**Effect of Adenosine on the Distribution of Renal Blood Flow in Dogs**

**WILLIAM S. SPIELMAN, STEVEN L. BRITTON, AND MARY J. FIksen-Olsen**

**SUMMARY** Previous reports have shown that the intrarenal infusion of adenosine results in a relatively greater fall in superficial nephron glomerular filtration rate (GFR) than whole kidney GFR. This nonuniform decrease in GFR occurred despite a concomitant increase in total renal blood flow (RBF); thus, the present study was undertaken to assess the effect of intrarenally administered adenosine on the distribution of RBF. RBF distribution was measured with radiolabeled microspheres (15 μm) in anesthetized dogs (n = 8) before and during the intrarenal artery infusion of adenosine (0.3 μmol/min). In dogs with elevated plasma renin activities (PRA), adenosine infusion produced no significant change in outer cortical blood flow (4.36 ± 0.50 vs. 4.41 ± 0.63 ml/min per g), whereas absolute inner cortical blood flow increased by 94% (1.54 ± 0.34 vs. 2.99 ± 0.52 ml/min per g). In dogs with low PRA, outer cortical blood flow was only minimally affected by adenosine infusion (6.39 ± 0.44 vs. 5.88 ± 0.33 ml/min per g), whereas inner cortical blood flow was increased from 4.91 ± 0.43 to 6.06 ± 0.38 ml/min per g. Although adenosine resulted in a deep cortical vasodilation in dogs with both high and low PRA (94% vs. 23%), the relative change was greater in the animals with high PRA. Additional experiments were performed in indomethacin- (or meclofenamate-) treated (n = 14) or phenoxybenzamine-treated (n = 5) dogs to determine whether the deep cortical vasodilation is mediated by increased prostaglandin production or by inhibition of norepinephrine release. The increase in deep cortical flow during adenosine administration was not affected by either the blockade of prostaglandin synthesis or α-adrenergic receptors. We conclude that the effect of adenosine to preferentially dilate vessels of the inner cortex is independent of a prostaglandin-related or sympathetic adrenergic mechanism.

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PREVIOUS reports hypothesize that intrarenal adenosine is a metabolic regulator of renal blood flow and glomerular filtration rate (GFR) (Osswald et al., 1978; Spielman and Osswald, 1978; Miller et al., 1978). Adenosine dilates most vascular beds (Hashimoto and Kumakura, 1965; Haddy and Scott, 1968) and relaxes smooth muscle of the small intestine (Ally and Nakatsu, 1976) and isolated renal artery strips (Walter and Bassenge, 1968); however, it produces vasoconstriction when injected as a bolus directly into the renal artery. On the other hand, the continuous infusion of adenosine into the renal artery results in a transient decrease in renal blood flow which wanes rapidly and returns to or increases above the preinfusion flow rate (Osswald et al., 1978).

Unlike renal blood flow, GFR remains depressed during the infusion of adenosine. This decrease in glomerular filtration is not uniform throughout the kidney, as evidenced by a relatively greater fall in superficial nephron GFR than whole kidney GFR (Osswald et al., 1978). Additionally, the effect of adenosine to decrease GFR may be related to the activity of the renin-angiotensin system, in that adenosine results in large decreases in GFR in animals maintained on a low-sodium diet, whereas little or no change occurs in animals on a diet high in sodium (Osswald et al., 1975).

A preliminary report (Ueda, 1972) suggests that adenosine infusion distributes a relatively greater than normal portion of total renal blood flow to the inner cortex. Other studies suggest that adenosine stimulates prostaglandin synthesis in the kidney (Spielman and Osswald, 1978) and have established that adenosine inhibits norepinephrine release from the renal sympathetic nerves (Hedqvist and Fredholm, 1976). Either of these two modulators of RBF might participate in the mechanism whereby deep cortical blood flow is increased by adenosine. Thus, the present study was undertaken (1) to assess the effects of adenosine on the distribution of renal blood flow in dogs with both high- and low-renin levels and (2) to investigate if the increase in renal deep cortical blood flow produced by adenosine is the result of an interaction between adenosine and the renal prostaglandins or the renal sympathetic nervous system.

