Effect of Posthemorrhagic Anemia on the Renal Circulation of the Unanesthetized Rabbit


The effects of anemia on the renal circulation have been studied in a variety of preparations and species,1-11 but the results obtained have not been uniform. For example, the renal blood flow in anemia has been reported to be decreased,1-3 unchanged4 or increased5-11 by different investigators. Factors which may have contributed to these contradictory results include variation in the cause and duration of anemia, changes in total blood volume, and differences in the surgical and anesthetic procedures employed. In some series,1,3,5-7 the renal blood flow may have been underestimated. In these the renal blood flow was derived from the para-aminohippurate (PAH) clearance with the implicit assumption that no change in renal PAH extraction ratio had occurred. However, Pappenheimer and Kin-ter8-10 and Thompson et al.4 have demonstrated a reduction in renal PAH extraction ratio in anesthetized cats and dogs in acute anemia.

In severe anemia the reduction in red cell concentration results in decreased blood viscosity12 and some degree of tissue hypoxia.13 The purpose of the present investigation was to determine the effects of anemia on the renal circulation and renal PAH extraction ratio of the unanesthetized rabbit, and to assess separately the parts played by reduction in red cell concentration and by renal hypoxia in producing these effects.

Methods

ANIMALS

Experiments were carried out on 61 hutch-bred, male, New Zealand white rabbits ranging in weight from 2.0 to 3.2 kg. Animals were fed on a diet of rabbit pellets and given greens on alternate days. Apart from ensuring an adequate supply of drinking water during and after bleeding, no special dietary measures were taken.

OPERATIVE PROCEDURES

One to four days before all experiments in which renal clearances were determined, the renal vein was catheterized, using general anesthesia. The technique of renal vein catheterization differed from that described previously for the rabbit.14 After injection of 500,000 units of crystalline penicillin intravenously, the animal was anesthetized with sodium pentobarbital (Veterinary Nembutal, Abbott: 40 mg/kg) and, observing aseptic precautions, a constant lumbar vein tributary of the left renal vein was catheterized using 20-gauge Transflex tubing. The catheter was tied firmly to the adjacent psoas muscle so that its siliconated tip lay within the lumen of the renal vein and sampled only renal vein blood (fig. 1). It was brought to the exterior through a stab wound in the left flank, filled with heparin solution (5,000 units/ml) and protected by strapping it to the skin and binding a light cloth harness around the abdomen. Heparin solution in the catheter was replenished daily. The position of the catheter within the renal vein was always

FIGURE 1

Anatomy of left renal vein and its tributaries in rabbit shown schematically with the renal vein catheter in position.
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checked at autopsy, and the kidneys examined for macroscopic evidence of infarction.

On the day of renal clearance measurements the bladder was catheterized, and the central ear artery and vein cannulated using local (lidocaine) anesthesia. Details of these procedures have been given elsewhere.14

MEASUREMENT OF RENAL BLOOD FLOW (RBF), GLOMERULAR FILTRATION RATE (GFR), RENAL VEIN O2 SATURATION, ARTERIAL BLOOD PRESSURE, AND HEART RATE

All observations were carried out at least 12 hours after recovery from general anesthesia with the animals in a state of moderate water and mannitol diuresis.14 RBF was calculated from PAH clearance and renal PAH extraction ratio; GFR was measured as the creatinine clearance.* The compositions of priming and sustaining infusions were as described previously.14 The sustaining infusion was given at a rate of 0.7 ml/min; it was administered for one hour before commencing measurements of RBF and GFR. Each estimate of RBF and GFR was based on three consecutive 10-minute urine collection periods. Arterial and renal vein blood samples (1.1 ml each) were withdrawn into tuberculin syringes moistened with heparin, at the midpoint of the first and third collection periods. Plasma PAH and creatinine concentrations were determined from these samples as described previously.14 Hematocrit ratio and hemoglobin were determined from an arterial blood sample taken at the midpoint of the second collection period. Hematocrit ratio was read from Wintrobe tubes without correction for plasma trapping or body hematocrit, after centrifuging 3,000 rev/min, and 13.5 cm radius. Hemoglobin was measured using the method of Drabkin and Austin.15 Renal venous and arterial O2 saturations were determined from 1 ml blood samples drawn at the midpoint of the second urine collection period; O2 contents being measured by the method of Van Slyke and Neill16 using 0.5 ml blood. Arterial blood pressure and pulse rate were recorded from the ear artery using a Statham P23AC pressure transducer and a Grass polygraph, at the midpoint of each urine collection period.

