RENAL VASCULAR RESPONSES TO DOPAMINE:
HAEMODYNAMIC AND ANGIOGRAPHIC
OBSERVATIONS IN NORMAL MAN

N. K. HOLLENBERG, D. F. ADAMS, P. MENDELL,
H. L. ABRAMS AND J. P. MERRILL

Departments of Medicine and Radiology, Peter Bent Brigham Hospital and
Harvard Medical School, Boston, Mass., U.S.A.

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SUMMARY

1. The renal vascular response to intravenously administered dopamine was
assessed in normal man by selective renal arteriography and xenon washout. Infusion
of 3 μg min⁻¹ kg⁻¹ induced renal vasodilatation with an increase in the cortical com-
ponent of blood flow. Arterial blood pressure was not influenced and a systemic effect
was not demonstrable. Lower doses did not induce a renal response. Increasing dosage
raised arterial blood pressure and induced subjective symptoms, but did not result in
a further increase in renal blood flow.

2. Renal vascular resistance increased with increasing age in the normal subjects.
A significant inverse relationship was found between the initial vascular resistance
and the renal vasodilator response to dopamine. It thus appears that the vascular
effects of increasing age (nephrosclerosis) may limit the dilator response to dopamine.

3. It is concluded that dopamine is an effective renal cortical vasodilator when
administered intravenously at doses which are free from other systemic cardio-
vascular effects. The dose–response relationship must be considered in attempts at
reversal of conditions characterized by renal vasoconstriction.

Key words: vasodilators, radioxenon, nephrosclerosis.

Dopamine (3,4-dihydroxyphenethylamine) is a naturally occurring catecholamine which is
generally considered to be a precursor of noradrenaline; it differs from the sympathetic neural
transmitter only in the absence from the side chain of an aliphatic hydroxyl group (Horny-
kiewicz, 1966). This structural difference results in a profound change in biological activity as
dopamine is an effective renal vasodilator when given intravenously at doses which otherwise
have minimal systemic effects (McNay, McDonald & Goldberg, 1965; Goldberg, 1972); it
appears to act upon receptors in the renal vascular bed which are unrelated to the classical
alpha or beta loci (Goldberg & Yeh, 1971). A combination of pharmacologic characteristics

Correspondence: Dr Norman K. Hollenberg, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston,
Mass. 02115, U.S.A. 

733
which includes a positive inotropic action on the heart and a vasodilator action on the splanchnic and renal vascular beds has been considered useful therapeutically. The renal response, since it is associated with a diuresis, has led to exploration of the therapeutic use of dopamine in patients with shock (Talley, Goldberg, Johnson & McNay, 1969), congestive heart failure (Goldberg, McDonald & Zimmerman, 1963), the hepatorenal syndrome (Barnardo, Baldus & Maher, 1970) and acute renal failure (Talley, Forland & Beller, 1970). There are, however, significant species differences in its cardiovascular effects and few reports on the characteristics of the renal vascular response to this agent in normal man (Goldberg, 1972). The demonstration of a decrease in p-aminohippurate (PAH) extraction in association with the vasodilatation has raised the question of a relative increase in medullary flow to account for the diuresis (Breckenridge, Orme & Dollery, 1971). In this study we have investigated the renal vascular effects of dopamine in normal potential kidney donors with radioactive xenon and renal angiography, which provide some insight into intrarenal blood flow distribution. The dose–response characteristics are potentially relevant to the use of this agent in the conditions noted above.

METHODS

The characteristics of the normal human subjects, all potential kidney donors in the transplant programme who required selective renal arteriography as part of their assessment, have been described in earlier reports, along with details of their clinical assessment prior to the haemodynamic evaluation (Rosen, Hollenberg, Dealy & Merrill, 1968; Hollenberg, Epstein, Rosen, Basch, Oken & Merrill, 1968). In this study the effects of an intravenous infusion of dopamine hydrochloride (Intropin; Arnar Stone) were assessed in fourteen subjects, who were admitted sequentially for evaluation as potential kidney donors. Twelve were found to be perfectly normal. One was otherwise healthy but had mild essential hypertension which does not preclude kidney donation in this centre. The other had moderately severe hypertension with advanced nephrosclerosis: the intravenous pyelogram showed a discrepancy in renal size sufficient to indicate arteriography. Only the data in the twelve normal subjects is included in the subsequent analysis.

