Hyperosmotic NaCl and severe hemorrhagic shock

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VELASCO, I. T., V. PONTIERI, M. ROCHA E SILVA, JR., AND O. U. LOPES. *Hyperosmotic NaCl and severe hemorrhagic shock.* Am. J. Physiol. 239 (Heart Circ. Physiol. 8): H664–H673, 1980.—Intravenous infusions of highly concentrated NaCl (2,400 mosmol/l; infused volume 4 ml/kg, equivalent to 10% of shed blood), given to lightly anesthetized dogs in severe hemorrhagic shock, rapidly restore blood pressure and acid base equilibrium toward normality. No appreciable plasma volume expansion occurs for at least 12 h, indicating that fluid shift into the vascular bed plays no essential role in this response. Initial effects were sustained indefinitely: long term survival was 100%, compared to 0% for a similar group of controls treated with saline. Hemodynamic analysis of the effects of hyperosmotic NaCl showed that these infusions substantially increase mean and pulse arterial pressure, cardiac output and mesenteric flow, whereas heart rate was slightly diminished. These effects immediately follow infusions with no tendency to dissipate with time (6-h observation). We conclude that hyperosmotic NaCl infusions increase the dynamic efficiency of the circulatory system, enabling it to adequately handle oxygen supply and metabolite clearance, despite a critical reduction of blood volume.

hypovolemic shock; hyperosmotic solutions; survival; cardiac output; mesenteric flow; acid base equilibrium; capacitance vessels; shock therapy

INTRAVENOUS INFUSIONS of sodium salts have been known for at least 60 yr to produce beneficial effects in the treatment of patients with hemorrhagic shock (25), but the mechanisms underlying this response are still poorly understood. It has been suggested that shock reduces the total functional sodium pool (7, 24) because of adsorption of sodium ions to collagen (7, 29). However, it is agreed that hyperosmotic infusions (electrolyte or nonelectrolyte) increase myocardial contractility, as well as myocardial stiffness, both in vivo (23, 32, 33) and in vitro (16, 21). It is also accepted that increased osmolarity induces a widespread precapillary dilation (9, 19, 20), but the intensity and persistence of this response varies widely as a function of the infused solute or of the perfused region (10). This vasodilator response is independent of intact nervous supply (9) and has been confirmed in vitro on isolated portal vein strips, which exhibit characteristics of precapillary vessels (15).

A fourth frequently suggested explanation for the beneficial effects of hyperosmolarity in the treatment of shock is compartmental redistribution, with fluid shift into the vascular bed and consequent plasma expansion (2, 5, 22). It must be noted however that direct proof of its occurrence, after hyperosmotic shock treatment, has never been produced. The exploration is merely based on analogical inference: it is known that shock increases blood sugar concentrations (3), and this in turn is the major cause of the increased plasma osmolarity that follows severe blood loss. In recent years Jarhult et al. (13, 14) elegantly showed that this increase in plasma osmolarity is largely if not solely responsible for the so-called internal transfusion (6) that occurs during the early stages of shock.

Because of these established or presumed properties, hyperosmotic solutions have been widely tested both experimentally and clinically as interim or adjuvant treatment for severe blood loss (1, 2, 4, 8, 22). Published reports cover a variety of infused solutes (glucose, mannitol, NaCl, $NaHCO_3$) over a wide range of volumes (3–46 ml/kg) at variable osmotic strengths (600–1,800 mosmol/l). Such infusions increase mean and pulse arterial pressure, cardiac output, mesenteric flow, and oxygen consumption, whereas they reduce vascular resistance. For the acid-base equilibrium, effects are reportedly dependent on the infused solute: $NaHCO_3$ corrects acidosis, whereas NaCl aggravates it (1, 2). The reversal of shock produced by hyperosmotic infusions alone is invariably described as transient. Consequently in all clinical trials and in practically all experimental tests, such infusions are followed by replacement of lost or removed blood with permanent reversal of shock in a high percentage of cases.

The present report examines the effects of small volumes of highly concentrated NaCl infusions used as sole treatment for severe blood loss in dogs. We find that such infusions induce complete and permanent reversal of shock; we also find that fluid shift into the vascular bed plays no essential role in this response. A preliminary report of some of these findings has been published elsewhere (18).

METHODS

Experiments were performed on 44 mongrel dogs (26 males, 18 females) weighing 8–22 kg fed on standard dog chow and water ad lib. for at least 7 days. Food was removed 16 h and water 1 h before preanesthetic administration. Morphine (2 mg/kg sc) was given 30 min before pentobarbital sodium, 10–15 mg/kg iv. Supplementary doses of pentobarbital, 10–15 mg, were given whenever

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required, typically at 2- to 3-h intervals. Two different procedures, designated as survival test and hemodynamic analysis, were performed on two sets of different dogs.

Survival test (24 dogs). An endotracheal tube was inserted, but animals were allowed to breath spontaneously for the duration of the experiment. A femoral artery was cannulated and connected to a Y-shaped tube, one branch of which was connected to a strain gauge transducer (Statham Instruments model P23Db) in turn connected to a galvanometric pen recorder (Beckman Instruments model R611). Pulse pressure was recorded on one channel, attenuated mean pressure on a second channel, and heart rate (pressure signal fed to a cardiotachometer coupler model 9857B) on a third. The second branch of the Y-shaped tube was used for bleeding and arterial sampling. A femoral vein was cannulated for infusions and injections. An interval of 90–120 min was allowed between anesthetic induction and initial bleeding, which was preceded by an intravenous injection of heparin (500 IU/kg) and carried out at the rate of 2.5–3.0 $ml \cdot min^{-1} \cdot kg^{-1}$, which was adjusted to reduce mean arterial pressure to 40 mmHg over 15 min. The moment at which pressure first declines to 40 mmHg is defined as experimental zero time. From 0 to 30 min postzero, mean arterial pressure was held at 40 mmHg by means of controlled bleeding into an overhanging reservoir. At 30 min postzero, the connection to the reservoir was interrupted and shed blood was discarded. An intravenous infusion of NaCl, 300 mosmol/l (control group 10 dogs), or 2,400 mosmol/l (test groups 10 dogs), preheated to 37°C, was given over a 10-min interval. The infusion volume was made equivalent to 10% of total shed blood. At 6-h postzero, survivors were given intravenous protamine chloride, 10–20 mg; they were decannulated and returned to the kennel. At 12 h postzero, they were offered water ad lib.; after 24 h postzero, they were fed normally.

