Effect of Hemodilution on the Distribution of Renal Blood Flow

By Stephen Migdal, Edward A. Alexander, Frank J. Bruns, Arthur L. Riley, and Norman G. Levinsky

ABSTRACT

We evaluated the effects of hemodilution, expansion of intravascular volume, and expansion of interstitial volume on the distribution of cortical renal blood flow, utilizing the microsphere technique. Hemodilution without volume expansion (saline exchange) produced an increase in fractional blood flow in zone 1 (outermost zone) of the cortex from 34 ± 1% to 43 ± 2% and a decrease in fractional blood flow in zone 4 (innermost zone) from 16 ± 2% to 13 ± 2%. Hemodilution without volume expansion or a decrease in plasma protein concentration (isonicotic exchange) produced a similar redistribution in blood flow in zone 1 from 34 ± 2% to 41 ± 2% and in zone 4 from 14 ± 2% to 10 ± 1%. Hemodilution with intravascular volume expansion (hyperoncotic albumin infusion) also produced a superficial shift; blood flow in zone 1 increased from 27 ± 1% to 30 ± 1% and that in zone 4 decreased from 19 ± 2% to 15 ± 1%. Previous studies have demonstrated a redistribution to the juxtamedullary area after saline expansion. Our data demonstrate that hemodilution causes flow to redistribute to the superficial rather than the deep cortex. This superficial shift appears to be secondary to decreased hematocrit rather than to dilution of plasma proteins or expansion of intravascular volume. The deep shift in cortical blood flow which occurs during saline loading is presumably a consequence of expansion of interstitial volume.

KEY WORDS
volume expansion, dog, radioactive microspheres, renal blood flow, axial streaming

Acute saline infusion increases blood flow to the inner cortex of the kidney proportionately more than it increases flow to the superficial zones (1–3). Among the changes during saline loading that could cause this redistribution of blood flow are: (1) hemodilution, (2) expansion of intravascular volume, and (3) expansion of interstitial volume. We designed experiments in dogs to study the separate effects of these changes on the distribution of cortical blood flow. We found that decreased hematocrit caused flow to redistribute to the superficial rather than the deep cortex. Dilution of plasma proteins and expansion of intravascular volume appeared to have no major effect on blood flow distribution. The deep shift of cortical blood flow during saline infusion is presumably a consequence of expansion of the interstitial volume.

Methods

Dogs weighing 11–23 kg were anesthetized with sodium pentobarbital (30 mg/kg, iv) and ventilated with a Harvard respirator through a cuffed endotracheal tube. Blood pressure was measured through a catheter placed in the thoracic aorta via the brachial artery. Microspheres were injected into the left ventricle through a catheter passed via the brachial or femoral artery. Both ureters were catheterized near the renal pelvis through bilateral retroperitoneal flank incisions. All experiments were begun at least 1 hour after the completion of surgery. In the dogs undergoing cross perfusion, one catheter was passed into the thoracic inferior vena cava via the femoral vein and one into the opposite iliac vein. In these dogs, renal blood flow was determined by placing an appropriately sized (2.5–3.5 mm, i.d.) Biotronex series 5000 flow probe on the right renal artery with a balloon distal to the probe for zero flow calibration. Measurements were recorded continuously with a Biotronex 610 flowmeter and a Hewlett Packard 7702B recorder but are presented for statistical purposes as a mean value for each clearance period. At the conclusion of each experiment, the flow probe was calibrated in vivo by direct collections from a renal artery catheter.

The dogs were divided into three groups.

Group 1: Hemodilution without Volume Expansion (Saline Exchange).—In seven dogs, four control urine collections were obtained, and cross

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circulation was begun. Blood was pumped from the iliac vein into a siliconized, heparinized reservoir that contained a volume of 0.85% saline equal to 5% of the dog’s weight. Fluid from the reservoir was simultaneously infused by gravity into the thoracic inferior vena cava at a rate which kept the level of fluid in the reservoir constant. Cross perfusion was continued until hematocrit and plasma protein measurements were equal in the dog’s blood and the reservoir. This equilibration was accomplished in 30–60 minutes. Thirty minutes after the cessation of cross circulation, clearance collections were repeated. During the second clearance collection of both the control and experimental periods, 4–10 x 10^5 differently labeled radioactive microspheres (15 ± 5 μ) (3M Co.) were injected.

