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Rapid Saline Infusion Produces Hyperchloremic Acidosis in Patients Undergoing Gynecologic Surgery

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Background: Changes in acid-base balance caused by infusion of a 0.9% saline solution during anesthesia and surgery are poorly characterized. Therefore, the authors evaluated these phenomena in a dose-response study.

Methods: Two groups of 12 patients each who were undergoing major intraabdominal gynecologic surgery were assigned randomly to receive 0.9% saline or lactated Ringer's solution in a dosage of $30 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. The pH, arterial carbon dioxide tension, and serum concentrations of sodium, potassium, chloride, lactate, and total protein were measured in 30-min intervals. The serum bicarbonate concentration was calculated using the Henderson-Hasselbalch equation and also using the Stewart approach from the strong ion difference and the amount of weak plasma acid. The strong ion difference was calculated as serum sodium + serum potassium - serum chloride - serum lactate. The amount of weak plasma acid was calculated as the serum total protein concentration in $\text{g/dl} \cdot 2.43$.

Results: Infusion of 0.9% saline, but not lactated Ringer's solution, caused a metabolic acidosis with hyperchloremia and a concomitant decrease in the strong ion difference. Calculating the serum bicarbonate concentration using the Henderson-Hasselbalch equation or the Stewart approach produced equivalent results.

Conclusions: Infusion of approximately $30 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ saline during anesthesia and surgery inevitably leads to metabolic acidosis, which is not observed after administration of

lactated Ringer's solution. The acidosis is associated with hyperchloremia. (Key words: Acid-base balance; crystalloid infusion; hyperchloremia; metabolic acidosis; Stewart approach.)

DESPITE the common practice of crystalloid infusion during surgery, few data have been published that describe acid-base changes associated with infusion of 0.9% saline. The recognition that 0.9% saline contains chloride in a nonphysiologic concentration led to the introduction of lactated Ringer's solution.¹ Only a few experimental data²⁻⁴ and some recent case reports⁵⁻⁸ exist that support the occurrence of metabolic acidosis in the course of large 0.9% saline infusions. This acidosis is still called "dilutional acidosis."⁹ All published studies are based on traditional knowledge of the acid-base balance.¹⁰ By comparing two groups of patients who received 0.9% saline or lactated Ringer's solution, we assessed the influence of crystalloid infusion on acid-base changes. We planned to compare the changes in serum bicarbonate concentration (Bic), as calculated by the Henderson-Hasselbalch equation with those calculated using the Stewart equations. Fifteen years ago, Stewart developed a mathematically derived approach to acid-base chemistry.¹¹

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Materials and Methods

We studied 24 women without apparent cardiac, pulmonary, or renal diseases (classified as American Society of Anesthesiologists physical status I or II) who were scheduled for elective lower abdominal gynecologic surgery. Written informed consent was obtained from each patient before surgery, and the protocol was approved by the ethics committee of our institution. During the study, no patient received colloids, plasma products, or blood transfusions. The patients were assigned randomly to receive either 0.9% saline (saline group, $n = 12$) or lactated Ringer's solution (Ringer's group, $n = 12$). The saline solution contained 154 mm sodium and 154 mm chloride; the lactated Ringer's solution contained 130

mm sodium, 5.4 mm potassium, 1.8 mm calcium, 112 mm chloride, and 27 mm lactate.

General anesthesia was induced with intravenous thiopental, sufentanil, and cisatracurium. After tracheal intubation, anesthesia was maintained with isoflurane, 0.4–1.5 vol% in an oxygen–nitrous oxide mixture of 1:1, and additional doses of sufentanil and cisatracurium as appropriate. Radial arterial and central venous catheters were inserted. Mechanical ventilation was performed to maintain the arterial oxygen tension (P_{aO_2}) at 250–300 mmHg and the arterial carbon dioxide pressure (P_{aCO_2}) as close as possible to 40 mmHg. Intraoperative monitoring included end-tidal P_{aCO_2} , cardiac electric activity, central venous pressure, arterial blood pressure, pulse oximetry, and esophageal temperature. During the operative period, the patient's temperature was kept constant using fluid warmers and warming blankets.

