Effect of Hematocrit and Colloid-Induced Changes in Blood Viscosity on Renal Hemodynamics and Renin Release in the Dog

By Keith M. McDonald

ABSTRACT
This study compared the effects on the kidney of two major determinants of blood viscosity, the hematocrit and the plasma colloid content. In anesthetized dogs, blood viscosity was raised 30% by increasing hematocrit or infusing isoncotic Dextran 500 while blood volume was kept constant. Neither form of hyperviscosity altered blood pressure, but both forms caused a decrease of about 35% in cardiac output and a comparable rise in total peripheral resistance. Renal blood flow decreased minimally (<10%) in the group of dogs with increased hematocrit but fell more than 30% in the group given Dextran 500. Reciprocal changes occurred in renal vascular resistance. The increase in hematocrit was accompanied by an increase in renin secretion from 146 units/min to 416 units/min (P<0.001), but Dextran 500 caused a decrease from 167 units/min to 107 units/min (P<0.025). Sodium and potassium excretion both decreased similarly in the two groups. The data suggest that increased hematocrits are accompanied by renal vasodilatation so that renal vascular resistance rises less than blood viscosity. Dextran hyperviscosity, however, causes no compensatory vasodilatation. This difference in renal vascular response might explain the difference in renin secretion; afferent arteriolar dilatation might stimulate renin release during a rise in hematocrit, and the absence of vasodilatation in colloid hyperviscosity might explain its failure to stimulate renin.

KEY WORDS
plasma colloid hyperviscosity sodium excretion blood rheology dextran systemic hemodynamics

One of the well-documented responses to renal artery constriction is an increase in renin secretion by the kidney (1, 2). This observation implies that the mechanisms controlling renin secretion are responsive to changes in renal vascular resistance, although how the response is mediated is still a source of controversy (3, 4). Blood vessel diameter is of prime importance in determining flow resistance, but another determinant, blood viscosity, also contributes significantly to resistance, as predicted by the Poiseuille equation. The question arises, therefore, whether changes in blood viscosity might also influence renin secretion.

Whole blood viscosity is determined chiefly by the hematocrit and the colloidal components of plasma (5). In a recent preliminary report, McDonald and Smith (6) have shown that an acute rise in hematocrit in the dog results in an increase in renin secretion. The present study was designed to examine the mechanisms mediating this response and to compare it with the effects of colloid-induced hyperviscosity. In one group of dogs the hematocrit was increased, and the magnitude of the resulting rise in blood viscosity was measured by cone-plate viscometry. In another group of dogs similar changes in viscosity were produced by infusing high-molecular weight dextran, while blood volume and hematocrit were kept constant. This procedure allowed a comparison to be made between the effects of hematocrit-induced and colloid-induced changes in blood rheology on renin secretion, renal hemodynamics, and sodium excretion.

Methods
Mongrel dogs of either sex (12–18 kg) were allowed water but no food for 18 hours before the experiments. Anesthesia was induced with sodium pentobarbital (30 mg/kg, iv). Additional small doses were given as required to maintain light anesthesia during the experiment. Respiration was controlled by a mechanical respirator attached to an endotracheal tube.

Both ureters were cannulated through a midline incision, and polyethylene catheters were placed in one or both renal veins. The left renal vein was catheterized through the left gonadal vein, and the right renal vein was catheterized with a specially moulded catheter passed retrograde from the left femoral vein. Arterial blood pressure was monitored continuously.
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through a femoral artery catheter attached to a Statham transducer and recorded on a Grass multichannel recorder. Mean pressures were calculated electronically.

When the surgical preparation was complete, the dog was given a loading infusion of isotonic saline (10 ml/kg, iv) over a period of 20 minutes. The infusion was then slowed to a rate of 4-6 ml/min and kept constant for the remainder of the experiment. After the saline infusion had been established, a loading intravenous dose of creatinine was administered and a constant infusion of creatinine and para-aminobiphenyl (PAH) was initiated at a rate sufficient to produce plasma concentrations of these substances appropriate for clearance measurements. At least 45 minutes was allowed for equilibration and establishment of a steady urine flow. Then a series of control clearance periods was measured.

