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INTRARENAL DISTRIBUTION OF BLOOD FLOW AND THE CONTROL OF SODIUM EXCRETION

by
James Robert Cant

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Physiology)
in The University of Michigan
1973

Doctoral Committee:

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I. INTRODUCTION

Congestive heart failure is characterized in part by an inappropriate renal retention of sodium and water. Because the mechanism of this fluid retention is not clear--it often exists in patients with normal levels of aldosterone and normal glomerular filtration rates--it has stimulated a search for other mechanisms having a role in the determination of sodium excretion. One possible mechanism has been suggested by Barger (1966; Barger et al., 1965) who has extensively studied congestive heart failure in a canine model of the disease. Sparks, working in Barger's laboratory, demonstrated a marked alteration in the distribution of blood flow within the kidneys of dogs with heart failure (Barger et al., 1966; Sparks et al., 1972). The existence of a similarly altered pattern of flow distribution in other experimental situations characterized by reduced sodium excretion, such as renal nerve stimulation, carotid sinus reflex (Pomeranz et al., 1968) and hemorrhage (Carrière, 1966) led Barger to propose that redistribution of renal blood flow may lead to a decrease in sodium excretion.

Distribution of flow is also of interest in the broader question of the regulation of sodium excretion in general. Since DeWardener's (DeWardener et al., 1961) demonstration that factors other than changes in glomerular filtration rate and levels of aldosterone can alter sodium excretion, there has been an appreciable effort to determine the nature of such factors.

Barger's proposal is one of three mechanisms which have received considerable attention as possible "third factors." Another, which comes directly from DeWardener's work, concerns the possibility of a natriuretic hormone which alters tubular reabsorption of sodium. The evidence for or against such a hormone comes almost entirely from studies considering the natriuresis which accompanies an acute expansion of blood volume. The other hypothesis deals with the role of physical factors in the control of sodium excretion and was first stated by Early and Friedler (1964); here work has dealt predominantly with the role of hemodynamic alterations accompanying renal vasodilation or volume expansion. In contrast to these two mechanisms, studies which support the redistribution of flow theory usually involve anti-natriuretic states.

This dissertation reports investigations designed to test the hypothesis that intrarenal distribution of blood flow is an important determinant of sodium excretion. Before further considering the background of the problem, a word should be said about what is meant by the intrarenal distribution of flow and how it is estimated. The kidney is an organ of distinct anatomical areas which are perfused at quite different flow rates, though the rate of flow in any area is relatively uniform. The outer cortex of the kidney has the highest flow rate (approximately 450 ml/min/100 g) and receives the major portion (greater than 90%) of total renal blood flow. The juxtamedullary cortex and outer medulla have a slower flow rate (approximately 120 ml/min/100 g) and the inner medulla a yet slower rate; these areas also receive a proportionately smaller portion of the total renal flow (Thorburn et al., 1963). Estimates of these flow rates given by different techniques are

in reasonable agreement (Thurau, 1964). (Recently the outer cortex itself has been shown to be heterogeneous in its rate of flow (Slotkoff et al., 1971; McNay and Abe, 1970); however, the degree of heterogeneity within the outer cortex of normal kidneys is less than that for the entire kidney.)

The method of estimating the intrarenal distribution of blood flow used in the various studies which support the hypothesis being considered and which is used in the present study is the inert gas washout method developed by Thorburn et al. (1963). This technique estimates the various flow rates and the portions of total renal blood flow flowing at each rate by observing the disappearance of an intra-arterial bolus of a radioactive tracer whose clearance is flow limited. From autoradiographs, these parameters can be attributed to specific anatomic areas of the kidney.

Many studies using the inert gas washout method have demonstrated that in a variety of situations exhibiting reduced sodium excretion, flow is distributed in a particular manner which is different from the normal distribution. This pattern of redistribution is characterized by two findings; first, there is a shift of some portion of the total renal blood flow away from the outer cortex and toward the inner cortex or outer medulla so that these latter regions receive a greater portion of the total flow than normally at a time when sodium excretion is lowered. Second, the rate of flow (in ml/min/100 g) is increased in the inner cortex and outer medulla. Together, these two changes can be referred to as a shift or redistribution of flow from the outer or superficial region of the kidney to the inner or deeper region. Because the flows in inner cortex and outer medulla are at times similar, it is

often convenient to refer to these collectively as the juxtamedullary area of the kidney.

Situations in which this pattern of redistribution of flow has been observed and in which reduced sodium excretion would be expected include experimental congestive heart failure in dogs (Sparks et al., 1972), congestive failure in humans (Dell et al., 1973), constriction of the vena cava--a model of congestive failure (Newsome et al., 1971; Kilcoyne and Cannon, 1971), increased renal sympathetic activity achieved via direct nerve stimulation, reflex stimulation through carotid sinus hypotension or chronically by anastomosis of the phrenic nerve to the splanchnic ganglion (Pomeranz et al., 1968), hemorrhage (Carrière, 1966), restriction of salt intake in humans (Hollenberg et al., 1970), and intrarenal arterial infusion of norepinephrine (Carrière, 1968). It is evidence of this sort, the demonstration of a correlation between a redistribution of flow from outer to inner regions of the kidney and reduced sodium excretion, that led Barger to propose that redistribution of renal blood flow might be an important controller of sodium excretion.

Some possible mechanisms by which changes in distribution of flow could alter sodium excretion have been proposed (Pomeranz et al., 1968). These mechanisms are based on various anatomic or functional differences between nephrons of outer and inner cortex that could result in the latter population of nephrons being relative "salt savers" while the former might be relative "salt losers." For example, Pomeranz points out that the deeper, or juxtamedullary nephrons may be capable of a greater reabsorption of tubular fluid since they have larger loops of Henle than the more superficial nephrons. It has also been suggested

that increases in medullary flow may decrease the hypertonicity of the interstitium surrounding these deep nephrons and thereby lower sodium excretion by reducing passive back diffusion into the tubular lumen. One provocative study which supports the idea of salt losing and salt saving populations of nephrons is the work of Horster and Thurau (1968). They demonstrated that restriction of dietary sodium in rats led to an increase in juxtamedullary and a fall in superficial single nephron glomerular filtration rates with little change in overall glomerular filtration rate; however, data which contradict this finding have recently been reported (Coelho and Bradley, 1973).

Thus, it seems that there is a reasonable basis for the hypothesis that intrarenal distribution of blood flow may play a significant role in the regulation of sodium balance. There are, however, major shortcomings with the body of data presented above. One is that the data from these studies are, at best, only consistent with the hypothesis and, since in each case there are other possible mechanisms which could have affected sodium excretion, cannot establish the validity of this theory. Also, many of the studies cited above do not present data on renal function so it is not possible to consider the quantitative contributions of other known determinants of sodium excretion. Possible changes in glomerular filtration rate are particularly important since in those situations with a redistribution of flow to the inner regions of the kidney, one would also expect a reduced glomerular filtration rate. It is the intent of the present study to investigate the relationship between intrarenal distribution of blood flow and sodium excretion while attempting to control other variables, particularly glomerular filtration rate.

This problem does not appear to lend itself to a straight-forward experimental approach that would produce a clear answer. Ideally, one would like to alter the intrarenal distribution of blood flow in the manner suggested by the hypothesis being tested, have no changes in other variables which would confound the experiment, and observe the changes in sodium excretion. The rub is that experimental maneuvers of a degree which causes a redistribution of flow, cause changes in these other variables, especially glomerular filtration rate. This necessitated a slightly more complicated experimental design which permits an evaluation of the quantitative contribution of various mechanisms, including redistribution of flow, to reductions in sodium excretion.

The strategy in the first of two series of experiments which this study comprises was to lower glomerular filtration rate equally by two different experimental maneuvers, only one of which caused changes in distribution of flow. Sodium excretion could then be observed in two situations with equal glomerular filtration rates and different distributions of flow. By comparing the reductions in sodium excretion occurring with two such manipulations one can estimate the contribution of redistribution of blood flow to the decreased sodium excretion. Because glomerular filtration rate falls equally with each maneuver, the portion of the decreased sodium excretion attributable to this mechanism should be equal in the two situations. If redistribution of renal blood flow has any significant anti-natriuretic effect, beyond that due to the concurrent fall in glomerular filtration rate, a greater decrease in sodium excretion should occur with that maneuver which redistributed flow. In addition, the contralateral (non-manipulated) kidney serves as a control for the influence of systemically circulating factors which might alter sodium excretion.

One of the two maneuvers was an intra-arterial infusion of norepinephrine which decreased glomerular filtration rate and produced the redistribution of flow described in the hypothesis being tested. The other maneuver was to reduce renal perfusion pressure by constricting the renal artery to produce a fall in glomerular filtration rate equivalent to that occurring with norepinephrine. Flow was redistributed much less by this maneuver. The reduction in sodium excretion was not greater with norepinephrine--it was, in fact, significantly less--which suggests that redistribution of flow did not make a quantitatively important contribution to the reduction of sodium excretion.

The second series of experiments attempted to dissociate changes in sodium excretion, glomerular filtration rate, and distribution of flow on a dose dependent basis by employing a smaller dose of norepinephrine than was used in the first series. Separation of these variables on a dose dependent basis would allow a stronger statement regarding the relation of distribution of flow to sodium excretion. A change in both sodium excretion and distribution of flow without changes in glomerular filtration rate would be evidence supporting the hypothesis. Also, this experiment represents a milder perturbation of the normal physiological state and may be more representative of the magnitude of alterations in renal function occurring naturally. In the second experimental series, a low dose of norepinephrine reduced sodium excretion without significantly changing the intrarenal distribution of flow or reducing glomerular filtration rate.

The results of this study do not provide evidence that the redistribution of renal blood flow from the superficial to the deeper regions of the kidney contributes significantly to a reduction of sodium excretion.

II. METHODS

This study consisted of two series of experiments in which the relationship of changes in intrarenal distribution of blood flow to concurrent changes in sodium excretion and glomerular filtration rate were assessed. In Series I, renal arterial constriction and an intra-arterial infusion of norepinephrine were used to alter the above variables and the changes from control levels produced by these two manipulations were compared. In Series II, the effects of an intrarenal infusion of a relatively small dose of norepinephrine on these renal functions were observed.

The aspects of the experiments common to both Series I and II will be described together and the particular experimental protocols will be described separately.

Preparation of the Experimental Animal

Acute mongrel dogs were fasted overnight but allowed free access to water. They were anesthetized with sodium pentobarbital, 25-30 mg/kg, i.v., with supplementary doses as required. A cuffed endotrachial tube was inserted. The brachial artery was cannulated for measurement of systemic arterial pressure and blood sampling. Intravenous infusions were given via the brachial vein.

At the beginning of the surgery, the animals in Series I received a loading dose of creatinine in approximately 150 ml 0.9% saline; this dose gave a plasma creatinine concentration of approximately 0.3 mg/ml. A sustaining infusion of creatinine in saline at 2 ml/min was then begun.

In Series II, the loading volume averaged 45 ml and the sustaining infusion, 0.82 ml/min.

The left kidney was exposed by a retroperitoneal flank incision. Both ureters were cannulated with polyethelene tubing. An umbilical tape was placed loosely around the left renal pedicle and a 5 mm Doppler ultrasonic flow probe was placed around the left renal artery at its origin, care being taken not to damage the renal nerves. A small (.03 o.d.) polyvinyl catheter was inserted in the renal artery immediately distal to the flow probe using the method described by Herd and Barger (1964). This catheter was used for intra-arterial infusions and injections of ^{85}Kr.

In the experiments of Series I, a small, adjustable screw clamp was placed around the renal artery in order to constrict the vessel. A second small polyvinyl catheter was placed distal to this clamp, either in the artery or in a major branch, to monitor renal perfusion pressure.

Blood pressures were monitored with Statham pressure transducers. Pressure and flow meter outputs were recorded on a Grass Model 7 polygraph. The output of the flowmeter was also put through an audio speaker because the quality of the sound resulting from the audio frequency signal of the Doppler flow probe is useful in assuring that good coupling between artery and probe exists and that no mechanical artifacts are being recorded as flow signals.

Measurement of Intrarenal Distribution of Blood Flow

The inert gas washout method of Thorburn et al. (1963) was used to measure intrarenal distribution of blood flow. A bolus of ^{85}Kr dissolved in saline was injected into the renal artery and then flushed

in with saline. Enough ^{85}Kr to give a peak activity of 100,000 to 200,000 cpm was used; the total injection was less than 1.5 ml. Disappearance of activity from the kidney was monitored by a Nuclear Chicago gamma counter with a digital ratemeter using an external probe placed over the flank of the dog. Curve analysis is described below.

Any flow transient caused by the injection was indicated by the Doppler flow meter. Curves with such transients were discarded since the krypton method is unreliable in such instances (Mowat et al., 1972).

At the conclusion of the experiment, the kidney was removed for preparation of an autoradiograph. A bolus of ^{85}Kr was injected into the artery and the renal pedicle ligated by tying the umbilical tape at a predetermined time following this injection. The renal vessels were clamped, and the kidney was removed and rapidly frozen in a mixture of dry ice and acetone.

Autoradiagraphs were prepared at a later time by taking a transverse slice about 4 mm thick through the hilum of the frozen kidney and smoothing and polishing the surfaces with a disposable microtome blade (Thorburn, 1963). Kodak Type AA industrial X-ray film was placed against the faces of the slice and clamped between plastic plates with two pieces of rubber to cushion the slice. Two or three autoradiographs of different densities were prepared from each slice by varying the exposure times.

Protocols

There were two protocols used in this study: Series I and II. Series I will be described in detail and Series II more generally with the differences from Series I noted. (Examples of these protocols are presented in Figures 3 and 4 which represent a sample experiment from each Series.)

Series I: Each experiment in this series consisted of four one-hour periods; the first and third were control while the second and fourth were experimental maneuvers. One hour elapsed following surgery before the beginning of the first period and 30-45 minutes elapsed between the beginning of a subsequent maneuver and the first collections. Within each one-hour period, a 60-minute ^{85}Kr washout curve was obtained and urine outputs for renal clearances were collected in four fifteen-minute intervals with an arterial blood sample taken near the middle of each interval. Values of mean arterial pressure, perfusion pressure, and Doppler flow rate were averaged over the time of each clearance collection interval. During the control periods (1 and 3), 0.9% saline was infused into the renal artery at 0.2-0.3 ml/min which was approximately the infusion rate with the norepinephrine.

In one of the experimental periods, norepinephrine in saline was infused into the renal artery at a concentration of 20 ug/ml. The rate was adjusted to reduce the Doppler flow by approximately 25% of control levels; the average dose was 5.1 ug/min. During the hour of norepinephrine infusion, flow was kept constant by making small adjustments in the infusion rate when needed.

In the other experimental period, the renal perfusion pressure was reduced by constricting the renal artery with the small clamp until the perfusion pressure fell to approximately 75 mmHg. Saline was also infused during this experimental period. Small fluctuations of about 5 mmHg occurred spontaneously and the clamp was adjusted to keep the pressure variations within this range. In 10 of 16 experiments norepinephrine was the first experimental maneuver (second one-hour period) and reduced perfusion pressure, the second maneuver (fourth period);

the order was reversed in the remaining experiments. At the end of the fourth period, the kidney was removed for an autoradiograph.

In analysing these experiments, values for data collected in the four fifteen-minute clearance intervals were averaged over the entire one-hour period. These average values for each experimental period were compared to those for the immediately preceding control period. Data from norepinephrine and decreased perfusion pressure periods were also compared to each other both directly and as a per cent of their respective controls. There were sixteen animals in Series I; data were not collected on the right (control) kidney in the first five of these.

Series II: In these experiments, only one experimental maneuver was used which was alternated with control periods. This maneuver was to infuse norepinephrine at a dose which just caused a detectable change in flow measured by the Doppler flow probe. This change was either a small (less than 10%), sustained decrease in Doppler flow or an increase in flow following a momentary interruption of the infusion. Two or three norepinephrine infusion periods were done for each animal, making a total of four or six periods (each with an ^{85}Kr curve and renal clearances). At the end of the last maneuver the kidney was removed for preparation of an autoradiograph.

