

Dopamine, Dobutamine, and Dopexamine

A Comparison of Renal Effects in Unanesthetized Human Volunteers

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Background: Recently, dopexamine (DX), which acts *via* adrenergic β_2 and dopaminergic DA_1 receptors, has been introduced in the treatment of low cardiac output states. However, the renal effects of DX have not been compared to those produced by equipotent inotropic doses of dopamine (DA), which predominantly stimulates DA_1 and DA_2 receptors, and of dobutamine (DB), which stimulates β_1 but not DA receptors. The current study tested the null hypothesis that, with equal increases in cardiac output, DX, DA, and DB would have similar effects on renal function.

Methods: Each drug was given for 2 h on three different occasions to eight normal subjects in doses adjusted to produce a similar 30–35% increase in cardiac output. Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were measured as renal clearances of ^{131}I -hippuran and ^{99m}Tc -DTPA, respectively. Lithium clearance (C_{Li}) was used as an index of proximal tubular outflow.

Results: Doses of DA, DX, and DB were 2.90 ± 0.19 , 1.00 ± 0.02 , and $4.92 \pm 0.40 \mu g \cdot kg^{-1} \cdot min^{-1}$, respectively. Dopamine and DX increased ERPF by 23% and 10%, respectively, whereas ERPF remained unchanged during DB. The increase in ERPF was smaller during DX compared with DA. The GFR remained unchanged during DA and DB, but increased during DX (7%).

The C_{Li} increased by 35% and 30% during DA and DX, respectively, but was not changed by DB. Calculated absolute proximal reabsorption rate ($APR = GFR - C_{Li}$) decreased by 13% during DA, but remained unchanged during DB and DX. Dopamine increased sodium clearance (C_{Na}) by 103%, but the changes during DX and DB were not significant. Only DA decreased fractional distal reabsorption ($FDR_{Na} = 1 - C_{Na}/C_{Li}$).

Conclusions: The findings are consistent with a specific, renal-vasodilating effect of DA and DX. However, in the current doses, this effect of DX was of lesser magnitude compared with that of DA. Only DA significantly increased C_{Na} , and the decreases in APR and FDR_{Na} indicate that an effect on tubular reabsorption rate contributed to the natriuresis. (Key words: Kidney: function. Sympathetic nervous system, catecholamines: dobutamine; dopamine; dopexamine.)

THE sympathomimetic amines dopamine and dobutamine are commonly used to augment cardiac output in clinical conditions of endangered vital organ function. Low doses of dopamine ($1-5 \mu g \cdot kg^{-1} \cdot min^{-1}$) predominantly stimulate dopaminergic DA_1 and DA_2 receptors, and the inotropic effect is associated with a marked increase in renal blood flow and sodium excretion.¹⁻⁴ Increasing the infusion rate will, in a dose-dependent manner, also involve stimulation of adrenergic β_1 and α receptors.⁵ In contrast to dopamine, dobutamine does not stimulate dopaminergic receptors, but predominantly acts *via* cardiac β_1 receptors.⁶⁻⁸ Recently, the dopamine analog dopexamine has been introduced in the treatment of low cardiac output states.⁹ This drug predominantly stimulates adrenergic β_2 and dopaminergic DA_1 receptors.¹⁰⁻¹²

The renal effects of low-dose dopamine can be explained as secondary to renal vasodilation by stimulation of dopaminergic receptors in the renal arterioles, and, in addition, specific tubular effects may play a role.^{1-4,13-15} Although some studies have indicated that dopexamine may increase renal blood flow and the excretion of sodium and water,¹⁶⁻¹⁹ renal effects of dopexamine have not been compared with those produced by equipotent inotropic doses of dopamine.

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The purpose of the current study was to compare overall renal effects of dopamine and dopexamine in equipotent doses producing a similar increase in cardiac output of 30–35% in normal humans. Because the evaluation of specific renal effects of inotropic drugs may be confounded by indirect effects secondary to the increase in cardiac output, we also investigated the renal effects of equipotent doses of dobutamine, which does not have specific effects on renal hemodynamics.^{6,20} Thus, the current study tested the null hypothesis that, with equal increases in cardiac output, dopamine, dopexamine, and dobutamine will have similar effects on renal function.

Materials and Methods

Subjects and Experimental Protocol

Eight healthy men, 23–38 yr of age, entered the study after they had given their written informed consent. The study was approved by the regional scientific ethical committee. Each subject was studied on three different occasions separated by an interval of at least 7 days with either dopamine, dopexamine, or dobutamine, in a random order. The protocols for the three study days were identical, and were conducted at the same time of the day. After an overnight fast, water diuresis was induced by orally administered water with a fixed rate of 200 ml every 20 min without an initial load. The subjects abstained from nicotine and caffeine-containing drinks. Except for briefly standing when voiding, the subjects were confined to a resting supine position. A venous catheter was inserted into an antecubital vein in each arm for infusion and blood sampling, respectively. The subjects were instructed to void every 20 min, and steady state was considered to be achieved when urine flow rates approximately equaled water intake. Thereafter, a 1-h control period (baseline) was followed by an intravenous infusion of either dopamine, dopexamine, or dobutamine, which was continued during two consecutive 1-h periods. Initial infusion rates of dopamine, dopexamine, and dobutamine were 3, 1, and 5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, respectively. During the first 1-h infusion period, the doses were adjusted to produce a 30–35% increase in cardiac output and, thereafter, were kept constant for measurements in the second 1-h infusion period.