Each period was timed exactly, and the average duration was 15 minutes. Urine was collected from the ureteral catheters into separate graduated tubes. A 7-ml sample of blood was drawn from the arterial catheter and from one of the renal vein catheters at the midpoint of each period. When only one renal vein was catheterized, a sample was drawn from it in each period. When both were catheterized, each was sampled in alternate periods.

In most experiments, four control periods were obtained. All blood and urine samples were analyzed for sodium, potassium, creatinine, and PAH. In the second and fourth control periods, blood samples were also drawn for renin determinations. Blood (12 ml) for renin assay was drawn from the arterial and renal venous catheters into chilled heparinized syringes and transferred to test tubes standing in crushed ice. The plasma was immediately separated by centrifugation at 4°C and frozen. The volume of blood sampled was replaced by infusing an equivalent amount of "reconstituted blood," which consisted of packed red cells freshly obtained from a donor dog and suspended in either normal saline or plasma previously harvested from the experimental dog.

In the final control period, whole blood viscosity and plasma viscosity were measured in a 1.5-ml sample of fresh heparinized arterial blood kept at 37°C. Viscosity measurements were performed using a cone-plate viscometer (Wells-Brookfield microviscometer) (7) at shear rates of 230, 115, 46, 23, and 11.5 sec⁻¹.

At the end of the final control period one of four types of exchange transfusion was performed depending on which protocol was being followed.

PROTOCOLS

Increased Hematocrit Group.—Packed red blood cells were obtained immediately before each experiment by exsanguinating a donor dog into plastic blood bags containing acid citrate dextrose (ACD) anticoagulant. The cells were separated by centrifugation in a Sorvall RC-3 centrifuge at 4°C and warmed to 37°C in a water bath just before the exchange transfusion. In some experiments donor dogs were selected by cross-matching their blood with that of the prospective experimental dogs. This procedure proved unnecessary, presumably because naturally occurring isoantibodies are very weak in the dog (8). The packed cells were washed repeatedly with sterile saline in several experiments, but no detectable difference in experimental results occurred. The exchange transfusion was conducted by infusing the packed cells with a 50-ml plastic syringe into a short, wide-bore catheter in a jugular vein. Simultaneously, an equivalent volume of whole blood was withdrawn from the femoral artery catheter at the same rate at which the packed cells were being infused. The exchange was continued until the hematocrit had risen approximately 15% above the control value. The average volume of packed cells infused was 400 ml over an average time of 20 minutes.

Decreased Hematocrit Group.—The hematocrit was reduced an average of 15% by an isovolemic exchange transfusion in which the infusate was the dog's own plasma harvested by multiple bleedings over a 2-3-week period before the experiment. At each bleeding 100-200 ml of whole blood was withdrawn from the unanesthetized dog into sterile blood bags containing 20 ml of ACD anticoagulant. The plasma was separated and immediately frozen. The red cells were suspended in an equal volume of sterile isotonic saline and infused back into the dog. When 400 ml of plasma had been accumulated, the dog was left undisturbed for at least 1 week before the experiment was performed. The experimental protocol was identical to that for the group with increased hematocrit except that the infusate was the dog's own plasma rather than homologous red cells. Before the plasma was infused, it was filtered through glass wool to remove fibrin clots which occasionally appeared after thawing. Creatinine and PAH were added to the plasma to provide concentrations similar to those in the circulating plasma. Samples were saved for measurement of viscosity, protein concentration, and renin activity. The average volume of plasma infused in the exchange procedure was 350 ml over a period of 20 minutes.

Dextran 500 Group.—The infusate consisted of a 5.4% (w/v) solution of Dextran 500 (i.e., mean molecular weight 500,000) in normal saline. This concentration was estimated to be isoncotic with normal dog plasma by calculations shown in Appendix 1. The isoncotic Dextran 500 solution was infused through a femoral vein catheter with a 50-ml plastic syringe. At the same time that the Dextran 500 solution was being infused into a femoral vein, packed cells were infused through a jugular vein catheter. These packed cells were prepared in the same way as were those used in the group with increased hematocrit. The ratio of Dextran 500 solution to packed cells was adjusted to correspond to the hematocrit of the experimental dog. The exchange was continued until the whole blood viscosity measurements had risen by an amount approximating the increment produced by a 15% rise in hematocrit. The average volumes of Dextran 500 solution and packed cells infused were 200 ml and 150 ml, respectively, over a period of 20 minutes.