In Series II three fifteen-minute collections were made during each period and the ^{85}Kr curves were only 45 minutes long. This permitted three experimental periods in most animals. Since arterial blood samples were not taken during the second collection of each maneuver, plasma values for creatinine were interpolated from those of the first and third periods (plasma creatinine concentration did not vary more than 5%).

Data for the three fifteen-minute intervals within each forty-five-minute period were averaged.

In Series II, each infusion of norepinephrine was considered a separate observation and was compared to its controls. The mean of the period preceding (pre-control) and following (post-control) was used as the control value in statistical comparisons. When an observation was the last one of the experiment, the pre-control alone was used. Eighteen observations (with controls) of renal clearances were obtained in seven dogs; for intrarenal distribution of flow, there were thirteen observations in five dogs.

Analysis of Clearance Data

Creatinine in urine and plasma was determined on an autoanalyzer; sodium in urine and plasma was measured by internal standard flame photometry.

The Doppler flowmeter was not calibrated in every experiment. When it was calibrated, in situ, by cannulating the renal artery distal to the flow probe and making timed collections, the flow meter was linear over the range of flows encountered in the experiment. Figure 1 is an example of such a curve. Because of this linearity, changes in the Doppler signal are directly related to renal artery volume flow within an individual animal and can be treated statistically as if they were actual flow measurements. In these experiments, the mean Doppler signal during the first control period was taken as 100 and the remaining flows normalized with respect to this value. Because the slope of the line relating the flowmeter reading to volume flow varied from dog to dog, due to differences in the diameter of the arterial lumen, comparisons

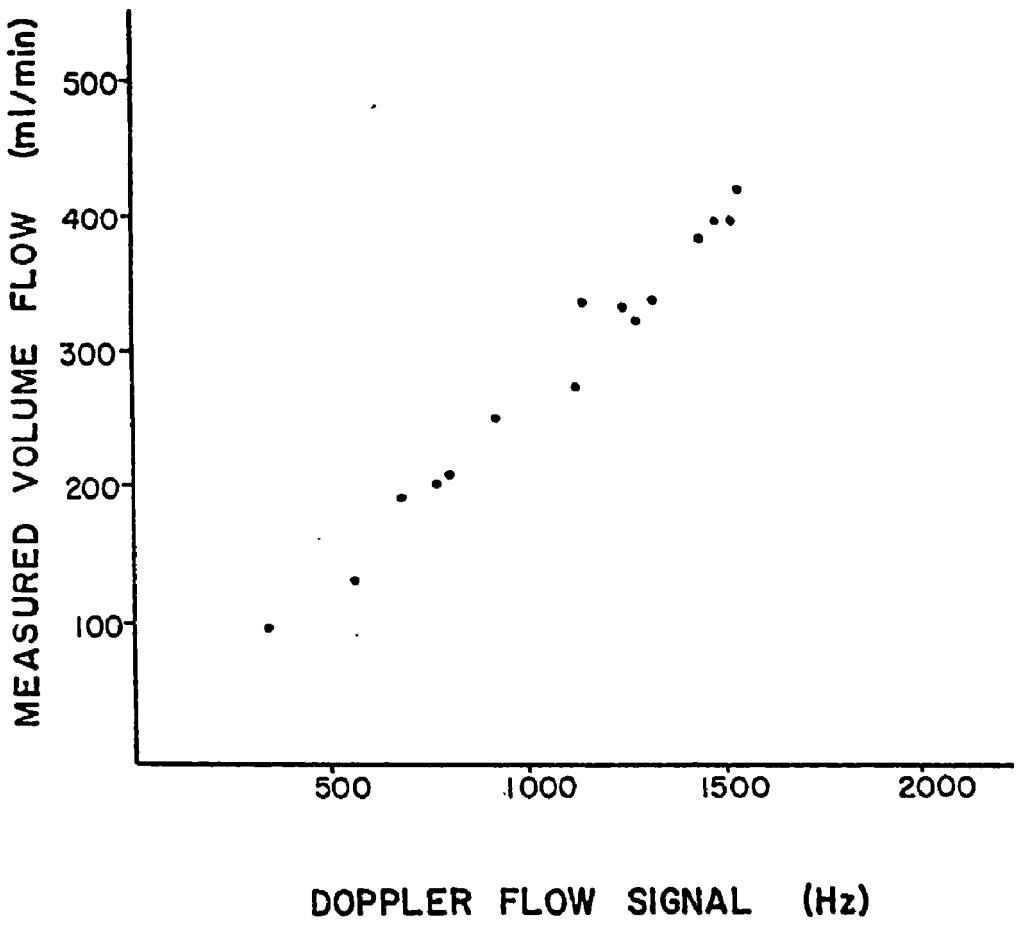


Figure 1. Calibration curve of Doppler flow probe. The linear relationship of volume flow to the Doppler flow signal was determined by cannulating the renal artery distal to the probe and making timed collections.

of actual volume flows cannot be made between dogs although changes in flow (per cent of control) can be compared.

Analysis of Distribution of Flow

The krypton washout curves which reflect intrarenal distribution of blood flow were described as a sum of four exponentials as originally described by Thorburn et al. (1963). The activity A(t) remaining in the kidney at any time following a bolus injection of tracer is given by the equation

$$A(t) = \sum_{n=1}^{4} A(0)_i \, e^{-k_i \cdot t}$$

In this model, the kidney is viewed as a parallel four compartment system in which each compartment is uniformly perfused at a constant flow rate. The $A(0)_i$ are the initial activities of each compartment (amount of tracer delivered at t = 0) and the k_i are the flows per volume (reciprocal of mean transit time) for that compartment and will be expressed as ml/min/100 g of compartment weight. Each $A(0)_i$ is determined by the distribution of the total renal blood flow among the various compartments; therefore, the expression

$$A(0)_i \; / \sum_{n=1}^{4} A(0)_i$$

is the fraction of the bolus entering the i^{th} compartment which is the fraction of total renal blood flow going to that compartment.

In this study, only the two fastest compartments (highest flows) are considered since about 95% of the renal blood flow is distributed to these compartments both in normal and experimental conditions (Thorburn

et al., 1963; Pomeranz et al., 1968; Sparks et al., 1972). The slower compartments represent flow in the papilla (compartment 3) and perirenal fat (compartment 4) (Thorburn et al., 1963) in which the study of blood flow is respectively unreliable by the ^{85}Kr method (Thorburn et al., 1963) and uninteresting. We will consider the sum of $A(0)_1$ and $A(0)_2$ to represent 100% of renal blood flow and present the data for these parameters of the ^{85}Kr curves as A_I, the fraction of that portion of renal blood flow entering the two fastest compartments ($A(0)_1$ plus $A(0)_2$) which enters the most rapid compartment, compartment I. The analogous quantity A_{II} is given by the expression 100% - A_I and will not be explicitly considered in this study since any mathematical or statistical statement regarding A_I must hold as well for A_{II}.

From the parameters A_I, A_{II}, k_I, and k_{II}, it is possible to calculate, using the technique developed by Dobson and Warner (1957), the relative volumes V_I and V_{II} of the kidney corresponding to these two compartments; only data for V_I (in per cent) will be presented since the relationship between V_I and V_{II} is the same as that for A_I and A_{II}. When the relative volumes of distribution are known, the total flow F_T in ml/min/100 g kidney weight can be calculated.

Figure 2 shows plots of two krypton washout curves and of those single exponentials which represent the first three components of each curve. The curves are a control curve and a curve made during the intra-arterial infusion of norepinephrine; the difference between them illustrates the pattern of redistribution described in the introduction. The decrease in A_I and the increase in A_{II} represent the shift of a portion of the total flow away from the outer cortical areas to the juxtamedullary area. The increase in k_{II}, the rate constant of

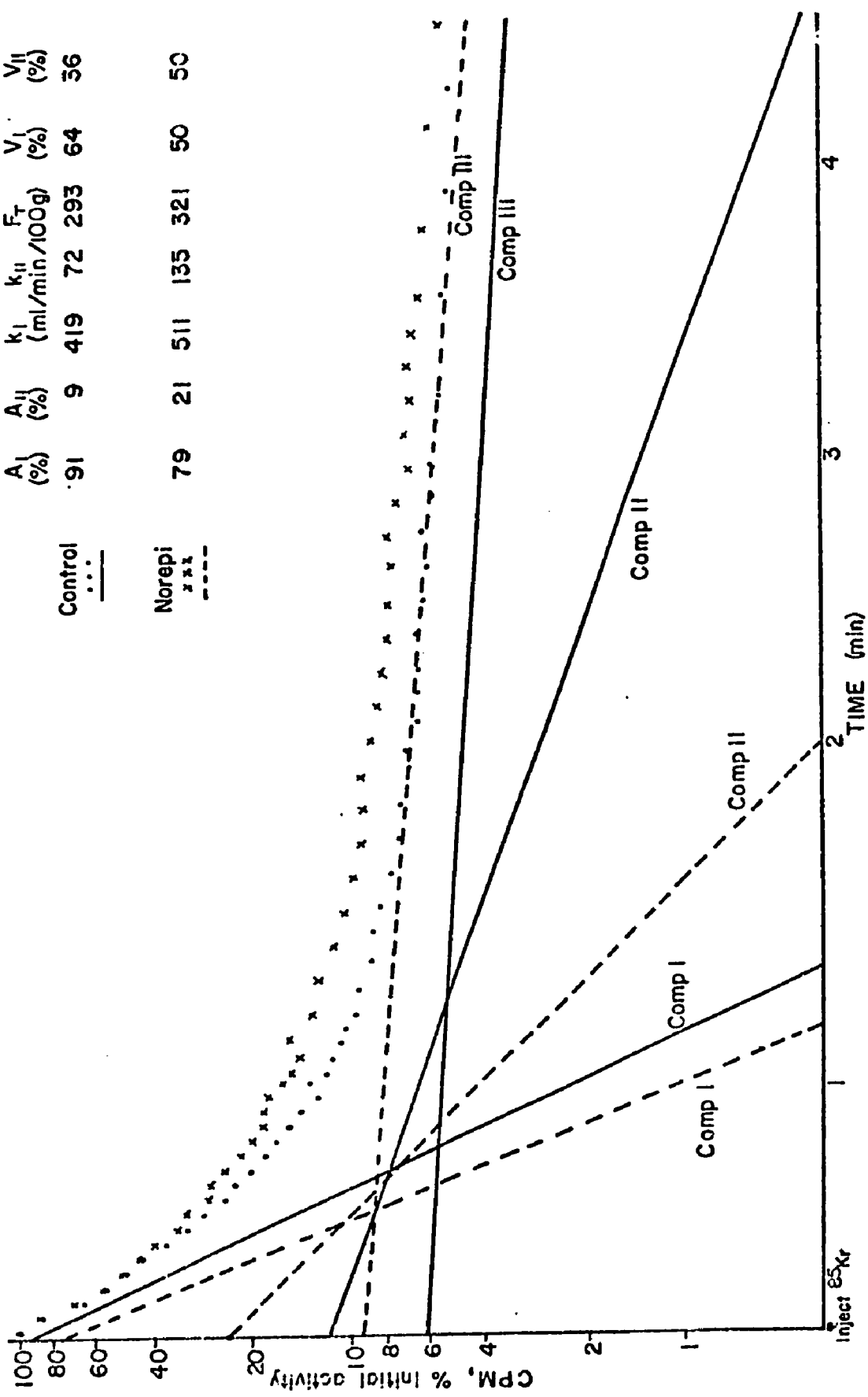


Figure 2. Typical ^{85}Kr washout curves illustrating redistribution of flow. Components I, II, and III are shown for each of the two ^{85}Kr curves plotted above. The decrease in A_I and increase in k_{II} best characterize the pattern of redistribution caused by norepinephrine.

component II represents an increase in the rate of juxtamedullary blood flow.

A word regarding terminology and the relationship of the ^{85}Kr curves to actual anatomic areas of the kidney is important. The terms compartment, component, A_I, k_I, etc., refer only to the ^{85}Kr curves and describe a compartmental model whose behavior produces clearance curves like the ones obtained from the kidney. Correlations between specific anatomic regions of the kidney and the parameters of the ^{85}Kr curve can be made on the basis of autoradiographs; this correlation varies with different experimental situations. In this study, the autoradiographs showed that component I always represents only cortical flow, and that component II always represents juxtamedullary cortical and outer medullary flow. In one instance, component II, in addition, represents a portion of cortical flow. Because of this general relationship, component I at times will be equated with the cortex and component II with the juxtamedullary cortical region. Similarly, k_I will be used interchangeably with cortical flow rate, etc. For simplicity, we will use the term juxtamedullary flow to refer to flow through the juxtamedullary cortex and outer medulla.

Values for the flows (k's) and relative distribution (A's) were determined from the krypton washout curve by finding those values or parameter estimates for the $A(0)_i$ and k_i which gave a best fit for the sum of four exponentials to the data according to a weighted least squares criterion. The number of counts in each counting interval was expressed as activity (cpm) and background was subtracted; the time for each point was taken as the midpoint of the counting interval. The terminal, monoexponential portion of the curve (beyond thirty minutes)

was first fitted by a least squares method with a single exponential which was extrapolated to zero time. The values for this fourth or slowest component were subtracted from the corresponding data points and the resulting reduced curve fitted as described below. This method was used to estimate the fourth component because it substantially reduced computer costs; the same parameter estimates are obtained for the first two components if four components are fitted to the original curve.

The first three components were then determined simultaneously by an iterative technique (Chandler, 1971) which found the values that minimized the following function which is the weighted least squares criterion:

$$X^2 = \sum_{i=1}^{n} [y(t)_i - \{A(0)_1 e^{-k_1 t_i} + A(0)_2 e^{-k_2 t_i} + A(0)_3 e^{-k_3 t_i}\}]/y(t)_i$$

where the $y(t)_i$ are the n data points. The $y(t)_i$ in the denominator is the weighting factor and is assumed proportional to the variance of the data points; this weighting is necessary because the data points are known to be heteroscadastic.

Only the portion of the curve prior to the terminal part that was fitted by the single exponential was used in the parameter estimation. Dell(1973) using a similar approach (but a different algorithm) has shown that parameters of the sum of exponentials are not sensitive to excluding the terminal portion of the curve beyond twenty minutes.

The validity of this method was tested by constructing curves from known parameters and then adding randomness to each point in

proportion to its value in order to simulate scatter in the data. When such curves were fitted, the program would return the parameters used to construct the curve. The parameter estimates returned by the program were not sensitive to their initial estimates in the parameter optimization, either for constructed curves or for real data. If four components were fitted to a constructed three-component curve, one of the four components returned by the program would be trivial in that its rate constant would duplicate another or its zero time intercept would be small so that the component made a negligible contribution to the entire curve. The program was therefore capable of determining "fusion" in the krypton curve where the two most rapid components have a similar rate constant and are represented by a single exponential (see discussion).

Statistics

Standard statistical techniques were used throughout. Tests for significance of difference were done by the paired t test against the null hypothesis that the mean difference was zero.

III. RESULTS

In Series I, both norepinephrine infusion and decreased perfusion pressure caused reductions in sodium excretion and glomerular filtration rate when compared to controls. The fall in sodium excretion was significantly greater when perfusion pressure was lowered than when norepinephrine was infused; the accompanying fall in glomerular filtration rate with decreased perfusion pressure was smaller than but not significantly different from that with norepinephrine infusion. Norepinephrine increased the rate of flow in the slower compartment (k_{II}, juxtamedullary cortex) and, in addition, caused a shift in flow from the faster to slower compartment (decreased A_I). Autoradiographs indicated that this decrease in A_I was due to localized areas of low flow (at approximately the rate of k_{II}) in the cortex. Decreasing perfusion pressure increased k_{II} in the same proportion as did norepinephrine but did not shift the relative distribution of flow (A_I) between the two compartments.

In Series II, norepinephrine caused a significant decrease in sodium excretion without a marked change in glomerular filtration rate; there were no significant changes in any of the parameters which describe the krypton curves; the autoradiographs were not different from control.