The methods utilized for selective renal arterial catheterization, the assessment of intrarenal flow distribution with xenon, and renal arteriography have been described in detail (Rosen et al., 1968; Hollenberg et al., 1968). In brief, one renal artery was catheterized selectively under fluoroscopic guidance with a percutaneous technique. Renal blood flow and its intrarenal distribution was assessed by xenon washout, as described in detail in earlier publications. Radioactive xenon in progressively larger quantities (150–1500 μCi in 0.144 ml of saline) was injected into the catheter as a bolus. The transit of xenon through kidney was monitored by external counting with a scintillation probe. Mean flow was calculated from the initial disappearance slope. Compartmental analysis resolves the data as the sum of a series of decreasing exponential functions, the largest and most rapid of which probably represents cortical perfusion in the normal kidney. The percentage of flow entering the compartment is calculated from its zero-time intercept, and the local flow rate from its slope.

A power injector (Viamonte–Hobbs) was used to deliver 8 ml of contrast agent [meglumine diatrizoate (Renografin 60)] in 1 s. The films were obtained on a serialographic roll film changer (Franklin) with a standard programme: initially four films per second for 2 s, then at increasing
Dopamine and renal blood flow in normal man

intervals so that twenty films were obtained over 19 s. The injector and film changer were triggered simultaneously by the 'R' wave of the patient's electrocardiogram so that the contrast agent was infused at a constant time-interval from patient to patient and from injection to injection in the individual patient. With this technique extremely reproducible renal angiographic sequences are obtained routinely. Selective arteriograms were obtained twice in each subject: the first prior to administration of dopamine and the second following the last blood-flow determination during the vasodilator infusion.

A similar protocol was utilized in every subject, modified only to allow the assessment of the dose-response characteristics of dopamine. An intravenous infusion of 150 mmol of sodium chloride/l was initiated prior to the control selective arteriogram and xenon washout study. The drug infusion was then started with a motor-driven syringe (Harvard Instruments) set to deliver the appropriate dose of dopamine at infusion rates of 0.7–1.9 ml/min. A rheostat control on the pump allowed incremental log-dose changes in the amount of drug infused without interrupting the infusion. During the infusion, blood-flow measurements were made serially; the first was made 3 min after the initiation of the infusion, and then 12–15 min and 25–30 min thereafter. In five normal subjects the infusion was initiated with 3 μg min⁻¹ kg⁻¹ and continued at this dose throughout the 30 min infusion. In three subjects the infusion was initiated at 3 μg min⁻¹ kg⁻¹ and the dosage gradually increased at 6 min intervals to a maximum of 9 μg min⁻¹ kg⁻¹. Another four subjects received smaller doses: in two the dose was initially 0.3 μg min⁻¹ kg⁻¹ and was increased to 1.0 μg min⁻¹ kg⁻¹ after 6 min. The others received an initial dose of 1 μg min⁻¹ kg⁻¹, which was then increased to 3 μg min⁻¹ kg⁻¹.

Arterial blood pressure, heart rate and the electrocardiogram were monitored continuously throughout the procedure on an oscilloscope and recorded on an Electronics for Medicine recorder.

Mean values are reported with the standard error of the mean (SEM) as the index of dispersion. Statistical significance was assessed with the t-test; paired-data analysis was used where applicable. Ordinal data, especially those derived from the roentgen studies, were assessed by the Fisher direct probability test and the Wilcoxon Rank sum test for non-parametric data.

The protocols have been approved by the Human Experimentation Committee of the Peter Bent Brigham Hospital. Consent for the investigation was obtained after a detailed description of the procedure.

RESULTS

Dopamine did not induce changes in renal perfusion or the arteriogram in patients receiving 1 μg min⁻¹ kg⁻¹ or less. All of the subjects receiving a dose of 3 μg min⁻¹ kg⁻¹ or more responded with renal vasodilatation which was evident both in the xenon washout studies and in the arteriograms. A typical haemodynamic response is shown in Fig. 1, where the slope of the first component of xenon washout from the kidney is clearly increased. Average values for the response are shown in Fig. 2. Within 3 min dopamine induced a significant increase in mean blood flow from 280 ± 10 to 417 ± 34 ml min⁻¹ 100 g⁻¹. This response was associated with an increase in rapid-flow-component flow rate from 390 ± 21 to 572 ± 40 ml min⁻¹ 100 g⁻¹ and an increase in the percentage entering that component from 70.4 ± 4.1 to 81.8 ± 3.3%. The response increased with time during the infusion so that after 25–30 min mean flow had risen to 469 ± 21 ml min⁻¹ 100 g⁻¹ with a rapid-component flow rate of 615 ± 21 ml 100 min⁻¹ g⁻¹, represent-
Fig. 1. Semi-logarithmic display of the first 3 min of xenon washout in a normal subject (J.B.), (a) prior to dopamine infusion and (b) during the infusion of 3 μg min⁻¹ kg⁻¹: •, washout from kidney; ○, rapid component of this curve. Note the more rapid disappearance of isotope from the kidney during dopamine infusion which is attributable to increased flow in the rapid component.

