Propylbutyldopamine: Hemodynamic Effects in Conscious Dogs, Normal Human Volunteers and Patients with Heart Failure

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SUMMARY The cardiovascular actions of a dopamine analog, propylbutyldopamine (PBDA), were examined for the first time in conscious dogs, normal human volunteers, and patients with congestive heart failure. PBDA lowered blood pressure without reflex increases in heart rate, increased renal blood flow, and decreased renal vascular resistance in dogs previously instrumented to allow measurement of arterial pressure and regional vascular flows in the conscious, unrestrained state. Pretreatment of the dogs with (S)-

saltpride, an antagonist selective for the dopamine receptor located on noradrenergic neurons (DA₂),

attenuated the reduction in arterial pressure but not the increase in renal blood flow produced by PBDA at a dose of 20 μg/kg/min. The emetic potency of this dopamine analog also was examined in conscious dogs; the drug caused vomiting on two of 22 occasions at an i.v. infusion rate of 20 μg/kg/min and on six of 11 occasions at a dosage of 40 μg/kg/min. In contrast to its effects in conscious dogs, PBDA in nonemetic dosages (20–40

μg/kg/min) failed to lower blood pressure in three normal volunteers but slightly increased heart rate and
doubled renal blood flow as measured by changes in the clearance of p-aminohippurate. Pretreatment of the volunteers with metoclopramide, 20 mg i.v., antagonized the increase in both heart rate and renal blood flow produced by PBDA. In 11 patients with congestive heart failure not due to valvular or congenital heart
disease, i.v. infusion of PBDA at 5, 10 and 20 μg/kg/min resulted in dose-dependent reductions in mean arterial pressure, left ventricular filling pressure and pulmonary and systemic vascular resistances, and increases in cardiac index, without changes in either stroke work index or heart rate. The demonstration that PBDA decreases systemic vascular resistance and blood pressure in patients with heart failure and increases renal blood flow in dogs and normal volunteers introduces a new class of drugs with unique mechanisms of action and advantages for the treatment of conditions such as congestive heart failure and hypertension. The possibility that this drug class acts through activation of peripheral DA₂ presynaptic and

DA₁ postsynaptic dopamine receptors appears strong and further studies with this and similar agonists should stimulate the study of DA₂ receptors in man.

MANY therapeutic advances have occurred through development of drugs selective for specific adrenergic, histaminergic or cholinergic receptors. These achievements have stimulated the current interest in identifying specific dopaminergic receptors that might be involved in the pathogenesis of a variety of cardiovascular diseases or useful in their treatment.¹-⁷

An ideal dopaminergic agonist should possess both presynaptic (DA₂) adrenergic inhibitory activity and postsynaptic (DA₁) vascular dilating activity in the renal bed without having cardiac chronotropic (β₁) or vascular constrictor (α₁) effects. The last two actions limit the use of dopamine itself in the treatment of heart failure and hypertension.

However, how or where putative dopaminergic drugs act is not clear, and it is not known whether DA₂ receptors on peripheral adrenergic neurons even exist in man. For example, the dopamine agonist bromocriptine decreases blood pressure in man.⁷-⁸ Explanations of the hypotensive effects of bromocriptine have postulated an interaction with peripheral DA₂ receptors,⁹,¹⁰ although more recent studies have led to the conclusion that the drug may act mainly through a central rather than peripheral mechanism because its hypotensive effects are inhibited only by dopamine antagonists that enter the central nervous system.¹¹-¹³

In addition, bromocriptine is not an agonist for DA₁ vascular receptors in the dog¹⁴ and, therefore, does not possess one of the main attributes that make dopaminergic agonists uniquely attractive for treating cardiovascular diseases — the ability to maintain renal blood flow despite a reduction in systemic blood pressure.