Measurement of Cardiac Output

Cardiac output was measured by the carbon dioxide-rebreathing method, using a cardiopulmonary gas ex-

change monitoring device (CPX-system, Medical Graphics, St. Paul, MN).^{21–23} This microcomputerized system consists of an infrared absorption analyzer for carbon dioxide, and a pneumotachometer attached to ± 2 cmH₂O for gas flow measurements. The accuracy is $\pm 0.1\%$ for analysis of carbon dioxide between 0 and 10%, and $\pm 3\%$ for volumes between 0.050 and 10.0 l. The rapid response time (<175 ms) for the sensor makes it possible to obtain breath-to-breath measurements of carbon dioxide excretion (VCO_2), which is then expressed as the average of eight breaths. The gas analyzer was calibrated before each study by two-point calibration with room air and a known gas mixture of carbon dioxide, and the pneumotachometer was calibrated with a known volume (3 l) during mechanical inhalation and exhalation. The end-tidal carbon dioxide partial pressure (PETCO_2) was measured to calculate the partial pressure of carbon dioxide in the pulmonary artery (PaCO_2) by the formula $\text{PaCO}_2 = 5.5 + (0.9 \times \text{PETCO}_2) - (0.0021 \times \text{Vt})$ mmHg, where Vt = the tidal volume. The mixed venous partial pressure of carbon dioxide (PvCO_2) was calculated according to Collier²³ as $\text{PvCO}_2 = \text{PeqCO}_2 = \text{FeqCO}_2 \times (\text{Pb} - 47)$ mmHg, where PeqCO_2 and FeqCO_2 = the partial pressure and the fraction of carbon dioxide during equilibrium, respectively, and Pb = the barometric pressure. The PeqCO_2 was obtained during rebreathing from a bag containing a volume of 1.5 times the tidal volume and with a carbon dioxide concentration 2–3% higher than PETCO_2 in 35% O₂, until an equilibrium in carbon dioxide was reached. During the rebreathing procedure, the end-tidal carbon dioxide fraction and equilibrium curve was displayed, and accepted as satisfactory, when the equilibrium curve was horizontal after 10–15 s of rebreathing. The difference in carbon dioxide content between mixed venous blood (CvCO_2) and arterial blood (CaCO_2) was calculated as $11.02 \times (\text{PvCO}_2^{0.396} - \text{PaCO}_2^{0.396})$. Cardiac output was then calculated as $\text{VCO}_2 / (\text{CvCO}_2 - \text{CaCO}_2)$.

Cardiac output at baseline and in the second infusion period was determined as the mean of at least two measurements. During the first infusion period, measurements were repeated until the increased cardiac output had reached a new steady state, as judged by at least two measurements.

Hemodynamic and Renal Measurements

Arterial blood pressure (measured manually by sphygmomanometry) and heart rate were determined at baseline and at the middle of the second infusion

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period. Body weight was measured before induction of water diuresis, at the end of the baseline period, and immediately after termination of amine infusion. Renal clearance of lithium (C_{Li}) was used as an index of the delivery of sodium and water from the proximal tubule to the thin descending loop of Henle.^{24,25} A test dose of lithium carbonate (600 mg, 16.2 mEq) was given orally on the evening before each investigation. Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were measured by a constant infusion technique with urine collections, using ^{131}I -hippuran and ^{99m}Tc -DTPA in a total average dose of 0.10 mCi (3.6 MBq) and 0.73 mCi (27.0 MBq), respectively.²⁶ After an equilibration period of at least 1 h, renal clearances of ^{131}I -hippuran, ^{99m}Tc -DTPA, lithium, and sodium (C_{Na}) were determined at baseline and during the second hour of amine infusion. Each clearance value was calculated from the 1-h urinary excretion rates and the plasma values from three samples drawn at the start, the middle, and the end of each 1-h clearance period. Packed cell volume (PCV), plasma renin activity (PRA), and plasma aldosterone concentration (PAC) were measured at the end of each period.

Analytical Methods

Plasma and urinary lithium concentrations were measured by atomic absorption spectrophotometry (model 403; Perkin-Elmer, Norwalk, CT). Activities of ^{131}I -hippuran and ^{99m}Tc -DTPA in plasma and urine were determined in a well counter. Plasma sodium was measured with a Technicon RA 1000 instrument (Tarrytown, NY), and urinary sodium with a Technicon RA-Xt instrument. Plasma renin activity was measured by a double antibody radioimmunoassay, according to the principles described by Giese *et al.*²⁷ Intra- and inter-assay coefficients of variation were 5% and 10%, respectively. Plasma aldosterone concentration was measured as described by Lund *et al.*²⁸ Intra- and interassay coefficients of variation were 4% and 23%, respectively.