During stable anesthetic conditions and at the time of surgical incision, the investigation was started and arterial blood was withdrawn to measure baseline values (time = 0 min). The samples were analyzed for P_{aO_2} , pH, P_{aCO_2} (using standard electrodes), the concentrations of serum sodium (Na^+), potassium (K^+), chloride (Cl^-) (using ion-selective electrodes), and serum lactate (Lac^-) (using the enzymatic method, quantification of hydrogen peroxide) all integrated using a Radiometer analyzer (Radiometer ABL 620 GL; Radiometer Company, Copenhagen, Denmark). In addition, the serum total protein concentration was determined using the Biuret method. After the baseline blood samples were collected, the crystalloid infusion (0.9% saline vs. lactated Ringer's solution) was started. We planned an infusion rate of $30 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in both groups using a common infusion device. Every 30 min, new blood samples were taken, urine production and temperature were measured, and blood loss was estimated. When K^+ was less than 3.3 mm, 20 mmol potassium chloride solution, 1 M, was infused with the next infusion bottle. This was necessary in eight patients in the 0.9% saline group and in two patients in the Ringer's solution group.

For each sample, the strong ion difference (SID) was calculated as $Na^+ + K^+ - Cl^- - Lac^-$. The amount of weak plasma acid was calculated as the product of the serum total protein concentration (g/dl) and the empirically derived factor 2.43, according to van Slyke¹² and called "Prot⁻." The Bic (Bic_{HH}) and base excess (BE) were taken from the blood gas analyzer, which uses the Henderson-Hasselbalch equation and the formula of Siggaard-Andersen.¹⁰ In addition, the Bic was calculated as the difference between SID and Prot⁻ (Bic_s) using the

Table 1. Patient Characteristics

	Saline Group (n = 12)	Ringer Group (n = 12)
Age (yr)	46 ± 14	53 ± 5
Height (cm)	165 ± 7	165 ± 8
Weight (kg)	68 ± 13	77 ± 20
Body surface area (m ²)	1.79 ± 0.20	1.89 ± 0.28
Time of infusion (min)	135 ± 23	138 ± 20
Crystalloid infusion after		
120 min (ml/kg)	71 ± 14	67 ± 18
Estimated blood loss (ml)	962 ± 332	704 ± 447
Urine production (ml)	717 ± 459	1,075 ± 799

Values are mean ± standard deviation.

Stewart model. The anion gap was calculated as $Na^+ + K^+ - Cl^- - Bic_{HH}$.

Statistical Analysis

Because all measured and calculated data described before were normally distributed (according to the Kolmogorov–Smirnov test), they are presented as mean values with standard deviations. For demographic data, Student *t* tests for unpaired data were performed. Two-way repeated-measures analysis of variance compared intragroup and intergroup differences at 30, 60, 90, and 120 min of crystalloid infusion with 0 min. *Post hoc* testing was performed according to the Student–Newman–Keuls method for multiple comparisons. $P < 0.05$ was considered significant.

Results

Table 1 presents patient characteristics. There were no significant differences in weight, height, body surface area, and time of infusion. Because of differences in the duration of surgery, individual differences occurred in infusion times. The total amount of fluid infused during this time was similar and amounted to a mean of approximately 6,000 ml in both groups. Because data for all patients are only complete to 120 min of infusion time, beyond that point no mean values are presented (fig. 1). As shown in table 1, at this point, the volume of crystalloid infusion in relation to body weight also was not significantly different in either groups and was in line with our planned infusion volume (noted previously). Furthermore, there were no significant differences between the groups with respect to estimated blood loss and urine production. The hemoglobin concentration decreased from approximately 12 g/dl to 9 g/dl in both

