EFFECTS OF ELECTROLYTE ALTERATIONS ON BLOOD PRESSURE IN SPINALLY BLOCKED DOGS

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ABSTRACT

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By

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In a previous report (Emerson et al., 1968) the blood pressure effects in dogs of five minute IV infusion at 10 ml/Kg/min of solutions designed to alter plasma electrolyte concentrations were described. Infusion of a Ringer's solution, which caused no electrolyte changes, was without effect on arterial blood pressure (ABP). Infusion of a solution which decreased $[K^+]$, decreased $[Mg^{++}]$, decreased Osmolarity (Os), increased $[Ca^{++}]$, and increased pH resulted in a rise in ABP (single electrolyte changes resulted in smaller rises in ABP) and the opposite electrolyte changes caused a fall in ABP (see Table). In the present study, possible participation of the neurological compensatory system in buffering the above blood pressure effects was evaluated in anesthetized (sodium pentabarbital) dogs by creating the same electrolyte changes as in the earlier study. Complete spinal anesthesia was achieved with injection of 9 ml of a 2% procaine solution in the cisterna magna. The following table compares the current findings (2) with those of the earlier study (1) when the major combined changes were created.

	N	Os (mOsm /l)	$[K^+]$	$[Mg^{++}]$	$[Ca^{++}]$	pH	Hct	Mean Blood Press. C (mm Hg)	Δ	Δ Relative to Control Response
1	26	0	0	0	-0.3	0	-15*	129	9	--
2	13	0	-0.2	0.1	-0.4	0	-14*	89	45*	--
1	10	-16*	-0.5*	-0.5*	0.9*	0.2*	-12*	131	37*	28*
2	10	-16*	-0.5*	-0.6*	1.5*	0.2*	-13*	97	66*	21*
1	10	28*	1.9*	1.2*	-1.2*	-0.1*	-17*	133	-19*	-28*
2	10	39*	3.9*	1.9*	-1.8*	-0.1*	-18*	103	-35*	-70*

*= $P < 0.05$; [ ] = mEq/l; C = control.

Group 1 -- Emerson et al., 1968; Group 2 -- present study.

These data show that the blood pressure responses to the infusions are greater after neural blockade and, in addition, suggest that the nervous system partly masks the cardiovascular actions of depressor combinations of elelctrolyte abnormalities.

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DEDICATION

To Mom and Dad

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INTRODUCTION

The effects of various electrolyte abnormalities on the cardiovascular system have been the concern of many investigators over the past few years.

It is well known that most of the major blood cations are vasoactive. Studies completed in isolated vascular beds clearly indicate that single or multiple electrolyte concentration changes affect vascular resistance (Haddy, 1963; Haddy and Scott, 1965; Haddy and Scott, 1968; Scott et al., 1968). Later work showed that these electrolyte changes when made systemically, cause significant effects upon the blood pressure of the intact animal (Haddy et al., 1969). Furthermore, when multiple changes were created (e.g. $\downarrow[K^+]$, $\downarrow[Mg^{++}]$, $\uparrow[Ca^{++}]$, $\downarrow$Os, $\uparrow$pH), systemic blood pressure increased to a much greater extent than was the case with the single changes. The opposite combination ($\uparrow[K^+]$, $\uparrow[Mg^{++}]$, $\downarrow[Ca^{++}]$, $\uparrow$Os, $\downarrow$pH) yielded the reverse effect on arterial blood pressure.

Alteration of systemic blood pressure can be effected by changing one or both of its two direct determinants, cardiac output and total peripheral resistance. Therefore,

if cardiac output remains constant, any change in total peripheral resistance would be reflected by a corresponding change in systemic blood pressure. Likewise, any alteration in cardiac output will shift blood pressure, provided total peripheral resistance is held constant. In the intact animal, however, systemic blood pressure remains the function of not one, but both determinants. It is the net additive result of variations in both cardiac output and total peripheral resistance.

Varying resistance is most often achieved by changing the vessel radius, this being normally accomplished by the activation or de-activation of smooth muscle cells within the vessel wall. Strip studies as well as *in situ* perfusion studies show that the contractile state of vascular smooth muscle can be affected by electrolyte and osmolar concentrations on both the inside and outside of the cells (Friedman *et al.*, 1959; Haddy, 1963).

Cardiac output is also affected by electrolyte and osmolar abnormalities. The striking effects of electrolytes on cardiac muscle have long been recognized (Bayliss, 1901; Hoff, *et al.*, 1939; Winkler, *et al.*, 1940; Haddy, *et al.*, 1963). Electrolyte changes affect the cardiac output by acting upon stroke volume (primarily by varying cardiac strength) and heart rate. Thus, cardiac output can be increased or decreased according to the changes evoked in heart rate and stroke volume.

Of course, in the normal intact animal, these mechanisms rarely act alone. The neurological barostatic regulatory system attempts to neutralize most variations in blood pressure and keeps the body in a relatively steady-state situation. A review of these reflex control mechanisms can be consulted for details on how this regulatory system operates (Heymans and Neil, 1958). Adjustment to achieve homeostasis is accomplished by altering both determinants of systemic arterial blood pressure. Needless to say, these two factors are in a dynamic, ever-changing state in the normal intact animal. Examining exactly what extent the neurological barostatic system buffers the vascular effects of both electrolyte and osmolar abnormalties was the purpose of this study. In particular, the study was an expansion of earlier work by Emerson et al. (1968). A paired comparison between this study and the study of Emerson et al. (1968) is included, as well as the intrinsic analysis of the current study.

The application of much of the information obtained from research in this field is now being used in various clinical disorders in man. Of much interest has been the realization of a possible close relationship between concentration alterations of some of these blood components and certain hypo- and hypertensive disease states (Haddy, 1959; Haddy and Overback, 1962; Haddy, 1964). This potential relationship provided the stimulus for much of the current research done in this field. Examples of diseases which

have, as characteristics, one or more electrolyte concentration alterations associated with high blood pressure, are: primary aldosteronism ($\uparrow[Na^+]$, $\downarrow[K^+]$, $\downarrow[Mg^{++}]$, and $\downarrow[H^+]$); Cushings disease ($\uparrow[Na^+]$, $\downarrow[K^+]$, and $\downarrow[H^+]$); hyperparathyroidism ($\uparrow[Ca^{++}]$, $\downarrow[Mg^{++}]$).

LITERATURE SURVEY

Scientific interest in the cardiovascular effects of various ions stems back to experiments carried out in the latter part of the nineteenth century. Sidney Ringer conducted a group of experiments on amphibian ventricular muscle contraction, ". . . designed to ascertain the influence each constituent of the blood exercises on the contraction of the ventricle" (Ringer, **1883**). He tested the effects of sodium chloride, serum albumin, potassium chloride, and a dried blood mixture--all of these thought to be constituents of blood. Later, he realized that the supposedly "distilled water" he had used, turned out to be ordinary pipe water, which contained calcium, magnesium, sodium, potassium, chloride, and bicarbonate ions (Ringer, **1884**). Ringer concluded that most of his results were due to the action of these inorganic constituents. The actions of potassium, sodium, calcium, bicarbonate, and chloride ions on the heart were then reported with amazing accuracy. Ringer summed up his experiments by observing that ". . . a perfect contraction can be obtained with a neutral circulating fluid composed of a saline solution with a minute trace of calcium chloride and potassium chloride."

Sytemic Effects of Single Electrolyte Alterations

Other substances, including other cations, have been implicated in systemic blood flow regulation. Gaskell (1877) presented the first description of changes in blood flow following exercise or active hyperemia. In an attempt to explain the mechanisms behind such changes, Gaskell (1880) and Roy and Brown (1879) implicated metabolically linked vasoactive chemicals (including some cations) as causes for blood flow changes. Subsequent studies further developed this hypothesis and extended its application to various body organs.

The relationship between blood pressure changes and plasma electrolyte concentrations was first examined by Hoff, Smith, and Winkler (Hoff et al., 1939; Winkler et al., 1940). Cationic salt solutions were infused intravenously into dogs and cats. Within physiological ranges, potassium and calcium salts produced minor, insignificant blood pressure changes. Magnesium salts lowered arterial blood pressure. Both magnesium and potassium depressed cardiac functions, whereas calcium ions had the opposite effect. These findings supplemented the earlier findings of Katz and Lindner (1938). Their method involved the use of a Langendorff canine heart preparation to study electrolyte effects on the coronary vascular bed.

Research in this area expanded to encompass the specific singular effects of numerous electrolytes and blood properties

on blood pressure, cardiac output, and peripheral resistance. Various isolated vascular beds in the body were used.

Local Effects of Single Electrolyte Alterations

Potassium

Dawes (1941) offered the first true delineation of the vasoactive characteristics of potassium. In the isolated hindlimb of the adrenalectomized dog or cat, small doses of KCl were shown to cause vasodilation, while larger doses resulted in vasoconstriction. He also found that hyperkalemia caused vasoconstriction of rabbit ear skin vessels but had very little effect on lung or intestinal vessels in the dog. It should be taken into account that the author fails to state potassium ion concentration for the effect of vasoconstriction. The vasodilator properties cited above have been observed in other vascular beds, e.g., forelimb (Emanuel et al., 1959; Overbeck et al., 1961), kidney (Scott et al., 1959; Frohlich et al., 1962), myocardium (Scott et al., 1961) and intestine (Dabney et al., 1967; Textor et al., 1967). However, the liver has been shown to be unresponsive to locally induced potassium increase (Chou and Emerson, 1968).

Generally, potassium decrease causes arteriolar constriction (Haddy and Scott, 1965). Increased resistance (in response to hypokalemia) has been reported in the forelimb (Haddy et al., 1963), kidney (Haddy et al., 1963), and

gracilis muscle (Skinner and Powell, 1967; Roth, et al., 1969) vascular beds.

Hydrogen

Another monovalent cation possessing vasoactivity is hydrogen. The acute local effect of excess hydrogen ion concentration in plasma (pH = 7.30) is generally vasodilation. Acidosis produced by either decreasing respiration (and thus increasing plasma carbon dioxide tension and hydrogen ion concentration) or intra-arterially infusing acids produces dilation. Resistance in the vascular beds of the heart (Daugherty et al., 1965; Daugherty et al., 1967), intestine (Mohamed and Bean, 1951; Pals and Steggerda, 1966), brain (Emerson and Heath, 1969), forelimb (Daugherty et al., 1967) falls in response to respiratory decrease of pH. In response to infusion of acid into the vascular beds of the skin (Deal and Green, 1954), forelimb (Molnar et al., 1962a), hindlimb (Kester et al., 1952), heart (Elek and Katz, 1942) and brain (Geiger and Magnes, 1947), there is also a fall in resistance. Because the vascular effects of respiratory and metabolic acidosis are similar, some investigators have hypothesized that hydrogen ion vasoactivity, rather than changes in CO_2 tension, is the causative agent behind the resistance effect in both conditions.

Alkalosis can also be either respiratory or metabolic in origin. When respiration is increased and followed by hypocapnia and increased pH, vascular resistance is increased

in the forelimb (Daugherty et al., 1967; Molnar et al., 1962b), intestine (Mohamed and Bean, 1951), and kidney (Daugherty et al., 1967; Molnar et al., 1962a). The response to local alkali infusion is more difficult to demonstrate. The particular alkali compound used apparently determines what vascular effects are elicited (Haddy and Scott, 1968; Emerson et al., 1969). Increases in pH, within the range 7.40-7.60, produce little resistance change. With greater pH increases, the perfused canine gacilis muscle (Emerson et al., 1969) and canine forelimb (Scott and Haddy, 1963) react with an increase in resistance using NaOH or Na_2CO_3 as the alkalotic agent. However, unless the pH change is large, little change is seen using $NaHCO_3$ as the alkalotic agent (Scott and Haddy, 1963; Emerson et al., 1969). Long-term $NaHCO_3$ infusion studies on a dog gracilis muscle failed to show a different response or explain the above discrepancy (McKeag, Unpub. observ.).

Sodium

Sodium is another monovalent ion to be considered. All available evidence seems to indicate that the sodium ion per se has no direct effect on vascular smooth muscle. In the forelimb (Haddy, 1960; Overbeck et al., 1961) renal (Gazitua et al., 1967), mesenteric (Textor et al., 1967), and coronary (Scott et al., 1961) vascular beds, acute increase or decrease of the sodium concentration, via intra-arterial infusion, had little effect upon pre-capillary

small vessel resistance other than that attributable to changes in plasma tonicity.

Osmolarity

The changes in resistance that were initially attributed to the action of the sodium ion have been shown to be related to osmolarity changes (Haddy, 1960), rather than to the sodium ion per se. Intra-arterial infusion of a hyperosmotic salt or dextrose solution causes a resistance fall in the dog hindlimb (Marshall and Shepherd, 1959; Reed et al., 1960; Mellander et al., 1967), forelimb (Haddy, 1960; Overbeck et al., 1961; Frohlich et al., 1962), kidney (Gazitua et al., 1967) and heart (Scott et al., 1961).

Conversely, hypo-osmolarity increases resistance to flow through the vascular beds of the kidney (Gazitua et al., 1967) and forelimb (when compared to an equal-volume infusion of an iso-osmotic solution) (Overbeck et al., 1961). Haddy and Scott (1965) found that intra-arterial injection of distilled water into the canine forelimb increases resistance. Furthermore, this increase still occurs following near-maximal blood vessel constriction with epinephrine.

Calcium

The two major bivalent cations (calcium and magnesium) in the blood exhibit vasoactivity. Either moderate or marked hypercalcemia results in active vasoconstriction in various vascular beds (Frohlich et al., 1962). Specifically, an increase in resistance occurs following local

intra-arterial infusion in the renal (Frohlich et al., 1962), forelimb (Frohlich et al., 1962; Overbeck et al., 1961; Haddy, 1960) and coronary (Scott et al., 1961) vascular beds. No effect on resistance was seen in the liver (Chou and Emerson, 1968), whereas variable changes were noted in the ileum (Dabney et al., 1967). Increased calcium ion concentration caused a resistance fall in the gastric bed (Textor et al., 1967). Decreasing gastric wall tension causing a passive dilation of the gastric vessels appears to be the reason for the above cited occurrence. Normally, the effects of calcium are limited to the arterioles.

Plasma calcium reduction causes local vasodilation in the dog forelimb and kidney (Haddy et al., 1963).