These patterns of changes in renal function are illustrated by selected individual experiments shown in Figures 3 and 4. Figure 3 shows sodium excretion and glomerular filtration rate for experimental and control kidneys and Doppler flow and perfusion pressure for the

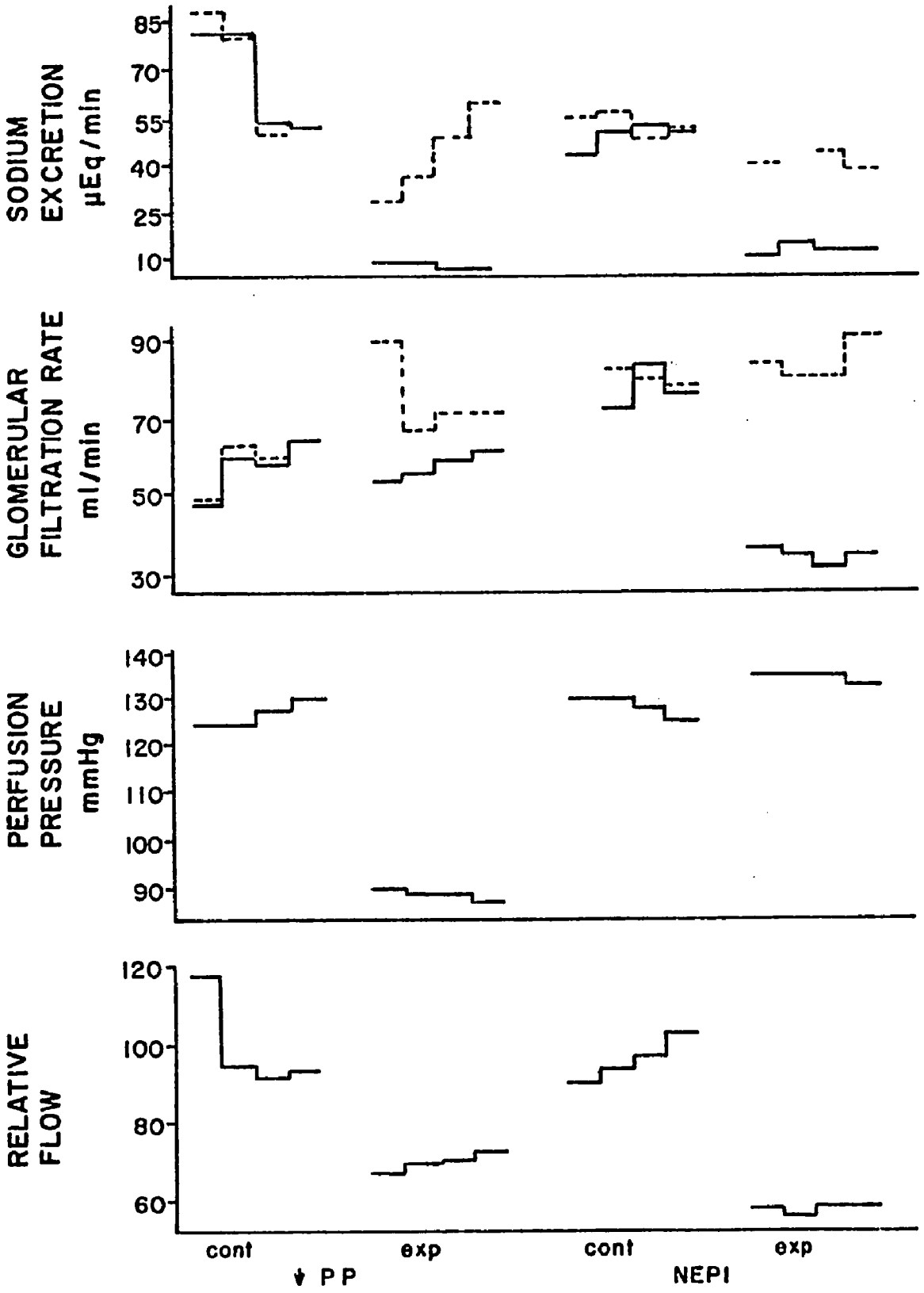


Figure 3. Renal function data from a representative experiment of Series I. Individual values are for fifteen-minute collection intervals in each of four periods. Solid lines represent the experimental kidney; dashed lines, the contralateral, unmanipulated kidney. cont = control period exp = experimental periods

experimental kidney of an experiment in Series I. Values for each of four clearance collections in the two control and two experimental periods are shown. Sodium excretion fell with both maneuvers but more with decreased perfusion pressure. Glomerular filtration rate, in contrast, was reduced much more with norepinephrine infusion. Changes in blood flow paralleled those for glomerular filtration rate. The right kidney showed no marked changes.

Figure 4 presents similar data on renal function for an experiment from Series II; shown are three individual clearance collections in alternating control periods and periods of norepinephrine infusion. In this experiment, there was a tendency for sodium excretion to decrease over the day. Norepinephrine infusion, however, did cause further decreases in sodium excretion when compared to the mean of the preceding and following controls. Glomerular filtration rate decreased somewhat with norepinephrine (this fall being greater than the average for all experiments). There are fluctuations but no consistent changes in perfusion pressure and flow.

Series I, Renal Function Data

Infusing norepinephrine at an average rate of 5.1 μg/min reduced sodium excretion by 39% of control values (from 74 ± 12 to 46 ± 11 μEq/min) when compared to the immediately preceding control period. At the same time, glomerular filtration rate fell by 35% of control (from 43 ± 4 to 29 ± 4 ml/min) (Figure 5, Table 1). A decrease in both urine flow rate (from 0.44 ± .08 to 0.37 ± 0.8 ml/min) and sodium concentration (from 171 ± 15 to 107 ± 11 mEq/l) accounted for the fall in sodium excretion. Blood pressure rose slightly but significantly from 129 ± 3 to 139 ± 2 mmHg with the infusion (Table 1).

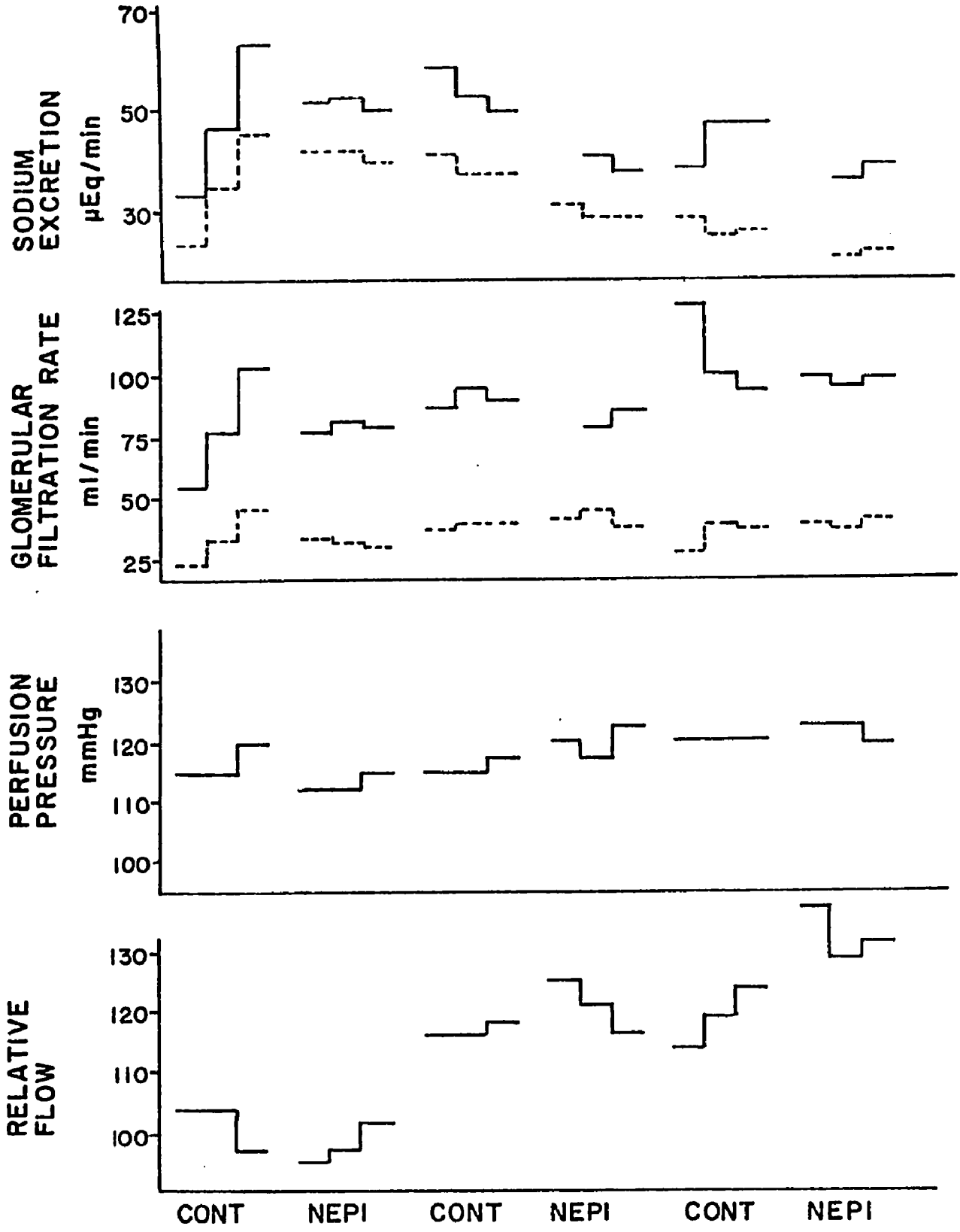


Figure 4. Renal function data from a representative experiment of Series II. Individual values are for fifteen-minute collection intervals in each of six periods. Solid lines represent the experimental kidney; dashed lines, the contralateral, unmanipulated kidney. cont = control period nepi = norepinephrine infusion

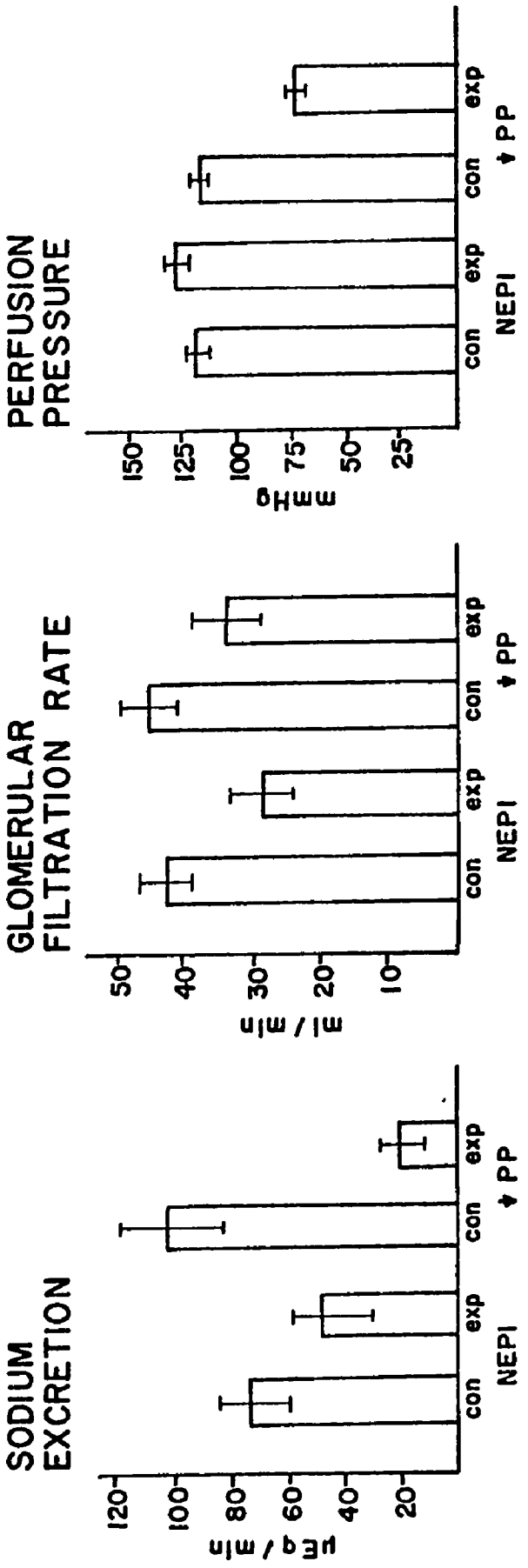


Figure 5. Averages of renal function data from the experiments of Series I. Means ± SEM for each of four periods. NEPI = norepinephrine infusion ↓PP = decreased perfusion pressure con = control period exp = experimental period

Table 1

Renal Function Data, Series I

	Norepinephrine[a]		Dec. Perf. Press.[a]		p values[b] (sample sizes)			
	Cont	Exp	Cont	Exp	Cont/Cont	Nepi/↓PP	Cont/Nepi	Cont/↓PP
Left Kidney								
Sodium Excretion								
uEq/min	73.5 ± 12	46.1 ± 11	105 ± 21	23 ± 7.6	.25 (13)	.05 (13)	.01 (14)	.001 (12)
% Control	100	62 ± 9.9	100	21 ± 5.3		.01 (12)		
Glom. Filt. Rate								
ml/min	42.5 ± 4.9	29.1 ± 3.8	46.4 ± 5.0	34.5 ± 4.2	.35 (13)	.19 (13)	.001 (14)	.08 (12)
% Control	100	65 ± 8.1	100	83 ± 7.7		.33 (12)		
Urine Volume								
ml/min	.44 ± .076	.37 ± .075	.77 ± .146	.23 ± .036	.04 (13)	.07 (16)	.43 (16)	.003 (12)
% Control	100	95 ± 13	100	36 ± 5.9		.01 (12)		
$[Na^+]_U$								
mEq/l	171 ± 14	107 ± 11	154 ± 20	75 ± 14	.17 (13)	.02 (13)	.001 (14)	.001 (12)
% Control	100	62 ± 5.1	100	53 ± 7.4		.35 (12)		
Perfusion Pressure								
mmHg	129 ± 3	139 ± 2	120 ± 3	75 ± 4	.34 (9)	.001 (11)	.02 (12)	.001 (10)
% Control	100	107 ± 2	100	62 ± 12		.001 (19)		
Right Kidney								
Sodium Excretion								
uEq/min	95 ± 21	106 ± 21	72 ± 11	80 ± 16	.35 (9)	.35 (10)	.55 (9)	.44 (10)
% Control	100	135 ± 32	100	112 ± 12		.35 (9)		
Glom. Filt. Rate								
ml/min	48.0 ± 4.7	48.5 ± 6.1	47.3 ± 4.0	42.7 ± 5.3	.35 (13)	.46 (12)	.77 (12)	.43 (11)
% Control	100	97 ± 5.3	100	92 ± 5.3		.40 (11)		
Urine Volume								
ml/min	.43 ± .11	.55 ± .08	.53 ± .13	.52 ± .12	.59 (13)	.76 (16)	.17 (16)	.13 (13)
% Control	100	165 ± 32	100	119 ± 9.2		.35		
$[Na^+]_U$								
mEq/l	203 ± 22	176 ± 18	187 ± 26	177 ± 23	.37 (9)	.98 (10)	.16 (9)	.32 (10)
% Control	100	89 ± 7.7	100	101 ± 8.4		.21 (9)		

[a] All values are mean ± SEM

[b] The p values shown are for paired t tests which compare 1) the control values for norepinephrine and decreased perfusion pressure (Cont/Cont), 2) the experimental values for norepinephrine and decreased perfusion pressure (Nepi/↓PP), 3) the control and experimental values for norepinephrine (Cont/Nepi), and 4) the control and experimental values for decreased perfusion pressure (Cont/↓PP).

When renal perfusion pressure was reduced to an average pressure of 75 ± 4 mmHg, sodium excretion fell by 80% of control (from 105 ± 21 to 23 ± 8 μEq/min). This decrease was significantly greater than that resulting from norepinephrine infusion, both in terms of per cent of control and the absolute level of sodium excretion during the experimental period. The control sodium excretion for decreased perfusion pressure was higher than for norepinephrine but not significantly different. In this situation, both urine volume and sodium concentration were reduced with respect to control (from 0.77 ± 0.15 to 0.23 ± 0.21 ml/min and from 154 ± 20 to 75 ± 14 mEq/l respectively). With lowered perfusion pressure, glomerular filtration rate fell less (by 17% of control, from 46 ± 5 to 35 ± 4 ml/min) to an experimental value which was slightly higher than that during norepinephrine; neither the per cent change nor final glomerular filtration rate were significantly different from those during norepinephrine infusion (Figure 5, Table 1). With decreased perfusion pressure, mean systemic pressure rose slightly but significantly from 126 ± 3 to 134 ± 2 mmHg (Table 1).