To determine whether significant changes in plasma volume occurred as a result of the Dextran 500 exchange procedure, plasma volume was measured before and after the exchange, using 125I-labeled human serum albumin.

Sham-Exchange Group.—Two types of control exchange procedures were performed. In five dogs the exchange consisted simply of removing a 25-ml sample of
blood from a femoral artery and reinventing it immediately into a femoral vein. The procedure was repeated until a total volume of blood similar to that involved in the three test groups had been exchanged, i.e., approximately 400 ml. In another three dogs the exchange was conducted with reconstituted blood as the infusate. This reconstituted blood consisted of washed red cells obtained immediately before the experiment from a donor dog and suspended in plasma harvested in small samples from the recipient dog over a 2-3-week period prior to the experiment as described for the group with decreased hematocrit. The hematocrit of this reconstituted blood was adjusted to correspond to that of the recipient dog at the time of the experiment.

Following each type of exchange procedure, 15–30 minutes was allowed for equilibration and then the 15-minute clearance periods were resumed. At least three postexchange periods were measured. Blood and urine samples were obtained and analyzed as they were in the preexchange periods. Blood for renin assay was obtained in the first and third postexchange periods. The blood and plasma viscosity measurements were repeated after the second postexchange period.

**Cardiac Output Studies.**—Serial cardiac output determinations were performed on five dogs before and after the exchange procedure described for the group with increased hematocrit and in another five dogs undergoing the Dextran 500 exchange. Indocyanine green dye was injected into the right atrium in amounts of 1.0–1.5 mg. Arterial dye concentration was detected with a Waters dichromatic densitometer (MD-4 Module with XC-302 cuvette) in blood drawn from the aortic arch and was recorded on a Waters 447 oscillograph. The densitometer was calibrated with each dog’s blood both before and after the exchange procedure. Dye concentrations of 5 and 10 mg/liter were used for the calibrations. No change in the sensitivity of the densitometer was noted over the range of hematocrits encountered in the group with increased hematocrit; this finding is in agreement with that of Cropp (19) with respect to the Waters dichromatic densitometer. Calibrations before and after the Dextran 500 exchange also showed that no change in sensitivity resulted from the presence of the high-molecular weight dextran in the blood.

**ANALYTICAL PROCEDURES**

Urine and plasma concentrations of PAH were measured by the method of Bratton and Marshall (10), creatinine was measured by the method of Hare (11), and sodium and potassium were measured by flame photometry. Hematocrit measurements were done in duplicate by the microcapillary method.

Plasma renin activity was measured by the method of Skinner (12). The incubated plasma was sampled at least three times at appropriate intervals for up to 48 hours. The angiotensin concentration of the samples was assayed in pentolinium-treated rats using the bracket assay technique (13) with synthetic angiotensin II (Ciba) as the standard. The addition of Dextran 500 to plasma in vitro had no effect on the velocity of generation of angiotensin. From the statistical evaluation proposed by Hosie et al. (14), the smallest detectable difference between the renin activities of two samples was 15%. This degree of precision was adequate for measuring renal venoarterial differences in plasma renin activity in almost all pairs of samples. In some of the Dextran 500 experiments plasma renin “concentration” was measured by the method of Skinner (12) with renin substrate prepared from nephrectomized sheep plasma.

**Calculations**

Exogenous creatinine clearance was used as a measure of glomerular filtration rate. Renal plasma flow (RPF) was calculated from PAH clearance (C\textsubscript{PAH}) and the PAH extraction ratio (E\textsubscript{PAH}) according to the formula: \( RPF = C_{PAH} \times \frac{E_{PAH}}{Q} \). Renal blood flow (RBF) was calculated from the formula: \( RBF = \frac{RPF}{1 - \text{hematocrit}} \). Renal vascular resistance was calculated by dividing mean arterial blood pressure by renal blood flow. Renin secretion rate was calculated for individual kidneys by multiplying the venoarterial difference in renin activity by the renal plasma flow. Plasma renin activity in the arterial and venous samples was expressed as ng angiotensin/ml plasma hour\(^{-1}\) incubation. However, when expressing renin secretion rate, these units became awkward since they had to be divided by renal plasma flow (ml/min). Renin secretion rate was, therefore, expressed as renin units/min. One renin unit was defined as the concentration of renin required to generate 1 ng of angiotensin in 1 ml of plasma during 1 hour of incubation at 37°C.

