EFFECTS OF HYPOKALEMIA AND HYPOMAGNESEMIA PRODUCED BY HEMODIALYSIS ON BLOOD PRESSURE IN THE DOG

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ABSTRACT

EFFECTS OF HYPOKALEMIA AND HYPOMAGNESEMIA
PRODUCED BY HEMODIALYSIS ON
BLOOD PRESSURE IN THE DOG

By

Walter Joseph Hoppe

We previously reported that hypokalemia or hypomagnesemia, produced within five minutes by a dilutional technique, raises arterial pressure (Emerson *et al.*, 1970). We now report effects when the ionic changes are produced more slowly by a non-dilutional technique. Hypokalemia (n=10) or the combination hypokalemia and hypomagnesemia (n=10) were created by hemodialysis (Kiil Dialyzer) against a modified Ringer's solution lacking the cation(s) in question. The protocol involved three sequential steps: (1) dialysis against a normal modified Ringer's solution for 30 min (control); (2) dialysis against a solution lacking the experimental cation(s) for 30 min (experimental); (3) dialysis against a solution containing an excess of the experimental ion(s) to re-establish a normal plasma concentration (post control). In a control series (n=9), dialysis was against a normal Ringer's solution for 1-1/2 hrs.

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Decreasing plasma K^+ by 1.0 mEq/l or K^+ and Mg^{++} simultaneously by 1.1 and 0.5 mEq/l, respectively, did not significantly alter systolic, diastolic, or mean arterial blood pressures or heart rate relative to control dogs in which no plasma cation abnormalities occurred. In another group of dogs, the neurologic barostatic system was rendered inoperable by spinal anesthesia. Decreasing plasma K^+ (n=10) or K^+ and Mg^{++} (n=10) simultaneously still did not alter blood pressure significantly when compared to control spinally blocked dogs (n=9). In three unblocked dogs, dp/dt values during the hypokalemic period were not significantly different from the normokalemic values. In two of three spinally blocked dogs, dp/dt values increased during the hypokalemic period; dp/dt in the third animal was unchanged. These data suggest that hypokalemia or the combination hypokalemia and hypomagnesemia does not alter blood pressure significantly in the normal or spinally blocked animal. Since the magnitude of the ionic changes were similar to those produced in the earlier study, the difference in the blood pressure response must result from some other unknown factor, perhaps related to time or dilution.

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To my wife, Patricia Anne,

and my son, Michael Thomas.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

The hemodynamic effects of altering the concentration of potassium and magnesium, singly and combined, in blood perfusing isolated organs have been investigated extensively over the past several years. Experimental evidence has shown that these naturally occurring cations are locally vasoactive and that this vasoactivity is limited mainly to the arterial side of the capillary (Haddy and Overbeck, 1962; Haddy *et al.*, 1963; Haddy and Scott, 1965; Haddy *et al.*, 1967; Haddy and Scott, 1968; Scott *et al.*, 1968).

Acute local elevation of the plasma potassium concentration to levels less than twice the normal value produced arteriolar dilation in the forelimb (Emanuel *et al.*, 1959; Frohlich *et al.*, 1962; Haddy, 1960; Overbeck *et al.*, 1961), skeletal muscle (Dawes, 1941; Skinner and Powell, 1967), kidney (Frohlich *et al.*, 1962; Scott *et al.*, 1959), heart (Scott *et al.*, 1961), skin (Dawes, 1941), stomach (Textor *et al.*, 1967), and mesenteric (Textor *et al.*, 1967; Dabney *et al.*, 1967) vascular beds. In contrast, an acute local decrease in the plasma potassium concentration (as low as 1.85 mEq/liter) by a hemodilutional technique produced arteriolar constriction in the forelimb (Haddy *et al.*, 1963),

renal (Haddy *et al.*, 1963), and skeletal muscle (Skinner and Powell, 1967) vascular beds of the dog. Similarly, in the pump perfused isolated gracilis muscle, altering plasma potassium concentration in the range 0.2-4 mEq/liter by hemodialysis, a non-dilutional technique, resulted in arteriolar constriction (Roth *et al.*, Anderson *et al.*, 1972).

Arteriolar dilation has been shown to occur during acute local hypermagnesemia in many of the isolated vascular beds responsive to hyperkalemia (Haddy, 1960; Overbeck *et al.*, 1961; Scott *et al.*, 1961; Frohlich *et al.*, 1962; Textor *et al.*, 1967; Haddy *et al.*, 1967; Dabney *et al.*, 1967; Chou and Emerson, 1968). However, a vascular effect associated with local hypomagnesemia alone is small or insignificant (Haddy *et al.*, 1963; Anderson *et al.*, 1972).

In addition to their vascular effects, potassium and magnesium affect cardiac muscle. Both hyperkalemia (Haddy *et al.*, 1963; Sarnoff *et al.*, 1966; Scott *et al.*, 1968; Logic *et al.*, 1968; Surawicz *et al.*, 1967) and hypermagnesemia (Uchiyama, 1968) have been shown to decrease myocardial contractility. Recent evidence suggests that both acute hypokalemia (Haddy *et al.*, 1963; Sarnoff *et al.*, 1966; Gilmore and Gerlings, 1968; Scott *et al.*, unpublished observations; Cohn *et al.*, 1967) and chronic dietary hypokalemia (Bahler and Rakita, 1971) produce an increase in myocardial contractile force.

Pertinent to the present study is the enhanced effect seen in the presence of combined hypokalemia and hypomagnesemia on the resistance to blood flow in perfused organs (Haddy *et al.*, 1963). A 30% reduction in plasma potassium concentration in combination with a 50% reduction in plasma magnesium concentration by the hemodilutional technique in the blood perfusing the dog forelimb or kidney produced a much greater increase in resistance than occurred when either ion was reduced singly to the same level (Haddy *et al.*, 1963). However, the response of acute hypokalemia in the presence of hypomagnesemia was not enhanced when plasma potassium concentration was decreased 86% by hemodialysis in the isolated gracilis muscle (Anderson *et al.*, 1972). In addition to the vascular effects, this acute alteration of both ions by hemodilution of the blood perfusing the coronary vascular bed, increased myocardial contractile force more than either ionic alteration did singly (Haddy *et al.*, 1963).

All of these acute local studies suggest that generalized plasma electrolyte alterations in an intact animal would change arterial blood pressure by affecting both the heart and peripheral vasculature. Consequently, several groups have investigated the effects of single and in many cases combined acute generalized plasma potassium and magnesium alterations on blood pressure in the intact dog (Hoff *et al.*, 1939; Winkler *et al.*, 1940; Maxwell *et al.*,

1965; Surawicz *et al.*, 1967; Haddy *et al.*, 1969; Emerson *et al.*, 1970). Other investigators have looked at the effects of chronic generalized dietary potassium depletion in intact dogs and rats (Freed and Friedman, 1951; Friedman *et al.*, 1962; Bahler and Rakita, 1971).

Acute generalized hyperkalemia and hypermagnesemia were easily produced without altering other plasma constituents by infusing small volumes of isotonic concentrated KCl and $MgCl_2$ solutions (Hoff *et al.*, 1939; Maxwell *et al.*, 1965). Under these conditions hypotension was observed. With more difficulty, however, hypokalemia and hypomagnesemia were produced acutely by hemodilution in the presence of hypervolemia or with a potent diuretic, furosemide (Emerson *et al.*, 1970; Haddy *et al.*, 1969) or chronically by dietary depletion (Freed and Friedman, 1951; Friedman *et al.*, 1962; Bahler and Rakita, 1971). These studies have shown that acute hypokalemia produced hypertension, while chronic dietary potassium depletion resulted in hypotension.

Since the blood pressure changes during acute, systemic hypokalemia and hypomagnesemia were opposite to the changes during chronic dietary studies, it was decided to study the vasoactivity of these ions further. To do this we used the technique of hemodialysis which gradually and selectively created hypokalemia and hypomagnesemia without producing changes in hematocrit, viscosity, nonelectrolytes, or other electrolyte concentrations.

LITERATURE SURVEY

Gaskell, Roy, Brown, and Ringer, late nineteenth century investigators, stimulated a scientific interest in the cardiovascular effects of various ions. Ringer (1883), working with an isolated frog-heart preparation, clearly demonstrated that contraction of the heart muscle was dependent upon the electrolyte composition of the perfusing fluid. He tested the effects of sodium chloride, serum, albumin, potassium chloride, and a dried blood mixture. Through further experimentation he came to realize that the "distilled water" he had used was ordinary pipe water, which contained calcium, magnesium, sodium, potassium, chloride, and bicarbonate ions (Ringer, 1884). This prompted his conclusion that most of the observations resulted from the action of these inorganic constituents. Subsequent research has served to enhance and expand these initial basic observations.

