Dopamine and dobutamine were administered to 12 patients who had undergone open cardiac operations. To eliminate the effects of variation in systemic blood flow upon renal function the drug infusion rates were adjusted to achieve equal cardiac outputs. Under conditions of equivalent systemic pressure and flow, dopamine (5.0 ± 1 µg·kg⁻¹·min⁻¹) and dobutamine (3.5 ± 1.8 µg·kg⁻¹·min⁻¹) had similar effects upon glomerular filtration rate (80 ± 29 vs. 83 ± 27 ml·min⁻¹·1.73 m⁻²) and effective renal plasma flow (375 ± 119 vs. 357 ± 126 ml·min⁻¹·1.73 m⁻²). However, dopamine administration resulted in a significantly greater diuresis (2.8 ± 2.7 vs. 1.0 ± 0.3 ml/min), kaliuresis (0.22 ± 0.39 vs. 0.07 ± 0.10 mEq Na⁺/min), and kaliuresis (0.15 ± 0.06 vs. 0.10 ± 0.05 mEq K⁺/min) (P < 0.05). In patients with modest depression of cardiac performance and renal vasconstriction, dopamine's selective renal vasodilator effects were not evident. Furthermore, these data suggest that dopamine inhibits tubular solute reabsorption directly. Thus, the diuresis and kaliuresis that frequently accompany dopamine administration may occur independently of any effects of dopamine upon renal blood flow. (Key words: Heart; cardiac output; Kidney; blood flow; diuresis; function. Pharmacology: dopamine; dobutamine. Sympathetic nervous system: catecholamines, dopamine.)

Dopamine is a naturally occurring catecholamine and a potent myocardial inotropic agent. The rapid growth in its therapeutic use has been due both to its inotropic potency and to its salutary renal effects, which include vasodilatation, diuresis, and natriuresis. Renal vasodilatation generally has been attributed to specific renal vascular receptors, while the diuresis and natriuresis have been considered secondary to renal vasodilatation.¹⁻³ This latter inference may not be entirely correct. Reductions in renal vascular resistance in cardiac patients and volunteers during dopamine infusion invariably have been associated with, and may have resulted from, increments in cardiac output. Failure of dopamine to increase renal blood flow, while still initiating a natriuresis in patients with congestive heart failure,⁶ raises the possibility that dopamine-induced diuresis may result from direct tubular inhibition of solute reabsorption. This latter interpretation is consistent with a considerable body of data indicating that catecholamines exert a direct effect upon tubular solute transport.¹⁰⁻¹⁷

The present study was designed to determine whether or not the cardiovascular and tubular actions of dopamine could be dissociated in patients with a low cardiac output state following cardiac surgery. Because it is not possible, in our view, to isolate the renovascular effects of dopamine from its simultaneous effects on cardiac performance and the systemic circulation, we did not compare the respective renal responses before and during dopamine infusion. Instead, the effects of dopamine infusion on renal vasomotion and urinary cation excretion were compared with those of an infusion of dobutamine of equivalent inotropic potency. Dobutamine, a synthetic catecholamine and potent myocardial inotropic agent,²¹⁻²⁰ has been shown to have no direct effect upon the renal vasculature.²¹,²² Accordingly, a comparison of the effects of dopamine and dobutamine at equivalent systemic flow (and pressure) should permit any selective renal effects of dopamine to be identified easily.

Materials and Methods

Patient Population

Informed consent was obtained preoperatively from patients scheduled for open cardiac operation who had depressed preoperative left ventricular performance, with inotropic support anticipated postoperatively. Twelve of these patients subsequently required inotropic support with dopamine and were studied. Age ranged from 44 to 71 yr, averaging 61.6 yr. Five patients had valve replacement surgery, and seven had coronary revascularization procedures. The patients were volume expanded with crystalloid and colloid infusions intraoperatively and in the early postoperative period, such that an average increase of 5.2% above preoperative weight was observed at the time of study. Studies were performed with patients breathing spontaneously or
mechanically ventilated; the mode of ventilation was not changed during the study. Fluid administration rates and other patient care variables also were changed as little as possible during the study. Consent procedures and study techniques conformed to appropriate ethical standards and were approved by the Committee on the Use of Human Subjects in Research at Stanford.

PROTOCOL

Measurements of hemodynamic and renal function were made 12–36 h postoperatively. Initially, hemodynamic dose–response curves for dopamine and dobutamine were determined. An infusion rate of either catecholamine, which resulted in a clear increment in cardiac output, was selected. The order of drug administration was arbitrary; in seven patients dopamine infusion preceded that of dobutamine, while the order was reversed in the remaining five patients. Following a 60-min period for equilibration of drug and clearance markers, renal function was measured. Hemodynamic measurements then were performed in duplicate. Administration of the second drug was initiated and the rate increased until the identical cardiac output was obtained. A second equilibration period of 60 min was followed by repeat measurement of hemodynamic and renal function.