**Group 2: Hemodilution with Volume Expansion or a Decrease in Plasma Protein Concentration (Isoneotic Exchange).**—These six dogs were treated identically to those of group 1 except that they were hemodiluted with a solution of bovine albumin in saline with a protein concentration equal to that of the dog’s control serum.

**Group 3: Hemodilution with Expansion of Blood Volume (Hyperoncotic Albumin Infusion).**—In six dogs, hemodilution was produced by intravenous injection had been made, 100 ml of 30% bovine albumin. In these dogs, renal plasma flow (RPF) was calculated from the clearance of para-aminohippuric acid (PAH) and extraction ratios obtained in comparable experiments performed in our laboratory (4) and by Knox et al. (5); the values were 0.80 control and 0.72 after albumin. Renal blood flow (RBF) was calculated from the formula RBF = RPF/1 – hematocrit.

At the termination of all experiments, the kidneys were removed and sectioned; the microsphere radioactivity was determined by methods that have been previously described (1). Briefly, four zones of cortex of equal thickness were cut; they are described as zones 1-4, outermost to juxtamedullary. Ten tissue samples from each zone were counted separately. The percent distribution of flow to each zone was calculated as mean counts per minute per gram for that zone divided by the sum of the counts per minute per gram for all four zones (1). Inulin clearance, PAH clearance, and plasma protein concentration were determined as previously described (6). Student’s t-test was used to determine statistical significance. All values are given as means ± SE.

**Results**

All of the data from the present experiments are summarized in Tables 1 and 2; microsphere data from saline infusion experiments reported previously (1) are shown in Table 2 for comparison.

**GROUP 1**

After exchange with 0.85% saline, hematocrit was reduced by 23% and serum protein concentration by 30% (P < 0.01). Hemodilution resulted in a significant increase in the fractional blood flow to zone 1, 34 ± 1% to 43 ± 2% (P < 0.01), and a significant decrease in fractional blood flow to zone 4, 16 ± 2% to 13 ± 2% (P < 0.05). These changes were comparable in all seven dogs studied. This shift in blood flow distribution occurred despite a 15% fall in total renal blood flow (P < 0.01) and a 12% fall in blood pressure (P < 0.01).

**TABLE 1**

Summary of Clearance and Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (N = 7)</th>
<th>Group 2 (N = 6)</th>
<th>Group 3 (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>E</td>
<td>C</td>
</tr>
<tr>
<td>C&lt;sub&gt;K&lt;/sub&gt; (ml/min)</td>
<td>38 ± 2</td>
<td>37 ± 2</td>
<td>35 ± 2</td>
</tr>
<tr>
<td>RBF (ml/min)</td>
<td>203 ± 17</td>
<td>170 ± 14*</td>
<td>198 ± 26</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>116 ± 5</td>
<td>119 ± 5*</td>
<td>120 ± 6</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>48 ± 2</td>
<td>37 ± 2*</td>
<td>46 ± 2</td>
</tr>
<tr>
<td>Protein (g/100 ml)</td>
<td>5.3 ± 0.2</td>
<td>4.0 ± 0.1*</td>
<td>6.3 ± 0.3</td>
</tr>
<tr>
<td>Resistance (mm Hg/ml min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.70 ± 0.1</td>
<td>0.74 ± 0.1</td>
<td>0.64 ± 0.2</td>
</tr>
</tbody>
</table>

Values are means ± SE. Abbreviations: C = control period, E = experimental period, C<sub>K</sub> = clearance of inulin, RBF = renal blood flow, BP = blood pressure, Hct = hematocrit, Protein = serum protein concentration, and Resistance = renal vascular resistance.