Magnesium

The magnesium ion (Mg^{++}) has the opposite effects on resistance compared to the calcium ion. Acute local hypermagnesemia directly causes arteriolar dilation in the liver (Chou and Emerson, 1968), forelimb (Haddy, 1960; Overbeck et al., 1961), intestine (Dabney et al., 1967) and heart (Scott et al., 1961).

It is surprising to note that the hypomagnesemia alone does not produce any measurable effect on resistance to flow through the isolated forelimb (Haddy, 1960; Haddy et al., 1963), renal (Haddy et al., 1963), or coronary (Haddy et al., 1963) vascular beds. However, when hypomagnesemia is combined with other electrolyte abnormalities, the resistance

increase seen is greater than that increase produced as a result of only the other abnormalities (Haddy, 1960; Haddy et al., 1963). Therefore, in combination with other electrolyte alterations, hypomagnesemia has an effect upon resistance.

Table I shows a summary chart of the vascular effects of single electrolyte changes as they have heretofore been reviewed.

Local Effects of Combined Electrolyte Alterations

In view of the findings associated with single electrolyte abnormalities, it became a natural extension of the previously cited studies to investigate the effect of combined electrolyte changes on the blood vascular system. Haddy et al. (1963) examined this question using a method by which small multiple electrolyte abnormalities were acutely created in the blood perfusing various vascular beds, viz., forelimb, renal, and coronary beds. When hypokalemia, hypomagnesemia, hypercalcemia, and alkalosis were simultaneously produced, the net result was a greater constriction than seen with any one of the aforementioned electrolytes alone. Furthermore, the electrolyte alterations created were relatively small. From the normal concentrations in the blood, the ionic concentrations varied only slightly ($[K^+]$ = 1.0 mEq/l, $[Mg^{++}]$ = 1.2 mEq/l, $[Ca^{++}]$ = 6.5 mEq/l, and pH = 7.54). Later work (Scott et al., 1968) verified the fact that, indeed, very small changes in

Table I. Cardiovascular effects of single electrolyte changes.

Electrolyte Change (or Osmolarity)	Vascular Resistance	Myocardial Contractile Force
$\uparrow K^+$	$\downarrow$ ($\uparrow$[1])	$\downarrow$
$\uparrow Mg^{++}$	$\downarrow$	$\downarrow$
$\uparrow H^+$ ($\downarrow$pH)	$\downarrow$	$\downarrow$
$\uparrow Na^+$	<—>	$\downarrow$[2]
$\uparrow Ca^{++}$	$\uparrow$[3]	$\uparrow$
$\uparrow$Os	$\downarrow$	
$\downarrow K^+$	$\uparrow$	$\uparrow$
$\downarrow Mg^{++}$	<—>	
$\downarrow H^+$ ($\uparrow$pH)	$\uparrow$[4]	$\uparrow$
$\downarrow Na^+$	<—>	$\uparrow$[2]
$\downarrow Ca^{++}$	$\downarrow$	$\downarrow$
$\downarrow$Os	$\uparrow$	

[1] $[K^+]$ greater than 8 mEq/l.

[2] Guyton, 1966.

[3] Exception-gastric bed, where $\uparrow[Ca^{++}]$ causes $\downarrow$R.

[4] Inconsistent response - dependent upon agent used to produce the alkalosis.

electrolyte plasma concentrations are capable of producing a measurable alteration in vascular resistance.

To add further support to the importance of this research, it was discovered that the four-electrolyte combinations mentioned above ($\downarrow[K^+]$, $\downarrow[Mg^{++}]$, $\uparrow[Ca^{++}]$, $\uparrow$pH) produced more intense constriction than the combined action of only three changes - $\downarrow[K^+]$, $\uparrow[Ca^{++}]$, and $\uparrow$pH. This seemed to indicate that while the condition of hypomagnesemia does not seem to have any intrinsic effect on vascular resistance, it still causes vasoconstriction in the presence of the other three abnormalities (Haddy and Scott, 1965).

This enhanced effect of electrolyte combinations also seems to exist, with opposite electrolyte changes. For example, in the isolated forelimb, hyperkalemia and hypermagnesemia produce vasodilation of greater magnitude than either change generated alone (Haddy and Scott, 1965).

Skinner and Costin (1970) have shown this same type of potentiated effect while studying the vasodilatory effects of hypoxia, hyperkalemia, and hyperosmolarity on an isolated dog gracilis muscle.

Systemic Effects of Combined Electrolyte Alterations

Since minute local concentration changes of one or more cations effect both vascular smooth muscle and cardiac muscle, then a correspondingly small, single generalized electrolyte change might have a similar effect on systemic arterial blood pressure. However, several investigators

reported that this was not the case. For example, acute hyperkalemia (up to 10 mEq/l) in an intact dog results in a slight bradycardia with little effect on blood pressure (Hoff et al., 1939). Other ion concentration changes did not seem to regularly affect blood pressure, perhaps due to the concurrent action of compensatory mechanisms of the blood pressure buffering systems. Dale and Evans (1922) suggested that the lack of a pressure response following acute generalized alkalosis could be explained by the antagonism of a generalized sympathico-adrenal discharge.

Scott et al., (1968) reported the effects of generalized plasma electrolyte changes, both single and combined, on systemic blood pressure. Two methods were used, both employing a diuretic, furosemide, to reduce water and plasma electrolyte concentrations. With the hypervolemic diuretic method, the fluid volume loss caused by the furosemide was replaced by a bolus injection of the desired solution. Creation of the abnormalities $\downarrow[K^+]$, $\downarrow[Mg^{++}]$, $\uparrow[Ca^{++}]$, and $\uparrow$pH caused a large rise in systemic blood pressure, with corresponding increases in systolic and diastolic pressures and a decrease in heart rate. When the opposite changes were created, a decrease in blood pressures (mean, systolic, and diastolic) was seen. While a control solution did slightly increase blood pressure, this could be explained by the amount of hypervolemia induced.

A second type of diuretic study was also used. This was an isovolemic method and called for essentially the

same overall procedure as used in the first study with the exception that urine volume loss was immediately replaced in the dog milliliter for milliliter (Haddy et al., 1969). Spinal anesthesia, using procaine hydrochloride, was instituted to eliminate any possible influence of neurologically mediated baraostatic mechanisms. Hypokalemia and hypomagnesemia caused an increase in blood pressure. This blood pressure rise was not enhanced by superimposing hypercalcemia and alkalosis. When the opposite electrolyte changes were made, a fall in systemic blood pressure, due to hypermagnesemia and possibly hypocalcemia and acidosis, was seen. Complete spinal anesthesia, while failing to effect blood pressure in the presence of the hypertensive combination ($\downarrow[K^+]$, $\downarrow[Mg^{++}]$, $\uparrow[Ca^{++}]$, $\uparrow$pH), did reduce pressure in the presence of the opposite hypotensive cation combinations. Partial buffering by the baroreceptor mechanisms of the blood pressure effects of the electrolytes was evident (Haddy et al., 1969). Complete spinal anesthesia apparently "unmasks" the potent vasoactivity of electrolyte abnormalities.

A third method of studying the effects of acute multiple electrolyte changes has been investigated (Emerson et al., 1970). It is a non-diuretic method involving the infusion of various test solutions at 10cc/Kg/min for 5 minutes. Thus, by the termination of the experiment, hypervolemia has become a significant factor. Infusion of a solution to simultaneously

create $\downarrow[K^+]$, $\downarrow[Mg^{++}]$, $\uparrow[Ca^{++}]$, $\uparrow$pH, and $\downarrow$Os caused a 30 percent rise in mean blood pressure. Infusion of a solution causing the opposite electrolyte changes of $\uparrow[K^+]$, $\uparrow[Mg^{++}]$, $\downarrow[Ca^{++}]$, $\downarrow$pH, and $\uparrow$Os resulted in a 15 percent decrease in pressure. The control solution failed to alter pressure by more than 4 percent. Attempts were made to determine the contribution of each single abnormality to the response produced by the total hypertensive combination. While each abnormality ($\downarrow[K^+]$, $\downarrow[Mg^{++}]$, $\uparrow[Ca^{++}]$, $\uparrow$pH, and $\downarrow$Os) produced a significant rise in blood pressure, not one of these electrolyte changes produced a response equal to that of the total hypertensive solution. Further, the effect of any one electrolyte change was not significantly different from another. Combinations such as ($\downarrow[K^+]$, $\downarrow[Mg^{++}]$, $\uparrow$pH), ($\downarrow[K^+]$, $\downarrow[Mg^{++}]$), and ($\downarrow[K^+]$, $\uparrow[Ca^{++}]$) produced the same results - each lesser combination produced a significant response compared to normal, but much less of a response than seen with the original hypertensive combination.

METHODS

Experimental Set-up

Eighty-six mongrel dogs of various sizes (average wt. = 14.1 Kg; range - 10-20 Kg), and both sexes were used for these experiments. Anesthesia was induced using an intravenous injection of sodium pentobarbital (30 mg/Kg). Coagulation was inhibited with heparin (5 mg/Kg). The dogs were ventilated with a positive pressure respirator (Model 607, Harvard Apparatus Co.) *via* an endotrachial tube. The respirator was adjusted to obtain a minute respiratory volume which would give a near normal pH (7.40 ± 0.02 units). The two common carotid arteries were isolated and looped loosely with ligatures. Both femoral arteries and veins were cannulated and the catheters were advanced into the abdominal aorta and inferior vena cava. One arterial catheter was used for monitoring mean arterial, systolic, and diastolic blood pressures, the other for obtaining blood samples. Electrolyte solutions were infused through the two venous catheters. Central vein pressure was measured by advancing a catheter through an external jugular vein to a point in or near the right atrium. PE 240 polyethylene tubing was used for all cannulae. Blood pressures were

measured *via* physiological pressure transducers (Statham Laboratories, Model P23Gb) which served as input into a six-channel Sanborn polygraph. Both strain gauges were routinely calibrated using a mercury manometer. Heart rate was monitored using five EKG electrodes, implanted subcutaneously, and recorded *via* a Sanborn Cardiotach preamplifier. The carotid sinus reflex was elicited by occluding both common carotids *via* the looped ligatures.

Spinal anesthesia was achieved using a 20 gauge 1 1/2 inch needle inserted into the cisterna magna. An average of 6 ml of cerebrospinal fluid were withdrawn and 6 ml of 2% procaine hydrochloride (Abbott Laboratories) were slowly infused over a 3 to 4 minute period. Arterial pressure usually stabilized 35-40 mm Hg below control level following procaine infusion. The carotid sinus reflex was again tested to determine the effectiveness of the block. After an additional 5-minute stabilization period, a control 10 ml arterial blood sample was taken.

The solutions infused (specifically, their composition and predicted plasma electrolyte changes) are listed in Table II. These solutions were infused I.V. at 10 ml/Kg/min for five minutes (Sigmamotor pump, Zero-Max Co.). Only one solution was used per experiment. When hypercalcemia was desired (solutions 1 and 7 in Table II) isotonic $CaCl_2$ was infused separately but simultaneously at an infusion rate of 0.5 ml/Kg/min (Infusion/Withdrawal Pump, Model 901, Harvard Apparatus Co.), to achieve the desired calcium ion

Table II. Makeup of solutions.

Solution	Na^+ (mEq/l)	K^+ (mEq/l)	Mg^{++} (mEq/l)	Ca^{++}** (mEq/l)	HCO_3^- (mEq/l)	Cl^- (mEq/l)	Osmolarity (mOsm/l)	Predicted Plasma Change
1. Hypertensive	104	0	0	0*	104	0	207	$\downarrow K^+$, $\downarrow Mg^{++}$, $\uparrow Ca^{++}$, $\uparrow$pH, $\downarrow$Os
2. Hypotensive	232	27	10	0	0	269	528	$\uparrow K^+$, $\uparrow Mg^{++}$, $\downarrow Ca^{++}$, $\downarrow$pH, $\uparrow$Os
3. Control	144	4	2	5	21	128	305	None
4. Hypo-osmolar	99	4	3	5	27	70	203	$\downarrow$Os
5. Hypokalemic	151	0	2	5	26	120	301	$\downarrow K^+$
6. Hypomagnesemic	148	4	0	5	25	125	307	$\downarrow Mg^{++}$
7. Hypercalcemic	146	4	2	0*	26	126	304	$\uparrow Ca^{++}$
8. Alkalotic	149	4	2	5	107	40	298	$\uparrow$pH

*Isotonic $CaCl_2$ infused separately but simultaneously at 0.5 ml/Kg/min.

**Calcium in solution was present as calcium gluconate.

concentration changes. All solutions were kept at 37°C in a water bath until shortly before infusion.

Just before the end of the five minute infusion period, blood sample #2 was drawn. Immediately following infusion, the carotid sinus reflex was again tested. The animal was allowed to return to a normal steady state for 15 minutes. At this point, the third blood sample was drawn and the carotid sinus reflex again tested. To further test the spinal block, the animal was then allowed to breathe voluntarily, but, due to spinal anesthesia, respiration failed to take place, even when blood pressure fell drastically.

The three blood samples were analyzed for the following: pH, hematocrit, osmolarity, $[K^+]$, $[Mg^{++}]$, $[Ca^{++}]$, and $[Na^+]$. These parameters, their units of measure, the instruments used to determine them, and the confidence limits of these instruments are depicted in Table III.

The results from these experiments have been analyzed and will be presented in two ways. First, data obtained from these experiments were analyzed intrinsically, i.e. within itself. Then, this same set of data was extrinsically examined, i.e. compared with earlier studies (Emerson et al., 1968). The latter analysis was necessary to determine the effect of barareceptor blockade which is the main purpose of this study.

Table III. Blood parameter measurement information.

	Parameter	Units of Measure	Instrument	Confidence Limits
1)	pH	*units	pH meter 22 - Astrup Radiometer	±0.02
2)	Hct	%	Micro hematocrit centrifuge	±0.5
3)	Osmolarity	mOsm/l	Advanced Osmometer (freezing point depression)	±5
4)	$[Ca^{++}]$	mEq/l	Perkin-Elmer Atomic Absorber (Model 290B)	±0.04
5)	$[Mg^{++}]$	mEq/l	Perkin-Elmer Atomic Absorber (Model 290B)	±0.018
6)	$[Na^{+}]$	mEq/l	Beckman Flame Photometer (Model 105)	±1
7)	$[K^{+}]$	mEq/l	Beckman Flame Photometer (Model 105)	±0.1

*Indirect measurement of $[H^{+}]$ mEq/l -- pH = -log $[H^{+}]$.

