Redistribution of Renal Intracortical Blood Flow during Dopamine Infusion in Dogs

By William T. Hardaker, Jr., and Andrew S. Wechsler

ABSTRACT
We determined the effect of intravenous and renal intra-arterial infusion of dopamine on the distribution of intracortical blood flow in kidneys of anesthetized dogs. Total renal and renal intracortical blood flows in dogs receiving dopamine intravenously were quantified by the radioactive microsphere technique with reference sampling. In dogs receiving dopamine by renal intra-arterial infusion, total renal and renal intracortical blood flows were determined from radioactive microsphere and electromagnetic flowmeter data. Tissue perfusion rates for the total kidney, the renal cortex, the renal outer cortex, and the renal inner cortex increased following either intravenous or direct renal intra-arterial infusion of dopamine. Dopamine infusion by either method caused a relative redistribution of renal blood flow from the outer two-thirds to the inner one-third of the renal cortex. During direct dopamine infusion into the renal artery, no significant changes in renal hemodynamics occurred in the contralateral kidney. No changes in arterial blood pressure occurred during dopamine infusion by either method. These observations imply that the change in the fractional distribution of renal intracortical blood flow following dopamine infusion is not dependent on a systemic mode of action. This pattern of flow redistribution suggests that the intrarenal dopamine-specific receptor may be in higher number in the inner cortex or that the redistribution of cortical flow after dopamine infusion may reflect differing initial physiological states of the inner and outer cortical receptors for dopamine.

KEY WORDS
radioactive microspheres intrarenal blood flow vascular responsiveness renal cortical blood flow nonadrenergic vascular receptors dopamine vascular receptors

Naturally occurring and synthetic amines are routinely used to support the circulatory system in the treatment of various forms of shock; they improve cardiac performance, restore arterial blood pressure, and augment tissue perfusion. Although norepinephrine, epinephrine, and isoproterenol all increase cardiac contractility, they do not increase, and in some cases they decrease, renal blood flow (1-4).

Dopamine, a naturally occurring catecholamine and the direct biochemical precursor of norepinephrine, has evoked considerable interest in recent years. Dopamine has a positive cardiac inotropic action (5-8) and causes selective renal vasodilation in both man and animals (9, 10). This combination of properties, unique among clinically useful catecholamines, has prompted investigations suggesting that dopamine is an attractive agent for treatment of patients with low cardiac output states in which oliguria is a major component of the shock syndrome (11-14).

Although previous investigators have documented the renal vasodilation caused by dopamine, no studies have examined possible effects of dopamine on the distribution of intrarenal blood flow. Therefore, in the present investigation the radioactive microsphere technique was used to determine the effect of dopamine on the distribution of renal intracortical blood flow.

Methods
Healthy adult mongrel dogs of both sexes (18-35 kg) were medicated with morphine sulfate, (3 mg/kg, im), anesthetized with sodium pentobarbital (25 mg/kg, iv), and ventilated using a Harvard respirator with room air through a cuffed endotracheal tube. A polyethylene catheter was sutured into the left atrium through a left thoracotomy, and the chest was closed. Central aortic pressures were obtained from a catheter threaded up the femoral artery and connected to a Statham P23db pressure transducer. Mean aortic blood pressure was calculated as diastolic pressure plus one-third pulse pressure. The opposite femoral artery was also cannulated to provide a site for withdrawal of the reference sample.
In dogs in which direct intra-arterial infusions of dopamine were made, the left kidney was exposed through a retroperitoneal flank incision. Minimum dissection of the renal pedicle was made, and all nerves supplying the kidney were left intact. In these experiments left renal blood flow was measured continuously with a Micron RC1000 electromagnetic flowmeter. The zero base line and phase adjustments of the flowmeter were performed at application of the probe and at intervals throughout the experiment by mechanical occlusion of the renal artery distal to the probe. Flow transducers were calibrated by placing them on a segment of excised artery of comparable size suspended between plastic cannulas in a saline bath. Timed collections of saline passing through the vessel lumen were used to calibrate the probes.