Blood pressure and heart rate were continuously monitored, up to 6 h postzero; arterial pH and blood gases (pH/Blood Gas Analyzer, Instrumentation Laboratory model 113), arterial hematocrit (microhematocrit), and arterial plasma osmolarity (Fiske Osmometer model OM) were measured before initial bleeding (in duplicate), at zero time, at 30 min postzero, then hourly thereafter, to 6 h postzero. Arterial hematocrit and plasma osmolarity were additionally measured 12 and 24 h postzero, and 2, 7, and 14 days postshock. Plasma volume was measured by the Evan's blue dilution technique (27) 3 days preshock, 1 and 6 h postzero, and 2, 7, and 14 days postshock. Erythrocyte volumes were estimated from plasma volumes and hematocrit readings. Reticulocyte counts were taken 7 and 14 days postshock. A complete postmortem examination was carried out on all but three dogs.

Hemodynamic analysis (20 dogs). In addition to the preparation described above, the following surgical steps were carried out. Under positive pressure breathing an electromagnetic flow probe (Statham Instruments model SP7505, 10–14 mm ID) was placed around the root of the aorta. The thoracic cavity was drained and sealed and animals were returned to spontaneous breathing. Intrapleural pressure was monitored by means of an immersed tip catheter; animals incapable of exerting an inspiratory pleural pressure of -5 cmH_2O were rejected. A second electromagnetic flow probe (3–5 mm ID) was placed around the root of the cranial mesenteric artery through a lumbar incision. The flow probes were connected to a twin-channel electromagnetic flowmeter (Statham Instruments model SP2202), which was connected to the pen recorder. The nonocclusive zero readings of the instrument were checked at regular intervals against an occlusive zero produced by an artery occluder placed around the mesenteric artery or against the base-line diastolic aortic flow, respectively. An interval of 90–120 min was allowed between the end of the surgical procedure and the start of bleeding. The experimental sequence was as described above, but mean arterial pressure was brought to 50 mmHg at zero time and held between 45 and 50 mmHg between zero and 30 min postzero. Blood in the reservoir was likewise discarded at 30 min postzero, and each dog received an intravenous infusion of 6 ml/kg NaCl, 300 mosmol/l (saline group 10 dogs) or 2,400 mosmol/l (hyperosmotic group 10 dogs), administered over an interval of 3–5 min. Arterial pressure, heart rate, cardiac output, and mesenteric flow were monitored to 6 h postzero, but other readings described above were omitted. At 6 h postzero, all survivors were killed, and a macroscopical postmortem was performed on all dogs.

Statistical analysis. Data were processed according to a covariance analysis routine: between dogs, control vs. test, and between times. Two separate analysis were performed for each parameter: *effect of hemorrhage* from prehemorrhage to 30 min postzero and *effect of infusion* for the period after the infusion. The latter analysis was confined to the interval during which a sufficient number of control survivors still existed (up to 2 h postzero for hemodynamic analysis, up to 4 h postzero for the survival test). Where analysis of variance was impractical, a *t* test was performed (30).

RESULTS

Hemodynamic analysis. The total volume of blood in the reservoir at 30 min postzero averaged 23.1 ± 2.1 ml/kg for the 20 dogs taken jointly. There was no difference between the two groups ($t = 0.786$; $P > 0.4$). Figures 1–3 show the effects of hemorrhage and infusions on various hemodynamic parameters. No difference was detected for any of them between the two groups or from control to 30 min postzero, so they can be treated as a homogeneous population. Relevant statistical differences ($P < 0.01$) caused by the infusions are indicated in the figure legends. Figure 1 shows blood pressure and heart rate. From control to 30 min postzero, mean arterial pressure fell from 105 to 48 mmHg, whereas heart rate increased from 121 to 190 min^{-1}. The saline infusion did not appreciably alter these values, at 35 min postzero (end of infusion), but thereafter blood pressure fell steadily. In contrast, hyperosmotic infusions were followed by an immediate recovery of mean arterial pressure to 80 mmHg, which remained practically unchanged up to 6 h postzero. Systolic pressure practically recovered to con-

trol levels, whereas diastolic pressure remained relatively low at 55–60 mmHg. The substantial increase in pulse pressure is evident in the Fig. 1. Hyperosmotic infusions also caused a sustained fall in heart rate.

Cardiac output and mesenteric flow (Fig. 2) were both reduced by bleeding, but output fell to 42% of control, whereas mesenteric flow was more drastically reduced to 5.5% of control. Saline infusions only slightly increased these flows at 35 min postzero; afterward they gradually declined toward zero. Hyperosmotic infusions immediately restored output to control levels, whereas mesenteric flow overshot the initial level by 67% to an average 355 ml/min. Both recoveries were sustained over the rest of the observation period. Figure 3 represents calculated values for total vascular conductance, mesenteric conductance, and stroke volume. Bleeding reduced total vascular conductance only slightly but caused very intense mesenteric vasoconstriction. Saline infusions had no appreciable effects on these parameters, but hypertonic infusions increased both: total conductance by 50% and mesenteric conductance by 134%. Mesenteric conductance remained very high for 6 h. At the end of the observation period, it was still almost twice as high at the control level. Stroke volume decreased from 13.0 to

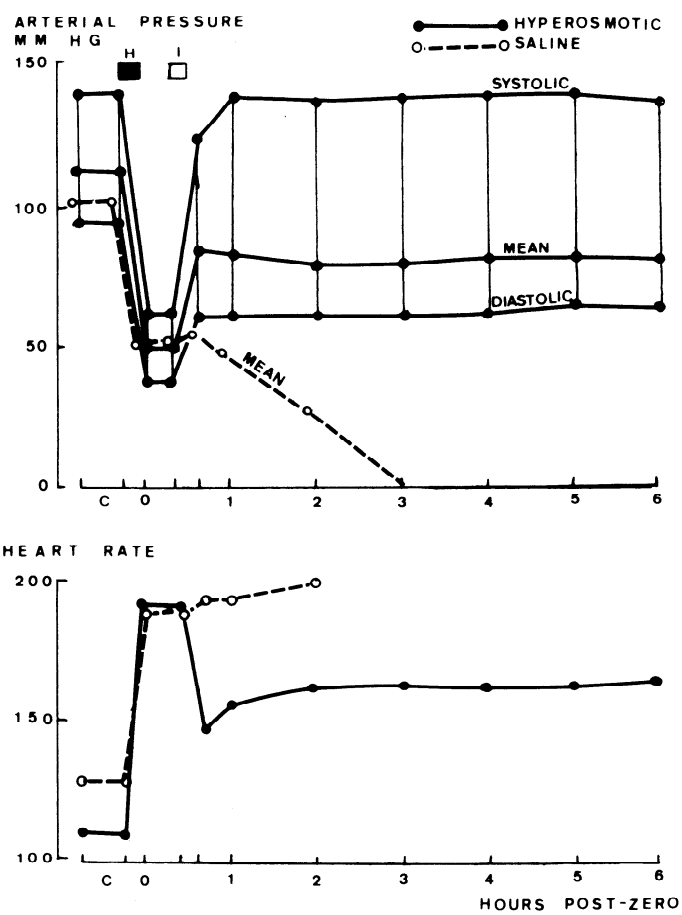

FIG. 1. Effects of hemorrhage and infusions on arterial pressure and heart rate. C, prehemorrhage duplicate readings; H, initial bleeding; I, infusion. Systolic and diastolic pressures are shown for hyperosmotic dogs only. Significant differences ($P < 0.01$) occurred between saline and hyperosmotic dogs, after infusions, for mean arterial pressure and heart rate.