Smith, Hoff, and Winkler (Hoff *et al.*, 1939; Winkler *et al.*, 1940) infused cationic salt solutions intravenously into dogs and cats in an attempt to determine the relationship between blood pressure changes and plasma electrolyte concentrations. Within physiological ranges, potassium

salts produced minor, insignificant systemic blood pressure changes while magnesium salts lowered systemic arterial blood pressure. Both potassium and magnesium salts depressed cardiac function. These observations in light of the earlier findings of Katz and Lindner (1938) were the focal point of an expanding amount of research in an attempt to understand the relationship between electrolyte abnormalities and blood pressure, cardiac output, and peripheral resistance changes. Research was conducted with various isolated vascular beds as well as intact animals.

Potassium Local Effects

Using the isolated hindlimb of the adrenalectomized dog or cat, Dawes (1941) showed that small doses of KCl caused vasodilation, while larger doses caused vasoconstriction. Further work on his part showed that hyperkalemia caused vasoconstriction of vessels in the rabbit ear, but had very little effect on lung or intestinal vessels in the dog. However, he failed to state what potassium concentration caused vasoconstriction. Haddy (1963) stated that an increase in the local plasma concentration over the range 4 to 8 mEq/l caused arteriolar dilation, while concentrations above 8 mEq/l resulted in constriction of the larger arteries. This constriction overshadowed the arteriolar dilation resulting in a net increased resistance to flow above control (Haddy, 1963).

The arteriolar vasodilation caused by small, acute increases in plasma potassium concentration has been observed in other vascular beds by other investigators, e.g., forelimb (Emanuel *et al.*, 1959; Overbeck *et al.*, 1961) gracilis muscle (Skinner and Powell, 1967), kidney (Scott *et al.*, 1959; Frohlich *et al.*, 1962), heart (Katz and Lindner, 1938; Driscol and Berne, 1957; Scott *et al.*, 1961) and intestine (Dabney *et al.*, 1967; Textor *et al.*, 1967). However, Chou and Emerson (1968) failed to show a response in the liver to a locally induced potassium increase. Several strip studies using isolated segments of facial arteries from cattle have also shown that vascular tone was altered in the presence of small changes in extracellular potassium concentration (Konold *et al.*, 1968; Brecht *et al.*, 1969; Konold *et al.*, 1968). However, Norton and Detar (1972), working with helical strips from rabbit freewall left ventricular coronary arteries, found no changes in contractile tension when potassium concentration was altered in the medium.

The potassium ion is well known for its depressant effect on cardiac muscle (Gruber and Roberts, 1926; Scott *et al.*, 1968). Sarnoff and his colleagues observed in the isolated, supported dog heart preparation that when contractility decreased, there was a net gain of potassium in the heart (Sarnoff *et al.*, 1966). They also showed in this same preparation that infusions of 0.6-1.2 mEq/min of K^+

into the left coronary artery produced increased LVEDP and concluded that this was the result of decreased myocardial contractility. Two *in vivo* studies showed a similar depressed myocardial contractility when potassium, sufficient to increase the plasma concentration more than twofold, was infused either into the pulmonary artery (Surawicz *et al.*, 1967) or into each of the three major coronary arteries, namely, the left anterior descending artery, left circumflex artery, and right coronary artery (Logic *et al.*, 1968).

In contrast, a small, acute decrease in local plasma potassium concentration causes measurable arteriolar constriction (Haddy, 1963; Haddy and Scott, 1965). This increased vascular resistance in response to hypokalemia produced by a hemodilutional technique has been reported in constant flow preparations involving the forelimb (Haddy *et al.*, 1963), kidney (Haddy *et al.*, 1963), heart (Haddy *et al.*, 1963), and gracilis muscle (Skinner and Powell, 1967). Similar results were observed during acute local hypokalemia, produced by hemodialysis, a non-dilutional method, in the heart (Scott *et al.*, unpublished observations), and gracilis muscle (Roth *et al.*, 1969; Anderson *et al.*, 1972).

Hypokalemia during coronary perfusion at a constant flow resulted in an increased left ventricular contractile force but this difference was of questionable significance ($P = <0.1$) (Haddy *et al.*, 1963). More recently, several

investigators using isolated heart preparations reported enhanced myocardial contractility as a result of hypokalemia (Sarnoff *et al.*, 1966; Gilmore and Gerlings, 1968; Scott *et al.*, unpublished observations.

Potassium Systemic Effects

The local studies cited above have shown that small, acute changes in plasma potassium concentration affected both cardiac and vascular smooth muscle. In view of this, it would seem likely that a correspondingly small, generalized potassium alteration might regularly affect the systemic arterial blood pressure. However, an earlier work by Hoff, Smith, and Winkler (1939) and a more recent study by Haddy and associates (1969) have shown little or no blood pressure depression in response to generalized hyperkalemia, probably as the result of an effective buffering by the various remote compensatory mechanisms.

In contrast, acute hypokalemia resulted in an increased systemic blood pressure and enhanced myocardial contractility (Haddy *et al.*, 1969; Emerson *et al.*, 1970). Several methods of producing hypokalemia exist. One method lowers plasma potassium ion concentration acutely by dilution--a Ringer's solution lacking K^+ is infused or injected intravenously. However, this method produces hypervolemia (Haddy *et al.*, 1969; Emerson *et al.*, 1970). An isovolemic technique to produce acute hypokalemia utilizes a potent

diuretic (e.g., furosemide) and a simultaneous intravenous infusion of potassium free fluids equal to the urine loss (Scott *et al.*, 1968; Haddy *et al.*, 1969; Haddy and Scott, 1970). Hemodialysis can selectively and acutely remove potassium without altering other electrolytes or blood volume and without administering a drug (Goodyer *et al.*, 1967; Weller *et al.*, 1955). Lastly, dietary restriction produces chronic potassium depletion in the rat (Freed and Friedman, 1951; Friedman *et al.*, 1962; Krakoff, 1970) and in the dog (Bahler and Rakita, 1971; Knochel and Schlein, 1971). However, since dietary hypokalemia appears slowly, there is, in addition to a time factor, the possibility of other variables, active on pressure, entering the experiment. For example, a rise in systemic blood pressure during acute hypokalemia was observed, but a decrease was noted during chronic dietary hypokalemia (Friedman *et al.*, 1962; Freed and Friedman, 1951; Bahler and Rakita, 1971).

Magnesium Local Effects

The local effect of acute hypermagnesemia is dilation. Vascular resistance in the dog forelimb (Haddy, 1960; Overbeck *et al.*, 1961; Frohlich *et al.*, 1962), liver (Chou and Emerson, 1968), kidney (Frohlich *et al.*, 1962), intestine (Haddy *et al.*, 1967; Dabney *et al.*, 1967; Textor *et al.*, 1967), and heart (Scott *et al.*, 1961) decreases as a function of the plasma concentration of magnesium during

infusion of an isotonic solution of a magnesium salt into the arterial supply. Increased plasma magnesium concentration also attenuated the local levarterenol response in the forelimb and kidney (Haddy, 1960; Frohlich *et al.*, 1962). In the forelimb this attenuated response to levarterenol is observed even when the amount of magnesium administered is in itself insufficient to lower vascular resistance (Frohlich *et al.*, 1962). Altura and Altura (1971) using rabbit aortic strips also have shown that increased plasma magnesium concentration (5-20 mM) resulted in dose-dependent inhibition or attenuation of epinephrine-, serotonin-, and histamine-induced contractions.

A 33% to 84% decrease in plasma magnesium concentration has been shown to have little or no effect upon resistance to flow through forelimb, kidney, heart muscle (Haddy *et al.*, 1963), or gracilis muscle (Anderson *et al.*, 1972). However, in many cases, local hypomagnesemia combined with other local hypertensive electrolyte alterations resulted in a significantly greater resistance increase than seen with the other abnormalities alone (Haddy, 1960; Haddy *et al.*, 1963). Therefore, in combination with other electrolyte alterations, hypomagnesemia exhibited a potentiating effect.