Statistical Analysis

Statistical analysis of the data from these experiments was performed using an unpaired Student's "t" test. "P" values below the 0.05 level were considered significant. Further explanation of statistical evaluation is presented in the Appendix.

RESULTS

Intrinsic Analysis

Figure 1 is a summary of the average mean arterial blood pressure responses of all groups of electrolytes investigated. While Figure 1 encompasses much more, at this point discussion shall deal with the hypertensive solution ($\downarrow[K^+]$, $\downarrow[Mg^{++}]$, $\uparrow[Ca^{++}]$, $\downarrow$Os, $\uparrow$pH) and its relationship to control. Since both the hypertensive (Solution 1) and control (Solution 3) solutions significantly increased arterial blood pressure, we must begin to talk in terms of the difference between the above two pressure changes. While Solution I (see Table II) did increase mean blood pressure 66 mm Hg, it must be taken into account that an equivolume infusion of control Solution 3 caused a 45 mm Hg increase in pressure. Thus, Solution 1, creating the multiple electrolyte and water abnormalities of $\downarrow[K^+]$, $\downarrow[Mg^{++}]$, $\uparrow[Ca^{++}]$, $\downarrow$Os, and $\uparrow$pH, increased blood pressure 21 mm Hg more than the control Solution 3 ($p \leq 0.05$), which caused no electrolyte or osmotic abnormalities. The same responses for systolic and diastolic blood pressures were observed. The maximum pressure differences between the experimental and control solutions occurred at the 5th minute of infusion. This is also the time of maximum volume and electrolyte change.

Figure 1. Summary of mean arterial blood pressure (ABP) responses of all groups investigated. Responses are expressed as a percent change (%Δ) in blood pressure, relative to control, over the 5-minute infusion interval. Dashed lines = normal, intact studies; solid lines = spinally anesthetized studies.

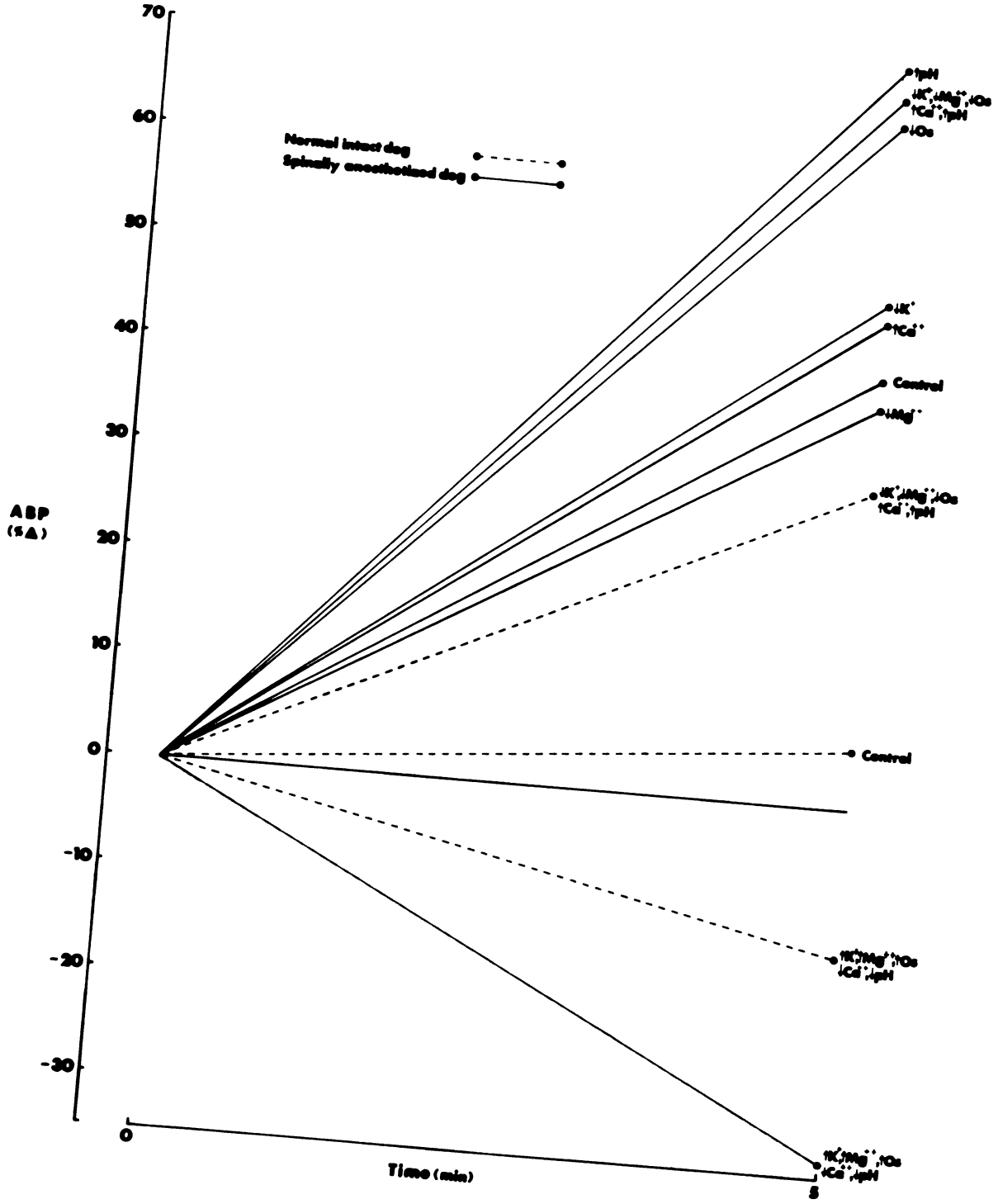
70
60
50
40
30
20
10
0
-10
-20
-30
ABP
(±Δ)
Normal intact dog
Spinally anesthetized dog
↑pH
↓Ca
↓K
↑Ca
Control
↓Mg
Control
0
Time (min)
5

Figure 1.

Figures 2a-c illustrate the pressure, rate, plasma electrolyte, and blood pressure changes that took place during the infusions of the hypertensive (Solution 1), hypotensive (Solution 2), and control (Solution 3) solutions. In Figure 2a, the differences between the hypertensive and control solutions for mean arterial, systolic, and diastolic blood presssures, at 5 minutes into the infusion, were 21, 24, and 23 mm Hg, respectively ($P \leq 0.05$). Central venous pressure increased steadily from 2 to 15 mm Hg with no significant difference between the hypertensive and control solutions. In fact, no solution used in this study caused any departure in CVP response from what was cited above. Heart rate increased 14 beats/minute, most of this in the last two minutes of infusion of the hypertensive solution. Infusion of approximately 700 ml of Solution 1 produced hypokalemia (-0.5 mEq/l), hypomagnesemia (-0.55 mEq/l), hypercalcemia (+1.5 mEq/l), hypo-osmolarity (-16 mOsm/l), and alkalosis (increased pH = +0.18 units), as seen in Figures 2 b-c. Hematocrit, associated with blood dilution by the infusate, fell 13%, which is approximately equal to the drop all solutions caused. In all cases, blood pressure and plasma parameters returned to near-normal values within 10-15 minutes after the infusion was stopped. Figure 3 shows a representative tracing illustrating the cardiovascular effects of a 5-minute infusion of hypertensive Solution 1.

Figure 2a. Pressure and rate changes that took place during infusion of hypertensive, hypotensive, and control solutions. Solid lines = hypertensive solution 1; dashed lines = hypotensive solution 2; dot-dashed lines = control solution 3.

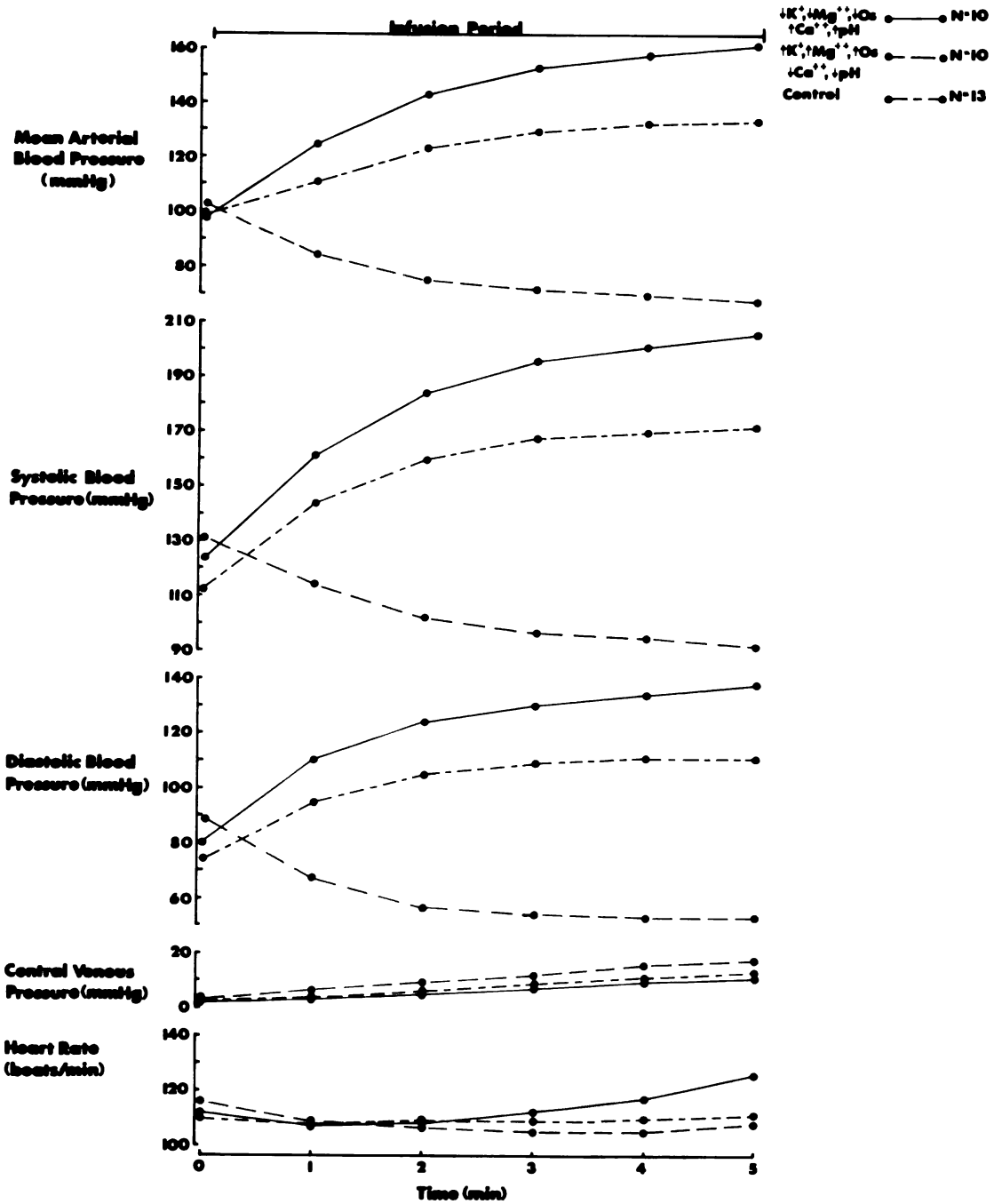
Infusion Period
↓K⁺,↓Mg⁺⁺,↓Os ↑Ca⁺⁺,↑pH N=10
↑K⁺,↑Mg⁺⁺,↑Os ↓Ca⁺⁺,↓pH N=10
Control N=13
Mean Arterial Blood Pressure (mmHg)
160
140
120
100
80
Systolic Blood Pressure (mmHg)
210
190
170
150
130
110
90
Diastolic Blood Pressure (mmHg)
140
120
100
80
60
Central Venous Pressure (mmHg)
20
0
Heart Rate (beats/min)
140
120
100
0
1
2
3
4
5
Time (min)

Figure 2a.

Figure 2b. Plasma electrolyte changes that took place during infusion of hypertensive, hypotensive, and control solutions. Line symbols are the same as for Figure 2a.

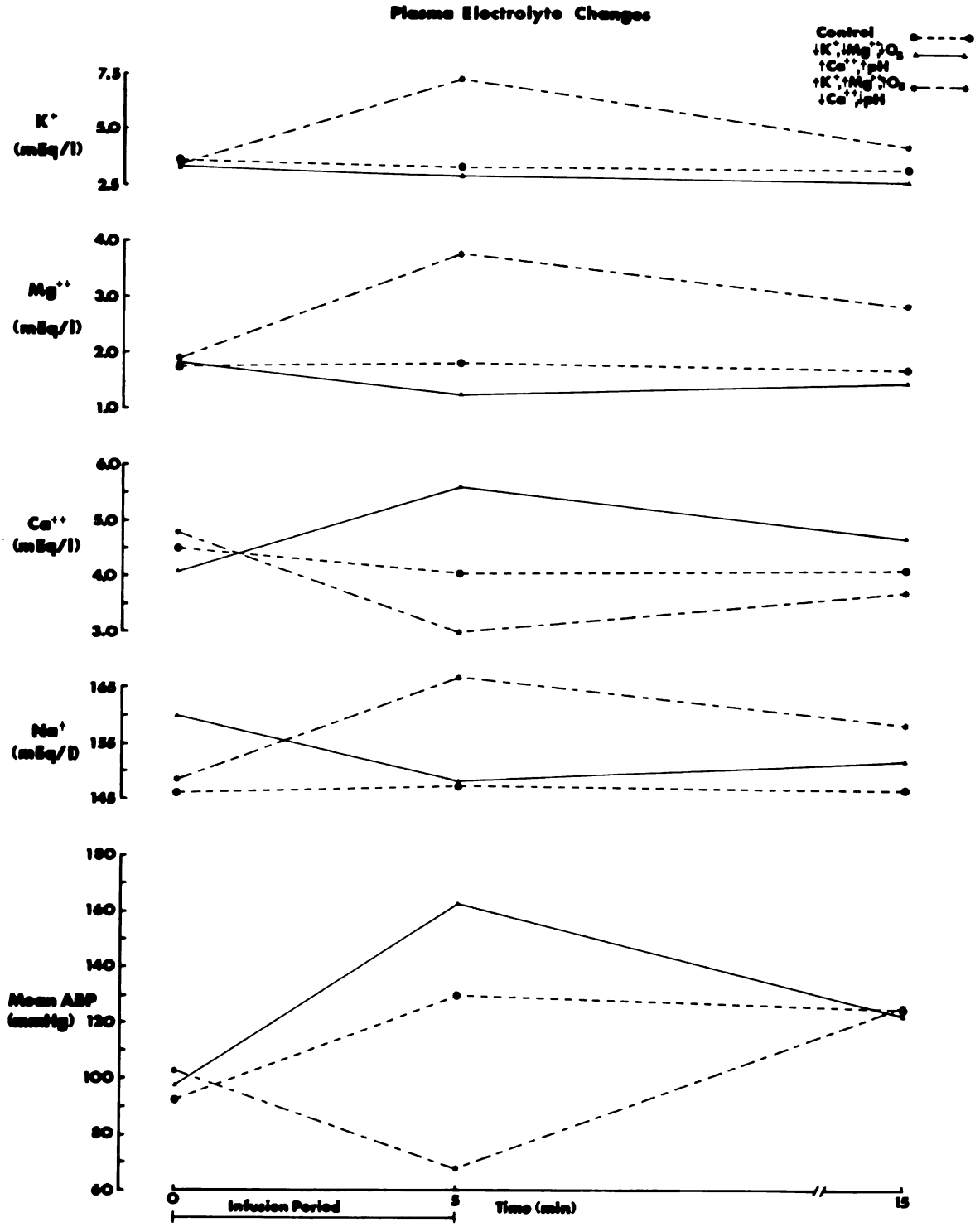
Plasma Electrolyte Changes
Control
↓K⁺,↓Mg⁺⁺,↑O₂
↑Ca⁺⁺,↑pH
↑K⁺,↑Mg⁺⁺,↑O₂
↓Ca⁺⁺,↓pH
K⁺ (mEq/l)
7.5
5.0
2.5
Mg⁺⁺ (mEq/l)
4.0
3.0
2.0
1.0
Ca⁺⁺ (mEq/l)
6.0
5.0
4.0
3.0
Na⁺ (mEq/l)
165
155
145
Mean ABP (mmHg)
180
160
140
120
100
80
60
0
Infusion Period
5
Time (min)
15

Figure 2b.