**Methods**

We studied dogs of either sex, weighing 14–21 kg. Dogs were maintained on diets either low or high in sodium content. Dogs receiving a low-sodium intake were given 100 mg of furosemide (intramuscularly) the first day of the dietary regimen and...
then were given a diet of <2 mEq/day of sodium for 5-8 days prior to experimentation. Dogs receiving a high-sodium intake were given daily injections of deoxycorticosterone acetate (25 mg) and the same diet as the low-sodium group to which 150 mEq of sodium had been added. Dogs were maintained on high-sodium intake and deoxycorticosterone for 14 to 21 days prior to the acute experiment.

Dogs were anesthetized with pentobarbital (30 mg/kg, iv); subsequent small doses were given as needed. Catheters (PE 160) were placed in the femoral artery and vein to measure arterial blood pressure (Statham strain gauge, P23Db, Gould Brush recorder 220) and to give systemic infusions. A thoracotomy was performed at the left 4th intercostal space, and a catheter (PE 160) was placed in the left atrium for microsphere injection. The dogs were placed in a metal frame which held them in a position approximating their normal standing posture. After tracheal intubation, each animal was ventilated mechanically with a Harvard respirator and the minute volume ventilation was selected by reference to the nomogram of Kleinman and Radford (1964). Body temperature was monitored with a rectal thermometer and was maintained between 37.5 and 39.0°C by a circulating water heating pad.

A retroperitoneal flank incision was made to expose the left renal artery for the placement of a noncannulating electromagnetic flow probe (Carolina Medical Electronics). The flow probe was calibrated by renal artery cannulation at the end of each experiment. On occasion, when the presence of a double renal artery precluded the use of the flow probe on the left side, the right renal artery was exposed through a contralateral flank incision. In these cases, the left flank incision was closed with sutures to avoid unnecessary evaporative fluid loss. A small curved infusion needle was placed into the renal artery just distal to the flow probe. The patency of the needle was maintained by a constant infusion of saline (1.91 ml/min). The same infusion rate was maintained at all times regardless of infusate.

Three groups of studies were performed:

Effect of Adenosine on the Distribution of Renal Blood Flow in Dogs with High or Low Plasma Renin Activity

Eight animals receiving a low-sodium diet and seven receiving a high-sodium diet were studied. Following surgical preparation, an interval of at least 45 minutes was allowed for stabilization as determined by steady blood pressure and renal blood flow recordings. Five minutes after a control injection of microspheres, the intrarenal infusion of saline was switched to adenosine (3.3 × 10⁻⁷ mol/min). Adenosine was infused for 10 minutes before injection of the second nuclide.

Effect of Prostaglandin Synthetase Inhibitors on the Distribution of Renal Blood Flow Produced by Adenosine

All dogs in this series were maintained on a low-sodium diet. Four experiments were performed on dogs given meclofenamate systemically (4 mg/kg, iv), and three experiments were performed on dogs given indomethacin directly into the renal artery (10 µg/min per kg). All experiments were performed exactly as described above, except an interval of 1 hour was allowed after administration of indomethacin or meclofenamate before the first microsphere injection. Blockade of prostaglandin synthesis was assessed in each dog by the direct injection of arachidonic acid (300 µg) into the renal artery pre- and post-indomethacin or meclofenamate administration.

Effect of α-Blockade on the Distribution of Renal Blood Flow Produced by Adenosine

All animals in this series were maintained on the low-sodium diet. Two dogs were given phenoxybenzamine systemically (10 mg/kg, iv), and in three dogs the drug was infused directly into the renal artery (0.18 µg/min per kg) to avoid the systemic effects of α-blockade. Experiments were performed as described above except that four nuclide species of microspheres were used so that the distribution of renal blood flow could be assessed four times. Following a control determination of renal blood flow with microspheres and the injection of another microsphere nuclide species during the infusion of adenosine, α-adrenergic blockade was performed. One hour after the administration of phenoxybenzamine, renal blood flow again was measured with microspheres both before and during the administration of adenosine. This experimental design allowed each dog to serve as its own control. Alpha-adrenergic blockade was verified by injection of norepinephrine (1 and 2 µg) into the renal artery pre- and post-phenoxybenzamine administration.

Radioactive microspheres (New England Nuclear), 15 µm in diameter, labelled with γ-emitting nuclides, were used to measure total and regional renal blood flow. In experiments that required two nuclide species, ¹²⁵Sn and ⁵⁷Co were used; in experiments that required four nuclide species, ⁴¹Ce, ⁵¹Cr, ¹¹⁸Sn, and ⁴⁶Sc were used. The sequence of nuclides used was random. The stock solution of microspheres came suspended in 10% dextran and contained 0.01% Tween 80 surfactant to prevent aggregation.

