Sodium and Potassium Shifts Associated with Peripheral Resistance Changes in the Dog

By James D. Jamieson, M.D., and Sydney M. Friedman, M.D., Ph.D.

The relation of cationic distribution to the tonus of vascular smooth muscle has become of increasing interest during the past few years. Acute rises and falls of blood pressure induced by a variety of agents have been shown to be consistently accompanied by inverse shifts of sodium out of or into the extracellular compartment. Tissue analysis has shown that these movements involve shifts of sodium into and out of vascular smooth muscle cells, usually, but not invariably, associated with inverse potassium transfers. Manipulation of the ionic environment of vascular tissue either in vitro or in vivo produces well defined changes in the tonus of vascular smooth muscle and underlines the direct relationship between ions and tonus. The description of sodium and potassium sensitive glass electrodes by Eisenman, Rudin, and Casby and their subsequent development for constant monitoring of these ions in the flowing blood stream has made more detailed studies possible. The present report deals with changes in blood sodium and potassium activity occurring in association with acute drug-induced blood pressure changes in the dog and their relation to the resistance of the peripheral vascular bed. Some experiments dealing with whole animal responses are presented for comparison with the more definitive responses obtained from the hind-limb vascular bed.

Methods

Cation Sensitive Glass Electrodes

The development and construction of ion specific glass electrodes for use in the blood stream have recently been reviewed. Briefly, tubes of Na and K preferring glass are prepared by thinning out a membrane area, then plating this with silver and copper. A fine copper wire incorporated into the copper deposit serves to connect the electrodes to the amplifier leads. The two electrodes are connected in line with a calomel reference electrode placed between them; the assembly is connected by polyethylene tubes into the blood stream. The electrode assembly is supported on a rigid plexiglass frame and ensnared in a shielded box. Potentials from the Na and K electrodes are amplified by a pair of Cary vibrating reed electrometers and the output is fed into a Grass polygraph for recording on paper.

The electrode pair is calibrated each day using buffered NaCl and KCl solutions at pH 7.4. In the present experiments, each electrode produced 50 to 58 mv. per log. unit change of cation concentration. The Na electrode preferred Na to K by a factor of about 250:1, while the K electrode preferred K to Na by about 5:1. Thus, the Na trace can be read directly, while interpretation of the K trace requires subtraction to correct for simultaneous Na effects. In vivo calibration was performed in all experiments using the fully controlled flow system described below. In these, the basal blood Na and K activities were determined as required during the course of an experiment and subsequent events measured as absolute quantities (fig. 1). For those experiments in which calculation of change was based on calibration carried out before the experiment, the results will be presented as estimated changes.

In vivo, the Na electrode is capable of detecting changes in Na activity (Na⁺) to the second decimal place on a base of 150 mEq./L. and the K electrode detects (K⁺) to the third decimal place on a base of 5 mEq./L. To simplify the calculation of shifts recorded and their presentation, all changes are referred to arbitrary bases, 150 mEq./L. for (Na⁺) and 5 mEq./L. for (K⁺).

Animal Procedures

Four female and nine male mongrel dogs, ranging in weight from 9.4 to 14.3 Kg., were used in this study. The animals were anesthetized with intravenous pentobarbital sodium (20 mg./Kg.) and heparinized with heparin sodium (10 mg./
SODIUM AND POTASSIUM SHIFTS

In vivo electrode calibration record. Base line for each electrode is given by limb venous blood flowing at constant rate.

Kg.). Surgical cutdowns were performed on the femoral vessels as required.

Flow Rate Measurement or Control

Whole Animal Responses

Since the electrodes respond to changes in flow rate (but not to pressure), cation changes can be assessed only by correction for a known flow rate change or by eliminating the effect entirely. Three methods were used in the initial experiments with whole animal responses to vasoactive agents (norepinephrine, epinephrine, and pitressin). At first, flow rate was measured with either a mechanical or electrical flowmeter and the data were used in interpreting the electrode responses. This procedure required long and tedious calculation and was replaced first by interposing a constant height reservoir between the femoral artery and electrode assembly and later by using a constant output Sigmamotor pump in the same position.

