BC= buffering capacity; HKCCPS= high potassium crystalloid cardioplegic solution; LR= Lactated Ringers; NS= normal saline; OCCPS= oxygenated crystalloid cardioplegic solution.

Table 2: Solution characteristics and facts

Solution	Relative overall BC (NS=1)	Original pH (pH unit)	NaOH used to titrate to pH=8.0 (mmole)	Vol. used to titrate to pH=8.0 (ml)	Hosp. cost of solution at (MUSC) ($/x ml)	Patient cost of solution at (MUSC) ($/x ml)
THAM™	11,849	8.6	*6.0	0.5	95/500ml	183/500ml
$NaHCO_3$	4,743	7.8	0.96	0.1	1.16/50ml	17.00/50ml
Bk. Blood	536	6.5	0.68	0.07	NA	†269/500ml
Fr. Blood	523	7.4	0.26	0.026	NA	NA
HKCCPS	447	7.3	0.27	0.027	115.00/l	258.00/l
AP	190	7.2	0.13	0.13	29.19/l	71.40/l
OCCPS	46	7.3	0.03	0.03	2.77/l	25.00/l
Plasma-Lyte™	7	7.4	0.004	0.04	2.20/l	5.80/l
LR	4.1	6.5	0.005	0.05	1.23/l	3.70/l
Hespan™	4	5.5	0.008	0.08	46/500ml	107/500ml
NS	1	5.0	0.0025	0.025	0.75/l	1.95/l

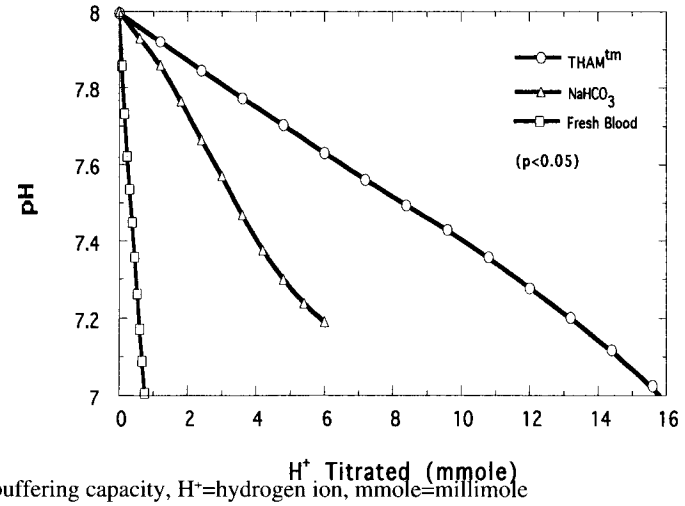
Data on the 11 solutions studied: Relative BC, starting pH, mmole and ml of NaOH titrated to obtain a starting pH of 8.0, and cost/ml.
*HCl was used to titrate THAM™ to a starting pH of 8.0
†Cost includes: type & screen, x-match, collection, storage, personnel and transfusion.
AP=adult prime; Bk.=banked; BC=buffering capacity, Fr.=fresh, HKCCPS=high potassium crystalloid cardioplegic solution; LR=Lactated Ringers; ml=milliliter; mmole=millimole; MUSC=Medical University of South Carolina; NS=normal saline; OCCPS=oxygenated crystalloid cardioplegic solution; Vol.=volume

DISCUSSION

Perfusionists are presently using a variety of solutions to prime their cardiopulmonary bypass (CPB) circuits. No one particular solution has been adopted as the "gold standard", or best solution for priming CPB circuits. Failure to adopt a standard priming solution may be due to the number of solutions available, the unique advantages/disadvantages each solution provides, and the lack of scientific information to make an informed decision.