Prior to injection, the stock solution of spheres was agitated mechanically and ultrasonicated. Approximately 7 × 10⁵ spheres were withdrawn from the stock solution and suspended in 2 ml of saline warmed to 37°C; this sphere solution was injected immediately into the left atrium and flushed with 10 ml of warmed, heparinized saline. To minimize
retention of microspheres in the injection system, the stopcock and hub of the left atrial catheter were replaced after each administration of microspheres. The kidneys were removed at the end of the experiment and the cortex was divided into four equal zones which will be designated as zones I-IV, going from the outer to inner cortex, respectively. The medulla and portions of the cortex in the renal poles, which could not be divided accurately into zones, were treated in the same manner as cortical zones so that total renal blood flow could be evaluated. Tissue samples were weighed and placed at equal heights in 10-cm plastic counting vials. The radioactivity of the samples was measured with a Searle γ counter and isotope separation was performed using the method of Rudolph and Heymann (1967). Flow (F) to each zone on a per gram basis was calculated using the following formula: $F = \frac{Q_T}{RT} \times RZ \times g^{-1}$, where $Q_T = \text{total renal blood flow as measured with flowmeter}$, $RT = \text{total radiation for the whole kidney}$, $RZ = \text{radiation for a particular cortical zone}$, and $g = \text{weight of cortical zone}$. Microsphere data computations were performed using a PDP 11/40 computer as described by Lydic et al. (1977).

Slotkoff et al. (1971) obtained results showing that 15 μm is an appropriate size of microsphere for measuring total and cortical renal blood flow distribution in the dog. A recent report by Fan et al. (1979) supports the choice of this size sphere for cortical blood flow determination. Slotkoff et al. (1971) have shown that with microspheres of this size: (1) shunting is minimal (<0.2%), (2) the measurements of both total and regional renal blood flow are reproducible, and (3) there is no impairment of renal function as assessed by examination of PAH clearance, inulin clearance, and the tubular maximum for glucose.

Accurate measurement of blood flow with microspheres requires that they become mixed uniformly with blood so that their distribution will be proportional to blood flow (Wagner et al., 1969). Adequate mixing of microspheres has been documented previously (Rudolph and Heymann, 1967; Hales, 1973). In preliminary experiments in our laboratory, adequate mixing was verified by the observation that blood flow values were equal on both sides of the brain (3.09 ± 0.21 vs. 3.13 ± 0.24 ml/min per g) and in both the right and left kidney (4.75 ± 0.27 vs. 4.81 ± 0.30 ml/min per g). Further validation of the technique in our laboratory was obtained by the simultaneous administration of different combinations of the species of nuclide microspheres into the left atrium. Similar values for both total and regional renal blood flow were obtained with each microsphere nuclide species when all microsphere nuclide species were administered simultaneously. Numerous other laboratories have confirmed the validity of the assessment of canine renal cortical blood flow with radioactive microspheres (McNay and Abe, 1970; Kirschenbaum et al., 1974; Riley et al., 1975; Hardaker et al., 1975; Stein et al., 1973).

Plasma renin activity was assessed by a radioimmunoassay using a method described in a previous study (Romero and Strong, 1977). The specificity and reproducibility of this method of measuring plasma renin activity in dogs also have been reported previously (Mancia et al., 1975). Samples for plasma renin activity were withdrawn through the arterial catheter immediately before starting the control period. Plasma renin activities are presented as ng/ml per hour to indicate the ng of angiotensin I generated per ml of plasma per hour of incubation.

Sodium meclofenamate (Parke-Davis) was prepared in normal saline (10 mg/ml), and indomethacin (Merck, Sharp & Dohme) was prepared in sodium phosphate buffer (10 mg/ml) and the pH adjusted to 7.4. Arachidonic acid (NuChek Prep., Inc.) was prepared in carbonate buffer (pH 8) and was kept in the dark in a nitrogen atmosphere until injected. Adenosine (Aldrich), phenoxymethylbenzamine (Smith, Kline & French), and norepinephrine (Winthrop) all were dissolved in isotonic saline. All drugs were prepared the day of the experiment.

Statistical analysis was performed using a Student's t-test for paired and unpaired saline, and the data are presented as means ± 1 SEM.