Magnesium Systemic Effects

Experimental evidence has shown that acute, generalized hypermagnesemia in intact animals has resulted in tachycardia and a fall in systemic blood pressure (Hoff *et al.*, 1939; Winkler *et al.*, 1940; Maxwell *et al.*, 1965). Hoff and his co-workers (1939) continuously injected an isotonic $MgSO_4$ solution intravenously and observed a progressive fall in blood pressure to zero as the plasma magnesium concentration was increased to 25 mEq/liter. Maxwell and his group (1965) injected intravenously a 10% solution of MgCl in one group of animals and infused the same solution (2 ml/kg body wt.) in the other animals to increase plasma magnesium concentration from 1.83 to 8.20 mEq/liter. In this range systemic blood pressure fell significantly; however, unlike local hypermagnesemia in the isolated heart, coronary flow was statistically unchanged (Maxwell *et al.*, 1965).

A few observations under hypervolemic conditions clearly showed that acute generalized hypomagnesemia alone in the intact animal raised systemic blood pressure (Haddy *et al.*, 1969; Emerson *et al.*, 1970). Hypomagnesemia in these cases was created in the presence of hypervolemia by a dilution technique, namely, a Ringer's solution lacking Mg^{++} was injected or infused intravenously (Haddy *et al.*, 1969; Emerson *et al.*, 1970). Supportive evidence for the

hypertensive effect of hypomagnesemia stems from experimentation where magnesium is lowered in the presence of other hypertensive electrolyte alterations (Scott *et al.*, 1968; Haddy *et al.*, 1969; Haddy and Scott, 1970; Emerson *et al.*, 1970). These studies have shown that hypomagnesemia increased further the already elevated systemic blood pressure.

Local Effects of Combined Potassium and Magnesium Alterations

In light of the more impressive vascular responses observed when only potassium was altered, the question asked most often was what effect will an added magnesium alteration have on the various vascular beds. Acute local studies in many of the vascular beds cited above have shown that hyperkalemia and hypermagnesemia or hypokalemia and hypomagnesemia produced a greater vascular response than did either ionic alteration singly (Haddy *et al.*, 1963; Haddy and Scott, 1965). However, a more recent work by Anderson and colleagues (1972), using a constant flow isolated gracilis muscle preparation and hemodialysis, showed that hypokalemia alone could account for the hypertensive response seen in the presence of the hypokalemia and hypomagnesemia combination. But, this observation is based on a very large reduction in plasma potassium (86%), while the other studies dealt with smaller (30%) plasma potassium concentration changes.

Electrolyte alterations in a constant flow in situ heart preparation which included the combination hypokalemia and hypomagnesemia produced a greater increase in contractile force than was seen with either electrolyte abnormality alone (Haddy *et al.*, 1963).

Systemic Effects of Combined Potassium and Magnesium Alterations

Since small, local changes in concentration of both potassium and magnesium affected the resistance of the various vascular beds cited above and also the myocardial contractile force, a similar generalized electrolyte alteration likewise might directly affect the peripheral vasculature and myocardinal contractility and thus change systemic arterial blood pressure. Scott *et al.* (1968) and Haddy *et al.* (1969) demonstrated that acute, multiple alterations of plasma electrolytes affected systemic blood pressure. A potent diuretic, furosemide, was injected intravenously to reduce water and plasma electrolyte concentrations. After a 90 minute period, the urinary fluid loss was replaced with different solutions to create the electrolyte abnormalities. Electrolyte changes which included hypokalemia and hypomagnesemia raised systolic and diastolic pressures and produced bradycardia, while the opposite changes lowered systolic and diastolic pressures. Emerson *et al.* (1970), with a non-diuretic method, infused various test solutions at a rate of 10 ml/kg/min for 5

minutes to produce electrolyte changes by hemodilution. Hypokalemia and hypomagnesemia in combination increased mean, systolic, and diastolic blood pressures while hyperkalemia and hypermagnesemia in the presence of other hypotensive plasma electrolyte abnormalities significantly decreased mean, systolic, and diastolic blood pressures (Emerson *et al.*, 1970).

Using an isovolemic diuretic study, Haddy *et al.* (1969) observed a rise in mean arterial blood pressure as a result of hypokalemia and hypomagnesemia in combination. The superimposition of other hypertensive electrolyte alterations did not augment the already increased pressure. At this point, complete spinal anesthesia failed to affect blood pressure significantly. When the opposite electrolyte changes were made, a fall in systemic blood pressure was noted.

Abnormalities in other plasma cations, namely, hydrogen, sodium (osmolarity), and calcium resulted in cardiovascular changes. The effects of these abnormalities have been studied extensively; but, since the plasma concentration of these vasoactive substances was not altered in the present study, a detailed review of their activity will not be presented. Many of the studies cited above have shown that the hydrogen ion and osmolarity have vasoactivity similar to potassium, while calcium has the

opposite effect. In contrast, the sodium ion *per se* has been shown to have no direct effect on vascular smooth or cardiac muscle (Scott *et al.*, 1961; Haddy and Scott, 1965; Haddy and Scott, 1971).

METHODS

Sixty-four mongrel dogs of both sexes, anesthetized with sodium pentobarbital (30 mg/kg) and anticoagulated with heparin (5 mg/kg), were used for this study. Average dog weight was 15.5 kg (range, 10-20 kg). The dogs were ventilated with a mechanical positive pressure respirator (Model 607, Harvard Apparatus Co.) via an endotrachial tube. The respirator was adjusted so that blood pH averaged 7.34 (range, 7.10-7.48).

Both femoral arteries and veins were isolated and cannulated and the catheters advanced into the abdominal aorta and inferior vena cava, respectively. The left femoral arterial catheter was used for monitoring mean, systolic, and diastolic blood pressures and heart rate and for obtaining blood samples for analysis. The left femoral vein catheter, placed near the right atrium, was used for drug injections and for measuring central venous pressure. The right femoral artery and vein catheters were used for hemodialysis. Blood pressures were recorded using Statham pressure transducers and a Sanborn direct-writing recorder. The pressure transducers were routinely calibrated using a mercury manometer. Before each set of hemodynamic measurements, the catheters were flushed and zero pressures recorded.

Plasma electrolyte changes were produced with the use of a Western Kiil 7200 Dialyzer (Western Gear Corporation, Medical Systems Division). A constant displacement blood pump (Model RE 161, The Holter Co., Division of Extrocorporeal Medical Spec. Inc.) was interposed between the right femoral arterial catheter and the hemodialyzer. Blood out-flow from the dialyzer was directed to the left femoral vein (see Figure 1). Flow was held constant at 150 ml/min. Initially, the dialyzer was flushed with saline and then filled with cross-matched blood (240 ml) from a donor dog. The dialyzer consisted of three polypropylene boards "sandwiched" together with two sheets of semipermeable cuprophane PT 150 membrane inserted between each board, providing a two-layer blood compartment. Each board contained finely machined pyramids which supported the membranes and permitted the dialysate to pass along the external surfaces of the membranes. Blood flowed internally between the membranes countercurrent to dialysate flow.

The experimental protocol used in all the groups to be reported consisted of three sequential 30 minute periods of dialysis during which the animals' arterial blood was dialyzed against three separate dialysate solutions contained in a water bath kept at 37°C. The dialysate solutions were changed from one to the other with uninterrupted flow by means of a valving arrangement. Ten ml blood

Figure 1. Schematic diagram shows the blood circuit and dialysate circuit. The temperature of the dialysate solution is maintained at 37°C in a constant temperature water bath.

