Hyperosmotic sodium salts reverse severe hemorrhagic shock: other solutes do not

M. ROCHA E SILVA, I. T. VELASCO, R. I. NOGUEIRA DA SILVA, MARIA A. OLIVEIRA, G. A. NEGRAES, AND MARLY A. OLIVEIRA
Research Division, Heart Institute, Faculdade de Medicina, Universidade de São Paulo, 05499 São Paulo, Brazil

ROCHA E SILVA, M., I. T. VELASCO, R. I. NOGUEIRA DA SILVA, MARIA A. OLIVEIRA, G. A. NEGRAES, AND MARLY A. OLIVEIRA. *Hyperosmotic sodium salts reverse severe hemorrhagic shock: other solutes do not.* Am. J. Physiol. 253 (Heart Circ. Physiol. 22): H751–H762, 1987.—Severe hemorrhage in pentobarbital-anesthetized dogs (25 mg/kg) is reversed by intravenous NaCl (4 ml/kg, 2,400 mosmol/l, 98% long-term survival). This paper compares survival rates and hemodynamic and metabolic effects of hypertonic NaCl with sodium salts (acetate, bicarbonate, and nitrate), chlorides [lithium and tris(hydroxymethyl)aminomethane (Tris)], and nonelectrolytes (glucose, mannitol, and urea) after severe hemorrhage (44.5 ± 2.3 ml/kg blood loss). Sodium salts had higher survival rates (chloride, 100%; acetate, 72%; bicarbonate, 61%; nitrate, 55%) with normal stable arterial pressure after chloride and nitrate; near normal cardiac output after sodium chloride; normal acid-base equilibrium after all sodium salts; and normal mean circulatory filling pressure after chloride, acetate, and bicarbonate. Chlorides and nonelectrolytes produced low survival rates (glucose and lithium, 5%; mannitol, 11%; Tris, 22%; urea, 33%) with low cardiac output, low mean circulatory filling pressure, and severe metabolic acidosis. Plasma sodium, plasma bicarbonate, mean circulatory filling pressure, cardiac output, and arterial pressure correlated significantly with survival; other parameters, including plasma volume expansion or plasma osmolarity, did not. It is proposed that high plasma sodium is essential for survival.

arterial pressure; cardiac output; canine; chlorides; hemodynamics; hemorrhage; glucose; mannitol; therapy; urea

HYPERTONIC CRYSTALLOID SOLUTIONS have been used since World War I (14) as initial or accessory treatment for severe blood loss because they induce increased myocardial contractility (23), widespread precapillary dilation (6), and expanded plasma volume through an osmotic fluid shift into the vascular compartment. Hypertonic sodium chloride and bicarbonate have been used in concentrations of up to 1,800 mosmol/l (2) and glucose up to 2,500 mosmol/l (10), but positive effects were always described as transient and requiring conventional fluid replacement not long after the initial hypertonic therapy.

In 1980, however, we described results (22) showing that severely bled dogs could be permanently reversed with an intravenous bolus of very hypertonic NaCl (7.5%, equivalent to 2,400 mosmol/l, 4 ml/kg). No other treatment or intravenous fluid replacement was required to sustain the response until the animal itself restored its blood volume, at first by plasma expansion then later by red cell formation. Unpublished data from our laboratory show that the rat and the cat also recover from severe blood loss with hypertonic NaCl as sole treatment. Nakayama et al. (13), however, have shown that severely bled conscious sheep do not exhibit permanent recovery after 2,400 mosmol/l NaCl.

The basic pattern of the cardiovascular response to intravenous hypertonic NaCl includes a restoration of mean arterial pressure, cardiac output, acid-base equilibrium, and mean circulatory filling pressure to stable, near control levels in spite of the transient nature of plasma volume expansion (9, 22). Regional flows are diversely affected; muscular and cutaneous resistance vessels constrict, whereas renal, mesenteric, portal, and coronary vessels all dilate in response to hypertonic NaCl injections (18). The successful use of hypertonic solutions in human hypovolemia (1, 3) and burn shock (11) have been reported.

A number of points, however, remain unanswered; there are no data on plasma electrolyte levels, blood glucose, or plasma proteins. Plasma osmolarity patterns were described in the original paper (22), but these data were subsequently challenged (24). The transient nature of plasma volume expansion was also described, but a continuous analysis of plasma-red cell volume changes after the use of hypertonic solutions is still lacking.

Other hypertonic solutions at 2,400 mosmol/l have also been used; we (9) reported that no survival follows 50% glucose, whereas Jeffrey-Smith et al. (7) described the use of 7.2% NaCl combined to various solutes, including sodium acetate and Dextran 70. The 7.2% NaCl-6% Dextran 70 combination is striking in that it produced a sustained plasma volume expansion. The use of isolated hypertonic acetate has also been reported with results comparable to NaCl (20): mean arterial pressure ran lower, but cardiac output was higher and acid-base equilibrium correction was quicker.

The present paper describes the effects of monovalent sodium salts and chlorides, as well as nonelectrolytes, all at 2,400 mosmol/l and 4 ml/kg in severely bled dogs. Results establish common and diverse properties of these solutions and clarify a number of points regarding the mechanism of action of hypertonic solutions.

METHODS

Experiments were performed on male mongrel dogs (14–18 kg) fed on standard dog chow and water ad libitum for at least 1 wk in the divisional kennel. Food was removed 16 h before experiments but replaced with 500 ml of 10% glucose, which was in turn withdrawn, together with water, 1 h before anesthetic induction (pentobarbital sodium, 25 mg/kg, supplemented with 50–75 mg whenever necessary). A tracheal cannula was inserted, but animals were allowed to breathe spontaneously throughout the experiments. Animals were divided into two groups according to the experimental procedure.

Hemodynamics, blood gases, and biochemical determinations. The left femoral artery and vein were dissected and cannulated. The arterial cannula was connected to a Hewlett-Packard (HP) model 1280C strain-gauge transducer coupled to a HP model 4568-C galvanometric recorder. A 7-Fr Swan-Ganz catheter was inserted through a dissected left external jugular vein, and its tip was placed in a pulmonary arterial branch under radioscopic monitoring.

The experimental protocol (22) was the following. Forty minutes after the end of the surgical procedure heparin (500 U/kg) was given intravenously, and initial bleeding was carried out at a rate adjusted to reduce mean arterial pressure to 40 mmHg in 15 min. This pressure was then maintained for 30 min more by controlled bleeding or reinfusion. At the end of this interval the total volume of removed blood was noted and discarded. Each animal was then given an intravenous bolus (through a central venous catheter over a 2-min interval) of 4 ml/kg of one of nine possible hypertonic solutions. Animals were then observed for a further 180 min. Arterial pressure was monitored continuously, and cardiac output (thermal dilution; American Edwards model 9520A cardiac output computer) was measured at the start of the experiment, at the end of initial bleeding, immediately before and 5 min after hypertonic injection, then at 1-h intervals for 3 h. At these same times (except at the end of initial bleeding) arterial blood samples were collected for determination of pH and blood gases; plasma Na^+, K^+, and Cl^-; proteins and osmolarity; blood glucose; and urea. A sample of removed blood was also kept for all determinations except blood gases. Plasma volume was determined by the dye dilution (Evans blue) method (16); red cell volume was estimated through the hematocrit. At the end of the observation period survivors were decannulated, sutured, and returned to the kennel. They were offered water 6 h after hypertonic treatment and food on the following morning. Four-day survival rates were recorded. Time of death was recorded to the nearest hour over the first 6 h, then to the nearest 12 h posttreatment. The following solutions were given: *1*) NaCl at 2,400 mosmol/l (7.5%); *2*) other monovalent sodium salts at 2,400 mosmol/l, i.e., bicarbonate (10.7%), acetate (10.5%), and nitrate (10.9%); *3*) other monovalent chlorides at 2,400 mosmol/l, i.e., lithium (5.4%) and tris(hydroxymethyl)aminomethane (Tris) chloride (19.7%); and *4*) nonelectrolytes at 2,400 mosmol/l, i.e., glucose (50%), mannitol (40%), and urea (15%).

In this series, each solution was given to 12 dogs in a random blinded sequence, injections being prepared in advance and stored under a code number.

Measurement of mean circulatory filling pressure. One week before the experiment, a vessel occluder was implanted around the root of the pulmonary artery through a third intercostal space thoracotomy. Experiments were then performed as described above with the following alterations: *1*) no Swan-Ganz catheter was introduced; *2*) the left femoral artery cannula was used exclusively for bleeding; *3*) the right femoral artery and vein were cannulated with large-bore polyvinyl tubing, and these were connected to each other through a high-rate (50 ml/s) roller pump (Instituto do Coração model HC-1); the tips of these cannulas were placed in the aorta and inferior vena cava, respectively, at the approximate level of the diaphragm; *4*) a wide-bore polyvinyl cannula was introduced through the left external jugular vein with its tip in the right atrium; and *5*) the left external carotid artery was cannulated. Carotid and jugular cannulas were connected to two perfectly matched HP model 1280C strain-gauge transducers, coupled to a HP model 4568-C galvanometric photographic recorder calibrated to a gain of 1 mmHg/cm beam deflection. Hemorrhage and hypertonic administration were performed as described above. Arterial and central venous pressure were monitored continuously; mean circulatory filling pressure was determined before initial bleeding, immediately before and 10 min after hypertonic injections, and then at 1-h intervals for 3 h by occlusion of the pulmonary artery while the roller pump was activated. The intersection of arterial and central venous pressures was taken as mean circulatory filling pressure (9). All readings were obtained within 5 s of pulmonary artery occlusion. Each solution was given to six dogs in a randomized blinded sequence as described above. At the end of the 3-h observation period dogs were decannulated, removed to the kennel, and observed for 4 days. Time of death or 4-day survival were recorded as above.

Blood gas, osmolarity, and biochemical determinations. Blood gases and pH were determined in an Instrumentation Laboratory model IL-110 blood-gas analyzer. Plasma sodium and potassium were measured by flame photometry; chloride was determined colorimetrically (Labtest Clinical Diagnostic System); blood urea nitrogen and glucose were measured with Abbot Laboratories diagnostic kits; total plasma protein concentrations were determined with a Miles Laboratory Sera-Pak kit; and plasma osmolarity was measured by freezing-point depression on an Advanced Instruments osmometer. Hematocrits were measured in microhematocrit tubes. All determinations were performed blindly on code-numbered samples by the central laboratory of the hospital.