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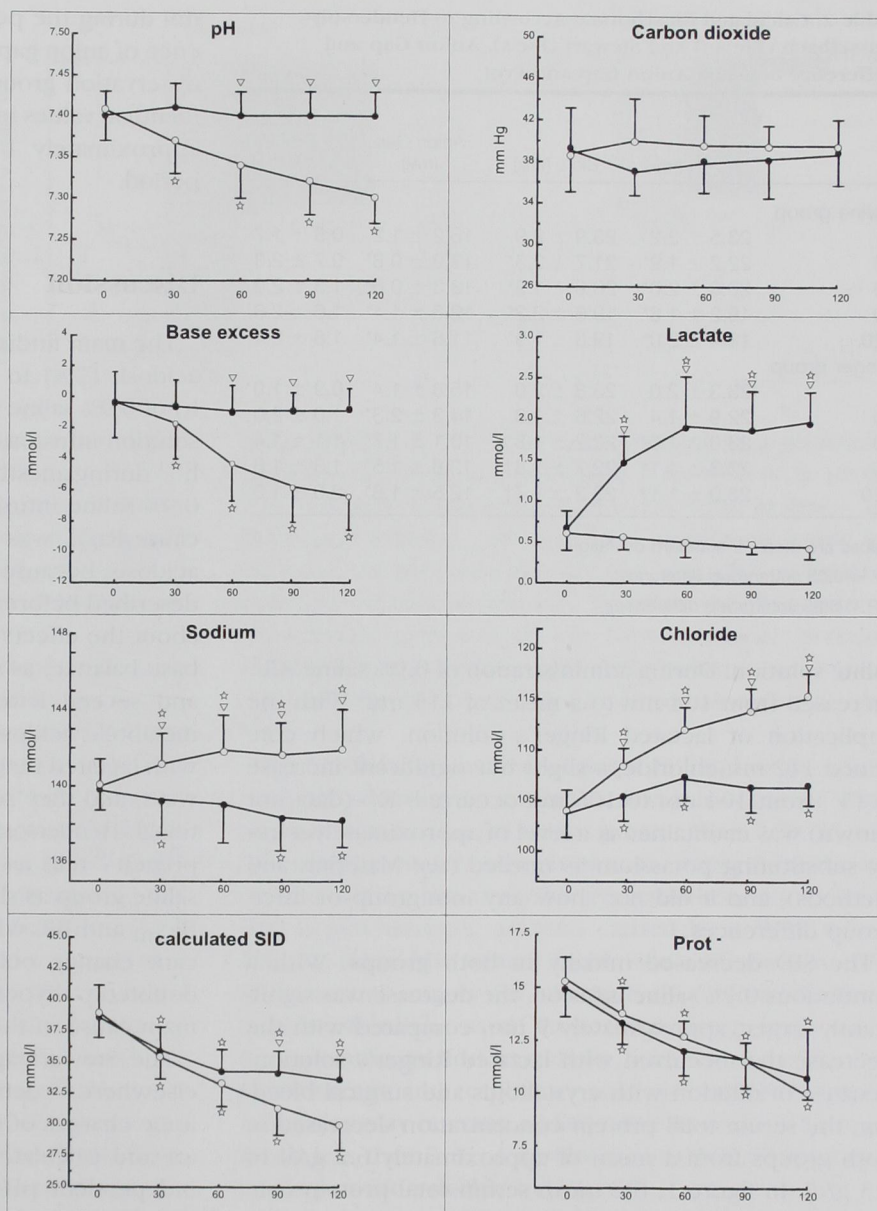


Fig. 1. Measured and calculated values (mean \pm SD) at the different measuring points. Saline group = white dots; Ringer's group = black dots. Star = intra-group differences, $P < 0.05$; triangle = intergroup differences, $P < 0.05$.

groups (intergroup comparisons, $P > 0.05$; data not shown).

In figure 1, pH, P_{aCO_2} , BE, Lac^- , Na^+ , Cl^- , SID, and $Prot^-$ are shown at the various measuring points described before. During infusion of the crystalloid solution, pH decreased significantly from 7.41 to 7.28 in the saline group. No major pH changes were observed in the patients who received Ringer's solution. In both groups, P_{aCO_2} did not show major deviations from 40 mmHg. Changes in BE were similar to changes in pH. In the saline group, starting from a control value of -0.4 mm,

BE decreased to -6.7 mm at 120 min. There were no major changes in BE in the Ringer's group. In the saline group, starting from a low level of 0.6 mm, Lac^- decreased to a mean of 0.4 mm. During the infusion of lactated Ringer's solution, Lac^- increased slightly to approximately 2 mm. Infusion of 0.9% saline solution led to a slow and continuous increase in Na^+ . There was a slight but significant decrease in Na^+ in the Ringer's group, in which the infused solution contained only 130 mm sodium. Cl^- increased in both groups, but this increase was by far larger with the application of the 0.9%

Table 2. Calculated Bicarbonate According to Henderson-Hasselbalch (Bic_{HH}) and Stewart (Bic_S), Anion Gap and Difference between Anion Gap and Prot⁻