Recently, limited structure activity studies in our laboratories have shown that a newly synthesized dopamine analog, N-n-propyl-N-n-butyl dopamine (PBDA), demonstrates these desirable cardiovascular and renal actions in anesthetized dogs.¹⁵,¹⁶ The drug decreased blood pressure and heart rate (HR) primarily through activation of specific DA₂ receptors located in

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the peripheral rather than central nervous system. Simultaneously, it increased renal blood flow by agonism of DA, vasodilatory receptors. On the N,N-di-substituted dopamine analogs that were examined, propylbutyldopamine had the highest therapeutic ratio (efficacy/toxicity), mainly because of less vomiting. We now report our studies of the hemodynamic and renal effects of propylbutyldopamine in conscious, chronically instrumented dogs, in normal volunteers and in patients with congestive heart failure.

**Methods**

**Studies of Hemodynamics and Renal Blood Flow in Conscious Dogs**

**Surgical Preparation**

Ten healthy mongrel dogs (20–33 kg) were used. The dogs were anesthetized with sodium pentobarbital, 25 mg/kg body weight i.v., and mechanically ventilated through a cuffed endotracheal tube. Through a thoracotomy incision in the left fifth intercostal space, a miniaturized pressure transducer (Konigsberg P-22, Konigsberg Instruments, Inc.) was implanted in the left ventricle through a stab wound in the apex and secured with a pursestring suture. Similarly, a second miniaturized pressure transducer was implanted in the thoracic descending aorta. Both transducers were calibrated against a mercury manometer before implantation and again at 37°C after implantation but before closing the thoracotomy incision. Through a flank incision a pulsed Doppler flow probe was secured around the left renal artery with care to avoid vessel constriction. Wires from the transducers and flow probe were tunneled subcutaneously, brought through the skin, and secured at the nape of the neck.

The dogs were allowed at least 1 week to recover from the surgical procedure and to become adapted to the laboratory before experimentation. Postoperatively, they received daily injections of procaine penicillin for 5 days as antibiotic prophylaxis. Skin sutures were removed on the fifth to seventh postoperative day.

**Hemodynamic Measurements**

Left ventricular systolic and end-diastolic pressures (LVSP and LVEDP), maximal rates of left ventricular pressure rise (LV dp/dt), and systemic phasic and mean (MAP) arterial pressures were obtained from the Konigsberg transducers. The pulsed Doppler flow probe was calibrated in terms of Doppler frequency shift. A linear relationship between flow and frequency shift for ultrasonic crystals of this type has been established in vivo. After establishing a baseline zero, values for renal vascular flow were recorded in hertz and subsequently converted to ml/min from previously derived calibration charts for these flow probes over the full range of sizes used (2–5-mm external vessel diameter). Renal vascular resistance was calculated by dividing MAP by renal blood flow.

**Experimental Protocol**

All hemodynamic measurements were made in awake, unrestrained dogs trained to lie quietly on a mat in the laboratory. On the day of experiments, a poly-ethylene catheter was inserted percutaneously into the saphenous vein for infusion of drugs. All transducers and flow probes were connected to an eight-channel Gould series 200 recorder and calibrated. Phasic and mean steady-state control observations then were made continually for at least 10 minutes before beginning infusion of either PBDA or sodium nitroprusside (NP). The sequence of drug administration was random. PBDA was infused at dosages of 10, 20 or 40 μg/kg/min. These three dosages were demonstrated previously to decrease MAP 4 ± 0.8%, 9 ± 1.3%, and 14 ± 2.1% (mean ± SEM), respectively, from control values in anesthetized dogs. Each dosage was infused for 10 minutes before measuring hemodynamics, and a second drug infusion was not started until hemodynamic values had returned to control values for at least 10 minutes after discontinuing the previous drug infusion. Drug infusion was terminated if a dog vomited during PBDA infusion, and the dog was allowed to recover completely from the hemodynamic changes, predominantly tachycardia, associated with vomiting before other studies were performed. To compare the hemodynamic effects of PBDA with those of a direct-acting vasodilator, NP was infused i.v. in concentrations of 10, 20 or 40 μg/min for 15 minutes each, after which time hemodynamic measurements were made. Preliminary observations indicated that the reduction in LVSP and MAP produced by NP at doses of 20 and 40 μg/min were similar to those during PBDA infusion at 10 and 20 μg/kg/min, respectively. In some experiments, dogs were pretreated with (S)-sulpiride before PBDA infusion because of this enantiomer's selective antagonism of DA, receptors in the doses used. The (S)-sulpiride was given as a single i.v. injection in progressively larger doses of 0.025, 0.05 and 0.1 mg/kg. PBDA infusion was started 2 minutes after each sulpiride injection and continued for 6–8 minutes before measuring hemodynamics.