Statistical analysis. Data were processed through analysis of variance. Serially collected data were subjected to two comparisons between treatments: *1*) from prehemorrhage to the last reading before hypertonic treatment (effect of hemorrhage) and *2*) from the first to the last reading after hypertonic injection (effect of treatment). The volume of removed blood was compared between treatments and between survivors vs. nonsurvivors. Selected parameters were correlated to the survival rates

observed for the various treatments. Statistical significance levels are given in the legends of illustrations.

RESULTS

Survival. Table 1 displays the total volume of removed blood and survival rates for all groups. No statistically significant differences ($P > 0.25$) occurred for bleeding volume between different solutions nor between survivors and nonsurvivors. Survival after NaCl is significantly better than after the other three sodium salts, being the only hypertonic solute to produce 100% survival. Acetate, bicarbonate, and nitrate produced significantly lower rates (55–72%) in comparison with sodium chloride ($P < 0.05$) with no significant differences between them. Chlorides and nonelectrolytes produced much lower survival rates (5–33%) in comparison to sodium salts ($P < 0.01$) but no differences among themselves.

Hypertonic sodium salts. The effects of hypertonic sodium salts are displayed in Figs. 1–4. No differences were detected between the four groups for any of the 14 parameters before hypertonic treatment. Hypertonic sodium chloride and nitrate produced high stable levels of mean arterial pressure (Fig. 1) over the 3-h observation period; acetate promoted only a poor initial recovery of pressure, which, however, tended to improve with time. Bicarbonate, in contrast, effected a very good initial but transient recovery; at the end of the observation period bicarbonate-treated dogs had the lowest average mean arterial pressure. Cardiac output (Fig. 1) recovered initially to high comparable levels in all four hypertonic sodium groups with the best initial performance resulting from acetate. However, over the next 3 h cardiac output fell in all groups with the smallest loss occurring in NaCl treated dogs, which retained 76% of control output, compared with 48–53% for the other three sodium salts. Arterial pH and base excess showed a tendency toward metabolic acidosis during hemorrhage. This was immediately reversed by bicarbonate and acetate. Bicarbonate in fact induced intense metabolic alkalosis. Sodium chloride promoted a steady recovery toward near normality, whereas nitrate merely prevented the progress toward severe acidosis. Figure 2 displays plasma electrolytes (Na^+, K^+, Cl^-, and HCO_3^-) throughout these experiments. Hemorrhage did not affect the plasma levels of Na^+ or Cl^-, but K^+ exhibited a slight rise, whereas HCO_3^- fell sharply from a normal level of 19.5–11.7 meq/l, a clear sign of the onset of metabolic acidosis. Plasma Na^+ was increased after all four hypertonic injections, but Cl^- was raised by hypertonic sodium chloride alone. Plasma K^+ declined immediately after hypertonic injections (as a result of plasma dilution) but gradually increased back. Plasma HCO_3^- rose sharply to 34 meq/l immediately after hypertonic $NaHCO_3$ but declined gradually back to near normal levels at 3 h. Acetate produced a lesser, delayed HCO_3^- increase (12), which also returned gradually to control levels at 3 h. Sodium chloride and nitrate produced little initial impact on plasma HCO_3^-, but a gradual recovery to near normal levels ensued. Thus all four sodium salts ultimately restored normal acid-base equilibriums. Figure 3 displays plasma proteins, hematocrit, plasma, and red cell volumes. Hemorrhage diluted plasma proteins, an indication of fluid shift into the vascular compartment; this was confirmed by the fact that the sum of removed and remaining plasma volume exceeded the total initial volume. Hematocrit varied irregularly from dog to dog but on average tended to remain unchanged in response to initial bleeding. Coupled to plasma protein dilution, this was an indication of red cell recruitment that was confirmed by the fact that the sum of removed and remaining red cell volumes was also greater than the total initial volume. Resuscitation affected these parameters in a similar manner; in immediate response to treatment, plasma proteins were even further diluted, the hematocrit was reduced, and plasma volume expanded by 18 ± 4 ml/kg (no difference between groups), whereas red cell volumes remained unchanged. Over the next 3 h plasma proteins, hematocrit, and plasma volume all reverted toward preinjection levels, whereas the red cell volume still remained unchanged. There was good agreement between plasma volume determined by use of Evans blue or by the variation of plasma proteins; the latter method tended to underestimate plasma volumes by 13 ± 8%. Figure 4 illustrates blood glucose and urea, plasma osmolarity, and mean circulatory filling pressure. Glucose was increased by hemorrhage but partially reduced by hypertonic injections with no differences between treatments; urea increased throughout the experiments but exhibited a slight transient decrease immediately after treatment. Plasma osmolarity, which was increased in response to hemorrhage (mainly because of hyperglycemia), was further elevated by all four sodium salts but decreased partially over the 3-h observation period. Mean circulatory filling pressure was intensely reduced from 6.8 ± 0.4 to 2.0 ± 0.3 mmHg by hemorrhage; hypertonic sodium chloride, acetate, and bicarbonate all restored filling pressure to near normal levels in contrast to sodium nitrate, which caused a further reduction to very low levels throughout the rest of the observation period.

Hypertonic chlorides. The effects of hypertonic chlorides are shown in Figs. 5–8. No differences were detected between the three groups for control and hemorrhage

TABLE 1. *Bleeding volumes and survival rates of 162 dogs submitted to hemorrhage and hypertonic treatment*

Solute	Bleeding Volume, ml/kg	Survival Rate, %
Sodium chloride	45.3±4.9	100 (18/18)
Sodium acetate	43.2±2.6	72 (13/18)
Sodium bicarbonate	46.2±2.7	61 (11/18)
Sodium nitrate	42.7±2.5	55 (10/18)
Tris chloride	44.1±2.8	22 (4/18)
Lithium chloride	43.3±3.1	5 (1/18)
Urea	43.9±2.5	33 (6/18)
Mannitol	45.2±3.5	11 (2/18)
Glucose	43.5±3.1	5 (1/18)
Survivors ($n = 66$)	44.6±1.7	
Nonsurvivors ($n = 96$)	44.1±1.8	

Values in parentheses are survivors/total subjects. All solutes were 2,400 mosmol/l and dose was 4 mg/kg. Tris, tris(hydroxymethyl)-aminomethane.

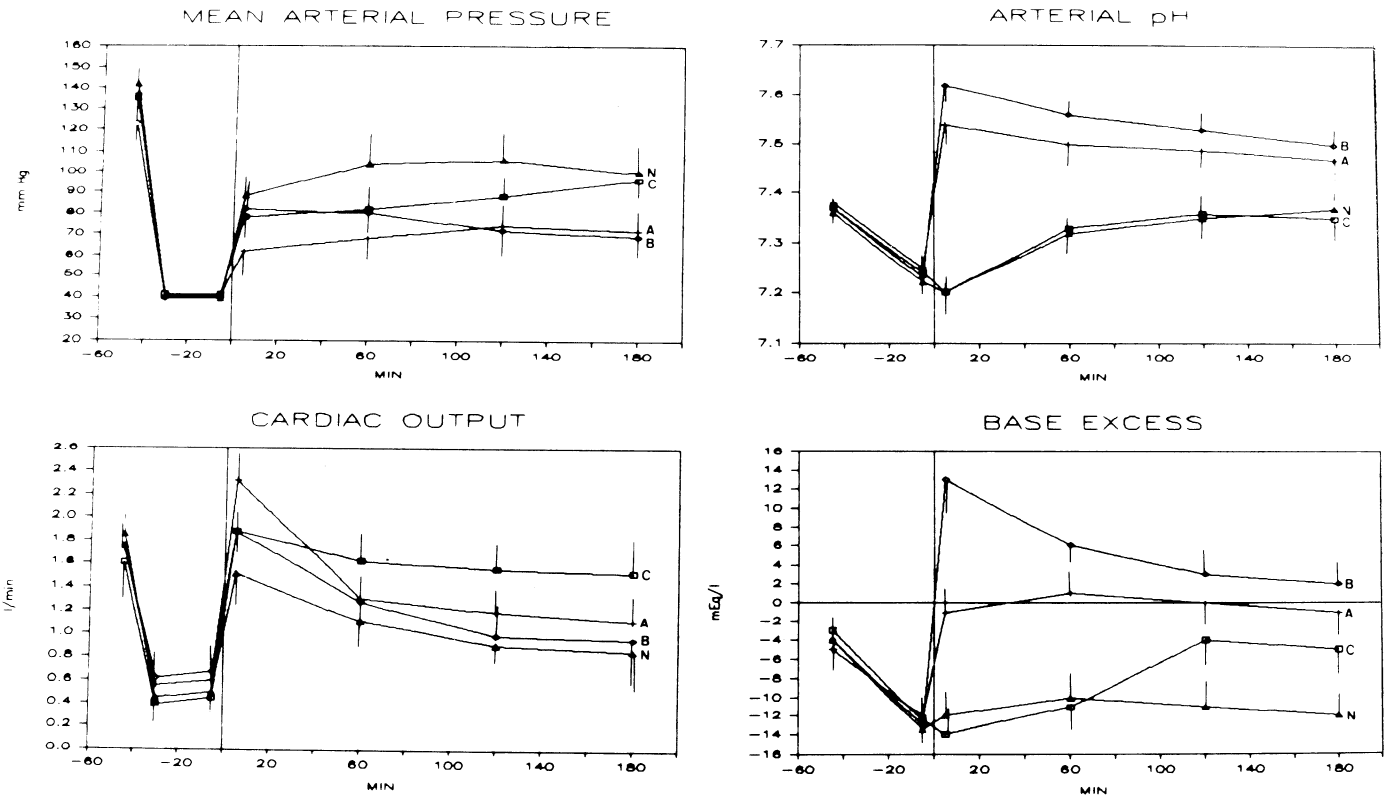

FIG. 1. Effects of hemorrhage (from −45 to 0 min) and hypertonic treatment (at zero) with sodium acetate (A), sodium bicarbonate (B), sodium chloride (C), and sodium nitrate (N) on mean arterial pressure, cardiac output, arterial pH, and base excess. Means and SE of 18 observations for each solute. Acetate produced a significantly lower arterial pressure in contrast to other solutes ($P < 0.05$); chloride produced a significantly higher output vs. other solutes ($P < 0.01$). Bicarbonate and acetate produced significantly higher ($P < 0.001$) arterial pH and base excess in contrast to chloride and nitrate.

readings. Arterial pressure (Fig. 5) was initially restored to high, comparable levels by sodium and lithium chlorides, but initial recovery after Tris was very poor. At 3 h, however, lithium-treated dogs were back to shock levels, whereas Tris had produced a steady pressure rise to near normal levels. Cardiac output showed only a partial initial recovery after lithium and Tris chlorides and even this was transient; at 3 h, output was virtually back to pretreatment levels in both groups. Arterial pH and base excess demonstrate the progression of metabolic acidosis after lithium and Tris treatment. Figure 6 displays plasma electrolyte levels. Plasma Na^+ only rose in response to NaCl treatment; lithium and Tris actually produced a fall in plasma Na^+, doubtlessly because of dilution. Plasma Cl^- rose in response to all three treatments. Plasma K^+ tended to run higher, whereas HCO_3^- was consistently lower after lithium and Tris injections. Figures 7 and 8 show that plasma proteins, hematocrit, plasma and red cell volumes, glucose, urea, and plasma osmolarity all followed similar courses after the three chlorides. Once again plasma volume determinations through Evans blue or plasma proteins give relatively similar results. Mean circulatory filling pressure, which recovered to near normal levels after sodium chloride, remained very low after lithium or Tris.