**Results**

**Effect of Adenosine on the Distribution of Renal Blood Flow in Dogs with High or Low Plasma Renin Activity**

In the dogs with high PRA [mean plasma renin activity of 11.3 ± 4.2 ng/ml per hour as compared to 5.9 ± 1.1 ng/ml per hour for dogs (n = 20) in our laboratory on an ad libitum sodium intake], adenosine produced an increase in total renal blood flow (2.61 ± 0.29 to 3.22 ± 0.41; $P < 0.05$) and had no effect on systemic arterial blood pressure (121.1 ± 3.3 to 118.2 ± 3.5 mm Hg). Adenosine produced no effect on blood flow in outer cortical zones I and II in these dogs (Fig. 1). Adenosine produced vasodilation in the inner cortex as evidenced by the 38% and 94% increases in blood flow in zones III and IV, respectively (Fig. 1). Total blood flow and its distribution in the contralateral kidney were not altered by the infusion of adenosine into the experimental kidney.

In the dogs with low PRA [mean plasma renin activity of 0.2 ± 0.04 ng/ml per hour], total kidney blood flow and cortical blood flow to all zones were significantly higher than the same parameters in the dogs with high PRA (Table 1 and Fig. 1). Adenosine infusion into these dogs produced statistically significant increases in blood flow to zones III and IV, while zones I and II were not affected. Although inner cortical blood flow (zones III and IV) was increased in each dog, this change was not reflected as a significant change in total renal blood
flow since directionally opposite changes in blood flow to the outer cortical zones were observed in several dogs (Table 1). Although the absolute increases in blood flow of zones III and IV produced by adenosine were similar in both groups of dogs, the relative increase of zones III and IV (percent change in absolute flow) was much greater in dogs with high PRA as compared to those with low PRA (Fig. 2). No change in mean arterial pressure (Table 1) or contralateral blood flow (total or zonal) was observed during the infusion of adenosine in the dogs with low PRA. Control mean arterial blood pressure was significantly higher ($P < 0.05$) in the dogs with high PRA ($121.1 \pm 3.3$ mm Hg) as compared to those with low PRA ($97.7 \pm 3.1$ mm Hg).

**Effect of Prostaglandin Synthetase Inhibitors on the Distribution of Renal Blood Flow by Adenosine**

Results of these studies are summarized in Table 2 and Figure 3. [Mean plasma renin activity of the combined prostaglandin synthetase inhibitor group was $8.6 \pm 1.4$ ng/ml per hour, not statistically different from the nontreated dogs given low-sodium diet ($11.3 \pm 4.2$ ng/ml per hour).] In all animals given meclofenamate or indomethacin systemically, there was an increase in mean arterial pressure within 10-15 minutes of administration of the drug which persisted throughout the period of study. This change in blood pressure was from $129 \pm 4$ to $149 \pm 2$ mm Hg in the four meclofenamate-treated dogs, and from $122 \pm 5$ to $139 \pm 7$ mm Hg in the seven indomethacin-treated dogs. Total renal blood flow was decreased by meclofenamate treatment in each of the four dogs ($181 \pm 16$ vs. $145 \pm 15$ ml/min) and in all seven dogs treated with indomethacin ($165 \pm 13$ vs. $139 \pm 15$ ml/min). All animals given systemic meclofenamate or indomethacin were challenged with 300 μg of arachidonic acid administered directly into the renal artery pre- and post-meclofenamate or indomethacin administration. Systemically administered meclofenamate and indomethacin were effective in block-
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Effect of Adenosine on the Distribution of Renal Blood Flow in the Dog with Low PRA

Table 1

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>C</th>
<th>A</th>
<th>C</th>
<th>A</th>
<th>C</th>
<th>A</th>
<th>C</th>
<th>A</th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>Total renal blood flow (ml/min per g)</th>
<th>Flow to cortical zone (ml/min per g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
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<td></td>
<td></td>
<td>IV</td>
</tr>
</tbody>
</table>
| C = control; A = adenosine. * P < 0.025.