EXPERIMENTAL PRODUCTION OF ANEMIA

In preliminary experiments it was observed that the animals tolerated the bleeding and plasma replacement procedures better if the hematocrit was reduced, in a given experiment, by not more than half of its initial value. Accordingly two groups of animals were used in the experiments.

Group I

In six animals initial measurements of RBF, etc. were made at their normal hematocrit (range 38 to 30%). Following these measurements the sustaining solution was stopped. The animal was then allowed to bleed (20 to 25 ml/kg) slowly from the ear artery catheter while 80 to 100% of the blood lost was replaced simultaneously by infusion of plasma freshly collected from a donor animal. This process lasted 30 to 45 minutes. The sustaining infusion was started again and after one hour the second set of observations of RBF etc. was carried out. The range of hematocrits during these observations was 24 to 18%.

Group II

In 23 animals an initial state of moderate anemia was induced by two preliminary bleeds of 15 ml/kg/day from the marginal ear vein. Two days after the second bleed, renal vein catheterization was carried out, and on the following day initial measurements of RBF etc. were made. The range of hematocrit values was 29 to 15%. The procedure of acute bleeding and plasma replacement was carried out as described for Group I, and a second set of measurements of RBF etc., was made with hematocrit values ranging from 15 to 8%. In two animals the process of bleeding and plasma replacement was repeated and the animals were thus studied at three levels of hematocrit. In ten animals a third set of measurements was carried out after breathing 100% O2 for 30 minutes.

ADMINISTRATION OF GAS MIXTURES

The effects of breathing 0.2% and/or 0.3% carbon monoxide in air were studied in 11 animals. The animals were placed in a gas-tight lucite box, and the catheters were brought to the exterior through rubber seals. Gas was drawn through this box from a 100-liter Douglas bag at the rate of 4 to 6 liters/min, using a water suction pump. During the control period, room air was drawn through the box and subsequently the animals breathed 0.2% CO or 0.3% CO for 30 minutes before commencing measurements of RBF, etc.

In ten experiments in Group II animals, following observation of the effects of severe anemia breathing room air, 100% O2 was administered and renal measurements repeated after 30 minutes. In these animals a tracheotomy tube was inserted at the beginning of the experiment and the animals breathed room air, or 100% O2 through the respiratory valve assembly as described previously.14

In a separate series of 11 experiments in four animals, creatinine and inulin clearances were measured simultaneously under several different conditions (normal, anemic, and during TM determination).

Inulin clearance averaged 17.07 ml/min and creatinine clearance 17.13 ml/min, the difference for within animal comparisons being 0.3 ±2.1 (SE)%.

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MEASUREMENT OF BLOOD VOLUME

The effect of the bleeding and plasma replacement procedure on blood volume was determined in five animals. In these, renal vein catheterization and renal clearance estimations were not carried out. The animals were given the same infusion solutions and were bled and given plasma in the same way as animals used for the renal circulatory studies. The blood volume was measured as the sum of separate plasma and red cell volumes before and after bleeding in each animal. Plasma volume was measured using the dye T-1824. The dye was not extracted from the plasma, but T-1824 standards were prepared from the plasma blank of each animal. The dose of T-1824 injected was 50 mg in each estimation and samples were taken at 10, 15, and 20 minutes following injection. The plasma was diluted 1 in 100 (including blank and standards) before reading on the Beckman model DU spectrophotometer at a wavelength of 620 μm. Plasma concentration at zero time was obtained by semilogarithmic extrapolation.

Red cell volume was determined from the 10-minute sample, after injecting the animal's own cells labelled with Cr⁺⁺ at the same time as the T-1824.¹⁷

ADMINISTRATION OF GANGLION-BLOCKING AGENT

In two animals, measurements of RBF, etc., were carried out before, during, and after infusion of the ganglion-blocking agent, trimethylene thiophanium d-camphorsulphonate (Arfonad - Roche) given at a constant rate of 2 mg/min.