Means ± se were calculated for the control and the postexchange data for all variables. All P values were based on paired Student’s t-tests, and values in the control and the postexchange period in each dog were treated as paired data.

**Results**

**Sham-Exchange Group.**—Data for eight dogs undergoing the sham-exchange procedures are shown in Table 1. Each value shown for the preexchange and postexchange periods in this table and the following tables represents a mean of two to four periods. In the first five dogs (Table 1, Sham), the exchange consisted simply of withdrawing blood in 25-ml samples from a femoral artery and immediately reinventing it into a femoral vein. The only variables which showed a significant change after the exchange were the plasma protein concentration and the urinary sodium excretion. Both these changes were slight, and they can be explained by the moderate degree of saline loading during the experiment. Systemic blood pressure remained constant as did the various parameters of renal hemodynamics. There was a slight but insignificant decrease in renin secretion. Mean arterial plasma renin activity rose slightly from 4.54 ± 1.3 ng/ml hour\(^{-1}\) before the exchange to 5.30 ± 1.7 ng/ml hour\(^{-1}\) after the exchange, and renal venous hemodynamics remained unchanged.
plasma renin activity rose from 6.48 ± 1.3 ng/ml hour⁻¹ to 6.82 ± 1.6 ng/ml hour⁻¹. Neither of these increases in plasma renin activity was significant, the P values derived from the paired t-test being > 0.1 and > 0.2, respectively.

In the second sham-exchange group (Table 1, Sham Reconstituted Blood) consisting of three dogs, the sham-exchange procedure was performed using reconstituted blood as the infusate. In this group, none of the measured variables changed significantly. Renin secretion rate was almost constant. Mean arterial plasma renin activity before the exchange was 8.0 ± 3.2 ng/ml hour⁻¹, and after the exchange it was 7.4 ± 2.9 ng/ml hour⁻¹. The mean renal venous plasma renin activity was 13.9 ± 4.5 ng/ml hour⁻¹ before the exchange and 12.9 ± 4.7 ng/ml hour⁻¹ after it. The changes in arterial and renal venous plasma renin activity were not significant.

The serum sodium and potassium concentrations are not shown in Table 1 or the subsequent tables. These concentrations were within the normal ranges in all experiments and were unaffected by the exchange procedures in the sham-exchange group and in all of the test groups.

Increased Hematocrit Group.—Data from nine experiments in this group are summarized in Table 1. Following the exchange the hematocrit rose by an average of 14%. Plasma protein concentration fell slightly, presumably due to the modest saline loading that occurred during the experiment. Mean arterial blood pressure rose slightly. The decreases in urine flow and sodium and potassium excretion were also very similar to those observed in the group with increased hematocrit. The decreases in urine flow and sodium and potassium excretion were also similar to those observed in the group with increased hematocrit. The decreases in urine flow and sodium and potassium excretion were also very similar to those observed in the group with increased hematocrit.

Renin secretion rate decreased in each experiment. The arterial plasma renin activity fell slightly from a preexchange mean of 7.1 ng/ml hour⁻¹ to 6.4 ± 0.9 ng/ml hour⁻¹ after the exchange (P < 0.1). Renal venous plasma renin activity fell from 16.6 ± 3.5 ng/ml hour⁻¹ to 11.0 ± 2.2 ng/ml hour⁻¹ (P < 0.025). The somewhat higher control values of plasma renin activity in these dogs and in the dogs exchange transfused with reconstituted blood are assumed to be the result of the multiple plasmaphereses over the 3 weeks prior to the experiment.

Dextran 500 Group.—The results of 12 experiments in this group are shown in Table 1. In contrast to the preceding two groups, there was only a minor change in hematocrit after the exchange (39% to 38%). Plasma protein concentration decreased sharply as expected (3.9 g/100 ml to 2.7 g/100 ml); plasma volume, however, did not change significantly. Mean arterial blood pressure was also quite constant. The striking differences between this group and the group with increased hematocrit were in renal blood flow and renal vascular resistance. Blood flow fell more consistently and resistance increased much more than it did after the hematocrit had been increased. The decrease in renal plasma flow and the increase in filtration fraction, however, were quite similar to the changes observed in the group with increased hematocrit. The decreases in urine flow and sodium and potassium excretion were also very similar to those which followed the increase in hematocrit.