**Studies of Hemodynamics and Renal Blood Flow in Normal Volunteers**

The effects of PBDA infusion on blood pressure, HR and renal blood flow also were studied in three healthy normal volunteers. An Investigational New Drug Application was approved by the Food and Drug Administration and the Baylor College of Medicine Institutional Review Board for Human Research. Blood pressure was recorded every minute in a semisupine position using the Roche Arteriosonde ultrasound technique. Renal plasma flow was estimated by the clearance of p-aminohippurate (CPAH) (Merck, Sharp, and Dohme, Inc.) under conditions of maximal free water excretion. CPAH was determined during three 15-minute control periods, during i.v. administration of PBDA at 20 and 40 μg/kg/min and again after administration of the dopamine-receptor antagonist metoclopramide (Reglan, A.H. Robins), 20 mg i.v., with continued PBDA infusion.

**Studies of Hemodynamics in Patients with Heart Failure**

Patients at the Ben Taub General Hospital with clinical evidence of congestive heart failure scheduled to
undergo diagnostic cardiac catheterization were invited to participate in the study. Approval to carry out this portion of the study was obtained from both the Food and Drug Administration and the Baylor College of Medicine Institutional Review Board for Human Research. The experimental protocol was explained to each patient, and each gave written, informed consent before the study. Patients with valvular or congenital heart disease were excluded. The study group consisted of 11 patients, four females and seven males. Six had chronic coronary artery disease (two with diabetes mellitus), four congestive heart failure secondary to hypertension (one with diabetes mellitus), and one idiopathic cardiomyopathy. Nine of the 11 patients were in New York Heart Association functional class III or IV before admission. Each patient had a left ventricular ejection fraction of 0.40 or less. The mean cardiac index for the group was 2.3 ± 0.2 l/min/m² and the left ventricular filling pressure (LVFP) was 29 ± 3 mm Hg. A summary of individual clinical and hemodynamic characteristics of these patients is listed in table 1.

Studies were conducted in a fasting state (> 8 hours) with i.v. diazepam, 2-5 mg, as premedication. Baseline hemodynamics were measured at least 30 minutes after administration of angiographic contrast material. Digitalis or diuretic medication regimens were not altered in the 48 hours preceding the study and were not administered on the day of the study. All long-acting nitrates were discontinued at least 12 hours and systemic vasodilators (prazosin and hydralazine) at least 24 hours before the study. Catheterization was performed either from a right brachial artery cutdown or through a femoral artery percutaneous approach using introducer sheaths. Pressure measurements were obtained from the left ventricle using #7F pigtail catheters (Cordis) or #8F Sones (USCI). When the approach was from the femoral artery, arterial pressure was obtained directly from the sidearm of the introducer sheath (#8F, Cordis). Pulmonary artery and right atrial pressures were recorded using a Swan-Ganz flow-directed, balloon-tipped catheter introduced through the femoral or a brachial vein and cardiac output was measured by standard thermodilution computer technique (mean of five values) (Edwards Laboratories). Pressure measurements were recorded on an Electronics for Medicine multichannel oscilloscope recorder using Statham P23ID transducers with zero reference level at the midaxillary line with the patient supine. When ventricular irritability precluded continuous pressure recording from a catheter in the left ventricle (two patients), pulmonary capillary wedge pressure was monitored instead. In both cases, LVEDP and pulmonary wedge pressure were identical before the administration of drug. Cardiac index (CI) was calculated by dividing cardiac output by body surface area. Systemic (SVR) and pulmonary (PVR) vascular resistances were calculated in dyn-cm-sec⁻⁵ by dividing mean systemic or pulmonary arterial pressures by cardiac output and multiplying the result by 80. Stroke volume index (SVI) was calculated by dividing CI by HR. Stroke work index (SWI) was calculated as

\[
\text{SVI} \times (\text{LVSP} - \text{LVFP}) \times 1.36 \times 100 = \text{g-min/m}^2.
\]