Hypertonic nonelectrolytes. Hypertonic glucose, urea, and mannitol are compared with sodium chloride in Figs. 9–12. Once again, no differences were detected between groups before treatment. Arterial pressure (Fig. 9) showed similar initial recoveries after all four solutes but only the sodium-chloride effect was sustained. Final levels after urea, glucose, and mannitol were very low. A similar observation applies to cardiac output. Arterial pH and base excess indicate a progressive metabolic acidosis after glucose and mannitol but a more stable condition after urea. Plasma electrolytes are displayed in Fig. 10. Plasma Na^+ rose in response to sodium chloride, fell slightly in response to urea, but fell intensely in response to mannitol and glucose; these effects may again be attributed to dilution. Plasma Cl^- rose after NaCl but tended to run steady after the nonelectrolytes. Plasma K^+ followed a similar course after the four treatments, but HCO_3^- allowed a differentiation; at 3 h it was practically normal in response to hypertonic sodium chloride but declined steadily after the nonelectrolytes. Figure 11 shows that the initial plasma volume expansion produced by hypertonic administration was maximal after glucose and mannitol but minimal after urea. The dilution of plasma proteins and the fall of hematocrit both confirm this observation. The very transient plasma volume expansion after hyperosmotic urea should be attributed to its high diffusion rates across membranes, which weakens its tonic pull on extravascular water. Figure 12 shows the large hyperglycemia after hypertonic glucose and the large uremia after urea; osmolarity tends to higher levels after glucose, mannitol, and urea, in that order, compared with NaCl. Mean circulatory filling pressure is only transiently recovered after glucose and mannitol, effects

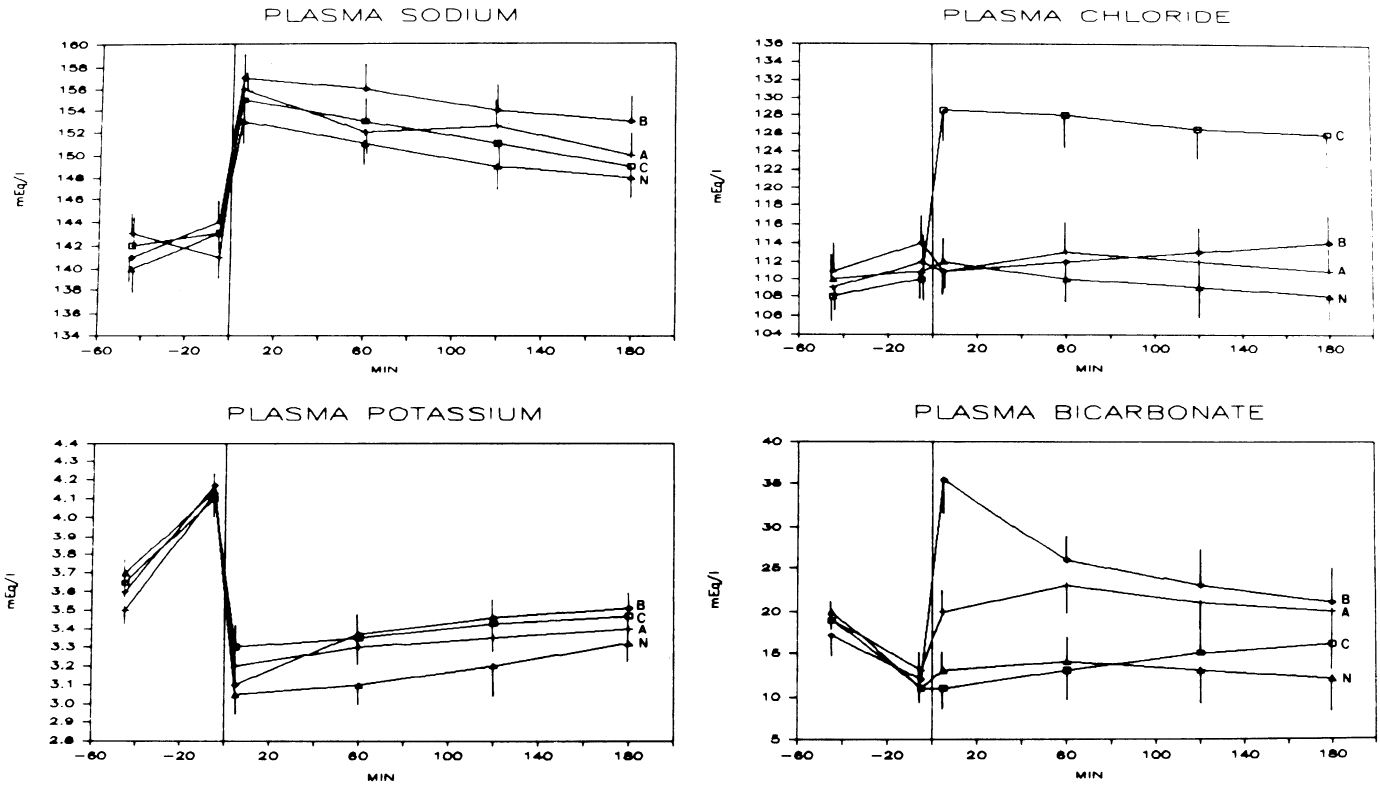

FIG. 2. Effects of hemorrhage (from −45 to 0 min) and hypertonic treatment with sodium salts (at 0 min) on plasma electrolytes. Only NaCl raises plasma Cl ($P < 0.001$ vs. other solutes), whereas bicarbonate and acetate raise plasma bicarbonate ($P < 0.001$ vs. chloride and nitrate). See Fig. 1 for conventions and abbreviations.

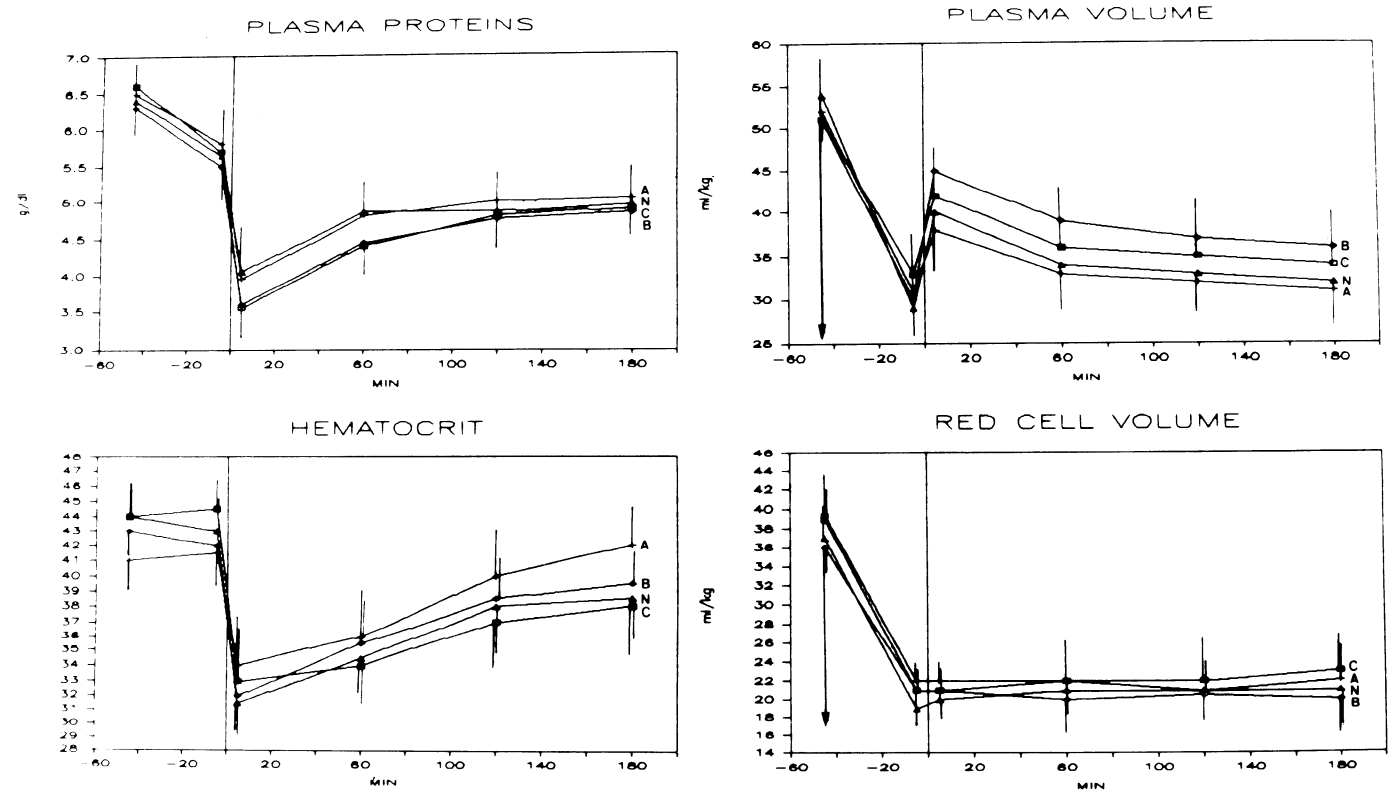

FIG. 3. Effects of hemorrhage (from −45 to 0 min) and hypertonic treatment with sodium salts (at 0 min) on plasma proteins, hematocrit, plasma, and red cell volumes. No differences occur between treatments. *Arrows* indicate the volume of plasma or red cells removed. See Fig. 1 for conventions and abbreviations.

