HEMODIALYSIS STUDIES OF THE EFFECTS OF LOW BLOOD POTASSIUM AND LOW BLOOD MAGNESIUM ON SKELETAL MUSCLE VASCULAR RESISTANCE TO BLOOD FLOW

Thesis for the Degree Of M. S.

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ROBERT A. BRACE

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ABSTRACT

HEMODIALYSIS STUDIES OF THE EFFECTS
OF LOW BLOOD POTASSIUM AND LOW BLOOD MAGNESIUM
ON SKELETAL MUSCLE VASCULAR RESISTANCE TO BLOOD FLOW

By

Robert A. Brace

The ionic composition of plasma directly effects vascular resistance to blood flow. Arterioles, the major resistance to blood flow, respond to changes in the plasma concentration of the potassium ion, hydrogen ion, and calcium ion by actively changing their diameter, and thereby altering resistance to flow. Many diseases that are associated with hypertension or hypotension are characterized by chronic abnormalities in plasma ionic composition.

The purposes of these studies were to determine the effect produced upon vascular resistance to blood flow through skeletal muscle by low plasma magnesium ion concentration (hypomagnesemia), both singly and in combination with low plasma potassium ion concentration (hypokalemia).

The collateral-free, gracilis muscle of the dog was utilized in this study. Plasma concentrations of potassium and/or magnesium were lowered by interposing a small hemodialyzer in the blood supply to the gracilis muscle. Flow was held constant in any given experiment. Initially, blood flowing to the muscle was dialyzed against

a Ringer's solution which contained all the major ions of the plasma in approximately equal concentrations. Response to low plasma ion concentration was determined by switching to another isoosmolal dialysate lacking the 4 meq/liter of K^+ and/or the 2 meq/liter of Mg^{++} and observing changes in pressure required to pump the constant volume of blood through the muscle.

The gracilis muscle was electrically stimulated via the gracilis nerve for 3 minutes before switching from the control dialysate to the dialysate lacking the potassium ion. After one hour of hypokalemic perfusion, the muscle was again electrically stimulated for 3 minutes to determine the effect of K^+ depletion upon change in response during active hyperemia.

Our findings from this study show reduction in plasma magnesium ion concentration by up to 85% causes no immediate change in vascular resistance in the dog gracilis muscle. Reduction of plasma magnesium ion concentration in combination with low plasma potassium ion concentration appears to produce a response not different from low potassium ion concentration alone. Furthermore, removal of 10% of the potassium in the gracilis muscle does not appreciably change the active hyperemia response. In addition, it was shown that the absolute level of plasma potassium ion concentration is not alone responsible for the changes in vascular resistance during active hyperemia.

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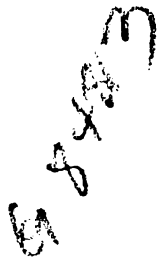

To my loving wife Catherine

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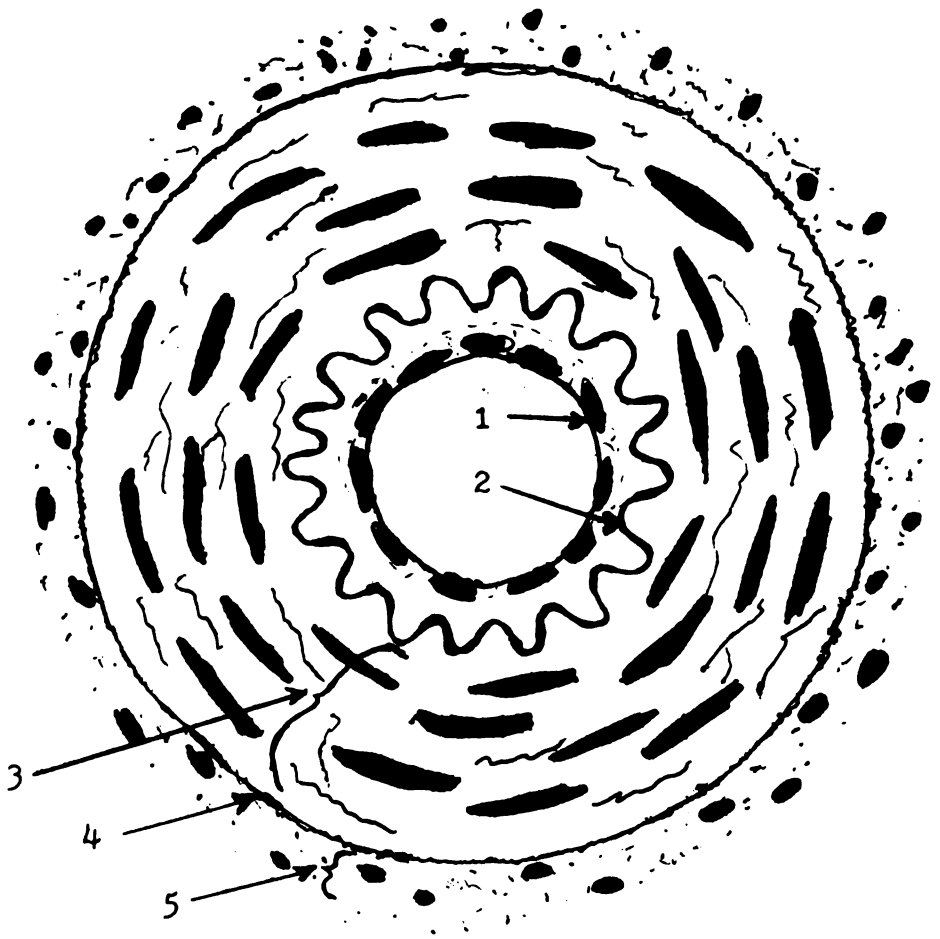
INTRODUCTION

The effect of ions upon resistnace to blood flow has been the subject of a great deal of research, both when ion concentrations are above and below their normal values. Data from that research have increased our knowledge and understanding of specific ion importance in blood flow regulation, mechanism of blood flow regulation, nature of diseases characterized by abnormal plasma ionic compositions, and also the ion's role in life's processes.

Under normal conditions, the arterioles are primarily responsible for local blood flow regulation. Their structure is illustrated in Figure 1. (Note that arterioles are distinguished from other blood vessels by their relatively thick muscular wall in relation to the small inner diameter.) The smooth muscle walls of arterioles respond to three different types of stimuli that regulate blood flow. First, they respond to the chemical composition of the blood and surrounding interstitial fluid, decreasing flow when a vasoconstrictor is introduced and increasing flow in the presence of a vasodilator. Second, they respond to the local needs of the tissues, increasing blood flow when the supply of nutrients to the tissues falls too low and decreasing the flow when the nutrient supply becomes too great. Third, autonomic nerve impulses have a profound effect on the degree of contraction of arterioles.



1. Inner layer of endothelium cells.
2. Wavy internal elastic layer.
3. Thick layer of smooth muscle.
4. External elastic layer.
5. Fibrous tissue.

Outer diameter of arterioles is typically 70 to 100 microns.

Figure 1. Schematic Representation of Arteriole Structure

Decreased plasma concentrations of hydrogen ion and potassium ion and increased concentration of calcium ion cause active decreases in arteriole inner diameter. Changes in arteriole diameter result in altered resistance to flow as shown by the Hagen-Pouseville equation for laminar flow through a tube:

$$\Delta P = \frac{128\ v\ L\ Q}{g_c\ \pi\ D^4} \cdot \qquad (1)$$

Since pressure drop across a vascular bed and blood viscosity are normally relatively constant, blood flow rate through that vascular bed will vary directly as a function of diameter to the fourth power. The very strong muscular wall of the arteriole is constructed in such a manner that the diameter can change as much as 3- to 5-fold (1). With resistance inversely proportional to the fourth power of vessel diameter, it becomes obvious that the resistance to blood flow through arterioles can be changed as much as several hundred fold by simply relaxing or constricting the smooth muscle walls. This ability to make such drastic changes in resistance is an effective means of controlling local blood flow.

BACKGROUND

Vascular Effects of Potassium and Magnesium Ions

Tremendous amounts of research have been done in the medical and physiological fields with the potassium ion and a somewhat lesser amount with the magnesium ion. Data pertinent to this study was given in a report by Haddy et al.(2). They indicate that, over a time period of a few minutes, low plasma potassium ion concentration results in active constriction in canine forelimb and kidney while low plasma magnesium ion concentration has no observeable effect, except possibly in combination with other abnormalities.

Experimental Techniques

In order to determine the effect an ion has on resistance to blood flow, the ion must be either removed from or added to the blood so that its plasma concentration changes. If this blood and normal blood are alternately passed through a vascular bed, a change in resistance may be observed. In *in vivo* experiments, increasing the blood concentration of most ions is conveniently accomplished by infusion of the ion in an isoosmolal solution. Decreasing the blood concentration of a single ion while producing no other change is very difficult. Researchers have resorted to the dilutional technique(2) and *in vitro* studies(3) in an attempt to determine the

local effect of low blood ion concentration on resistance and vascular smooth muscle activity, respectively.

However, the dilutional technique used to produce concentration changes presents some disadvantages. Dilution produces secondary changes in other variables such as hematocrit, viscosity, protein binding, nonelectrolyte concentrations, etc. Local responses are interpreted by comparison with infusion of a control solution that produces all of the changes, except that under study.