Hematocrit ratio in relation to renal blood flow (RBF), glomerular filtration rate (GFR), ear artery blood pressure (BP), and filtration fraction. Solid circles: Determinations in Group I animals before and after bleeding with plasma replacement. Open circles: Determinations in Group II animals before and after bleeding with plasma replacement. Results from one animal are joined by a straight line.
RESULTS

Changes in the Renal Circulation in Anemia

Hemodynamic Effects

Figure 2 shows results obtained in four animals from Group I and 17 animals from Group II, studied in each case at two levels of hematocrit (at three levels in two animals). There was no significant change in RBF as a result of anemia, but there was significant reduction in GFR ($P < 0.02$) and filtration fraction ($P < 0.001$) with the more severe grades of anemia (Group II). Other changes noted were a significant fall in arterial pressure in Group II animals, and a slight but significant tachycardia (mean 109.3 ± 2.7 (SE) % of control value) in this group.

There was a reduction in resistance to blood flow in severe anemia (i.e., maintenance of RBF despite a fall in arterial pressure). This may have been due in part to the reduction in blood viscosity. The fall in filtration fraction suggests that changes may have occurred also in the ratio of pre- to postglomerular resistance.

Renal Venous $O_2$ Saturation and Renal $O_2$ Consumption

Figure 3 shows that there was significant reduction in renal venous $O_2$ saturation and renal $O_2$ consumption in anemia. These findings suggest an increasing degree of tissue hypoxia with increasing severity of anemia.*

Renal PAH Extraction Ratio

Figure 4 illustrates the relationship of renal PAH extraction ratio to the hematocrit in 85 tests obtained from 56 animals. In tests carried out with the hematocrit above 30%, the renal PAH extraction ratios averaged 96.2 ± 0.4 (SE) %. There was little change in extraction ratio down to hematocrit values of about 20%, but below this there was progressive reduction in extraction ratio which reached an average of 84.3 ± 2.3 (SE) % for hematocrit values below 10%.

In 26 animals the extraction ratio was deter-

* The renal oxygen consumption of the rabbit per gram of kidney is higher than has been reported for man and the dog. It bears, however, a similar relationship to total body oxygen consumption as is found in those species.14 The explanation of the higher absolute values lies in the fact that the mean body temperature of the rabbit is 40°C (range 39.5 to 41°C).
mined at two levels of hematocrit in the same animal, thus permitting a better quantitative assessment of the effects of anemia on renal PAH extraction. In six experiments on Group I animals the renal PAH extraction was 96.9% and 95.2% (0.1 < P < 0.2) when the hematocrit was reduced from 34.5% to 20.4%. In 20 animals from Group II there was a significant reduction in extraction ratio from 95.0% to 91.3% (P < 0.001) when the hematocrit was reduced from 22.5% to 11.5%. The results of these comparisons within animals are in agreement with those of the whole series (fig. 4), and it is evident that the effect of anemia on renal PAH extraction was relatively slight except where the degree of anemia was severe (i.e., hematocrit below 10%).

**EVALUATION OF SOME FACTORS INFLUENCING THE RENAL CIRCULATION IN ANEMIA**

An attempt has been made to assess the part played by renal tissue hypoxia, fall in red cell concentration, fall in arterial pressure, and variation in arterial PAH concentration on the various renal circulatory findings in anemia in this series. In addition, the effect of bleeding with plasma replacement on total blood volume was investigated.

**CONTRIBUTIONS OF RENAL HYPOXIA AND CHANGE IN RED CELL CONCENTRATION**

In anemia there is a reduction both in the blood O₂ carrying capacity and in the number of circulating red cells, leading to a decrease in O₂ available to the tissues on the one hand, and a decreased blood viscosity and possibly an alteration in the distribution of red cells and plasma in certain vascular beds, on the other. The part played by these two factors was investigated (1) by administration of 100% O₂ to severely anemic animals, (2) by administration of graded low concentrations of carbon monoxide in air to animals with a normal hematocrit.

Breathing 100% O₂ increases the amount of dissolved oxygen and thus the O₂ content of the arterial blood. At normal hematocrits the proportionate increase in oxygen available to the tissues is slight, but in severe anemia with low hematocrit ratios this effect is greater, and presents a means of relieving tissue hypoxia with little or no change in hematocrit or blood viscosity.