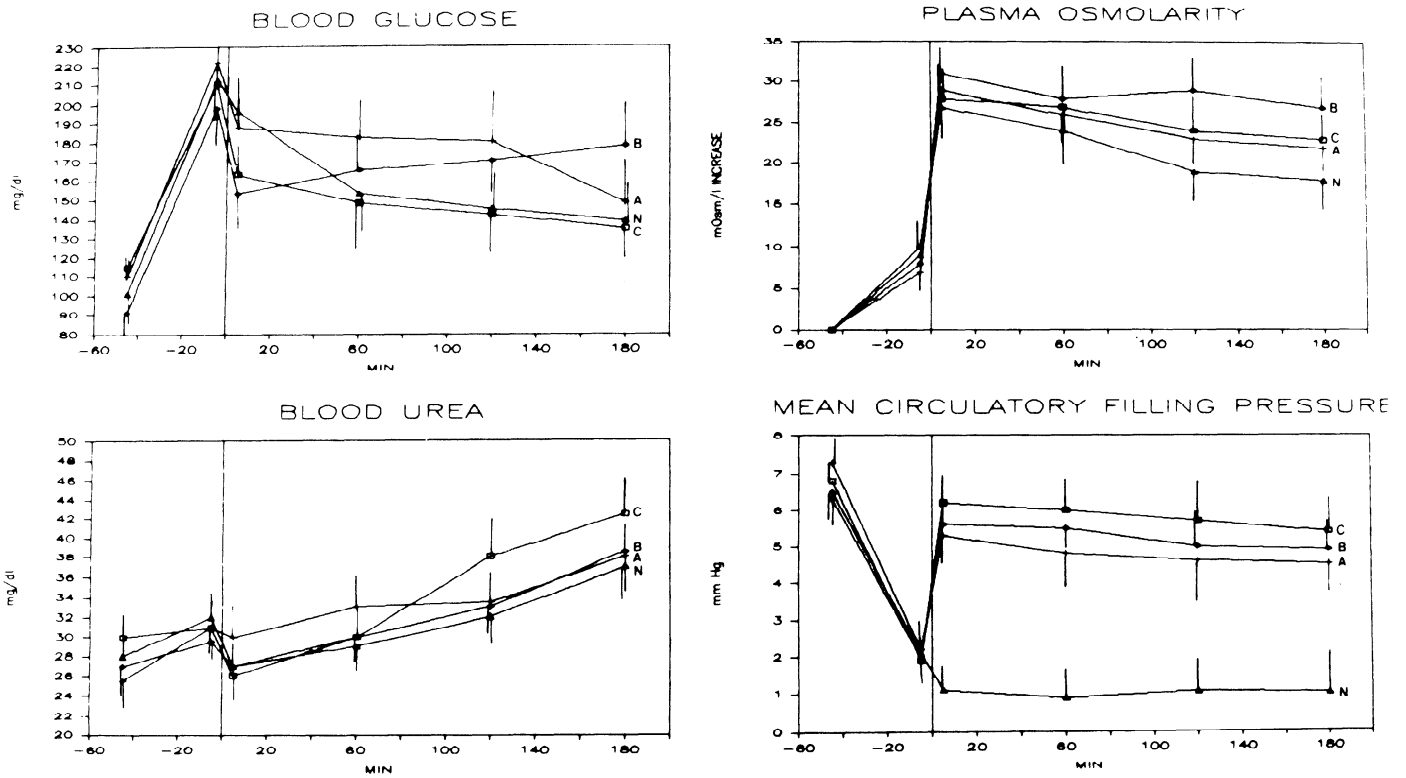

FIG. 4. Effects of hemorrhage (from −45 to 0 min) and hypertonic treatment with sodium salts (at 0 min) on plasma glucose, urea, osmolarity, and on mean circulatory filling pressure. No differences occur except for filling pressure ($P < 0.001$, nitrate vs. other solutes). Mean circulatory pressure values are from 6 observations for each solute. See Fig. 1 for conventions and abbreviations.

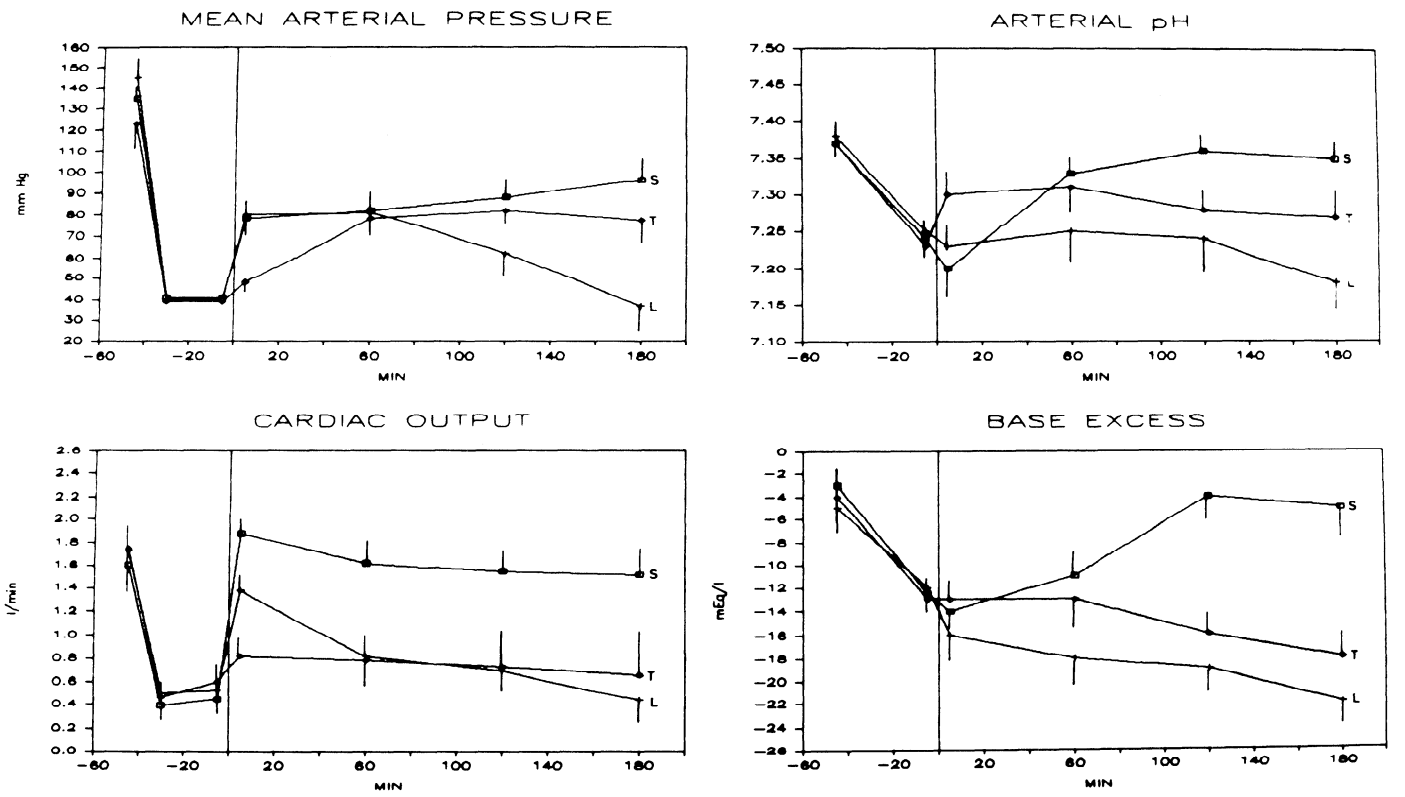

FIG. 5. Effects of hemorrhage (from −45 to 0 min) and hypertonic treatment with sodium (S), lithium (L), or tris(hydroxymethyl)aminoethane (T) chloride (at 0 time) on mean arterial pressure, cardiac output, arterial pH, and base excess. Arterial pressure for lithium chloride is significantly lower ($P < 0.05$); cardiac output and base excess for sodium chloride significantly higher ($P < 0.001$). See Fig. 1 for conventions.