Figure 2c. Blood parameter changes that took place during infusion of hypertensive, hypotensive, and control solutions. Line symbols are the same as for Figure 2a

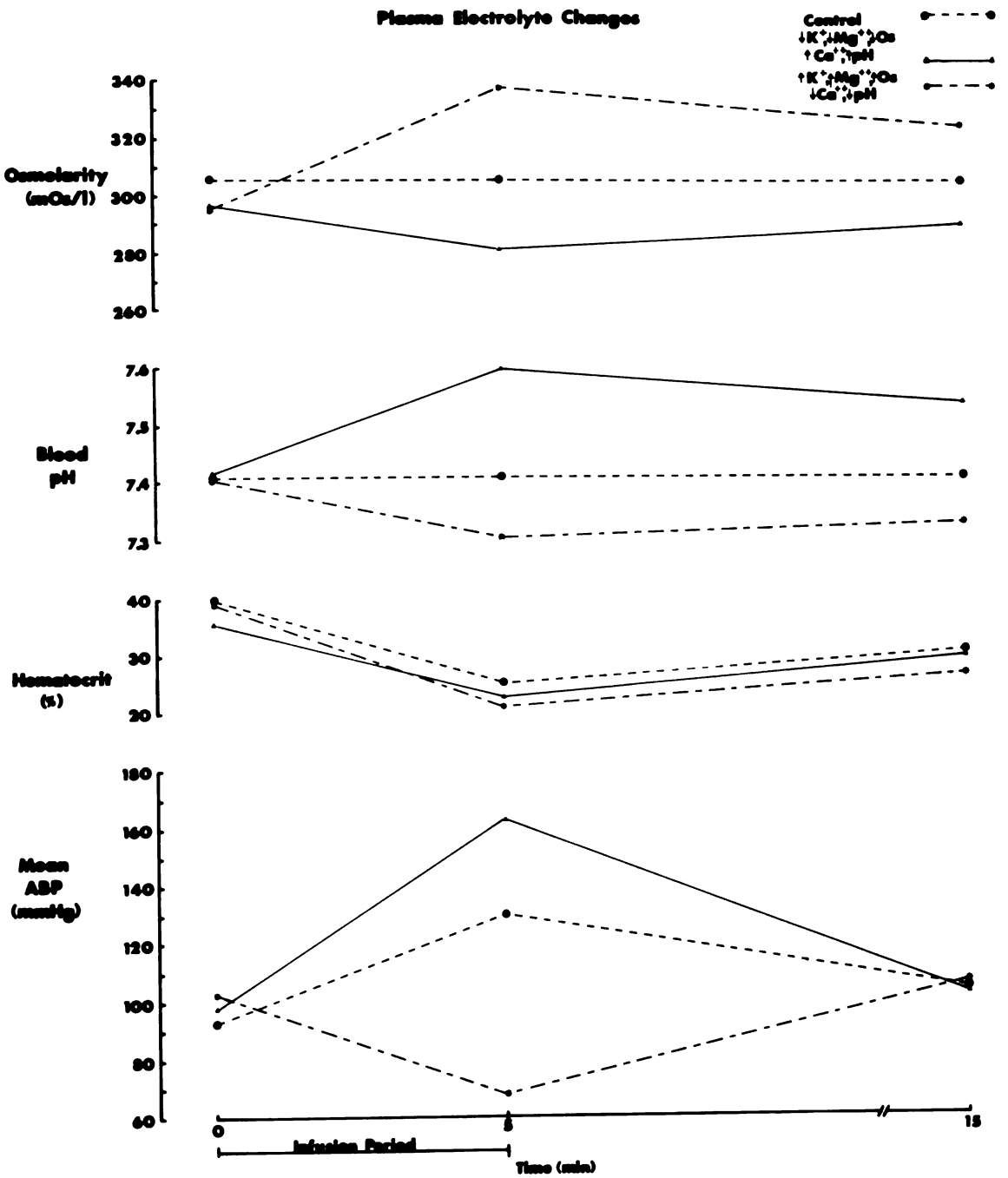
Plasma Electrolyte Changes
Control
↓K⁺,↓Mg⁺⁺,↑Os
↑Ca⁺⁺,↑pH
↑K⁺,↓Mg⁺⁺,↑Os
↓Ca⁺⁺,↓pH
Osmolarity (mOs/l)
340
320
300
280
260
Blood pH
7.6
7.5
7.4
7.3
Hematocrit (%)
40
30
20
Mean ABP (mmHg)
180
160
140
120
100
80
60
0
5
15
Infusion Period
Time (min)

Figure 2c.

Figure 3. Representative tracing showing the cardiovascular effects during 5-minute infusion of hypertensive solution 1 (causing hypokalemia, hypomagnesemia, hypercalcemia, hypo-osmolarity, and alkalosis).
ABP = arterial blood pressure; CVP = central vein pressure; HR = heart rate.

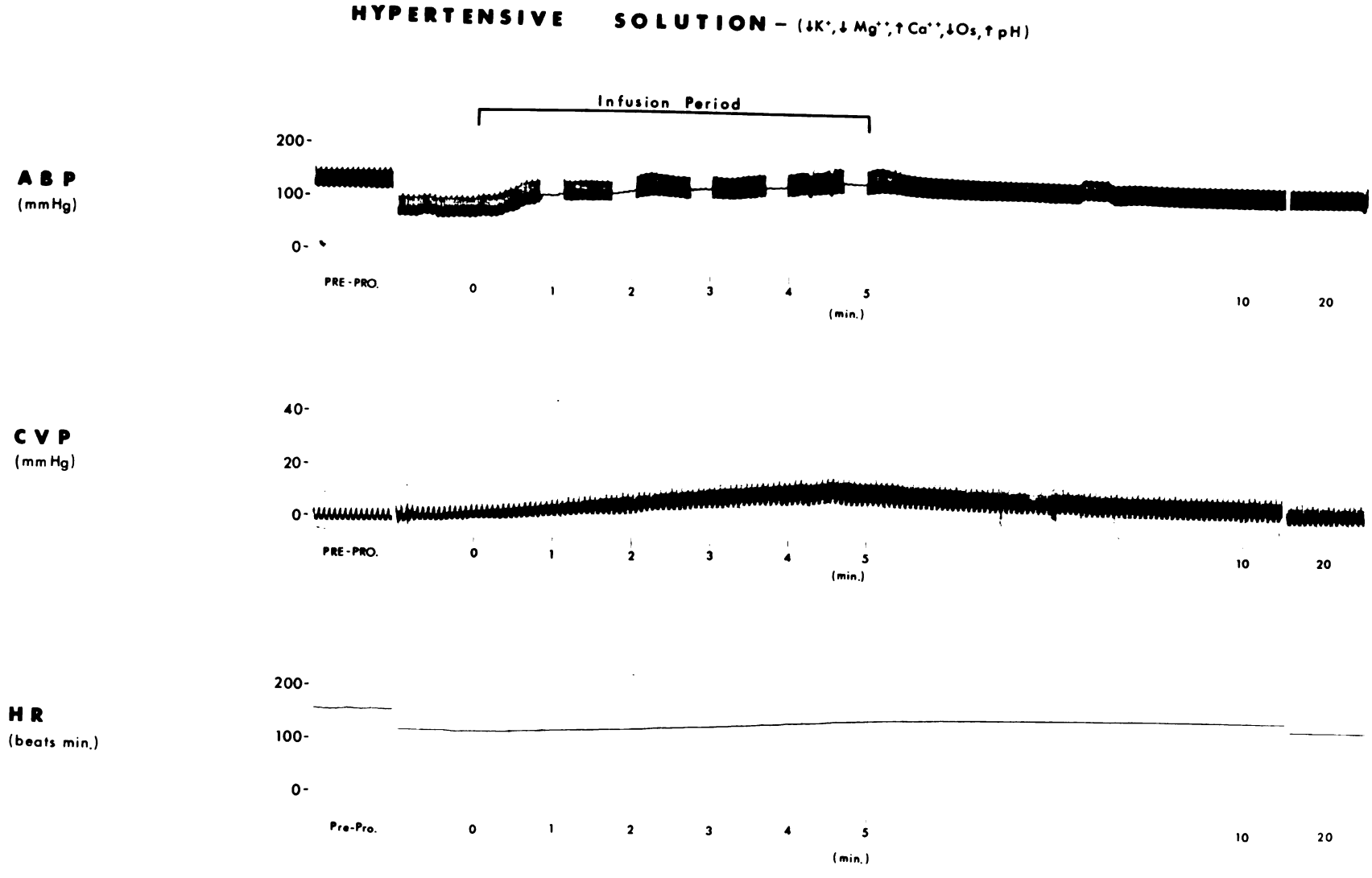
HYPERTENSIVE SOLUTION – (↓K⁺, ↓ Mg⁺⁺, ↑ Ca⁺⁺, ↓Os, ↑ pH)
Infusion Period
ABP
(mmHg)
200-
100-
0-
PRE-PRO.
0
1
2
3
4
5
(min.)
10
20
CVP
(mmHg)
40-
20-
0-
PRE-PRO.
0
1
2
3
4
5
(min.)
10
20
HR
(beats min.)
200-
100-
0-
Pre-Pro.
0
1
2
3
4
5
(min.)
10
20

Figure 3.

The hypotensive solution (Solution 2) created the opposite electrolyte charges ($\uparrow[K^+]$, $\uparrow[Mg^{++}]$, $\downarrow[Ca^{++}]$, $\uparrow$Os, $\downarrow$pH) and elicited the opposite effect on blood pressure. Examination of Figure 1 shows Solution 2 caused a 34% drop in blood pressure from a control pre-infusion level. Relative to control, Solution 2 caused, at the end of the 5-minute infusion period, close to an 80% drop in the blood pressure.

Figures 2 a-c again show the large pressure decreases caused by the hypotensive solution. In Figure 2a, the differences between the hypotensive and control solutions for mean arterial, systolic, and diastolic blood pressures were 80, 98, and 71 mm Hg, respectively. Heart rate decreased 8 beats/minute, but this was not significant. As noted in Figures 2 b-c, hyperkalemia (+3.9 mEq/l), hypermagnesemia (+1.90 mEq/l), hypocalcemia (-1.8 mEq/l), hyperosmolarity (+39 mOsm/l), and acidosis (decreased pH = -0.11 units) were produced upon I.V. infusion of 700 ml of Solution 2. The hematocrit fell 18%, but this drop was indistinguishable from those caused by the control and other solutions. Figure 4 is a representative tracing illusrating the cardiovascular effects of infusion of hypotensive Solution 2.

Infusion of the control Ringer's solution produced a mean blood pressure rise of 45 mm Hg, a systolic blood pressure rise of 59 mm Hg, and a diastolic blood pressure rise of 35 mm Hg, as seen in Figure 2a. Figures 2 b-c clearly show that 700 ml infusion of this control solution

Figure 4. Representative tracing showing the cardiovascular effects during 5-minute infusion of hypotensive solution 2 (causing hyperkalemia, hypermagnesemia, hypocalcemia, hyperosmolarity, and acidosis). Symbols are the same as for Figure 3.