Perfused Hind-Limb Preparation

The main body of quantitative experimentation with which this report is concerned was carried out in eight dogs with the following controlled procedure modified after Haddy. A Sigmamotor pump perfused the animal's hind limb with its own blood from the proximal femoral artery at a constant flow rate. The recording Na and K electrode assembly was interposed in the femoral vein to sample the venous effluent from the limb. The blood was fed back into the proximal end of the femoral vein. After three dogs were studied, it became evident that venous return might have varied with the vasoactive materials used. To obviate this difficulty, the venous blood was pumped back into the proximal femoral vein at constant rate. In this way, complete control of flow was achieved, the limb and electrode assembly receiving and discharging a constant amount of blood determined by the pump speed. Vascular resistance on the arterial side of the perfused limb was measured as pressure with a transducer interposed between the pump and the limb. Systemic blood pressure was recorded in the opposite limb. The perfusion pressure to the test limb was maintained at a level comparable to the control limb by appropriate adjustment of the pump speed.

Injections of drugs were given intrarterially in the pump line to the limb. The drugs were administered in isotonic saline at 37 C. and for any given drug were contained in a constant volume, between 0.05 and 0.10 cc. In the perfused limb preparation the doses of drugs were selected to be below threshold for a systemic effect.

Results

Pressor Agents

Norepinephrine

A total of 37 injections of norepinephrine were given in doses ranging from 0.14 to 5.0 μg./Kg. intravenously in the whole animal. The responses were measured by the methods described. At all dose levels and with all procedures, the pressor response was always associated with a rise in (K+) and almost al-
ways (32/37) with a fall in (Na⁺). In about half the trials, the (Na⁺) response was biphasic, showing an initial rise preceding the more prolonged fall (fig. 2).

Quantitative estimation of the data was possible in 20 trials. The fall in (Na⁺) measured in 15 of these ranged from −0.65 to −6.0 mEq./L, and the initial rise in eight from 1.5 to 3.0. The (K⁺) rise observed in all ranged from 0.16 to 1.5 mEq./L. Diastolic blood pressure rose 25 to 100 mm. Hg, but no correlation of ion shift with pressure rise could be attempted.

In the perfused limb preparation, all flow effects are eliminated and, hence, the results are more meaningful. Intra-arterial injections of norepinephrine were given in 28 trials to seven dogs. The doses ranged from 0.01 to 0.90 µg./Kg., sufficient only to produce vasoconstriction in the limb but not systemically. Responses were obtained in two of the animals before and after ganglionic blockade with chlorisondamine chloride (Ecolid, Ciba). A typical trace of electrode potentials associated with blood pressure changes is shown in figure 3. The (K⁺) changes, although appearing small on the trace, must be corrected for the simultaneous (Na⁺) fall and are quite significant.

In the unblocked animals, 20/23 of the vasoconstrictor responses were accompanied by a fall in plasma sodium of −0.30 to −2.30 mEq./L. In 13 of these, an initial transient rise in (Na⁺) of 0.10 to 1.80 mEq./L. was observed. In three trials, only the small rise in (Na⁺) was seen. In general, the biphasic response was associated with the larger doses of norepinephrine (0.2 to 0.9 µg./Kg.) which gave limb diastolic blood pressure rises of between 50 and 100 mm. Hg. The smaller doses of less than 0.20 µg./Kg. produced pressure changes between 20 and 50 mm. Hg. There seemed to be no correlation between magnitude of limb pressure rise and magnitude of sodium fall.

Blood (K⁺) rose in 14/22 of the trials by 0.05 to 0.20 mEq./L., fell in 7/22 by −0.10 to −0.25 mEq./L., and did not change in one. It is interesting that those responses in which (K⁺) fell were associated with large doses of

Figure 3
Limb venous (Na⁺) and (K⁺) following intra-arterial norepinephrine. Controlled arterial inflow and outflow rates.

Figure 4
Limb venous (Na⁺) and (K⁺) following intra-arterial epinephrine. Controlled arterial inflow and outflow rates.
norepinephrine in which the initial rise of 
(Na⁺) tended to be marked. The time elapsing 
for the total electrolyte response was between 
three and five minutes. In general, longer 
times were associated with larger electrolyte 
shifts. It is difficult to construct a dose re-
sponse curve due to the variability of the re-
sponses in different animals.