Effect of α-Adrenergic Blockade on the Distribution of Renal Blood Flow by Adenosine

The results of these studies are summarized in Table 3. The infusion of adenosine in the control portion of the experiment produced a response in cortical blood flow (zones I-IV) similar to that which occurred in the dogs with high PRA as shown in Figure 1. After the first adenosine infusion, dogs no. 1 and 2 (Table 3) were given phenoxybenzamine systemically. In both dogs, phenoxybenzamine decreased renal vascular resistance. Infusion of adenosine resulted in 32 and 22% increases in zone IV flow in dogs 1 and 2, respectively, which compared to 38 and 98% increases in zone IV flow prior to α-blockade. In one dog (no. 2, Table 3) α-blockade decreased mean arterial blood pressure from 145 to 80 mm Hg. This decrease in arterial blood pressure might have affected blood flow distribution; therefore, subsequent experiments were performed using an intrarenal infusion of phenoxybenzamine to avoid the systemic effect of α-blockade. In the three dogs given phenoxybenzamine intrarenally, the ef-

Table 2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>Total renal blood flow (ml/min per g)</th>
<th>Mean arterial blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>A</td>
<td>C</td>
<td>A</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>Meclofenamate</td>
<td>5.84</td>
<td>5.32</td>
<td>5.01</td>
<td>5.14</td>
<td>3.50</td>
<td>4.47</td>
</tr>
<tr>
<td>(n = 4)</td>
<td>±1.06</td>
<td>±0.63</td>
<td>±0.44</td>
<td>±0.08</td>
<td>±0.28</td>
<td>±0.46</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>4.26</td>
<td>4.27</td>
<td>4.13</td>
<td>4.19</td>
<td>3.14</td>
<td>3.69</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>±0.46</td>
<td>±0.63</td>
<td>±0.36</td>
<td>±0.56</td>
<td>±0.56</td>
<td>±0.29</td>
</tr>
</tbody>
</table>
| Intrarenal indo-
| 4.79  | 5.04  | 4.51  | 5.31  | 3.41  | 5.17  | 1.93  | 3.79  | 2.83  | 3.73  | 112.7 | 110.5 |
| methacin        | ±0.35 | ±0.24 | ±0.47 | ±0.31 | ±0.54 | ±0.42 | ±0.29 | ±0.27 | ±0.21 | ±2.7  | ±3.2  | ±0.33 | ±0.38 |
| (n = 3)         |       |       |       |       |       |       |       |       |       |       |       |       |       |

Results are expressed as mean ± SEM.
C = Control; A = adenosine.
### Table 3  Effect of \( \alpha \)-Adrenergic Blockade on the Distribution of Renal Blood Flow by Adenosine

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Flow to cortical zone (ml/min per g)</th>
<th>Total renal blood flow (ml/min per g)</th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>Flow to cortical zone (ml/min per g)</th>
<th>Total renal blood flow (ml/min per g)</th>
<th>Mean arterial blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5.20  5.82  4.10  5.18  5.34  5.94  1.93  4.10</td>
<td>3.03  4.23  95  100  6.31  6.61  5.21  5.90</td>
<td>4.75  6.84  274  447  3.83  4.79  107  110</td>
<td>5.20  5.82  4.10  5.18  5.34  5.94  1.93  4.10</td>
<td>3.03  4.23  95  100  6.31  6.61  5.21  5.90</td>
<td>4.75  6.84  274  447  3.83  4.79  107  110</td>
</tr>
<tr>
<td>4</td>
<td>5.31  5.69  4.73  5.20  5.94  5.87  2.48  4.38</td>
<td>3.30  4.16  105  105  5.91  5.96  5.39  5.38</td>
<td>4.87  6.45  312  4.87  3.83  4.44  105  110</td>
<td>5.31  5.69  4.73  5.20  5.94  5.87  2.48  4.38</td>
<td>3.30  4.16  105  105  5.91  5.96  5.39  5.38</td>
<td>4.87  6.45  312  4.87  3.83  4.44  105  110</td>
</tr>
<tr>
<td>5</td>
<td>5.18  3.66  3.82  4.63  3.23  4.58  1.72  2.56</td>
<td>2.37  3.07  118  123  3.01  4.38  3.71  5.73</td>
<td>3.44  5.98  1.97  3.83  120  123</td>
<td>5.18  3.66  3.82  4.63  3.23  4.58  1.72  2.56</td>
<td>2.37  3.07  118  123  3.01  4.38  3.71  5.73</td>
<td>3.44  5.98  1.97  3.83  120  123</td>
</tr>
</tbody>
</table>

| CSEM | ±0.45  | ±0.46  | ±0.34  | ±0.29  | ±0.20  | ±0.38  | ±0.33  | ±0.24  | ±0.36  | ±0.25  | ±0.33  | ±0.21  | ±0.24  | ±0.26  | ±0.71  | ±0.67  | ±0.65  | ±0.61  | ±0.44  | ±0.28  | ±0.33  | ±0.21  | ±0.24  | ±0.26  | ±0.71  | ±0.67  |

C = control; A = adenosine.