Renin secretion differed significantly between the group infused with Dextran 500 solution and that with increased hematocrit. In none of the Dextran 500 experiments did renin secretion rise. In fact, there was a consistent slight decrease. Arterial
Effect of Exchange Procedures on Renal Hemodynamics, Urine Flow, Cation Excretions, and Renin Secretion

TABLE 1

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Pre refers to values before the exchange and Post refers to values after the exchange. Abbreviations for this and the subsequent two tables are as follows: Hct = hematocrit, Pₚ = plasma protein concentration, MABP = mean arterial blood pressure, RBF = renal blood flow, RVR = renal vascular resistance, RPF = renal plasma flow, GFR = glomerular filtration rate, FF = filtration fraction, V = urine flow, UₜK = potassium excretion, UₜNa = sodium excretion, RSR = renin secretion rate, RSR by PRC = renin secretion calculated from renin concentration measurements, and PV = plasma volume.

plasma renin activity remained almost constant at 2.60 ± 0.30 ng/ml hour⁻¹ before the exchange and 2.55 ± 0.31 ng/ml hour⁻¹ afterwards (P < 0.4). Renal venous plasma renin activity fell slightly from 4.31 ± 0.37 ng/ml hour⁻¹ to 4.03 ± 0.37 ng/ml hour⁻¹ (P < 0.05).

In four experiments (Table 1, Dextran 500), renin secretion rates were estimated from plasma renin concentrations in arterial and renal venous plasma. These secretion rates also showed a slight decrease after the exchange.

Table 2 shows the response of renin secretion to intravenous injections of furosemide in five normal anesthetized dogs and five dogs which had just undergone the Dextran 500 exchange. The rise in renin secretion was comparable in the two groups.

**Blood and Plasma Viscosity.**—The changes in whole blood viscosity in the group with increased hematocrit, the group given Dextran 500, and the group with decreased hematocrit are shown in Table 2.
### TABLE 3

**Effect of Increased Hematocrit and Dextran 500 Hyperviscosity on Systemic Hemodynamics**

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<th>Hct (%)</th>
<th>$P_{Pr}$ (g/100 ml)</th>
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<th>PN (centipoise)</th>
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**Increased Hematocrit**

**Dextran 500**

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<td>6.24</td>
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<td>$P$</td>
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WBN = whole blood viscosity measured at a shear rate of 230 sec$^{-1}$, PN = plasma viscosity measured at shear rate of 230 sec$^{-1}$, CO. = cardiac output, and TPR = total peripheral resistance. See Table 1 for other abbreviations.
Effect of increased (↑Hct) and decreased (↓Hct) hematocrit and of Dextran 500 (Dex 500) on whole blood viscosity. Viscosity is elevated in the group with increased hematocrit and in the group given Dextran 500 and reduced in the group with decreased hematocrit. The differences from control values are highly significant (P < 0.001) at all shear rates in the three groups. There is no significant difference between the values in the group with increased hematocrit and that given Dextran 500 at any of the shear rates. Each point on the curves is the mean for the group, and bars indicate ± se. Since the control values in each group did not differ significantly from each other, they were pooled in this graph. The P values, however, were derived from the paired t-test in which the values before and after the exchange in each experiment were treated as paired data.

Figure 1. It is of particular importance to note that the degree of elevation of blood viscosity was very similar in the group with increased hematocrit and the group given Dextran 500. Moreover, the shear-rate dependency of the viscosity at low shear rates was similar in these two groups.

Figure 2 shows the elevation of plasma viscosity induced by Dextran 500. The groups with increased or decreased hematocrits did not show any change in plasma viscosity after the exchange.