Ganglionic blockade with chlorisondamine, 
200 μg./Kg., did not alter the electrolyte re-
sponse pattern.

Epinephrine
A total of 16 injections of epinephrine were 
given using doses from 0.07 to 1.20 μg./Kg. 
intravenously in the whole animal. The results 
were similar qualitatively and quantitatively 
to those obtained with norepinephrine. A con-
sistent depression of blood (Na⁺) and elevation of 
(K⁺) were observed in association with 
the rise in blood pressure.

In the perfused limb preparation, 19 in-
jections of epinephrine in doses ranging from 
0.009 to 0.90 μg./Kg. were given intra-arteri-
ally to two dogs before and after chlorisonda-
mine. A typical trace in an unblocked animal 

In six trials in unblocked animals, the ad-
mistration of epinephrine in doses of 0.07 
to 0.9 μg./Kg. was followed by a temporary 
rise of (Na⁺) of 0.50 to 1.75 mEq./L, and 
then a more sustained fall of —0.55 to —1.30 

mEq./L. In one case (Na⁺) rose 1.50 mEq./ 
L. and did not fall. A rise of (K⁺) was ob-
served in three of the six trials (0.03 to 0.75 

mEq./L.) and no change occurred in three. 
The limb diastolic blood pressure rose 80 to 
150 mm. Hg at this dose range. In general, 
larger cation changes occurred with larger 
doses.
In 13 trials after ganglionic blockade, epinephrine in doses of 0.009 to 0.9 μg./Kg. produced the usual fall of (Na⁺) 11 times. This ranged from —0.25 to —0.60 mEq./L. and was always preceded by a transient rise of 0.25 to 3.20 mEq./L. In two cases, only a rise in (Na⁺) was observed. Blood (K⁺) rose in eight trials by 0.05 to 0.14 and fell in five by —0.18 to —0.65 mEq./L. It is interesting that in one of the two dogs used for this series, (K⁺) rose consistently after epinephrine injection before blockade and then fell just as consistently with the same doses after blockade. Limb diastolic pressure rose by 25 to 50 mm. Hg in the dose range used.

Serotonin (5-Hydroxytryptamine)

This agent was given intra-arterially eight times in the perfused limb preparation in doses of 0.9 to 2.9 μg./Kg. Blood (Na⁺) fell in six trials by —0.30 to —1.15 mEq./L., did not change in one trial, and in the remaining trial rose 0.55 mEq./L. after a transient fall. Blood (K⁺) responded inconsistently, falling less than —0.1 mEq./L. in two trials, rising by a similar amount in two, and remaining unchanged in four. Limb diastolic pressure rose by 25 to 50 mm. Hg in the dose range used. A typical tracing is shown in figure 5.

Angiotensin

Synthetic angiotensin was administered 12 times in four perfused limb preparations. The doses ranged from 0.025 to 0.50 μg./Kg. intra-arterially and although only small limb pressure rises of 10 to 60 mm. Hg were produced, it seemed impossible to achieve these without at the same time inducing a systemic effect even at the smallest dose used. Blood (Na⁺) fell by —0.30 to —0.80 in 10 trials, rising initially in 4 of these by 0.15 to 0.65 mEq./L. A simple rise was noted in one trial and no change in another. Blood (K⁺) was inconsistent, occasionally rising or falling by less

Figure 7

Limb venous (Na⁺) following intra-arterial pitressin. Controlled arterial inflow rate with monitoring of venous outflow rate. Electrode placed distal to femoral artery pump to monitor arterial (Na⁺) was unshielded and noisy but serves to show that Na effect of top trace is entirely local. The sharp dip in the arterial (Na⁺) trace is an artifact.

Figure 8

Limb venous (Na⁺) and (K⁺) following intra-arterial isoproterenol. Controlled arterial inflow and outflow rates.
than 0.2 mEq./L., but usually remaining unchanged. Because of the superimposed systemic effects, these data cannot be referred exclusively to the limb. A typical tracing is shown in figure 6.