Thirty to 60 minutes after diagnostic catheterization, control hemodynamic measurements were obtained. PBDA was then infused intravenously in progressively larger doses of 5, 10 and 20 µg/kg/min in all 11 patients and to 40 µg/kg/min in three of the 11 patients. The choice of these infusion rates for PBDA in patients was based on our observation that most conscious dogs tolerated 20 µg/kg/min without vomiting. Hemodynamic effects of PBDA were usually obvious within 4 minutes of onset of the infusion. Hemodynamic measurements were made during steady state 8 minutes after beginning the infusion of each dose of PBDA. Ten minutes after completing the infusion of the final drug dose, recovery measurements were repeated.

**Table 1. Clinical and Hemodynamic Characteristics of Patients Receiving Propylbutyldopamine**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Race/Sex</th>
<th>ISC</th>
<th>HPT</th>
<th>DM</th>
<th>PCM</th>
<th>DIG</th>
<th>DIUR</th>
<th>VD</th>
<th>FC</th>
<th>LVFP (mm Hg)</th>
<th>CI (l/min/m²)</th>
<th>EF (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>WF</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>IV</td>
<td>13</td>
<td>1.4</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
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<td></td>
<td>+</td>
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<td></td>
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<td>+</td>
<td></td>
<td>IV</td>
<td>22</td>
<td>2.6</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>WM</td>
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<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>III</td>
<td>35</td>
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<td>40</td>
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<td>+</td>
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<td></td>
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<td>+</td>
<td>+</td>
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<td></td>
<td>+</td>
<td>+</td>
<td></td>
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<td>20</td>
<td>1.9</td>
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<td>9</td>
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<td>BF</td>
<td>+</td>
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<td>+</td>
<td>+</td>
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<td>III</td>
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<td>2.0</td>
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<td>49</td>
<td>BM</td>
<td></td>
<td>+</td>
<td></td>
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<td>+</td>
<td></td>
<td>II</td>
<td>14</td>
<td>2.4</td>
<td>40</td>
</tr>
<tr>
<td>11</td>
<td>53</td>
<td>BM</td>
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<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>II</td>
<td>34</td>
<td>2.2</td>
<td>28</td>
</tr>
</tbody>
</table>

Abbreviations: ISC = ischemic heart disease; DM = diabetes mellitus; PCM = idiopathic cardiomyopathy; DIG = receiving digitalis; DIUR = receiving diuretics; VD = received vasodilators up to 24 hours before study; FC = New York Heart Association functional class; LVFP = left ventricular filling pressure (left ventricular end-diastolic or pulmonary capillary wedge pressure); CI = cardiac index; EF = left ventricular ejection fraction.
Laboratory and Statistical Methods

The PBDA used in this study was synthesized by James Z. Ginos using methods previously published. 22 For administration to patients, the drug was prepared in sealed ampules containing 25 mg/ml PBDA in water with 1% sodium metabisulfite as preservative. The pH of the solution was adjusted to 7.0. The drug was tested for purity, sterility, stability and absence of pyrogenicity before administration to man. The drug was diluted with 5% dextrose in water just before infusion. ND (Nipride, Hoffman-LaRoche) was obtained commercially.

