

Acidosis Associated with Perioperative Saline Administration

Dilution or Delusion?

THE hypothesis that saline administration results in dilutional acidosis was advanced by Shires and Holman in 1948.¹ The antithesis, that physiologic defense mechanisms prevent reduction of bicarbonate concentration ($[\text{HCO}_3^-]$) to the extent predicted by simple dilution, followed approximately 20 yr later and generally was accepted by 1975.²⁻⁴ In the 1990s, a variety of case reports⁵⁻⁷ and clinical studies^{8,9} showed that perioperative administration of clinically relevant volumes of 0.9% saline was associated with substantial hypobicarbonatemia and hyperchloremia. However, if the concept of dilutional acidosis were valid, reductions of $[\text{HCO}_3^-]$ should be proportional to the extent of dilution. In the current issue of ANESTHESIOLOGY, three clinical studies¹⁰⁻¹² suggest that actual $[\text{HCO}_3^-]$ is similar to changes in $[\text{HCO}_3^-]$ predicted on the basis of dilution. Together, they provide a sound basis for the synthesis that the term "dilutional acidosis" is not only an important clinical entity, but also an appropriate physiologic term.

In the context of perioperative fluid administration, dilutional acidosis is metabolic acidosis that results from rapid administration of fluids that contain near-physiologic concentrations of sodium accompanied by anions (usually chloride) other than bicarbonate or bicarbonate precursors, such as lactate. The magnitude of acidosis is a consequence of several factors: the baseline volume and composition of plasma volume and extracellular volume (ECV); the volume, rate, and composition of administered fluid; the volume, rate, and composition of fluid losses; and physiologic modification of changes in

extracellular composition (e.g., *via* transmembrane shifts, excretion, or metabolism). Although animal studies have involved volume expansion,¹⁻³ hypervolemia is not necessary for the diagnosis of dilutional acidosis.

Data previously reported in dogs undergoing rapid volume expansion with saline provide a useful background for clinical studies (table 1). In nephrectomized dogs, infusion of 50, 75, or 100 ml/kg saline decreased $[\text{HCO}_3^-]$ by less than half of that predicted based on dilution of ECV.² Similarly, infusion of 105 ml/kg saline over 2 h decreased actual $[\text{HCO}_3^-]$ by only approximately one third of the predicted decrease.³

In contrast, each of the three studies in this issue of ANESTHESIOLOGY reports a reduction of $[\text{HCO}_3^-]$ by saline or other high-chloride solutions that approximates what would have been predicted based on simple dilution of extracellular $[\text{HCO}_3^-]$ (table 2). These reports build on previous perioperative studies^{8,9} in which the effects of saline infusion were potentially confounded by the effects of surgery and blood loss. Waters and Bernstein,¹⁰ Rehm *et al.*,¹¹ and Liskaser *et al.*¹² chose experimental designs that more completely controlled important factors that could influence dilutional acidosis. Waters and Bernstein¹⁰ induced acute hypervolemia in volunteers with use of a 30-min colloid infusion (hetastarch in 0.9% saline or albumin in an unquantified diluent) and measured results immediately after infusion. Rehm *et al.*¹¹ assessed acid-base changes 20 min after isovolemic hemodilution with colloid (hetastarch in 0.9% saline or albumin in a solution resembling 0.9% saline). This approach did not expand blood volume but expanded ECV and removed approximately 20 mEq bicarbonate. Liskaser *et al.*¹² cleverly took advantage of the unique circumstances at the beginning of cardiopulmonary bypass, when priming volume is added short-term to the circulation. They evaluated acid-base status 2 min after initiation of cardiopulmonary bypass with a priming solution that contained either 151 mEq/l chloride or 98 mEq/l chloride plus acetate and gluconate. Measurements so soon after the onset of bypass permitted minimal time for equilibration throughout ECV, physiologic modification of acid-base status, or confounding fluid losses.