**Pitressin**

Limb injections of pitressin were carried out in four dogs, one trial each, with doses ranging from 1.8 to 3.9 mU/Kg., using monitored but not controlled flow procedures. While limb pressure rises in three of four trials were small (5, 10, and 20 mm. Hg) and threshold in the fourth, in all cases (Na⁺) fell by —0.95 to —2.30 and (K⁺) rose by 0.12 to 0.75 mEq./L. Figure 7 shows the limb arteriovenous (Na⁺) difference following femoral artery injection of a very small dose of pitressin.

Depressor Agents

**Isoproterenol (Isuprel)**

This agent was administered intra-arterially 20 times in three perfused limb preparations. The doses ranged from 0.001 to 2.5 μg./Kg. and depressed limb diastolic pressure —5 to —50 mm. Hg. In all cases (Na⁺) rose by 0.2 to 0.9 mEq./L. In 6 of the 20 trials, (K⁺) fell by —0.04 to —0.50 mEq./L. but did not change in the remaining 14 instances. The degree of rise of (Na⁺) was correlated with the degree of fall of limb resistance (fig. 8). The total time for the electrolyte response was three to four minutes. The response was not altered by ganglionic blockade.

**Acetylcholine**

In the perfused limb, acetylcholine administered intra-arterially 20 times in three dogs produced results similar to those observed
with isoproterenol. Doses ranging from 0.05 to 100 μg./Kg. depressed limb diastolic pressure —5 to —60 mm. Hg. Blood (Na+) rose in 18 of the 20 trials by 0.35 to 1.45 mEq./L. and remained unchanged in two instances. In general, the larger rises were associated with larger falls of limb resistance. Blood (K+) responded variably, rising less than 0.2 mEq./L. in four trials, falling by the same amount in 12, and remaining unchanged in 4. The time course was three to four minutes, and the response was unaffected by previous ganglionic blockade. A typical tracing is shown in figure 9.

**Histamine**

In the perfused limb, histamine was administered intra-arterially 14 times in two dogs and produced results similar to those obtained with isoproterenol and acetylcholine. The doses ranged from 0.01 to 1.0 μg./Kg. and these depressed limb diastolic pressure —5 to —40 mm. Hg. Blood (Na+) rose in 12 of the 14 trials by 0.15 to 0.60 mEq./L. and did not change in 2. Blood (K+) did not change at all in 9 trials and rose or fell less than 0.1 mEq./L. in 5. A typical record is shown in figure 10.

**Discussion**

The first evidence that changes in peripheral resistance might be associated with changes in ionic distribution was provided by Muirhead, Goth, and Jones who demonstrated a fall in plasma sodium during the infusion of norepinephrine. Unfortunately, the significance of this finding was obscured by the fact that these workers used near-toxic doses. A few years later, Tobian and Fox infused smaller amounts of norepinephrine and measured sodium and potassium in the femoral arterial wall after 30 minutes of sustained blood pressure elevation. They observed a definite, but not entirely consistent, gain in intracellular sodium and a consistent loss of potassium. Considering that the measurement of sodium has an appreciable error, these authors produced remarkably good evidence for an association between ion distribution and peripheral vasconstriction, at least for norepinephrine.

Shortly after this, we observed a mass migration of sodium ions out of and potassium ions into the extracellular space in the rat as a rapid sequel to the intravenous injection of pitressin. These observations with pitressin, added to the earlier observations with norepinephrine, suggested to us that we were dealing with a general phenomenon of association between ionic shifts and changes in peripheral resistance.

Systematic studies were then undertaken both in the rat and dog, and evidence accumulated to indicate that as blood pressure rises under the influence of a variety of pressor agents, sodium leaves the extracellular space and enters it as pressure falls. Potassium, generally but not consistently, moves inversely to sodium.

The fact that sodium and potassium ions surge into or out of blood samples does not prove that these necessarily reflect changes in vascular smooth muscle itself. To be sure, this had been shown for norepinephrine but not for other agents. Daniel and co-workers then completed the demonstration by measuring the counterpart changes in the rat aorta during acute rises and falls of blood pressure induced with a variety of agents.