Calculations

Mean arterial blood pressure (MABP) was calculated as the diastolic pressure plus one-third of the pulse pressure. Total peripheral resistance (TPR) was determined as MABP divided by cardiac output. Renal vascular resistance (RVR) was estimated as MABP divided by the renal blood flow calculated as $ERPF/(1-PCV)$, and the renal fraction by dividing renal blood flow by cardiac output. Effective renal plasma flow, GFR, C_{Li} , and C_{Na} were calculated using standard formulae, and

all clearance values were corrected to 1.73 m² body surface area. Filtration fraction was determined as $GFR/ERPF$. Segmental renal tubular reabsorption rates were calculated based on the assumption that C_{Li} provides an accurate measurement of the rate of end-proximal delivery of fluid to the thin descending limb of Henle:^{24,25} absolute proximal reabsorption rate (APR) = $GFR - C_{Li}$, fractional proximal reabsorption (FPR) = $1 - (C_{Li}/GFR)$, absolute distal reabsorption rate of sodium (ADR_{Na}) = $(C_{Li} - C_{Na}) \times P_{Na}$ (where P_{Na} = plasma sodium concentration), and fractional distal reabsorption of sodium (FDR_{Na}) = $(C_{Li} - C_{Na})/C_{Li}$. Fractional excretions of sodium (FE_{Na}) and lithium (FE_{Li}) were calculated as C_{Na}/GFR and C_{Li}/GFR , respectively.

Statistical Analysis

Differences between study days were analyzed by a two-way ANOVA. If unequal ($P < 0.05$), paired *t* tests were used to analyze differences between corresponding baseline periods and infusion periods, respectively. Differences within study days between the baseline period and the second-hour infusion period were analyzed by paired *t* tests. Values are presented as means \pm SEM.

Results

Cardiac Output

On the three study days, dopamine, dopexamine, and dobutamine produced a similar increase in cardiac

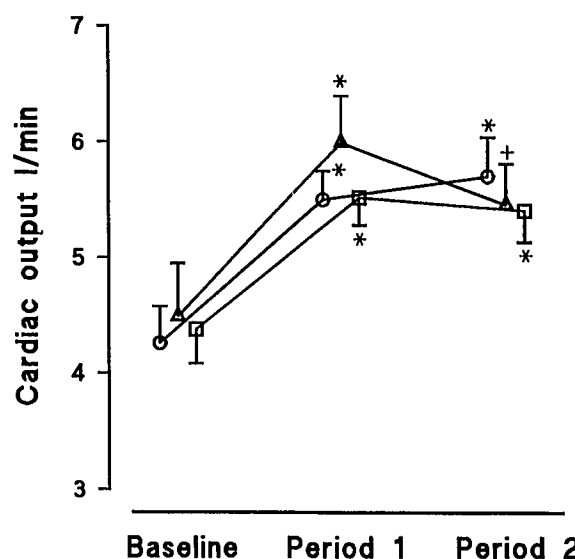


Fig. 1. Cardiac output at baseline and during infusion of dopamine (○), dopexamine (□), or dobutamine (△) in two consecutive 1-h periods. Values are means \pm SEM. N = 8. * $P < 0.01$; + $P < 0.05$ compared with baseline.

output (fig. 1). Infusion rates were 2.90 ± 0.07 (dopamine), 1.00 ± 0.02 (dopexamine), and 4.92 ± 0.14 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (dobutamine), respectively.

Hemodynamic Effects

Heart rate increased on all study days without significant changes between study days (table 1). The MABP increased significantly during dobutamine infusion, but remained unchanged during dopamine and dopexamine (table 1). None of the drugs changed diastolic blood pressure, but dopexamine and dobutamine significantly increased systolic blood pressure (table 1). The MABP and systolic pressure were significantly higher during dobutamine compared with dopamine and dopexamine. The TPR decreased significantly during dopamine and dopexamine, but remained unchanged with dobutamine (table 1). However, differences between study days were not significant. Only dopamine decreased RVR significantly, but values during both dopamine and dopexamine were significantly lower compared with dobutamine, which tended to increase RVR ($P = 0.066$; table 1). Renal fraction of cardiac output was decreased by dobutamine (table 1).