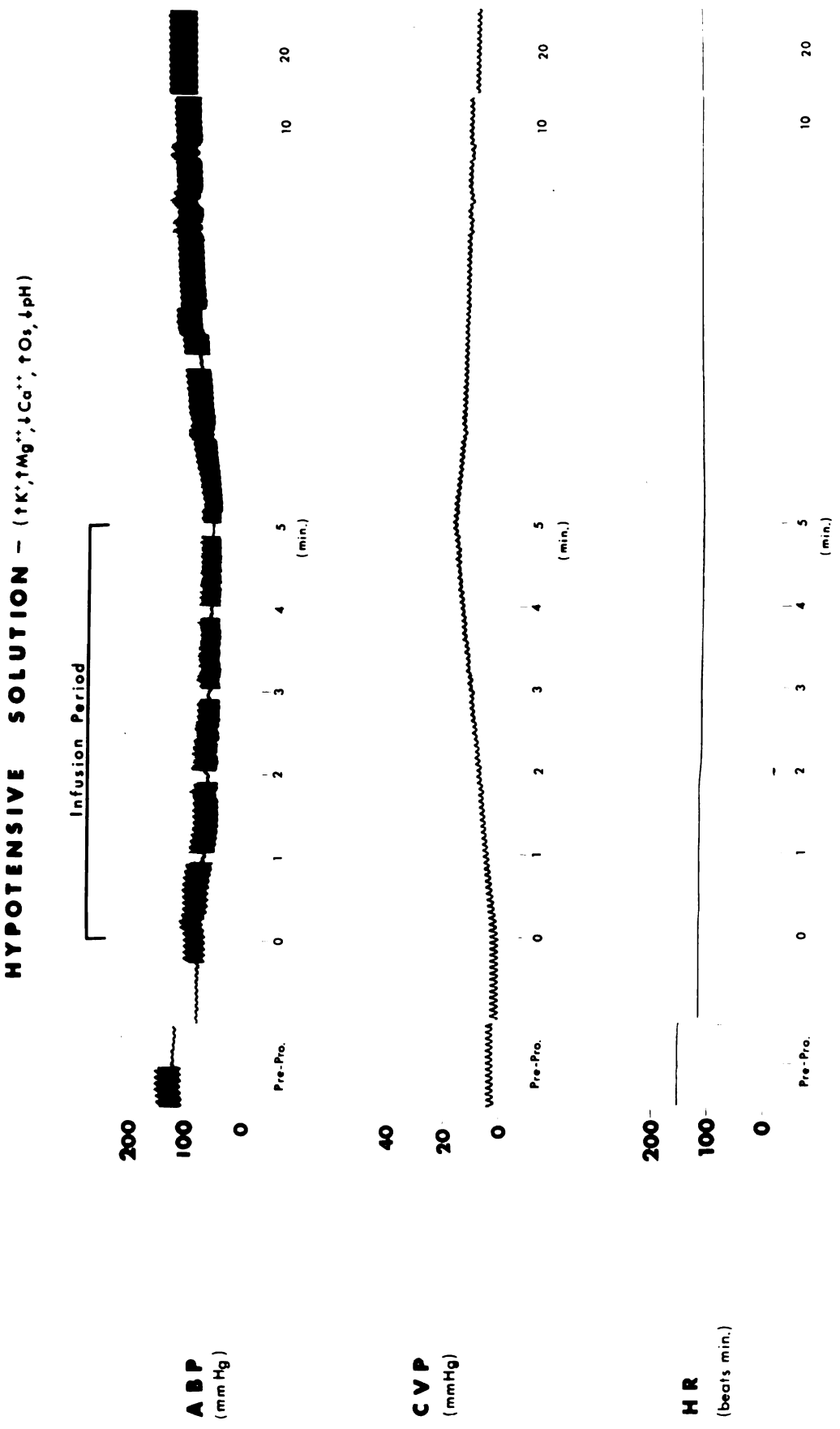
HYPOTENSIVE SOLUTION – (↑K⁺, ↑Mg⁺⁺, ↓Ca⁺⁺, ↑Os, ↓pH)
Infusion Period
ABP
(mm Hg)
200
100
0
Pre-Pro.
0
1
2
3
4
5
(min.)
10
20
CVP
(mmHg)
40
20
0
Pre-Pro.
0
1
2
3
4
5
(min.)
10
20
HR
(beats min.)
200
100
0
Pre-Pro.
0
1
2
3
4
5
(min.)
10
20

Figure 4.

produced no significant electrolyte alterations. Heart rate stayed constant and hematocrit decreased an insignificant 14%. A representative tracing of the cardiovascular effects of infusion of control Solution 3 is seen in Figure 5.

Analysis of each individual electrolyte change, i.e. hypokalemia, hypomagnesemia, hypercalcemia, hypo-osmolarity, or alkalosis, showed no significant increases in any electrolyte measured, except, of course, the one in question.

Specifically, a decreased $[K^+]$ of 0.6 mEq/l caused a net mean arterial blood pressure increase of 49 mm Hg, which proves to be no different from the response of the control solution. Figure 6 graphically compares the pressure changes occurring during infusion of the hypokalemic and control solutions. Neither systolic nor diastolic blood pressures varied significantly from the control solution. Heart rate, although starting at a higher rate, did not vary.

Likewise, a decreased $[Mg^{++}]$ of 0.67 mEq/l caused little, if any, deviation from control solution pressure values (refer to Figure 7). Hypercalcemia (+1.3 mEq/l) failed to produce any distinguishable pressure effect. However, heart rate, as a direct result of cardiac stimulation by calcium, did increase 12% over control (refer to Figure 8).

Infusion of a hypo-osmolar solution, causing an osmolarity decrease of 16 mOsm/l in the plasma, produced a significant effect on blood pressure. Figure 9 shows that mean blood pressure increased 57 mm Hg or 12 mm Hg

Figure 5. Representative tracing showing the cardiovascular effects during 5-minute infusion of control solution 3 (causing no electrolyte or osmolarity changes). Symbols are the same as for Figure 3.

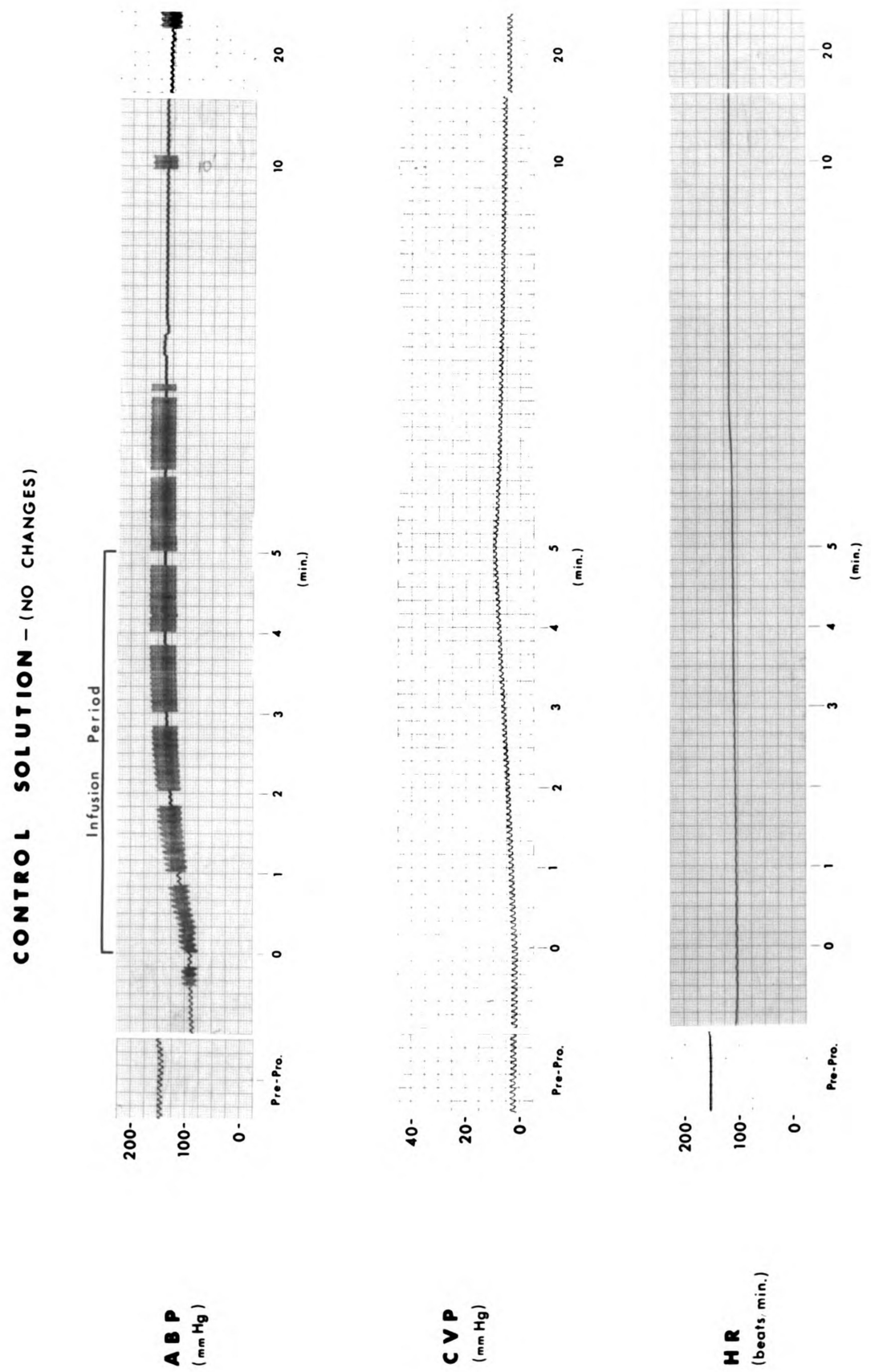
CONTROL SOLUTION – (NO CHANGES)
Infusion Period
ABP
(mm Hg)
200-
100-
0-
Pre-Pro.
0
1
2
3
4
5
(min.)
10
20
CVP
(mm Hg)
40-
20-
0-
HR
(beats min.)

Figure 5.

Figure 6. Average pressure and rate changes caused by the plasma electrolyte change $\downarrow[K^+]$ and compared with the control curve. Dashed lines = control; solid lines = electrolyte change curve.

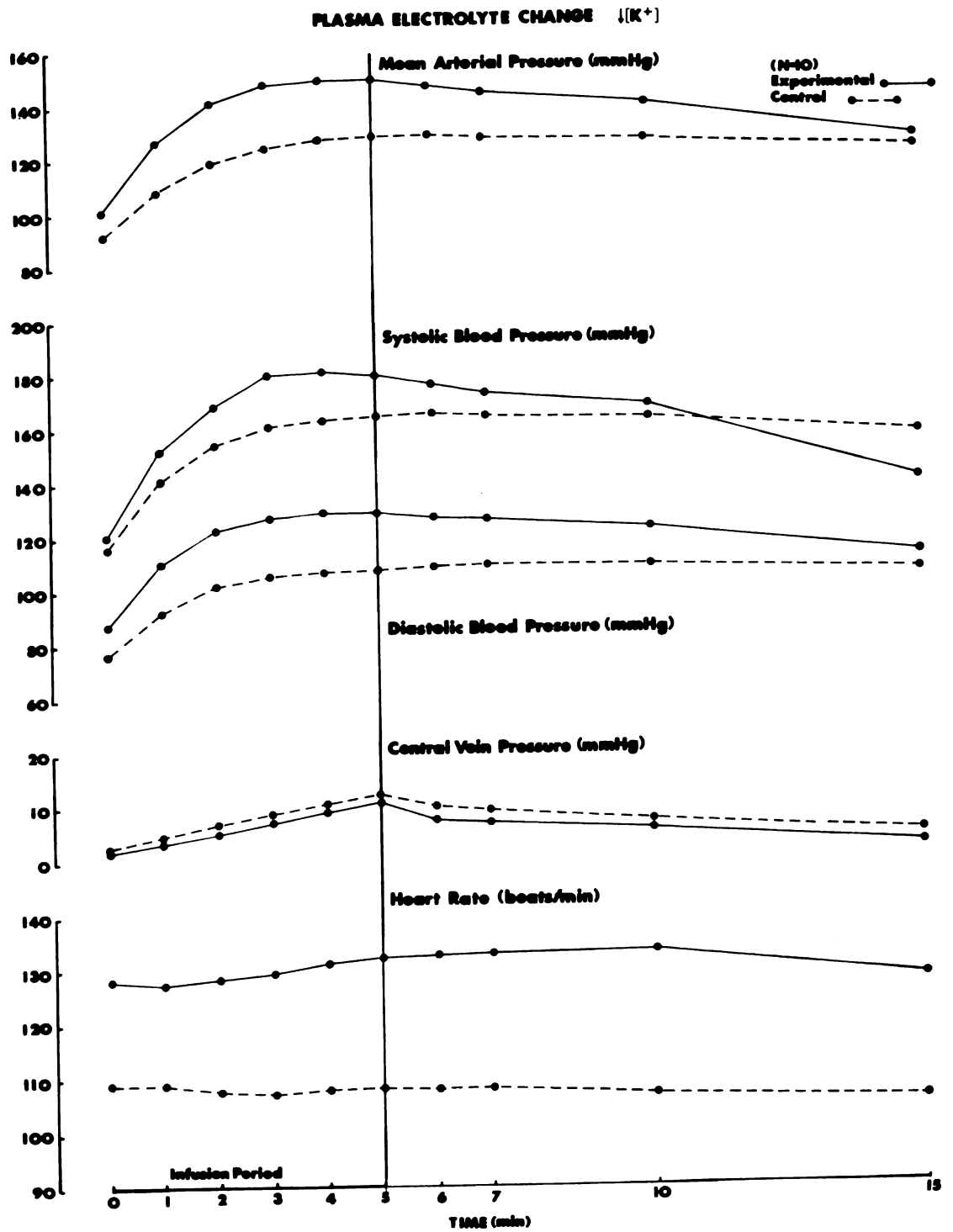
PLASMA ELECTROLYTE CHANGE ↓[K+]
Mean Arterial Pressure (mmHg)
(N=10)
Experimental
Control
160
140
120
100
80
Systolic Blood Pressure (mmHg)
200
180
160
140
120
100
80
60
Diastolic Blood Pressure (mmHg)
Central Vein Pressure (mmHg)
20
10
0
Heart Rate (beats/min)
140
130
120
110
100
90
Infusion Period
0
1
2
3
4
5
6
7
10
15
TIME (min)

Figure 6.

Figure 7. Average pressure and rate changes caused by the plasma electrolyte change $\downarrow[Mg^{++}]$ and compared with the control curve. Symbols are the same as for Figure 6.