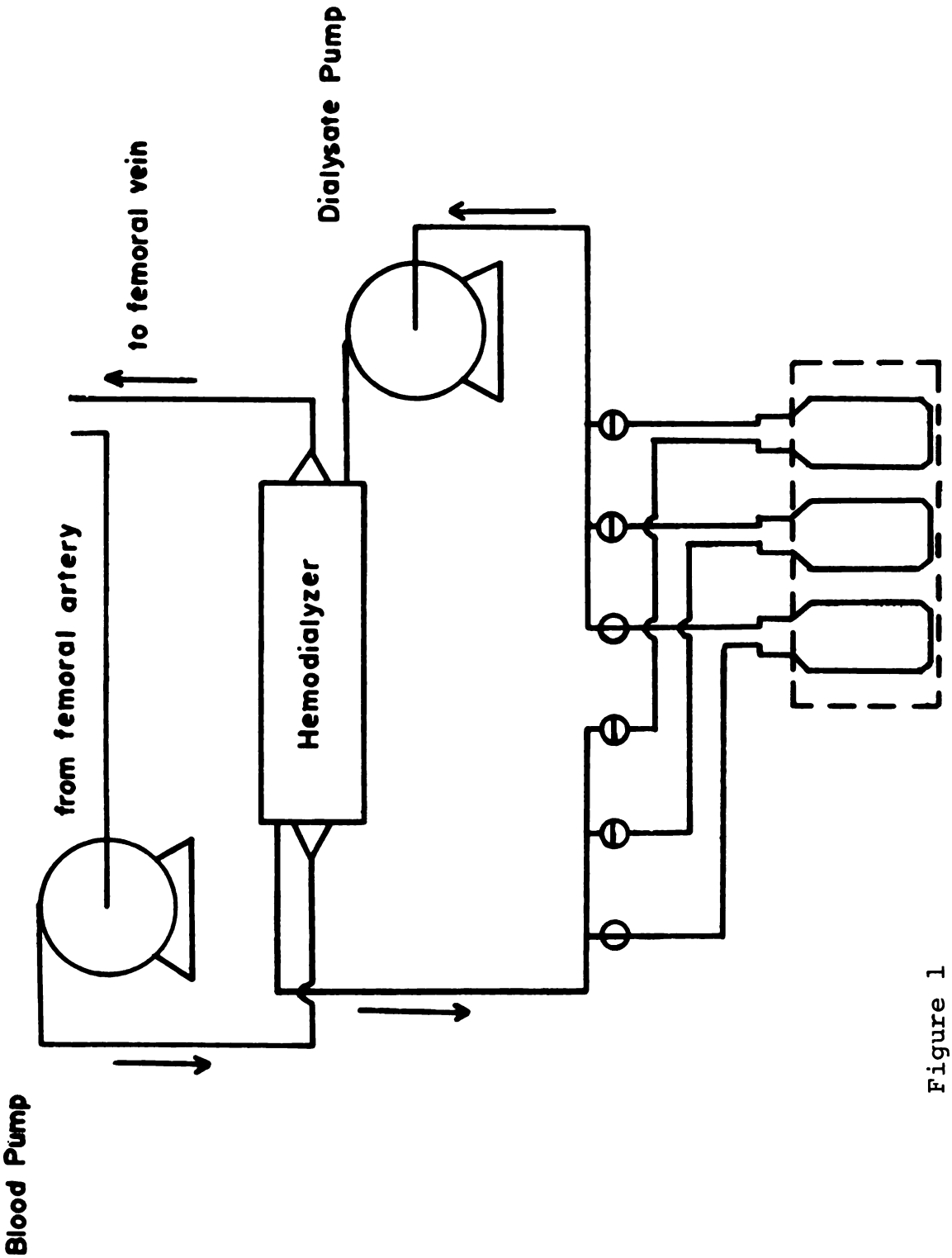
Blood Pump
from femoral artery
to femoral vein
Dialysate Pump
Hemodialyzer

Figure 1

samples were taken for electrolyte measurements and hemodynamic parameters (pressure and heart rate) recorded at the end of the first 30 minute period and every 15 minutes thereafter. The blood samples were centrifuged and the plasma electrolyte concentrations were determined in duplicate as follows: K^+ and Na^+ by flame photometry (Bechman model 105), Mg^{++} and Ca^{++} by atomic absorption (Perkin-Elmer atomic absorption spectrophotometer, model 290 B). Blood hematocrit and plasma osmolarity were determined with a microhematocrit centrifuge and with an advanced osmometer (freezing-point depression), respectively. Arterial blood pH was measured with a pH meter (22-Astrup Radiometer).

In the first group, consisting of 9 dogs, the three dialysate solutions were a modified Ringer's solution (concentration in mEq/liter: Na^+, 146; Mg^{++}, 2; K^+, 4; Ca^{++}, 5; Cl^-, 131; HCO_3^-, 21; osmolality, 300). Since the electrolyte concentrations in these solutions were the same as in normal plasma, dialysis did not create ionic abnormalities and hence, these experiments served as a control for subsequent experiments.

In a second group of experiments, consisting of 10 dogs, the blood was dialyzed against the modified Ringer's solution for the first 30 minutes just as in the dogs described above. However, during the second 30 minute period, the dialysate was a modified Ringer's solution in

which the K^+ was replaced by Na^+. This solution was designed to create hypokalemia. During the third 30 minute period, the dialysate was a modified Ringer's solution containing 7 mEq/liter of K^+. This solution was designed to re-establish a normal plasma concentration in the animal.

In a third group of experiments, consisting of 10 dogs, the blood was dialyzed against a modified Ringer's solution for the first 30 minutes. During the second 30 minute period, the dialysate was one in which the K^+ and Mg^{++} were replaced by Na^+. This solution was designed to create the combination hypokalamia and hypomagnesemia. During the third 30 minute period, the dialysate contained 7 mEq/l of K^{++} and 3.5 mEq/l of Mg^{++}. This solution was designed to re-establish a normal plasma concentration in the animals.

Blood pressure and heart rate were also investigated in three additional groups of animals, involving the same protocol and the same number of dogs in each group noted above, except these animals had their neurologic barostatic mechanism rendered inoperable by spinal anesthesia. The block was achieved by inserting a 20 gauge 1-1/2 inch needle into the cisterna magna. An average of 7 ml of cerebro-spinal fluid were withdrawn and an equal amount of 2% procaine hydrochloride solution (Abbott Laboratories) was infused slowly over a 4 to 5 minute period. A lesser amount

was withdrawn and infused to maintain complete spinal anesthesia as the experiment progressed. To test the effectiveness of the spinal block, the carotid sinus reflex was elicited by bilateral occlusion of the previously isolated common carotid arteries, both before and after spinal anesthesia. A lack of response after procaine administration indicated an effective block. This test was performed periodically throughout the experiment. At the end of the experiment, the spinal block was further checked by allowing the dog to breathe voluntarily. Failure of spontaneous respiration was further evidence of an effective spinal block.

While using the same experimental protocol described above, the chests of six additional dogs were opened surgically. Through a small midline incision just posterior to the sternum, a blunt 13 gauge needle, attached to two Statham pressure transducers via a non-pulsatile plastic "Y" tube, was inserted through the apex of the heart into the left ventricle to measure left ventricular maximal rate of pressure rise (LV dp/dt) and left ventricular end-diastolic pressure (LVEDP). The first derivative of the pressure pulse was determined by an RC differentiator (Sanborn 350-16).

Statistical analysis of the data was performed using Student's "t" test modified for paired replicates for within group comparison and the standard Student's "t" test for comparison of means between groups.

RESULTS

Figures 2-5 graphically illustrate both control and experimental average mean arterial blood pressures and heart rates as per cent change. Average control and experimental plasma potassium and magnesium concentrations are represented as actual values. Data shown in Figures 2 and 3 represent the results of intact (unblocked) animals, while data shown in Figures 4 and 5 represent the results of intact (blocked) animals, namely, those whose neurologic barostatic system had been rendered inoperable by spinal anesthesia.

Figure 2 shows graphically that the average changes in mean blood pressure associated with hypokalemia (-1.0 mEq/l) were not significantly different from those occurring in the control group in which the plasma potassium concentration was unaltered. However, average mean blood pressure in both groups fell progressively and simultaneously with time, a total of 13% for the experimental group and 10% for the control group. Heart rate tended to decrease equally in both groups; thus, the experimental group was not significantly different from the control group.

Figure 3 illustrates graphically that the average mean blood pressure changes associated with hypokalemia

Figure 2. Summary of mean arterial blood pressure (ABP) and heart rate (HR) responses during hypokalemia. Responses are expressed as a percent change (%Δ), relative to 0 minutes, over the 60 minute dialysis interval. Potassium changes are expressed as actual concentrations. Dashed lines = control animals; solid lines = experimental animals.