In the three studies, the results that were interpreted most easily were those caused by infusion of hetastarch in 0.9% saline or initiation of bypass using the higher chloride priming solution. After rapid volume expansion

This Editorial View accompanies the following three articles: Liskaser FJ, Bellomo R, Hayhoe M, Story D, Poustie S, Smith B, Letis A, Bennett M: The role of pump prime in the etiology and pathogenesis of cardiopulmonary bypass-associated acidosis. ANESTHESIOLOGY 2000; 93:1170-3; Rehm M, Orth V, Scheingraber S, Kreimeier U, Brechtelsbauer H, Finsterer U: Acid-Base changes due to 5% albumin *versus* 6% hydroxyethylstarch solution in patients undergoing acute normovolemic hemodilution: A randomized prospective study. ANESTHESIOLOGY 2000; 93:1174-83; and Waters JH, Bernstein CA: Dilutional acidosis following hetastarch or albumin in healthy volunteers. ANESTHESIOLOGY 2000; 93:1184-7.

Accepted for publication June 20, 2000. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

Key words: Acid-Base; bicarbonate concentration; blood volume expansion; extracellular volume.

Table 1. Predicted *versus* Reported Changes in [HCO₃⁻] after Saline Infusion in Dogs

| First Author | Before Infusion | | Infusion | | After Infusion | | |
|------------------------|-----------------|--|----------------|--|-------------------|--|---|
| | ECV (l) | [HCO ₃ ⁻] (mEq/l) | Volume (ml/kg) | [HCO ₃ ⁻] (mEq/l) | Estimated ECV (l) | Predicted [HCO ₃ ⁻] (mEq/l) | Actual [HCO ₃ ⁻] (mEq/l) |
| Rosenbaum ² | 4* | 24† | 50 | 0 | 5.0 | 19.2 | 21.6 |
| | 4* | 24† | 75 | 0 | 5.5 | 17.5 | 21.5 |
| | 4* | 24† | 100 | 0 | 6.0 | 16.0 | 21.0 |
| Garella ³ | 3.9‡ | 22 | 105§ | 0 | 5.6‡ | 15.4 | 19.8 |

* Weight range 14–25 kg; mean not provided; assumed extracellular volume (ECV) = 20% of mean body weight of 20 kg. † Baseline not reported; only change reported; baseline assumed to be 24 mEq/l. ‡ Measured using chloride space. § 2,100 ml administered over 2 h; not adjusted for weight; mean weight assumed to be 20 kg.

[HCO₃⁻] = serum bicarbonate concentration.

with hetastarch in saline or isovolemic hemodilution with hetastarch in saline, the predicted and actual [HCO₃⁻] were similar. Two minutes after initiation of bypass, equilibration of the higher chloride priming solution within ECV seemed incomplete. The reported [HCO₃⁻] at 2 min (20.4 mEq/l) was between the predicted [HCO₃⁻] when the entire ECV had been diluted in 2 min (22.9 mEq/l) and the predicted [HCO₃⁻] when only plasma [HCO₃⁻] had been diluted (16.6 mEq/l). Using similar assumptions to predict changes in [HCO₃⁻] in ECV in previous clinical studies^{8,9} also provides estimates that closely approximate actual reductions (table 2). Therefore, predictions of postinfusion hypobicarbonatemia based on simple dilution of [HCO₃⁻] perform robustly across a wide variety of perioperative clinical situations if sufficient time for equilibration is available.

There are no obvious explanations for the apparent differences between the canine^{2,3} and clinical^{8–12} experiments. The authors of the previous canine studies proposed a variety of mechanisms to explain reductions in [HCO₃⁻] that were smaller than predicted. These included intracellular buffering and shifts of electrolytes across cellular membranes. In dogs, hypervolemia increased gastric secretion of volume and acid both,¹³ but the quantities secreted were insufficient to explain the blunted changes in pH and [HCO₃⁻].