*P < 0.01.

tP < 0.05.
HEMODILUTION AND INTRARENAL BLOOD FLOW

TABLE 2
Summary of Cortical Blood Flow Distribution

<table>
<thead>
<tr>
<th></th>
<th>Zone 1</th>
<th>Zone 2</th>
<th>Zone 3</th>
<th>Zone 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (saline exchange)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>34 ± 1</td>
<td>29 ± 1</td>
<td>21 ± 1</td>
<td>16 ± 2</td>
</tr>
<tr>
<td>E</td>
<td>43 ± 2*</td>
<td>29 ± 2</td>
<td>17 ± 1*</td>
<td>13 ± 2†</td>
</tr>
<tr>
<td>Group 2 (isoncotic exchange)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>34 ± 2</td>
<td>30 ± 1</td>
<td>22 ± 1</td>
<td>14 ± 2</td>
</tr>
<tr>
<td>E</td>
<td>41 ± 2†</td>
<td>30 ± 1</td>
<td>18 ± 1†</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>Group 3 (albumin exchange)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>27 ± 1</td>
<td>31 ± 1</td>
<td>23 ± 1</td>
<td>19 ± 2</td>
</tr>
<tr>
<td>E</td>
<td>30 ± 1†</td>
<td>31 ± 1</td>
<td>24 ± 4</td>
<td>15 ± 1*</td>
</tr>
<tr>
<td>Saline expansion †</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>29 ± 2</td>
<td>32 ± 3</td>
<td>23 ± 1</td>
<td>16 ± 2</td>
</tr>
<tr>
<td>E</td>
<td>30 ± 1</td>
<td>27 ± 3*</td>
<td>21 ± 1†</td>
<td>22 ± 2*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Abbreviations are the same as they are in Table 1.
*P < 0.01.
†P < 0.05.
†Data from a previous study (1).

GROUP 2

After exchange with isoncotic albumin in 0.85% saline, there was a 39% fall in hematocrit (P < 0.01) without a significant change in serum protein concentration. In this group, as in group 1, there was a significant redistribution of blood flow to the superficial cortex in all of the dogs studied; fractional blood flow in zone 1 increased from 34 ± 2% to 41 ± 2% (P < 0.05). In five of the six dogs, there was a decrease in fractional blood flow to the deeper zones 3 and 4. Renal blood flow tended to increase, although blood pressure remained unchanged.

GROUP 3

Intravascular expansion with hyperoncotic albumin resulted in a fall in hematocrit of 23% (P < 0.01), but serum protein concentration was not significantly changed. As in groups 1 and 2, there was a significant increase in fractional blood flow to zone 1 in all of the dogs studied from 27 ± 1% to 30 ± 1% (P < 0.05). Zone 4 flow decreased in all of the dogs from a mean of 19 ± 2% to 15 ± 1% (P < 0.01). Renal blood flow and blood pressure were not significantly changed.

Discussion

The purpose of this study was to compare the effects of hemodilution, expansion of intravascular volume, and expansion of interstitial volume on the distribution of cortical blood flow, utilizing the microsphere technique. The validity of this technique has been extensively discussed recently (1, 7-9), and it appears to be quite adequate for the measurement of alterations in cortical renal blood flow.

It has been demonstrated by several investigators (1-3) that saline expansion produces a redistribution of cortical blood flow to the deep or juxtamedullary area. For reference purposes, we have included in Table 2 some data from our laboratory that have been published previously in different form (1). These data were obtained from ten hypopenic dogs before and after expansion with isotonic saline equal to 10% of the dog's weight. It is unclear from previously published data (1-3) whether the deep shift in blood flow distribution is secondary to volume expansion alone or to the possible effects of hemodilution. The experiments in groups 1 and 2 were designed to produce a degree of hemodilution, as judged by reduction in hematocrit, comparable to that which occurs with saline loading (31% [1]), but without volume expansion. When this condition was accomplished, there was a superficial shift in blood flow. This result was all the more impressive in group 1, since renal blood flow and blood pressure fell modestly, probably because of the dilution of plasma protein and, hence, a reduction in intravascular volume. Previous studies have demonstrated...
a deep shift in blood flow during reductions in renal blood flow or blood pressure (7, 9). It is unlikely, therefore, that the 12-15% decrements in total renal blood flow and blood pressure can account for the opposite effect, i.e., the superficial shift we noted.