PHYSIOLOGIC MEASUREMENTS

The physiologic measurements used standard techniques and calculations as previously described.25,24 Briefly, measurements were performed after the patients were rewarmed completely and hemodynamically stable. No diuretics were administered in the 6 h prior to study; hyperoncotic volume expansion and changes in fluid administration rates were avoided during clearance measurement periods. Cardiac output was measured in duplicate by indocyanine green dilution using a Waters’ cuvette densitometer (D-400) (Waters Instrument Corporation, Rochester, Minnesota) and cardiac output computer (CO-4) (Waters Instrument Corporation). Pulmonary artery and pulmonary capillary wedge pressures were measured through a Swan-Ganz® 7F thermodilution catheter (Edwards Laboratories, Inc., Santa Ana, California). Heart rate and mean arterial pressure (MAP) were measured using standard transducers and bedside monitors (Hewlett-Packard, Palo Alto, California).

Glomerular filtration rate and effective renal plasma flow were determined by the clearances of inulin and para-aminohippurate (PAH), respectively. A bolus of 24 mg/kg inulin and 3.5 mg/kg PAH was followed by a sustained infusion of 375 mg/h of inulin and 200 mg/h of PAH. This resulted in stable plasma concentrations of inulin and PAH of 8.5 ± 2.5 mg/dl and 0.6 ± 0.2 mg/dl, respectively. After equilibration of these markers, three 20-min urine collections were performed. The bladder was emptied completely at the start and end of each collection period by flushing 60–120 ml of air through an indwelling Foley catheter under sterile conditions and allowing complete gravity drainage of the residual urine. Heparinized blood samples were obtained at the beginning and end of each collection period. In addition to inulin and PAH, osmolality, sodium, and potassium concentrations and oncotic pressure were determined from the blood and urine samples. The clearance of PAH was corrected, assuming a PAH extraction value of 0.9, and renal blood flow was calculated by dividing the corrected PAH clearance by (1-hematocrit). The fractional excretion of sodium was calculated by dividing the sodium clearance by the inulin clearance and multiplying by 100, the renal fraction by dividing renal blood flow by cardiac output and multiplying by 100, and the filtration fraction by dividing the clearance of inulin by the clearance of PAH. Average clearance values for inulin and PAH were determined as a time-weighted average from the values for the three collection periods, normalized, and expressed in ml·min⁻¹·1.73 m⁻². Urine flow also was derived from the three collection periods, however, values for electrolyte excretions were derived from a single collection period.

Calculation of Efferent (Postglomerular) Oncotic Pressure

Efferent oncotic pressure is the major Starling force favoring the uptake of tubular fluid by the peritubular capillary circulation.25,26 In an effort to determine the oncotic pressure prevailing in the postglomerular circulation during the administration of dopamine and dobutamine, respectively, we used a membrane osmometer to determine the oncotic pressure in radial arterial plasma.27 This oncotic pressure is taken to be the same as that in the afferent (preglomerular) arteriole (πa). With the formation of a protein-free ultrafiltrate, protein concentration, and hence oncotic pressure, rises during axial blood flow along the glomerular capillary network. Efferent protein concentration (Ce) can be estimated from afferent protein concentration (Ca) and the filtration fraction (FF) using the equation

\[ C_e = C_a / (1 - FF) \]  

We previously have shown that over the protein concentration range prevailing in the glomerular capillary network (5 < C < 9 g%), the relationship between protein concentration and oncotic pressure is described in the quadratic relation24:

\[ \pi = a_1 C_a + a_2 C_a^2 \]  

Downloaded From: http://anesthesiology.pubs.asahq.org/pdaccess.ashx?url=/data/journals/jasa/931419/ on 04/29/2017
TABLE 1. Hemodynamic Effects of Dopamine and Dobutamine with Infusion Rates Adjusted to Achieve Equivalent Cardiac Indices

<table>
<thead>
<tr>
<th></th>
<th>Dopamine</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion rate</td>
<td>5.0 ± 1.8</td>
<td>3.5 ± 1.8</td>
</tr>
<tr>
<td>(µg·kg⁻¹·min⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac index</td>
<td>2.7 ± 0.7</td>
<td>2.7 ± 0.7</td>
</tr>
<tr>
<td>(l·min⁻¹·m⁻²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular stroke work index (g·m⁻³)</td>
<td>30 ± 10</td>
<td>28 ± 10</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>87 ± 9</td>
<td>83 ± 9</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mmHg)</td>
<td>18.0 ± 4.5*</td>
<td>16.4 ± 4.2</td>
</tr>
<tr>
<td>Systemic vascular resistance index (mmHg·min·m⁻²·l⁻¹)</td>
<td>28 ± 7</td>
<td>27 ± 8</td>
</tr>
</tbody>
</table>

*P < 0.05.

where a₁ = 1.629 mmHg and a₂ = 0.2935 mmHg, respectively.