Radioactive $^{141}$Ce, $^{51}$Cr, $^{55}$Sc, and $^{99}$Sc carbonized microspheres with a diameter of $15 \pm 5\mu$ were used to quantify intrarenal blood flow distribution. The microspheres were obtained as 1 mc of nuclide in 10 ml of 10% dextran to which one drop of Tween-80 was added to minimize clumping. The specific activities for the isotopes were 11.6 mc/g for Ce, 32.54 mc/g for Cr, 7.2 mc/g for Sr, and 7.0 mc/g for Sc. An ultrasonic bath (Nuclear Products, 3M Company) was used to place the microspheres in suspension, and immediately before injection the suspension was further agitated for 20 seconds by a vibrating mixer (Super Mixer, Lab Line Instrument, Inc.). No shattering or clumping of microspheres was observed microscopically.

Injections of approximately 400,000 microspheres suspended in 1 ml of 10% dextran were made into the left atrial catheter and immediately flushed through the catheter with 20 ml of heparinized saline. Renal blood flow was calculated using a modification of the reference-sampling method described by Domenech et al. (15). The reference sample was collected at a flow rate of 9.89 ml/min with a Harvard infusion-withdrawal pump. Collection was initiated 3 seconds prior to injection flush. There was no change in heart rate or blood pressure during the microsphere injection and the concomitant withdrawal of the reference sample.

Dopamine hydrochloride (Intropin) was freshly prepared for each experiment: 40 mg of dopamine was diluted with 5% dextrose or 0.9% NaCl to make a stock solution of 240 $\mu$g/ml. The rate of infusion was regulated by a Harvard 952 pump, and the highest rate of dopamine infusion that could be administered without elevating blood pressure was used. The mean rates of intravenous and intra-arterial infusions are indicated in Tables 1 and 2.

**INTRAVENOUS ADMINISTRATION**

In eight experiments, after a control microsphere injection, dopamine was infused through a polyethylene catheter in the brachial vein. Ten minutes were allowed for peak responses to develop, and the infusion rate was adjusted, if necessary, to maintain the control mean aortic pressure. A second microsphere injection was then made. In six dogs the infusion rate was further increased to provoke a rise in mean aortic pressure, and an additional microsphere injection was made.

**INTRA-ARTERIAL ADMINISTRATION**

The effects of intra-arterial dopamine infusion were studied in six experiments in which no elevation of arterial blood pressure was observed. Following control injection of microspheres, dopamine was infused through a 25-gauge needle inserted into the left renal artery proximal to the flow probe. Results were compared with those for the contralateral (right) kidney and with control values for the left kidney.

**TISSUE COUNTING**

After the dogs had been killed, their kidneys were excised, and the capsule was gently removed by blunt dissection. Representative coronal sections, 5 mm thick, were taken from each kidney. After separation of the renal cortex from the medulla by sharp dissection, samples were taken of the outer two-thirds and the inner one-third of the cortex. These tissue slices, as well as the remainder of the kidney, were washed, weighed, and counted in a well scintillation counter. Isotope separation was achieved by using a computer program especially designed to solve a multiple equation-multiple unknown matrix.

**CALCULATIONS AND ANALYSIS OF DATA**

Renal and intrarenal blood flows in dogs receiving dopamine intravenously were calculated using the reference-sample technique (15). This method has been validated for many organs and experimental protocols (16–18). Briefly stated, if microspheres are well mixed in the left atrium, distributed in proportion to blood flow, and completely trapped in the capillary beds of the organs in one pass through the circulation, then their fractional distribution to any organ or tissue will be a function of the fraction of cardiac output going to that organ or tissue. Therefore, if the flow and the radiouclide counts for any organ are known, the flow to any other organ can be determined. In this technique the reference sample represents a mock-organ with a known flow ($Q_f$) (withdrawal rate) and a reactivity ($C_r$) that can be determined. Since the radioactivity in the selected tissue ($C_t$) is known, the flow to that tissue ($Q_t$) can be calculated using the following expression: $Q_t/C_t = Q_r/C_r$. Solving for $Q_t$, $Q_t = C_tQ_r/C_r$.