The technique used in this study, hemodialysis, allows transfer of selected ions to and from plasma with little or no change in hematocrit, viscosity, and plasma protein concentrations. With all variables except the one under consideration approximately constant, there is a quantitative response that should provide insight into the mechanisms that control resistance to blood flow.

Hemodialysis

Hemodialysis may be defined as the removal from blood of substances by means of diffusion through a semipermeable membrane. The membrane is semipermeable in the sense that it is permeable to small particles such as the metal cations and impermeable to large particles such as red blood cells and plasma proteins.

In a hemodialyzer, blood flows through a membrane envelope. A water solution which contains all the major

ions that are in blood, in approximately equal concentrations, flows on the membrane side opposite to blood. This is called the dialysate fluid.

The substance being removed from the blood diffuses to and permeates the membrane according to its concentration gradient. In clinical hemodialysis, such substances as urea and creatinine are dialyzed from the blood. In experimental hemodialysis, an ion of interest or other permeable substance is added to or deleted from a second dialysate solution while keeping all other concentrations the same as in the first solution. Osmolality is kept constant by adjusting sodium chloride concentration. The ionic concentration of blood is changed by switching the fluid bathing the membrane from the first to the second dialysate fluid. The feature of hemodialysis is that an ion can be selectively removed from blood while keeping variables such as other electrolyte concentrations, hematocrit, viscosity, protein binding, etc., essentially constant.

In a parallel-plate hemodialyzer, blood flows between two membranes in a thin film. Thickness of the film is adjusted by using spacers of appropriate thickness. The dialysate fluid flows on the outside of the membrane through the structure of the membrane support. Performance of a parallel-plate hemodialyzer can be adequately predicted from theory. Detailed theory of design and

performance of parallel-plate dialyzers, as well as discussion of membrane support can be found in L. Grimsrud's thesis(4).

In a coiled tube dialyzer, blood flows through a coil of tubular cellulose membrane which is bathed in a dialysate fluid. Since blood flows via the path of least resistance through the collapsed membrane tube, considerable channeling results and the dialyzer has a low efficiency.

APPARATUS

Dialyzers

Two parallel-plate dialyzers similar in design to that developed by Babb and Grimsrud(4,5,6,7) as an artificial kidney were used. The design is illustrated in Figure 2. In this design, the unique feature is the foam nickel metal* used to support the membrane. The porous metal (nominal density of 3% of solid nickel) allows the dialysate fluid to flow through its structure while maintaining rigid support for the membrane. Rigid support is necessary in order for the dialyzer to attain a high efficiency and have the desireable low blood volume holdup. With sagging membranes, blood volume holdup increases and efficiency decreases. If the membrane has rigid support, dialyzer performance can be adequately predicted from theory (See references 4,5,6,7).

Dialysis Membranes

Cuprophane PT 150 membranes of regenerated cellulose were used in this study. They have a dry thickness of 0.5×10^{-3} inch and swell when submersed in water to a wet thickness of 1.0×10^{-3} inch. Molecules and ions permeate the membrane if their sizes and shapes are

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*Available commercially from Metallurgical Products Department, General Electric Company, Detroit, Michigan.

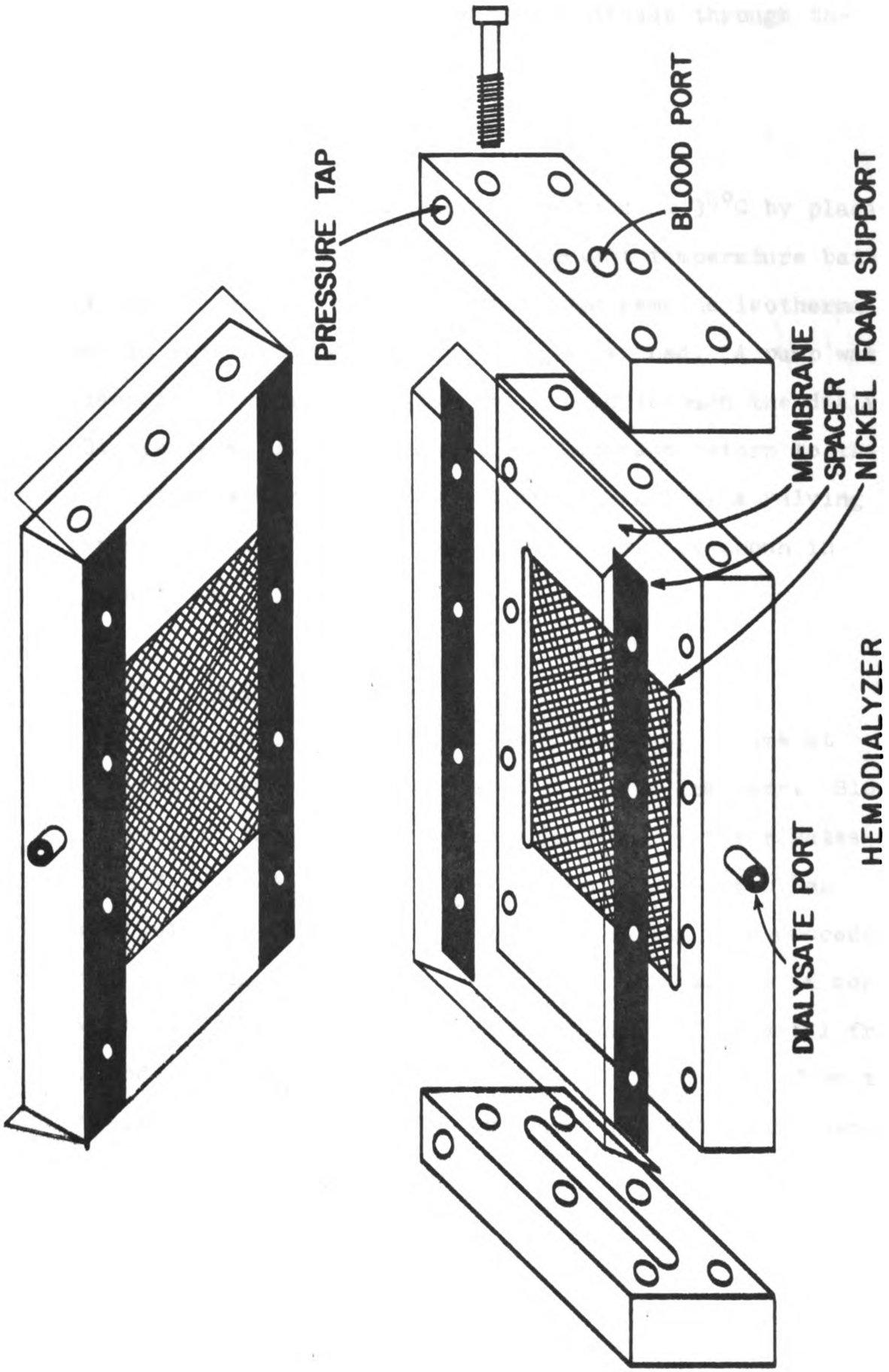


FIGURE 2. EXPLODED VIEW OF HEMODIALYZER

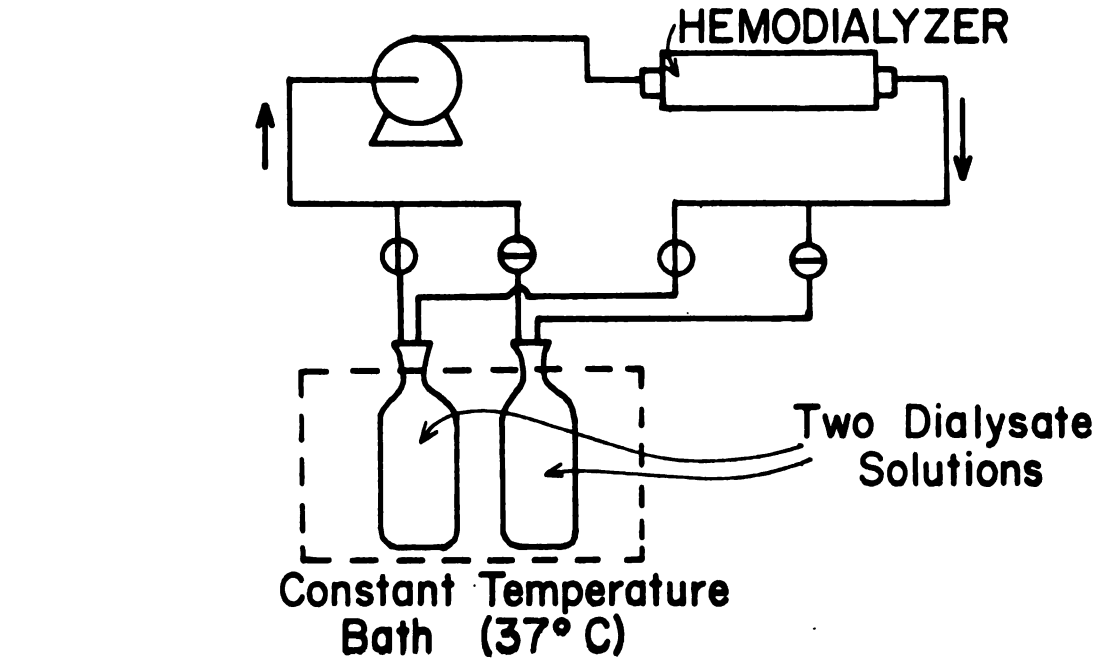
sufficiently small to allow their passage through the membrane's pores.