In the contralateral kidney control sodium excretion for this maneuver was lower than in the experimental kidney; glomerular filtration rate was the same. There were no significant changes in this kidney with reduced perfusion pressure although there was a slight rise in sodium excretion and fall in glomerular filtration rate.

Series I, Flow Data

Infusion of norepinephrine caused a decrease in total renal blood flow, measured by the Doppler flow probe, of 31% of control levels (Figure 6, Table 2).

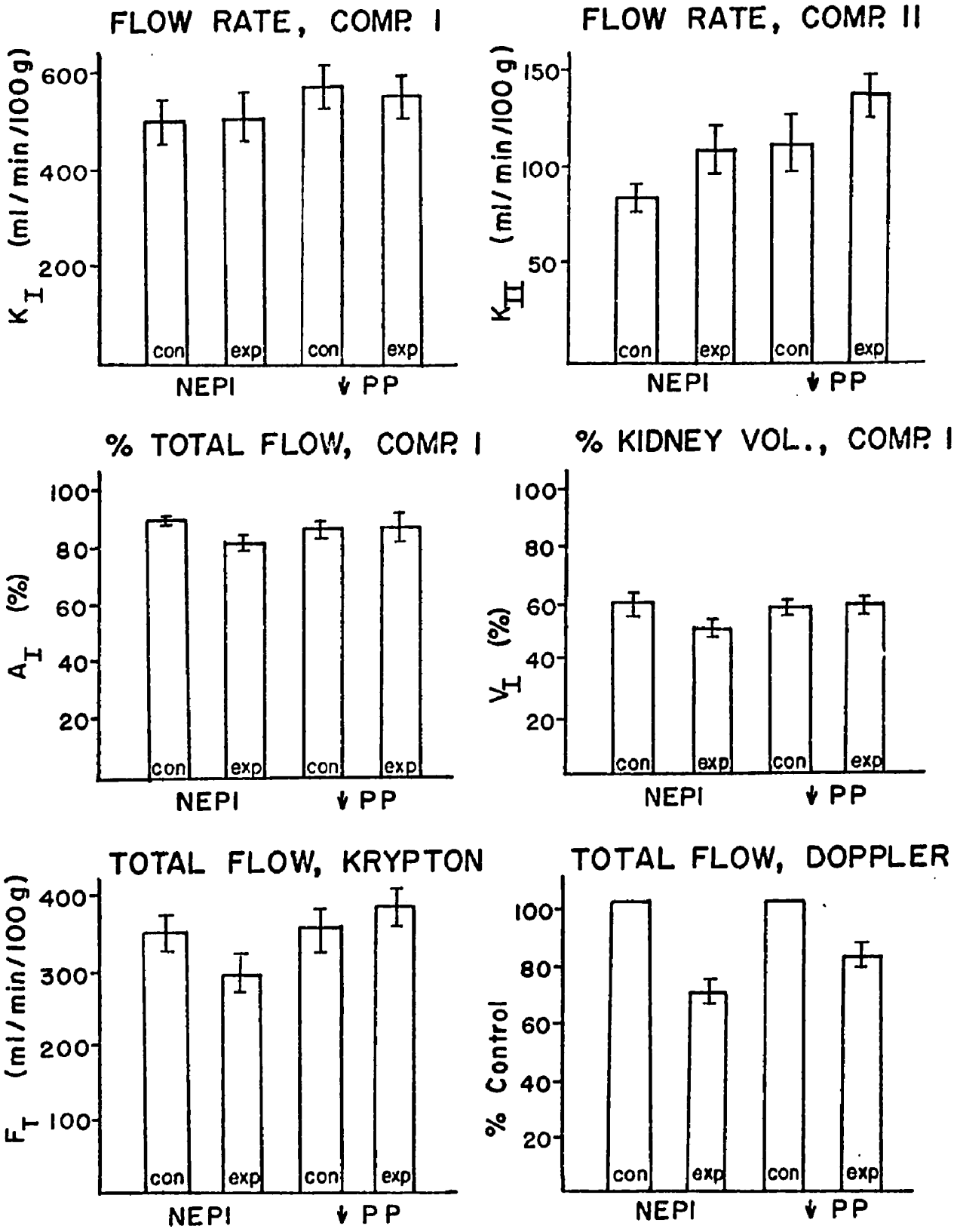


Figure 6. Averages of data for total blood flow and intrarenal distribution of flow, Series I. Means ± SEM for each of four periods. NEPI = norepinephrine infusion ↓PP = decreased perfusion pressure con = control exp = experimental

Table 2

Flow Data, Series I

	Norepinephrine[a]		Dec. Perf. Press.[a]		p values[b] (sample sizes)			
	Cont	Exp	Cont	Exp	Cont/Cont	Nepi/+PP	Cont/Nepi	Cont/+PP
A_I (%)	90.6 ± .86	81.7 ± 1.8	87.2 ± .97	85.9 ± 1.0	.057 (12)	.017 (14)	.001 (14)	.16 (12)
% Control	100	90.4 ± 2.0	100	97.3 ± 1.9		.004 (10)		
V_I (%)	61.0 ± 1.9	49.0 ± 2.3	58.8 ± 1.7	60.3 ± 1.7	.51 (12)	.002 (14)	.001 (14)	.99 (12)
% Control	100	81.0 ± 4.1	100	101 ± 4.9		.0001 (10)		
k_I (ml/min/100 g)	501 ± 32	509 ± 37	553 ± 39	546 ± 40	.14 (12)	.17 (14)	.63 (14)	.67 (12)
% Control	100	105 ± 6.5	100	104 ± 6.3		.93 (10)		
k_{II} (ml/min/100 g)	83 ± 6.8	106 ± 12.4	112 ± 9.7	134 ± 12	.07 (12)	.06 (14)	.07 (14)	.07 (14)
% Control	100	134 ± 15	100	140 ± 17		.80 (10)		
F_t (ml/min/100 g)	336 ± 20	289 ± 21	346 ± 28	371 ± 24	.64 (12)	.007 (13)	.09 (14)	.11 (11)
% Control	100	89.3 ± 6.3	100	119 ± 10		.014 (9)		
Doppler flow								
% Control	100	69.1 ± 4.1	100	79.5 ± 4.0		.001 (8)		

A_I is the percent of total renal flow distributed to the faster compartment.

V_I is the percent of total renal volume perfused at the faster flow rate.

k_I is the flow rate of the faster compartment; it represents cortical flow in both controls and in decreased perfusion pressure and the major fraction of cortex with norepinephrine.

k_{II} is the flow rate of the slower compartment; it represents juxtamedullary flow for both controls and decreased perfusion pressure and some areas of cortex as well with norepinephrine.

F_t is total renal blood flow as measured by krypton.

Doppler flow is expressed only as percent of the respective control periods.

[a] All values are mean ± SEM

[b] The p values shown are for paired t tests which compare 1) the control values for norepinephrine and decreased perfusion pressure (Cont/Cont), 2) the experimental values for norepinephrine and decreased perfusion pressure (Nepi/+PP), 3) the control and experimental values for norepinephrine (Cont/Nepi), and 4) the control and experimental values for decreased perfusion pressure (Cont/+PP).

Norepinephrine caused a greater portion of the total renal blood flow to be distributed to the deeper region of the kidney and increased the flow per volume of this region of the kidney.

The fraction of blood flow entering the fast compartment, A_I, was reduced 10% from 90 $\pm$ 1% to 82 $\pm$ 2% of the total renal blood flow. The fraction of total kidney volume perfused by this faster component, V_I, decreased during norepinephrine infusion by 19% of control from a value of 61 $\pm$ 2% to 49 $\pm$ 2% of the kidney volume. There were complementary changes in these variables for the second component of the krypton curves.

The rate of flow in the faster compartment, k_I, was insignificantly increased by 5% of control value. Rate of flow for the slower compartment, k_{II}, increased significantly to 134% of control value (from 83 $\pm$ 7 to 106 $\pm$ 12 ml/min/100 g). Total flow calculated from the krypton curves fell 11% from a control value of 336 $\pm$ 20 ml/min/100 g to 289 $\pm$ 21 ml/min/100 g when norepinephrine was infused (Table 2, Figure 6). This was significantly smaller than the 31% drop indicated by the Doppler flow.

In contrast, reducing perfusion pressure caused an increase in k_{II} with no significant change in other parameters. K_{II} increased by 40% of control flows (112 $\pm$ 92 to 134 $\pm$ 12 ml/min/100 g) which was the same relative rise as with norepinephrine infusion. Both control and experimental values for k_{II} were higher than the corresponding values during norepinephrine..

A_I fell by only 3% of control (from 87 $\pm$ 1% to 86 $\pm$ 4%) and V_I increased by 1% from 59 $\pm$ 2 to 60 $\pm$ 2%. Although control values of A_I were slightly less than for norepinephrine, the values during the

experimental period were higher (smaller fall) than for norepinephrine. The rate of flow in the faster compartment, k_I, increased 4% from 553 $\pm$ 39 to 546 $\pm$ 40 ml/min/100 g (Table 2, Figure 5). Doppler flow (Figure 5, Table 2) was reduced by 21 $\pm$ 4% which was smaller than the change with norepinephrine though not significantly so.

For each experimental maneuver, autoradiographs were prepared from kidneys removed at several different times following the intra-arterial injection of ^{85}Kr and were used to anatomically localize the components of the krypton washout curves. This is done by comparing the distribution of krypton (which exposes the film more where it is more concentrated) within the kidney at the various points in time at which the kidneys were removed. An example of such a series of autoradiographs is shown in the upper panel of Figure 10; these were taken from an earlier study in this laboratory (Carlson and Sparks, 1970) and illustrate the normal control distribution of flow in acute, anesthetized dogs.

The kidney removed 30" after injection of ^{85}Kr has an even distribution of ^{85}Kr throughout the cortex, somewhat less ^{85}Kr in the outer medulla and almost none in the papilla. The kidney removed one minute after injection of ^{85}Kr has much less ^{85}Kr in the outer cortex than in the juxtamedullary cortex and outer medulla. Autoradiographs of kidneys removed two minutes after injection of ^{85}Kr show that ^{85}Kr is partially removed from the outer medulla and juxtamedullary cortex but completely removed from the outer cortex. Thus, the most rapid component of the washout curve (Component I) represents flow through outer cortex. In kidneys removed after 6 minutes (not shown in Figure 10; see Figure 7), only the perirenal fat and papilla contain ^{85}Kr. Thus Component II must represent flow through juxtamedullary cortex and outer medulla.

In the autoradiographs taken soon (less than 30 seconds) after injection of ^{85}Kr, the areas of greatest density represent areas of high flow per volume because a larger portion of the bolus is delivered to them. In autoradiographs of kidneys taken at successively later times, the areas of high flow appear less dense because the high flow has cleared these areas of krypton, decreasing its concentration, while the tracer remains in the areas of slower flow. In this manner, areas of successively slower flow rates can be identified as those areas that are cleared at successively later times. It should be noted that only the relative densities of different areas can be compared; absolute density is not proportional to the absolute amount of krypton present because of variations in the exposure time.

Autoradiographs prepared from kidneys taken during norepinephrine infusion demonstrate that the most rapid flow, k_I, was localized to the renal cortex (Figure 7). This is seen by comparing the relative densities in the 60" autoradiographs where the light cortical areas indicate areas from which the majority of the krypton present at 15" has been cleared and therefore represent regions perfused at the most rapid rate of flow in the kidney. The juxtamedullary cortex and outer medulla as well as considerable areas of the outer cortex are perfused at a slower rate, k_{II}. Krypton is still present in these areas at 60" but is well cleared by 6 minutes. At this later time, krypton remains only in the perirenal fat and the papilla.

Comparison of the autoradiographs taken during decreased perfusion pressure 5" and 60" after injection of ^{85}Kr shows that the entire cortex is uniformly cleared of krypton at a time when activity remains in the juxtamedullary cortex and outer medulla (Figure 7). Component I therefore

Figure 7. Autoradiographs indicating the anatomic localization (distribution) of the various flow rates represented in the krypton washout curves of Series I. These autoradiographs were prepared from kidneys removed at the indicated times following an intra-arterial bolus of ^{85}Kr during either norepinephrine infusion or decreased perfusion pressure.

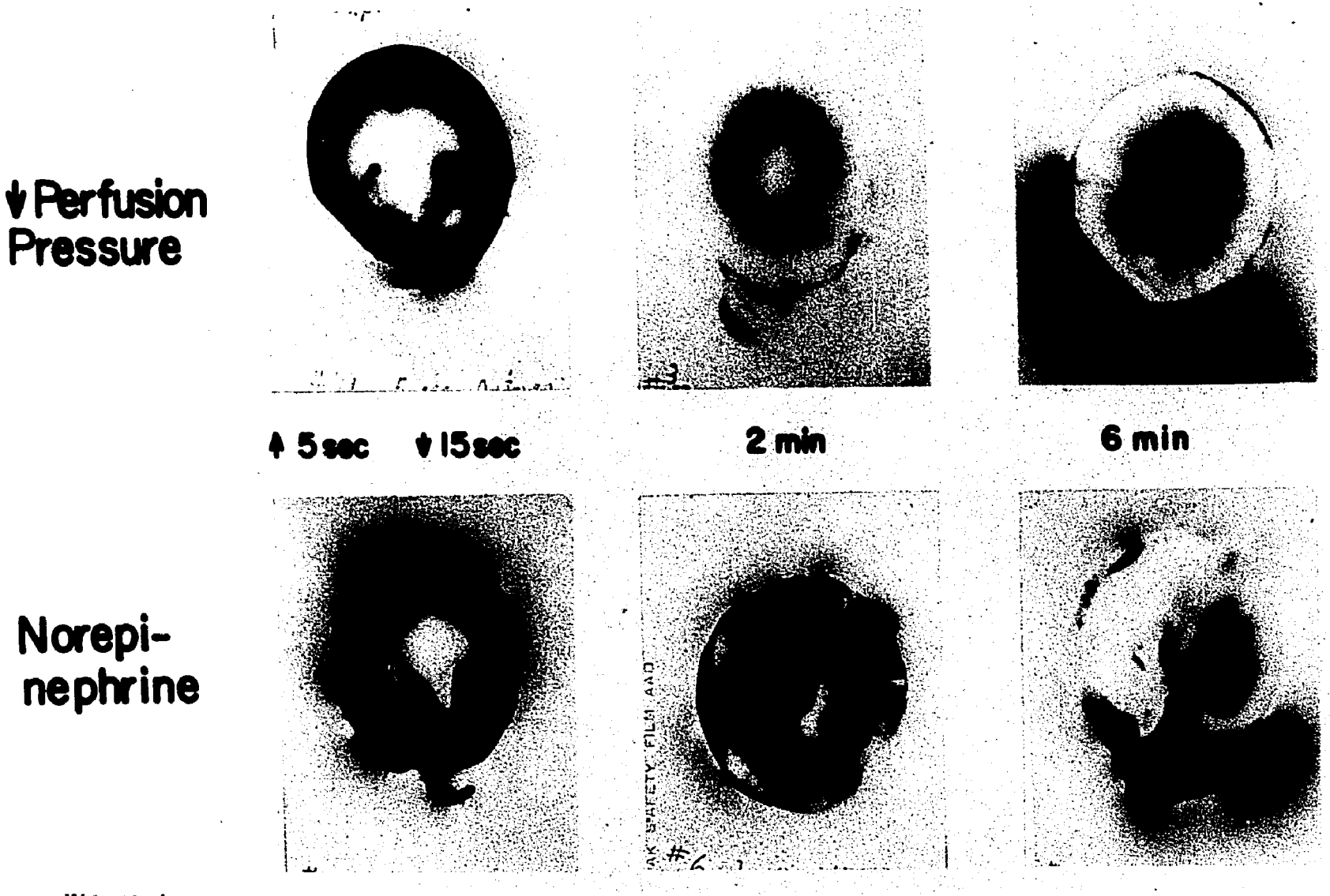


Figure /.

perfuses the entire outer cortex. The juxtamedullary cortical and outer medullary areas are cleared next by component II (one and two minute autoradiographs) whereas fat and renal papilla are cleared more slowly.