Effective Renal Plasma Flow and Glomerular Filtration Rate

Both dopamine and dopexamine increased ERPF, which remained unchanged during infusion of dobutamine. Values during dopamine were significantly higher than during dopexamine and dobutamine (fig. 2). On the study day with dopexamine, baseline GFR was significantly higher compared with baseline conditions before infusion of dobutamine (fig. 2). In contrast to the other drugs, dopexamine caused a small, but significant, increase in GFR (fig. 2). Filtration fraction decreased with dopamine (from $20.5 \pm 0.9\%$ to $17.0 \pm 1.1\%$, $P < 0.001$ vs. baseline, $P < 0.05$ vs. values during dopexamine and dobutamine), but remained unchanged with dopexamine (from $22.3 \pm 2.2\%$ to $22.0 \pm 2.0\%$) and dobutamine (from $20.5 \pm 0.9\%$ to $20.7 \pm 0.7\%$).

Segmental Tubular Function

Dopamine and dopexamine caused similar increases in C_{Li} and FE_{Li} , which remained unchanged during dobutamine (fig. 3). Dobutamine had no effect on calculated tubular reabsorption rates (fig. 4). The APR

Table 1. Hemodynamic Effects

	Dopamine	Dopexamine	Dobutamine
Heart rate (beats/min)			
Baseline	51 \pm 2	52 \pm 3	52 \pm 3
Infusion	57 \pm 3*	62 \pm 3*	61 \pm 3†
Diastolic pressure (mmHg)			
Baseline	73 \pm 2	77 \pm 3	76 \pm 1
Infusion	70 \pm 3	74 \pm 3	81 \pm 3
Systolic pressure (mmHg)			
Baseline	119 \pm 5	121 \pm 2	126 \pm 4
Infusion	128 \pm 5 ^a	139 \pm 4 ^{a,b}	162 \pm 5§
MABP (mmHg)			
Baseline	88 \pm 2	91 \pm 2	93 \pm 1
Infusion	90 \pm 3 ^a	96 \pm 4 ^b	108 \pm 3*
TPR (mmHg \cdot min \cdot l ⁻¹)			
Baseline	21.5 \pm 1.8	21.6 \pm 1.7	23.3 \pm 3.8
Infusion	16.1 \pm 1.3*	17.9 \pm 0.8†	20.3 \pm 1.4
RVR (mmHg \cdot min \cdot l ⁻¹)			
Baseline	88.8 \pm 5.6	98.3 \pm 7.9	100.2 \pm 4.5
Infusion	73.8 \pm 8.4 ^{a,†}	95.0 \pm 9.3 ^b	114.8 \pm 2.8
Renal fraction (%)			
Baseline	25.0 \pm 2.5	23.1 \pm 2.8	22.7 \pm 2.7
Infusion	23.0 \pm 2.2 ^b	19.9 \pm 1.9	17.8 \pm 1.4†

Values are means \pm SEM; n = 8.

MABP = mean arterial blood pressure; TPR = total peripheral resistance; RVR = renal vascular resistance.

* $P < 0.01$, † $P < 0.05$, § $P < 0.001$ compared with baseline.

^a $P < 0.001$, ^b $P < 0.05$ compared with values during infusion of dobutamine.

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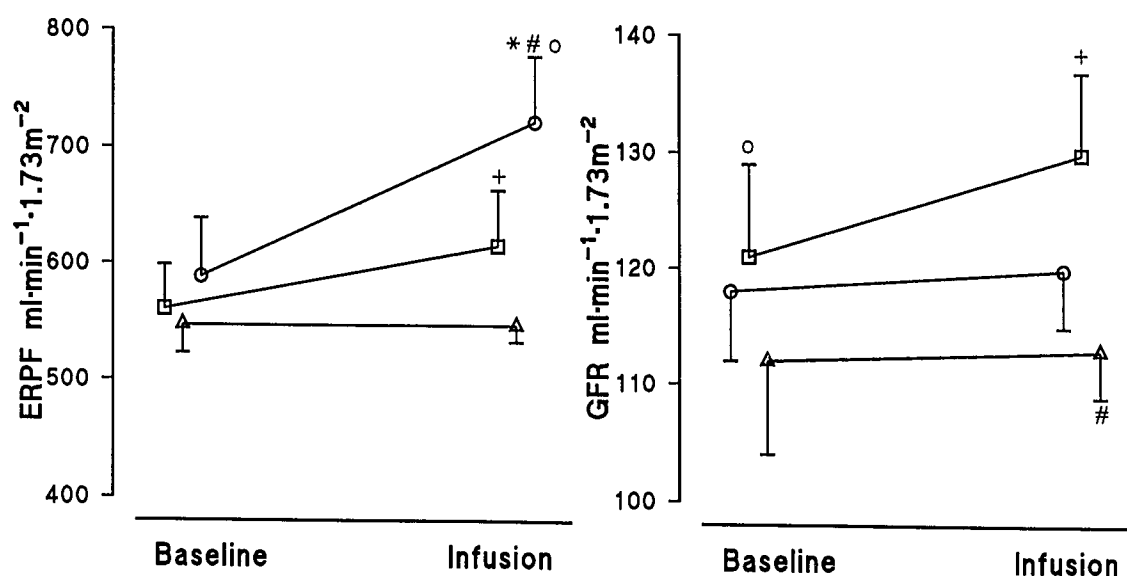


Fig. 2. Effective renal plasma flow and GFR at baseline and during the second-hour infusion period with dopamine (○), dopexamine (□), or dobutamine (△). Values are means ± SEM. N = 8. * $P < 0.05$; * $P < 0.01$ compared with baseline. * $P < 0.05$ compared with dopexamine. ° $P < 0.01$ compared with dobutamine.

only decreased significantly during dopamine infusion, but both dopamine and dopexamine significantly depressed FPR. These drugs also induced a similar increase in ADR_{Na} , whereas FDR_{Na} only decreased with dopamine. However, dobutamine tended to elevate FDR_{Na} , and values were significantly higher compared with both dopexamine and dopamine.