Cardiac Output.—Table 3 shows the cardiac output values before and after the Dextran 500 exchange and the increase in hematocrit. The blood pressure, total peripheral resistance, hematocrit, and blood viscosity are also given. As in the experiments shown in Table 1 for the group with increased hematocrit and that given Dextran 500, the increments in whole blood viscosity were comparable in the two groups. Viscosity increased 36% in the group with increased hematocrit and 39% in the group given Dextran 500. Neither exchange procedure significantly affected blood pressure. The cardiac output also responded similarly in the two groups, decreasing by an average of 39% in the group with increased hematocrit and 30% in the group given Dextran 500 (P < 0.1). Total peripheral resistance rose more in the group with increased hematocrit than it did in the group given Dextran 500 (69% vs. 50%), although the difference between the two groups was not significant (P < 0.1). These changes in cardiac output and peripheral resistance were different from the effects seen in the kidney where blood flow fell and resistance rose much more in the group given Dextran 500 than it did in the group with increased hematocrit.

Discussion

This study was designed to examine the effects of blood viscosity on renal hemodynamics and renin...
BLOOD VISCOSITY AND THE KIDNEY

secretion. Two of the most important determinants of blood viscosity are the hematocrit and the macromolecular substances in plasma (5). The effects on the kidney of changes in hematocrit have been intensively studied (15-18). In a recent preliminary report, McDonald and Smith (6) extended these observations by showing that an acute increase in hematocrit was a stimulus for renin secretion.

The effects on the kidney of colloid-induced changes in blood viscosity have not been studied as systematically as have changes in hematocrit. Infusions of colloidal solutions are normally accompanied by plasma volume expansion and decreases in hematocrit (16). Moreover, unless the infusate is isocotic with plasma, large shifts of fluid occur between the interstitial and the intravascular compartment. All of these factors are likely to have major hemodynamic consequences quite independent of blood viscosity. For these reasons, the Dextran 500 protocol in the present study was designed to produce an increase in blood viscosity without altering plasma volume or hematocrit.

From the measurements obtained by cone-plate viscometry (Fig. 1), it is apparent that the hematocrit-induced and Dextran 500-induced elevations in blood viscosity were very similar. This similarity was consistent over the entire range of shear rates measured, showing that in both groups the non-Newtonian characteristics of blood at moderately low shear rates were comparable. Conversely, at the higher shear rates, blood viscosity was virtually constant.

One of the most striking differences in the effects of the two forms of hyperviscosity was on the rate of renin secretion. The increase in hematocrit stimulated it, but the Dextran 500-induced increase failed to do so and even suppressed it slightly. Several control studies were performed to determine whether this difference was due to nonspecific effects of foreign red cells on the one hand or of high-molecular weight dextran on the other, quite independent of their effects on blood viscosity. The control studies failed to support such nonspecific effects. Immunologic reactions to foreign red cells were not involved, since such cells were given not only to the group with increased hematocrit but to the group receiving Dextran 500 and to some of the sham-exchange group as well. The fact that the effects on the kidney of a decreased hematocrit were opposite to those of an increased hematocrit provides further evidence that the change in hematocrit and not an effect of foreign red cells was the important determinant.

It is conceivable that renin failed to rise during Dextran 500-induced hyperviscosity because the dextran directly impaired the secretory capacity of the juxtaglomerular cells. This possibility was excluded by the demonstration of a normal response of renin secretion to furosemide injections in dogs which had received Dextran 500. The Dextran 500 exchange procedure might also have obscured a rise in renin secretion by lowering plasma renin substrate concentration. The latter does influence the results of the plasma renin activity assay (12). However, renin secretion was calculated on the basis of venoarterial differences in plasma renin activity across the kidney. Since the blood samples were drawn simultaneously from the aorta and the renal vein, their substrate concentrations would be the same. Moreover, in the assay procedure, plasma renin activity calculations were based on initial reaction velocities (13), which required a linear relationship between angiotensin generation and incubation time. Substrate exhaustion during incubation could be detected by a decrease in reaction velocity in the later stages of the incubation. This decrease occurred infrequently and only in samples with very high plasma renin activity. Incubations for shorter periods of time were always repeated in these instances. A most conclusive piece of evidence against changes in substrate concentration being important in the group given Dextran 500 is the fact that, when exogenous substrate was added and renin measured as plasma renin concentration, there was still no change in the response of renin secretion to Dextran 500-induced hyperviscosity.

All of the preceding considerations indicate that the changes in renin secretion and renal hemodynamics showed in this study were the result of alterations in blood viscosity. The question arises as to how the changes in viscosity exerted their influence on the kidney.

There was a marked similarity between the effects of the two forms of hyperviscosity on systemic blood pressure and cardiac output. Therefore, it is unlikely that the disparity in effects on the kidney was the result of differences in systemic hemodynamics.