Dialysate Supply System

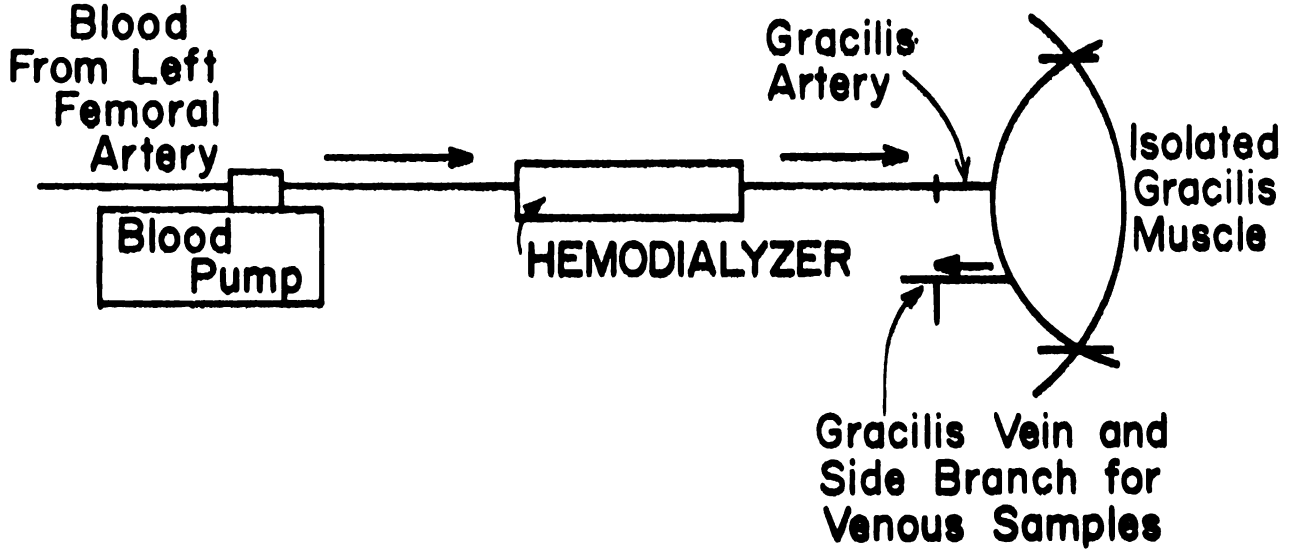
The dialysate solutions were held at 37°C by placing the dialysate containers in a constant temperature bath. With the dialysate at 37°, the blood remains isothermal as it enters the experimental vascular bed. A pump was used to circulate the dialysate fluid through the dialyzer. Dialysate solution supply to the pump and return to the container was rapidly changeable by means of a valving arrangement. The dialysate flow circuit is shown in Figure 3a.

Blood Supply System

A blood pump which outputs a constant volume at varying pressures was used to supply the dialyzer. Blood flows into the dialyzer header channel and distributes itself in a thin film (thickness normally controlled at 0.01 inch) across the dialyzer. As the flow procedes, the blood encounters the section of the membrane in contact with the foam metal support and transfer of material from blood to dialysate occurs. The blood then flows from the dialyzer into the experimental vascular bed. This blood flow circuit is shown in Figure 3b.



(a) Dialysate Circuit



(b) Blood Circuit

Figure 3.

EXPERIMENTAL PROCEDURE

Experimental Vascular Bed Preparation

Dogs ranging in weight from 20 to 40 kg were anesthetized by intravenous injection of sodium pentobarbitol (33mg/kg) and ventilated with a mechanical positive pressure respirator via an intratracheal tube. The right hindlimb gracilis muscle was surgically exposed (For detailed procedure see reference 8). The muscle was isolated, except for the main gracilis artery, vein and nerve, from trunk and leg attachments with ligatures. This was followed by an intravenous injection of sodium heparin(5mg/kg). A cannula was placed in a side branch of the gracilis vein to allow for sampling of venous blood. The left femoral artery was ligated and a constant displacement blood pump was interposed between the proximal segment of the femoral artery and the hemodialyzer. Initially the dialyzer was flushed with saline and then filled with arterial blood. Blood leaving the dialyzer entered the gracilis muscle (as shown in Figure 3b) and blood flow rate was adjusted so that the perfusion pressure was at or slightly above systemic pressure. Flow rate ranged from 5 to 25 ml/min in different experiments, depending on muscle size and initial resistance, but was maintained constant in any given experiment. Inlet dialyzer pressure as well as perfusion pressure and systemic pressure were monitored continuously on a

direct writing oscillograph. Three pressure transducers were used and all tubes and needles were flushed periodically with heparinized saline.

Dialysate Solutions

Blood concentration changes were achieved by using different dialysate solutions. Table 1 compares the ionic concentrations of the modified Ringer's solution used as control with blood. In the hypokalemia experiments, the dialysates were the control solution and another in which the 4 meq/liter of K^+ were replaced with Na^+. Similarly for the hypomagnesemia experiments, Mg^{++} was replaced with Na^+. For the combination of hypokalemia and hypomagnesemia, both K^+ and Mg^{++} in the dialysate were replaced with Na^+.

The dialysate solution volume (6 liters) was sufficiently large so that at no time did the K^+ concentration (dialyzed from blood) in the K^+ free dialysate reach 10% of the blood concentration. All solutions were maintained at 37°C, keeping the blood isothermal.

Testing for Change in Resistance to Blood Flow

The gracilis muscle was perfused with blood dialyzed against the control solution until pressure was steady and then, by means of a valving arrangement, the control solution was changed to the dialysate solution lacking the ion(s) of interest. After a new steady state perfusion

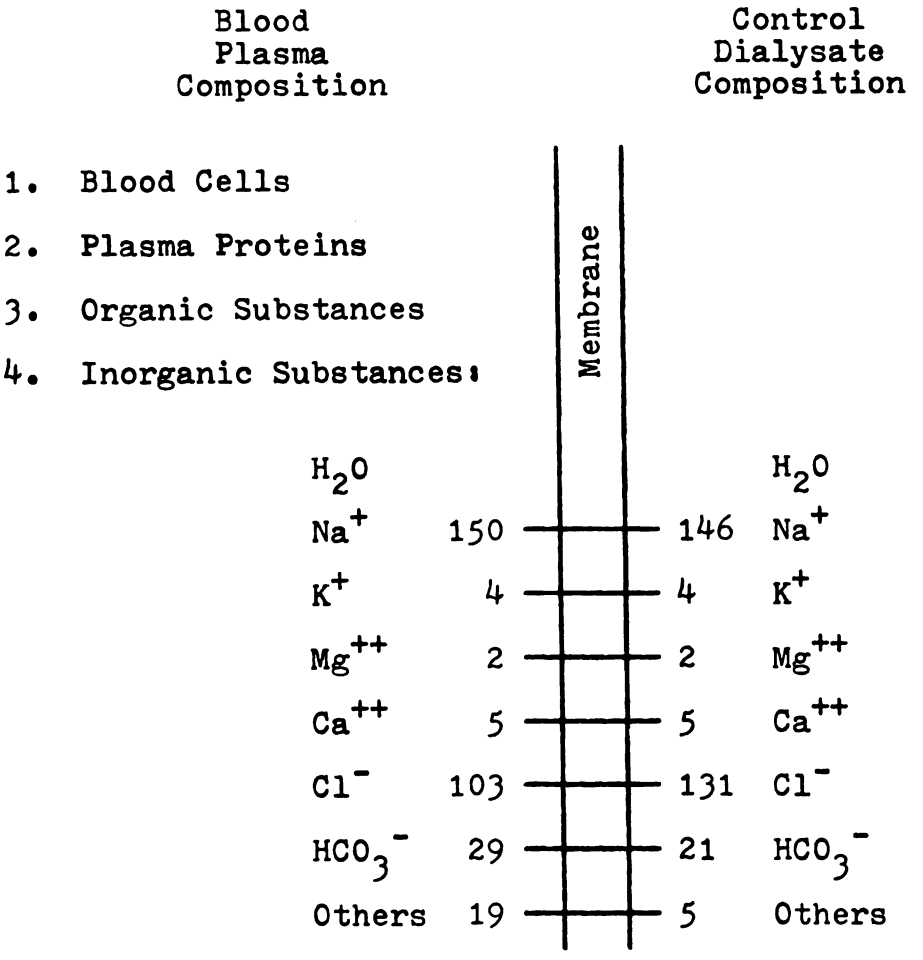


Table 1. A Comparison Of Blood Plasma Composition and Control Dialysate Composition

pressure had been reached, samples were drawn from blood entering the dialyzer, as well as arterial blood entering and venous blood leaving the gracilis muscle. These samples were analyzed for plasma potassium concentration with the Beckman flame photometer and/or magnesium concentration with the Perkin-Elmer atomic absorption. Osmolality, determined with the Advanced osmometer, pH and hematocrit were checked periodically and found to be unchanged by the dialyzer.