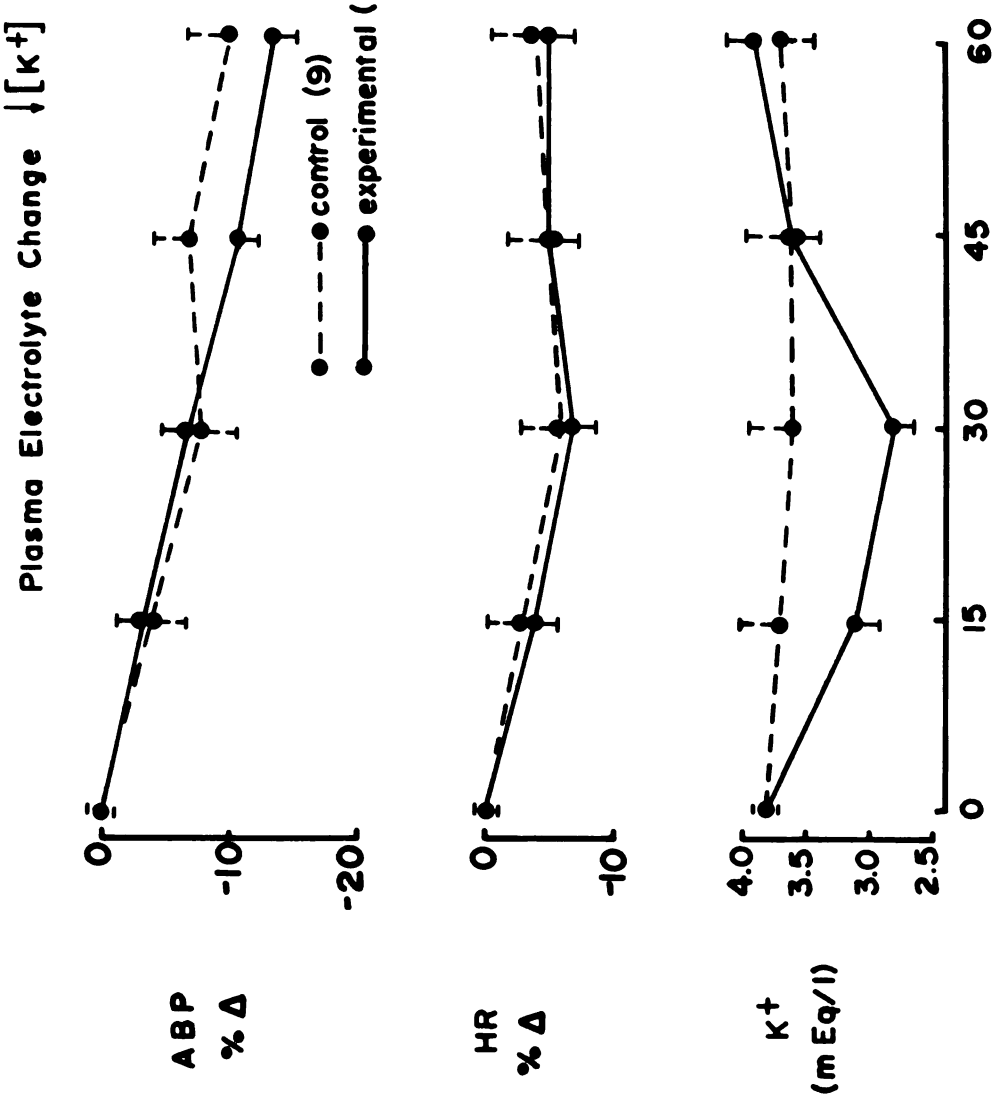
Plasma Electrolyte Change ↓[K+]
control (9)
experimental (10)
ABP
% Δ
0
-10
-20
HR
% Δ
0
-10
K+
(m Eq/l)
4.0
3.5
3.0
2.5
0
15
30
45
60
Time (min)

Figure 2

Figure 3. Summary of mean arterial blood pressure (ABP) and heart rate (HR) responses during hypokalemia and hypomagnesemia. Responses are expressed as a percent change (%Δ), relative to 0 minutes, over the 60 minute dialysis interval. Potassium and magnesium changes are expressed as actual concentrations. Dashed lines = control animals; solid lines = experimental animals.

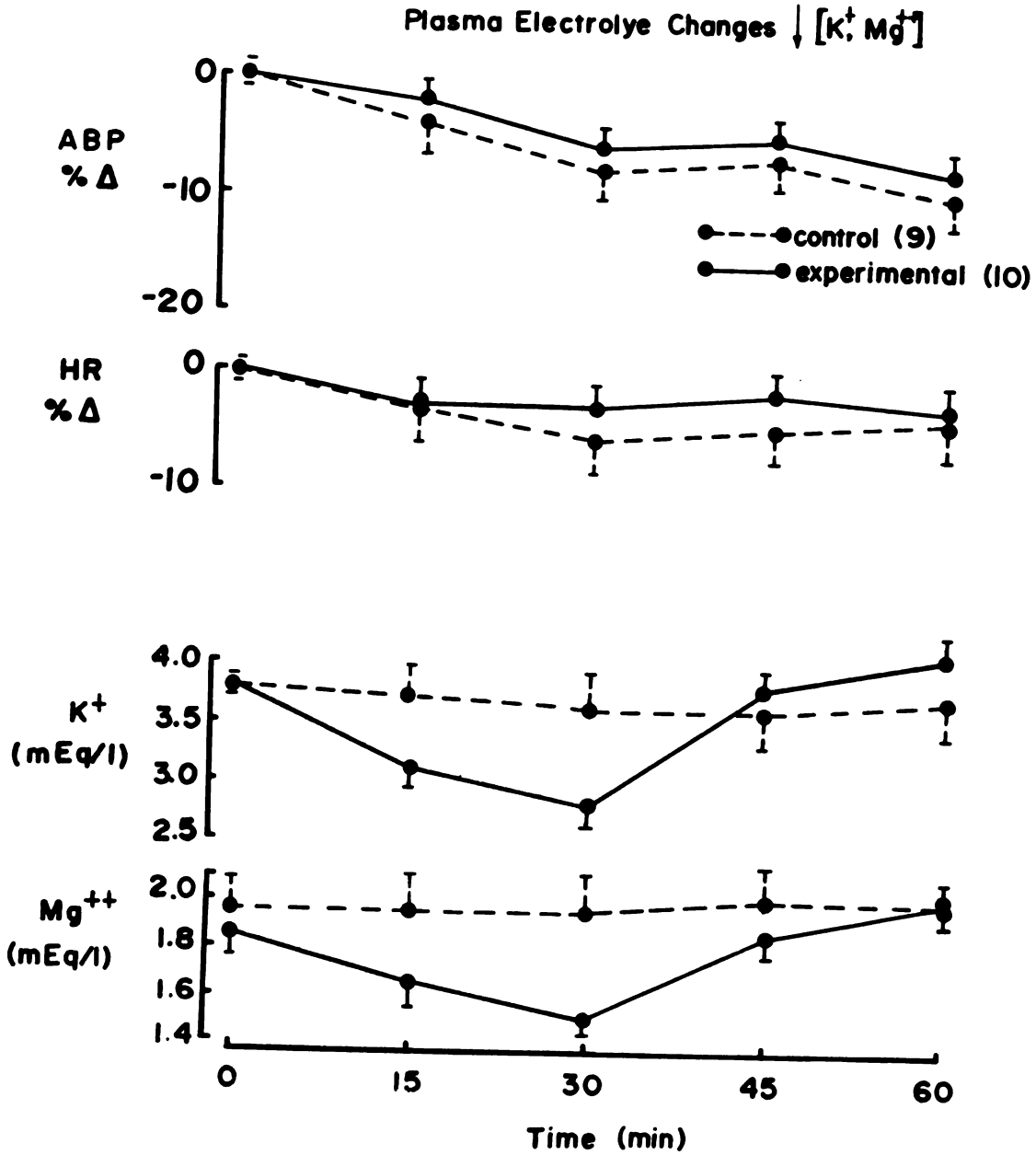
Plasma Electrolye Changes ↓ [K+, Mg++]
ABP
%Δ
0
-10
-20
control (9)
experimental (10)
HR
%Δ
0
-10
K+
(mEq/l)
4.0
3.5
3.0
2.5
Mg++
(mEq/l)
2.0
1.8
1.6
1.4
0
15
30
45
60
Time (min)

Figure 3

(-1.0 mEq/l) and hypomagnesemia (-0.45 mEq/l) were not significantly different from those occurring in the control group. Average mean blood pressure in both groups fell progressively and simultaneously with time, a total of 8% for the experimental group and 10% for the control group. Heart rate in the experimental group was not significantly different from the heart rate in the control group.

Figure 4 shows that the average changes in mean blood pressure associated with hypokalemia (-0.9 mEq/l) were not significantly different from those occurring in the control group in which the plasma potassium concentration was unaltered. Average mean blood pressure in both groups fell progressively and simultaneously with time, a total of 16% for the experimental group and 14% for the control group. Heart rate in the experimental group decreased initially, but not significantly, when compared with an unchanged control.