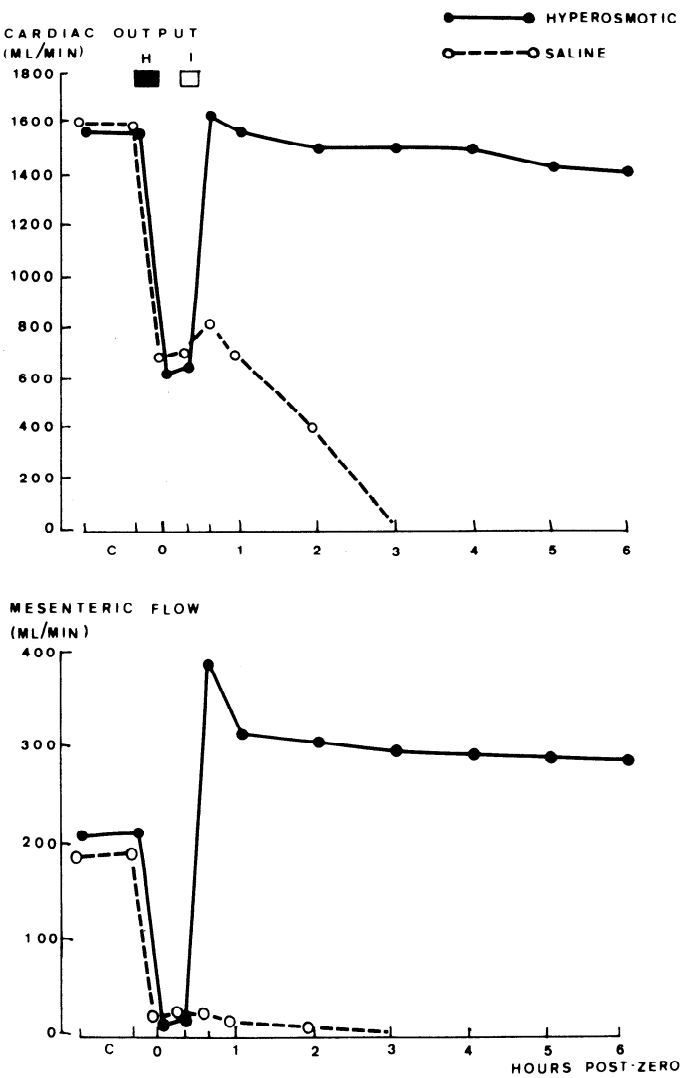

FIG. 2. Effects of hemorrhage and infusions on cardiac output and mesenteric flow. Symbols as in Fig. 1. Significant differences occurred between groups, after infusions, for both parameters.

3.5 ml, as a consequence of hemorrhage, but increased to 10–11 ml after hyperosmotic infusions.

All the saline-infused dogs died between 2 and 3 h postzero. Postmortem examination showed that death was caused by hemorrhagic enteritis: severe at the duodenal end, mild in the distal ileum, and large amounts of blood in the lumen. The 10 hyperosmotic dogs were killed at 6 h postzero; no evident pathological alterations were found.

Survival test. Preliminary experiments showed that similar results could be obtained by infusing 6 or 4 ml/kg hyperosmotic NaCl, but that 2 ml/kg produced a smaller survival rate. We therefore describe the detailed results of 4 ml/kg infusions, because this appeared to be the minimum effective dose in terms of a high survival rate. The most striking difference between control (saline treated) and test dogs is the survival rate. The last of the controls died at 6.5 h postzero, whereas all 10 test animals survived indefinitely. A recovery of various reflexes or even of spontaneous activity was noticeable within 30 min of the end of the hyperosmotic infusions; anesthetic supplements were necessary in every experiment. Such