In dogs in which direct intra-arterial infusions of dopamine were made, renal and intrarenal blood flows were calculated from flow-probe data. All renal and intrarenal blood flows are expressed as ml/g min$^{-1}$. Flow rates before dopamine infusion were termed control. Analysis of the effects of dopamine were based on three methods of assessing change in flow. (1) The absolute renal blood flow, total cortical flow, outer cortical flow, and inner cortical flow before and after dopamine infusion were compared by Student’s t-test for paired data. (2) The percent changes in renal blood flow, total cortical flow, outer cortical flow, and inner cortical flow following dopamine infusion were compared by analysis of variance. (3) The distribution of
intrarenal blood flow before and after dopamine infusion was assessed by comparing the ratio of outer cortical flow to inner cortical flow, the ratio of outer cortical flow to total cortical flow, and the ratio of inner cortical flow to total cortical flow using Student’s t-test for paired data.

**Results**

**EFFECT OF INTRAVENOUS DOPAMINE INFUSION ON RENAL AND INTRARENAL BLOOD FLOW**

When dopamine was infused at an average rate of 4.6 μg/kg min⁻¹, no changes in mean or phasic aortic pressure occurred in the eight dogs studied. Dopamine increased renal blood flow (RBF), total cortical flow (TCF), outer cortical flow (OCF), and inner cortical flow (ICF) (Table 1). During dopamine infusion mean RBF and mean TCF increased approximately 50%. Although dopamine increased both mean OCF and mean ICF, it did so to different degrees; mean OCF increased 38%, and mean ICF increased 92%.

This change in distribution of renal intracortical blood flow during dopamine infusion is illustrated in Figure 1. The mean OCF-ICF ratio and the mean OCF-TCF ratio both decreased, although the mean ICF-TCF ratio increased. The control mean OCF-ICF ratio fell from 2.16 ± 0.16 to 1.47 ± 0.05 during dopamine infusion (P < 0.0001). Similarly, the OCF-TCF ratio decreased from a control mean of 1.21 ± 0.02 to 1.12 ± 0.01 (P < 0.0001). The mean ICF-TCF ratio increased from 0.60 ± 0.03 to 0.77 ± 0.02 (P < 0.0001).

**EFFECT OF INTRA-ARTERIAL DOPAMINE INFUSION ON RENAL AND INTRARENAL BLOOD FLOW**

Dopamine, infused into the left renal artery at a mean infusion rate of 1.6 μg/kg min⁻¹, produced increases in renal and intrarenal blood flows in the left kidney similar to those observed in dogs receiving dopamine intravenously. RBF, TCF, OCF, and ICF all increased in the experimental (left) kidney. No significant changes in these flow parameters were noted in the contralateral (right) kidney (Table 2). No change in mean phasic aortic pressure was observed during intra-arterial dopamine infusion in the six dogs studied.

Intra-arterial dopamine was associated with a change in the distribution of intracortical blood flow in the experimental kidney as shown in Figure 2. The mean OCF-ICF ratio decreased from a control mean of 1.51 ± 0.09 to 1.19 ± 0.05 (P < 0.003) during dopamine infusion. The mean OCF-TCF ratio fell from 1.12 ± 0.02 to 1.05 ± 0.01 (P < 0.003), but the mean ICF-TCF ratio increased from 0.75 ± 0.03 to 0.89 ± 0.03 (P < 0.001). These data parallel the redistribution of intrarenal blood flow observed following intravenous administration of dopamine (Fig. 1). The mean OCF-TCF and ICF-TCF ratios in the contralateral
### TABLE 1

<table>
<thead>
<tr>
<th>Dog</th>
<th>Kidney AP (mm Hg)</th>
<th>RBF (ml/g min⁻¹)</th>
<th>TCF (ml/g min⁻¹)</th>
<th>OCF (ml/g min⁻¹)</th>
<th>ICF (ml/g min⁻¹)</th>
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<td>Dopamine</td>
<td>Control</td>
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<td>3.04</td>
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<td>5.42</td>
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Mean = 8,