The experimental program consisted of dialyzing the blood alternately against the control dialysate and the zero potassium and/or zero magnesium dialysate for 5 to 10 minutes and calculating changes in vascular resistance from the steady state perfusion pressures. In addition, the experimental procedure included challenging the muscle for an extended period, one hour, with blood dialyzed against the zero potassium dialysate to determine if the acute response to hypokalemia was altered with time. Also, the effect of potassium depletion upon gracilis muscle response to levarterenol was examined by injecting 0.1 ml of levarterenol (conc. 1 ug/ml) into the blood perfusing the muscle when dialyzed against normal Ringer's and comparing this response to that due to levarterenol injection at 5, 30, and 45 minutes into a one hour potassium depletion.

In a second series of experiments (n=10), the gracilis nerve was electrically stimulated (6 volts - 1.6 msec -

6 cps) for three minutes to induce active hyperemia. At 2.5 to 3.0 minutes into the stimulation period, the dialysate was switched from the control to K^+ free Ringer's and the muscle was perfused with hypokalemic blood for one hour. The muscle was stimulated again for 3 minutes, examining the effects of K^+ depletion on response to active hyperemia. Arterial and venous samples were taken before, during and after stimulation. These were analyzed for K^+ concentration and osmolality.

RESULTS AND DISCUSSION

Short Term Response to Hypokalemia

The amount of potassium removed from the blood depends mainly on the blood flow rate and the transfer area available in the dialyzer. Blood flow rates to the gracilis varied from about 5 to 25 ml/min and the two dialyzers had transfer areas of approzimately 200 and 1000 cm^2. The combination of the low flow rate with the larger dialyzer makes it possible to remove in excess of 95% of the normal potassium from the perfusing blood in a single pass through the dialyzer.

Figure 4 is a tracing from a typical hypokalemia experiment. The arrow indicates the point at which the dialysate solution was switched from normal Ringer's to zero potassium. Note the time lag, about one minute, before the muscle is perfused with hypokalemic blood and the vascular resistance increases. Initially there is no rise in perfusion pressure after switching dialysate sources since the gracilis muscle continues to be perfused with blood from the connecting tubing and outlet header of the hemodialyzer which contained normal K^+. After this period, hypokalemic blood entered the gracilis and the perfusion pressure rose rapidly to a new level.

Figure 5 summarizes the results of short term hypokalemia including that reported by Roth(9,10). Each point represents one gracilis muscle preparation and

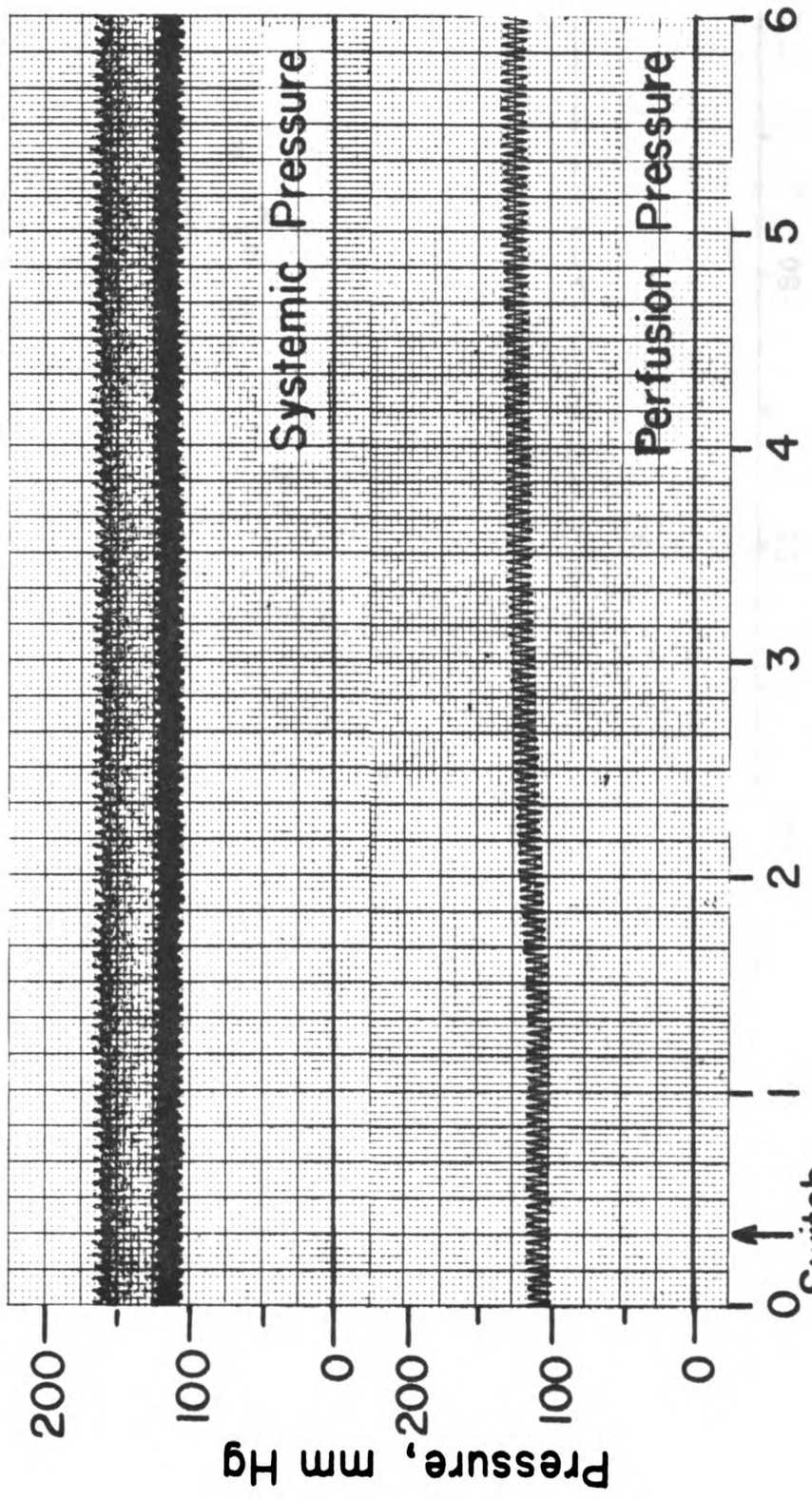


Figure 4. Typical Response of Gracilis Muscle to Hypokalemia.

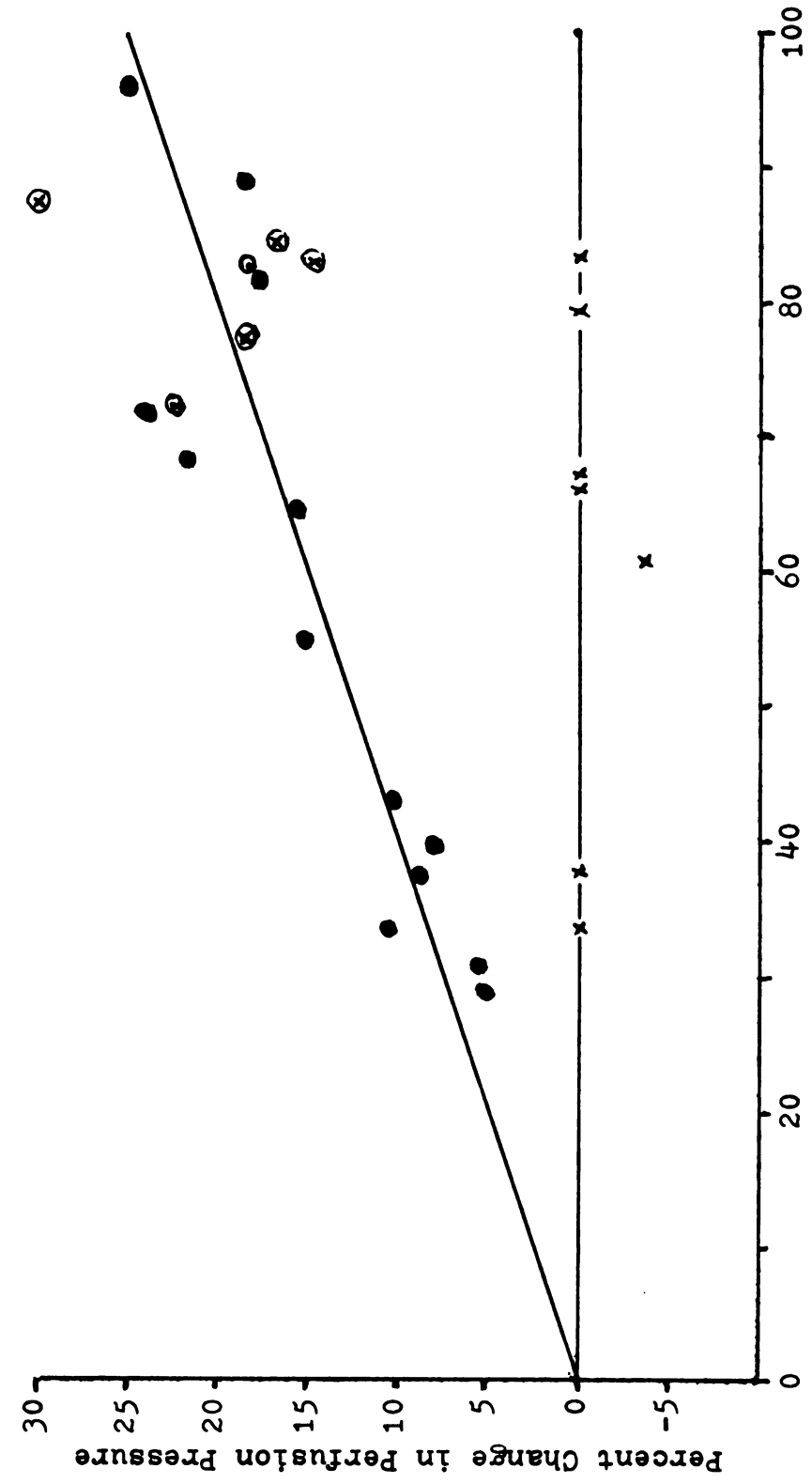


Figure 5. Percent Change in Perfusion Pressure as a Function of Change in Potassium and Magnesium Ion Concentrations. Circles ⊙, K^+ data; filled circles ●, Roth's K^+ data; crosses ×, Mg^{++} data; cross-filled circles ⊗, combination K^+ and Mg^{++} data, plotted as P vs. K^+.