Accordingly, a value for cₐ was derived from measured cₐ using equation 2. The value for cₑ then was calculated using equation 1 and reconverted to oncotic pressure (πₑ) (equation 2).

STATISTICAL ANALYSIS

Data are reported as the mean ± standard deviation. Student's t-test for paired data was used to evaluate the significance of the differences observed.

RESULTS

Adjustment of dopamine (5.0 ± 1.8 µg·min⁻¹·kg⁻¹) and dobutamine (3.5 ± 1.8 µg·min⁻¹·kg⁻¹) infusion rates to achieve equal cardiac outputs in individual patients resulted in average values for cardiac index that were below normal values at 2.7 l·min⁻¹·m⁻² and identical (table 1). Similarly, the average values for mean arterial pressure, heart rate, left ventricular stroke work index, and systemic vascular resistance index were comparable. Pulmonary capillary wedge pressure was slightly, but significantly, lower during dobutamine infusion.

Dopamine and dobutamine infusions were associated with an essentially identical renovascular response to the low cardiac output state (table 2). In all but three patients, the renal fraction (renal blood flow to cardiac output ratio) was below the normal value of 20%, averaging 15 ± 5 and 14 ± 4% during dopamine and dobutamine infusion, respectively, indicating a selective increase of renal relative to systemic resistance. As measured by PAH or diodrast clearance, renal (cortical) plasma flow in men in the sixth and seventh decades of life approximates 500 ml·min⁻¹·1.73 m⁻². Neither dopamine nor dobutamine was associated with renal plasma flows in this range, the respective values averaging 375 ± 119 and 357 ± 126 ml·min⁻¹·1.73 m⁻².

By contrast, the corresponding average values for glomerular filtration rate of 90 ± 29 and 85 ± 27 ml·min⁻¹·1.73 m⁻², respectively, were close to the age-adjusted normal range. Affenter oncotic pressure averaged 20.5 ± 1.6 mmHg during dopamine infusion and was slightly lower during dobutamine infusion (19.6 ± 2.4 mmHg).

Despite equivalent values for renal plasma flow, filtration fraction, and πₑ, dopamine infusion was associated with a 2.8-fold increase in urine flow and a 4.6-fold increase in urinary sodium excretion relative to dobutamine infusion (table 3). The fractional excretion of sodium also increased during dopamine infusion, potassium excretion was enhanced, and the urine was less concentrated as measured by the urine to plasma inulin and osmolality ratios.

DISCUSSION

An increase in cardiac output due to dopamine administration would increase renal blood flow, glomerular filtration rate, and solute and water excretion. At issue

TABLE 3. Comparison of Indices of Solute and Water Excretions Between Dopamine and Dobutamine

<table>
<thead>
<tr>
<th></th>
<th>Dopamine</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine flow (ml/min)</td>
<td>2.8 ± 2.7*</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>Na excretion (mEq/min)</td>
<td>0.32 ± 0.39*</td>
<td>0.07 ± 0.10</td>
</tr>
<tr>
<td>Fractional excretion of sodium (%)</td>
<td>2.54 ± 2.97*</td>
<td>0.66 ± 0.87</td>
</tr>
<tr>
<td>K excretion (mEq/min)</td>
<td>0.15 ± 0.06*</td>
<td>0.10 ± 0.08</td>
</tr>
<tr>
<td>Fractional excretion of potassium (%)</td>
<td>45.8 ± 21.6</td>
<td>37.5 ± 11.0</td>
</tr>
<tr>
<td>Urine/plasma osmolality</td>
<td>1.6 ± 0.3*</td>
<td>2.0 ± 0.4</td>
</tr>
<tr>
<td>Urine/plasma inulin</td>
<td>48 ± 50*</td>
<td>83 ± 32</td>
</tr>
</tbody>
</table>