The y axis shows radioactivity (c.p.m.) obtained from external counting over the kidney.

ing 83±1.8% of the total flow. No systemic effects of doses at or below 3 μg min⁻¹ kg⁻¹ were evident. Systolic, diastolic and mean arterial blood pressure and heart rate were stable; the shape of the pulse contour, however, suggested an inotropic effect as the upstroke of systolic pressure became steeper.

Attempts at increasing the dosage above 3 μg min⁻¹ kg⁻¹ resulted in subjective and objective systemic effects in every subject. Nausea eventually occurred at doses between 5 and 9 μg min⁻¹ kg⁻¹, but never before the study at 12–15 min. Prior to the development of nausea, a reproducible increase in heart rate and systolic arterial pressure occurred with increasing dosage in every subject, and they all became aware of an increase in force of contraction of their heart. The inotropic effect was apparent in the pulse contour where the rate of rise of systolic pressure showed a large increase. The renal haemodynamic response to increasing doses of dopamine was uniform. The increase in blood flow between the third and fifteenth minute was less than that seen in subjects given 3 μg min⁻¹ kg⁻¹ in two cases, and in one there was a fall (Fig 3). The responses to increased doses were decreased significantly ($P<0.05$; Wilcoxon rank sum test).

The coefficient of variation for mean blood flow after 3 min of infusion was 24.7%, which is considerably greater than the usual 12–15% associated with this technique. It was 13.4% in the control state in these subjects. Two significant, and probably related, regression relationships were defined which appeared to account for the variability. The renal vascular resistance...
Dopamine and renal blood flow in normal man

Fig. 2. The renal vascular response to dopamine in normal man and its time-course. Note the parallel increase in mean flow and rapid-component flow rate, and the progressive increase between the value at 3 min and 25–30 min. The bars represent ± SEM.

prior to infusion ranged from 0.25 to 0.37 unit, calculated as the ratio of mean pressure (diastolic plus one-third pulse pressure) to mean flow. A major determinant of the resting resistance in the normal subjects appeared to be age. The relationship between age in years \((x)\) and mean blood flow in \(\text{ml min}^{-1} \text{100 g}^{-1}\) \((y)\) was \(y = 385 - 2.6x (r = 0.55; f = 5.50; P<0.05)\). There was a statistically significant inverse relationship between the vascular resistance prior to administering dopamine \((x)\) and the mean flow \((y)\) at a dose of 3 \(\mu\text{g min}^{-1} \text{kg}^{-1}\) \((y = 9.07 - 16.1x; r = 0.78; f = 10.96; P<0.02)\). The relationship is shown in Fig. 4. Thus, with increasing age, decreasing renal blood flow and an increasing calculated resistance, the dilator response to dopamine fell.

The angiographic features of a typical response to dopamine are shown in Fig. 5. A consistent increase in renal size and in the calibre of the arterial vessels followed doses of 3 \(\mu\text{g min}^{-1} \text{kg}^{-1}\) or more. A 20% increase occurred in the diameter of the distal interlobar arteries \((0.15 \pm 0.009 \text{ mm versus } 0.18 \pm 0.01 \text{ mm}; P<0.005)\) and 11% increase in second order arteries \((0.46 \pm 0.03 \text{ mm versus } 0.51 \pm 0.02 \text{ mm}; P<0.005)\). The velocity of contrast-agent transit through the kidney was assessed by four indices (Table 1). Three indices including the time to arterial
FIG. 3. Change in mean renal blood flow between the third and fifteenth minute of infusion: the responses to increasing doses (5–9 µg min⁻¹ kg⁻¹) are significantly less ($P<0.05$) than the responses to the lower dose.

FIG. 4. The relationship between the renal vascular resistance prior to dopamine infusion and the blood flow achieved with 3 µg of dopamine min⁻¹ kg⁻¹. There is a significant inverse relationship ($r = 0.78; P < 0.02$) which primarily reflects the effects of increasing age. The higher the resting resistance, the smaller the blood flow increase induced by dopamine. BP, blood pressure.
Dopamine and renal blood flow in normal man

Fig. 5. The angiographic features of the normal renal vascular response to dopamine. (a) Control run 1.5 s after injection of the contrast agent. (b) Same phase of arteriogram during infusion of dopamine. Note the striking dilatation of all orders of the arterial tree.