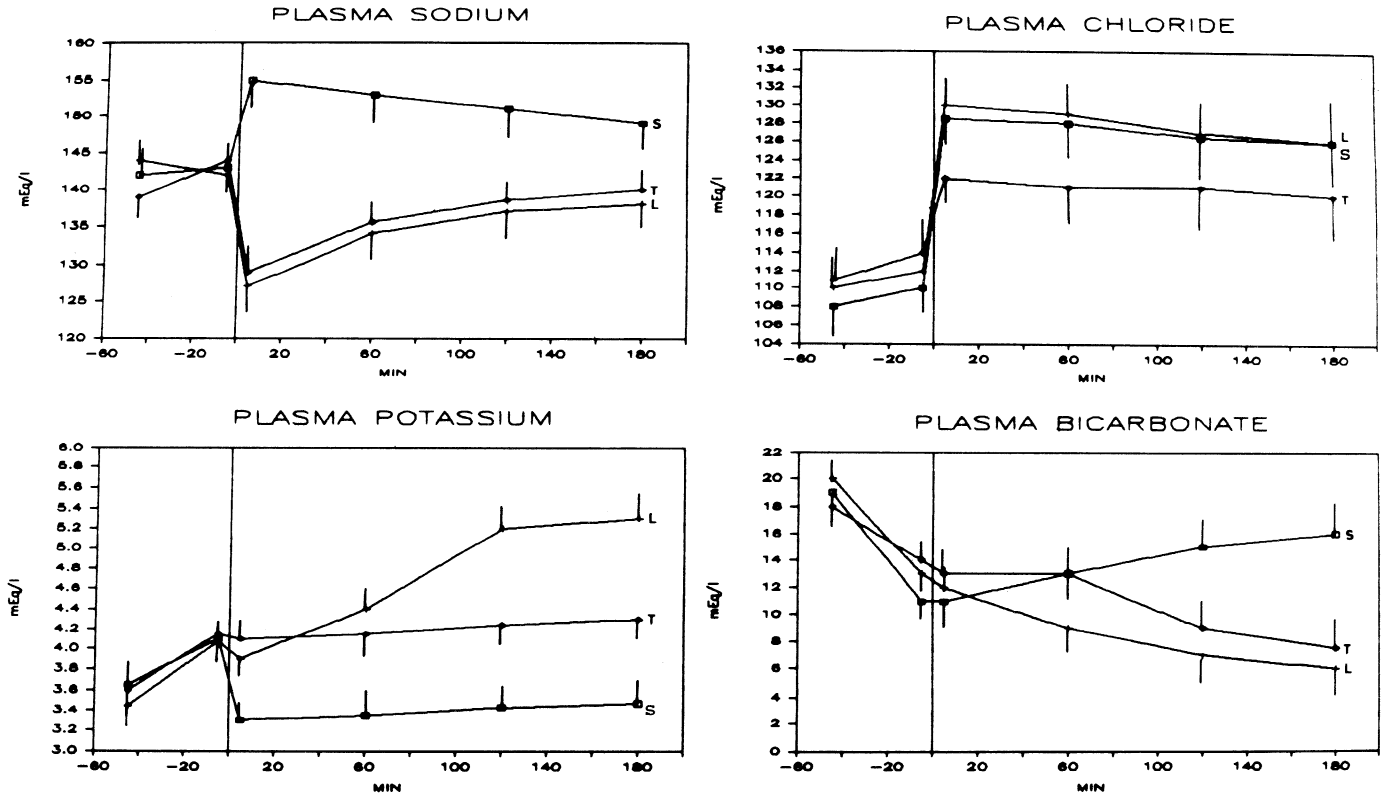

FIG. 6. Effects of hemorrhage (from −45 to 0 min) and hypertonic treatment with chlorides (at 0 min) on plasma electrolytes. Only NaCl raises Na^+ ($P < 0.001$) and restores HCO_3^- ($P < 0.01$). See Fig. 1 for conventions, Fig. 5 for abbreviations.

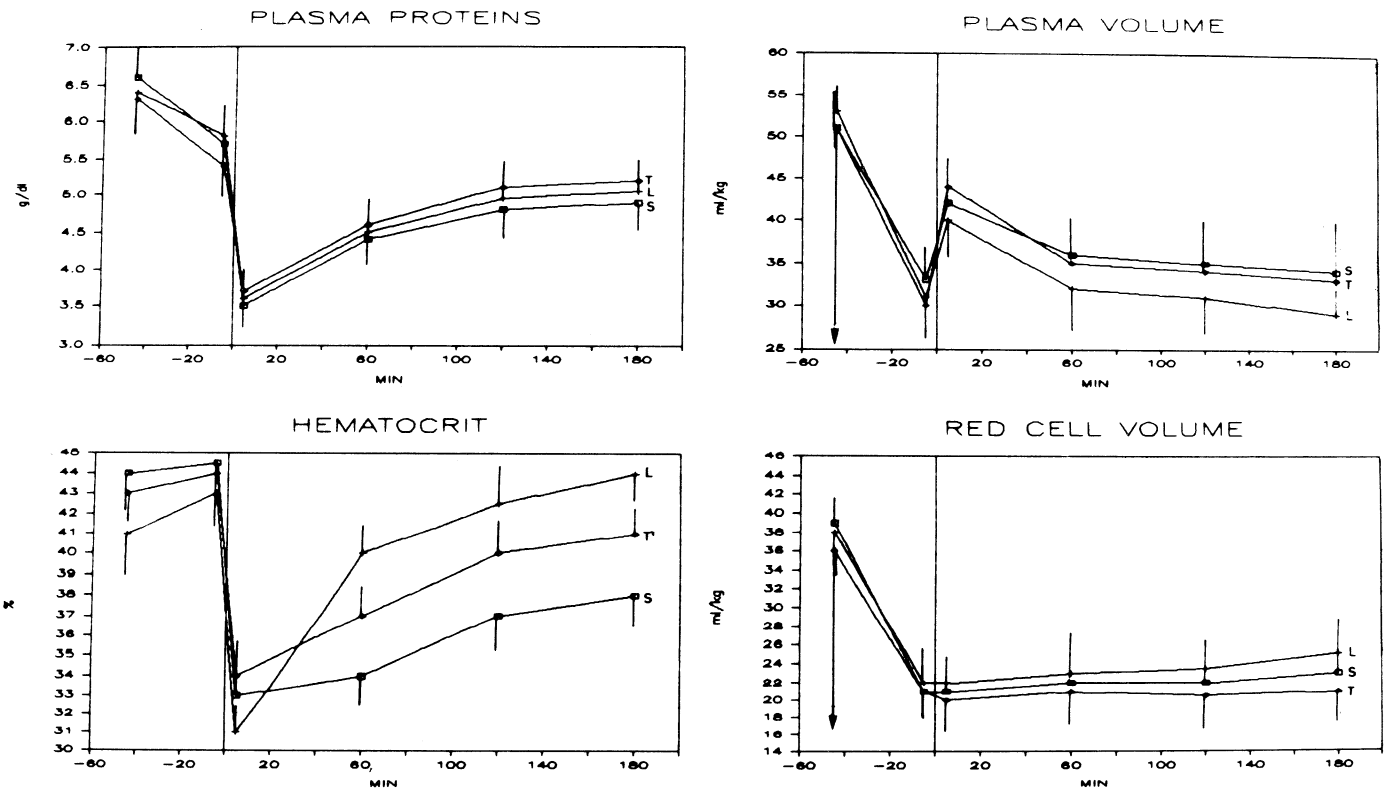

FIG. 7. Effects of hemorrhage (from −45 to 0 min) and hypertonic treatment with chlorides (at 0 min) on plasma proteins, hematocrit, and plasma and red cell volumes. No differences occur between treatments. See Figs. 1 and 3 for conventions, Fig. 5 for abbreviations.

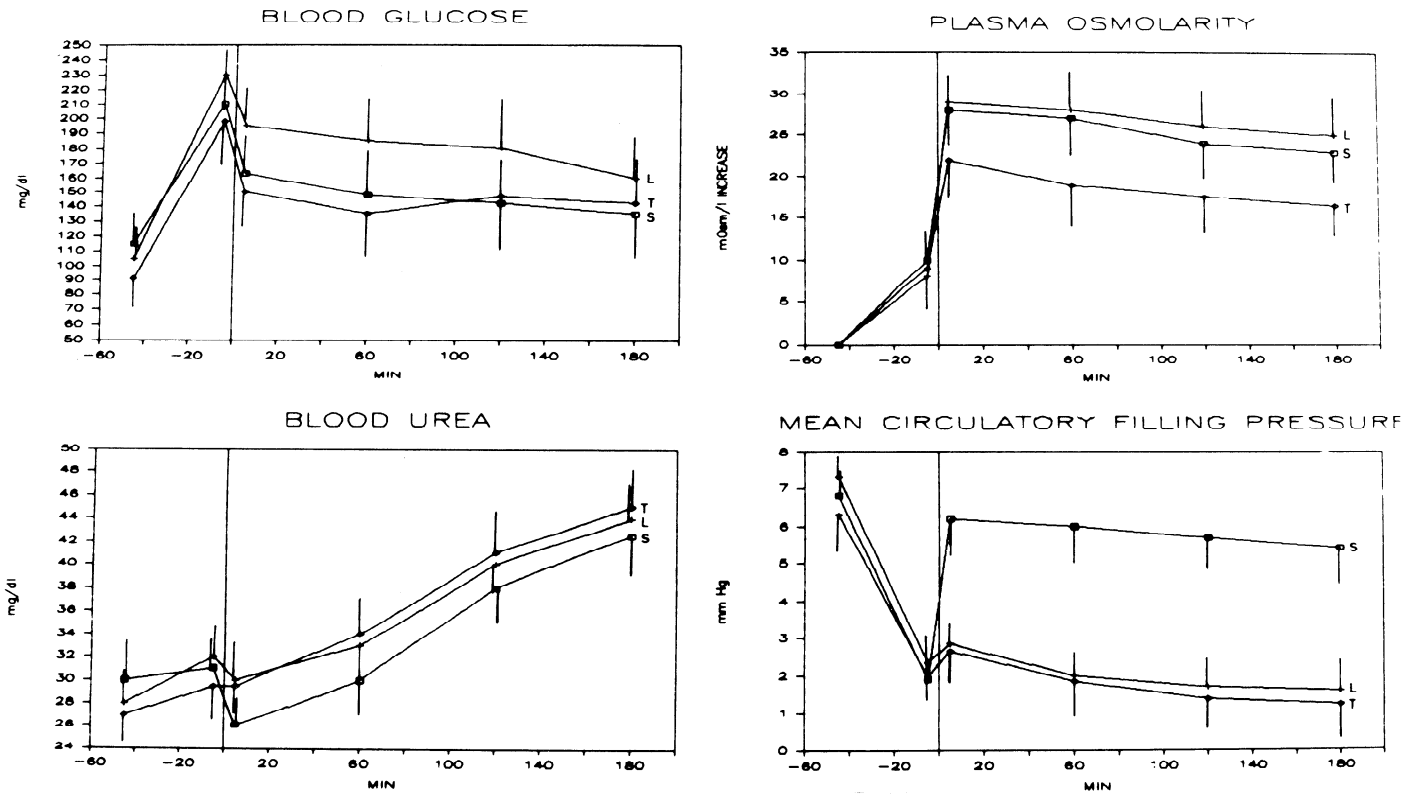

FIG. 8. Effects of hemorrhage (from −45 to 0 min) and hypertonic treatment with chlorides (at 0 min) on plasma glucose, urea, osmolarity, and mean circulatory filling pressure. Mean circulatory pressure after NaCl treatment is significantly different ($P < 0.001$) from other treatments. See Figs. 1 and 4 for conventions, Fig. 5 for abbreviations.