Conversely, breathing low concentrations of carbon monoxide affords a method of studying increasing degrees of tissue hypoxia in

**TABLE 1**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>(A) Breathing 21% O₂</th>
<th>(B) After bleeding: breathing 21% O₂</th>
<th>(C) After bleeding: breathing 100% O₂</th>
<th>SE of difference (B — C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit %</td>
<td>20.7</td>
<td>10.2</td>
<td>9.6</td>
<td>±0.7</td>
</tr>
<tr>
<td>H_PAH %</td>
<td>93.2</td>
<td>88.3†</td>
<td>89.6†</td>
<td>±1.5</td>
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<td>Blood pressure (mm Hg)</td>
<td>76.0</td>
<td>57.2†</td>
<td>61.3†</td>
<td>±7.7</td>
</tr>
<tr>
<td>Heart rate per min</td>
<td>286</td>
<td>313†</td>
<td>305†</td>
<td>±8.8</td>
</tr>
<tr>
<td>RBF (ml/20g/min) *</td>
<td>135</td>
<td>148†</td>
<td>136†</td>
<td>±2.5</td>
</tr>
<tr>
<td>Renal vascular resistance*</td>
<td>45.3</td>
<td>29.3†</td>
<td>34.5†</td>
<td>±2.5</td>
</tr>
<tr>
<td>GFR (ml/min)*</td>
<td>15.7</td>
<td>12.4†</td>
<td>13.1†</td>
<td>±0.4</td>
</tr>
<tr>
<td>RPF (ml/min)*</td>
<td>86.5</td>
<td>120†</td>
<td>112†</td>
<td>±7.3</td>
</tr>
<tr>
<td>Filtration fraction*</td>
<td>0.177</td>
<td>0.108†</td>
<td>0.130†</td>
<td>±0.007</td>
</tr>
<tr>
<td>Renal venous S_O₂ %</td>
<td>33.8</td>
<td>43.3†</td>
<td>76.3†</td>
<td>±3.15</td>
</tr>
<tr>
<td>Renal V_O₂ (ml/min STPD)*</td>
<td>2.56†</td>
<td>3.11†</td>
<td>±0.14*</td>
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</tr>
</tbody>
</table>

(A) during moderate chronic anemia while breathing room air (21% O₂); (B) after bleeding with plasma replacement while breathing room air; (C) after bleeding with plasma replacement while breathing 100% O₂. Treatments were carried out consecutively in each animal and the standard errors shown are based on comparisons within animals.

* Based on six measurements (within animals).
† Treatment effect (A — B or B — C) significant (P<0.05).
‡ 0.05<P<0.1.
the presence of a normal hematocrit and normal blood viscosity. Carboxyhemoglobin is formed and there is consequently a reduction in the hemoglobin available for O\textsubscript{2} transport without change in arterial O\textsubscript{2} pressure.

**Effects of Breathing 100% O\textsubscript{2}**

Measurements of RBF etc., were obtained in ten animals with the hematocrit approximately 20%, whilst the animals were breathing room air (column A, table 1). The hematocrit was reduced to approximately 10% by the usual method of bleeding and plasma replacement and this resulted in the usual significant reduction in arterial pressure, GFR, filtration fraction, renal vascular resistance, renal PAH extraction ratio, renal venous O\textsubscript{2} saturation, and renal O\textsubscript{2} consumption (column B, table 1).

In these animals the O\textsubscript{2} capacity of the arterial blood averaged 3.8 ml/100 ml of blood with the hematocrit ratio 10%. Breathing 100% O\textsubscript{2} increased the amount of O\textsubscript{2} in physical solution in the arterial blood by approximately 2 vol/100 ml of blood, and thus increased the amount of O\textsubscript{2} available to the tissues by approximately 50% in these severely anemic animals. The effects observed are shown in column C of table 1. In these animals the hematocrit ratio was 10.2% while breathing 21% O\textsubscript{2}, and 9.6% while breathing 100% O\textsubscript{2}. There was thus a negligible change of blood viscosity in these two treatment periods.

Breathing 100% O\textsubscript{2} produced no significant changes in RBF and GFR. The filtration fraction increased significantly, and the renal vascular resistance increased in five out of six animals, the overall effect being small but probably significant. These results observed in the presence of constant blood viscosity suggest that part of the reduction in filtration fraction and renal vascular resistance was due to hypoxic postglomerular vasodilatation.

There was a large increase in the renal venous O\textsubscript{2} saturation and the value reached was greater than before bleeding. There was a significant increase in renal O\textsubscript{2} consumption, though this did not return to its initial value (columns A and C, table 1).