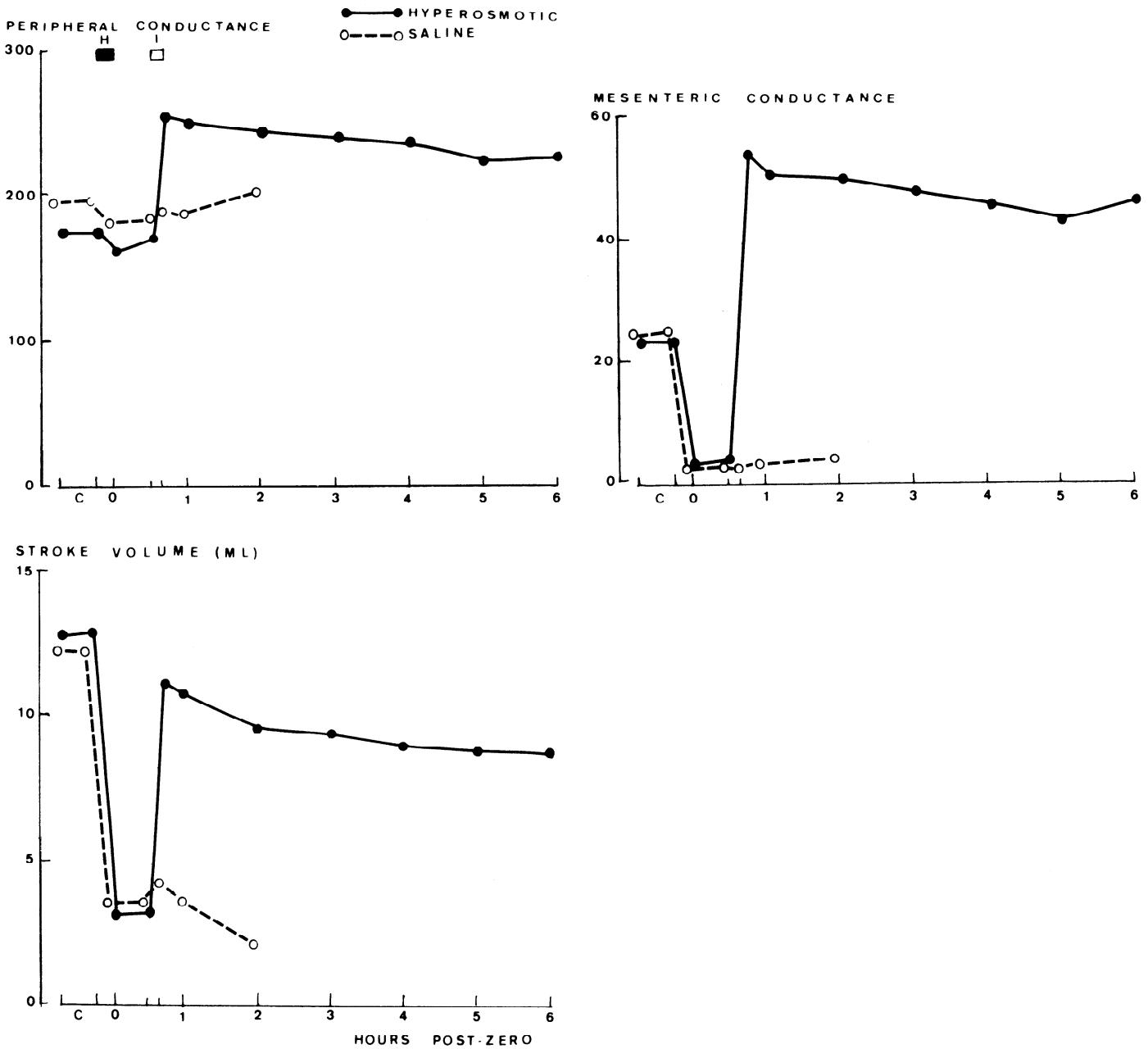

FIG. 3. Effects of hemorrhage and infusions on total peripheral vascular conductance and mesenteric conductance (expressed as $dyn^{-1} \cdot cm^5 \cdot s^{-1} \times 10^{-6}$), and on stroke volume. Symbols as in Fig. 1. Statistically significant differences occurred between groups, after the infusions, for 3 parameters.

supplements were given in sufficient amounts to abolish spontaneous activity, but not segmental reflexes. Animals were kept lying on one side unrestrained except for a loose tie around the cannulated leg. In contrast, none of the control dogs ever required or received anesthetic supplementation. At 12 h postzero test dogs had invariably recovered to stand in their cages unaided; at this stage, water was offered and every dog drank 40–60 ml/kg within 30 min. At 24 h all dogs stood and walked alertly. Their reflexes were normal, and 8 of 10 dogs accepted solid food. From 2 days postshock and afterward, they became undistinguishable from normal dogs.

The total volume of blood in the reservoir at 30 min postzero averaged 40.7 ± 1.4, equivalent to 43.2% of initial blood volume for the 20 dogs taken jointly. There was no significant difference between controls and tests ($t = 0.91$; $P > 0.3$). Figures 4–7 show the effects of hemorrhage and infusions on various parameters; again no difference was found between groups up to 30 min postzero (effect of hemorrhage). Relevant statistical data from the second analysis (effect of infusions) are indicated in the figure legends.

Figure 4 shows the effects of hemorrhage and infusions on mean arterial pressure and heart rate; these results are basically similar to those shown in Fig. 1 but two minor differences may be noted: *1*) the recovery of mean arterial pressure in the test group in Fig. 4 is slightly better than that of the hyperosmotic group in Fig 1, and *2*) the effect of the hyperosmotic infusion on the heart rate is also slightly different in that in these experiments

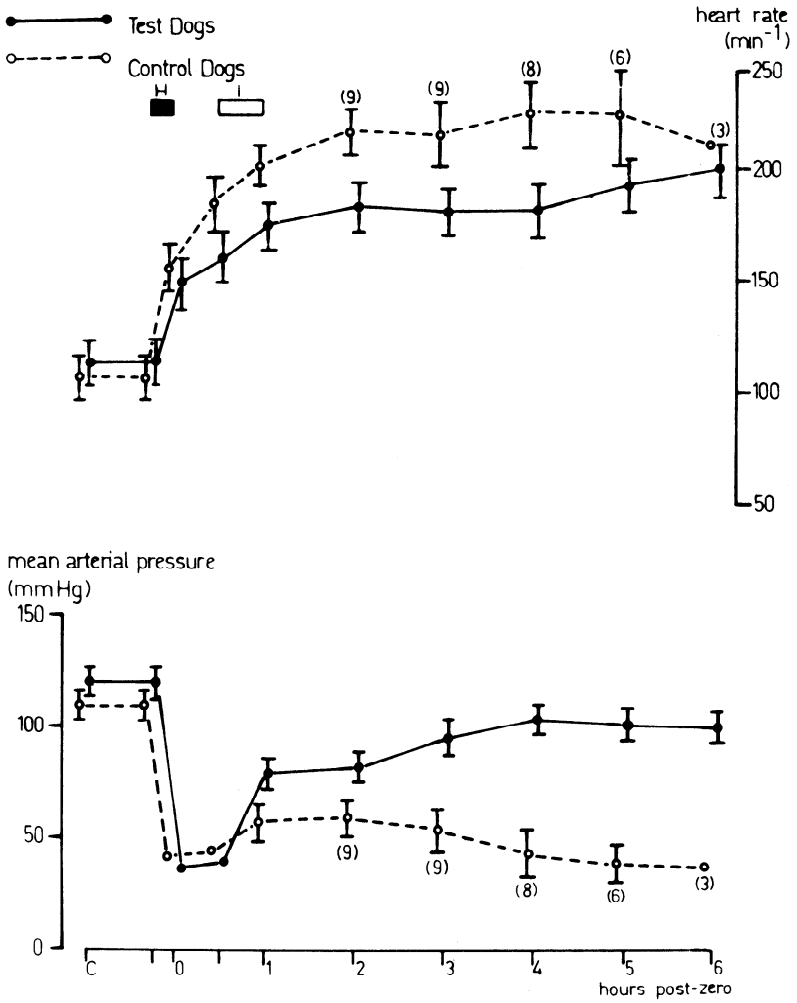

FIG. 4. Effects of hemorrhage and infusions on heart rate and mean arterial pressure (survival test experiments). Symbols as in Fig. 1. Statistically significant differences occurred between tests and controls, after infusions. Numbers in parentheses along control group traces indicate number of survivors at any given time.

there is no initial fall in heart rate, as observed in the hemodynamic analysis. This difference is partly due to the fact that in the survival tests we take no reading immediately after the end of the infusion as was done in the hemodynamic analysis experiments.

Figure 5 displays arterial blood gases and pH, as well as calculated values for base excess. Up to infusion time, all dogs develop comparable levels of metabolic acidosis. Arterial pH remains practically unaltered but at the expense of compensatory hyperventilation, and CO_2 tension (P_{CO_2}) fell from an initial 47.7 to 28.5 mmHg at 30 min postzero. Base excess at this stage had dropped to −8.5 meq/l. After the infusion, at 1 h postzero, arterial pH dropped sharply in both groups, but for different reasons. In control dogs the P_{CO_2} remains low at 29.6 mmHg, and in test dogs it rises to 35.4 mmHg. These data indicate that control dogs are still actively hyperventilating, whereas test dogs have reduced their breathing rate. These different responses are reflected in the respective base excess levels at 1 h: control dogs sink deeper into metabolic acidosis (base excess −11.8 meq/l), whereas test animals begin to recover toward normality (base excess −6.8 meq/l). This trend persists over the following hours; test dogs recovered to a base excess level of −4.6 meq/l at 6 h, whereas controls sank progressively deeper into severe metabolic acidosis with correspondingly lower levels of P_{CO_2}. No important differences in O_2 tension levels were observed between groups throughout these experiments.