In any individual dog or patient, a single value for each hemodynamic variable during each observation was determined by averaging the values from at least 10 consecutive cardiac cycles. The mean ± SEM for a particular hemodynamic measurement during each observation period were then calculated from the individual values for all conscious dogs or patients in that group. Mean hemodynamic values measured during the control period were compared with those obtained during drug infusion by t test for paired data and by analysis of variance. Differences were considered significant if p < 0.05. The effect of PBDA on vomiting was evaluated statistically by Fisher’s exact test.

Results

Studies of Hemodynamics and Renal Blood Flow in Conscious Dogs

The influence of PBDA and NP on left ventricular hemodynamics and MAP are summarized in table 2. The reduction in LVSP and MAP produced by PBDA at 10 and 20 µg/kg/min were similar to those produced by NP at 20 and 40 µg/kg/min, respectively. The small reduction in LVEDP was statistically significant only at a PBDA infusion rate of 20 µg/kg/min. Despite the reduction in left ventricular and aortic pressures induced by PBDA, no significant change in HR or contractility occurred as reflected by LV dP/dt. After NP, significant increases in both HR and cardiac contractility were seen. The onset of effect of PBDA was usually noted after 2–4 minutes of infusion at each concentration; loss of drug effect was equally rapid upon termination of drug infusion.

The changes in renal blood flow and renal vascular resistance observed during PBDA and NP infusion are summarized in table 2. PBDA infused at 10 and 20 µg/kg/min produced small but consistent increases in renal blood flow and decreases in renal vascular resistance. In contrast, the changes in renal blood flow and renal vascular resistance produced by NP were more variable and not statistically different from control values.

The effects of pretreatment with (S)-sulpiride on PBDA-induced changes in blood pressure and renal blood flow in a smaller group of dogs are summarized in table 3. Pretreatment with a DA2-receptor antagonist, (S)-sulpiride, 0.1 mg/kg, antagonized the reduction in MAP produced by PBDA infusion at both 10 and 20 µg/kg/min. Sulpiride blunted the increase in renal blood flow observed during PBDA infusion at 10 µg/kg/min but did not alter the increase produced by 20 µg/kg/min.

On two of 22 occasions dogs vomited while receiving PBDA at 20 µg/kg/min, whereas none vomited at 10 µg/kg/min. Vomiting occurred on six of 11 occasions at a dose of 40 µg/kg/min. Pretreatment with (S)-sulpiride, 0.025 µg/kg, was effective in blocking vomiting in each of six dogs during PBDA infusion up to a dose of 40 µg/kg/min (p < 0.05). No dog vomited during NP infusion.

Studies of Hemodynamics and Renal Blood Flow in Normal Volunteers

Unlike its effects in conscious and anesthetized dogs, PBDA did not reduce MAP in normal subjects, but did consistently increase HR (table 4). As in conscious dogs, PBDA increased renal plasma flow. Pretreatment with the dopamine-receptor antagonist metoclopramide, 20 mg i.v., prevented the increase in renal

<table>
<thead>
<tr>
<th>Drug</th>
<th>MAP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>LV dP/dt (mm Hg/sec)</th>
<th>HR (beats/min)</th>
<th>RBF (ml/min)</th>
<th>RVR (mm Hg/ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBDA (n = 20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>98 ± 4</td>
<td>7 ± 1</td>
<td>2474 ± 694</td>
<td>95 ± 4</td>
<td>145 ± 5</td>
<td>0.71 ± 0.04</td>
</tr>
<tr>
<td>10 µg/kg/min</td>
<td>93 ± 4*</td>
<td>6 ± 1</td>
<td>2489 ± 167</td>
<td>100 ± 5</td>
<td>148 ± 6*</td>
<td>0.66 ± 0.04*</td>
</tr>
<tr>
<td>20 µg/kg/min</td>
<td>87 ± 5*</td>
<td>6 ± 1*</td>
<td>2415 ± 161</td>
<td>103 ± 6</td>
<td>166 ± 9*</td>
<td>0.55 ± 0.04*</td>
</tr>
<tr>
<td>NP (n = 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>95 ± 7</td>
<td>5 ± 1</td>
<td>2630 ± 199</td>
<td>102 ± 8</td>
<td>123 ± 5</td>
<td>0.77 ± 0.10</td>
</tr>
<tr>
<td>20 µg/min</td>
<td>89 ± 8*</td>
<td>4 ± 1</td>
<td>2689 ± 198</td>
<td>116 ± 10*</td>
<td>123 ± 6</td>
<td>0.72 ± 0.12</td>
</tr>
<tr>
<td>40 µg/min</td>
<td>87 ± 7*</td>
<td>3 ± 1</td>
<td>2808 ± 242*</td>
<td>129 ± 8*</td>
<td>129 ± 7</td>
<td>0.67 ± 0.11</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. 