Sodium and Water Excretion

Sodium clearance was significantly higher with dopamine and dopexamine infusions compared with dobutamine, which tended to decrease sodium excretion (fig. 5). However, compared with baseline, only dopamine significantly increased C_{Na} . A similar pattern was observed for FE_{Na} , where values during dopamine infusion tended to be significantly higher compared with dopexamine ($P = 0.056$; fig. 5). Urine flow rate increased to the same extent with dopamine and dopexamine, but remained unchanged with dobutamine (fig. 5). Body weight was decreased after dopamine infusion (from 75.4 ± 2.3 to 75.0 ± 2.3 kg, $P < 0.05$), but was unchanged after dopexamine (from 74.8 ± 2.2 to 74.8 ± 2.0 kg) and dobutamine (from 76.5 ± 2.2 to 76.2 ± 2.1 kg).

Renin and Aldosterone

None of the drugs significantly changed PRA or PAC (table 2). However, during infusion, values of PAC

were significantly higher with both dopamine and dobutamine compared with dopexamine.

Discussion

The current study compares renal effects of dopamine, dopexamine, and dobutamine in doses producing a similar increase in cardiac output. Adjustments of the infusion rates were guided by repeated measurements of cardiac output using the carbon dioxide-rebreathing method in association with a microcomputerized technology that allows values to be rapidly obtained. The method is based on the well established Fick principle, but relies on the function of the lung as an aerotometer to indirectly estimate arterial and mixed venous carbon dioxide tensions.²¹⁻²³ Several studies in healthy subjects and in patients with pulmonary and heart diseases have demonstrated a good agreement with the direct Fick method,^{22,23} and the current data obtained in resting subjects indicate that infusion rates on the three study days were successfully adjusted. However, as indicated by the difference between the drug effects on blood pressure, the similar increase in cardiac output may not be attributed solely to an equal inotropic potency, but may also have been influenced by different peripheral vascular drug effects.

Segmental tubular function was evaluated by the lithium clearance method.^{24,25} Lithium is reabsorbed in

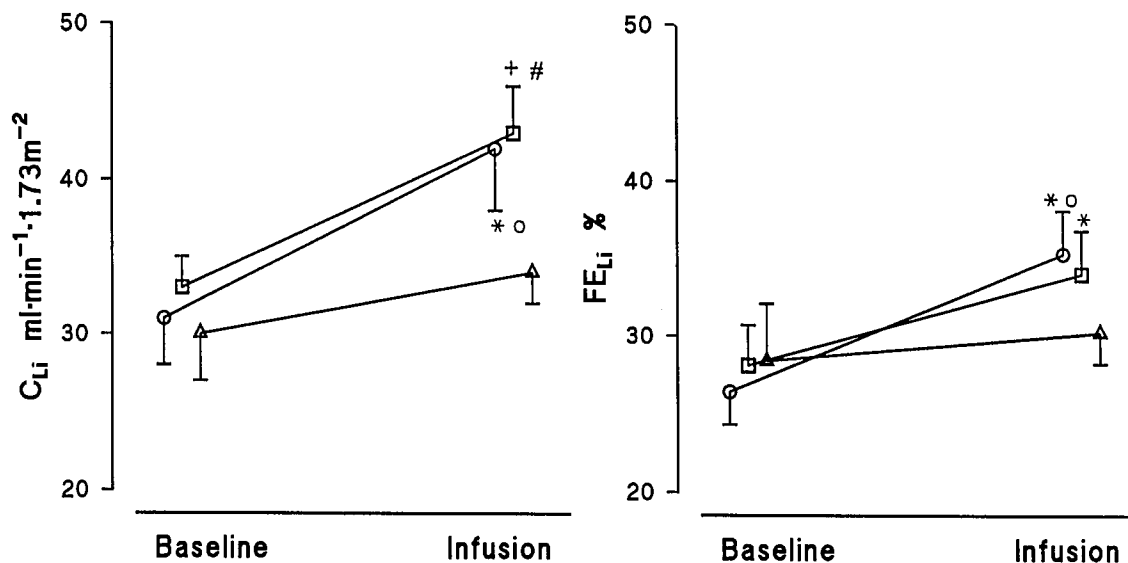


Fig. 3. Lithium clearance and FE_{Li} at baseline and during the second-hour infusion period with dopamine (○), dopexamine (□), or dobutamine (Δ). Values are means ± SEM. N = 8. * $P < 0.05$; * $P < 0.01$ compared with baseline. ° $P < 0.05$; ° $P < 0.01$ compared with dobutamine.