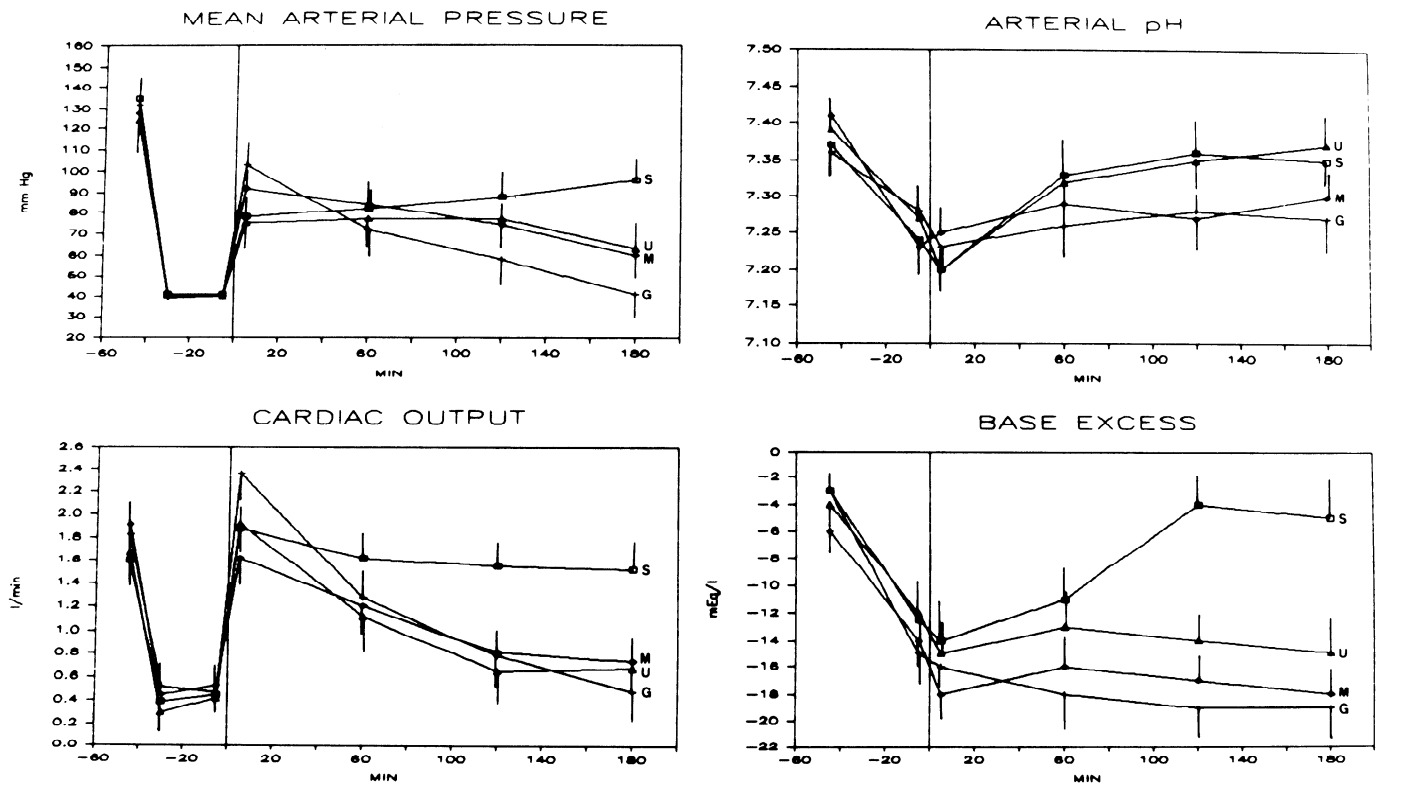

FIG. 9. Effects of hemorrhage (from −45 to 0 min) and hypertonic treatment (at 0 min) with sodium chloride (S), glucose (G), mannitol (M), or urea (U) on mean arterial pressure, cardiac output, arterial pH, and base excess. NaCl produces significantly higher levels of pressure ($P < 0.05$), output ($P < 0.001$), and base excess ($P < 0.01$). See Fig. 1 for conventions.

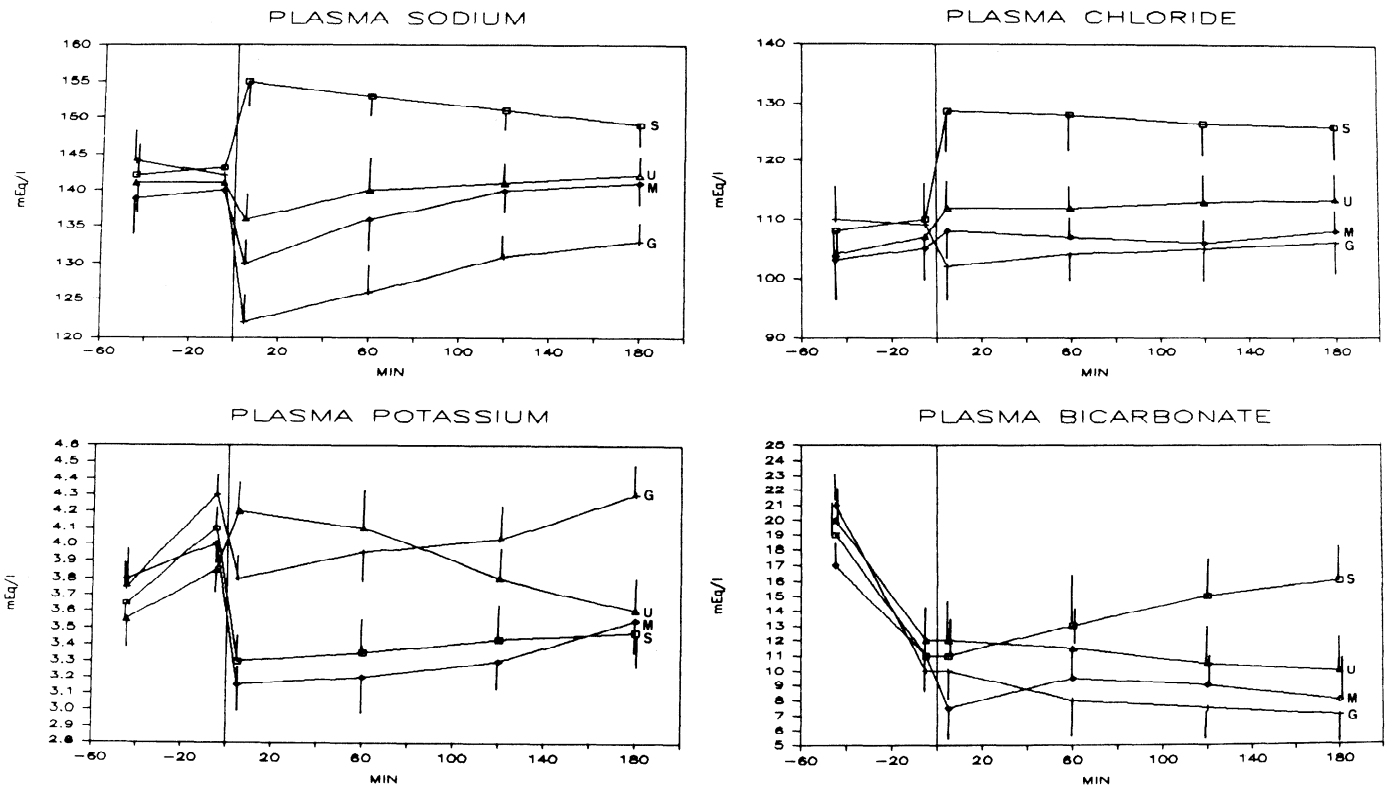

FIG. 10. Effects of hemorrhage (from −45 to 0 min) and hypertonic treatment with NaCl and nonelectrolytes (at 0 min) on plasma electrolytes. Only NaCl raises Na^+ ($P < 0.001$) and Cl^- ($P < 0.001$) or restores HCO_3^- ($P < 0.01$). See Fig. 1 for conventions, Fig. 9 for abbreviations.

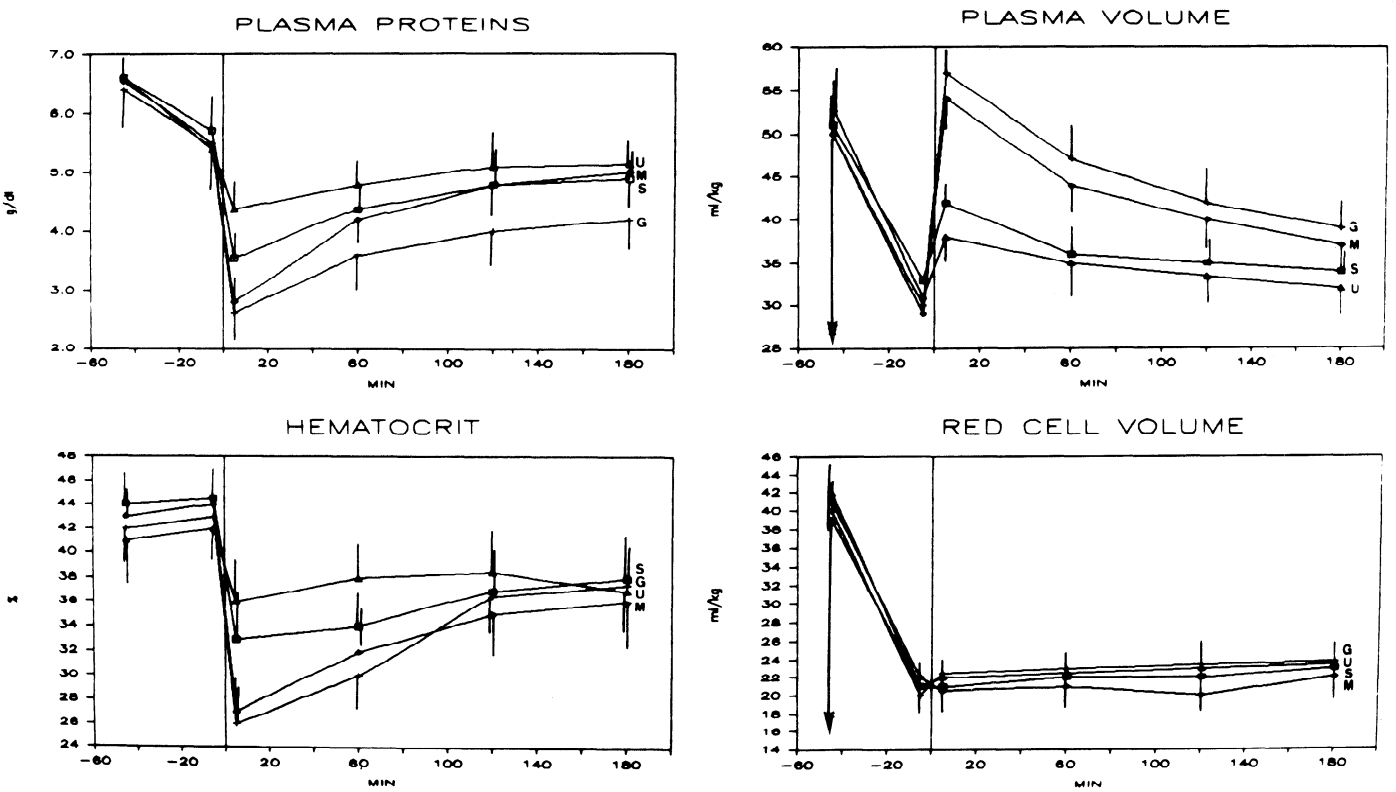

FIG. 11. Effects of hemorrhage (from −45 to 0 min) and hypertonic treatment with NaCl and nonelectrolytes (at 0 min) on plasma proteins, hematocrit, and plasma and red cell volumes. Glucose and mannitol produce significantly greater variations of all but red cell volume ($P < 0.05$). See Figs. 1 and 3 for conventions, Fig. 9 for abbreviations.