The renal PAH extraction ratio increased slightly in seven animals, remained unchanged in one, and decreased in two animals. The mean effect was small and not statistically significant (0.05 < P < 0.1).

In summary, there was an increase in renal venous O\textsubscript{2} saturation and renal oxygen consumption suggesting relief of renal hypoxia. The main hemodynamic effect in the severely...
anemic animal of breathing 100% O₂ was an increase in filtration fraction.

Effects of Breathing Carbon Monoxide

Figure 5 shows the changes produced in the renal circulation in rabbits breathing 0.1% to 0.3% carbon monoxide in air. The data comprise results reported previously, and in addition, results from 11 animals breathing 0.2% or 0.3% carbon monoxide in air. Despite minor technical differences in the procedures employed, the response in the two series was similar and the results have accordingly been pooled.

There were significant reductions in RBF, GFR, and arterial pressure in animals breathing carbon monoxide (fig. 5). Reference to figure 2 shows that the hemodynamic effects of breathing carbon monoxide differed somewhat from those produced by severe anemia. In animals breathing carbon monoxide, RBF and GFR were reduced in proportion to the blood pressure and there was little or no change in filtration fraction. In severe anemia, the fall in arterial pressure was approximately similar to that observed with carbon monoxide, and the GFR was also reduced. However, in anemia there was no reduction in RBF and a marked fall in filtration fraction.

Table 2 shows the effects observed with carbon monoxide on renal venous O₂ saturation, renal O₂ consumption, and renal PAH extraction ratio in animals breathing 0.2% and 0.3% carbon monoxide. There was a significant reduction in renal O₂ saturation with both mixtures and in renal O₂ consumption with 0.3% carbon monoxide. Though the renal venous O₂ pressure was not measured directly, it may be estimated approximately from the saturation data. Using the rabbit's oxyhemoglobin dissociation curve, and assuming a P₅₀ of 40 mm Hg and a body temperature of 40°C, the estimated renal venous P₅₀ averaged 23 ± 2.3 (SE) mm Hg in the experiments with 0.2% carbon monoxide and 17 ± 1.5 (SE) mm Hg in the experiments with 0.3% carbon monoxide. In severe anemia (Group II), the estimated renal venous P₅₀ (corresponding to a hematocrit of 10.8%) was 33 ± 1.1 (SE) mm Hg. Thus in animals breathing 0.2% and 0.3% carbon monoxide, there was probably a greater degree of renal hypoxia present than in the most severe degree of anemia observed in the present study.

Despite these differences in the estimated degree of renal hypoxia, there was a smaller effect on the renal PAH extraction ratio in the carbon monoxide experiments than in severe

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**Table 2**

Results for Renal PAH Extraction Ratio, Arterial Oxygen Saturation, Renal Venous Oxygen Saturation, and Renal Oxygen Consumption in Sixteen Animals

<table>
<thead>
<tr>
<th>No. of animals</th>
<th>Treatment</th>
<th>0.2% CO</th>
<th>0.3% CO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>T</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F₈₉H%</td>
<td></td>
<td>95.3</td>
<td>93.2*</td>
</tr>
<tr>
<td>Arterial O₂ Hb/total Hb %††</td>
<td>96.0**</td>
<td>56.1*</td>
<td>± 3.51</td>
</tr>
<tr>
<td>Renal venous S₉₀₂ %††</td>
<td>75.1</td>
<td>36.0*</td>
<td>± 4.73</td>
</tr>
<tr>
<td>Renal V₉₀₂ (ml/min STPD)‡</td>
<td>3.32</td>
<td>2.92</td>
<td>± 0.31</td>
</tr>
</tbody>
</table>

Each group breathed room air during the control period (C), but breathed 0.2% CO in air and/or 0.3% CO in air during the treatment period (T).

* Standard error based on comparisons within animals, each animal acting as its own control.
† Six animals from this group taken from previous series.
‡ Data from 10/12 animals in 0.2% CO group and 6/7 animals in 0.3% CO group.
§ Data from 7/12 animals in 0.2% CO group and 5/7 animals in 0.3% CO group.
* Treatment effect significant (P<0.05).
** Mean value from four animals only.
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anemia (table 2). With 0.2% carbon monoxide the mean reduction in renal PAH extraction ratio was only 2%, and only in animals breathing 0.3% carbon monoxide was a change in PAH extraction ratio observed comparable to that found in severe anemia. This point was investigated in more detail in four animals, where the responses to breathing 0.3% carbon monoxide and the responses to severe anemia were compared in the same animal. Following the initial set of observations with 0.3% carbon monoxide in air the animals were bled over a period of two to three days to make them moderately anemic. Severe anemia was then produced by the usual technique of bleeding and plasma replacement. The results in figure 6 demonstrate that in the carbon monoxide experiments the estimated renal venous O₂ pressure was lower than in severe anemia, but there was an approximately similar reduction in extraction ratio.