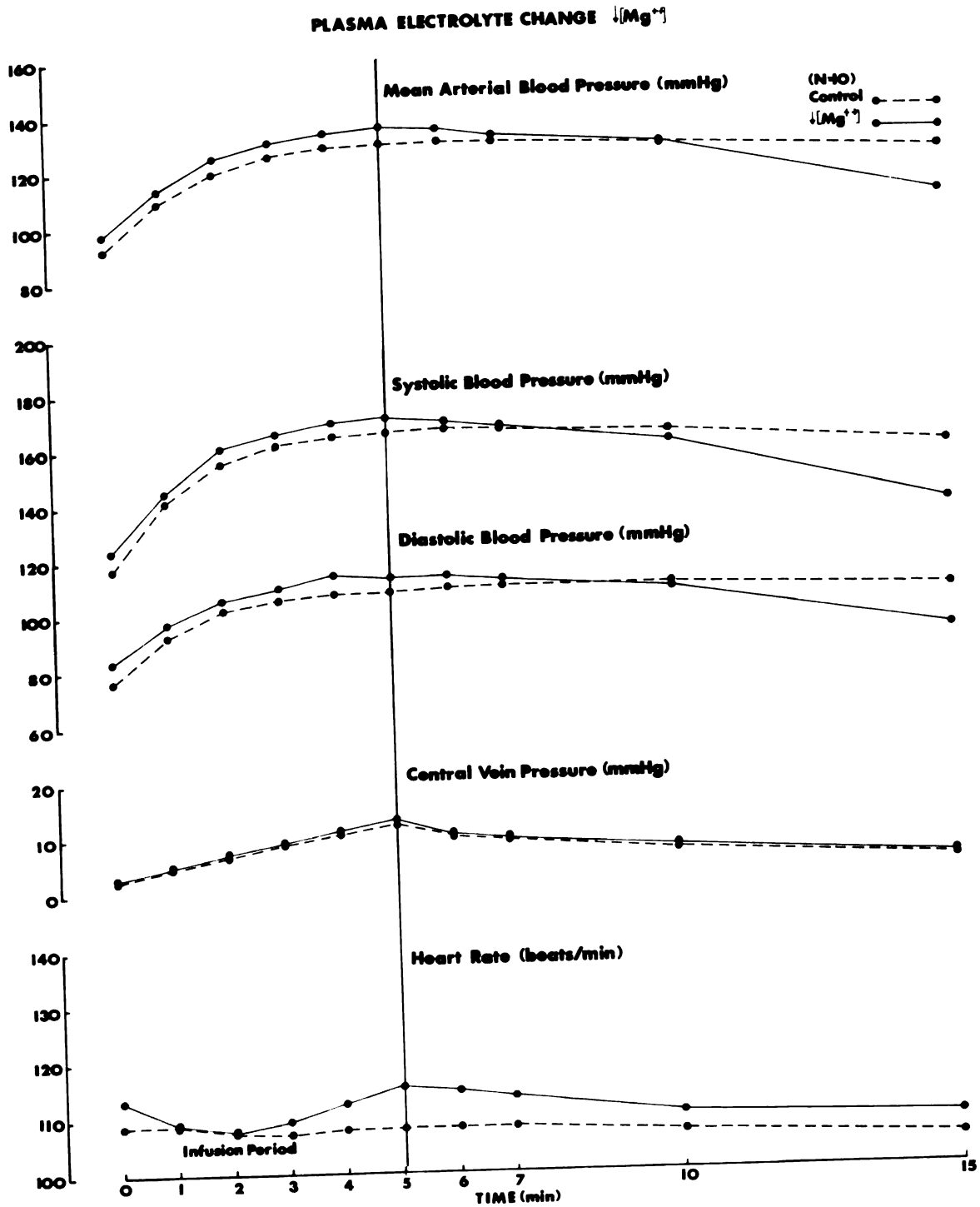
PLASMA ELECTROLYTE CHANGE ↓[Mg++]
Mean Arterial Blood Pressure (mmHg)
(N=10)
Control
↓[Mg++]
160
140
120
100
80
Systolic Blood Pressure (mmHg)
200
180
160
140
120
100
80
60
Diastolic Blood Pressure (mmHg)
Central Vein Pressure (mmHg)
20
10
0
Heart Rate (beats/min)
140
130
120
110
100
Infusion Period
0
1
2
3
4
5
6
7
10
15
TIME (min)

Figure 7.

Figure 8. Average pressure and rate changes caused by the plasma electrolyte change $\uparrow[Ca^{++}]$ and compared with the control curve. Symbols are the same as for Figure 6.

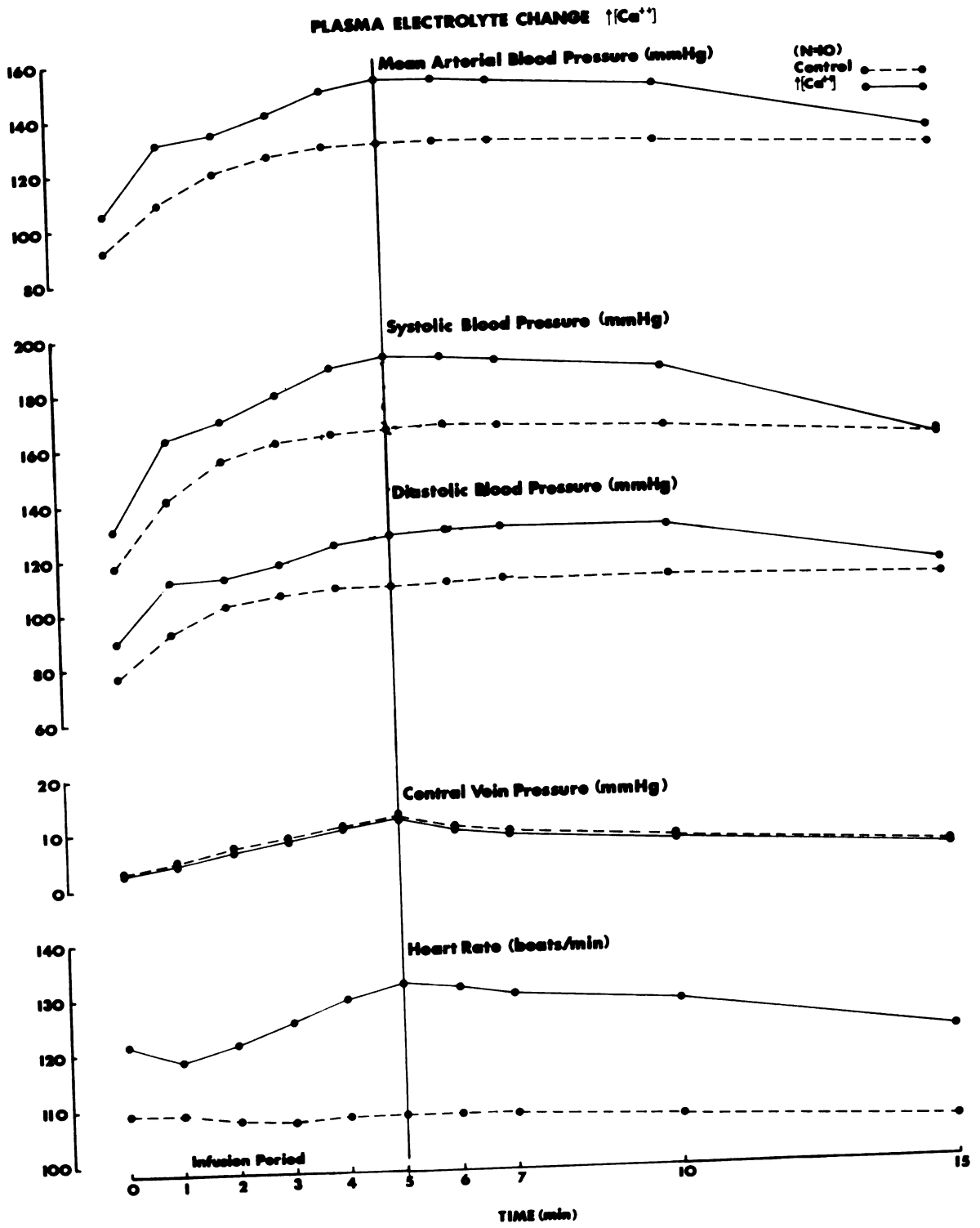
PLASMA ELECTROLYTE CHANGE ↑[Ca++]
Mean Arterial Blood Pressure (mmHg)
(N=10)
Control
↑[Ca++]
160
140
120
100
80
Systolic Blood Pressure (mmHg)
200
180
160
140
120
100
80
60
Diastolic Blood Pressure (mmHg)
Central Vein Pressure (mmHg)
20
10
0
Heart Rate (beats/min)
140
130
120
110
100
Infusion Period
0
1
2
3
4
5
6
7
10
15
TIME (min)

Figure 8.

Figure 9. Average pressure and rate changes caused by the blood parameter change ↓Os and compared with the control curve. Symbols are the same as for Figure 6.

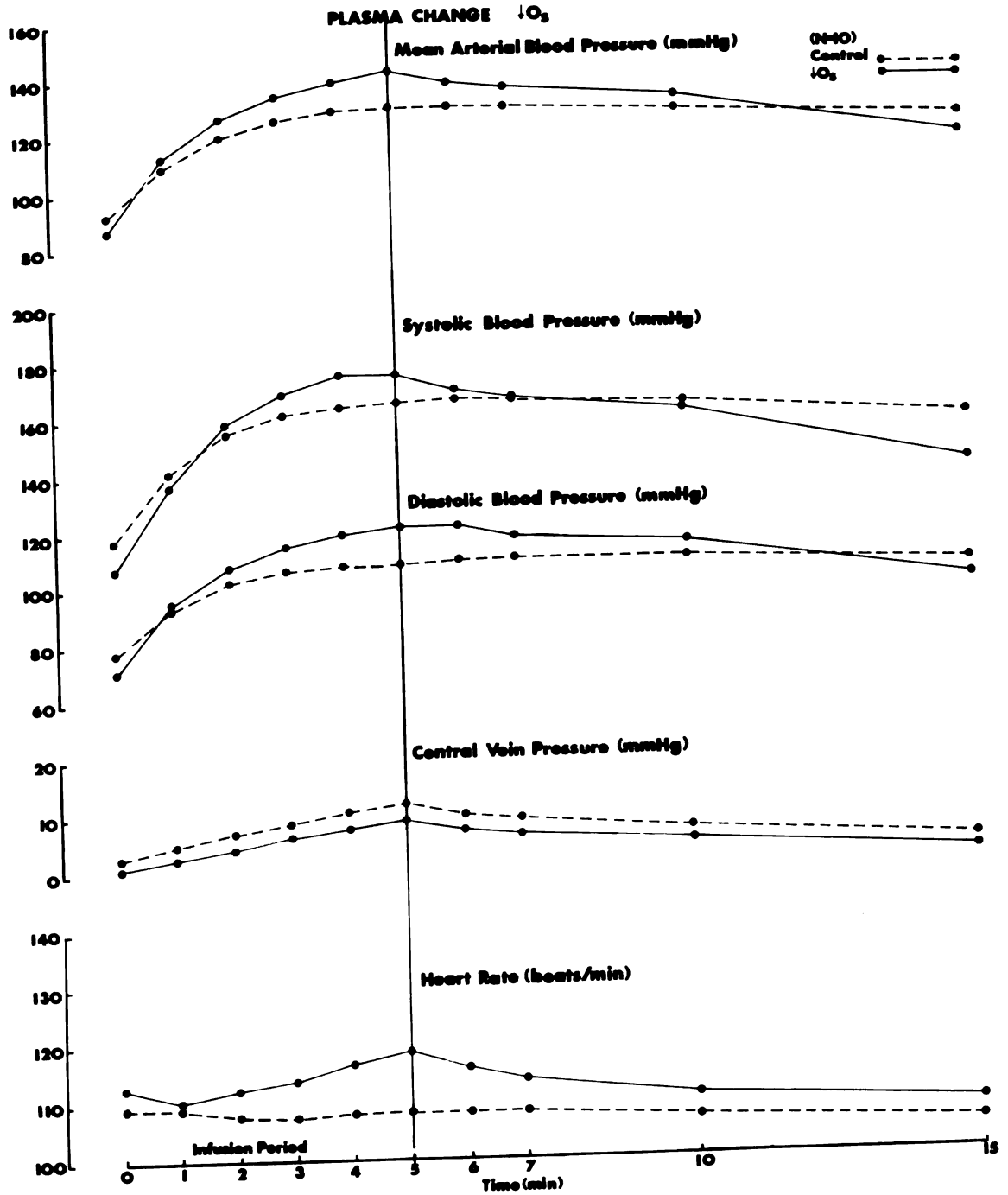
PLASMA CHANGE ↓O2
Mean Arterial Blood Pressure (mmHg)
(N=10)
Control
↓O2
160
140
120
100
80
Systolic Blood Pressure (mmHg)
200
180
160
140
120
100
80
60
Diastolic Blood Pressure (mmHg)
Central Vein Pressure (mmHg)
20
10
0
Heart Rate (beats/min)
140
130
120
110
100
Infusion Period
0
1
2
3
4
5
6
7
10
15
Time (min)

Figure 9.

above the control solution increase. Systolic and diastolic pressures increased 10 and 16 mm Hg over and above control values.

Infusion of an alkalotic solution, which increased pH about 0.2 units, caused a 65 mm Hg increase in mean blood pressure (20 mm Hg above control values). As evidenced in Figure 10, systolic and diastolic blood pressures increased significantly, as did heart rate.

The data from this experiment have been compiled into a summary table (Table IV) showing average values for pressures, blood parameters, and heart rates for all 8 solutions investigated. Table V depicts the average percent changes of blood pressures, heart rate, and measured blood parameters as created by infusion of the various test solutions. This table shows first the average control values for a particular solution, followed by the percent change elicited by that solution during infusion.

Extrinsic Analysis

Referring again to Figure 1, it should be noted that the percent change (i.e., the percentage of increase or decrease in pressure from the original pre-infusion starting blood pressure) in arterial blood pressure is, in all cases, of greater magnitude in the spinally-blocked studies than in the spinally-intact studies of Emerson et al. (1968). However, all these pressure changes are absolute when discussed in this way.

Figure 10. Average pressure and rate changes caused by the blood parameter change ↑pH and compared with the control curve. Symbols are the same as for Figure 6.