The evidence concerning this phase of the problem still contained two major gaps. In the first place, the changes measured applied to spaced intervals and involved the measurement of both sodium and inulin space. There was no evidence that any continuous change in blood sodium activity itself actually occurred. In the second place, the changes were measured in the whole animal, in the aorta or femoral artery, and did not necessarily apply to the peripheral vascular bed.

The development of the sodium and potassium electrodes has permitted both of these objections to be answered. In earlier studies in the whole animal we were able to monitor blood sodium activity (Na+), continuously during acutely induced rises and falls in blood pressure. In the present study, we have found that changes in peripheral vascular resistance are continuously co-ordinated with...
changes in blood (Na⁺) and less consistently with inverse shifts of (K⁺). The patterns obtained in the perfused dog hind limb preparation are, in general, less complex than those previously observed in the whole animal.

Blood (Na⁺) measured in the venous effluent from the limb falls consistently when vascular resistance of the limb is increased by a variety of dissimilar agents in doses too low to produce systemic effects. The fall in (Na⁺) is often preceded by a transient initial rise, and such a biphasic response usually occurs with the more marked degrees of vasoconstriction. It is quite possible that this initial rise of (Na⁺) reflects a prior shift of water into the vascular cells. Blood (K⁺) rises in association with vasoconstriction induced by norepinephrine, epinephrine, and pitressin but changes inconsistently if at all with serotonin or angiotensin. In general, agents which decrease limb vascular resistance produce the reverse changes.

These experiments have no direct bearing on the question of causality. In the first place, we can only infer from the work of others that peripheral vascular smooth muscle is involved in the exchanges observed. In the second place, in the procedure used, the injection of a sodium or potassium salt as marker produces an electrode response only after a delay of 30 to 40 seconds. Although the responses to vasoactive agents all occurred within this time interval, it is still quite impossible to decide on the precise time relation between vasoaction and ionic change. The results thus bear only on the basic point that the ionic changes previously measured in the whole animal reflect movements of sodium and potassium into and out of the peripheral vascular blood stream. These movements are continuously co-ordinated with changes in peripheral vascular resistance.

Observations from several laboratories including our own suggest that ionic exchanges are, in fact, causally related to vascular smooth muscle tension. Although this thesis remains to be definitely proved and the mechanisms explored, the present findings are consistent with this theoretical view.

**Summary**

The relation of changes in peripheral vascular resistance to blood sodium and potassium activity was studied in the dog hind limb. Arterial inflow was controlled by a constant output pump in the femoral artery line. Cations were monitored with glass-to-silver cannula electrodes in the venous outflow. Vasoactive drugs were administered intra-arterially in amounts sufficient only to affect the limb vasculature. Vasoconstriction induced by norepinephrine or epinephrine was associated with a fall in blood (Na⁺) and often with a rise of (K⁺). Larger doses tended to produce a biphasic response in (Na⁺), a transient initial rise preceding the fall. Vasoconstriction induced by serotonin or angiotensin was associated with a fall in blood (Na⁺) unaccompanied by any consistent change in (K⁺). Vasoconstriction induced by small amounts of pitressin (small series) produced a larger fall in (Na⁺) and rise in (K⁺) than with other agents producing an equal degree of vasoconstriction. Vasodilatation induced by isoproterenol, acetylcholine, or histamine was accompanied by a rise in blood (Na⁺) without any consistent change in (K⁺).

**Acknowledgment**

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**References**

6. Lasek, L.: Effect of potassium on muscle ten-


BOOK REVIEW


This marks the first complete publication of all reports and communications presented at a European Congress of Cardiology. Each article is printed in Italian, French, German, and English, so that the total proceedings are in four volumes. A suggestion for future congresses is to publish each volume in a single language, so that a reader can find a particular article without having to pass a repetition of the same article in three other languages. Some of the symposia dealt with the following: atherosclerosis, coronary circulation, extracorporeal circulation, congenital heart disease, radioisotopes, cardiopulmonary physiology, radiology, and pharmacology. The title page for the section on pharmacology has been wrongly identified as "miscellaneous" and includes two new coronary dilators.
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