* \( P < 0.01; \) † \( P < 0.05; \) ‡ \( P < 0.05.\)

Discussion

These experiments demonstrate that infusion of adenosine into the renal artery induced a preferential vasoconstriction in the outer cortical layer whereas little or no change occurred in blood flow to the inner cortex. A preliminary report by Ueda (1972) suggested that intrarenal infusion of adenosine decreased outer cortical blood flow, whereas following phenoxybenzamine blockade, the same individual experiments did not alter the pattern of blood flow distribution. In the present study, adenosine decreased outer cortical flow by 60 to 95%. Prior to \( \alpha \)-blockade, 2 \( \mu \)g of norepinephrine produced a 60 to 80% decrease in outer cortical blood flow, whereas following phenoxybenzamine, the response was diminished to 0% to 4%.

Regardless of the explanation, our previous conclusion that the decrease in superficial GFR due to adenosine was the result of a vasoconstriction of the outermost cortical slice (zone I) examined was fail to be detected with microsphere distribution if the afferent arteriolar vasoconstriction was localized to only the most superficial layer of cortex, it is possible that it might be sampled by micropuncture. If the afferent arteriolar vasoconstriction was localized to only the most superficial afferent arteriolar vasoconstriction. An adenosine infusion is difficult to reconcile with our data presented as a percent of total flow to a given area, as in the report by Ueda, one cannot distinguish whether a decrease reflects an actual change in absolute flow or merely an increase in flow to other areas. Our data suggest that the increase in flow to the outer cortex while it increased the percentage to the outer cortex as reported by Ueda derives from the cortical blood flow response to adenosine prior to phenoxybenzamine. Inspection of the data for all five does reveals that differences in the relative decrease in blood flow due to adenosine prior to or after a-blockade, compared to the cortical blood flow response to adenosine prior to phenoxybenzamine, were not different.

Adenosine-induced decrease in superficial nephron GFR during a decrease in deep cortical flow and not from the decrease in total flow. The failure to observe any decrease in deep cortical flow and not from the decrease in absolute flow to the outer cortex reported by Ueda (1972) is difficult to reconcile with our previous demonstration of an adenosine-mediated cortical arteriolar vasoconstriction. Adenosine infusion may be offered based on the relatively large compared to the area of vasoconstriction.

A previous study from our laboratory reported that the decrease in superficial GFR due to adenosine infusion was the result of a vasoconstriction of the outermost cortical zone as reported by Ueda, one cannot distinguish whether a decrease reflects an actual change in absolute flow or merely an increase in flow to other areas. The apparent difference in the effect of adenosine on outer cortical blood flow (zones I-IV) in the report by Ueda and the present study may reflect the difference in data presentation. With the data presented as a percent of total flow to a given area, as in the report by Ueda, one cannot distinguish whether a decrease reflects an actual change in absolute flow or merely an increase in flow to other areas. Our data suggest that the increase in flow to the outer cortex while it increased the percentage to the outer cortex as reported by Ueda derives from the cortical blood flow response to adenosine prior to phenoxybenzamine.
the afferent arteriole, cannot be extended to the rest of the kidney as an explanation for the adenosine-mediated decrease in whole kidney GFR.

Previous studies report that intrarenal infusion of adenosine results in a decrease in the rate of glomerular filtration (Osswald, 1975; Tagawa and Vander, 1970) and that this decrease in GFR is larger in animals maintained on diets low in sodium as compared to animals on high-sodium intakes (Osswald et al., 1975). Comparison of the effect of adenosine on renal blood flow distribution in dogs with high and low PRA reveals that adenosine results in deep cortical vasodilation in both groups of dogs, and that the absolute change in deep cortical flow of the two groups is not statistically different. The most apparent difference between the two groups of dogs is the relative distribution of blood flow during the preadenosine infusion (control) period. Cortical blood flow was significantly higher in each of the four zones in the dogs with low PRA as compared to the dogs with high PRA. This difference in the magnitude of blood flow was greatest in the inner zones of the cortex. When the effect of adenosine is analyzed as the percent change in absolute flow (Fig. 2), a greater response is observed in the dogs with elevated PRA as compared to dogs with low PRA. Several investigators (Tagawa and Vander, 1970; Ueda, 1972; Osswald et al., 1978) observed that adenosine reduced GFR while RBF was unchanged or increased, which led to the conclusion that adenosine acts primarily to vasodilate the efferent arteriole. These findings suggest that the effect of adenosine to decrease GFR in the dog with elevated PRA is the result of a greater deep cortical, efferent arteriolar vasodilation, compared with the animal with low PRA.