Figure 5 graphically illustrates that the average mean blood pressure changes associated with hypokalemia (-1.1 mEq/l) and hypomagnesemia (-0.40 mEq/l) were not significantly different from those occurring in the control group in which the plasma potassium and magnesium concentrations were unaltered. Average mean blood pressure in both groups fell progressively with time, a total of 7% for the experimental group and 14% for the control group. Heart rate remained essentially unchanged in both groups.

Figure 4. Summary of mean arterial blood pressure (ABP) and heart rate (HR) responses during hypokalemia in spinally anesthetized animals. Responses are expressed as a percent change (%Δ), relative to 0 minutes, over the 60 minute dialysis interval. Potassium changes are expressed as actual concentrations. Dashed lines = control animals; solid lines = experimental animals.

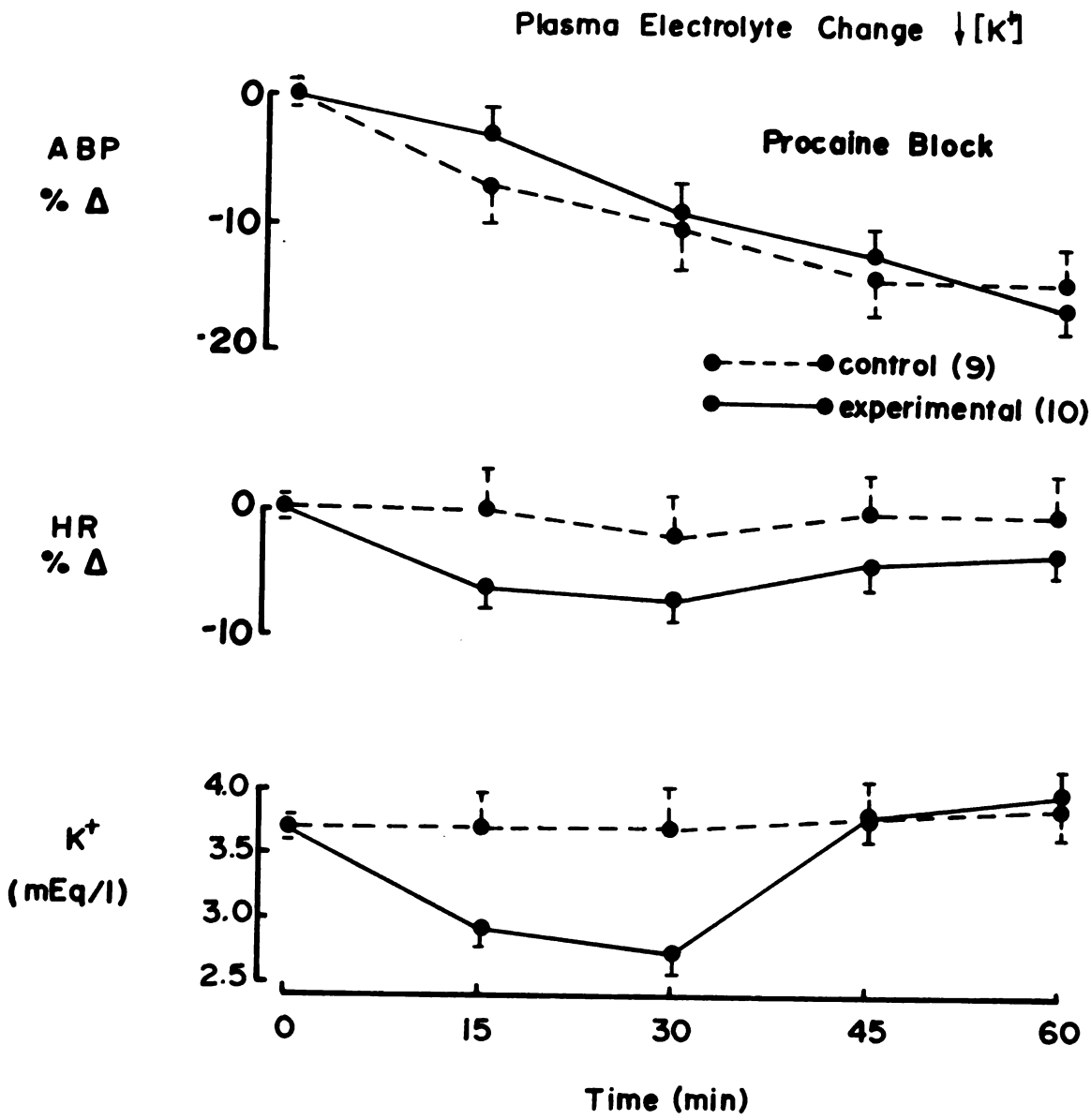
Plasma Electrolyte Change ↓[K+]
ABP
% Δ
0
-10
-20
Procaine Block
control (9)
experimental (10)
HR
% Δ
0
-10
K+
(mEq/l)
4.0
3.5
3.0
2.5
0
15
30
45
60
Time (min)

Figure 4

Figure 5. Summary of mean arterial blood pressure (ABP) and heart rate (HR) responses during hypokalemia and hypomagnesemia in spinally anesthetized animals. Responses are expressed as a percent change (%Δ), relative to 0 minutes, over the 60 minute dialysis interval. Potassium and magnesium changes are expressed as actual concentrations. Dashed lines = control animals; solid lines = experimental animals.

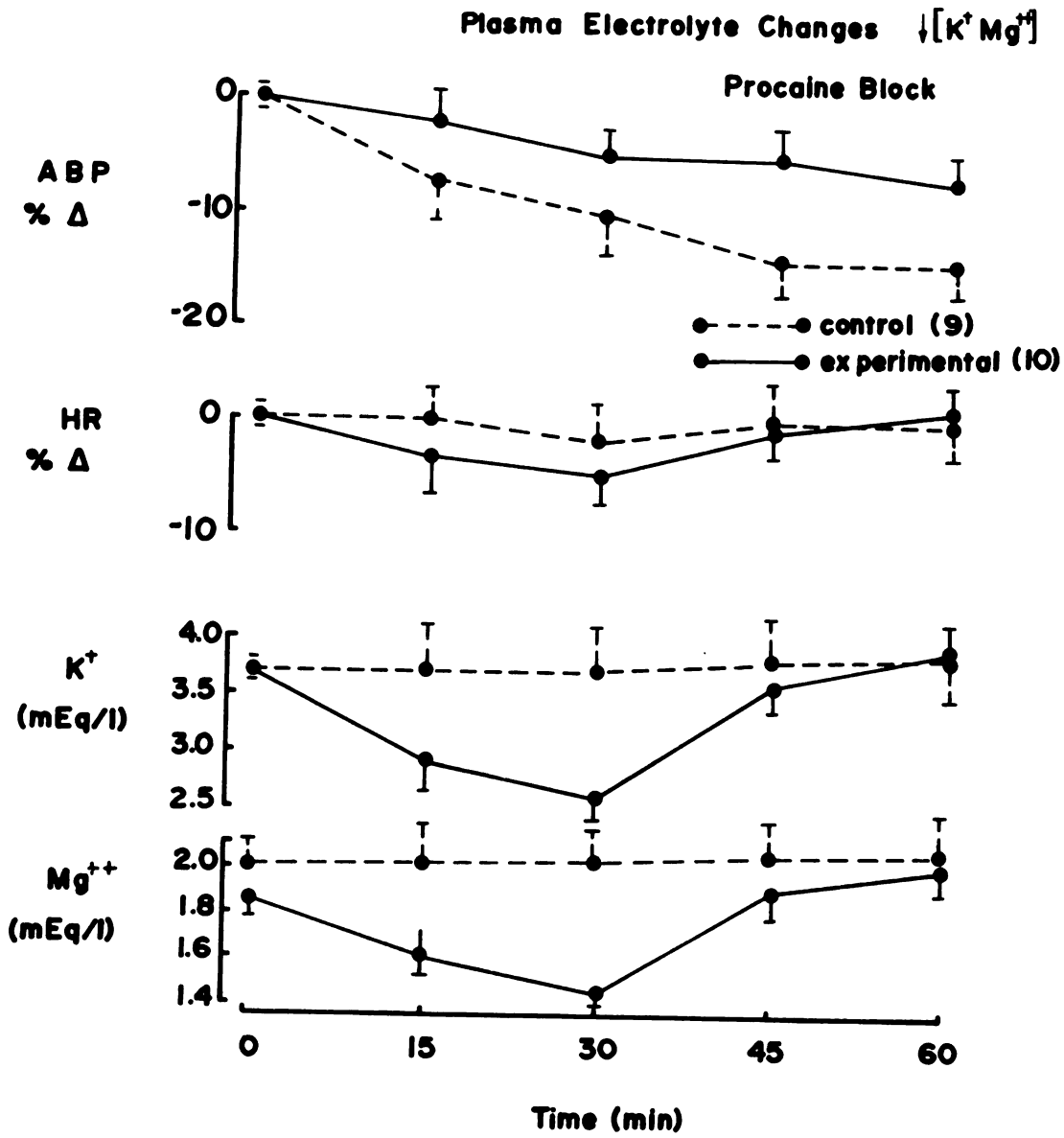
Plasma Electrolyte Changes ↓[K⁺ Mg⁺⁺]
Procaine Block
ABP
% Δ
0
-10
-20
control (9)
experimental (10)
HR
% Δ
0
-10
K⁺
(mEq/l)
4.0
3.5
3.0
2.5
Mg⁺⁺
(mEq/l)
2.0
1.8
1.6
1.4
0
15
30
45
60
Time (min)