(Facing p. 738)
Dopamine induced a reproducible increase in renal blood flow at a dosage of 3 \( \mu \text{g min}^{-1} \text{kg}^{-1} \). The dose–response range was surprisingly narrow. A dose of 1 \( \mu \text{g min}^{-1} \text{kg}^{-1} \) or less failed to induce a recognizable response. Doses exceeding 3 \( \mu \text{g min}^{-1} \text{kg}^{-1} \) uniformly resulted in systemic effects and were associated with a decrease in renal blood flow from the peak noted at 3 \( \mu \text{g} \). At 3 \( \mu \text{g min}^{-1} \text{kg}^{-1} \) the haemodynamic response was uniform: there was an increase in mean blood flow and in both absolute and percentage flow in the rapid-flow component without systemic effects.

Evidence supporting the concept that the rapid-flow component represents cortical perfusion has been reviewed elsewhere (Hollenberg et al., 1968; Rosen et al., 1968). The response is compatible with a uniform increase in cortical perfusion with either a less-striking or absent effect on medullary perfusion. In a study on the effects of acetylcholine on renal perfusion in normal man (Rashid, Hollenberg, Adams, Solomon, Abrams & Merrill, 1972), the maximal effective dose of acetylcholine infused into the renal artery was 100 \( \mu \text{g min}^{-1} \) and this increased mean renal blood flow to 592±28 ml min\(^{-1} \) 100 g\(^{-1} \), which is significantly greater than the maximal mean flow response to dopamine (469±21 ml min\(^{-1} \) 100 g\(^{-1} \); \( P<0.05 \)). The angiographic changes with acetylcholine were also qualitatively similar to those induced by dopamine, but were more marked. The findings in this study suggest that the maximal renal dilator effect of dopamine is very similar to that induced by lower doses of acetylcholine where the response suggested an effect primarily on the cortical vessels. Unfortunately, data are not available for comparison with the more-direct analyses of intrarenal flow distribution which are possible only in animal models. Acetylcholine, prostaglandin E1 and bradykinin induce an identical peak renal blood flow, suggesting that each is capable of inducing maximal renal dilatation.

### DISCUSSION

**Table 1. Angiographic responses to dopamine**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>+Dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Arterial washout time (s)±SEM</td>
<td>2.1±0.1</td>
<td>1.7±0.1(^{(1)})</td>
</tr>
<tr>
<td>Venous appearance (s)</td>
<td>4.9±0.6</td>
<td>3.9±0.5</td>
</tr>
<tr>
<td>Maximum venous opacification (s)</td>
<td>9.2±0.6</td>
<td>7.6±0.3(^{(1)})</td>
</tr>
<tr>
<td>Reflux to aorta</td>
<td>Median: ++</td>
<td>+(^{(1)})</td>
</tr>
<tr>
<td>(0 to 3+)</td>
<td>Mode: ++</td>
<td>0(^{(1)})</td>
</tr>
</tbody>
</table>

\(^{(1)}\) \( P<0.05 \) by paired-data \( t \) test for interval data and by Wilcoxon rank sum test for ordinal data.

washout\( (P<0.025) \), time to maximal opacification of the renal vein\( (P<0.05) \) and the amount of reflux to the aorta after arterial injection\( (P=0.027) \) indicated a more rapid transit. The average venous appearance time also fell, but the decrease did not achieve statistical significance\( (P<0.2) \). Venous appearance time, however, is the most difficult index to define in the arteriogram. Its extremely large coefficient of variation, 36.3%, in the control run probably reflects this difficulty. The only exception to this pattern of renal vascular response was in the essential hypertensive with advanced nephrosclerosis in whom dopamine induced only minimal changes.
Bradykinin also induces a larger maximal increase in renal blood flow than does dopamine in the dog (McNay & Goldberg, 1966). It is clear, therefore, that dopamine does not induce maximal renal vasodilatation in either species.