\(\text{Mean} = 115 = 4.7\)

\(\begin{align*}
\text{RBF} &\approx 0.20 \\
\text{TCF} &\approx 0.21 \\
\text{OCF} &\approx 0.29 \\
\text{ICF} &\approx 0.29 \\
\end{align*}\)

\(\text{RBF} &\approx 0.29 \\
\text{TCF} &\approx 0.29 \\
\text{OCF} &\approx 0.36 \\
\text{ICF} &\approx 0.33 \\
\end{align*}\)

\(\text{P} < 0.0001 < 0.0001 < 0.0001 < 0.0001\)

\(\text{AP = mean arterial pressure, RBF = renal blood flow, TCF = total cortical flow, OCF = outer cortical flow, ICF = inner cortical flow, L = left, and R = right. Dopamine infusion rate was set to maintain mean arterial pressure constant (mean dopamine infusion rate = 4.6 \mu g/kg min⁻¹). P values were obtained using Student's t-test for paired data and are for the change from control.}\)
TABLE 2

Distribution of Intracortical Blood Flow before and after Administration of Dopamine Hydrochloride into Left Renal Artery and Comparison with Contralateral (Right) Kidney

<table>
<thead>
<tr>
<th>Dog</th>
<th>Kidney AP (mm Hg)</th>
<th>Kidney AP (mm Hg)</th>
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</thead>
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<td>RBF (ml/g min⁻¹)</td>
<td>TCF (ml/g min⁻¹)</td>
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<td>Control</td>
<td>Dopamine</td>
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<td>3.39</td>
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<tr>
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<td>138</td>
<td>2.87</td>
</tr>
<tr>
<td>5</td>
<td>120</td>
<td>3.55</td>
</tr>
<tr>
<td>6</td>
<td>130</td>
<td>3.69</td>
</tr>
</tbody>
</table>

**P** values were obtained using Student's t-test for paired data and are the change from control.

**AP** = mean arterial pressure, **RBF** = renal blood flow, **TCF** = total cortical flow, **OCF** = outer cortical flow, **ICF** = inner cortical flow, and **ns** = not significant. Dopamine infusion rate was set to maintain mean arterial pressure constant (mean dopamine infusion rate = 1.6 µg/kg min⁻¹).
Distribution of intrarenal blood flow before and after administration of dopamine hydrochloride at constant mean aortic pressure into the left renal artery. Comparisons of change in the OCF-ICF ratio, change in the OCF-TCF ratio, and change in ICF-TCF ratio in the experimental (left) and the contralateral (right) kidneys are given. Means ± 1 se are shown beside the individual groups. See Figure 1 for abbreviations.

kidney showed no significant changes; however, the mean OCF-ICF ratio did change slightly in the contralateral kidney. This change probably represents minor recirculation of the drug from the experimental kidney.

Changes in heart rate following intravenous infusion of dopamine were highly variable. Four dogs had mean increases of 5% over control rates, one dog had a mean decrease of 3% from the control rate, and three dogs showed no change in rate.

In six dogs receiving intravenous infusion of dopamine, the infusion rate was increased to produce an elevation in mean aortic pressure. A mean infusion rate of 14 μg/kg min⁻¹ was associated with a 14 ± 5.7% mean increase in aortic pressure. Mean RBF increased 65 ± 7.8%, mean TCF increased 60 ± 7.6%, mean OCF increased 45 ± 5.8%, and mean ICF increased 139 ± 25.4%. In these dogs the pattern of redistribution of intrarenal blood flow was the same as that observed in the studies involving intravenous and intra-arterial dopamine infusion with arterial blood pressure held constant. The control OCF-ICF ratio decreased from 2.28 ± 0.20 to 1.41 ± 0.05 (P < 0.0008), the OCF-TCF ratio decreased from 1.22 ± 0.02 to 1.10 ± 0.10 (P < 0.0001), and the ICF-TCF ratio increased from 0.58 ± 0.04 to 0.50 ± 0.02 (P < 0.0001).