Effect of Bleeding with Plasma Replacement on Blood Volume

Figure 7 shows that the technique of bleeding with plasma replacement used to produce anemia caused minimal changes in total blood volume in four out of five animals where the blood volume was measured; in one animal there was an increase in blood volume of 26%. It seems likely that the technique of bleeding with plasma replacement minimized changes in total blood volume.

Effect of Reduction of Arterial Pressure

Two animals with normal hematocrit ratios were given the ganglion-blocking drug Arfonad by constant intravenous infusion. These experiments were carried out to examine the possibility that the fall in arterial pressure observed in anemia might contribute to the reduction in renal PAH extraction ratio. The arterial pressure was lowered from 80 to 64 mm Hg in one animal, and from 70 to 50 mm Hg in the second animal. In neither
animal was there any significant change in RBF, GFR, renal venous $O_2$ saturation, or renal PAH extraction ratio. It is thus unlikely that reduction in arterial pressure alone accounts for any of the findings in anemia.

**Effect of Changes in Arterial PAH Concentration on Renal PAH Extraction Ratio**

In all the above experiments the arterial plasma PAH concentration varied between 1 and 3 mg/100 ml. In further experiments the relationship of renal PAH extraction ratio to hematocrit was examined over a wider range of arterial PAH concentrations. This was done in order to investigate the possibility that the fall in extraction ratio observed in anemia might be due to a minor change in arterial PAH concentration between the taking of control measurements and measurements in anemia. In addition the experiments were designed to test whether reducing the renal tubular PAH load might diminish the effect of severe anemia on the PAH extraction of the kidney.

In three animals the plasma PAH concentration was increased stepwise, and simultaneous arterial and renal vein specimens were taken when the PAH level had become stable at each infusion rate. The results for renal PAH extraction ratios at three different hematocrit values in each animal (i.e., approximately 35%, 20%, and 10%) are shown in figure 8. At hematocrit values of about 20%, the renal PAH extraction ratio differed from normal only at higher arterial PAH concentrations, but at low hematocrit values (mean 9.8%) it was reduced at all arterial PAH levels in all three animals. At any level of hematocrit the extraction ratio was only slightly affected by variation of arterial PAH concentration in the range 1 to 3 mg/100 ml.

**Discussion**

In renal circulation in anemia there was no change in RBF, and a decrease in GFR, filtration fraction, renal PAH extraction ratio, renal venous $O_2$ saturation, and renal $O_2$ consumption.

The changes observed in anemia differed from those reported previously in unanesthetized rabbits with normal hematocrits in other types of hypoxia. In contrast to the fall in filtration fraction in anemia there was no change in filtration fraction with carbon monoxide. This may represent differences in the effects of these treatments on the pre- and postglomerular circulation. It is unlikely that the different effects observed in the carbon monoxide experiments and in anemia depend on differences in renal $P_{(0)}$ in anemia since the arterial $P_{(0)}$ is essentially normal in anemia, and is only slightly altered when breathing carbon monoxide in man and in the rabbit (unpublished observations). The arterial $P_{(0)}$ is normal both in anemia and with carbon monoxide, and the $O_2$ carrying capacity of the blood is reduced in both types of experiment. The differences in hemodynamic findings in anemia and in the carbon monoxide experiments.
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thus probably depend on the differences in the red cell concentrations in the two types of experiment.

The contribution of changes in blood viscosity to the decreased renal vascular resistance in anemia is difficult to assess quantitatively in the absence of general agreement regarding the distribution of intrarenal blood flow in anemia. The relative blood viscosity in the isolated perfused hindlimb is reduced by less than 10% with a fall of hematocrit from 20% to 10% (the range of Group II animals). This would account only for a part of the observed fall in renal vascular resistance.