A major determinant of the degree of vasodilatation induced by dopamine in the normal population was the initial renal vascular resistance, which reflected primarily increasing age of the subjects. A significant inverse relationship between the dilator response induced by dopamine and both age and initial resistance was defined. It seems likely that organic, fixed changes in the renal vasculature which characterize the normal senescent process were responsible for the progressive decrease in the flow response with increased resistance. The regression relationship is the opposite of that apparent in the data of Breckenridge et al. (1971), who studied a population of hypertensives. Recalculation of the data provided in their Table 2 reveals a significant inverse relationship between resting renal blood flow and the increase in blood flow induced by dopamine at 2 μg min"⁻¹ kg"⁻¹ (y = 226 - 24x where y = percentage increase in blood flow and x = control flow; r = 0.54; P < 0.05). Thus the hypertensives showed a larger flow increase when resting flow was decreased, whereas the normal subjects in this study displayed a decreased response. While the differences could be methodologic, the single uncomplicated essential hypertensive assessed in this study showed a similar phenomenon: his flow response was almost twice that predicted from the regression relationship between the initial resistance and the blood flow response of normal subjects to dopamine. Thus the normal ageing process seems to decrease the renal vascular response to dilators, whereas patients with hypertension may show an increased response. Whether this reflects a local, intrarenal influence of ageing and hypertension on the response cannot be determined, since the agent was administered intravenously in both studies.

Dopamine has been used in a number of clinical settings characterized by poor renal perfusion, sodium retention and oliguria. In the patient with congestive heart failure, the administration of dopamine resulted in natriuresis as an accompaniment of both an increase in renal plasma flow and glomerular filtration rate (McDonald, Goldberg, McNay & Tuttle, 1964). Normal subjects assessed in the same study showed a small increase in inulin clearance, and a striking increase in p-aminohippurate clearance with doses which ranged from 2.6 to 5.2 μg min"⁻¹ kg"⁻¹. The dose was selected so that mean arterial blood pressure did not change, but there was a small increase in heart rate and a marked increase in pulse pressure and cardiac output. It is of interest that the two patients in the study of McDonald et al. (1964) who received doses comparable to ours also showed only a small effect on pulse pressure but still had a striking increase in cardiac output. Although cardiac output was not measured in the present study, it seems likely that an increase in cardiac output occurred, on the basis of the observations cited. Barnardo et al. (1970) administered dopamine to a series of patients with cirrhosis. Patients with advanced renal failure were not assessed: none had an endogenous creatinine clearance of less than 25 ml/min. The dopamine dose they utilized for prolonged infusion was 75% of the minimal dose producing a recognizable increase in arterial pressure; a mean of 1.9 μg min"⁻¹ kg"⁻¹ was used with a range of 1.3–3.0 μg. It is difficult to compare doses in the two series because the inevitable presence of ascites and oedema in patients with advanced cirrhosis results in a relatively large extracellular fluid volume, and this is the probable initial volume of distribution. In the cirrhotic patients, dopamine induced a consistent increase in renal plasma flow, but little change in glomerular filtration rate despite a prolonged infusion. At most a modest diuresis and natriuresis was seen. It appears therefore that, although
dopamine increases renal blood flow in both patients with cirrhosis and those with congestive heart failure, it does not abolish the vascular factors responsible for sodium retention and decreased glomerular filtration rate in both: the vascular factors must differ. Barnardo et al. (1970) hypothesized a parallel effect on pre-glomerular and post-glomerular vessels so that glomerular capillary pressure was not increased *pari passu* with the increase in flow. Their interpretation seems reasonable. Dopamine was successful in inducing a reversal of the oliguric state in several patients in shock (Talley et al., 1969), which was attributed to the improvement in cardiac output and, in part, to the direct effect of dopamine on the renal circulation. In an abstract Talley et al. (1970) suggest that dopamine can potentiate the natriuretic effects of diuretics in established oliguric acute renal failure. The vascular responses were not described. Thus it appears that in some states characterized by renal vasoconstriction, the effect of dopamine on the renal vasculature is salutary; in others the renal vascular effects of dopamine are inadequate to reverse the syndrome. It seems unlikely from the information available that the responses were a simple function of either dose or duration of infusion, but the present study makes it clear that careful attention to both details must be given before a firm conclusion can be drawn. Doses greater than 3 μg min⁻¹ kg⁻¹ probably have an additional effect in the activation of alpha receptors with resultant renal vasoconstriction which counteracts the direct effect of lower doses on renal perfusion. The result is a progressive increase in systolic arterial pressure associated with a decrease in renal blood flow. Increasing the dose also results in unpleasant subjective symptoms.

In conclusion, dopamine is an effective renal vasodilator when administered intravenously at doses which have minimal systemic side effects. One of the major determinants of its renal vascular effects is the age of the patient, and this presumably reflects the degree of nephrosclerosis. The characteristics of the dose–response curve and the development of secondary effects at higher doses suggest that careful attention should be given to details of dosage in planning treatment for patients with impaired renal vascular perfusion.

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**REFERENCES**


HORNYKIEWICZ, O. (1966) Dopamine (3-hydroxytyramine) and brain function. Pharmacological Reviews, 18, 925–964.