the same proportion as sodium and water in the proximal tubule, but is neither reabsorbed or secreted in the distal tubules under normal physiologic conditions.²⁵ Lithium clearance has been shown to be a valid index of the delivery of fluid into the thin descending loop of Henle in rats,^{24,29} and indirect evidence obtained by diuretic drug effect studies indicates a similar renal handling of lithium in humans.^{25,30} Thus, simultaneous measurements of GFR, C_{Li} , and C_{Na} may allow estimates of proximal and distal reabsorption rates of sodium and water. Recent studies have demonstrated a natriuretic effect of the conventional lithium test doses used in clearance studies,^{31,32} and an interaction with renal dopaminergic mechanisms has been suggested.³³ However, this suggestion was not confirmed in more recent studies, in which lithium did not interfere with the renal effects of dopamine^{32,34} or the dopaminergic DA₁ agonist fenoldopam.³⁵ Although the use of lithium in the current study may have increased sodium excretion rate, baseline conditions were comparable on the three study days.

Maintenance of renal function is crucial in the treatment of the critically ill patient, and the use of dopamine in low cardiac output states has been established mainly because of its vasodilating effect and the beneficial effects on the renal function.^{1,36,37} However, indirect effects secondary to the increase in cardiac output have been proposed to contribute significantly to

the renal response of dopamine and dobutamine.^{15,17,37} Similar to the study of Hilberman *et al.*,¹⁵ we, therefore, included dobutamine for comparison of renal effects, because this drug does not stimulate dopaminergic receptors,³⁷ but predominantly acts on cardiac β_1 receptors to produce its inotropic effects.⁶⁻⁸ Furthermore, it is without direct vasodilating effects on renal vasculature.⁶ The current design, therefore, allows an extended interpretation of the relative significance of specific renal effects induced by sympathomimetic amines.

The current significant increase in MABP with dobutamine, not found with dopamine and dopexamine, was mainly caused by an increase in systolic pressure, and indicates a greater effect on cardiac contractility compared with the other drugs. Total peripheral resistance (TPR) decreased only with dopamine and dopexamine, and, in contrast to dobutamine, the increase in cardiac output with those drugs may be produced mainly as a result of vasodilation caused by stimulation of DA and β_2 receptors, respectively.^{1,2,9-12} As previously found in anesthetized dogs,²⁰ renal hemodynamics remained virtually unchanged with dobutamine, nor did dobutamine induce significant changes in renal excretory functions. In our volume-repleted, normotensive subjects, these findings argue against a contribution of indirect hemodynamic effects on the renal response to inotropic drugs after increased cardiac output (and

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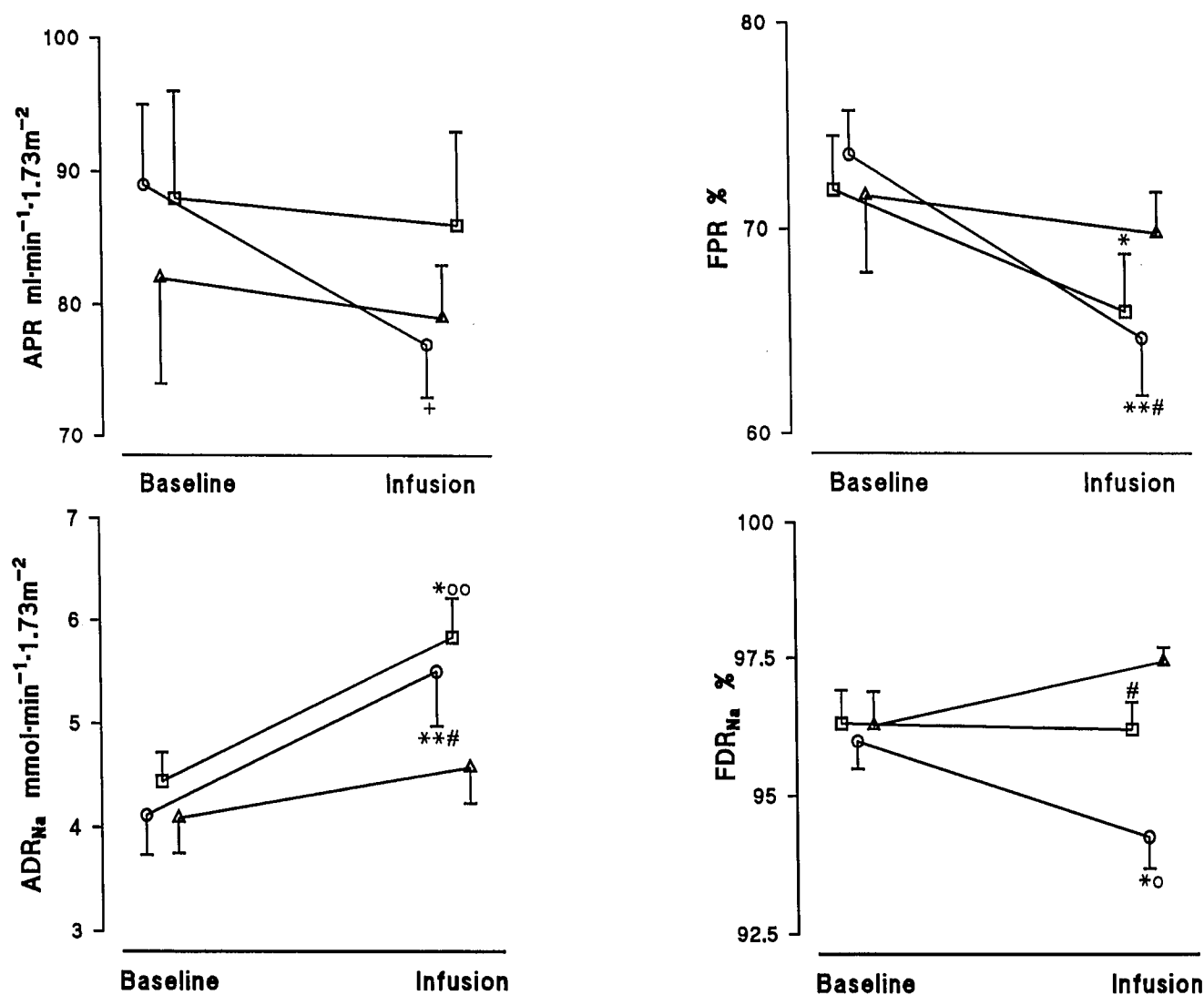