Series II, Renal Function Data

An intra-arterial infusion of norepinephrine at a relatively low dose, averaging 1.9 ug/min, significantly reduced sodium excretion with no changes in glomerular filtration rate (Figure 8, Table 3). Sodium excretion fell by 31% of control values (from 40 $\pm$ 6 to 30 $\pm$ 6 uEq/min) and glomerular filtration rate decreased 3% (from 48 $\pm$ 4 to 46 $\pm$ 3 ml/min). The fall in sodium excretion was due primarily to a decrease in concentration, although volume also fell slightly (Table 3).

There were no significant changes in any of these aspects in the right control kidney although there was a slight tendency for the glomerular filtration rate to increase. Also, there were no significant differences between pre- and post-control for any renal function parameter in either kidney (Table 3).

Series II, Flow Data

Infusion of these low doses of norepinephrine did not significantly alter any of the parameters of the krypton curves which describe intrarenal distribution of flow (Figure 9, Table 4). The fraction of total renal flow delivered to the faster compartment, A_I, was 89 $\pm$ 2% in control periods and 89 $\pm$ 2% with norepinephrine infusion; the volume of this compartment, V_I, was 61 $\pm$ 2% of the total kidney volume during control and 64 $\pm$ 3% with norepinephrine. Both flow rates fell slightly but insignificantly. With norepinephrine, k_I decreased 5 $\pm$ 5% of control

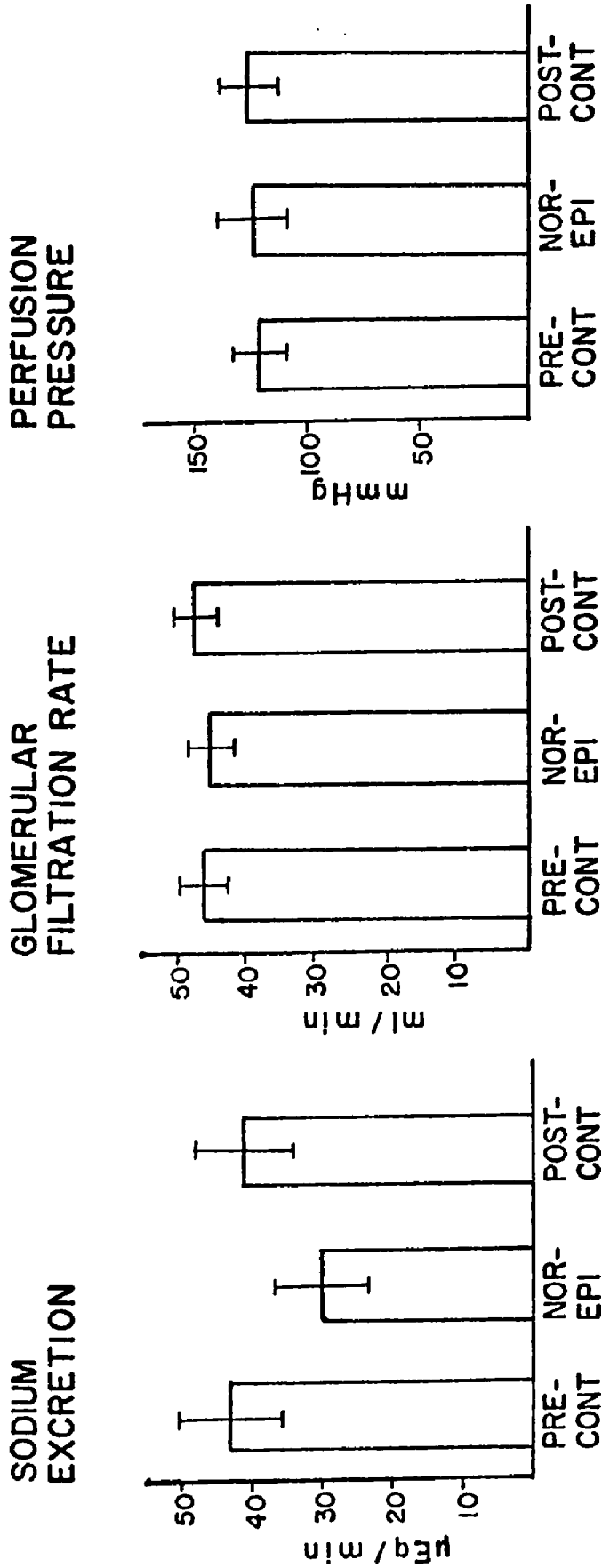


Figure 8. Average values of renal function data from the experiments of Series II. Means ± SEM during periods of norepinephrine infusion (NOREPI) and the preceding and following control periods (PRECONT, POSTCONT).

Table 3

Renal Function Data, Series II

	Pre-Control[a]	Norepi[a]	Post-Control[a]	Norepi vs Mean Control (p value)	Pre-Control vs Post-Control (p value)
Left Kidney[b]					
Sodium Excretion uEq/min	43.2 ± 7.3	29.9 ± 6.3	41.6 ± 6.8	0.02	0.26
% Cont		69 ± 9.7		0.005	
Glom. Filt. Rate ml/min	46.3 ± 2.8	45.5 ± 2.7	47.1 ± 2.6	0.41	0.47
% Cont		97 ± 4.9		0.62	
$[Na^+]_U$ mEq/l	147 ± 7.8	104 ± 18.6	144 ± 23.2	0.09	0.44
% Cont		73 ± 9.2		0.01	
Urine Volume ml/min	0.27 ± .02	0.24 ± 0.3	0.275 ± .03	0.04	0.62
% Cont		91 ± 6.4		0.03	
Right Kidney[b]					
Sodium Excretion uEq/min	31.4 ± 5.0	29.5 ± 5.3	27.7 ± 3.6	0.59	0.26
% Cont		98 ± 9.7		0.80	
Glom. Filt. Rate ml/min	46.6 ± 2.17	49.2 ± 2.19	46.6 ± 2.62	0.16	0.55
% Cont		106 ± 4.1		0.19	
$[Na^+]_U$ mEq/l	130 ± 18.6	127 ± 18.5	112 ± 19.3	0.48	0.17
% Cont		112 ± 13.8		0.42	
Urine Volume ml/min	0.235 ± .02	0.224 ± .03	0.225 ± .04	0.07	0.51
		107 ± 6.0		0.08	

[a] All values are mean ± SEM, n = 18

[b] % Cont is per cent of mean control

values (606 ± 29 vs 573 ± 37 ml/min/100 g), and k_{II} decreased 3 ± 8% (127 ± 77 vs 121 ± 10 ml/min/100g). This was a greater fall than for the Doppler flow which decreased significantly by 4 ± .02% of mean control values (Figure 9, Table 4).

Autoradiographs taken during norepinephrine infusion indicate that the cortex was uniformly perfused at the faster rate since the thirty second and one minute autoradiographs show the cortex is the first area cleared of ^{85}Kr, Component II, the slower rate, is attributed to the juxtamedullary region which contains the most of the ^{85}Kr present at one minute which is partially removed at two minutes. At two minutes the majority of ^{85}Kr is located in the papilla and fat.

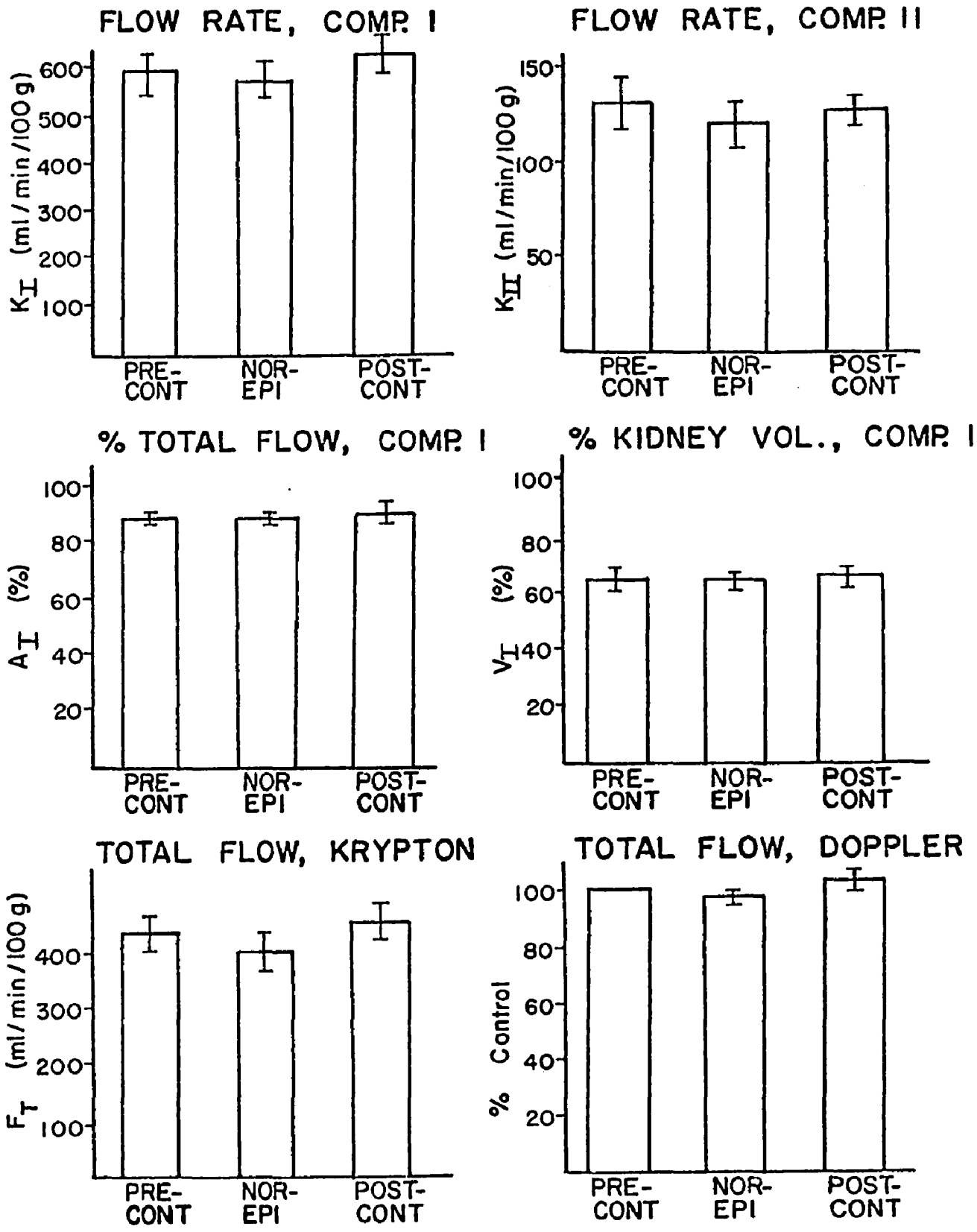


Figure 9. Averages of data for total blood flow and intrarenal distribution of flow, Series II. Means ± SEM during periods of norepinephrine infusion (NOREPI) and the preceding and following control periods (PRECONT, POSTCONT).

Table 4

Flow Data, Series II

	Pre-Norepi[a]	Norepi[a,b]	Post-Norepi[a]	Norepi vs Mean Control (p value)	Pre-Control vs Post-Control (p value)
$A(0)_I$ (%)	88.8 ± 1.65	88.9 ± 1.4	89.4 ± 1.8	0.89	0.69
% Control		100 ± 1.4		0.99	
$V(0)_I$ (%)	64.2 ± 2.1	64.4 ± 2.5	64.4 ± 3.0	0.90	0.92
% Control		101 ± 2.9		0.82	
k_I (ml/min/100 g)	597 ± 35	573 ± 37	622 ± 38	0.28	0.61
% Control		95 ± 4.0		0.28	
k_{II} (ml/min/100 g)	129 ± 13	121 ± 10	126 ± 7.1	0.68	0.76
% Control		97 ± 7.5		0.71	
F_t (ml/min/100 g)	434 ± 24	401 ± 22	455 ± 28	0.05	0.52
% Control		92 ± 3.7		0.04	
Doppler flow[c]					
% Pre-Control	100	96 ± 2.0	103 ± 5.0	0.04	0.61

$A(0)_I$ is the percent of total renal flow distributed to the faster compartment.

$V(0)_I$ is the percent of total renal volume perfused at the faster flow rate.

k_I is the flow rate of the faster component; it represents cortical flow for control and decreased pressure and a fraction of the cortex for norepinephrine.

k_{II} is the flow rate of the slower compartment; it represents juxtamedullary flow for control and decreased pressure and some areas of cortex as well as juxtamedullary flow for norepinephrine.

F_t is total renal blood flow as measured by krypton.

Doppler flow is expressed as a percent of the flow of the first control period.

[a] All values are mean ± SEM

[b] % Control is percent of mean control

[c] n = 18 for this variable only

Figure 10. Autoradiographs indicating anatomic localization (distribution) of the different rates of flow represented in the krypton washout curves of Series II. These autoradiographs were prepared from kidneys removed at the indicated times following an intra-arterial bolus of ^{85}Kr, either during control states or norepinephrine infusion. Control autoradiographs from Carlson and Sparks (1970).

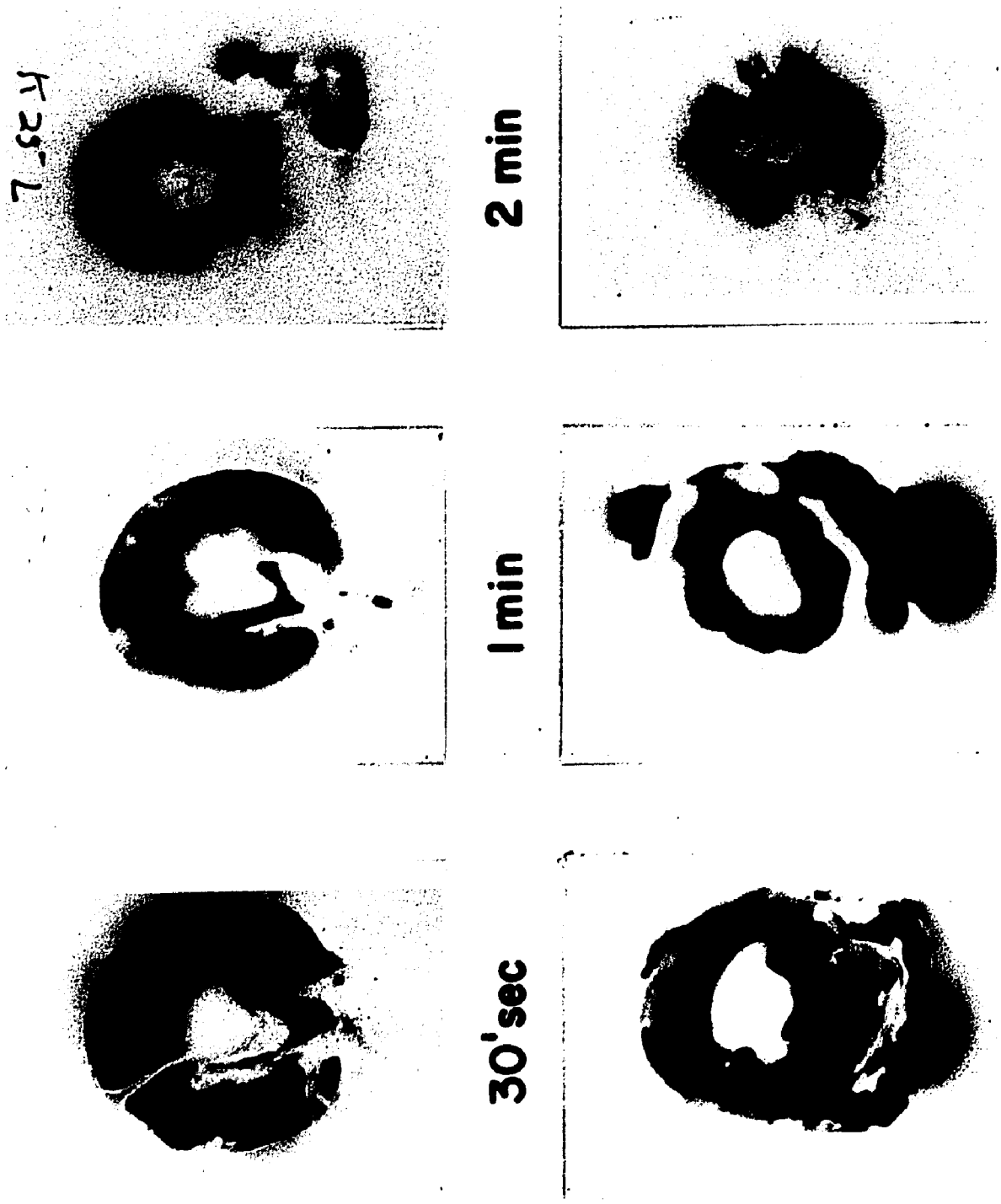


Figure 10.