A further consideration, to which this study lends no support, is the possibility that a rise in hematocrit and the administration of Dextran 500 altered the pattern of tubular sodium reabsorption differently so that sodium delivery to the macula densa was different. There is considerable, though conflicting, evidence that such an occurrence...
would influence renin secretion (4, 19) and even renal blood flow (4). It is impossible to rule out such a mechanism in these experiments. However, both the increased hematocrit and the Dextran 500 solution caused a drop in potassium excretion in conjunction with the decrease in sodium excretion. This finding suggests that both caused increased sodium reabsorption at a similar level of the tubule, i.e., proximal to the sodium-potassium exchange sites.

A more likely explanation for the disparity in the renin response to Dextran 500 and increased hematocrit can be found in the renal hemodynamic data. The outstanding difference was in the response of renal blood flow to the two exchanges. Dextran 500 produced a highly significant fall in renal blood flow, but an increase in hematocrit caused only a slight fall. This observation is analogous to that of Rosenblum (20) in relation to the cerebral circulation where Dextran 500 infusions reduce plasma transit time by a much greater degree than does an increase in hematocrit.

Since renal perfusion pressures remained constant in the present study, renal vascular resistance increased much more in the group given Dextran 500 than it did in the group with increased hematocrit. The relationships of renal vascular resistance to blood viscosity are presented in Figure 3, which shows that changes in viscosity resulting from wide variations in hematocrit were associated with very little change in total renal vascular resistance. The inference to be made from this observation is that as the hematocrit fluctuates there is a reciprocal change in the other major determinant of resistance, the radii of resistance vessels. The result is that during a hematocrit-induced rise in viscosity, renal vasoconstriction occurs and total resistance remains almost constant. Conversely, a fall in hematocrit is attended by sufficient vasodilation to maintain a nearly constant resistance. These effects of altered hematocrit on renal vascular resistance are somewhat less than those found by Schrier and Earley (18) using a very similar experimental model. However, their data also show that the changes in renal vascular resistance are proportionately less than the changes in blood viscosity. For example, in their saline-loaded animals, renal vascular resistance rose from 0.58 mm Hg/ml min⁻¹ to 0.63 mm Hg/ml min⁻¹ or by 8% during a rise in hematocrit from a control of 32% to a postexchange value of 40%. Although blood viscosity was not measured, data from my laboratory indicate that this increase in hematocrit would result in a 16–20% increase in blood viscosity. This increase is at least double the increase in renal vascular resistance and suggests that renal vasoconstriction occurred in response to the rise in hematocrit.

In the Dextran 500 experiments, the correlation between blood viscosity and renal vascular resistance is much different. As shown in Figure 3, resistance rose in a virtual one-to-one relationship with viscosity. This finding suggests that, unlike a rise in hematocrit, Dextran 500-induced hyperviscosity does not evoke a compensatory dilatation of renal resistance vessels.

These conclusions depend on the assumption that the in vitro measurements of blood viscosity accurately reflect those in vivo. For the renal circulation, this assumption is probably valid. The velocity of blood flow through the kidney is so great that high shear rates undoubtedly prevail. At shear rates above 100 sec⁻¹, as shown in Figure 1, blood behaves virtually as a Newtonian fluid. It is noteworthy that the rouleau formation that undoubtedly accompanied the Dextran 500 infusion did not significantly alter the relationship of shear rate to viscosity. This finding is in keeping with that
of Whitmore (21), who also showed that red cell aggregation made an insignificant contribution to flow resistance, at least at shear rates above 21 sec⁻¹. Therefore, the effective blood viscosity in the kidney should not differ substantially from values recorded in vitro at 230 sec⁻¹. In both situations shear rates are high enough to allow blood to behave virtually as a Newtonian fluid.

The available data provide no explanation for the difference in renal vascular response to the two forms of hyperviscosity. However, some possible mechanisms are worthy of speculation, because they may provide an explanation for the disparity in renin secretion.

One consideration is that the vasculature reacted differently because of the difference in renin secretion. This hypothesis is difficult to accept, since it implies that the increase in renin secretion caused the vasodilatation associated with the rise in hematocrit. Such vasodilatation would be paradoxical to the known effects of angiotensin on the kidney (22).