is an average value relative to control of several alternate responses to control and hypokalemic blood. For the range of plasma potassium concentrations considered, approximately 0.2 to 4.0 meq/liter, Roth fit his data to the straight line

$$\left(\frac{P_e - P_c}{P_c} \right) = -0.25 \left(\frac{K_e - K_c}{K_c} \right) \qquad (2)$$

with a coefficient of correlation of 0.90. P and K refer to the perfusion pressure and plasma potassium concentration entering the muscle, respectively. Subscripts e and c refer to the experimental and control values of the perfusion pressure and plasma potassium concentration entering the muscle. Each point represents an increase in vascular resistance or perfusion pressure when switching from control to hypokalemic blood and a decrease in vascular resistance or perfusion pressure when switching from hypokalemic blood to control. No significant difference is obtained when these responses are plotted separately. When change in resistance is compared to plasma potassium concentration leaving the muscle, there is less correlation (correlation coefficient = 0.20). Data for individual experiments are included in the Appendix.

It was common during these experiments for the gracilis muscle to respond more strongly to its second exposure to hypokalemia than to the first. Further

exposures to hypokalemia usually produced only small changes from the second exposure. Average percent change in perfusion pressure (n=7) for 3 exposures to hypokalemia are shown in Figure 6. Note that the amount of K^+ removed from the blood varied from one experiment to the next, but remained constant during any given experiment.

Long Term Response to Hypokalemia

One hour of hypokalemic perfusion produced an increase in perfusion pressure above the short term (5 to 10 minutes) response to hypokalemia in all but one experiment (n=10). At the end of one hour, perfusion pressure after switching from K^+ free to control Ringer's was above control in all experiments, averaging 38% higher as shown in Table 2.

After one hour of hypokalemic perfusion, the response of the muscle to short term hypokalemia was examined. When change in resistance is correlated with change in K^+ concentration in the perfusing arterial blood, correlation is poor (correlation coefficient = 0.20 for the best straight line).

Effect of Potassium Depletion on Response to Levarterenol

Figure 7 is a typical tracing showing gracilis perfusion pressure response to levarterenol. Injection of levarterenol during perfusion with normal blood produced the usual increase in vascular resistance.

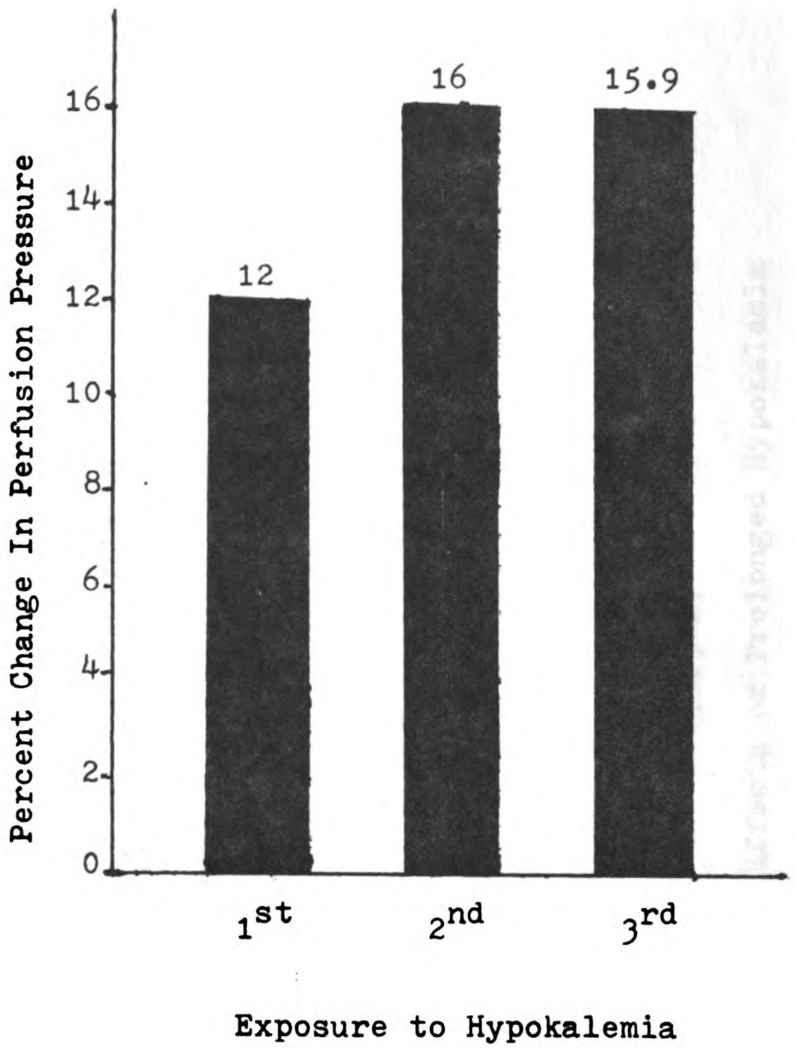


Figure 6. Change in Response to Hypokalemia Upon Repeated Exposures

time	dialysate	perfusion pressure	% above control
0	control Ringer's	114	—
5-10 min	K^+ free	132	15.8
1 hr	K^+ free	167	46.5
1 hr + 5-10 min	control Ringer's	156	37.9

Table 2.

Average Effects of Prolonged Hypokalemia

on Perfusion Pressure at Constant Flow (n=10)

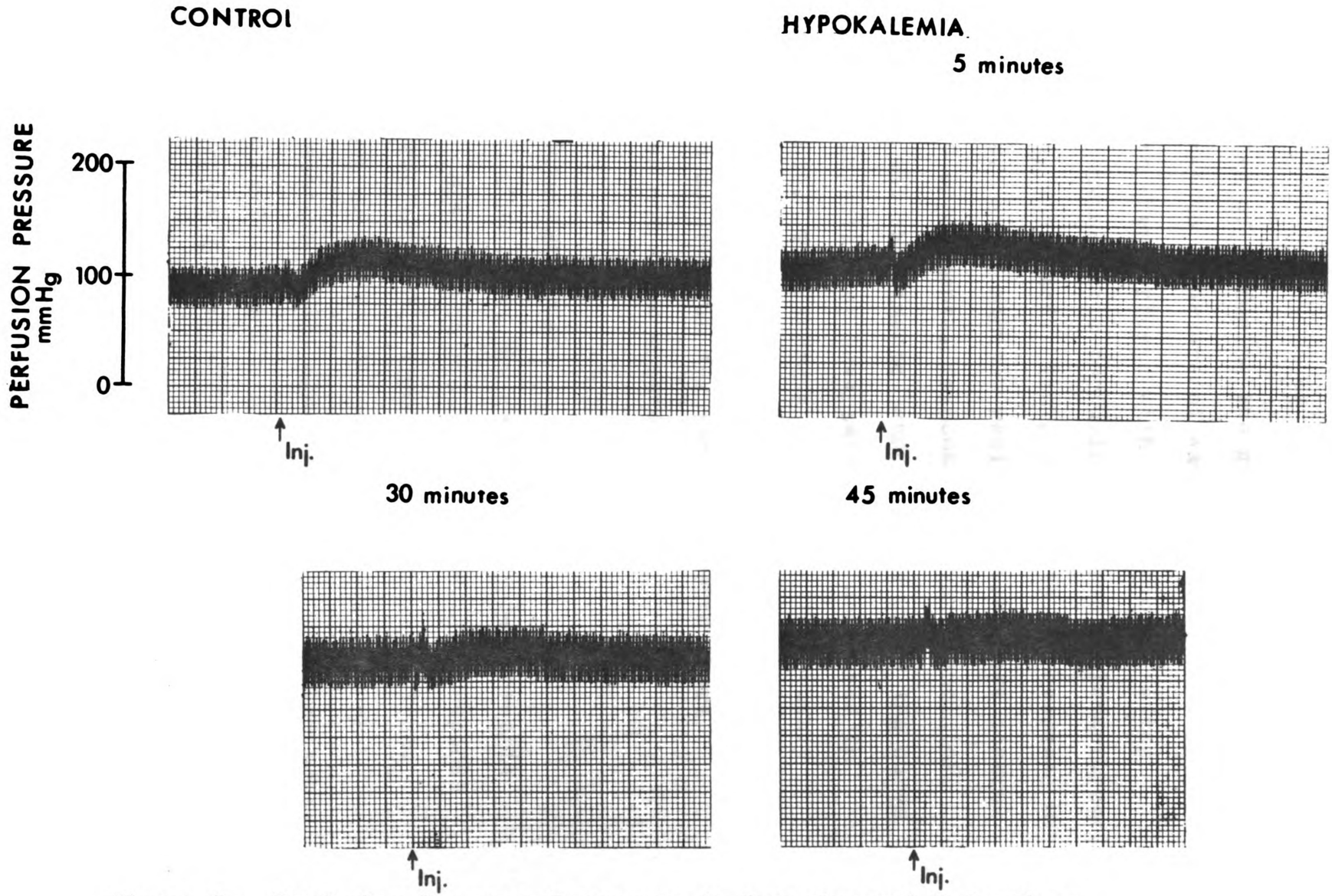


Figure 7. Perfusion Pressure Responses to Levarterenol Injections During Normal and Hypokalemic Blood Perfusion