IV. DISCUSSION

These experiments were done to test the hypothesis that redistribution of blood flow within the kidney, as determined by the inert gas washout method, contributes to the regulation of sodium excretion (Barger, 1966). The specific hypothesis is that either 1) a shift in the fractional distribution of blood flow from cortical to juxtamedullary (inner-cortical and outer-medullary) regions or 2) an increase in the rate of flow in the juxtamedullary region leads to a reduction of sodium excretion (Pomeranz et al., 1968; Sparks et al., 1972). A major criticism of the studies which suggest and support this proposition is that in situations in which such a redistribution of flow occurs, glomerular filtration rate would be expected to decrease and so lower sodium excretion. Changes in aldosterone may also occur, as for instance in congestive heart failure, and result in decreased sodium excretion. The objective of the current study was to consider the relationship of redistribution of flow within the kidney to changes in sodium excretion while controlling for these other determinants of sodium excretion.

The experiments in Series I were designed to observe this relationship in two experimental situations (decreased perfusion pressure and intra-arterial norepinephrine infusion) in which glomerular filtration rates are equal. In Series II, we infused a lower dose of norepinephrine than had been used for Series I in an attempt to dissociate changes in sodium excretion, distribution of flow, and glomerular filtration rate on the basis of dose dependent relationships. These series of experiments

taken either individually or together provide little or no evidence for a quantitatively important role for intrarenal distribution of blood flow as a determinant of sodium excretion.

Both experimental maneuvers of Series I produced redistribution of renal blood flow which, under the hypothesis being tested, should reduce sodium excretion. However, the quantitative relationships between the changes in the distribution of flow and the associated changes in sodium excretion fail to support the hypothesis. Norepinephrine produced a greater degree of redistribution than did reduced perfusion pressure; it lowered the fraction of total renal blood flow delivered to the faster compartment by 10% and increased the rate of flow in the second compartment, juxtamedullary flow, by 34%. Decreased perfusion pressure increased the rate of juxtamedullary flow in the same proportion, 40%, as did norepinephrine but did not change the portion of total renal blood flow perfusing the individual compartments.

If decreases in the portion of renal blood flow perfusing the outer cortex and increases in that perfusing juxtamedullary regions lead to reduced sodium excretion, we would expect a greater fall in sodium excretion with norepinephrine than with decreased perfusion pressure. But, in fact, the decrease in sodium excretion with decreased perfusion pressure was twice as great. Thus, this greater fall in sodium excretion could not be due to greater shifts of renal blood flow from cortical to juxtamedullary regions.

If increases in the rate of juxtamedullary cortical flow contribute to reduced sodium excretion, we would expect comparable changes in sodium excretion on the basis of changes in this parameter. Since the changes

in sodium excretion differed by a factor of two and glomerular filtration rate was decreased more with norepinephrine, if anything, this difference could not have been due to the increases in juxtamedullary flow which were relatively equal in the two situations.

Glomerular filtration rate fell, as expected, in each of these instances. Since the decrease in glomerular filtration rate was smaller with decreased perfusion pressure (but not significantly so, 11.9 vs. 13.4 ml/min), the greater decrease in sodium excretion occurring with this maneuver could not be due to a larger fall in glomerular filtration rate which overshadowed a sodium saving effect of the greater redistribution of flow that occurred with infusion of norepinephrine.

Since there were no significant changes in sodium excretion in the contralateral kidney, neither the observed decreases in sodium excretion nor the differences between the two situations can be easily explained by the effect of any systemically circulating substance. This eliminates from consideration changes in aldosterone, antidiuretic hormone, or any other circulating hormone which may affect sodium metabolism.

These data cannot completely exclude the possibility that redistribution of flow mediated in part the reductions of sodium excretion from control levels, particularly in the case of norepinephrine infusion. However, the possible quantitative contribution of the observed changes in distribution of flow to the decreases in sodium excretion can be evaluated relative to the contribution of other mechanisms.

If the decreased sodium excretion with norepinephrine was due solely to redistribution of flow, and not at all to glomerular filtration rate changes, then the mechanism which causes the excess reduction in sodium excretion when perfusion pressure is reduced (that is, the portion

of the fall in sodium excretion which is in excess of the fall caused by norepinephrine) must be at least as potent as redistribution of flow in saving sodium. That lowering perfusion pressure itself redistributed flow by increasing juxtamedullary flow does not alter the above argument since this maneuver only increased juxtamedullary flow rate; since this increase was not greater than that with norepinephrine, it could not have contributed to the excess reduction of sodium excretion.

Assume that the contribution of lowered glomerular filtration rate in reducing sodium excretion was the same with each experimental maneuver and that the contribution of redistribution of flow, if any, was greater in the case of norepinephrine infusion. For the moment, consider also that only these two mechanisms are involved in the norepinephrine response.

If this is the situation, then there must be a mechanism operating during reduced perfusion pressure which is responsible for the additional reduction of sodium excretion. This mechanism must be at least as potent a sodium conserving mechanism as the combined effects of lowered glomerular filtration rate and redistribution of flow in the latter situation because the total reduction with decreased perfusion pressure was twice as great as the total reduction seen with norepinephrine.

There were appreciable falls in glomerular filtration rate with each experimental maneuver which should contribute to the lowering of sodium excretion; the greater the effect of decreased glomerular filtration rate, the less the possible contribution of redistribution of flow. Although it is difficult to quantitate the effect of glomerular-tubular balance in determining the fall in sodium excretion that accompanies a given fall in glomerular filtration rate, we might assume

that the fall in sodium excretion would be proportional to the fall in glomerular filtration rate causing the change, that is, that a constant fraction of the filtered load would be excreted. If this is the case, it is possible to account for nearly all (94%) the reduction in sodium excretion seen with norepinephrine by the fall in glomerular filtration rate. This means the effect of redistribution of flow would be almost nil. Under this assumption, the additional mechanism involved in the case of reduced perfusion pressure must be as potent as changes in glomerular filtration rate in conserving sodium. In reality, it is impossible in any single situation, such as norepinephrine infusion, to separate the effects of redistribution of flow from those of concurrent reductions in glomerular filtration rate; this is the same problem that confronts us in trying to evaluate previous studies dealing with the distribution of flow hypothesis.

In the experiments of Series I, the greater redistribution of flow that occurred with norepinephrine infusion did not cause a greater reduction in sodium excretion than was seen when glomerular filtration rate was reduced to a similar degree by renal artery constriction. There was no evidence of any influence of a systemically circulating factor on sodium excretion. Further, the much greater fall in sodium excretion during lowered perfusion pressure demonstrates an important mechanism that cannot be explained by these data. Quantitative considerations indicate that if redistribution of flow plays any role at all, it is probably not of significant magnitude.

These data do not provide support for the hypothesis that redistribution of renal blood flow, either by decreasing the portion of renal blood flow perfusing the cortex, or by increasing the rate of

juxtamedullary blood flow, can lead to quantitatively important reductions in sodium excretion. In those aspects of these data where the effects of differences in glomerular filtration rate can be eliminated, intrarenal distribution of blood flow was eliminated as a mechanism conserving sodium.

The experiments of Series II were provoked by the results obtained with norepinephrine infusions of Series I. Here, the strategy was to separate changes in sodium excretion, glomerular filtration rate, and intrarenal distribution of blood flow by infusing norepinephrine intraarterially at a smaller dose than was used in Series I. If some variables changed without changes in others, stronger statements could be made regarding the importance of these variables as controllers of sodium excretion. In addition, the smaller changes which would be produced by the small dose would be more analogous to the magnitude of changes which might be expected to occur naturally in the day-to-day life of a dog as the animal goes about regulating its salt balance.

In this series, infusion of norepinephrine at one-third the dose used in the previous experiments reduced sodium excretion by about 30% of control values without significant changes in glomerular filtration rate. Since there were no changes in sodium excretion of the contralateral kidney, neither changes in glomerular filtration rate nor changes in any systemically circulating factor were responsible for this fall in sodium excretion.

Finally, norepinephrine did not significantly alter any parameter of the krypton curves which relate to distribution of flow and thus redistribution of renal blood flow is not the mechanism mediating this decrease in sodium excretion. The changes in these parameters are small

as are the standard errors and thus probably mean that the low dose was indeed without an effect. That is, this lack of a change is not merely a failure to achieve a statistically significant level of confidence because of a great degree of variance in an instance in which a physiologically important difference in the sample means exists.

The magnitude of the change in sodium excretion produced by these experiments is physiologically important; the sodium excretion in control periods is equivalent to a daily sodium intake of 90 mEq/day and this fell by about 30% with norepinephrine. Also, it is not unreasonable to have considered redistribution of flow as a possibility in this situation since previous studies are consistent with sympathetic activity being the means of redistributing flow (Pomeranz et al., 1968; Carrière, 1968; Sparks et al., 1972). Such activity, of course, mediates other changes in kidney function, such as generalized decreases in blood flow and decreases in glomerular filtration rate. Consequently, a change in the distribution of blood flow without changes in these other variables would have suggested a significant role for redistribution of renal blood flow in the control of sodium excretion.

Whether or not a redistribution of flow can alter sodium excretion cannot be determined from the experiments of Series II where redistribution did not occur. These results are, however, helpful in further assessing the possible quantitative importance that redistribution of flow might have in other situations such as the Series I experiments.

Because neither dose of norepinephrine (Series I or II) produced changes in the intrarenal distribution of blood flow in the absence of changes in other variables, particularly glomerular filtration rate, it appears that the physiological significance of alterations in the

distribution of flow in controlling sodium excretion must be considered with respect to changes in other determinants of sodium excretion.

The decrease in sodium excretion produced by the high dose of norepinephrine could in large part be attributed to the substantial fall in glomerular filtration rate rather than the redistribution of flow. Further, we would presume that the mechanism responsible for reducing sodium excretion at the low dose of norepinephrine (which is not decreased glomerular filtration rate) would also be operative at the higher dose. The larger the contribution of this mechanism in the latter situation, the smaller will be the possible contribution of the redistribution of renal blood flow.

The data with decreased perfusion pressure provide another approach to quantifying the effect of the change in glomerular filtration rate. This maneuver reduced glomerular filtration rate to the same or a lesser degree than did norepinephrine but reduced sodium excretion considerably more. In other words, the redistribution of flow toward the juxtamedullary region of the kidney, which occurred with norepinephrine, failed to enhance the effect of reduced glomerular filtration rate so that sodium excretion was lowered to a greater extent than that reached with decreased perfusion pressure which lowered glomerular filtration rate comparably but caused only minimal changes in the distribution of flow.

When the implications of both Series I and II are considered together, it seems extremely unlikely that redistribution of renal blood flow plays any important role in control of sodium excretion under the conditions of these experiments. Quantitative considerations relating the contributions of the different possible determinants of sodium

excretion suggest that any role of redistribution of flow is minor. To the extent that these experiments provide controls for other determinants of sodium excretion, there is no evidence to support the redistribution of flow hypothesis. These experiments also substantiate the existence of a mechanism(s) which is not glomerular filtration rate or any humoral mechanism and which is of considerable importance in the regulation of sodium excretion.

Important to the validity of the conclusions reached above is the soundness of the data upon which the arguments were based. We turn therefore to an appraisal of the data themselves and their relation to data reported in the literature.

In Series I, the changes produced by the two experimental maneuvers were compared presuming that the response to the second maneuver was not unduly affected or biased by the preceding maneuver. Varying the order of the experimental maneuvers in different animals partially controlled this problem. Comparing the control values for the two maneuvers also helps to evaluate this point; there are a few points that warrent comment.

Control sodium excretion (Table 1) is somewhat higher but not significantly different ($p = .25$) for decreased perfusion pressure than for norepinephrine infusions; this could be considered a predisposition for a greater fall in sodium excretion with decreased perfusion pressure, which did occur. This is unlikely because, although the fall was greater, the mean sodium excretion during decreased perfusion pressure was less than during norepinephrine. A statistical approach to this question, using analysis of variance, supports this interpretation. For each of

the two experimental maneuvers, separate linear regression analysis were performed which related the control level to the absolute fall in sodium excretion and also to the relative fall, expressed as percent of control. This analysis showed that the absolute decrease in sodium excretion was probably dependent on the preceding control value, but that the fractional fall was unrelated to control levels. Thus, a larger mean reduction in sodium excretion, which occurred with reduced perfusion pressure, would be expected on the basis of a systematically higher control value but a decrease that was proportionately greater would not be expected on this basis. Therefore, the proportionately greater fall in sodium excretion, to a lower absolute level, is probably not attributable to differences in control values for the two maneuvers.

A similar situation exists for the distribution of renal blood flow between cortical and juxtamedullary regions, A_I (Table 2). Here the control value is slightly higher ($p = .06$) for norepinephrine which produced the greatest fall. Since A_I was significantly lower during norepinephrine than during decreased perfusion pressure, it is unlikely that the greater change in this variable, which is the aspect of the data most descriptive of the degree of redistribution, is due to the slightly higher control value for norepinephrine.

Control juxtamedullary flow rates are also different ($p = .07$) in the two situations but here the interpretation is less straight-forward since the changes are equal with the two maneuvers. This is in contrast to the situation above in which the manipulation with the larger change in A_I was not associated with the larger change in sodium excretion as the intrarenal distribution of flow hypothesis would predict. However, as noted above, it seems unlikely that the equal (not significantly

different) changes in juxtamedullary flow could account for the marked (two-fold) difference in the two changes in sodium excretion. The higher rate of juxtamedullary flow during decreased perfusion pressure is associated with a lower sodium excretion when compared with the corresponding norepinephrine data. Since the glomerular filtration rates are equal, this observation favors the distribution of flow hypothesis. But this is countered by a similar consideration of the data in the two control situations in which, with equal glomerular filtration rates, the higher juxtamedullary flow is associated with the lower sodium excretion.

None of these considerations regarding disparities in control values would seem to affect the conclusion reached above. This is because differences in control values do not appear to explain any of the changes in the variables brought about by either maneuver and it is the changes upon which conclusions regarding the relationship between distribution of flow and sodium excretion depend.

Another point which must be evaluated in the case of norepinephrine infusion is the possible effect that the accompanying rise in blood pressure might have had on sodium excretion. If this rise in pressure had a natriuretic influence, it would have tended to offset the effects of other mechanisms, such as redistribution of flow, which in the absence of a rise in blood pressure, could have led to a lower sodium excretion than was observed. The effect of this 10 mmHg rise in perfusion pressure can be estimated by the sodium excretion in the contralateral kidney which increased significantly by 11 μEq/min with norepinephrine infusion.

If the effect of this rise in blood pressure on the experimental kidney was quantitatively similar, we would surmise that the decrease in sodium excretion due only to the other effects of norepinephrine--reduced glomerular filtration rate and redistribution of blood flow--

would have been greater than was observed by about this same amount. This, however, would account only for half of the 23 μEq/min difference in sodium excretion that was found between the two experimental states. This will not change any of the qualitative aspects of the data and thus would not negate any of the above arguments regarding the relationship between changes in the distribution of flow and changes in sodium excretion.