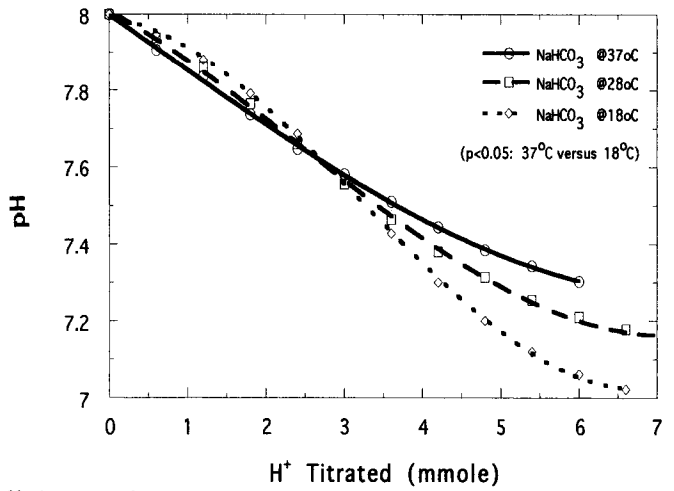
Perfusionists have an obligation to the patient to choose a priming solution with some knowledge of that particular solution's characteristics. Thus, an informed decision can be made regarding the particular advantages/disadvantages a solution affords a patient. Some of the important characteristics are BC, pH, and cost.

Figure 1: Ability of THAM™, $NaHCO_3$ and fresh blood to buffer H^+ titrated into solution. There was a significant difference in the BC of each of these solutions ($p<0.05$).



BC=buffering capacity, H^+=hydrogen ion, mmole=millimole

Figure 2: Ability of $NaHCO_3$ to buffer H^+ titrated into solution at three different temperatures. There was a significant difference in the BC of $NaHCO_3$ at 37°C versus 18°C ($p<0.05$).



BC=buffering capacity

From this study, we found that it would be advantageous to choose a priming solution in regards to its BC.

Our research found that there are significant differences in buffering capacities between all of the solutions we studied except for LR and Hespan™ (Table 1). Also of interest are the differences in starting pH and cost (Table 2). Solutions with a lower starting pH needed the addition of an alkalizing agent to bring the solution to a normal physiological pH. Cost may be a big deterrent, and even the deciding factor, regarding the use of a solution.

The study showed that THAM™ exhibited a BC 2.5 times that of $NaHCO_3$. Also, unlike $NaHCO_3$, THAM™ did not decrease significantly in BC as the temperature decreased from 37°C to 18°C. Therefore, THAM™ would be a better alkalizing agent to use in the prime and/or while on CPB to treat an acidotic condition or base deficit. The major disadvantage of THAM™ is its cost and the large volume (500 ml) in which it is sold (Table 2).

This study design provided no respiratory mechanism to blow off the increased production of CO_2 that occured with the titration of HCl into $NaHCO_3$. The HCO_3/H_2CO_3 equilibrium equation demonstrates that as additional H+ were added, more CO_2 was produced. Thus a point was reached when the solution became saturated with CO_2 resulting in the bubbling of CO_2 out of solution:

$$H_2O + CO_2 <==> H_2CO_3 <==> H^+ + HCO3^-$$

A pilot study which looked at controlled (PCO_2 40 mmHg) versus uncontrolled CO_2 in a solution of $NaHCO_3$, showed there was no significant difference in the BC when titrated from a pH of 8.0 to 7.2 with HCl.

M.U.S.C. perfusionists presently use LR, Hespan, and $NaHCO_2$ to prime the CPB circuit. LR and Hespan have a low starting pH, 6.5 and 5.5, respectively. Therefore, the alkalizing agent $NaHCO_3$ is needed to raise the pH to a normal physiological range. Study results demonstrated that Plasma-Lyte A™ had a better BC and a more physiological pH (7.4) than LR/Hespan™. Plasma-Lyte A™ is also lower in cost than a LR/Hespan™ mixture.Therefore, we recommend the use of Plasma-Lyte A™ instead of LR/Hespan™ because of its pH, lower cost, and greater BC.

Results from this study show that there are significant differences in the BC of solutions commonly employed during CPB. This method of acid titration, at varying temperatures, facilitates the ranking of the BC of solutions and alkalizing agents, including cardioplegic solutions, priming solutions, and blood. The results of this study give the perfusionist the ability to make an informed selection of the optimal solution or alkalizing agent to use while on CPB.

CONCLUSIONS

1. THAM™ had the highest BC, followed by $NaHCO_3$, banked blood, fresh blood, HKCCPS, AP, OCCPS, Plasma-Lyte A™, LR, Hespan™, and NS.

2. As the temperature decreased, the BC of $NaHCO_3$ decreased.

3. There was no significant difference in the BC of banked blood versus fresh blood, both having the highest BC of all the solutions studied excluding the alkalizing agents, THAM™ and $NaHCO_3$.