n = number of observations.

* p < 0.05 compared with control values by paired t test.

† p < 0.01 compared with control values by paired t test.

‡ p < 0.05 when change from control compared with corresponding NP change from control.

Abbreviations: MAP = mean arterial pressure; LV = left ventricular; LVEDP = LV end-diastolic pressure; HR = heart rate; RBF = regional blood flow; RVR = renal vascular resistance; PBDA = propylbutyldopamine; NP = nitroprusside.
plasma flow and attenuated the increase in HR produced by PBDA.

Studies of Hemodynamics in Heart Failure Patients
PBDA infusion at 5, 10, and 20 μg/kg/min produced a progressive fall in MAP from 102 ± 8 (mean ± SEM) to 93 ± 10, 88 ± 8 (p < 0.01) and 81 ± 3 (p < 0.01) mm Hg, respectively (fig. 1). This reduction was associated with a progressive increase in CI from a preinfusion value of 2.3 ± 0.2 to 2.4 ± 0.1 l/min/m² (p > 0.05) at a PBDA infusion rate of 5 μg/kg/min, to 2.6 ± 0.1 l/min/m² at 10 μg/kg/min (p < 0.05), and to 2.7 ± 0.2 l/min/m² at 20 μg/kg/min (p < 0.01). A concomitant, dose-related reduction in SVR also occurred, from 1847 ± 169 dyn-cm-sec⁻⁵ during the control period to 1546 ± 100 (p > 0.05), 1420 ± 111 (p < 0.05) and 1237 ± 79 dyn-cm-sec⁻⁵ (p < 0.01) after PBDA infusions at 5, 10 and 20 μg/kg/min, re-

<table>
<thead>
<tr>
<th>PBDA dose (μg/kg/min)</th>
<th>Mean arterial pressure (mm Hg) Before sulpiride</th>
<th>Mean arterial pressure (mm Hg) After sulpiride</th>
<th>Renal blood flow (ml/min) Control</th>
<th>(S)-sulpiride 0.1 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>102 ± 4 (7)</td>
<td>104 ± 7 (7)</td>
<td>148 ± 10 (7)</td>
<td>139 ± 9 (7)</td>
</tr>
<tr>
<td>10</td>
<td>96 ± 8 (6)*</td>
<td>103 ± 9 (6)†</td>
<td>160 ± 10* (6)</td>
<td>139 ± 8 (6)</td>
</tr>
<tr>
<td>20</td>
<td>87 ± 8 (6)*</td>
<td>105 ± 4 (7)†</td>
<td>162 ± 9* (6)</td>
<td>157 ± 10* (7)</td>
</tr>
</tbody>
</table>

Values are mean (± SEM) changes (in mm Hg) from pre-PBDA infusion values. Control = mean arterial pressure before PBDA infusion. Numbers in parentheses indicate number of observations.

*p < 0.05 compared with control values.
†p < 0.05 when PBDA effects on mean arterial pressure before and after pretreatment with (S)-sulpiride were compared.
Table 4. Effect of Propylbutyldopamine on Blood Pressure, Heart Rate and Effective Renal Plasma Flow in Three Normal Volunteers

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>PBDA</th>
<th>PBDA + MTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>1</td>
<td>102</td>
<td>97</td>
</tr>
<tr>
<td>Effective renal plasma flow</td>
<td>1</td>
<td>389</td>
<td>858</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>1</td>
<td>63</td>
<td>78</td>
</tr>
</tbody>
</table>

Abbreviations: PBDA = propylbutyldopamine at infusion rates of 40 μg/kg/min for subject 1 and 20 μg/kg/min for subjects 2 and 3; MTC = pretreatment with 20 mg metoclopramide 2 minutes before PBDA infusion.

respectively, with no change in HR. MAP, CI, and SVR all returned to values not significantly different from control within 10 minutes of terminating the drug infusion (fig. 1).