Figure 5

Table 1 is a summary showing the actual average values for blood pressures, heart rates, and blood parameters for the two control and four experimental groups. Groups 1-3 represent an unblocked animal series, while groups 4-6 represent a series where the dogs' neurologic barostatic system was rendered inoperable by spinal anesthesia. Analysis of the data for blood pressure and heart rate shows that no significant difference exists between the 0-30 minute intervals and the 30-60 minute intervals. Further analysis of the electrolyte data shows that the desired plasma electrolyte abnormalities were achieved in the presence of no change in the other blood parameters.

Table 2 presents the actual data of three single experiments showing values for dp/dt, LVEDP, and central venous pressure in addition to blood pressures, heart rate, and other blood parameters. Statistical analysis showed that while K^+ was significantly reduced after thirty minutes of dialysis, the other parameters were not significantly changed. The steady increase in dp/dt; mean, systolic, and diastolic blood pressures; and heart rate as the experiment progressed, probably resulted from a gradual lessening in the depth of anesthesia.

Table 3 presents actual data for the same parameters as Table 2; however, these three animals had their neurologic barostatic systems rendered inoperable by spinal anesthesia. Statistical analysis showed that in the

Table I. Average effects of control and experimental hemodialysis on blood pressures, heart rate, and measured blood parameters.

GROUP #	Event	N	Mean Blood Pressure (mmHg) 0 15 30 45 60	Systolic Blood Pressure (mmHg) 0 15 30 45 60	Diastolic Blood Pressure (mmHg) 0 15 30 45 60	Heart Rate (beats/min) 0 15 30 45 60	Hematocrit (%) 0 15 30 45 60	pH (Units) 0 15 30 45 60
1	Control	9	111 107 104 103 100	127 124 120 120 118	98 94 90 91 87	143 139 134 135 136	39 40 40 40 41	7.37 7.36 7.35 7.35 7.35
2	Hypokalemia	10	109 105 102 97 94	129 129 123 119 114	95 93 88 84 79	146 139 136 138 139	41 41 42 42 43	7.28 7.31 7.29 7.30 7.30
3	Hypokalemia Hypomagnesemia	10	110 108 103 104 100	129 130 121 122 119	97 93 89 90 86	143 138 138 140 138	39 40 42 43 43	7.28 7.25 7.24 7.22 7.23
4	Control	9	70 65 62 59 59	87 82 78 76 78	58 53 51 47 48	108 108 106 108 108	36 37 37 37 38	7.38 7.39 7.37 7.38 7.36
5	Hypokalemia	10	69 67 64 61 59	87 85 81 77 76	58 56 54 50 48	105 98 98 101 101	40 40 40 40 40	7.36 7.35 7.33 7.34 7.34
6	Hypokalemia Hypomagnesemia	10	68 66 64 65 64	83 81 80 83 82	56 53 52 54 52	113 109 107 111 113	39 40 41 41 42	7.34 7.32 7.32 7.31 7.32

GROUP #	Event	K^+ (mEq/l) 0 15 30 45 60	Mg^{++} (mEq/l) 0 15 30 45 60	Ca^{++} (mEq/l) 0 15 30 45 60	Na^+ (mEq/l) 0 15 30 45 60	Osmolarity (mOsm/l) 0 15 30 45 60
1	Control	3.8 3.7 3.6 3.6 3.7	1.96 1.96 1.97 2.00 2.00	4.5 4.5 4.5 4.5 4.5	150 150 151 150 151	299 298 299 299 299
2	Hypokalemia	3.8 3.1* 2.8 3.6 3.9	2.00 2.00 2.00 2.13 2.11	4.7 4.6 4.6 4.6 4.7	149 151 150 151 151	297 298 299 300 300
3	Hypokalemia Hypomagnesemia	3.8 3.1* 2.8 3.8 4.1	1.94 1.64* 1.49 1.87 2.01	4.6 4.6 4.5 4.5 4.5	148 148 149 149 149	299 299 300 300 301
4	Control	3.7 3.7 3.7 3.8 3.9	2.02 2.04 2.04 2.05 2.08	4.7 4.6 4.6 4.6 4.6	150 150 150 150 151	298 299 299 299 300
5	Hypokalemia	3.7 2.9* 2.8 3.8 4.0	1.92 1.94 1.95 1.95 1.94	4.5 4.6 4.6 4.6 4.6	150 152 153 152 152	299 299 299 300 301
6	Hypokalemia Hypomagnesemia	3.7 2.9* 2.6 3.6 3.9	1.86 1.60* 1.46 1.89 2.01	4.6 4.6 4.5 4.6 4.5	147 147 148 148 149	291 292 291 292 292

0, 15, 30, 45, 60 signifies duration of Experiment in minutes. Groups 1-3 represent an unblocked animal series; Groups 4-6 represent a spinally blocked series. * = $P < 0.05$ relative to the above control.

Table 2. Actual and average effects of hypokalemia on dp/dt, blood pressure, heart rate and measured blood parameters.

EXP	dp/dt (mmHg/sec)	LVEDP (mmHg)	Central Venous Pressure (mmHg)	Heart Rate (beats/min)	Mean Blood Pressure (mmHg)
ø	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60
1	1976 2423 2584 2736 2888	9 8 7 6 5	4 4 4 4 4	138 150 150 162 168	80 85 85 85 85
2	1672 1976 2128 2432 2432	3 3 3 3 3	1 1 1 1 1	138 138 138 144 150	105 105 105 115 110
3	1368 1520 1520 1824 1672	3 3 3 4 4	1 1 1 1 1	126 126 126 126 132	65 65 65 75 75
$\bar{x}$	1672 1973 2077 2330 2330	5.0 4.7 4.3 4.3 4.0	2 2 2 2 2	134 138 138 144 150	83 85 85 92 90

EXP	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Hematocrit (%)	Osmolarity (mOsm/l)	Ca^{++} (mEq/l)
ø	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60
1	125 135 135 130 130	60 60 55 60 60	35 37 39 41 41	305 307 307 311 311	4.1 4.4 4.5 4.5 4.6
2	115 120 120 135 125	90 95 95 100 105	30 32 33 35 35	299 301 300 305 309	4.2 4.1 4.2 4.2 4.1
3	75 75 75 85 90	55 55 55 65 70	37 35 33 32 32	298 301 301 301 303	4.1 4.1 4.0 4.0 3.9
$\bar{x}$	105 110 110 116 115	68 70 68 78 78	34 35 35 36 36	301 303 303 306 308	4.1 4.2 4.2 4.2 4.2

EXP	Mg^{++} (mEq/l)	K^{+} (mEq/l)	Na^{+} (mEq/l)	pH (Units)
ø	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60
1	1.92 2.14 2.11 2.30 2.24	3.6 2.9 2.7* 3.9 4.3	145 146 145 146 145	7.32 7.31 7.31 7.31 7.31
2	2.05 2.06 2.16 2.21 2.19	3.7 3.1 2.8* 3.8 4.2	141 140 141 141 140	7.42 7.39 7.31 7.34 7.34
3	1.81 1.81 1.86 1.88 1.88	3.1 2.7 2.4* 3.3 3.4	142 144 143 144 146	7.43 7.41 7.41 7.40 7.40
$\bar{x}$	1.93 2.00 2.04 2.13 2.10	3.5 2.9 2.6* 3.7 4.0	143 143 143 144 144	7.38 7.37 7.34 7.35 7.35

0, 15, 30, 45, 60 denotes duration of experiment in minutes. dp/dt = Left ventricular maximal rate of pressure rise. LVEDP = Left ventricular end-diastolic pressure. * = $P < 0.05$ relative to value at 0 minutes.