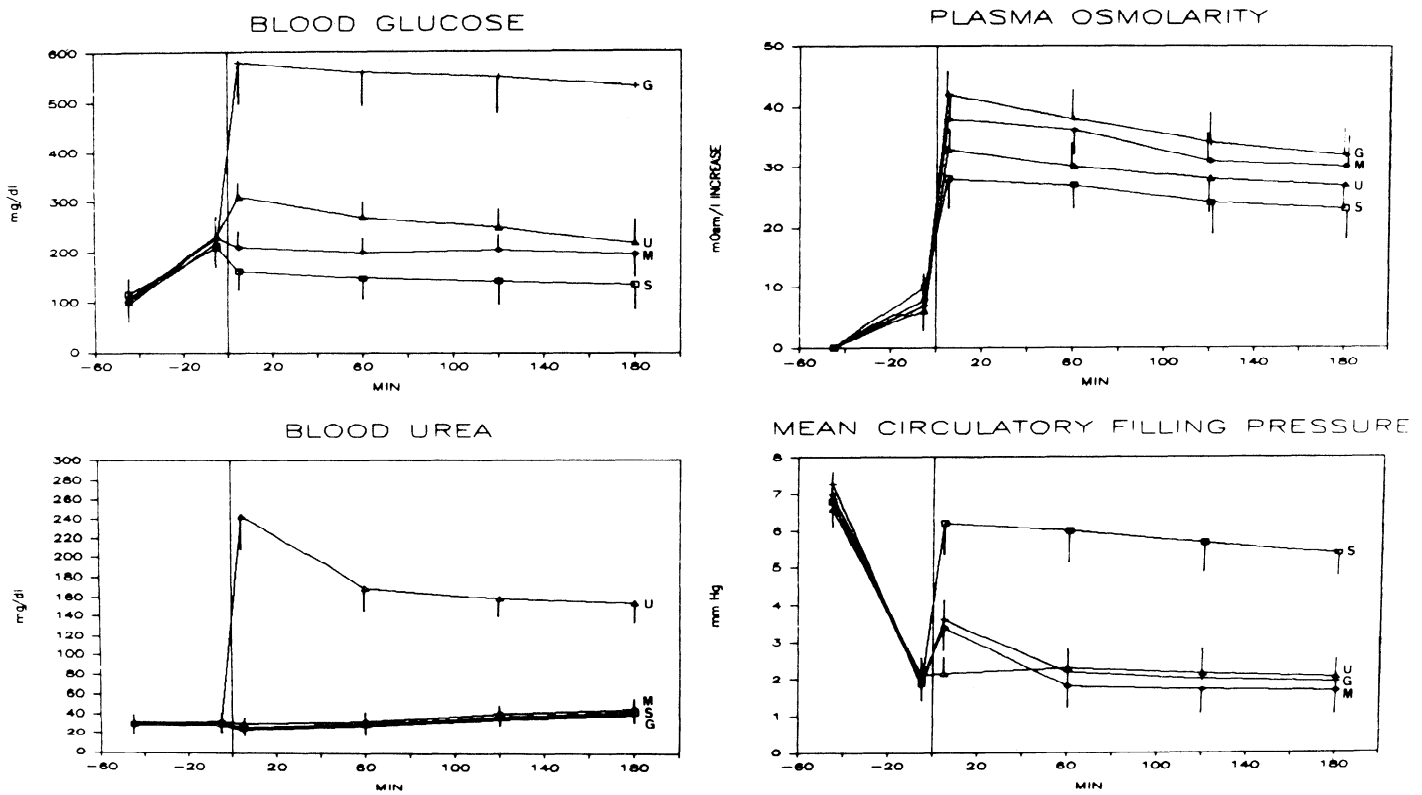

FIG. 12. Effects of hemorrhage (from −45 to 0 min) and hypertonic treatment with NaCl and nonelectrolytes (at 0 min) on plasma glucose, urea, osmolarity, and mean circulatory filling pressure. Glucose produces high plasma glucose ($P < 0.001$), urea produces high plasma urea ($P < 0.001$), all three nonelectrolytes produce higher osmolarities ($P < 0.05$ vs. NaCl), but NaCl produces higher mean circulatory filling pressure ($P < 0.001$ vs. nonelectrolytes). See Figs. 1 and 4 for conventions, Fig. 9 for abbreviations.

which may be attributed to the large volume expansion. At 3 h, filling pressure was again very low; hypertonic urea had virtually no effect on filling pressure.

Correlations. Figure 13 displays correlation coefficients between survival and some of the parameters displayed in Figs. 1–12. Correlations were calculated between survival rates for each treatment, on one hand, and "initial" (5 min) or "final" (3 h) values for each of the selected parameters, on the other. Five variables correlate with survival at a $P < 0.01$ confidence level, which are initial

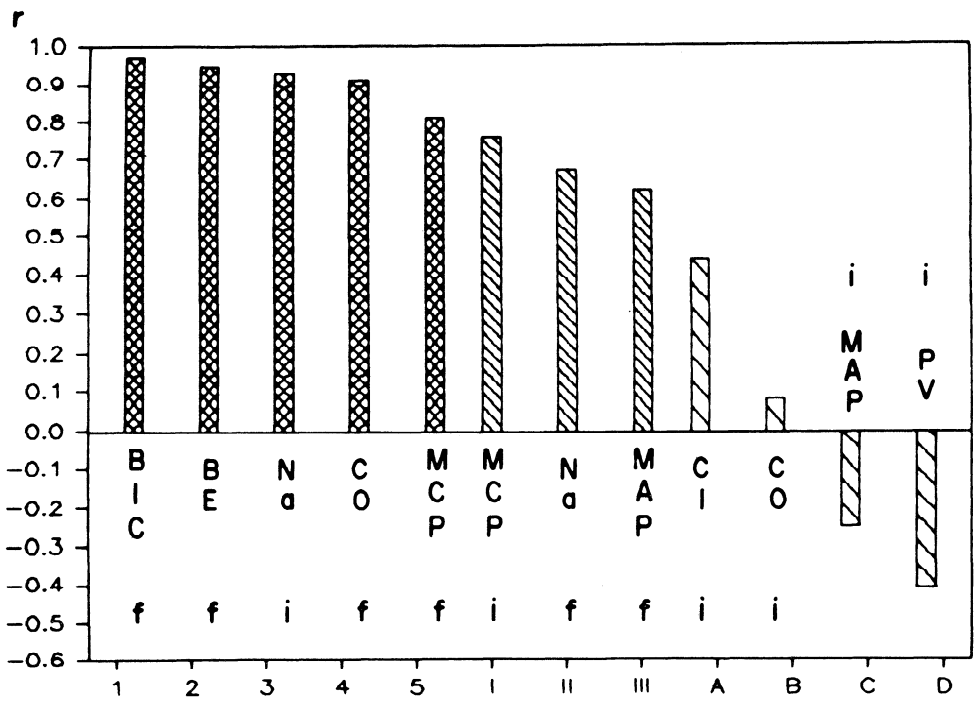

FIG. 13. Correlation coefficients (r) for selected parameters vs. long-term survival. *Bars* marked with arabic numerals exhibit a $P < 0.01$ significance level; roman numerals, $P < 0.05$; capital letters, no significant correlation; i, readings 5 min after hypertonic treatment; f, readings 3 h after treatment; BIC, Na, and Cl refer to respective plasma levels; CO, cardiac output; BE, base excess; MCP, mean circulatory filling pressure; MAP, mean arterial pressure; PV, plasma volume.

plasma Na, final plasma bicarbonate, base excess, cardiac output, and mean circulatory filling pressure. Three other parameters correlate at a $P < 0.05$ confidence level, which are initial mean circulatory filling pressure, final plasma sodium, and mean arterial pressure. Other parameters do not correlate; initial plasma volume actually came close to correlating negatively with survival.

DISCUSSION

In 1980, we reported (22) that severe hemorrhage in dogs can be reversed with indefinite survival by a small volume bolus of 7.5% NaCl. Later, we suggested (8) the existence of a reflex, starting from unidentified pulmonary receptors and running through the vagus, which was essential for survival. We also showed (9) that widespread venoconstriction, restoring mean circulatory filling pressure to normal levels, is also associated with survival and also requires intact vagal activity at the time of injection. The concept of a pulmonary-vagal reflex, critical for survival, has been confirmed by Younes et al. (24), who used dogs with unilaterally denervated lungs. In this preparation, hypertonic NaCl permanently restores normal circulatory function if given into the pulmonary artery to the innervated lung but is totally ineffective to the denervated side. Unpublished data from our laboratory suggest that a reflex also operates in the rat and cat, both of which can be reversed from severe blood loss with 7.5% NaCl as sole treatment. Nakayama et al. (13), however, have shown that conscious hypovolemic sheep do not exhibit permanent recovery after 2,400 mosmol/l NaCl, and this may mean that no pulmonary reflex operates in this species at this salt concentration.