Fig. 4. Absolute proximal reabsorption, FPR, ADR_{Na}, and FDR_{Na} at baseline and during the second-hour infusion period with dopamine (○), dopexamine (□), or dobutamine (△). Values are means ± SEM. N = 8. *P < 0.05; °P < 0.01; °°P < 0.001 compared with baseline. #P < 0.05; °#P < 0.01; °°#P < 0.001 compared with dobutamine.

MABP). Dobutamine decreased the renal fraction of cardiac output, and the results indicate the presence of adequate renal autoregulation after this drug.

Consistent with previous studies in healthy subjects,^{4,32,36,38} dopamine increased ERPF and decreased renal vascular resistance. *In vivo* studies in split hydronephrotic kidneys of rats have shown a direct vasodilating effect of dopamine on both afferent and efferent arterioles,³⁹ and strong evidence obtained by antagonist and radioligand binding studies exist to explain the effect as secondary to stimulation of specific DA₁

receptors.^{2,3,37,39} Also, dopexamine increased ERPF, but the increase was significantly smaller than with dopamine, and was not associated with significant changes in renal vascular resistance. In dogs, dopexamine was found to have approximately one-third the potency of dopamine in stimulating the renal vascular DA₁ receptor.¹⁰ The current results in humans agree with this finding. Only dopexamine increased GFR in the current study. However, this does not necessarily reflect a specific effect of dopexamine, because previous results obtained with dopamine^{4,32,38} and DA₁ agonists^{35,40} also

indicated small increases in GFR on the borderline of significance.

Previously, induction of natriuresis in the absence of changes in renal hemodynamics indicated specific tubular effects of dopamine,^{13,41} and a decrease in sodium transport has been demonstrated in the isolated perfused proximal straight tubule of the rabbit.¹⁴ Both DA₁ and DA₂ receptors have been identified in proximal tubules and cortical collecting ducts.^{3,42} Recent *in vitro* studies indicate that dopamine *via* the DA₁ receptor may decrease proximal tubular sodium reabsorption by inhibition of Na⁺-H⁺ antiport activity at the brush-border membrane⁴³ and by inhibition of Na⁺-K⁺-ATPase activity at the basolateral membrane.⁴⁴ In addition, measurements of proximal tubular fluid flow rates by micropuncture in rats⁴⁰ and by the lithium clearance method in humans^{4,32,34,38} have demonstrated that the DA₁ agonist fenoldopam and dopamine consistently increase proximal tubular outflow. The concomitant decrease in fractional proximal reabsorption (FPR), however, was not associated with marked decreases in absolute proximal reabsorption rate (APR),^{4,38,40,41} as would be expected if a direct proximal tubular effect of dopaminergic agents contributed significantly to the natriuresis.