The other data in the three clinical studies in this issue of ANESTHESIOLOGY also merit discussion. In volunteers undergoing short-term volume expansion with albumin,

there was no significant reduction of [HCO₃⁻]; however, the electrolyte composition of the albumin solution was not measured.¹⁰ Rehm *et al.*¹¹ specified that their albumin solution contained chloride in a concentration similar to that of the hetastarch solution and showed almost identical reductions in [HCO₃⁻]. By far, the most fascinating results, however, are those of Liskaser *et al.*¹² In the group receiving the lower chloride priming solution, the immediate dilution of [HCO₃⁻] was virtually identical to that in the higher chloride group. By the end of surgery, which permitted time for metabolism of the anions acetate and gluconate, [HCO₃⁻] exceeded the baseline value and was higher than that of the group receiving the higher chloride prime. These data suggest that dilutional acidosis usually is hyperchloremic because the increased chloride concentration is altered slowly, whereas other commonly infused anions are likely to be metabolized or excreted.

Is dilution of [HCO₃⁻], however arithmetically appealing, sufficient explanation for the metabolic acidosis that accompanies rapid expansion or replacement of bicarbonate-containing ECV with bicarbonate-free fluid? Advocates of the Stewart approach¹⁴ would, no doubt, argue that the essential difference is not dilution of bicarbonate but infusion of strong anions. Based on the concept that the independent variables—arterial carbon dioxide tension (Paco₂), the strong ion difference, and the total concentration of nonvolatile weak acids—influ-

Table 2. Predicted *versus* Reported Changes in [HCO₃⁻] after Saline Infusion in Humans

| First author | Before Infusion | | Infusion | | After Infusion | | |
|----------------------------|-----------------|--|----------------|--|-------------------|--|---|
| | ECV (l) | [HCO ₃ ⁻] (mEq/l) | Volume (ml/kg) | [HCO ₃ ⁻] (mEq/l) | Estimated ECV (l) | Predicted [HCO ₃ ⁻] (mEq/l) | Actual [HCO ₃ ⁻] (mEq/l) |
| Waters ¹⁰ | 14.7* | 27 | 14.9 | 0 | 15.8 | 25.1 | 25.0 |
| Rehm ¹¹ | 12.5* | 23.6 | 23.7 | 0 | 13.1† | 21.0 | 21.6 |
| Liskaser ¹² | 15.2* | 25.2 | 19.7 | 0 | 16.7† | 22.9 | 20.4 |
| McFarlane ⁹ | 11.6* | 25.0 | 53.4 | 0 | 14.2† | 20.4 | 21.0 |
| Scheingraber ^{9‡} | 13.6* | 23.5 | 71 | 0 | 17.1† | 18.6 | 18.4 |

* Estimated at 20% of mean body weight. † Estimated as baseline extracellular volume (ECV) minus plasma volume removed plus colloid infused¹¹; estimated as baseline ECV plus 1.5 l pump prime¹²; estimated as baseline ECV plus infused fluid minus plasma volume loss (urinary output not reported)⁸; estimated as baseline ECV plus infused fluid minus plasma volume loss minus urinary loss.⁹ ‡ Data at 120 min of surgery.

[HCO₃⁻] = serum bicarbonate concentration.

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ence the dependent variables pH and $[\text{HCO}_3^-]$, the Stewart approach provides an alternative to simple dilution as the explanation for acidosis. Thus, Liskaser *et al.*¹² describe the effects of the two pump primes as remarkably different and argue that the Stewart approach is necessary to understand the similar short-term changes in pH and $[\text{HCO}_3^-]$ produced by the differences in infused anions. An opposing viewpoint is that the effects of the two priming solutions at 2 min are remarkably similar in terms of dilution of $[\text{HCO}_3^-]$, despite the different compositions of the fluids. Rehm *et al.*¹¹ noted that the Stewart approach did not explain the decrease in $[\text{HCO}_3^-]$ in their hetastarch group and simple dilution of $[\text{HCO}_3^-]$.

In summary, the authors of the three articles in this issue of ANESTHESIOLOGY provide additional evidence that metabolic acidosis accompanying ECV expansion or replacement with 0.9% saline produces predictable, dose-dependent metabolic acidosis. While awaiting more definitive clarification of the actual mechanisms, the most appropriate term to describe this phenomenon is dilutional acidosis.

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