After 5 minutes of perfusing the gracilis with hypokalemic blood, response to levarterenol was not significantly different than when perfused with normal blood. After 45 minutes of hypokalemic perfusion response to levarterenol was noticeably decreased. Table 3 presents the averages of 9 experiments. At 45 minutes resistance was above control in 7 out of 9 experiments, response to levarterenol (ΔP) decreased in all experiments, and the area under the curve produced by injection of levarterenol was decreased in all experiments. The decrease in response is probably not related to the increased resistance since decreased response also occurred in the two experiments where resistance was not above control.

Response to Hypomagnesemia

Figure 5 also shows the result of 7 hypomagnesemia experiments. Again, each point is the averaged response relative to control for a single gracilis preparation. Removal of 33% to 84% of the plasma Mg^{++} produced no effect upon vascular resistance in all but one experiment. In that experiment the gracilis responded initially, but failed to respond upon further exposures to hypomagnesemia.

Response to Combination of Hypokalemia and Hypomagnesemia

Four of the above experiments included perfusing the gracilis muscle with hypokalemic and hypomagnesemic blood simultaneously. The data are plotted in Figure 5 as

hypokalemia perfusion	P_s	P_{p1}	P_m	ΔP	P_{p2}	mm^2 area
control	123	107	136	29	113	253
5 minutes	119	126	145	19	128	146
30 minutes	124	131	150	19	134	128
45 minutes	126	140	153	13	145	82
post control*	123	164	171	7	169	11

P_s = systemic blood pressure (mm Hg)

P_{p1} = preinjection perfusion pressure

P_m = maximum pressure attained after levarterenol injection

ΔP = $P_m - P_{p1}$

P_{p2} = post injection perfusion pressure

*post control (n=6) on normal Ringer's

Table 3.

Average Perfusion Pressure Responses to Levarterenol Injections During Normal and Hypokalemic Blood Perfusion

percent change in K^+ concentration vs. percent change in perfusion pressure. On as average we removed 64% of the Mg^{++} and 83% of the K^+ from the blood while producing a 20% change in perfusion pressure. From Figure 5 it can be seen that this increase in perfusion pressure corresponds to an 83% decrease in plasma K^+ concentration. Thus the potassium alone can account for the change in pressure.

Effect of K^+ Depletion on Response to Active Hyperemia

Active hyperemia is the increase in blood flow that accompanies an increase in metabolic rate in an organ. In the skeletal muscle, exercise results in an increase in metabolic rate and an increased flow. Experimental active hyperemia is produced by electrical stimulation of the nerve supply to a muscle. In these experiments, flow rate to the muscle was held constant during electrical stimulation so that the active dilation that accompanies active hyperemia could be examined through change in perfusion pressure.

Figure 8 is a tracing of the pressure response when the gracilis nerve is stimulated (6 volts - 1.6 msec - 6 cps) for three minutes while perfusing with normal blood. Just prior to stopping stimulation the dialysate was changed to K^+ free Ringer's. Thus hypokalemic blood entered the muscle approximately one minute after the end of stimulation.

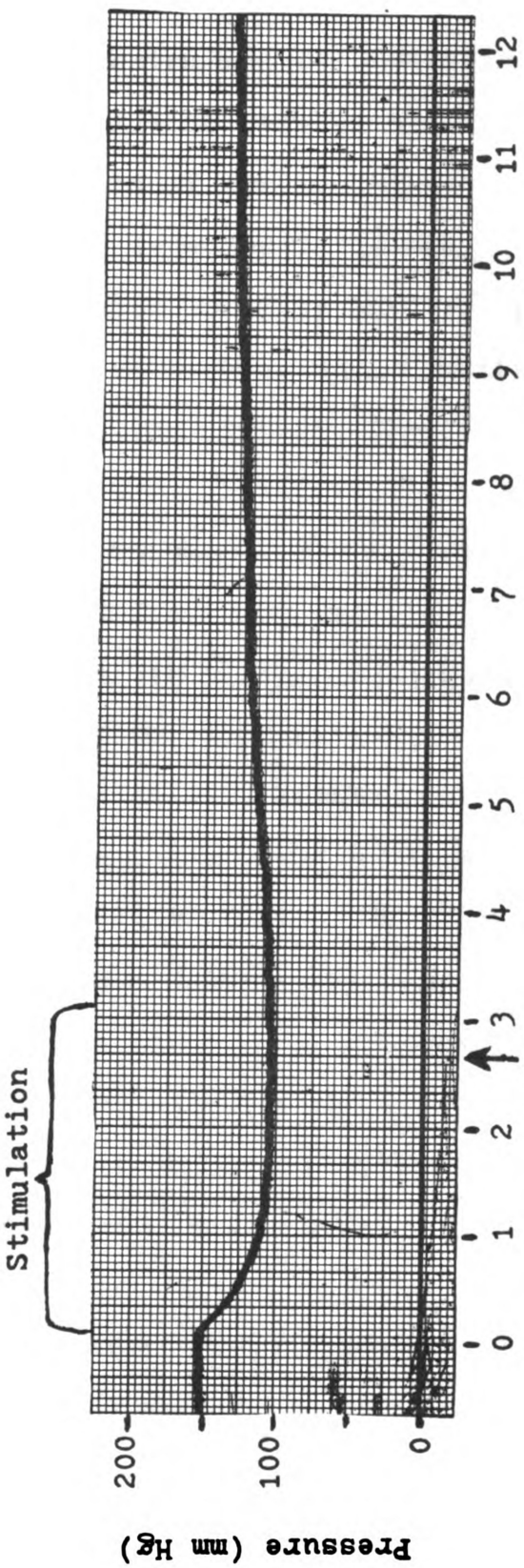


Figure 8. Typical Perfusion Pressure Response of Gracilis Muscle to Electrical Stimulation

The K^+ concentration was determined for blood entering and leaving the muscle before, during and after stimulation. A composite record of the concentration and perfusion pressures for 10 experiments is shown in Figure 9 and in Table 4. Perfusion pressure (initially 107 mm Hg) took several minutes to recover to a constant value (108 mm Hg). The K^+ concentration into the muscle decreased from 3.89 meq/liter to 0.94 meq/liter at approximately the time stimulation was stopped. The K^+ concentration out of the muscle increased from 3.92 meq/liter to 5.57 meq/liter when stimulation was begun and dropped to 1.52 meq/liter when stimulation was stopped and low K^+ dialysis started.

An estimate of the expected perfusion pressure due to the K^+ concentration changes alone can be made from Figure 5. The dotted line in Figure 9 corresponds to an arterial K^+ concentration change from 3.92 to 5.57 meq/liter at the onset of stimulation and a decrease from 5.57 to 0.94 meq/liter at its termination. Comparing the estimated with actual perfusion pressure, it is seen that the change in perfusion pressure due to hypokalemia is larger than the observed change in perfusion pressure.