In the current water-loaded subjects, dopamine and dopexamine elicited similar diuretic responses, but only dopamine significantly increased sodium excretion. The dopamine-induced increase in C_{Li} was of similar magnitude as found in previous studies,^{4,32,34,38} but GFR remained unchanged. Thus, calculated APR decreased by 13%, which indicates that a direct effect on

Table 2. Effects of Renin and Aldosterone

	Dopamine	Dopexamine	Dobutamine
PRA (mIU/l)			
Baseline	24 ± 3	26 ± 5	23 ± 3
Infusion	29 ± 4	25 ± 6	38 ± 6
PAC (pM)			
Baseline	242 ± 46	345 ± 105	328 ± 50
Infusion	290 ± 42*	198 ± 42	457 ± 86†

Values are means ± SEM; n = 8.

PRA = plasma renin activity; PAC = plasma aldosterone concentration.

* P < 0.05 compared with values during infusion of dopexamine and dobutamine.

† P < 0.01 compared with values during infusion of dopexamine.

proximal tubular sodium reabsorption contributed to the increase in C_{Li}. As indicated by the C_{Li} results, proximal tubular outflow increased to the same extent with dopamine and dopexamine, and both drugs decreased FPR. But, in view of the increased GFR without measurable changes in APR, dopexamine infusion would seem to change FPR as a secondary consequence to an increased filtered load.

The current increases in absolute distal sodium reabsorption with dopamine and dopexamine most probably reflect a load-dependent response to the increase in end-proximal fluid delivery.⁴⁵ However, in contrast to dopexamine, fractional distal reabsorption of sodium (FDR_{Na}) decreased with dopamine, indicating that incomplete distal tubular compensation for the increased delivery contributed to the dopamine-induced natriuresis.^{4,38} Similar results were found in rats given fenoldopam.⁴⁰ In the presence of similar effects on prox-

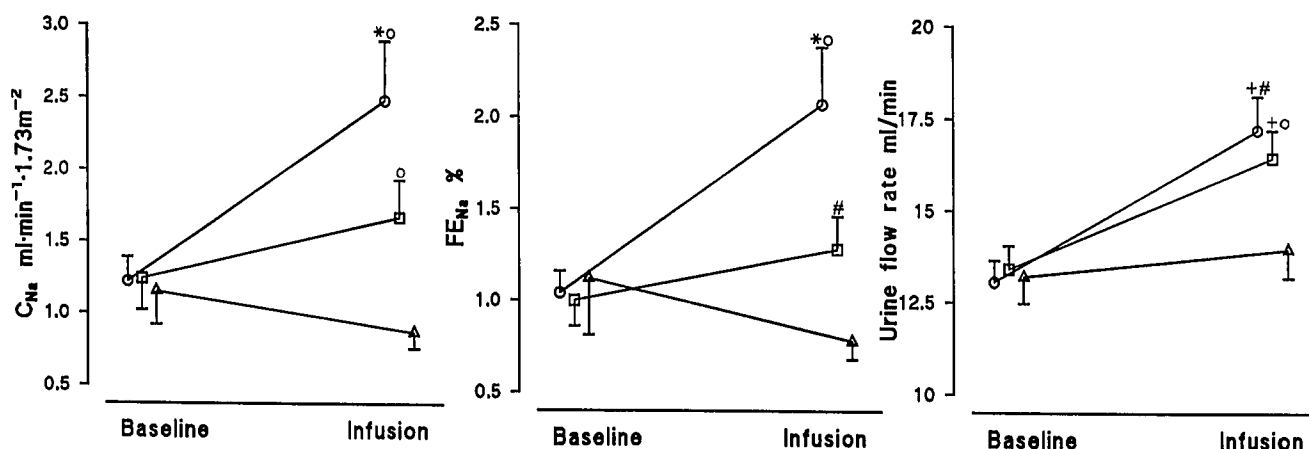


Fig. 5. Sodium clearance, FENa, and urine flow rate at baseline and during the second-hour infusion period with dopamine (○), dopexamine (□), or dobutamine (Δ). Values are means ± SEM. N = 8. * P < 0.05; * P < 0.01 compared with baseline. † P < 0.05; † P < 0.01 compared with dobutamine.

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imal tubular outflow, differences in distal tubular effects of dopamine and doxepamine may, therefore, have accounted for the observed differences in the natriuretic response.

Clearly, the null hypothesis that the three sympathomimetic amines would have similar renal effects when given in doses producing equal increases in cardiac output can be rejected. In summary, the current study reveals that a significant increase in cardiac output by either drug is associated with different cardiovascular and renal functional changes. In contrast to dobutamine, which did not change renal function, ERPF increased with dopamine and doxepamine consistent with a specific, vasodilating effect on renal vessels secondary to stimulation of DA receptors. However, in the current doses, the renal vasodilating potency of doxepamine was of lesser magnitude compared with dopamine. In spite of a similar diuretic response, a significant natriuresis only occurred with dopamine. The current lithium clearance studies indicate that dopamine inhibits sodium reabsorption in the proximal tubule and in more distal nephron segments, whereas renal tubular effects of doxepamine seemed to be predominantly caused by the increase in GFR. Further studies are warranted to clarify the renal effects of sympathomimetic amines in critically ill patients and patients with cardiac or renal disease.

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