Plasma osmolarity (Fig. 6) rises gradually in control dogs from an initial 302 to 318 mosmol/l, at 6 h postzero, unaffected by the infusion of saline. In test dogs, it rose sharply from 307 mosmol/l at 30 min to 333 mosmol/l at 1 h as a consequence of the hyperosmotic infusion. It declined slightly to 326 mosmol/l at 12 h, returning to the normal range of 300 mosmol/l after massive water ingestion.

The arterial hematocrit is also displayed in Fig. 6. Control dogs show no appreciable variations throughout the experiment. Test dogs exhibit a decline from 42.8% at 30 min to 35.5% at 1 h. This may be viewed as a reflection of plasma expansion due to the infusion. From 1 to 6 h postzero, however, the arterial hematocrit gradually rises back to 40.3%. At 12 h it declines slightly to 37%, but after water ingestion it drops to 30.1% at 24 h and to 28% at 48 h. These results should be examined jointly with those of Fig. 7, in which blood volumes for the test group are displayed. It is clear that prehemorrhage volume minus shed volume practically accounts for remaining volume at 1 h; red cell volumes balance out almost exactly, whereas plasmaa volumes show a small surplus at 1 h (~5 ml/kg). This matches the reduced hematocrit and must be attributed to fluid shift into the vascular bed. Over the next hours, however, this shift is

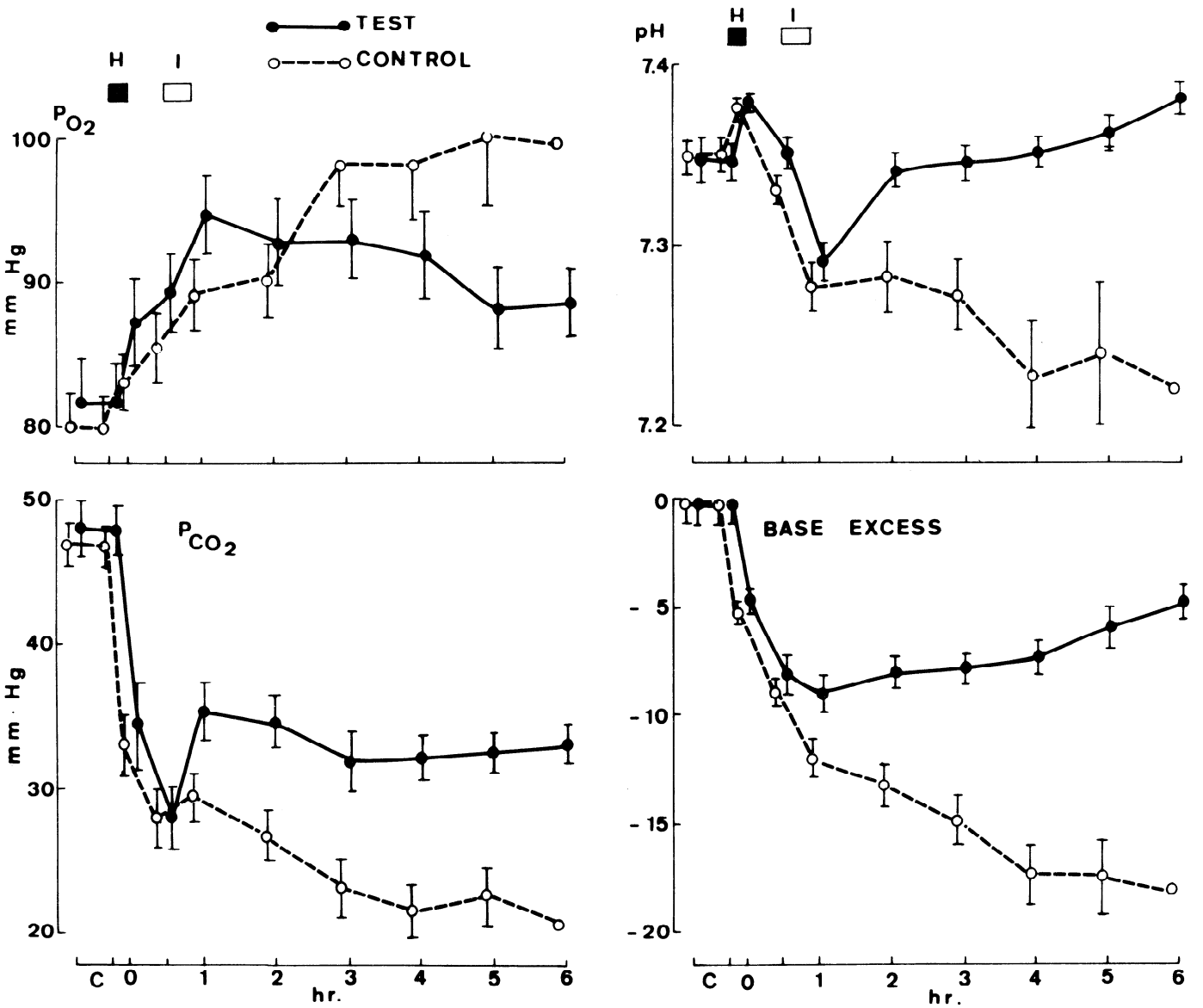

FIG. 5. Effects of hemorrhage and infusions on arterial P_{O_2} and P_{CO_2} (*upper* and *lower left*) and on arterial pH and base excess (*upper* and *lower right*). Symbols as in Fig. 1. Statistically significant differences occurred between tests and controls, after infusions, for P_{CO_2}, pH, and base excess ($P < 0.01$), but not for P_{O_2} ($P > 0.1$).

reversed. At 6 h postzero, the hematocrit is practically back to preinfusion levels, whereas plasma volume is almost exactly equal to prehemorrhage plasma volume minus shed plasma volume. The red cell volume remains unchanged. From 6 to 12 h there is a small decrease in arterial hematocrit, which corresponds to an estimated increase in plasma volume. It is only after massive water ingestion that plasma volume really expands, whereas the hematocrit drops below the 30% mark at 48 h. Seven and 14 days postshock, blood volume, as a whole gradually recovers towards normality, with an increase in red cell volume. Reticulocyte counts, at these stages show that immature red cells account for 30–40% of the total red cell population. To check whether water ingestion was indeed responsible for plasma expansion, four supplementary experiments were performed. In two of them, dogs were returned to the kennel at 1 h postzero. This allowed them to recover from anesthesia in time to be offered water at 7 h postzero. Water ingestion caused an immediate drop in the hematocrit from 41 and 43% to 34 and 32%, respectively. Two other dogs were only given water at 24 h postzero; their hematocrits were still high (38 and 36%), but dropped immediately after water ingestion to 31 and 30%, respectively.