The survival rates observed for the nine 2,400-mosmol/l solutes correlate with a limited set of parameters, which are plasma sodium and bicarbonate, base excess, cardiac output, mean arterial pressure, and mean circulatory filling pressure. However, we believe that significance must be attached to the fact that only plasma sodium and mean circulatory filling pressure correlate with survival immediately after treatment. Bicarbonate, cardiac output, and arterial pressure, which also correlate with survival, do so only 3 h after hypertonic injections. It may therefore be assumed that high plasma sodium and restored mean filling pressure are causal factors of survival, whereas the restoration of bicarbonate, cardiac output, and arterial pressure are more likely to be consequences of high sodium and normal filling pressure. In any case, it may be confidently stated that high sodium levels and normal mean circulatory filling pressure are the earliest reliable predictors of successful restoration of circulatory function. It is an established fact that sodium strongly influences the circulatory patterns observed in hypovolemia (4, 5, 21), but in the present context, the positive correlation clearly indicates that highly concentrated sodium ions, not merely hyperosmolarity, is essential for survival. There is an important quantitative difference between survival after sodium salts (>55%) or after the other solutes (<33%); in contrast, initial plasma volume came close to a significant negative correlation with survival. We have recently reported evidence indicating that the four sodium salts (2,400 mosmol/l, 4 ml/kg) actively trigger long lasting (3–15 min) saturating activity in pulmonary vagal afferents of anesthetized rats; in contrast, lithium and Tris chlorides as well as the nonelectrolytes were incapable of generating any comparable activity (17). These data confirm and extend a previous observation (15) obtained in single-fiber preparations of C-fiber pulmonary afferents of dogs treated with hypertonic NaCl. We therefore propose that highly concentrated sodium ions fire pulmonary receptors that induce venoconstriction (9) and selective muscular and cutaneous precapillary constriction (18) and that these combined effects restore cardiac output and normal metabolic exchanges in the continued presence of severe hypovolemia.

A number of differences were found in particular parameters among the four sodium salts. The most obviously important one relates to the inability of sodium nitrate to restore mean circulatory filling pressure, a predictable result, because nitrate is a powerful venodilator. It is not easy to reconcile venodilation with the relatively high survival (55%) produced by nitrate, but nitrate might conceivably evoke very intense muscular and cutaneous precapillary constriction and thus effectively shut out these territories, whereas renal and splanchnic circulations dilated. This idea is supported by the high pressure and low cardiac output found in nitrate-treated dogs, but regional flow measurements would be required to clarify the point.

A second important point relates to the reversal of metabolic acidosis. It could be anticipated that bicarbonate and acetate would efficiently correct metabolic acidosis, whereas nitrate and chloride might momentarily aggravate the condition. Both predictions were confirmed, but acetate turned out to be the best corrector of acidosis because of its gradual conversion to bicarbonate (12). Direct administration of bicarbonate produced an undesirable overshoot of plasma bicarbonate with potentially negative effects on respiration.

Cardiac output was very effectively corrected, immediately after treatment, by all the solutes, except Tris chloride. This correction must be attributed to the transient osmotic plasma volume expansion; glucose, and mannitol, the most impermeant molecules, induced maximal fluid shift and high initial levels of cardiac output and mean arterial pressure. Urea, with its low tonic activity, induced poor volume expansion but a relatively high initial level of output; in this case, however, there was no important initial pressure recovery, so that high output may have been caused by widespread arteriolar constriction. Regional flow should be measured to clarify this point. The salts were all very similar in their plasma expanding properties, but acetate and Tris produced very low initial pressures. Acetate is a well-known vasodilator agent and, in its case, low pressure associated to high output; Tris, however, produced low levels both of arterial pressure and cardiac output, no explanation being available at present. In the long run, cardiac output was only maintained at adequate levels by the sodium salts with chloride producing the best and nitrate the worst performance, in exact agreement with survival rate rankings.

The hyperglycemic response to blood loss has been associated to the increase in sympathetic activity (19). In these experiments, it was always observed before treatment. With the obvious exception of hypertonic glucose, hypertonic injections reversed the upward trend of glycemia, on account of the reversal of hypotension and output toward normal levels. Urea exhibited a continuous rise from start to finish, which was momentarily interrupted by hypertonic treatment (except of course when the injected solute was urea). Plasma potassium exhibited an almost identical pattern; it therefore appears that there may be impairment of renal function after treatment, a point that deserves further investigation. Finally, plasma chlorides rise to a plateau in response to hypertonic chlorides, but remain stable after the other solutes, and are unaffected by dilution.

In summary, we have demonstrated that reversal of severe hemorrhagic shock by small-volume hypertonic injections is dependent on the action of concentrated sodium ions, a result that conforms with data obtained by direct recordings of vagal activity after hypertonic injections. These results are consistent with the operation of a vagal pulmonary reflex triggered by high concentrations of sodium ions. The main effects of this reflex would be selective blood flow restriction to muscular territories (18) and widespread venoconstriction (9), both of which could be essential for restoring normal circulatory supply to critically endangered viscera.

This research was supported by grants from FINEP, FAPESP, and the E. J. Zerbini Foundation.

Received 22 September 1986; accepted in final form 12 May 1987.

REFERENCES

1. AULER, J. O. C., JR., M. H. C. PEREIRA, M. ROCHA E SILVA, A. D. JATENE, AND F. PILEGGI. Hemodynamic effects of hypertonic NaCl during surgical treatment of aortic aneurisms (Abstract). *Circ. Shock* 19: 94, 1985.
2. BAUE, A. E., E. T. TRAGUS, AND W. M. PARKINS. Effects of sodium chloride and bicarbonate in shock with metabolic acidosis. *Am. J. Physiol.* 212: 54–60, 1967.
3. DE FELIPPE, J., JR., J. TIMONER, I. T. VELASCO, O. U. LOPES, AND M. ROCHA E SILVA. Treatment of refractory hypovolemic shock by 7.5% sodium chloride injections. *Lancet* 2: 1002–1004, 1980.
4. FULTON, R. L. The adsorption of sodium and water by collagen during hemorrhagic shock. *Ann. Surg.* 172: 861–869, 1970.
5. FULTON, R. L., AND E. T. PETER. Metabolic and physiologic effects of sodium in the treatment of hemorrhagic shock. *Am. J. Surg.* 40: 152–160, 1974.
6. GAZITUA, S., J. B. SCOTT, B. SWINDALL, AND F. J. HADDY. Resistance responses to local changes in plasma osmolarity in three vascular beds. *Am. J. Physiol.* 220: 384–391, 1971.
7. JEFFREY-SMITH, G., G. C. KRAMER, P. PERRON, S. I. NAKAYAMA, R. A. GUNTHER, AND J. W. HOLCROFT. A comparison of several hypertonic solutions for resuscitation of bled sheep. *J. Surg. Res.* 39: 517–528, 1985.
8. LOPES, O. U., V. PONTIERI, M. ROCHA E SILVA, AND I. T. VELASCO. Hypertonic NaCl and severe hemorrhagic shock. Role of the innervated lung. *Am. J. Physiol.* 241 (*Heart Circ. Physiol.* 10): H883–H890, 1981.
9. LOPES, O. U., I. T. VELASCO, P. G. GUERTZENSTEIN, M. ROCHA E SILVA, AND V. PONTIERI. Hypertonic NaCl restores mean circulatory filling pressure in severely hypovolemic dogs. *Hypertension Dallas* 8, *Suppl.* I: I-195–I-199, 1986.
10. MCNAMARA, J. J., M. D. MOLOT, R. A. DUNN, AND J. F. STREMPLE. Effect of hypertonic glucose in hypovolemic shock in man. *Ann. Surg.* 176: 176–250, 1972.
11. MONAFO, W. W. The treatment of burn shock by intravenous and oral administration of hypertonic lactated saline solution. *J. Trauma* 10: 575–586, 1970.
12. MUDGE, G. H., J. A. MANNING, AND A. GIMAN. Sodium acetate as source of fixed base. *Proc. Soc. Exp. Biol. Med.* 71: 136–141, 1949.
13. NAKAYAMA, S., L. SIBLEY, R. A. GUNTHER, J. W. HOLCROFT, AND G. C. KRAMER. Small-volume resuscitation with hypertonic saline (2,400 mOsm/liter) during hemorrhagic shock. *Circ. Shock* 13: 149–159, 1984.
14. PENFIELD, W. G. The treatment of severe and progressive hemorrhage by intravenous injections. *Am. J. Physiol.* 48: 121–128, 1919.
15. PISARRI, T. E., A. JONZON, H. M. CLERIDGE, AND J. C. G. COLERIDGE. Pulmonary vagal afferents stimulated by arterial injection of hypertonic saline (Abstract). *Physiologist* 28: 305, 1985.
16. REEVE, E. B., M. I. GREGERSEN, T. H. ALLEN, AND H. SEAR. Distribution of cells and plasma in the normal and splenectomized dog and its influence on blood volume estimates with P^{32} and T-1824. *Am. J. Physiol.* 175: 195–203, 1953.
17. ROCHA E SILVA, M., E. M. KRIEGER, E. D. MOREIRA, AND R. I. NOGUEIRA DA SILVA. The effect of intravenous hypertonic injections (2400 mOsm/l) on afferent vagal activity of rats (Abstract). *Braz. J. Med. Biol. Res.* 19: 499A, 1986.
18. ROCHA E SILVA, M., G. A. NEGRAES, A. M. SOARES, V. PONTIERI, AND L. LOPPNOW. Hypertonic resuscitation from severe hemorrhagic shock: patterns of regional circulation. *Circ. Shock* 19: 165–175, 1986.
19. RUNCIMAN, W. B., AND G. A. SKOWRONSKI. Pathophysiology of hemorrhagic shock. *Anesth. Intensive Care* 12: 193–205, 1984.
20. SARAGOÇA, M. A., R. A. MULINARI, A. M. A. BESSA, S. A. DRAIBE, AND O. L. RAMOS. Hemodynamic and metabolic effects of hypertonic sodium acetate and chloride in severe hemorrhagic shock (Abstract). *Circ. Shock* 18: 339, 1986.
21. SLONIM, M., AND W. M. STAHL. Sodium and water content of connective tissue versus cellular tissue following hemorrhage. *Surg. Forum* 19: 53–58, 1968.
22. VELASCO, I. T., V. PONTIERI, M. ROCHA E SILVA, AND O. U. LOPES. Hypertonic NaCl and severe hemorrhagic shock. *Am. J. Physiol.* 239 (*Heart Circ. Physiol.* 8): H664–H673, 1980.
23. WILDENTHAL, K., D. S. MIERZWIAK, AND J. H. MITCHELL. Acute effects of increased serum osmolarity on left ventricular performance. *Am. J. Physiol.* 216: 898–904, 1969.
24. YOUNES, R. N., F. AUN, R. M. TOMIDA, AND D. BIROLINI. The role of lung innervation in the hemodynamic response to hypertonic sodium chloride solutions in hemorrhagic shock. *Surgery* 98: 900–906, 1985.