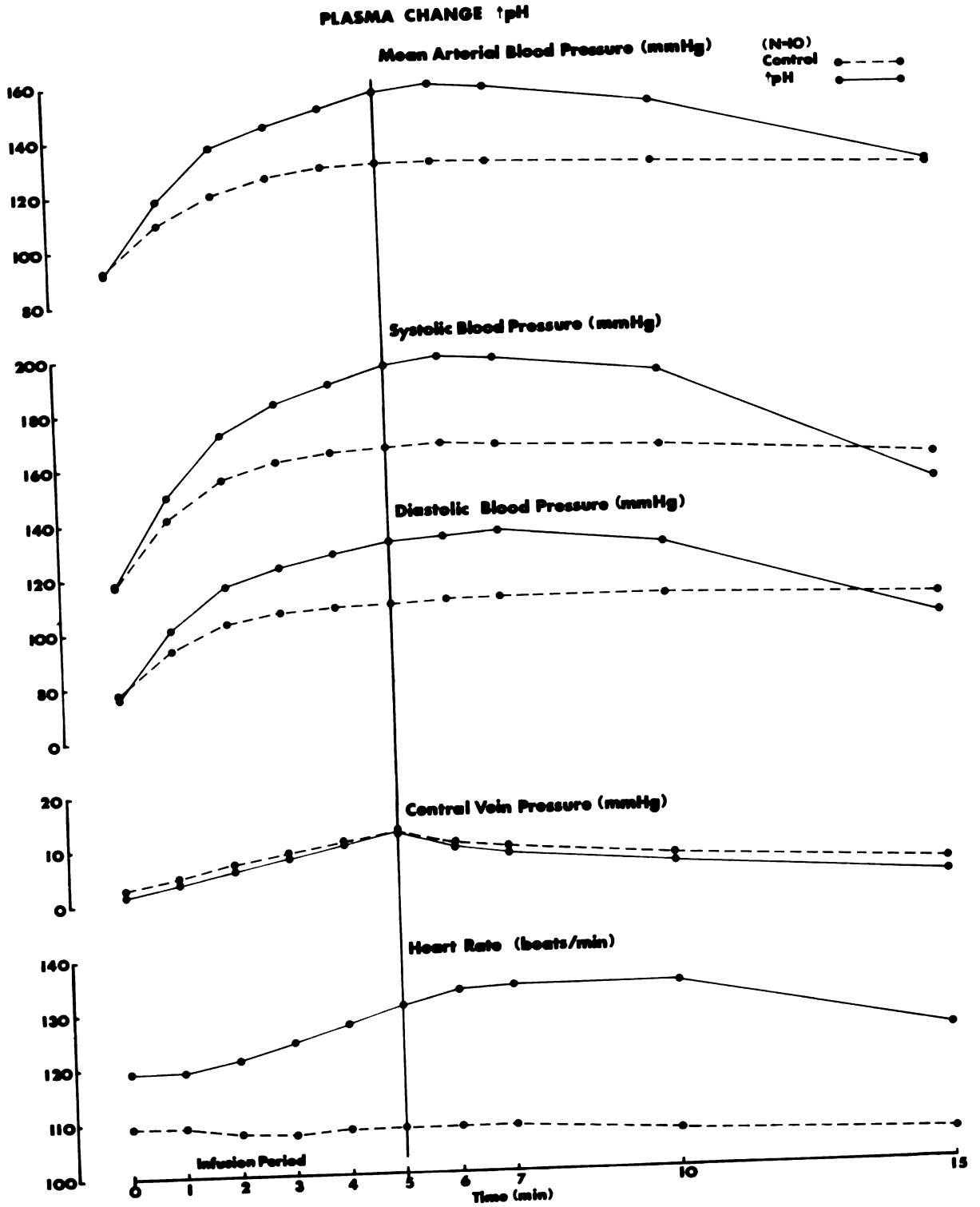
PLASMA CHANGE ↑pH
Mean Arterial Blood Pressure (mmHg)
(N=10)
Control
↑pH
160
140
120
100
80
Systolic Blood Pressure (mmHg)
200
180
160
140
120
100
80
Diastolic Blood Pressure (mmHg)
0
Central Vein Pressure (mmHg)
20
10
0
Heart Rate (beats/min)
140
130
120
110
100
Infusion Period
0
1
2
3
4
5
6
7
10
15
Time (min)

Figure 10.

Table IV. Average effects of I.V. infusion of test solutions on blood pressures, heart rate,

Solution	Plasma Change	N	Mean Blood Pressure (mmHg)			Systolic Blood Pressure (mmHg)			Diastalic Blood Pressure (mmHg)			Central Vein Pressure (mmHg)			Heart Rate (beats/min)		
			C	I	PI	C	I	PI	C	I	PI	C	I	PI	C	I	PI
1. Hypertensive	$\downarrow K^+, \downarrow Mg^{++}$ $\uparrow Ca^{++}, \uparrow pH, \downarrow Os$	10	97	163 **	123	123	206 **	154	80	158 **	104	1.4	11.1 *	2.2	112	126 *	116
2. Hypotensive	$\uparrow K^+, \uparrow Mg^{++}$, $\downarrow Ca^{++}, \downarrow pH, \uparrow Os$	10	103	68 **	126	131	92 **	153	89	53 **	106	3.2	17.2 *	7.9	116	108	110
3. Control	None	13	89	134 *	124	113	172 *	158	74	111 *	106	2.2	12.6 *	4.6	110	111	108
4. Hypo-Osmolar	$\downarrow Os$	10	86	143 **	116	106	175 **	142	71	122 **	101	1.1	9.1 *	2.6	113	119	107
5. Hypokalemic	$\downarrow K^+$	10	101	150 *	129	121	180 *	146	87	129 *	113	2.2	11.0 *	3.0	128	133	129
6. Hypomagnesemic	$\downarrow Mg^{++}$	10	98	135 *	109	123	170 *	137	83	113 *	92	2.8	13.0 *	4.9	114	115	111
7. Hypercalcemic	$\uparrow Ca^{++}$	10	104	153 *	130	130	191 *	158	90	126 *	113	2.7	11.9 *	4.8	122	132 *	122
8. Alkalotic	$\uparrow pH$	10	91	156 **	126	118	196 **	148	76	131 **	99	1.6	12.1 *	2.6	119	131 *	124

C = control values; I = values at 5th minute of infusion; PI = values 15 minutes post-infusion.
Values marked (*) are significant at the $P \leq 0.05$ level, relative to control values (C).
Pressures marked (**) are significant at the $P \leq 0.05$ level, relative to control solution 3.

and measured blood parameters in "procainized" dogs.

K^+ (mEq/l)			Mg^{++} (mEq/l)			Ca^{++} (mEq/l)			Na^+ (mEq/l)			Osmolarity (mOsm/l)			pH (Units)			Hemato-crit (%)		
C	I	PI	C	I	PI	C	I	PI	C	I	PI	C	I	PI	C	I	PI	C	I	PI
3.5	3.0 *	2.8	1.83	1.28 *	1.49	4.1	5.6 *	4.7	160	148 *	152	297	281 *	288	7.42	7.60 *	7.54	36	23 *	29
3.5	7.4 *	4.3	1.90	3.80 *	2.89	4.8	3.0 *	3.7	149	167 *	159	296	337 *	323	7.41	7.30 *	7.33	39	21 *	27
3.6	3.4	3.4	1.80	1.87	1.74	4.4	4.0	4.0	147	148	148	303	303	302	7.40	7.40	7.39	39	25 *	29
3.5	3.7	3.4	2.03	2.10	1.94	4.3	3.9	4.1	144	140	143	296	282 *	290	7.41	7.42	7.42	37	25 *	30
3.4	2.8 *	3.2	1.86	1.96	1.84	4.5	4.2	4.3	146	146	146	299	301	299	7.40	7.40	7.39	37	25 *	32
3.4	3.3	3.2	1.91	1.24 *	1.46	4.4	4.2	4.1	147	149	147	300	300	298	7.40	7.40	7.40	39	25 *	30
3.5	3.4	3.3	1.76	1.89	1.72	4.4	5.7 *	4.9	144	147	145	289	291	289	7.40	7.39	7.38	37	23 *	29
3.6	3.5	2.9	1.78	1.84	1.60	4.5	4.4	4.3	148	150	147	293	291	290	7.39	7.59 *	7.49	38	24 *	30

Table V. Average percent changes, relative to pre-infusion blood parameters as created by infusion of test

Solution	Plasma Change	N	Mean B.P.		Systolic B.P.		Dia-stolic B.P.		Heart Rate	
			Con (mm Hg)	% Δ	Con (mm Hg)	% Δ	Con (mm Hg)	% Δ	Con (mm Hg)	% Δ
1. Hyper-tensive	$\downarrow K^+, \downarrow Mg^{++}$ $\uparrow Ca^{++}, \uparrow pH, \downarrow Os$	10	97	68	123	68	80	72	110	13
2. Hypo-tensive	$\uparrow K^+, \uparrow Mg^{++}$ $\downarrow Ca^{++}, \downarrow pH, \uparrow Os$	10	103	-34	131	-30	89	-40	112	7
3. Control	None	13	89	45	113	52	74	50	116	0
4. Hypo-osmolar	$\downarrow Os$	10	86	66	106	65	71	72	113	5
5. Hypo-kalemic	$\downarrow K^+$	10	101	50	121	49	87	48	128	4
6. Hypo-magnesemic	$\downarrow Mg^{++}$	10	98	38	123	38	83	36	114	0
7. Hyper-calcemic	$\uparrow Ca^{++}$	10	104	47	130	47	90	40	122	12
8. Alkalotic	$\uparrow pH$	10	91	71	118	66	76	72	119	10

control values, of blood pressures, heart rate, and measured solutions.

K^+		Mg^{++}		Ca^{++}		Os		pH		Hct	
Con (mEq/l)	% Δ	Con (mEq/l)	% Δ	Con (mEq/l)	% Δ	Con (mOsm/l)	% Δ	Con (Units)	% Δ	Con (%)	% Δ
3.5	-14	1.83	-30	4.1	38	297	-5	7.42	2	36	-13
3.5	111	1.90	100	4.8	-38	298	13	7.41	-2	39	-18
3.6	-6	1.80	4	4.4	-9	303	0	7.40	0	39	-14
3.5	6	2.03	3	4.3	-9	298	-5	7.41	0	37	-12
3.4	-15	1.86	5	4.5	-7	299	1	7.40	0	37	-12
3.4	-3	1.91	-35	4.4	-5	300	0	7.40	0	39	-14
3.5	-3	1.76	7	4.4	30	289	1	7.40	0	37	-16
3.6	-3	1.78	3	4.5	-2	293	-1	7.39	3	38	-14

It is therefore imperative that these two sets of results be compared both relative to their own controls and relative to each other. Examining the differences between the effects of the hypertensive and control solution of this study and the effects of the hypertensive and control solution of the earlier intact study, no significant difference can be found. Using an unpaired "t" test, when similar multiple comparisons of mean, systolic, and diastolic blood pressures were conducted, no significant difference between the two studies was found. This was true for each individual electrolyte change analyzed.

Investigation and comparison of effects of Solution 2 (hypotensive solution) present an entirely different picture, however. Whereas, in the earlier normal study, Solution 2 caused a 19 mm Hg drop in blood pressure below control, the study showed an almost 70 mm Hg drop below control. This strikingly greater fall in arterial blood pressure becomes one of the major differences to emerge between these two studies.

Figure 11 offers some interesting results. With regard to the lower graph (heart rate versus time), it is clearly evident that the two sets of data start from different origins. A 35-45 beats/min drop is seen following injection of procaine into the cisterna magna of the animal. The spinal blockade initiated by the procaine dampens the heart rate throughout the entire experiment. Examination of the normal, intact dog heart rates renders the following

Figure 11. Time line graph depicting mean arterial blood pressure (upper graph) and heart rate (lower graph) for the duration of the experiment--i.e. infusion interval and recovery period. Dashed lines = normal, intact studies; solid lines= spinally anesthetized studies; 1 = hypertensive solution 1; 2 = hypotensive solution 2; 3 = control solution 3.

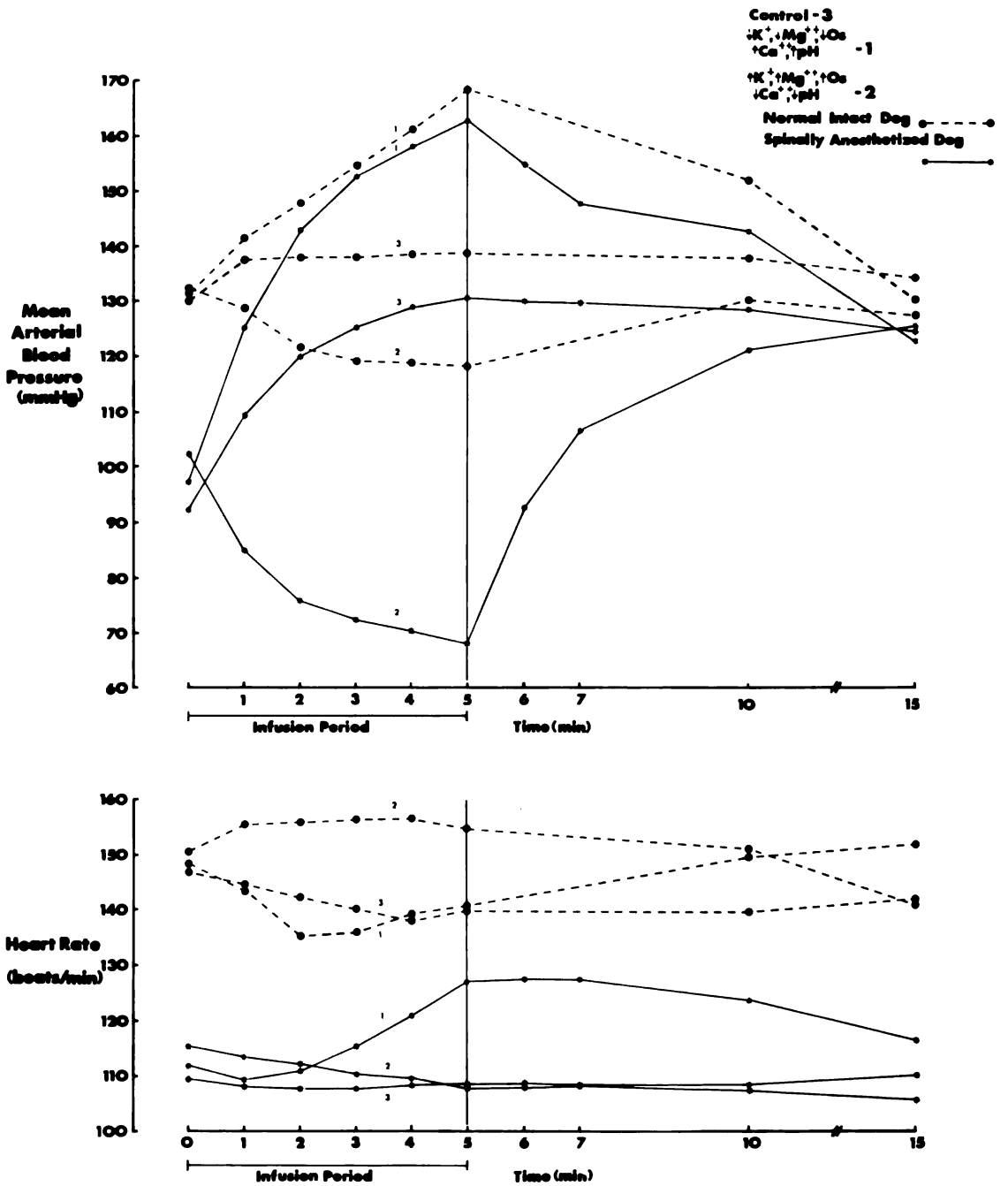
Control - 3
↓K⁺, ↓Mg⁺⁺, ↑Os
↑Ca⁺⁺, ↑pH - 1
↑K⁺, ↑Mg⁺⁺, ↑Os
↓Ca⁺⁺, ↓pH - 2
Normal Intact Dog
Spinally Anesthetized Dog
Mean Arterial Blood Pressure (mmHg)
170
160
150
140
130
120
110
100
90
80
70
60
1 2 3 4 5 6 7 10 15
Infusion Period
Time (min)
Heart Rate (beats/min)
160
150
140
130
120
110
100
0 1 2 3 4 5 6 7 10 15
Infusion Period
Time (min)

Figure 11.

observations:

(1) both the control and hypertensive solutions (Solutions 3 and 1) produced a slight reflex bradcardia ($0.05 \leq P \leq 0.10$),

(2) the hypotensive solution (Solution 2) infusion caused a slight increase in heart rate ($0.05 \leq p \leq 0.10$).