Peak LVSP decreased from a preinfusion mean value of 135 ± 11 to 125 ± 12, 121 ± 10 (p < 0.05) and 110 ± 11 mm Hg (p < 0.01) during infusion of PBDA at 5, 10 and 20 μg/kg/min, respectively. These changes in LVSP were paralleled by similar changes in both LVEDP and mean pulmonary artery pressure without a significant change in SWI (fig. 2). During the control period, LVFP in these patients was elevated (29 ± 3 mm Hg), consistent with the clinical diagnosis of left ventricular dysfunction. PVR also fell during PBDA infusion (fig. 2).

Side Effects During PBDA Infusion

Neither vomiting nor arrhythmias was associated with PBDA administration in man at doses up to 20 μg/kg/min. Two patients, however, developed transient hiccups at this dose. Two of the three volunteers vomited after PBDA at 40 μg/kg/min, but stopped immediately when the drug was discontinued. Three patients also received PBDA at 40 μg/kg/min. One vomited after 5 minutes of drug infusion at this dose, but the vomiting ceased within 1 minute of stopping the infusion. The onset of drug effect was rapid and apparent within 2–4 minutes at each dosage increment and loss of drug effect appeared equally rapid. No
evidence of rebound increase in HR or blood pressure during the recovery period was noted. Hematologic and biochemical measurements made 24 hours after drug infusion were not different from those before drug administration.

**Discussion**

Hemodynamic benefit from afterload reduction in patients with congestive heart failure was first demonstrated by Majid et al. Since then, an improvement in cardiac output after administration of a variety of agents with widely diverse pharmacologic actions but that all reduce SVR has suggested the important role of excessive vasoconstriction in perpetuating low cardiac output in these patients. In addition, greater impairment of blood flow to the kidney than to other regional vascular beds tends to increase the demands on the already compromised myocardium because the extra-cellular fluid volume expands due to impaired salt and water excretion by the kidney. An ideal vasodilator for treatment of such patients, therefore, should not only reduce total SVR, but also selectively improve renal blood flow.

Dopamine itself can produce such a selective increase in renal blood flow with a resultant diuresis at low doses. Evidence from studies in experimental animals supports the concept that this occurs by activation of specific vasodilatory (DA) dopamine receptors located on the renal and mesenteric vasculature. At these low doses, dopamine may also reduce blood pressure by activation of dopaminergic receptors located on adrenergic neurons (DA), which inhibit further release of norepinephrine. However, at doses of dopamine that maximally increase renal blood flow, this catecholamine also increases blood pressure and HR through activation of α-adrenergic vasoconstrictor and β-cardiac chronotropic receptors, which are undesirable drug effects in patients with congestive heart failure.

Recent studies have identified several N,N-dialkyl dopamine analogs that activate dopamine receptors without β-adrenergic stimulation and little or no α-adrenergic vasoconstrictor effect. Observations that these analogs produce a dose-dependent lowering of blood pressure in anesthetized dogs or cats not antagonized by propranolol or phenoxybenzamine but inhibited by sympathetic ganglionic blockade or by the dopamine receptor antagonist, domperidone, in doses which failed to prevent analog-induced increases in renal blood flow are consistent with a decrease in sympathetic neuronal release of norepinephrine occurring through activation of inhibitory DA receptors located on these neurons. Additional support for such a mechanism of action is provided by the observation that PBDA decreases both HR and coronary sinus norepinephrine secretion in a dose-dependent manner in spinally transected, vagotomized dogs during continuous electrical stimulation of the cardioaccelerator nerve. The effects of PBDA on both HR and coronary sinus norepinephrine secretion in this preparation were antagonized by (S)-sulpiride but not by phenotolamine.