The experiments with 100% O\textsubscript{2} indicate that tissue hypoxia also plays a part in some of the circulatory findings in anemia. Thus when animals with severe anemia breathed 100% O\textsubscript{2}, the renal venous O\textsubscript{2} saturation increased above its control level, and this was accompanied by a significant increase of filtration fraction and renal vascular resistance, although the latter measurements did not return to their control values. Since these effects were produced without alteration of blood viscosity, the results suggest that hypoxic postglomerular vasodilatation accounts for part of the fall in the renal filtration fraction.

The renal O\textsubscript{2} consumption was reduced in anemia. The changes observed in anemia appeared to be greater for a given reduction in renal P\textsubscript{O\textsubscript{2}} than those observed in the rabbit when breathing low oxygen mixtures or low concentrations of carbon monoxide in air. The present experiments throw no light on the mechanism of this apparently greater reduction in renal O\textsubscript{2} consumption in anemia. It is possible that reduction in O\textsubscript{2} consumption may have been associated with a decrease in GFR and a fall in sodium load available for reabsorption or with redistribution of intrarenal blood flow from areas of high oxygen consumption to areas of low oxygen consumption.

The observations concerning the renal PAH extraction ratio are of interest in relation to the findings of Kinter and Pappenheimer, and Thompson et al., obtained from anesthetized cats and dogs. In both the latter series the initial control extraction ratios at normal hematocrit values were much lower than in the present series. The present experiments demonstrate that there was no change in renal PAH extraction ratio in moderate anemia (hematocrit 20%), whereas there was a small but definite reduction in PAH extraction ratio in severe anemia (hematocrit 10%). In these experiments the fall in extraction ratio was approximately similar to that observed by Thompson et al., and was smaller than that observed by Kinter and Pappenheimer. At the lowest hematocrit values (3 to 10%) studied by Kinter and Pappenheimer, the PAH or diodrast extraction ratio was about 60% of the control value. In the present series the PAH extraction ratio was about 95% of the control value with a hematocrit of 11.5%, and was about 88% of the control value at hematocrits between 6 and 10%. Minor fluctuations in plasma PAH level did not contribute to the change in PAH extraction ratio in anemia, and the effect occurred over a wide range of tubular loads of PAH.

The effect of breathing 100% O\textsubscript{2} on PAH extraction ratio was slight and inconclusive. However, comparison of the results in anemia and in the carbon monoxide experiments demonstrated that at any given level of renal hypoxia there was a smaller reduction in renal PAH extraction ratio when the hematocrit was normal than when it was low. It was shown that only with very severe degrees of renal tissue hypoxia produced by breathing carbon monoxide was there a marked reduction in renal PAH extraction ratio. At the levels of renal venous P\textsubscript{O\textsubscript{2}} observed in anemia it seems that the reduction in red cell concentration was a factor in bringing about the reduction in renal PAH extraction ratio. The present results are thus consistent with the possibility of some shunting of PAH away from the renal tubules as proposed by Kinter and Pappenheimer, or with partition of blood flow between renal cortex and medulla, though they throw no light on the mechanisms by which these effects might be produced. How-
ever, the experiments indicate that any shunting of PAH away from the tubules is small even in the most severe grades of anemia studied here, and is negligible in moderate anemia.

The present observations suggest that renal tissue hypoxia and reduction in red cell concentration contribute in varying degrees to the changes observed in the renal circulation and PAH extraction ratio in anemia.

**Summary**

In the unanesthetized rabbit made acutely anemic by bleeding with plasma replacement, there was no change in renal blood flow (RBF), a reduction in glomerular filtration rate (GFR), and a reduction in renal vascular resistance with a fall in the filtration fraction. There was evidence of renal tissue hypoxia and reduction in renal PAH extraction ratio. The extraction ratio was 97% at a hematocrit ratio of 34.5%, 91% at a hematocrit of 11.5%, and 84% with hematocrits between 6 and 10%. The effects of carboxyhemoglobinemia at normal blood viscosity were compared with the effects of anemia; a smaller reduction in renal PAH extraction ratio was found and there was no reduction in filtration fraction. The reductions in renal vascular resistance and filtration fraction in anemia were partly reversed by breathing 100% O2, viscosity changes again being minimized. It was concluded that renal tissue hypoxia and reduction in red cell concentration contribute in varying degrees to the changes in the renal vascular bed and the PAH extraction ratio.

**References**