When the muscle was stimulated again after one hour of perfusion with hypokalemic blood, the perfusion pressure fell to the same level as it had during its initial stimulation (see Figure 9). Venous potassium increased from 1.52 to 3.42 meq/liter. (Note that arterial blood was still

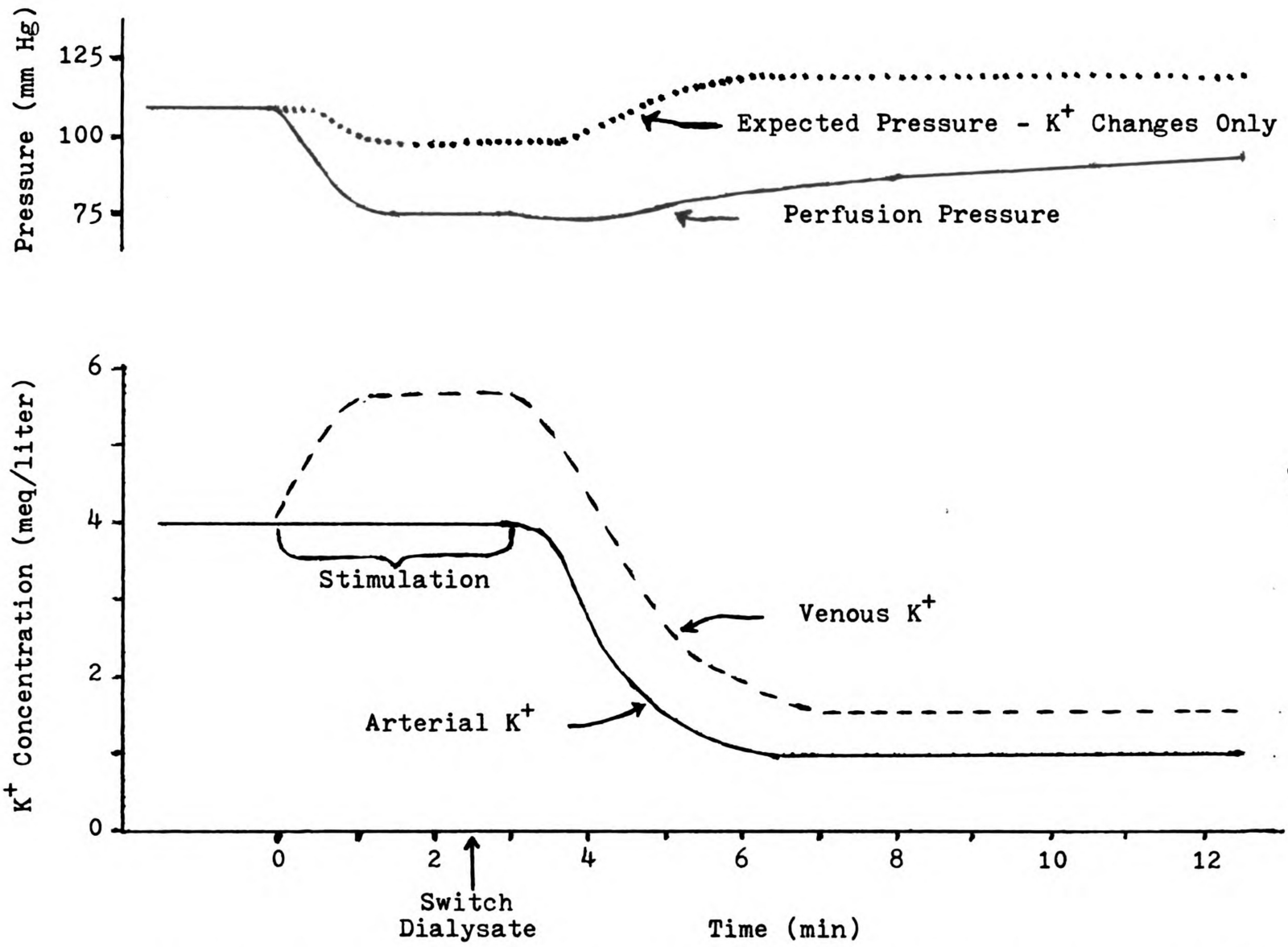


Figure 9. Average Changes in K^+ Concentration and Perfusion Pressure During Stimulation

stimulation time	dialysate	K^+_a	K^+_v	osm_a	osm_v	P	%ΔP	meq K^+ removed per gm muscle	flow ml/min
before	control	3.89	3.92	304	305	107		0	20.4
during	control		5.57		319	74	-31	0	20.4
before	1 hr low K^+	0.94	1.52	301	308	108		0.011	20.4
during	1 hr low K^+		3.42		320	72	-33	0.011	20.4

K^+_a = arterial K^+ concentration (meq/liter)

K^+_v = venous K^+ concentration

osm_a = arterial osmolality (milliosmoles/liter)

osm_v = venous osmolality

P = steady perfusion pressure

Table 4.

Effect of One Hour of Hypokalemic Perfusion

on Active Dilation During Electrical Stimulation

hypokalemic). Since this perfusion pressure response to stimulation was identical with the initial response while K^+ concentrations differed significantly, it was concluded that the absolute level of K^+ is not responsible for the response to active hyperemia.

The osmolality of the blood increased during stimulation as shown in Table 4. These are large increases in osmolality and their effect on perfusion pressure has to be examined. It is estimated that perfusion pressure change in response to such osmolality changes would be larger than the pressure change due to the changes in K^+ concentration alone(11).

Using the blood flow and the arterio-venous difference in K^+ concentrations as an indicator, an average of approximately 1.0 meq of potassium was removed from the muscle during the one hour of low potassium perfusion. The muscle was weighed at the conclusion of the experiment and it is estimated that an average of 11% of the cellular potassium was removed. Since perfusion pressure response to stimulation after 1 hour of hypokalemic perfusion was identical with that before the potassium depletion, it was concluded that K^+ depletion of up to 11% has no effect on response to active hyperemia.

SUMMARY AND CONCLUSTIONS

Prolonged Hypokalemia

Depleting a muscle of potassium by dialyzing the perfusing blood against a potassium-free Ringer's solution elevates vascular resistance to blood flow. As shown in Table 2, at the end of one hour of hypokalemic perfusion, vascular resistance is greater than the resistance of the nondepleted muscle when first exposed to hypokalemia. When the muscle is again perfused with normal blood, resistance remains above the control resistance before potassium depletion.

Response of the gracilis muscle to levarterenol injection decreases as potassium is depleted. As was shown in Table 3, the area under the perfusion pressure curve produced by levarterenol injection was progressively reduced as the time of hypokalemic perfusion increased. After one hour of hypokalemic perfusion, response to levarterenol injection was only 4% of the initial control response.

Hypomagnesemia

The results of this study show reducing the magnesium ion concentration of blood perfusing a muscle by up to 84% has no immediate effect upon skeletal muscle vascular resistance to blood flow. Change in vascular resistance due to the combination of low blood potassium ion and

low blood magnesium ion concentrations appears to be not different from that produced by low blood potassium ion concentration alone, as can be seen from Figure 5.

Potassium's Role in Active Hyperemia

Potassium does not appear to control change in vascular resistance during active hyperemia. Depletion of 11% of the cellular potassium from a muscle does not change perfusion pressure response to electrical stimulation when blood flow rate is constant. The amount of potassium in blood entering or leaving the gracilis muscle during active hyperemia is not the controlling factor which influences change in vascular resistance. As shown in Table 4, change in vascular resistance during electrical stimulation when arterial potassium ion concentration was 3.89 meq/liter and venous potassium ion concentration was 5.57 meq/liter was the same as the change in resistance observed when arterial potassium ion concentration was 0.94 meq/liter and venous potassium ion concentration was 3.42 meq/liter. The amount of potassium released during active hyperemia does not control resistance changes since the same resistance change occurred when 1.68 meq/liter and 2.50 meq/liter of potassium were released into the blood passing through the muscle. Note that more potassium was released from the muscle during stimulation after one hour of hypokalemia perfusion than before the potassium depletion.

RECOMMENDATIONS

As research progresses, an increasing amount of data is generated which shows the specific effects of individual ions and chemicals on resistance to local blood flow. One of the purposes of such research is to discover the as yet unknown mechanism by which changes in resistance occur. Since hemodialysis has been shown to be an effective method of studying the local effects of low blood ion concentrations, it is recommended that further hemodialysis studies be initiated to investigate the mechanism by which the observed changes in resistance to flow occur.

The active constriction caused by low plasma potassium ion concentration may be associated with the active transport of potassium into and sodium out of cells. Chemicals such as digitalis are known to partially block the active transport of sodium and potassium across the cell membrane. If digitalis is effective in changing vascular response to hypokalemia and hyperkalemia, some mechanistic explanation may be possible.

APPENDIX: TABULATED EXPERIMENTAL DATA

Exp. No.	%ΔP	Arterial %ΔK	Venous %ΔK	Q_B (ml/min)
1	10.3	44.0	27.5	13.0
2	15.8	64.3	42.9	-
3	21.8	68.4	18.1	8.4
4	5.85	30.7	23.1	19.0
6	9.35	33.8	5.0	15.2
7	8.9	37.5	29.2	16.2
9	7.9	39.6	31.0	15.7
10	5.2	29.0	25.7	20.5
11	15.2	55.0	39.2	8.6
12	24.2	72.0	53.6	13.5
13	17.6	81.6	38.5	8.5
14-1	25.1	96.0	63.5	7.9
14-2	18.4	89.0	70.3	12.4
15	18.2	82.8	23.5	-
16	22.6	72.2	32.3	-

Table 5.

Tabulated Results for the Short Term Vascular Response to Hypokalemia

Exp. No.	Arterial %ΔK	% Change in Perfusion Pressure		
		1st Exposure	2nd Exposure	3rd Exposure
2	64.3	11.9	19.5	14.3
6	33.8	10.5	11.8	11.2
7	37.5	11.8	11.5	14.1
9	39.6	1.77	3.68	9.41
11	55.0	9.8	17.7	20.7
12	72.0	20.1	35.0	25.6
13	81.6	12.1	12.8	15.2
avg.	54.6	11.99	16.0	15.88

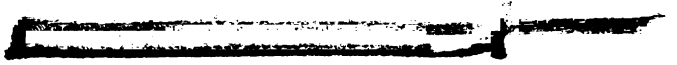
Table 6.