ACKNOWLEDGMENTS

I would like to thank the Extracorporeal Circulation Technology faculty and the Physiology Department faculty at the Medical University of South Carolina for their assistance in the development of the methodology and the data analysis of this study. A special thanks to Dr. Adam Smolka for the use of his lab and to his lab assistant, Peter Zwarych.

REFERENCES

1. Reed CC, Stafford TB. Cardiopulmonary Bypass. Texas: Surgimedics/TMP; 1985:207.
2. von Planta M, Bar-Joseph G, Wiklund L, Bircher NG, Falk JL, Abramson NS. Pathophysiologic and therapeutic implications of acid-base changes during CPR. Ann Emerg Med. 1993;22:404-410.
3. Adrogu'e HJ, Rashad MN, Gorin AB, Yacoub J, Madias NE. Arteriovenous acid-base disparity in circulatory failure: studies on mechanism. Am J Physiol. 1989;257:1087-1093.
4. Haber RJ. A practical approach to acid-base disorders. West J Med. 1991;155(2):146-151.
5. Julia PL, Buckberg GD, Acar C, Partington MT, Sherman MP. Studies of controlled reperfusion after ischemia. Reperfusate composition: superiority of blood cardioplegia over crystalloid cardioplegia in limiting reperfusion damage — importance of endogenous oxygen free radical scavengers in red blood cells. J Thorac Cardiovasc Surg. 1991;101(2):303-13.
6. Yoshida K, Marmarou A. Effects of tromethamine and hyperventilation on brain injury in the cat. J Neurosurg. 1991;74(1):87-96.
7. McLaughlin ML, Kassirer JP. Rational treatment of acid-base disorders. Drugs. 1990;39(6):841-855.
8. Nishikawa T. Acute haemodynamic effect of sodium bicarbonate in canine respiratory or metabolic acidosis. Br J Anaesth. 1993;70(2):196-200.
9. Ayus JC, Krothapalli RK. Effect of bicarbonate administration on cardiac function. Am J of Med. 1989;87:5-6.
10. Barner HB. Blood cardioplegia: a review and comparison with crystalloid cardioplegia. Ann Thorac Surg. 1991; 52(6):1354-67.
11. Benitez MJ, Company M, Arevalillo A, Jiménez JS. Comparative study of various hydrogen ion buffers to assay Zn_2^+-dependent beta-lactamases. Antimicrob Agents Chemother. 1991;35(7):1517-9.
12. Bidani A, Heming TA. Effects of perfusate buffer capacity on capillary CO_2-HCO_3^--H^+ reactions: theory. J Appl Physiol. 1991;71(4):1460-8.
13. Donnelly AJ, Djuric M. Cardioplegia solutions. Am J Hosp Pharm. 1991;48(11):2444-60.
14. Gazmuri RJ, von Planta M, Weil MH, Rackow EC. Cardiac effects of carbon dioxide-consuming and carbon dioxide-generating buffers during cardiopulmonary resuscitation. J Am Coll Cardiol. 1990;15(2): 482-90.
15. Love WB, Biswas S. Denture adhesives — pH and buffering capacity. J Prosthet Dent. 1991;66(3):356-360.
16. Kirschbaum B, Culpepper RM. The pK'1 of the carbonic acid-bicarbonate buffer system in hemodialyzed patients. Amer J Med Sci. 1989;298(4):237-242.
17. Mainwood GW, Lareau S, Whitehead K, Keon WJ, Deslauriers R. The effects of temperature and buffer concentration on the metabolism of human atrial appendages measured by ^{31}P and ^{1}H NMR. Adv Exp Med Biol. 1989;248:611-9.
18. Bersin RM, Chatterjee K, Arieff AI. Metabolic and hemodynamic consequences of sodium bicarbonate administration in patients with heart disease. Am J Med. 1989;87(1):7-14.
19. Gupta JM, Dahlenburg GW, Davis JA. Changes in blood gas tensions following administration of amine buffer THAM to infants with respiratory distress syndrome. Arch Dis Child. 1967;42(224):416-27.
20. Neethling WML, van den Heever JJ, Cooper S, Meyer JM. Interstitial pH during myocardial preservation: Assessment of five methods of myocardial preservation. Ann Thorac Surg. 1993;55(2):420-6.