To determine the effect of a reduction in hematocrit without a dilution of serum proteins, exchange with hyperoncotic albumin in saline was performed (group 2). Again a superficial shift of blood flow occurred. In this group, total renal blood flow, blood pressure, and, hence, renal resistance were not altered significantly. From these experiments, it seems most likely that the reduction in hematocrit produced the superficial shift in cortical blood flow. This conclusion was strengthened by the results noted with hyperoncotic albumin expansion (group 3). In these dogs, a reduction in hematocrit was accomplished along with intravascular volume expansion comparable to that which occurs with saline loading. Again blood flow was redistributed to the superficial cortex. We conclude from these data that a reduction in hematocrit produces a superficial shift in blood flow. Since the degree of shift in groups 1 and 3 was not different from that in group 2, reduction in serum protein concentration or expansion of intravascular volume probably has little if any direct effect on intrarenal blood flow distribution.

We have no definite explanation for the superficial shift observed in our experiments, but it seems reasonable to assume that it is a physiological response to hemodilution. McDonald (10) has recently shown that renin secretion decreases significantly when the hematocrit is reduced. Since renin is found in highest concentration in the superficial nephrons (11), reduced renin secretion during hemodilution could allow superficial vasodilation and increased superficial cortical blood flow. Another possibility is suggested by two recent preliminary reports (12, 13). Inhibitors of prostaglandin synthesis have been found to redistribute blood flow to the superficial cortex. It is possible that hemodilution inhibits prostaglandin synthesis. We have no data to support either possibility. An alternative explanation derives from the studies of Goldsmith (14) in artificial systems: when the hematocrit is lowered drastically to approximately 5%, there is a marked reduction in red cell-red cell collisions. These cell collisions produce a turbulence which prevents significant axial streaming. During hemodilution, these cell interactions are reduced, and there is a much greater potential for axial streaming. Thus, hemodilution in vivo might introduce a rheologic artifact which enhances microsphere distribution to the superficial cortex even though true renal plasma flow to this area is unchanged. However, the Goldsmith effect is significant only at extremely low hematocrits, and it is very unlikely to be a factor at the much higher levels at which our study was carried out.

Beyond the demonstration of superficial redistribution during hemodilution, our data bear on the mechanism of the deep shift during saline loading. Wallin et al. (15) have argued that the shift is a rheologic artifact. They have proposed that under control conditions there is significant streaming of microspheres to the superficial cortex which decreases after hemodilution with saline. Since we found that hemodilution without volume expansion (groups 1 and 2) caused superficial, not deep redistribution, our experiments are a potent argument against this hypothesis. Stein et al. (8) and Baehler et al. (16) have recently provided other evidence against streaming artifacts as the explanation of deep redistribution during saline infusion.

Our data suggest very strongly that the deep redistribution of blood flow during saline loading is related to interstitial expansion. During massive saline loading interstitial volume presumably increases markedly. During hyperoncotic infusion interstitial volume may fall (17) or remain unchanged (5), and during isoncotic exchange interstitial volume is probably also unaltered. During saline exchange interstitial volume may increase slightly due to hypoproteinemia, but any shift of fluid to the interstitium is probably limited by hypotension and is unlikely to approach that occurring during saline loading. Of the other factors which change during saline loading, decreased hematocrit causes a superficial shift, and decreased plasma protein concentration and plasma volume expansion appear to have no major effect on blood flow distribution. If expansion of interstitial volume is indeed the cause of the deep shift, it is tempting to speculate that the critical interstitial volume may be within the kidney itself. McGiff et al. (18) and
Attallah and Lee (19) have suggested that intrarenal production of prostaglandins, known to occur in the renal medulla, may serve a critical function with regard to the control of intrarenal blood flow distribution. Attallah and Lee (19) have shown that saline loading increases medullary production of prostaglandin. It is possible that the production of prostaglandin during saline loading occurs secondary to some alteration in renal interstitial pressure, composition (18), or volume. The release of a potent vasodilator such as a prostaglandin whose action may be restricted primarily to the corticomedullary and medullary areas (18) would lead to a deep shift in blood flow distribution. This concept is consonant with the suggestion of Stein et al. (7) that vasodilatation is a common feature in experimental models in which a deep shift occurs. Whatever the mechanism of the deep shift during saline loading, it is very potent, since it causes an overall redistribution of flow to the juxtamedullary cortex despite the tendency for a superficial shift in blood flow due to the concurrent hemodilution.

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