	Bic _{HH} (mM)	Bic _S (mM)	Anion Gap (mM)	Anion Gap - Prot ⁻ (mM)
Saline group				
0	23.5 ± 2.2	23.9 ± 2.9	16.2 ± 1.2	0.8 ± 1.7
30	22.2 ± 1.9*	21.7 ± 2.3*	13.9 ± 0.8*	0.7 ± 2.3
60	20.3 ± 2.0*	20.6 ± 1.9*	13.3 ± 0.6*	1.3 ± 2.0
90	19.2 ± 1.8*	19.6 ± 2.2*	12.6 ± 1.4*	1.6 ± 2.6
120	18.4 ± 2.0*	19.3 ± 1.9*	11.8 ± 1.4*	1.8 ± 2.4
Ringer group				
0	23.3 ± 2.0	23.8 ± 2.0	15.8 ± 1.4	0.9 ± 1.0
30	22.9 ± 1.4	22.6 ± 1.8	14.3 ± 2.3*	1.0 ± 2.0
60	23.0 ± 1.6†	22.2 ± 1.8†	13.1 ± 1.7*	1.1 ± 1.4
90	23.3 ± 1.1†	22.7 ± 1.8†	12.8 ± 1.5*	1.3 ± 1.6
120	23.0 ± 1.1†	23.2 ± 1.7†	12.5 ± 1.8*	2.0 ± 1.6

Values are mean ± standard deviation.

* $P < 0.05$ (intragroup difference).

† $P < 0.05$ (intergroup difference).

saline solution. During administration of 0.9% saline, Cl⁻ increased from 104 mM to a mean of 115 mM. With the application of lactated Ringer's solution, which contained 112 mM chloride, a slight but significant increase in Cl⁻ from 104 mM to 106 mM occurred. K⁺ (data not shown) was maintained at a level of approximately 4 mM by substituting potassium as needed (see Materials and Methods), and it did not show any intragroup or intergroup differences.

The SID decreased initially in both groups. With a continuous 0.9% saline infusion, the decrease was significantly larger, approximately 9 mM, compared with the decrease that occurred with lactated Ringer's solution. Because of dilution with crystalloids and surgical bleeding, the serum total protein concentration decreased in both groups from a mean of approximately 6.2 g/dl to 4.3 g/dl. In figure 1, the mean serum total protein concentration is presented as Prot⁻ calculated with the factor 2.43, as described before. In table 2, mean values for Bic_{HH}, Bic_S, anion gap, and the difference of anion gap and Prot⁻ are shown. The mean values for Bic_{HH} and Bic_S were virtually identical in both groups. It should be noted that Bic_{HH} represents the gold standard calculation using the Henderson-Hasselbalch equation, whereas Bic_S was obtained using only Na⁺, K⁺, Cl⁻, Lac⁻, and Prot⁻. In the saline group, Bic_{HH} and Bic_S decreased from approximately 23 mM to 18 mM. No major changes in Bic_{HH} and Bic_S occurred in the Ringer's solution group. The anion gap showed similar changes in both groups, with a decrease from approximately 16 mM to 12

mM during the period of crystalloid infusion. The difference of anion gap and Prot⁻ was slightly positive in both observation groups at all measuring points, with nearly identical values in both groups and a slight increase from approximately 1 mM to 2 mM during the observation period.

Discussion

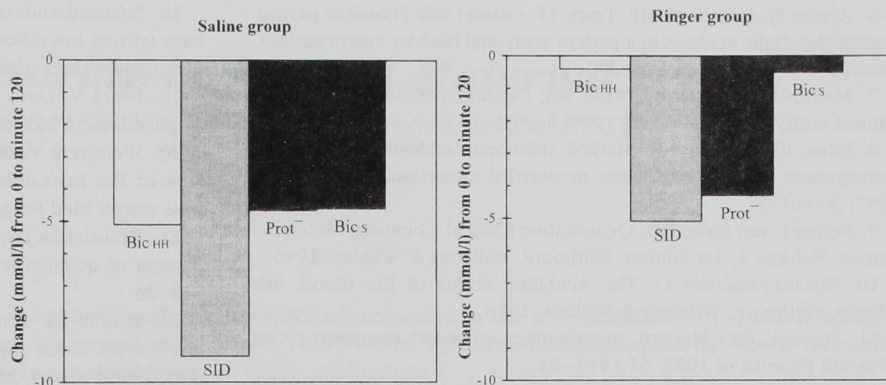
The main finding of this study was a rather impressive acidosis (7.41 to 7.28) after a relatively brief interval (2 h) of 0.9% saline infusion, but not after lactated Ringer's solution infusion at rates of approximately 35 ml · kg⁻¹ · h⁻¹ during anesthesia and surgery. This acidosis with the 0.9% saline infusion clearly had a metabolic origin, because Pa_{CO₂} was kept constant and there was no lactic acidosis, because Lac⁻ even decreased slightly. Although described before,²⁻⁴ there seems to be great uncertainty about the effects of large 0.9% saline infusions on acid-base balance, as shown by a few recent case reports⁵⁻⁸ and several letters to the editor.¹³⁻¹⁷ Our finding of metabolic acidosis associated with 0.9% saline, but not with lactated Ringer's solution, can be interpreted in two ways, and they seem to be contradictory.¹⁸ The conventional Henderson-Hasselbalch or Siggaard-Andersen approach¹⁰ tells us that metabolic acidosis occurred in the saline group as shown by constant Pa_{CO₂} and decreasing Bic_{HH} and BE, whereas in the Ringer's group no significant change occurred in the acid-base balance. Undoubtedly, hyperchloremia would be identified as the main cause of this metabolic acidosis.