In addition, the rise in mean sodium excretion of the control kidney is due solely to one aberrant observation; if this were omitted, the average sodium excretion would actually have fallen slightly. The likelihood of a value as aberrant as this particular one in a sample of the size considered is less than one in one thousand. Therefore, it is highly probable that the rise in blood pressure with norepinephrine infusion did not cause a rise in sodium excretion; rather, the increase is due to the occurrence of one spurious observation.

The contralateral kidney in Series I was used as a control for effect of systemically circulating factors on sodium excretion. Mean values for control sodium excretion do differ between kidneys but these differences are not so great as to reflect qualitative physiological differences that would invalidate the use of the contralateral kidney as a control. There are several likely explanations for these differences: the two kidneys may be intrinsically different, the surgical manipulations of the experimental kidney may have had some influence, the differences may have arisen because the data for the two kidneys are different samples since renal function measurements on the right kidney were not done in the earliest experiments.

In the experiments of Series II, there also are slight differences between control values in experimental and control kidneys but again not so great as to indicate different physiological conditions. Also, the small difference in sodium excretion between pre- and post-control suggest a trend over the course of the day but this trend is certainly not of a magnitude to explain the falls during norepinephrine infusion. Also comparing the data during norepinephrine infusion to the mean of pre- and post-control takes such trends into account.

Glomerular filtration rate of the control kidney tends to increase with norepinephrine (the average value was 106% of control, Table 3). Because this increase is associated with a slight decrease in sodium excretion, the question arises whether the fall of three percent in glomerular filtration rate caused by norepinephrine infusion on the experimental side should be compared to the slightly elevated glomerular filtration rate of the control kidney. When the difference in glomerular filtration rates for the two kidneys (experimental minus control) is considered as the variable of interest, the effect of norepinephrine on glomerular filtration rate is to increase this difference an average of 3.9 ± 1.7 SEM ml/min, $p = .04$. This change is larger than the 1.6 ml/min obtained when the decrease in the experimental kidney is compared to its own control values. Whether the former way of comparing glomerular filtration rate bears any relation to the changes in the sodium excretion occurring with norepinephrine infusion in the experimental kidney is difficult to ascertain. Whatever the relationship, it is not a simple one.

One possible interpretation is that these data for the control kidney indicate a tendency for glomerular filtration rate to rise with

a parallel rise in reabsorption and therefore without a concurrent rise in sodium excretion. Norepinephrine may then be thought of as leading to a fall in sodium excretion in the experimental kidney by preventing this rise in glomerular filtration rate while the increase in reabsorption is unaffected.

If this is true, the change in glomerular rate of the control kidney must be associated with norepinephrine infusion rather than another factor occurring over the course of the day such as increases in aldosterone levels, because the trend is not seen when the pre- and post-controls are compared. It is difficult to imagine a systemic effect of norepinephrine infusion that would affect the contralateral kidney; blood pressure was increased during norepinephrine, but by only 2 mmHg. (Also, if one animal with rather large changes in glomerular filtration rate in the control kidney is excluded, the change with infusion in the control kidney will be only one percent of control levels.)

The changes in intrarenal distribution of blood flow in this study agree in general with those reported by others using the inert gas washout method. There are some quantitative aspects which deserve discussion.

Stinson et al. (1969) showed that reduction of renal artery pressure to about 70 mmHg in two anesthetized dogs caused an increase only in the rate of Component II and no change in Component I or the relative distribution of flow between Components I and II. This is the same result as in Series I of the present study except that their absolute values for the two flow rates are considerably higher. Autoradiographs in both studies show that the anatomic distribution of Components I and II is the same in control situations. The authors do not consider the

relationship between distribution of flow and renal function in their discussion.

An interesting aspect of renal artery constriction is the change in total flow per kidney volume as determined by krypton washout which in Stinson's paper was unchanged by renal artery hypotension. In our study, this variable actually increased while the simultaneously measured Doppler flow showed a decrease of 20%. The most probable explanation of this dichotomy is that lowering perfusion pressure causes the kidney to shrink so that the volume of distribution of krypton decreases which leads to a higher krypton total flow per volume. This effect is important if one wants to equate krypton flow per volume to total renal blood flow or extrapolate from changes in flow (or the lack thereof) to changes in glomerular filtration rate.

The redistribution of flow with norepinephrine infusion in Series I is best compared to the similar experiment by Carrière (1968) and the renal nerve stimulations of Pomeranz et al. (1968); the redistributions of flow observed in all three studies are qualitatively the same. There are numerous other studies (Carrière, 1968; Newsome et al., 1971; Kilcoyne and Cannon, 1971; Sparks et al., 1972) which are pertinent in that similar changes in distribution of flow are probably mediated by sympathetic activity; they are, however, more complicated physiological situations and their interpretation less straight-forward.

Carrière infused norepinephrine intra-arterially in six animals at 4 μg/min. This decreased the percent of flow to Component I from 82% to 62% and increased the rate of Component II from 129 ml/min/100 g to 209 ml/min/100 g. Autoradiographic evidence showed that with norepinephrine, part of the cortex was flowing at the slower rate of

Component II. (In other instances, Carrière found "fusion" of Components I and II into a single exponential; this situation will be discussed below.) Component I flow and total flow, determined from the krypton curve did not change; no other estimate of total flow was made.

Pomeranz et al. produced redistributions of flow in anesthetized dogs either by stimulating the splanchnic nerves or through the carotid sinus reflex by bilaterally ligating the carotid artery and all its branches to reduce carotid sinus pressure to zero. The percent of renal flow delivered to the fastest component (A_I) decreased from control values of 90% to 60% with carotid occlusion and to 48% with splanchnic nerve stimulation. Component I flow rate was slightly lowered. Component II flow increased from 125 ml/min/100 g to 230 ml/min/100 g with carotid occlusion and to 210 ml/min/100 g with splanchnic stimulation. There were no independent measures of flow in these experiments.

The redistributions of flow in both Carrière's and Pomeranz's work were of greater magnitude than in the current study although there were no qualitative differences. One might wonder, therefore, whether they are comparable to the present study. It might be that redistribution of flow could have an effect on sodium excretion but that this becomes manifest only in situations with a more dramatic redistribution of flow than was obtained in our study. Unfortunately, sodium excretion was not measured in either of their experiments and so we do not know what the changes in this variable would be.

The quantitative discrepancy might be due to several factors. In Carrière's study, it is likely that experimental artifact may have affected measurement of distribution of flow. When vasoactive drugs are infused by the same catheter through which the bolus of krypton is

injected, a slug of drug can be introduced into the kidney at the same time as the krypton curve is begun and cause a flow transient during the early and most important part of the curve. As happened several times in our preliminary studies, a slug of norepinephrine can cause a substantial drop in flow (approximately 50%) that lasted approximately 60 seconds. An example of such a transient is shown in panel A of Figure 11. The flow record in panel B, taken from the same experiment, also during continuous norepinephrine infusion, shows no injection artifact. These transients of low flow result in krypton washout curves that would indicate a more marked degree of redistribution than was actually present during the steady state of the infusion (Mowat et al., 1972). That one half of Carrière's norepinephrine curves showed fusion in which Components I and II were represented by a single exponential with intermediate flow rate of 309 ml/min/100 g, increases the likelihood of these artifacts since fusion is the extreme case of this phenomenon. Also, Pomeranz's data for animals without an infusion and those of the present study in which the Doppler flow meter allowed us to reject cases with large flow transients never showed fusion. If transients of this nature do exist in Carrière's data, comparison with the present data would be inappropriate. Large volumes of cold solutions injected into the renal artery can also cause flow transients which cause a similar problem even when vasoactive drugs are not used (Mowat et al., 1972). The volume injected in the studies by the authors cited should not affect flow, but in the absence of a dynamic measure of flow, this is not certain.

In Pomeranz's study, the stimulus for renal vasoconstriction was probably much more profound than was the infusion of norepinephrine in our study since carotid sinus pressure was reduced to zero. Also the

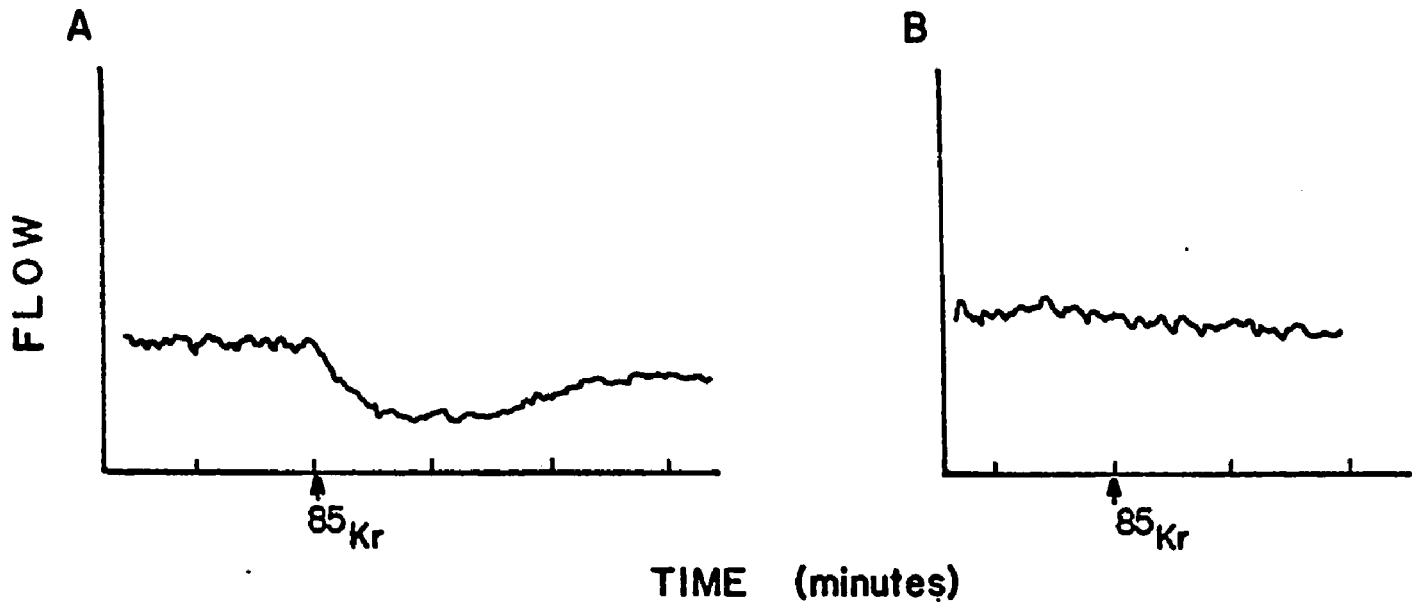


Figure 11. Flow transients resulting from accidental injection of norepinephrine concurrently with ^{85}Kr injection. Shown are flowmeter records of injections during intra-arterial infusions of norepinephrine. The transient decrease in flow (panel A) is due to drug contained in the dead space of the catheter; careful injection techniques (panel B) prevent this.

dog was bled into a reservoir to keep arterial pressure constant which would prevent buffering of sympathetic activity by aortic baroreceptors by blocking the reflex rise in blood pressure. Splanchnic stimulation also must have constituted a strong stimulus. The stimulation rate was 10 per second--near the physiological maximum for renal sympathetic nerves (Johannson et al., 1969). This degree of stimulation, applied to only a portion of the sympathetic efferents, was sufficient to raise the mean arterial blood pressure an average of 20 mmHg in dogs with intact baroreceptor systems. If the more drastic changes in distribution of flow in Pomeranz's study are the result of these much stronger stimuli, the quantitative differences in redistribution of flow may be appropriate.

There are two technical points which bear on the difference between the distribution of flow data of Series I and those of the other studies cited. The first point deals with the method of curve analysis. Carrière and Pomeranz, indeed, virtually all previous studies using the krypton method, employed graphical "peeling" techniques rather than the mathematical analysis used here. In a recent paper on the analysis of washout curves, Dell (1973) compares the results of graphical and mathematical techniques from 13 control curves in dogs and shows that the results can differ for particular parameters. He does not, however, give data comparing the two methods in evaluating changes in distribution of flow produced by experimental methods; this would be useful in considering the source of quantitative differences between various studies. This point is of more than just passing interest because of the weakness of the peeling technique (Dell, 1973; Riggs, 1963); this graphical method has limited power of resolution, has no criteria to assure the "best fit" and, most of all, the method is subjective in its most critical aspects.

The second point has to do with hydration of the experimental animals. The dogs in Series I received about 200 ml of saline at the beginning of the day and an infusion of 2 to 3 ml/min which was necessary to stabilize renal function over the several hours of an experiment. In contrast, Carrière's dogs received only an infusion of one ml/min and Pomeranz's animals, no fluids. It would not be surprising if this variation in the degree of hydration leads to quantitative changes in the parameters of the krypton curves since our infusions are sufficient to increase glomerular filtration rate 34% and sodium excretion several-fold when compared to the relatively low levels preceding the fluid administration. Also, changes due to experimental interventions might be blunted by hydration. Interestingly, the dogs of Series II received less saline at the time of surgery and had control values for k_{II} comparable to those of Carrière and Pomeranz.

To argue against the results of Pomeranz on the basis that the changes are too profound to be of physiological importance is perhaps specious. Such changes may be important in mediating the renal compensations in stressful or pathological situations. Hollenberg (1970) has shown in humans that lowering sodium intake from 200 to 10 μEq/day causes a redistribution similar to that seen by Pomeranz. Sparks et al. (1972) have shown a significant redistribution of flow in the established phase of experimental heart failure in dogs when ascites is present.

Despite these contrasts we have emphasized between our results and those of Carrière and Pomeranz, the results are more similar than not, particularly in regard to the changes produced by the experimental maneuvers upon which our arguments are based. Indeed, the differences

may well be accounted for by differences in hydration, severity of experimental intervention and techniques of curve analysis.

Recently radioactive microspheres have been used to estimate the distribution of flow within the renal cortex (McNay and Abe, 1970; Slotkoff et al., 1971). It is interesting to compare this technique to the inert gas washout method both from the viewpoint of differences in the methods themselves and differences in the results obtained with various experimental maneuvers.

In the microsphere method, the distribution of flow within the cortex is estimated by the distribution of radioactive, plastic microspheres which are injected into the arterial blood and subsequently trapped in the glomerular capillaries or afferent arterioles. Changes in the distribution of blood flow with different experimental maneuvers are estimated by using different isotopic labels on the 15 μ microspheres. The radioactivity per gram of tissue is determined at each of several levels of the cortex from capsule to medulla by slicing samples of the cortex into a number of layers. The resulting relative distribution of radioactivity is taken as a measure of the relative distribution of blood flow. If a separate measure of total flow is made, the regional flows can be expressed in ml/min/100 g.

There are several criteria which must be met for the microsphere method to be considered a true indicator of regional blood flow. First, they must be uniformly concentrated in the arterial blood; this is accomplished by injecting them into the left ventricle. Second, they must be totally extracted from the arterial blood in the first transit through the kidney. This is true for microspheres 15 μ or larger in

diameter (Slotkoff et al., 1971). Finally, their hemodynamic behavior must mimic that of blood; this means microspheres must not be subject to skimming phenomena which would lead to some glomeruli being perfused by blood with different concentrations of microspheres despite adequate mixing in the larger arteries. Since it is well known that red cells undergo axial streaming, this is a critical point in the behavior of the much larger microspheres.

Some authors have approached this important question by determining whether the distribution of flow is a function of microsphere size (McNay and Abe, 1970; Katz et al., 1971) or density (McNay and Abe, 1970). No statistical differences have been demonstrated although there are trends in the data that suggest that there may be some degree of skimming. Also, it might be the case that microspheres of different sizes are not skimmed relative to one another, but are skimmed relative to red cells or plasma. This is admittedly a difficult question to approach experimentally, but one which ought to be considered.

With the above constraints and cautions, the microsphere method appears to be a valid, workable one for estimating intracortical blood flow. It appears internally consistent in that the same results are obtained by different investigators. How closely it comes to being an ideal indicator of distribution of flow remains an open question. (The same might be said of the inert gas method.)