The alternative possibility is that changes in renal vascular tone were the cause rather than the result of changes in renin secretion. This hypothesis is more plausible. The almost constant total resistance in the kidney during wide fluctuations in hematocrit resembles the autoregulatory response to constriction of the renal artery. A major difference is that during renal artery constriction perfusion pressure is decreased, but during the increased hematocrit experiments arterial pressure was constant. However, an increase in blood viscosity would be expected to increase the rate of pressure drop between the main renal artery and the cortical arterioles. Thus, even though systemic pressure was unchanged, the pressure transmitted to the cortical arterioles would be reduced. The reduced intraluminal pressure should provide a stimulus for autoregulatory dilatation of the arterioles just as it does during mechanical constriction of the renal artery. Conversely, a reduction in hematocrit should enhance the transmission of systemic pressure into cortical arterioles and result in reactive vasoconstriction.

Such a purely autoregulatory response to changes in hematocrit may provide the mechanism controlling renin release. Vasodilatation involving the afferent arteriole, the site of the juxtaglomerular cells, may stimulate these cells to secrete renin. The recent report of Eide et al. (23) lends support to this possibility. They showed that a stepwise reduction in renal perfusion pressure produces a corresponding rise in renin secretion only as long as the pressure is within the autoregulatory range of the kidney. Reduction of pressure below this range causes a reduction in renal blood flow and no further increase in renin secretion. This phenomenon persists even while urine flow and sodium excretion are kept constant by a mannitol infusion. They concluded that the stimulus for renin secretion is dilatation of afferent arterioles during the process of autoregulation. When the arterioles have dilated maximally, there is no further stimulus to renin secretion.

The results of the present study conform to this theory. There is evidence in Figure 3 that an increase in hematocrit caused renal vasodilatation. Assuming that this effect involved afferent arterioles, it would account for the rise in renin secretion. A precise reversal of this mechanism would explain the results of the decreased hematocrit experiments. Furthermore, the absence of compensatory vasodilatation in the group given Dextran 500 would account for the failure of renin secretion to rise.

The present study leaves unresolved the question of why renal blood flow was not maintained more nearly constant during Dextran 500-induced hyperviscosity. It is conceivable that this large colloid directly affects responsiveness of vascular smooth muscle to changes in intraluminal pressure. Further studies are necessary to evaluate in more detail the effects of high-molecular weight dextrans on renal autoregulation, and to determine whether other large colloids, such as the macroglobulins, exert similar effects on the renal circulation. Of further importance in evaluating the effects of hematocrit-induced and colloid-induced hyperviscosity on the kidney would be a study of their effects on cortical blood flow distribution. The much higher renin content of the outer cortex compared with that of the inner cortex (24, 25) suggests that shifts in blood flow distribution may have potent effects on renin secretion. The disparity in the effects of Dextran 500 and an increased hematocrit on renin release may be partly due to a difference in their effects on cortical flow distribution, an effect which would go undetected by standard clearance studies.

Appendix 1

The oncotic pressure of normal dog plasma as measured by Zweifach and Intaglietta is $227 \pm 24$ (SD) mm H₂O (26). In the present study, it was necessary to
estimate the concentration of a Dextran 500 solution which would possess an oncotic pressure slightly below this range, since the dogs being studied received a saline load and, hence, were subjected to a mild dilution of plasma proteins. The oncotic pressure, \( \pi \), in mm H\(_2\)O of the Dextran 500 solution was calculated on the basis of the following equation (27):

\[
\pi = \frac{TRC}{M_n} + RTA_2C^2,
\]

where \( R \) is the gas constant and equals 8,500 when the colloid concentration, \( C \), is expressed in g/100 ml, \( M_n \) is the number-average molecular weight for Dextran 500 and equals half the mean molecular weight, \( T \) is the absolute temperature, and \( A_2 \) is the second viral coefficient which for Dextran 500 has been estimated by Cerny et al. (28) to be \( 2.53 \times 10^{-4} \). By setting the desired oncotic pressure \( (\pi) \) of the Dextran 500 solution at 250 mm H\(_2\)O, the calculated value for \( C \) in Eq. 1 is 5.4 g/100 ml. Therefore, this concentration was used in the infusate of the exchange transfusions.

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