The results of the present study confirm that PBDA can lower blood pressure without significant reflex tachycardia or negative inotropic effects (table 2) in conscious, unrestrained dogs in which sympathetic control of cardiovascular function is not influenced by anesthesia. The effects of PBDA on LVEDP in the dog were quite small (table 2) and underscore the difficulty in assessing the effectiveness of vasodilators in general and PBDA in particular for improving left ventricular performance in the normal heart.

Previous observations that the peripheral dopamine receptor antagonist domperidone antagonized the lowering of blood pressure, but not the increases in renal blood flow produced by PBDA in anesthetized dogs, suggested that these cardiovascular effects of the analog were mediated by different dopamine receptors. In the present study, (S)-sulpiride, a presumed selective antagonist of DA receptors, not only antagonized the hypotensive effects of PBDA in conscious dogs at infusion rates of both 10 and 20 μg/kg/min, but also blunted the increase in renal blood flow produced by PBDA at 10 μg/kg/min. It did not, however, inhibit the increase in renal blood flow produced by PBDA at 20 μg/kg/min (table 3). One explanation for these findings is that (S)-sulpiride has affinity for DA receptors in the renal vasculature. An alternative interpretation is that (S)-sulpiride is inhibiting that component of renal blood flow regulation under control of the renal sympathetic nerves by antagonism of inhibitory DA receptors. Although additional studies are required to determine which of these interpretations is correct, the results of the present study support the existence of pharmacologically distinct pre- and postsynaptic dopamine receptors in the dog.

Although the number of volunteers is small, the present studies suggest that PBDA is a renal vasodilator in man as it is in the dog. In man, as in the dog, this effect is presumably mediated by activation of dopamine receptors located on the renal vasculature since the PBDA-induced doubling of renal blood flow in human volunteers was antagonized by metoclopramide (table 4). In contrast to the conscious dog, however, PBDA had no consistent effect on blood pressure of normal volunteers, although it did produce a small but consistent increase in HR that was antagonized by pretreatment with metoclopramide. These findings suggest that the predominant effect of PBDA in normal volunteers was on DA receptors subserving renal vasodilation and that cardiac DA receptors were not selectively activated to prevent the reflex increase in HR. This reflex tachycardia may have prevented any reduction in blood pressure in these normotensive subjects.

In patients with congestive heart failure, in whom resting SVR is increased in comparison to normal subjects, PBDA produced a dose-dependent reduction in blood pressure and a concomitant increase in cardiac output that was not associated with reflex tachycardia. The elevated LVEDP in these patients with failing hearts was decreased in a dose-dependent manner by PBDA in contrast to the much smaller reduction in LVEDP produced by PBDA in dogs with normal
hearts. Unfortunately, prior administration of iodinated contrast material for angiography to heart failure patients precluded assessment of changes in renal blood flow in these patients. Thus, the net effect of PBDA on renal blood flow and renal vascular resistance in patients with congestive heart failure remains to be determined.

The demonstration in the present study that PBDA decreases SVR and blood pressure in heart failure patients and increases renal blood flow in conscious dogs and normal human volunteers introduces a new class of drugs with potentially unique mechanisms of action and advantages for the treatment of conditions such as hypertension and congestive heart failure. The possibility that this drug class acts through activation of peripheral DA, presynaptic and DA, postsynaptic dopamine receptors appears strong, and further studies with this and similar agonists should provide a probe for confirming the existence and importance of such receptors in man. The necessity of giving this drug intravenously and the proximity of the therapeutic dose to a potentially emetic dose will likely prevent its widespread clinical use. Nevertheless, the therapeutic implications of these studies are clear and highlight the need for development of additional dopamine-receptor agonists having similar hemodynamic properties but a lower affinity for the vomiting center.

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