The microsphere technique differs in several respects from the inert gas method. First, since the microspheres lodge in or proximal to the glomerulus, they measure only cortical flow and cannot directly estimate the medullary flow which is derived from the post-glomerular vessels of the inner cortex. The inert gas method does provide an

estimate of this flow since the clearance of tracer is determined by the capillary flow in peritubular capillaries or the vasa recta. Because flow in the outer medullary region is a major aspect of the hypothesis relating redistribution of flow to sodium excretion, both in terms of the pattern of redistribution reported using inert gas clearance and in terms of proposed underlying mechanisms, it is crucial that a method used to test this hypothesis be able to provide data bearing on this point.

One might assume that changes in medullary flow parallel those of the inner cortex; this may not be too extreme an assumption since medullary flow is derived from the glomerular blood flow of this region. On the other hand, the proportion of flow from inner-cortical glomeruli which enters the vasa recta of the outer medulla may change relative to that perfusing the peritubular capillaries. Differences in the rates of flow in these two regions might be apparent in ^{85}Kr clearance curves but would definitely be missed with the microsphere method.

Another difference is that microspheres measure flow in discrete areas of the cortex while with the inert gas method, all areas of flow of comparable rate are represented in a single component. This, coupled with the fact that the two methods do not measure the same portions of the kidney, makes quantitative comparisons of the two methods difficult.

Investigators who have compared these two methods (McNay and Abe, 1970; Slotkoff et al., 1971; Katz et al., 1972) have considered these contrasts. Neither method has been shown to invalidate the other, nor has one answered concerns regarding the methodological shortcomings of the other.

The pattern of flow in the normal or control state is roughly the same with both methods. With microspheres, the outer portion (two-thirds or three-fourths) of the cortex has a high rate of flow comparable to that of the rapid component of the ^{85}Kr clearance curves. The innermost part of the cortex has a slower rate similar to that of Component II of the ^{85}Kr curves (Stein et al., 1971; McNay and Abe, 1970; Katz et al., 1971; Slotkoff et al., 1971).

However, when changes in distribution of flow occurring with various experimental maneuvers are compared, the two techniques often show qualitatively different patterns of redistribution. We shall consider those studies relating most closely to the maneuvers employed in the present study.

Using microspheres, McNay and Abe (1970) studied the effect of reducing renal perfusion pressure to the lower limit of autoregulation (77 mmHg). This caused an inward redistribution of flow with about 12% of the total renal flow shifting from the outer one-fourth of the cortex to the inner half where the flow rate was approximately doubled. This is a much more marked change in distribution than was found in the present study and in that of Stinson et al. (1971) in which the only change was a smaller (about 40%) increase in the rate of juxtamedullary flow without shifts of appreciable percentages of the total flow.

With acetylcholine infusion, both the inert gas and microsphere methods show the same pattern of redistribution as they do when perfusion pressure is decreased. Stein et al. (1971) showed with microspheres that flow in the inner cortex increased proportionately more than total kidney flow. Carrière et al. (1971) using the krypton method found that only cortical flow rate was increased with no significant change in other

aspects of krypton clearance. The common aspect of these four studies is that microspheres show redistribution with decreases in vascular resistance while the inert gas method does not.

The effect of norepinephrine infusion, the second experimental maneuver used in this study, has been studied with microspheres by Rector et al. (1972). In contrast to the ^{85}Kr data of the present study and of Carrière (1968), no redistribution of flow was found.

In a related though more complex situation, hemorrhagic hypotension, both techniques demonstrate an inward redistribution; microspheres show that inner cortical flow is relatively well preserved (Logan et al., 1971; Rector et al., 1972); the krypton method shows an increase in juxta-medullary flow (Carrière et al., 1966). Stein et al. (1973) have also considered, using microspheres, the particular aspect of hemorrhage that is responsible for the redistribution of flow. They found that when the renal perfusion pressure was lowered to levels found during hemorrhage, intracortical flow was shifted in the manner seen with hemorrhage; with subsequent hemorrhage while maintaining perfusion pressure at the lowered value, there was no further redistribution. This points to the reduced pressure as the important aspect of hemorrhage rather than the changes in sympathetic activity. Other microsphere data cited above also suggest this interpretation. From the available inert gas data, it appears that a similar study would show the cause of redistribution to be the reflex sympathetic adjustments (Pomeranz et al., 1971; Carrière, 1968; the present study) rather than the hypotension (Stinson et al., 1971; present study). Therefore, agreement of these two methods regarding the patterns of redistribution with hemorrhage may be reflections of two different aspects of a complicated situation.

When all the data for these several experimental manipulations are considered, there is little concurrence between the redistribution of cortical flow as indicated with microspheres and that of renal blood flow found with the inert gas technique. It is interesting that the microsphere method, in general, shows changes in distribution of flow in states of decreased vascular resistance, but not increased vascular resistance, while the converse seems true for the inert gas method. That the redistributions of flow seen with separate methods appear to be mediated by different mechanisms, suggests that they may not measure the same thing. Thus, their incompatibility is probably because the two methods are not, even in theory, reflections of the same phenomena and therefore should not be expected to give the same answers.

There are several likely sources of this incompatibility. The increased rate of juxtamedullary flow sometimes seen using the inert gas method might be an artifact resulting from the averaging of similar flow rates into a single component. Autoradiographs prepared during norepinephrine infusion (Carrière, 1968; present study) and renal nerve stimulation (Pomeranz et al., 1968) show patches of cortex in which flow is appreciably lower than control levels. These areas are assigned to Component II which shows an appropriate increase in its volume of distribution in these situations. It could easily be that the rate of flow in these patchy areas in intermediate between that of the outer cortical and juxtamedullary cortical rates in the control state. Therefore, juxtamedullary flow could be increased, decreased or unchanged by these interventions, yet appear increased in ^{85}Kr curve analysis because it is averaged with the flow in the cortical areas of reduced flow. That juxtamedullary flow is relatively well preserved in such situations

is clear from the autoradiographic evidence; whether it is increased absolutely is open to question.

A further complicating aspect of krypton clearance is that the tracer is trapped by the countercurrent system of the outer medulla which slows its clearance. This gives a measure of an "effective" flow which is too low and a volume of distribution that is correspondingly overestimated. The relationship between volume flow and krypton clearance in this region may be such that changes in flow that are not apparent in the inner-cortical glomerular flow (measured by the microsphere method) would be apparent in the inert gas washout. Despite the difficulty of interpretation when countercurrent trapping is present, the inert gas method provides useful information since the renal handling of salt and water in the outer medulla is dependent on the efficacy of the countercurrent system.

One other point about the inert gas method is that occasionally experimental maneuvers will produce statistical differences in some parameters of some of the washout curves but not in certain other ones. This is troublesome because of the necessary mathematical relationship between parameters that results from viewing the kidney as a four compartment model. The corresponding changes must naturally occur, but they may be small and not statistically significant because of the degree of variance. When this occurs, as in the present study, in which the only significant change with reduced perfusion pressure is an increase in the rate of flow in Component II, a precise definition of the redistribution which occurred is difficult.

Another source of these incompatibilities is a possible change in the behavior of the microspheres in various experimental situations.

If the skimming phenomenon discussed above exists to any significant extent, changes in the degree of skimming could appear as redistribution of flow. Changes in vascular dimensions, pressures, or velocities could cause changes in skimming, for example, by causing laminar flow to become turbulent. The renal vasculature is complex and it is not easy to predict the effects of experimental interventions on these aspects of microsphere behavior. The question of skimming of microspheres in experimental situations has not been studied as thouroughly as in the control state. For that matter, completeness of trapping of spheres when the vascular bed is dilated has apparently never been evaluated.

Whatever the source of the discrepancy between the microsphere and inert gas methods, there is probably useful information to be gained with both techniques. Certainly, neither method invalidates results obtained with the other. It may be that these methods are reflections of different aspects of renal blood flow, the precise natures of which need to be further elucidated.

One additional aspect of the experiments reported here that deserves attention is the mechanism(s) governing those reductions in sodium excretion which were not explained by the data obtained. These are the reductions occurring with the low dose of norepinephrine (Series II) and that portion of the large fall in sodium excretion during reduced perfusion pressure which may not be attributable to the change in glomerular filtration rate. (One possibility which is ruled out by these data is a circulating "natriuretic" hormone; the lack of changes in sodium excretion in the control kidney eliminate this currently popular mechanism.)

One mechanism which might explain the norepinephrine result of Series II is a direct action of the catecholamine on the tubular epithelium. Gill and Casper (1971, 1972) provide some evidence for such a direct effect of adrenergic agents on the proximal tubule. Their experiments were done on acute, hypophysectomized dogs undergoing water diuresis; in this preparation it is assumed that urine volume represents the volume of tubular fluid delivered from the proximal nephron and indicates the degree of proximal reabsorption of glomerular filtrate. With this technique they conclude that isoproterenol infused intra-arterially into the alpha blocked kidney depresses proximal reabsorption and conversely, norepinephrine in the beta blocked kidney increases reabsorption. The actual changes they observe are small (a few percent) when considered as changes in the portion of glomerular filtrate that normally escapes reabsorption proximally. They argue against these agents acting through a hemodynamic mechanism because hemodynamic changes were small and not statistically significant.

It is difficult to say how closely these studies relate to more physiological situations. Stein (1972) studied the effect of isoproterenol on proximal reabsorption of hydropenic dogs using micropuncture techniques and found no effect except at doses that also caused changes in blood flow and glomerular filtration rate. It seems that if there is a direct tubular effect of catecholamines, it is small and probably unimportant when compared to their influence on sodium excretion which is mediated by their hemodynamic actions.

A mechanism more likely to be responsible for the unexplained changes in sodium excretion is a change in some physical factor which, in part, determines sodium reabsorption. This physical factor hypothesis,

first suggested by Early and Friedler (1965) and Lewy and Windhager (1968), can explain the increased reabsorption of sodium seen with reduced perfusion pressure and possibly that occurring with the low dose of norepinephrine in Series II. The theory considers the tubular reabsorption of salt and water as two processes in series. First, tubular fluid is reabsorbed into the interstitium by an active process of transepithelial transport; this is an example of Diamond's standing gradient model in which water and solute transport are coupled through the functional porperties of the lateral intercellular spaces (Diamond, 1964). Second, the balance of hydrostatic and colloidal osmotic forces across the capillary barrier determines the movement of this reabsorbed tubular fluid from interstitium to peritubular capillary blood according to the Starling-Landis hypothesis.

Physical factors are thought to change sodium reabsorption by initially changing the balance of Starling forces. Thus alterations in perfusion pressure, vascular resistances, and filtration fraction can all change the net movement of fluid into the peritubular capillary. In order for such changes to result in a change in overall tubular sodium reabsorption, they must also lead to changes in sodium movement across the tubular epithelium. These fluxes must be equal because they are arranged in series; if they are unequal, only transient changes in capillary reabsorption would occur and these are limited by the capacity of the renal interstitium to absorb or supply fluid to maintain capillary reabsorption at a rate different than that of the tubular epithelium.

It becomes apparent that the interstitium is a key part of the physical factor hypothesis since it is common to both fluxes; physical factors in the interstitium in effect serve to "couple" the transport

of water and solute across these two barriers. Since fluid reabsorbed across the capillary barrier is not changed in its composition of electrolytes, changes in Starling forces can only lead to changes in hydrostatic pressure and colloid osmotic pressure of the interstitial fluid; the tubular epithelium must therefore be capable of responding to these changes by altering the net flux of sodium and water for net changes in tubular reabsorption to occur. Earley et al. (1972) suggest a plausible modification of Diamond's original standing gradient model which shows this dependency. They propose that increased interstitial hydrostatic pressure distends tight junctions and permits diffusion of sodium from the intercellular spaces to the tubular lumen leading to natriuresis.

There is a growing body of evidence, both from micropuncture and from whole kidney studies, that indicates the physical factor hypothesis is a workable one. Brenner and Troy (1971) have shown that when peritubular capillaries of the rat kidney are perfused with hyper- or hypo-oncotic solutions, reabsorption from adjacent tubules is increased or decreased respectively. A very enlightening study that gets to the crux of the matter and which bears directly on the results of the present study is the measurement of renal interstitial pressure made by Ott et al. (1971). Using Guyton's implanted capsule technique for direct measurement of interstitial pressure, they determined the response of renal interstitial pressure to changes in arterial and venous pressure in dogs. They found that 3% of a decrease in arterial pressure, over the range of 140 to 50 mmHg, was transmitted to the interstitial fluid. This change probably occurred as a result of changes in Starling forces at the peritubular capillary. The work of Gazitua et al. (1969) showing that small vein pressure falls with decreased perfusion pressure supports this.

In our study, a similar decrease in interstitial pressure should have resulted from the fall in perfusion pressure. This experimental maneuver was associated with a large decrease in sodium excretion which was only partially explained by changes in glomerular filtration rate. This finding is consistent with the physical factor hypothesis as outlined above. That these changes in sodium excretion are of a physiologically important magnitude suggests that the role of physical factors in determining sodium reabsorption may be of major importance.

Physical factors may also play a role in the response to the low dose of norepinephrine where there were not large changes in overall renal hemodynamics. It is conceivable that this dose of norepinephrine caused changes at the level of the peritubular capillary that were too small to be reflected in the measurements made, yet could significantly alter sodium excretion.

The experiments described in this dissertation were designed to test the hypothesis that intrarenal distribution of blood flow is an important determinant of sodium excretion. This hypothesis is based on the observation that a common pattern of redistribution of flow to the deeper region of the kidney is present in several situations characterized by reduced sodium excretion. The present experiments are an attempt to determine whether this relationship holds when other determinants of sodium excretion, particularly glomerular filtration rate, are taken into consideration.

In one series of experiments, the reductions of sodium excretion accompanying either an intrarenal infusion of norepinephrine or a decrease in renal perfusion pressure were compared; these two maneuvers caused

equivalent reductions in glomerular filtration rate. Norepinephrine caused a significant redistribution of flow while decreased perfusion pressure did not. This redistribution of flow was not associated with a greater reduction of sodium excretion as the hypothesis would predict. In fact, decreasing perfusion pressure, which did not redistribute flow but which lowered glomerular filtration rate equivalently produced a significantly lower sodium excretion.

In a second series of experiments, a smaller dose of norepinephrine was used to see whether sodium excretion could be reduced and flow redistributed without changes in glomerular filtration rate. However, the lower dose reduced sodium excretion with a minimal fall in glomerular filtration rate and no change in the distribution of flow. Thus, it does not appear possible to produce changes in distribution of flow without concurrent changes in glomerular filtration rate.

In this study, alterations in the intrarenal distribution of flow were not associated with reductions in sodium excretion that were not more readily attributable to changes in glomerular filtration rate. It is concluded that intrarenal distribution of blood flow is not an important determinant of sodium excretion in the acute, anesthetized dog.

Finally, we have not yet considered the role of redistribution of blood flow in the chronic, long-term regulation of salt and water balance which is, after all, a physiologically more appropriate time frame in which to consider renal function. Little work has been done in this area but there are suggestions that changes in distribution of flow may be involved in such adjustments. (Curiously, no one has done the seemingly obvious experiment of chronically feeding animals different amounts of sodium and seeing whether there is a difference in the

distribution of flow.) Hollenberg et al. (1972) studied the time course of changes in flow distribution associated with sudden restoration of sodium balance following salt depletion in humans and found that it took at least two days for the pattern of flow distribution to return to normal.

Studies of congestive heart failure in dogs provide another example of long-term changes. When tricuspid insufficiency is produced in the dog, there is a transient redistribution of flow in the familiar manner which has returned to normal within a month. During this time, the animal has retained salt and water and come into positive sodium balance, but at the end of the month is in a new steady state in which renal excretion balances dietary intake (Sparks et al., 1972).

This is a very provocative observation and stimulates one to study the role of redistribution of flow in the control of sodium balance over longer time spans, taking into account concurrent changes in glomerular filtration rate, levels of aldosterone, and systemic hemodynamics. Such studies would provide interesting and useful information on pertinant phenomena which cannot be adequately considered in studies on acute experimental animals.

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