Discussion

Although the sympathomimetic amines, norepinephrine, epinephrine, isoproterenol, and dopamine, all increase cardiac contractility by a beta-adrenergic mechanism, each has a vastly different hemodynamic effect on the periphery. Isoproterenol causes beta-adrenergic vasodilation in all vascular beds; however, its most pronounced effects are manifest in skeletal muscle and the mesentery. Renal blood flow usually does not increase in the dog and man (2, 9). Epinephrine, although having both alpha and beta actions on the periphery, produces predominantly alpha vasoconstriction in the renal vascular bed (19). Norepinephrine has a strong generalized alpha-adrenergic effect on the periphery that leads to decreased renal blood flow (3, 9, 19). Dopamine reduces blood flow in skeletal muscle by an alpha-adrenergic mechanism, although it increases renal and mesenteric flow (6, 9, 19, 20).

The renal vasodilation produced by dopamine is not blocked by administration of antihistamines or atropine or by treatment with reserpine or monoamine oxidase inhibitors (20). Furthermore, this renal vasodilation cannot be prevented by use of alpha- or beta-blocking agents (19–21).

In addition to dopamine's already validated unique cardiovascular properties, our results clearly indicate that the increased renal blood flow
flowing dopamine administration is associated with a redistribution of renal intracortical blood flow. Although blood flow increased in both cortical zones, there was a relative shift in renal blood flow to the outer two-thirds to the inner one-third of cortex. This change in the fractional distribution of blood flow to the renal cortex occurred in the dogs receiving intravenously administered dopamine and in the kidneys of dogs receiving dopamine directly into the renal artery. In dogs receiving i-arterially administered dopamine, no significant changes were observed in the intrarenal hemodynamics of the contralateral kidneys. Lower dopamine infusions did not increase systemic arterial pressure in either group of dogs. These data support the conclusion of McNay et al. (9) and Hey and Goldberg (20) that dopamine has a renal vascular effect which is not secondary to systemic mode of action.

The selectivity of the vasodilator actions of dopamine strongly suggests that this amine acts at specific receptor sites within the renal and mesenteric vascular beds. The existence of a dopamine-specific, nonadrenergic, vasodilator receptor was first proposed by Eble (19). Van Rossum (24) suggested that haloperidol might be the specific dopamine antagonist defining such a receptor. Yeh and co-workers (25) demonstrated that haloperidol is a short-acting competitive antagonist of the dopamine mesenteric vasodilator effects of dopamine; this finding adds further support to the concept of a specific dilator receptor for dopamine. Our data indicated a significant difference in the response to dopamine infusion of the outer zone, the inner renal cortex. These data suggest that dopamine-specific dilator receptors are present in greater numbers in the outer zone of the inner cortex.

Our results do not, however, preclude the possibility of intrinsic myogenic differences in the renal responsiveness of the outer and inner cortical zones. Acetylcholine, although having many pharmacological and physiological properties distinct from those of dopamine, does produce renal vasodilation and a redistribution of intrarenal blood flow similar to that seen with dopamine (22, 23). The effects of both drugs on renal flow may therefore be secondary to the inherent physiological state of the arterioles in the different cortical zones rather than due to an anatomical disparity in receptor distribution.

Recent evidence has indicated that functional differences may exist between the nephrons occupying the outer two-thirds of the cortex and the juxtaglomerular nephrons of the inner one-third of the cortex (26-29). The physiological implications of dopamine-induced redistribution of renal intracortical flow remain to be determined. Nevertheless, certain physiological consequences of dopamine, such as natriuresis (10, 30-34), may be related to this redistribution of intrarenal blood flow.

Acknowledgment

We wish to express our thanks to Mr. George Quick for his technical assistance, to Mr. Robert Wesley and Dr. Craig Coulam for writing the computer programs used, and to Mrs. Janice Smart and Miss Phyllis Turner for their secretarial assistance.

References


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Circ Res. 1973;33:437-444
doi: 10.1161/01.RES.33.4.437

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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