Tabulated Results Showing Change in Response

to Hypokalemia with Repeated Exposures to Hypokalemia

Exp. No.	Arterial %ΔK	Perfusion Pressures (mm Hg) control 0 min	short term response 5-10 min	long term response 1 hr	post control 1 hr + 5-10 min
3	64.8	135	155	207	192
4	30.7	130	145	171	168
6	33.8	105	112	170	175
7	37.5	120	137	150	145
9	39.5	115	125	175	167
10	29.0	125	140	150	148
11	55.0	66	77	107	88
12	72.1	117	145	245	205
14	89.5	120	137	137	128
18	85.0	111	143	155	140

Table 7. Tabulated Perfusion Pressures Showing Effect of Hypokalemic Perfusion for One Hour Upon Perfusion Pressure During Hypokalemia and Post Control Perfusion Pressure



Exp. No.	P_s	P_{p1}	P_{pm}	ΔP	P_{p2}	mm^2 area
3	135	125	162	37	140	258
4	137	113	132	19	115	87
6	82	93	115	22	98	104
7	138	110	135	25	120	131
9	128	115	147	32	118	139
10	195	90	103	13	93	82
12	125	121	170	49	129	865
14	125	104	134	30	106	258
15	130	89	124	35	94	352
avg.	123	107	136	29	113	253

a) Control

P_s = systemic blood pressure (mm Hg)

P_{p1} = preinjection perfusion pressure

P_m = maximum pressure attained after levarterenol injection

ΔP = $P_m - P_{p1}$

P_{p2} = post injection perfusion pressure

area = area under perfusion pressure curve caused by injection of levarterenol

Table 8.

Tabulated Results for Vascular Response to Levarterenol Injected During Normal and Hypokalemic Perfusion for One Hour

Exp. No.	P_s	P_{p1}	P_{pm}	ΔP	P_{p2}	mm^2 area
3	133	170	175	5	170	85
4	127	145	157	12	150	41
6	85	113	135	22	110	41
7	138	125	150	25	133	138
9	90	123	140	17	135	56
10	120	75	86	11	83	77
12	125	143	170	27	133	357
14	125	137	153	16	133	88
15	129	102	139	37	102	378
avg.	119	126	145	19	128	146

b) After 5 Minutes of Hypokalemic Perfusion

Exp. No.	P_s	P_{p1}	P_{pm}	ΔP	P_{p2}	mm^2 area
3	145	180	190	10	190	22
4	133	135	150	15	143	44
6	87	143	152	9	145	32
7	138	148	165	17	148	48
9	107	138	167	29	138	117
10	122	90	97	7	90	22
12	125	134	160	26	137	416
14	130	129	146	17	129	132
15	132	84	119	35	87	319
avg.	124	131	150	18	134	128

c) After 30 Minutes of Hypokalemic Perfusion

Table 8. Tabulated Results for Vascular Response to Levarterenol Injected During Normal and Hypokalemic Perfusion for One Hour

Exp. No.	P_s	P_{p1}	P_{pm}	ΔP	P_{p2}	mm^2 area
3	146	205	210	5	217	0
4	135	148	157	9	153	35
6	82	158	162	4	162	23
7	138	150	165	15	163	0
9	111	143	150	7	147	55
10	123	90	100	10	95	0
12	125	152	175	23	153	264
14	130	133	147	14	132	99
15	140	81	109	28	86	262
avg.	126	140	153	13	145	82

d) After 45 Minutes of Hypokalemic Perfusion

Exp. No.	P_s	P_{p1}	P_{pm}	ΔP	P_{p2}	mm^2 area
3	146	205	210	5	223	0
4	132	160	165	5	158	19
6	70	183	185	2	185	0
7	138	173	187	14	180	0
9	119	175	177	2	175	0
10	130	90	100	10	90	49
avg.	123	164	171	6	169	11

e) Control After 1 Hour of Hypokalemic Perfusion

Table 8. Tabulated Results for Vascular Response to Levarterenol Injected During Normal and Hypokalemic Perfusion for One Hour

Exp. No.	%ΔMg	%ΔP	Flow (ml/min)
26	37.7	0	28.7
27	33.8	0	30.0
28	83.4	0	4.4
29	79.2	0	5.3
30	66.7	0	7.3
31	60.8	-3.7	14.4
32	66.8	0	15.2

Table 9.

Tabulated Data Showing Change in Perfusion Pressure When Arterial Magnesium Concentration is Lowered

Exp. No.	Arterial %ΔMg	Arterial %ΔK	%ΔP
30	72.6	87.5	30.2
31	59.1	84.2	17.0
32	64.0	83.0	14.5
33	60.9	77.0	18.6

Table 10.

Tabulated Results for Vascular Response to Simultaneous Perfusion with Hypokalemic and Hypomagnesemic Blood

exp. no.	stimulation time	dialysate	K^+_a	K^+_v	osm_a	osm_v	P	%ΔP
1	before	control		3.8		328	120	
	during	control		5.7		346	100	-16.7
	before	1 hr low K^+	1.6	1.9		326	115	
	during	1 hr low K^+		3.4		340	75	-34.9
2	before	control		4.0		300	108	
	during	control		5.1		306	78	-27.8
	before	1 hr low K^+	0.4	1.5		306	108	
	during	1 hr low K^+		2.6		312	100	-7.4
3	before	control	4.1	4.3	304	295	125	
	during	control		6.2		326	97	-22.4
	before	1 hr low K^+	0.5	1.1		298	145	
	during	1 hr low K^+		2.7		315	100	-31.0
4	before	control	3.8	4.0	315	321	127	
	during	control		5.7		326	79	-37.8
	before	1 hr low K^+	0.6	1.1	310	318	129	
	during	1 hr low K^+		2.4		315	83	-35.7
5	before	control	4.1	4.0	296	297	92	
	during	control		5.8		318	75	-18.5
	before	1 hr low K^+	2.0	2.0	287	301	110	
	during	1 hr low K^+		4.0		313	60	-45.5

Table 11. Tabulated Results Showing Vascular Response to Electrical Stimulation of Normal and Hypokalemic Perfused Gracilis Muscle

exp. no.	stimulation time	dialysate	K^+_a	K^+_v	osm_a	osm_v	P	%ΔP
6	before	control	4.2	4.0	306	304	110	
	during	control		5.3		317	75	-31.8
	before	1 hr low K^+	0.9	1.3	317	317	105	
	during	1 hr low K^+		3.9		335	65	-38.1
7	before	control	4.1	4.2	292	292	92	
	during	control		6.9		307	52	-43.6
	before	1 hr low K^+	0.6	1.3	287	289	60	
	during	1 hr low K^+		3.8		311	50	-16.7
8	before	control	3.8	3.8	309	309	95	
	during	control		5.8		322	63	-33.7
	before	1 hr low K^+	0.9	1.3	305	306	85	
	during	1 hr low K^+		3.4		320	50	-41.2
9	before	control	3.6	3.9	300	303	95	
	during	control		4.6		306	60	-36.8
	before	1 hr low K^+	1.2	1.9	302	303	115	
	during	1 hr low K^+		3.4		310	60	-47.8
10	before	control	3.4	3.2	313	297	110	
	during	control		4.6		320	60	-45.2
	before	1 hr low K^+	0.7	1.8		315	107	
	during	1 hr low K^+		4.6		329	72	-32.7

Table 11. Tabulated Results Showing Vascular Response to Electrical Stimulation of Normal and Hypokalemic Perfused Gracilis Muscle

exp. no.	dialysate	meq K^+ removed	meq K^+ removed per gm muscle	muscle wt (gm)	flow ml/min
1	control	0	0	128.1	29.0
	1 hr low K^+	1.134	.00885	167.3	29.0
2	control	0	0	109.0	13.0
	1 hr low K^+	0.999	.00916	125.0	13.0
3	control	0	0	74.6	14.2
	1 hr low K^+	0.895	.0120	86.9	14.2
4	control	0	0	68.3	15.9
	1 hr low K^+	0.813	.0119	87.4	15.9
5	control	0	0	103.0	52.0
	1 hr low K^+	1.290	.0125	118.0	52.0
6	control	0	0	84.2	14.0
	1 hr low K^+	0.770	.00915	94.9	14.0
7	control	0	0	67.0	6.4
	1 hr low K^+	0.567	.00845	89.6	6.4
8	control	0	0	89.5	16.5
	1 hr low K^+	0.940	.0105	112.0	16.5
9	control	0	0	81.3	26.9
	1 hr low K^+	1.550	.0203	76.3	26.9
10	control	0	0	106.8	15.0
	1 hr low K^+	0.870	.00744	117.5	15.0

Table 12. Tabulated Data Showing K^+ Removal from and Weight Change of Gracilis Muscle During a 3 Minute Stimulation and Following 1 Hour of Hypokalemic Perfusion

NOMENCLATURE

D - inner diameter

g_c - standard acceleration of gravity

K - plasma potassium ion concentration

L - tube length

Mg - plasma magnesium ion concentration

P - perfusion pressure

Q - flow rate (volume/time)

v - viscosity

Δ - change

Subscripts

B - blood

c - control

e - experimental

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