A previous report demonstrated that prostaglandin synthesis inhibitors increase the sensitivity of the renal vasculature to injected adenosine (Spielman and Osswald, 1978). We postulated that, following the initial vasoconstriction produced by the intrarenal infusion of adenosine, the gradual wane of the renal vasoconstriction might be the result of an increased prostaglandin synthesis. Our present observation that the return of total renal blood flow to or above control levels is a consequence of vasodilation of the deep cortex, a site where prostaglandins are known to affect blood flow (Kirschenbaum et al., 1974), is consistent with this hypothesis.

The present study tested this hypothesis by examining the effect of prostaglandin synthetase inhibitors on the distribution of renal blood flow produced by adenosine. Based on the findings of the present study, animals with elevated PRA were used to take advantage of their relatively greater response to adenosine. Infusion of adenosine produced an increase in deep cortical blood flow in the meclofenamate- or indomethacin-treated dogs that was not significantly different from that observed in the dogs with intact prostaglandin synthesis. Essentially the same response to adenosine was observed using either systemic meclofenamate or indomethacin or indomethacin given directly into the renal artery. Evidence that prostaglandin synthesis was inhibited was obtained from paired arachidonic acid challenges in each animal before and after treatment with meclofenamate or indomethacin. In each case, the vasodilator response to arachidonic acid was attenuated. Thus, despite the use of two different inhibitors of prostaglandin synthesis and verification of blockade of prostaglandin synthesis in each animal, adenosine still produced a vasodilation in the inner cortex, a finding that argues against a role for prostaglandins in this adenosine-mediated vascular response.

A second mechanism that could explain the wane of the initial vasoconstriction and the ensuing vasodilation during adenosine infusion is the withdrawal of sympathetic vascular tone. The basis for such a hypothesis stems primarily from a report by Hedqvist and Fredholm (1976) which demonstrated a dose-dependent and reversible inhibition by adenosine of norepinephrine release in the kidney. The effects of anesthesia and the stress of surgery might increase nerve traffic, increasing sympathetic vascular tone which, if inhibited by adenosine, would result in an increase in renal blood flow. Furthermore, volume-depleted dogs (i.e., high PRA) might be expected to have higher nerve activities than volume-loaded dogs (i.e., low PRA) (Shad and Seller, 1976). Inhibition of norepinephrine release, therefore, would have a greater effect on the volume-depleted dogs, thus explaining the relatively greater effect of adenosine on blood flow in the dogs with high, as compared to low, PRA.

The present study tested this hypothesis by investigating the effect of adenosine infusion on the distribution of renal blood flow in the α-adrenergically blocked dog. Alpha-adrenergic blockade would eliminate sympathetic vascular tone and, therefore, any subsequent inhibition of transmitter release by adenosine would be ineffective as a mechanism of vasodilation. Infusion of adenosine into dogs treated with phenoxybenzamine (either systemically or intrarenally) produced a deep cortical vasodilation that was indistinguishable from that in untreated dogs. Although this observation suggests that inhibition of norepinephrine release is not the mechanism responsible for the adenosine vasodilation, these findings do not preclude a role for adenosine in the regulation of transmitter release in the kidney.

In summary, adenosine infusion results in a renal vasodilation that is localized to the deep cortex. This effect is observed in both high- and low-renin states but is relatively greater in the animals with high PRA. This relative difference in response between these two groups of dogs may explain the previously observed difference in the effects of adenosine on GFR in animals with either elevated or decreased PRA. In addition, no evidence was obtained that increased prostaglandin synthesis or
an inhibition of sympathetic neurotransmission mediates the deep cortical vasodilation. Although adenosine is known to be a potent vasodilator in most vascular beds, it generally has been considered to be a vasoconstrictor in the kidney. We conclude that, with the exception of a transient vasoconstriction at the onset and a sustained vasoconstriction of the superficial cortex, intrarenal adenosine infusion does not produce renal vasoconstriction, but results in vasodilation of the deep renal cortex.

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