Postmortem examination of the control dogs revealed intense hemorrhagic enteritis with large amounts of blood in the lumen of the small gut. Microscopically, the mucosae of the duodenum and of the proximal jejunum were diffusely necrotic. Mild central lobular congestion was detected in the liver. No other significant histopathological alterations were found. Five test dogs were killed on the 7th day and two on the 14th day postshock. They were meticulously examined, but showed no significant macroscopical or histopathological alterations. Three dogs were kept alive for an extended period. After 1 mo their hematocrits had recovered to prehemorrhage levels and they appeared completely normal. Two of these dogs were submitted to a second identical procedure of hem-

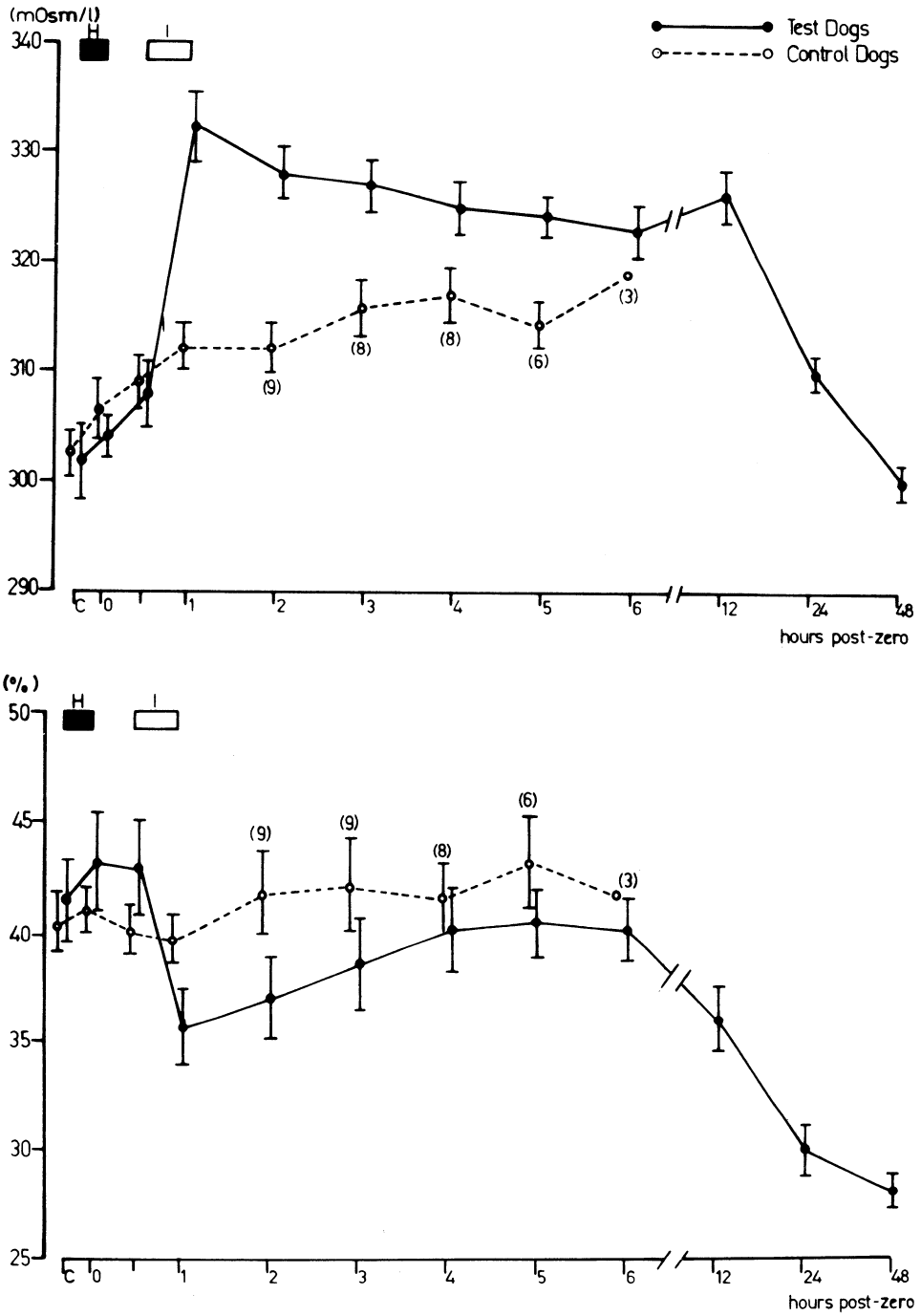

FIG. 6. Effects of hemorrhage and infusions on plasma osmolarity and on arterial hematocrit. Symbols as in Fig. 1. Significant differences occurred between tests and controls, after infusions, for osmolarity and hematocrit values.

orrhagic shock exactly 1 mo after the first one. The total volume of shed blood was slightly smaller than in the first trial (36.2 and 35.3 ml/kg as compared to 40.2 and 39.6 ml/kg, respectively). Hyperosmotic infusions again reversed the course of shock, much as it had done on the first occasion, and both dogs recovered. They were killed 14 days postshock, and no pathological alterations were found postmortem.

DISCUSSION

The most intriguing feature of these experiments is the chain of events starting from the infusion of hyperosmotic NaCl and stopping some hours later when dogs were finally able to make up for the lost volume by drinking large amounts of water. During these crucial hours, a quasinormal level of arterial pressure perfused a dilated precapillary bed; stroke volume was practically normal and oxygen supply adequate, because no fixed acid accumulated. All this happens despite the fact that nearly half the normal blood volume was missing and had not been replaced in any way. Plasma volume and arterial hematocrit measurements independently show that no appreciable or lasting expansion of plasma volume could account for the recovery of normal circulatory function. These results are confirmed by data obtained by Wolf (35), who showed that a rapid intravenous injection of 12 ml/kg NaCl at 833 mosmol/l (which is almost exactly identical to 4 ml/kg at 2,400 mosmol/l) induces a maximal plasma expansion at zero time. This expansion