Inspection of heart rate changes in spinally blocked dogs enables the following conclusions to be drawn:

(1) The control solution (Solution 3) infusion does not effect heart rate.

(2) The hypertensive solution (Solution 1) causes a tachycardia ($P \leq 0.05$).

(3) Infusion of the hypotensive solution (Solution 2) produces a non-significant slowing of heart rate ($P \geq 0.05$).

Significant bradycardia was evidenced in the normal intact dog study using the single electrolyte changes of hypokalemia and hypo-osmolarity. In the spinally blocked dog study, a statistically meaningful tachycardia was demonstrated using a hypercalcemic solution and an alkalotic solution (see Table IV). It appears that following spinal blockade, any possible reflex effect on the heart is opposite or absent entirely and only the direct action of the electrolyte alterations is seen.

Examination of the upper graph of Figure 11, plotting average mean arterial blood pressure against time, suggests

the following conclusions. While solutions 1, 2, and 3 qualitatively produced changes in the same direction in both experiments, quantitatively, changes were greater using spinally blocked dogs. Although the two sets of experiments started at time 0 with significantly different base lines, at time 5 (the end of infusion) the difference between the two sets of points became insignificant, with the exception of Solution 2. Solution 2 showed a very significant divergence throughout the whole experiment, the greatest difference coming at the end of infusion.

DISCUSSION

Acutely induced, small, generalized, single and multiple plasma electrolyte and osmolar alterations created striking changes in mean, systolic, and diastolic blood pressures in spinally anesthetized dogs. Of the five single changes studied ($\downarrow[K^+]$, $\downarrow[Mg^{++}]$, $\uparrow[Ca^{++}]$, $\uparrow$pH, and $\downarrow$Os), only two of these ($\downarrow$Os and $\uparrow$pH) significantly increased arterial blood pressure more than the increase produced by the control solution.

The blood pressure effects produced by the individual changes are somewhat in agreement with the findings of earlier studies concerning the effects of acute local plasma electrolyte and osmolar alterations on vascular resistance in isolated organs. Indeed, a stimulus that increased vascular resistance locally would be expected to increase blood pressure when produced systemically if there was not a concomitant fall in cardiac output. This, of course, assumes that all or a majority of the systemic vascular beds responded uniformly to the stimulus. Thus, hypokalemia, hypoosmolarity, hypercalcemia, or alkalosis were expected to increase total peripheral resistance (Overbeck et al., 1961; Haddy, 1963; Haddy and Scott, 1965; Scott et al., 1968) and, hence, blood pressure. Furthermore hypomagnesemia alone was

not expected to produce any effect on resistance or blood pressure (Haddy et al., 1963) and, in fact, did not significantly change blood pressure from the control response in the present study. The failure of decreased $[K^+]$ and increased $[Ca^{++}]$ to produce an evaluation in blood pressure might be related to 1) a rise in total peripheral resistance balanced by a fall in cardiac output and/or 2) a non-uniform response in some systemic vascular beds. The latter explanation seems likely in the case of hypercalcemia since this ion tends to dilate vessels of the gastric bed while increasing peripheral resistance in most other vascular beds (Textor et al., 1967).

The hypertensive effect caused by the control infusion clearly illustrates the importance of hypervolemia. Since blood viscosity is probably decreased by this infusion, with a resulting decrease in total peripheral resistance, the increase in blood pressure observed is likely due to an increase in cardiac output. This rise in cardiac output results when venous return to the heart is increased which, consequently, increases effective filling pressure and elevates end diastolic volume. This sequence of actions results in both an elevated stroke volume and cardiac output (Starling mechanism). Obviously, this necessitated that each series of experimental infusions be compared to the control series. Since all solutions, both control and experimental were infused at the same rate, it is reasonable to assume that the differences in responses produced can be attributed

to the electrolyte and/or osmolar alterations purposely created. This is further substantiated by data showing that central venous pressure and hematocrit responded in essentially the same manner for all series of experiments.

Using the control series as a reference, both combinations, hypertensive and hypotensive, significantly affected blood pressure. The hypotensive solution ($\uparrow[K^+]$, $\uparrow[Mg^{++}]$, $\downarrow[Ca^{++}]$, $\downarrow$pH, $\uparrow$Os) greatly decreased blood pressure, even in the face of a rise in total plasma volume which, in itself, would increase blood pressure (control solution). On the other hand, a large increase in arterial blood pressure resulted from the infusion of the hypertensive solution ($\downarrow[K^+]$, $\downarrow[Mg^{++}]$, $\uparrow[Ca^{++}]$, $\uparrow$pH, $\downarrow$Os). However, the single changes, alkalosis and hypo-osmolarity, also increased blood pressure to approximately the same level as the hypertensive solution. Thus, the effects of the five simultaneous alterations produced by the hypertensive solution did not affect blood pressure any more than did either alkalosis or hypo-osmolarity alone.

Before abandoning the intrinsic analysis of this study, one question needs to be considered. Are the blood pressure changes created by the electrolyte and osmolar abnormalities a result of total peripheral resistance changes, cardiac output alterations, or a combination of both? Although this study cannot answer this question, a recent study (Emerson and Jelks, 1970) indicates that the last alternative is probably the case. This study, by measuring venous blood

flow returning to the heart and systemic blood pressure, showed that a simultaneous increase in plasma $[K^+]$, $[Mg^{++}]$, and osmolarity caused a decrease in total peripheral resistance.

The major usefulness of this study lies not so much in the preceding analysis of the data itself, but rather in a comparison between the effects of acutely induced, small, generalized multiple electrolyte and osmolarity changes in spinally intact animals and spinally anesthetized animals. If both studies follow essentially the same procedure, then any difference noted in the results should be directly attributable to the functioning or lack of functioning of the barostatic compensatory mechanisms.

Comparisons of results seen following infusion of the control and hypotensive solutions indicate that the neurological barostatic mechanisms do, indeed, mask the blood pressure changes seen when electrolytes and osmolarity are altered. Apparently, the cardiovascular system becomes more responsive to blood volume changes due to absence of any functioning neurologic barostatic mechanisms (See Figs. 1 and 11). If it is more responsive to volume changes, then it might be expected to also be more responsive to electrolyte and osmolar alterations. However, only in the case of the hypotensive changes was this apparent (see Fig. 11). This does not seem to be true for the hypertensive solution. It is not clear why such a discrepancy exists. Possibly, the reflex barostatic mechanisms of the carotid

sinus and aortic arch were not activated by infusion of the hypertensive solution in the spinally intact animals. If, however, heart rate is examined, the reflex mechanisms seem to be functioning adequately during infusion of the hypertensive solution (see below). A second explanation might deal with the difference in the initial level of resistance present in the spinally intact and the spinally blocked dogs. Overbeck (1968) points out that in normotensive dogs there was a significant linear correlation between magnitude of response to angiotension and initial level of limb vascular resistance. Preliminary studies indicate that when systemic blood pressure is raised to pre-procaine-anesthesia control levels by continuous nor-epinephrine infusion, the resulting pressure responses due to hypertensive infusions seem to be of greater magnitude than those responses of the spinally intact or spinally blocked studies. Third, perhaps a 5-minute infusion period is too short for the full blood pressure effect to be elicited.

The heart rate response before and after spinal blockade tends to strengthen the contention that spinal anesthesia eliminates the neurological factors which normally allow an animal to compensate for variations in blood pressure. In the unblocked animals, one would expect to see a reflex bradycardia as a result of infusion of the hypertensive solution. Also, a reflex tachycardia, resulting from the drop in pressure caused by the hypotensive solution, should be noted. Both of these responses were, in fact, observed.

Spinal blockade reversed the heart rate responses. Instead of a reflex bradycardia during the hypertensive infusion, a marked tachycardia was seen. This perhaps due to the known cardiac stimulating properties of hypercalcemia and alkalosis. On the other hand, the hypotensive solution, which induced hypocalcemia and acidosis, caused a slight decrease in heart rate.

The possible mechanisms of actions of electrolytes and osmolarity on cardiac and vascular smooth muscle deserve mention. It definitely appears now that the free calcium ion is the essential final common requirement for all muscle contraction (Bohr et al., 1969). Calcium has a functional role in the excitation-contraction coupling in both smooth and striated muscle (Bohr, 1964). Magnesium seems to work by effecting the membrane excitability of smooth muscle, although a definite role has not been delineated (Bohr, 1964). The influence of potassium on cardiac and vascular smooth muscle is possibly mediated through its effect on membrane potential.

Furthermore, studies in isolated vascular smooth muscle indicate that hyper- or hypo-osmolarity are associated with the movement of water into or out of the cell (Mellander et al., 1967). This water movement causes concentration or dilution of intracellular potassium and would increase or decrease the intracellular-extracellular potassium gradient. This consequently altered membrane potential causes an increase in spike activity and muscle contraction. Another

possible mechanism involved is passive dilation, due to vessel wall dehydration and subsequent alterations in transmural pressure (Haddy and Scott, 1965). Finally, a third mechanism to be considered is a change in blood viscosity. Hyperosmolarity creates a reduction in blood viscosity due to the dilution of the blood with water from the extravascular compartment, vessel wall, and red blood cells and also due to a decrease in red cell size (Haddy and Scott, 1965).

The mechanism of action of hydrogen on muscle seems to be via an alteration in the membrane potential. A consistent and reversible increase in membrane potential was evidenced in muscle cells as the pH of the immersion fluid was lowered over a range of 7.1 to 5.8 (Mainwood and Lee, 1968). This hyperpolarization in skeletal muscle could be caused by following possible mechanisms: 1) decrease in transmembrane sodium conductance, or 2) an alteration in potassium or chloride membrane conductance. However, determination of the mechanism of action of hydrogen on cardiac and vascular smooth muscle has not been delineated.

SUMMARY AND CONCLUSIONS

It was the intent of this study to examine the buffering effect of the neurological barostatic reflex system on blood pressure changes caused by electrolyte and osmolar abnormalities. By comparing spinally intact studies (Emerson et al., 1968) with spinally blocked studies, the effects of this neurological reflex system can be determined. The following conclusions were drawn:

1) The blood pressure effects produced by the spinally blocked control solution were much greater in magnitude than the effects caused by the spinally intact control solution. Thus, the effects of hypervolemia seem to have been greatly masked in normal, spinally intact dogs.
2) The effects of all changes that increased blood pressure remained statistically the same in both spinally intact and blocked studies.
3) The effects of the hypotensive changes were markedly different, the spinally blocked studies producing a much greater effect on blood pressure than the spinally intact series. A buffering effect is clearly evident.

This study demonstrates that there exists at least partial buffering of the blood pressure changes elicited by electrolyte and osmolar alterations. The buffering effect seems to be mediated by a neurological barostatic system that can be blocked by means of spinal anesthesia.

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APPENDIX

STATISTICAL EVALUATION

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Statistical evaluation of the data obtained from this experiment was accomplished by means of the following methods. First of all, N, the number of experiments per treatment was arbitrarily set at 10. The confidence level of the data was also arbitrarily set at 95%, the standard level for most experiments done today and also the level used by Emerson et al. (1968). Having set these values, a maximum deviation limit was calculated. It was calculated using the maximum standard deviation obtained from the mean, systolic, and diastolic blood pressure data and produced the following claims:

1) The author is 95% confident that the average value of any of the mean, systolic, or diastolic blood pressure readings at any point in time in any of the series of experiments falls no more than 13.4 mm Hg above or below the true statistical mean pressure in any particular medium-sized dog (10-20 kg).

2) The same statement can be applied to heart rate at a level of ±13 beats/min and to central venous pressure at a level of ± 2.5 mm Hg.

Data differences within a particular experiment were evaluated *via* a paired T test. Thus, time level differences were analyzed in this way. Included in this category are all significant differences noted as such in Table IV.

Raw data was analyzed by the Control-Data 3600 Fortram computer at Michigan State University, East Lansing, Michigan. The statistical test used was a one-way analysis of variance with equal replication. The choice between two-way and one-way analysis of variance was made once it was determined that blocking out of differences between dogs could be performed. The hypothesis used to test the differences between treatments (i.e. solutions 1-8) was

$$H_0: \mu_{sol\ 1} = \mu_{sol\ 2} = \cdots\cdots = \mu_{sol\ 8},$$

with the alternate hypothesis being

$$H_1: \mu_{sol\ 1} \neq \mu_{sol\ 2} \neq \cdots\cdots \neq \mu_{sol\ 8}.$$

It is a one-tailed test. Statistical assumptions made included randomness of variables, additivity of the experimental model, normal distribution of data, homogeneity of variances, and independence of means and variances. One major biological assumption made was that a spinal blockage was indeed, effected.

Analysis of earlier data (Emerson *et al.*, 1968), compared parameter for parameter and treatment for treatment with the data from this study, was carried out using the same one-way analysis of variance test (essentially identical to an unpaired Students' "T" Test). Additional biological assumptions that must be made here are:

1) The dogs used in the intact studies (Emerson et al., 1968) came from essentially the same population as the dogs used in this study.

2) The data of both experiments were collected at the same times and by the same type of instruments.