The Stewart approach, which is discussed in detail elsewhere,¹⁹ defines Pa_{CO₂}, SID, and the sum of all anionic charges of weak plasma acids (called A_{tot} by Stewart and calculated in the way we calculated Prot⁻) as independent pH-regulating variables, whereas pH and the Bic are dependent variables.¹¹ The Stewart approach has been applied less commonly in the last decade. Only a few studies in exercise medicine,^{20,21} experimental medicine,²² and critical care medicine²³⁻²⁶ have used this model. In discussing this model, two methodologic aspects are important: our method of measuring lactate, and the estimation of the anionic component of weak plasma acids in conjunction with the problem of undefined cations and anions.

First, the lactate electrode incorporated in the blood gas and electrolyte analyzer used in this study measures L (+) lactate, which is the form that naturally occurs in blood. The lactated Ringer's solution used in this study

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Fig. 2. Changes in the serum bicarbonate concentration shown using the Henderson-Hasselbalch equation (Bic_{HH}) or the Stewart formula (Bic_s) and of the strong ion difference and $Prot^-$ after 120 min of 0.9% saline or lactated Ringer's solution compared with respective baseline values.



(27 mM lactate) is racemic, with L (+) lactate being the dominant fraction. Analyzing this product provided lactate values of approximately 21 mM for pure solution, approximately 12 mM for a 1:1 dilution with normal saline, and 2.5 mM for a 1:10 dilution with saline. Therefore, the values for Lac^- shown in figure 1 and used to calculate SID might be correct indeed.

Second, estimating the net anionic charges of weak plasma acids by multiplying the serum total protein concentration (g/dl) by 2.43, according to van Slyke,¹² is a simplification. Figge *et al.*^{27,28} have shown that only plasma albumin, but not the globulins, bear negative charges. The authors developed a rather complicated mathematical model to calculate the weak acid component from plasma albumin and plasma phosphate concentrations. However, Kowalchuk and Scheuermann²¹ used both ways to estimate the weak acid component in heavily exercising humans and did not find relevant differences between measured and calculated values of pH and the Bic using the van Slyke factor *versus* the Figge model. Another indication that our values for $Prot^-$ might be a reasonable estimate of the weak acid component of our patients comes from the finding that, in this study, the anion gap closely reflected changes in serum total protein concentration and therefore $Prot^-$ (table 2). The fact that throughout the study period there was only a slightly positive mean difference between the anion gap and $Prot^-$ of 1 or 2 mM in both groups also implies that there should have been a nearly equal amount of unidentified cations and anions in our patients.

Figure 2 illustrates changes in Bic_{HH} and Bic_s , and therefore in pH, in the context of SID and $Prot^-$, according to the Stewart model. Variables in figure 2 were calculated using mean values of the two groups after 120 min of crystalloid infusion time compared with the corresponding baseline values. With the 0.9% saline infu-

sion, changes in Bic were accompanied by a profound decrease in SID by approximately 9 mM and were probably attenuated by a simultaneous decrease in $Prot^-$. In the Ringer's group, SID and $Prot^-$ decreased nearly to the same amount, and the Bic was virtually unchanged with the crystalloid infusion. Whether the Henderson-Hasselbalch approach or the Stewart model is more valuable in interpreting and understanding acid-base changes resulting from crystalloid infusion can be debated.

Hyperchloremic acidosis caused by large 0.9% saline infusions seems to be benign, unless it is confused with hypoperfusion. The pH values greater than 7.20 do not seem to have major pathophysiologic implications in the clinical setting we describe. Nevertheless, we believe that hyperchloremic acidosis caused by a 0.9% saline infusion should be treated to provide a BE close to zero at the end of surgery (or, alternatively, lactated Ringer's solution should be used). In our experience in the early postoperative period, metabolic acidosis caused by hyperchloremia and respiratory acidosis caused by opiate analgesics may become additive and result in pH values much less than 7.20. A systematic analysis of this topic might provide valuable information.

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