*P < 0.05.
is whether the diuresis that accompanies dopamine administration is explained entirely by its well-recognized inotropic potency, or whether selective renal vasodilation (which would increase the renal fraction of total blood flow), or a direct effect of dopamine on tubular solute transport are also involved. To minimize the indirect effects of cardiac output changes upon renal function, dopamine administration was compared with that of dobutamine, a newer synthetic inotropic agent that does not cause selective renal vasodilation.\textsuperscript{21,22} The improvement in renal blood flow and renal function observed with dopamine administration is sustained up to 10 μg·kg\textsuperscript{-1}·min\textsuperscript{-1}.\textsuperscript{6,22} Evidence of renal vasoconstriction is not evident until 20 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} are administered.\textsuperscript{22} Therefore, the 5 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} dose employed in this study was well within the “dopaminergic” range. Dopamine and dobutamine infusion rates were adjusted successfully to achieve equal systemic blood flows in patients with depressed left ventricular performance. Thereafter, the effects of dopamine and dobutamine upon systemic and renal hemodynamics were nearly indistinguishable. Most striking, despite the similarities in renal and systemic perfusion and glomerular filtration during the infusion of these two agents, the diuretic, natriuretic, and kaliuretic effects of dopamine were still evident.

The failure of glomerular filtration rate to decrease in proportion to the reduction in renal plasma flow, seen in our patients, is a typical renal response to cardiac failure.\textsuperscript{50–52} These changes closely mimic the effects of several pressor hormones on the glomerular filtration process, including angiotension II, vasopressin, and noradrenaline.\textsuperscript{33–36} Increased plasma levels of these pressor hormones have been observed in cardiac failure.\textsuperscript{37–39} The high filtration fraction observed during the infusion of both dopamine and dobutamine suggests the presence of efferent vasoconstrictor hormones in these postoperative patients with modest depression of cardiac performance. In this setting selective renal vasodilation by dopamine was not demonstrable.

Given the nearly identical glomerular filtration rates with the two drug regimens and the increase in the fractional sodium excretion during dopamine infusion, there remain three mechanisms that might explain the observed diuresis and natriuresis: first, the Starling forces governing tubular fluid reabsorption could be altered by renal vasodilation; second, an intrarenal redistribution of blood flow to nephrons with less reabsorption capacity could occur; and, third, a direct tubular inhibition of solute reabsorption could occur.

That dopamine did not cause greater renal vasodilation than dobutamine is evidenced by the equal PAH clearances, renal vascular resistances, and filtration fractions. This result depends upon normal (or equivalent) PAH extraction. Previous studies of patients following cardiac operation or with poor cardiac performance consistently have demonstrated a normal PAH extraction ratio of between 80 and 90%.\textsuperscript{30–32,40} As judged by the level of glomerular filtration rate, renal function (and presumably proximal tubule cell function) in our experimental population was relatively normal. Furthermore, plasma PAH concentrations deliberately were kept low (0.6 ± 0.2 mg/dl) to avoid saturating proximal tubule PAH extraction capacity. Therefore, we may assume the PAH clearances are valid. We directly demonstrated that the Starling forces favoring reabsorption of tubular fluid were not diminished by dopamine infusion. Of the physical forces responsible for peritubular uptake of reabsorbed tubule fluid, postglomerular oncotic pressure (π\textsubscript{e}) is by far the largest.\textsuperscript{23,41} π\textsubscript{e} during dopamine infusion did not differ from that during dobutamine infusion and, therefore, cannot explain the fourfold increment in fractional sodium excretion observed during dopamine relative to dobutamine infusion.

An intrarenal redistribution of blood flow could account for the changes observed. Such a change cannot be excluded by our data but is not an attractive explanation for our results. First, it has been shown that the inert gas techniques used for measuring renal blood flow distribution in intact humans are not accurate.\textsuperscript{42,43} Secondly, our data indicate that no change in total blood flow occurred, and changes in the regional distribution of renal blood flow (measured by inert gas or microsphere techniques) always have been accompanied by changes in total blood flow (although the reverse is not true).\textsuperscript{42}

The effects of catecholamines upon renal solute and water handling have been reviewed.\textsuperscript{10–12} There exist good correlations between urinary sodium and dopamine excretion,\textsuperscript{13} between dopamine synthesis and urinary sodium excretion,\textsuperscript{14} and between dietary sodium and plasma dopamine levels.\textsuperscript{15} These indirect observations in humans have received strong support from in vitro studies on isolated rabbit proximal tubule that demonstrate that dopamine inhibits solute flux.\textsuperscript{17} Given this evidence and the absence in our patients of a suitable alternative explanation, we propose that the observed dopamine-related diuresis, kaliuresis, and natriuresis is best explained by a direct action of dopamine on tubular solute transport.

Why do our results differ from earlier studies on dopamine? Most importantly, the availability of dobutamine, a new synthetic catecholamine of similar myocardial inotropic potency,\textsuperscript{2,16–20} permitted us to devise a protocol in which the systemic hemodynamic effects of dopamine could be imitated by a drug that lacked
RENAL PROPERTIES OF DOPAMINE

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References

18. Tuttle RR, Mills J: Development of a new catecholamine to