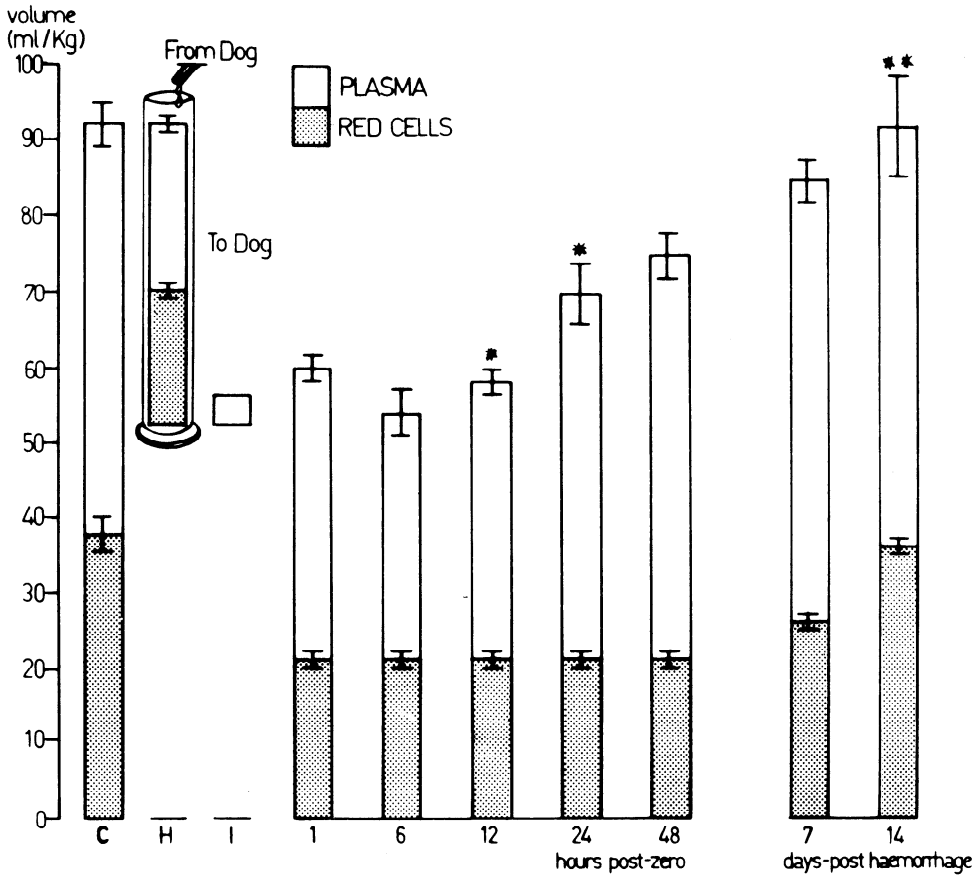

FIG. 7. Red cell, plasma, and total blood volume during course of 10 hemorrhagic shock experiments (test group, hyperosmotic NaCl infusions; means ± SE for each reading). Corresponding readings for 10 control dogs, prehemorrhage values only were: plasma volume, 59.1 ± 2.1 ml/kg; red cell volume, 37.7 ± 1.1 ml/kg. *Rectangle inside cylinder* marked *from dog* represents total volume of shed blood; *rectangle* marked *to dog* represents volume of infused hyperosmotic NaCl. *Estimated values obtained from effectively measured arterial hematocrits and interpolation of red cell volumes between 6 and 48 h postshock; ** means ± SE for 5 dogs.

is transient, however. At 30 min postinjection (equivalent to 1 h postzero in our experiments); expansion is already down to 25%, and at 90 min it has further dropped to 10%. The decay appears to follow first-order kinetics. These data adjust perfectly to the present findings. At 1 h postzero, plasma expansion is approximately 20%, and judging from hematocrit variations over the next hours, the decay could follow first-order kinetics. It thus appears that one may discount the idea of plasma expansion due to osmotically driven fluid shift into the vascular bed, because it can play no essential role in the overall response of the cardiovascular system. We must turn instead to the hemodynamic effects of hyperosmolarity for adequate explanations.

It has been repeatedly demonstrated that hyperosmolarity increases myocardial contractility and cardiac efficiency both in normotensive and in shocked subjects (2, 33, 34). Though no direct measurements of cardiac contractility were performed in the present experiments, the large increase in pulse pressure that follows hyperosmotic infusions is compatible with the concept of increased myocardial contractility. The same applies to the effect of hyperosmolarity on precapillary resistance vessels (2, 10), which are obviously dilated by the infusions. The novelty of this report, where these matters are concerned, lies in the duration of the response. Published reports of experiments, in which concentrations no higher than 1,800 mosmol/l have been infused, describe a transient increase in myocardial efficiency and vascular conductance. In the present experiments, NaCl concentration has been raised to 2,400 mosmol/l, a concentration apparently never tried before in connection with hemorrhagic shock. It does appear that this higher concentration is required to trigger off a long-lasting stable recovery.

It must however be apparent that increased myocardial contractility and a widely dilated precapillary bed cannot, in themselves, account for the observed functional recovery, because we may no longer invoke fluid shifts to restore intravascular volume. No matter how efficient the heart may be, under circumstances in which half the blood volume is missing, a dilated precapillary bed must entail low arterial pressure unless vascular capacitance is duly adjusted. Hyperosmolarity has been repeatedly shown to induce constriction of capacitive systemic and pulmonary vessels (4, 10, 11); but to our knowledge these facts have never been acknowledged in the field of hyperosmotic treatment of hemorrhagic shock.

The hemodynamic response outlined above may not be the only significant effect of hyperosmotic NaCl. One must therefore consider the possibility of metabolic actions, such as stabilization of lysosomal membranes and the prevention of toxic factor formation, such as the myocardial depressant factor (17). If present, such an action might help to explain the very long sustained effect of hyperosmotic infusions.

The full picture that seems to emerge from these results may be summarized as follows. In response to an intravenous infusion of highly concentrated NaCl, myocardial contractility, and consequently cardiac efficiency are increased, precapillary vessels dilate, and ca-

TABLE 1. *Effects of intravenous injections of 4 ml/kg NaCl on arterial pressure, heart rate, cardiac output, plasma volume and osmolarity, arterial hematocrit and pH,and base excess of 10 nonshocked dogs*