Table 3. Actual and average effects of hypokalemia on dp/dt, blood pressure, heart rate, and measured blood parameters in spinally blocked dogs.

EXP	dp/dt (mmHg/sec)	LVEDP (mmHg)	Central Venous Pressure (mmHg)	Heart Rate (beats/min)	Mean Blood Pressure (mmHg)
#	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60
1	1824 2052 2204 2052 1824	5 5 5 5 5	1 1 1 1 1	114 114 110 120 120	75 85 80 75 65
2	1368 1368 1368 1520 1520	3 3 3 3 3	1 1 1 1 1	120 123 120 130 130	50 50 45 50 50
3	2204 2356 2356 2300 2204	3 3 3 3 3	1 1 1 1 1	108 108 104 108 108	75 75 75 85 85
$\bar{x}$	1798 1925 1976 1957 1849	3.7 3.7 3.7 3.7 3.7	1 1 1 1 1	114 115 111 119 119	67 70 67 70 67

EXP	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Hematocrit (%)	Osmolarity (mOsm/l)	Ca^{++} (mEq/l)
#	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60
1	90 100 95 85 75	65 75 65 63 55	33 36 36 36 37	302 302 302 302 304	4.5 4.5 4.6 4.6 4.6
2	65 65 55 65 65	40 40 34 40 40	35 38 38 39 40	299 300 300 301 302	4.4 4.6 4.4 4.3 4.3
3	100 100 100 110 110	60 60 60 70 70	37 38 38 40 41	304 300 304 307 309	4.1 4.0 4.0 3.9 3.9
$\bar{x}$	85 88 83 87 83	55 58 53 58 55	35 37 37 38 39	302 301 302 303 305	4.3 4.4 4.3 4.3 4.3

EXP	Mg^{++} (mEq/l)	K^{+} (mEq/l)	Na^{+} (mEq/l)	pH (Units)
#	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60	0 15 30 45 60
1	2.09 2.20 2.29 2.38 2.35	3.4 2.5* 2.5* 3.4 3.6	149 144 143 143 141	7.46 7.44* 7.46 7.47 7.48
2	1.89 2.01 2.02 2.06 2.20	2.6 2.0* 2.0* 3.1 3.2	140 143 141 143 144	7.43 7.36* 7.36* 7.38 7.35
3	1.87 1.90 1.99 2.08 2.09	3.1 2.5* 2.3* 3.4 3.6	144 144 143 141 143	7.39 7.39 7.37 7.37 7.37
$\bar{x}$	1.95 2.03 2.10 2.17 2.21	3.0 2.3* 2.3* 3.3 3.5	144 144 142 142 143	7.43 7.39* 7.39* 7.40 7.40

0, 15, 30, 45, 60 denotes duration of experiment in minutes. dp/dt = Left ventricular maximal rate of pressure rise. LVEDP = Left ventricular end-diastolic pressure. * = P 0.05 relative to value at 0 minutes.

presence of a significantly reduced concentration of plasma potassium, no significant change was noted in dp/dt, blood pressures, heart rate, or other blood parameters. Average dp/dt for the three animals, however, showed a slight increase during the decreased plasma potassium concentration.

DISCUSSION

The results obtained in this study suggest that the blood pressure changes associated with slowly induced, mild generalized hypokalemia alone or in combination with hypomagnesemia in intact, anesthetized dogs with either functioning or non-functioning neurogenic barostatic mechanisms are not significantly different from those occurring in the control group in which the plasma potassium and magnesium concentrations were unaltered.

The many acute local and systemic electrolyte abnormality studies cited earlier have demonstrated that blood pressure increased in the presence of either hypokalemia or hypokalemia and hypomagnesemia. Therefore, the failure of blood pressure to increase in the present study was not expected since the cationic alterations were relatively short in duration and similar in magnitude to the previously reported dilutional studies. However, careful analysis of the earlier dilutional acute plasma electrolyte alteration studies in the whole dog shows that the peak blood pressure responses occurred rapidly (about 5 minutes) and returned quickly to control even though the electrolyte abnormalities in many instances never returned to control

levels (Scott *et al.*, 1968; Emerson *et al.*, 1970). In contrast, the electrolyte changes seen in the present hemodialysis study were created more slowly (about 30 minutes). Perhaps these blood vessels became acclimated or sensitized to the reduced plasma potassium or magnesium concentrations and thus were unable to elicit a response, that is, an increased blood pressure. Perhaps the long time involved during chronic dietary potassium depletion desensitized the blood vessels further and thus accounted for the fact that dietary hypokalemia significantly lowered systemic blood pressure (Bahler and Rakita, 1971). Are these differences in blood pressure related to the length of time during which the abnormalities are created or does electrolyte depletion through dietary means possibly allow other pressure active variables to enter the experiment and influence the vascular responses? If time is a contributing factor to the differences in the blood pressure responses, then perhaps the more slowly reduced plasma potassium and magnesium concentrations in the present experiments, in contrast to the very rapid electrolyte reduction in the acute studies, accounted for the failure of blood pressure to increase.

Hemodilution is another factor to consider in regard to the generalized acute studies of ionic abnormalities. Perhaps the blood pressure responses seen in the earlier dilutional works were influenced by changes in hematocrit,

blood viscosity, non-electrolytes, or other vasoactive substances. The present data show that hypokalemia and hypomagnesemia were created gradually and selectively over a 30 minute period in the absence of any other blood parameter alterations. Thus, the factors of time and dilution could account for the differences in response since the magnitude of the ionic changes in the present study were similar to those produced in the earlier acute and chronic studies.

In the presence of functioning barostatic mechanisms, the present data demonstrate that gradually inducing a generalized hypokalemia alone or in combination with hypomagnesemia did not change systemic blood pressure or heart rate significantly when compared to the control group. Furthermore, when the neurologic barostatic mechanism was rendered inoperable by spinal anesthesia, hypokalemia did not change systemic blood pressure significantly when compared to the control group. Heart rate decreased initially as plasma potassium concentration was reduced, however, this was not significant. Bahler and Rakita (1971) observed a decreased heart rate in the presence of chronic hypokalemia. Again this difference may have been time related or a result of other bradycardic variables entering a dietary depleted animal. In other comparably blocked dogs, the combination hypokalemia and hypomagnesemia produced no significant

change in average mean arterial blood pressure or heart rate when compared to control.

The fact that blood pressure in all groups, control and experimental, waned with time in the presence of unchanged measured blood parameters suggests that hemodialysis removes some naturally occurring vasopressor or vasodilator-suppressive substance(s). However, only those substances small enough to pass through the semipermeable membrane of the dialyzer could be removed from the animal. The inability to add these postulated vasopressor or vasodilator-suppressive substance(s) to the dialysate would allow their continual removal from the animal as dialysis progressed. This progressive depletion could very well account for the observed steady decline in all the control and experimental blood pressures.

The average progressive increase in dp/dt; mean, systolic, and diastolic blood pressures; and heart rate during a normal, significantly decreased, and back to normal plasma potassium concentration in three unblocked animals probably was related to a gradual lessening in the depth of anesthesia and not hypokalemia. However, in the presence of an unchanged blood pressure, two spinally anesthetized animals demonstrated an increase in dp/dt in conjunction with a significant decrease in plasma potassium concentration. Dp/dt measurements were unchanged in a third animal of this small series. This observation parallels the

results of an earlier acute local study by Haddy *et al.* (1963) which demonstrated that mild hypokalemia tended to increase myocardial contractile force. Furthermore, it is compatible with the results of a moderately severe, chronic dietary potassium depletion study by Bahler and Rakita (1971) and a hemodialysis-induced acute hypokalemic study by Goodyer *et al.* (1967) which demonstrated a significantly increased contractile force.

Perhaps the lack of significant changes in blood pressure responses is the net effect of opposite changes in cardiac output and peripheral resistance. This study cannot answer this question since cardiac output was not measured; however, many of the studies cited earlier indicate that both of these immediate determinants of arterial blood pressure are probably involved.

SUMMARY

Potassium and magnesium were dialyzed gradually and selectively from the blood of intact unblocked and spinally blocked anesthesized dogs, while monitoring blood pressures and heart rate. Dp/dt was measured in six additional dogs. The results have shown that mild hypokalemia alone or in combination with hypomagnesemia does not significantly change mean, systolic, or diastolic blood pressures or heart rate. Dp/dt measurements suggest that mild hypokalemia tends to increase myocardial contractile force.

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