		Control	Time After Start of Hyperosmotic Infusions						
			30 s	10 min	30 min	1 h	2 h	4 h	12 h
Mean art press, mmHg	*A*	90 ± 7	95 ± 7	100 ± 9	105 ± 9	110 ± 8	115 ± 6	110 ± 7	
	B	105 ± 9	75 ± 6	110 ± 9	125 ± 10	125 ± 9	120 ± 8	120 ± 8	
Pulse press, mmHg	*A*	45 ± 2	45 ± 2	50 ± 3	50 ± 3	50 ± 2	50 ± 2	45 ± 2	
	B	50 ± 2	40 ± 2	90 ± 3	90 ± 2	85 ± 3	75 ± 2	60 ± 3	
Cardiac output, ml/min	*A*	1,530 ± 200		1,950 ± 310	1,830 ± 280	1,620 ± 205	1,510 ± 190	1,560 ± 205	
	B	1,580 ± 180		2,230 ± 360	2,210 ± 290	1,850 ± 270	1,620 ± 170	1,590 ± 190	
Heart rate, min^{-1}	*A*	100 ± 20	135 ± 25	120 ± 20	130 ± 20	115 ± 20	110 ± 20	115 ± 25	110 ± 15
	B	105 ± 15	180 ± 35	120 ± 15	120 ± 15	115 ± 20	115 ± 25	110 ± 25	110 ± 20
Plasma vol, ml/kg	*A*	56.5 ± 7.1		73.1 ± 8.1*	58.7 ± 7.3	56.1 ± 6.1*	54.1 ± 5.0*	51.7 ± 4.9*	55.9 ± 6.3
	B	54.3 ± 4.8		98.5 ± 6.2*	76.2 ± 6.7	70.3 ± 8.2*	65.1 ± 7.3*	53.2 ± 6.1*	56.3 ± 7.1
Hematocrit, %	*A*	41.2 ± 2.3		33.1 ± 2.1	35.2 ± 2.7	38.3 ± 2.1	41.2 ± 2.7	43.7 ± 2.1	40.7 ± 2.0
	B	38.1 ± 3.1		24.1 ± 3.2	29.3 ± 2.9	35.8 ± 2.9	37.3 ± 3.2	39.7 ± 3.1	38.3 ± 2.0
Osmolarity, mosmol/l	*A*	301 ± 4		329 ± 6	321 ± 5	319 ± 4	319 ± 3	313 ± 3	300 ± 5
	B	303 ± 5		351 ± 9	340 ± 7	335 ± 5	332 ± 6	327 ± 2	297 ± 6
pH	*A*	7.36 ± 0.02		7.32 ± 0.01	7.34 ± 0.02	7.35 ± 0.02	7.35 ± 0.02	7.35 ± 0.03	7.39 ± 0.01
	B	7.37 ± 0.01		7.25 ± 0.03	7.27 ± 0.03	7.30 ± 0.03	7.32 ± 0.02	7.32 ± 0.02	7.37 ± 0.02
Base excess, meq/l	*A*	−0.4 ± 0.2		−2.3 ± 1.1	−2.7 ± 0.9	−2.5 ± 0.4	−2.3 ± 0.2	−1.9 ± 0.2	−0.2 ± 0.1
	B	0.1 ± 0.3		−7.8 ± 1.7	−6.5 ± 1.4	−5.3 ± 1.0	−5.1 ± 0.9	−4.8 ± 0.5	−0.9 ± 0.2

Values are means ± SE; $n = 5$. *A*, 2,400 mosmol/l; *B*, 4,800 mosmol/l. * Estimated as described in Fig. 7.

pacitance vessels constrict. A slight and transient shift of fluid into the vascular bed may play a role in the first 30 min of the response. The recovery of circulatory function, without blood volume expansion, can last for as long as 24 h, during which time an adequate oxygen supply is ensured, as judged from the level of base excess. Before the infusion diminishing base excess levels indicate anaerobic metabolism, with fixed acid accumulation; after the infusion this trend is reversed. This also conflicts with some of the published reports, in which hyperosmotic NaCl infusions reportedly aggravate acidosis (1, 2). In our experiments we do find an initial decrease in arterial pH, but this is accompanied by a rise in P_{CO_2}. Baue et al. (1, 2) also observed a fall in pH and a rise in P_{CO_2} after infusions of hyperosmotic NaCl (1,800 mosmol/l), but apparently failed to appreciate the significance of the interaction probably because of the short duration of the effect.

One final point should be made. Because oxygen transport is a linear function of hematocrit, whereas blood viscosity is an exponential function of red cell concentration, an optimal hematocrit value must exist in terms of oxygen transport efficiency. It has been demonstrated that this optimal hematocrit level is 30% (12). In the present experiments, the hematocrit drops naturally to the 30% range after water ingestion and remains at this level until at least 2 wk have elapsed after the initial blood loss.

APPENDIX

To evaluate possible cardiovascular effects of hyperosmotic NaCl injections in normotensive normovolemic dogs submitted to the same procedure used in the survival tests, 10 supplementary experiments were performed in which the survival test protocol was followed, except for the hemorrhage procedure. Additionally, cardiac output was determined by thermal dilution (St Thomas' Hospital Cardiac Output Computer, Devices, UK). Ninety minutes after anesthetic induction, an intravenous injection of 4 ml/kg NaCl, 2,400 mosmol/l (5 dogs) or 4,800 mosmol/l (5 dogs), was given. Four hours later, all dogs were decannulated and removed to kennel cages where they were observed for a period of 7 days.

Table 1 summarizes the main observations of this experimental series. Intravenous injectionss of the lower dose of 2,400 mosmol/l NaCl produce only small and transient effects on a few parameters. *a*) Heart rate peaks 35% above control at 30 s, but promptly drops back to control levels. *b*) Cardiac output is slightly increased over the first 0.5 h. *c*) Plasma volume peaks 29% above control at 10 min, but shrinks back to control at 30 min. *d*) Although not shown, red cell volume remains practically unaltered. *e*) Plasma osmolarity peaks at 329 mosmol/l at the end of the injection, then drops to the 320 mosmol/l range where it remains for 4 h. At 12 h after water ingestion it returns to control levels. *f*) A very mild metabolic acidosis prevailed from injection time to 4 h but disappeared at 12 h. Every dog survived the procedure.

It must be noted, however, that this is not an entirely valid control for the survival tests. Normovolemic dogs have roughly twice the plasma volume of the shocked dogs described above; this means that 4 ml/kg NaCl at 2,400 mosmol/l will dilute in a larger pool (hence at a lower concentration) in the normovolemic animal. This idea is confirmed if one compares plasma osmolarity of shocked dogs with that of *group A*. Thus a new group, in which the concentration of salt was doubled, is also presented in Table 1. Plasma osmolarity is now in the range obtained in shocked dogs, and results are more evident. *a*) A slight short-lasting hypotension is observed within 30 s of the start of the injection. *b*) Pulse pressure is practically doubled from the end of the injection to 4 h. *c*) Heart rate increases by 70% at 30 s, but also drops back to control levels at 10 min. *d*) Cardiac output peaks 41% above control at the end of the injection, but gradually decreases thereafter. *e*) Plasma volume peaks 81% above control at the end of the injection. At 30 min this expansion is down to 40%, and at 2 h down to 20%. Red cell volume is again unaltered. *f*) Metabolic acidosis is more severe and persists over the 4-h period, subsiding after water ingestion. Every dog survived the procedure.

In conclusion, an exactly identical injection of hyperosmotic NaCl given to normovolemic dogs is practically without effects. It is not, however, a valid control for the shock procedure, as seen above. If the total injected salt load is doubled, then comparisons are possible, and general cardiovascular effects appear to be of the same nature as those observed during shock: increased pulse pressure and cardiac output, transient plasma expansion, and hemodilution. It should also be noted that the purely hemodynamic effects last for a shorter period in the normovolemic dog. This may of course be due to the fact that homeostatic mechanisms operate to antagonize the effects of hyperosmotic NaCl in the normotensive animal but in synergism with these effects in hypotensive shocked dogs.

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