The haemodynamic and myocardial effects of dopexamine: a new $\beta_2$-adrenoceptor and dopaminergic agonist

B. E. JASKI*, W. WIJNS, R. FOULDS** & P. W. SERRUYS
The Catheterization Laboratory, Thoraxcentre, Erasmus University, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands

1 Dopexamine increases inotropic state and rate of relaxation independent of changes in heart rate.
2 Dopexamine has a chronotropic effect and results in a decrease in systemic vascular resistance.
3 Dopexamine has a spectrum of action that should be useful in patients with severe heart failure.

Keywords dopexamine catecholamine vasodilator inotrope

Introduction

Dopexamine is a recently developed chemical analogue of dopamine (Figure 1) that acts as a peripheral arterial vasodilator, retains the beneficial renal vasodilating effects of dopamine, yet is free of $\alpha$-adrenoceptor agonist activity (Brown et al., 1984a).

In vitro screening of dopexamine at adrenergic and dopaminergic receptors has been reported (Brown et al., 1984a,b). The compound is a highly specific $\beta_2$-adrenoceptor agonist with only very weak $\beta_1$-adrenoceptor agonist activity (less than 1/10,000 of the potency of isoprenaline). In addition, it is equipotent with dopamine at vasodilating renal vascular receptors. The compound lacks any activity at $\alpha_1$- or $\alpha_2$-adrenoceptors.

In animal studies, intravenous dopexamine administration is followed by a moderate fall in blood pressure, an increase in heart rate and left ventricular peak dP/dt·P$^{-1}$, and renal and mesenteric vasodilation (Brown et al., 1984b, 1985a,b).

Recent studies have shown that $\beta_2$-receptors are present in atrial and ventricular myocardium in many species including man (Hedberg et al., 1980; Heitz et al., 1983; O'Donnell & Wanstal, 1979; Brodde et al., 1983; Wilson, 1984). Activation of these receptors should enhance $\beta_2$-adrenoceptor stimulation of the heart following catecholamine administration. Therefore, in addition to a decrease in afterload, it is possible that dopexamine administration could lead to a primary direct increase in inotropic state. A single drug that combined the beneficial inotropic, systemic vasodilator and specific renal vasodilator effects of presently available catecholamines would be useful and, in some cases, eliminate the need for multiple drug combinations to achieve optimal haemodynamic effect.

This study was designed to investigate the left ventricular and haemodynamic effects of dopexamine in patients undergoing cardiac catheterization. In order to assess effects independent of changes in heart rate, comparisons were made at both spontaneous heart rate and at one of a range of pacing rates individually matched to the heart rate following dopexamine administration.

Present addresses: *Cardiovascular Division, Brigham and Women's Hospital, Boston, Mass., USA and **Clinical Pharmacology Department, Fisons plc – Pharmaceutical Division, Loughborough, England
Correspondence: Dr P. W. Serruys, Catheterization Laboratory, Thoraxcentre, P.O. Box 1738 Rotterdam, The Netherlands

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Methods

Study population

Ten patients (nine males, one female) with a mean age of 52 years (range 27–69 years) undergoing routine cardiac catheterization for evaluation of presumed coronary disease were studied. The mean ejection fraction was 54 ± 5% (range 37–75%). One patient with atypical chest pain had normal coronary arteries. β-adrenoceptor blockers and vasodilators were discontinued at least 24 h before study. One patient inadvertently received one dose of a β-adrenoceptor blocker on the morning of the study.

Informed consent was obtained from all patients prior to catheterization. Patients were studied after an overnight fast without premedication preceding routine diagnostic angiography.

Data collection

Catheterization was performed via a right brachial or right femoral approach. An 8F double micromanometer-tipped catheter (Millar Instruments, Houston, Texas) was advanced into the left ventricle and a 7F Swan-Ganz thermodilution catheter was advanced into the pulmonary artery. A 7F pacing catheter was placed in the right atrium.

Left ventricular pressure was analyzed using a previously described on-line system to determine the following parameters (Meester et al., 1974, 1975): heart rate HR, beats min⁻¹1, left ventricular peak systolic (LVsys, mm Hg) and end-diastolic pressures (LVEDP, mm Hg), peak positive and negative rates of left ventricular pressure change (dP/dt, mm Hg s⁻¹), maximum measured dP/dt/P or peak measured velocity of the contractile element (peak VCE, s⁻¹), Vmax (VCE linearly extrapolated to 0 mm Hg), and T1 (ms) the exponential time constant for the first 40 ms of left ventricular isovolumic relaxation (Brower et al., 1983).

Aortic (Ao, mm Hg) and pulmonary artery (PA, mm Hg) pressures were measured and mean arterial pressures determined by digital integration. Cardiac output (CO, 1 min⁻¹) was determined by duplicate thermodilution measurements. Cardiac index (CI, 1 min⁻¹ m⁻²) was calculated as CO/body surface area, stroke volume index (SVI, ml m⁻²) was calculated as CI × 1000/HR and stroke work index (SWI, g m m⁻²) was calculated as SVI × (Ao-LVEDP) × .0136. Total systemic vascular resistance (SVR, dyn s cm⁻⁵) was calculated as 80 × Ao/CO and total pulmonary vascular resistance (PVR) was calculated as 80 × PA/CO.

Dopexamine blood concentration at the end of the ten minute infusion was measured by h.p.i.c. with electrochemical detection. This method provides an accurate and specific determination with a limit of detection of 2 ng ml⁻¹ and a lower limit of determination of 5 ng ml⁻¹ (personal communication, Fisons plc. Details of the assay methodology will be the subject of a separate publication).
Protocol

Following placement of catheters, stable left ventricular pressures were obtained. All haemodynamic and left ventricular function measurements were then determined at control spontaneous heart rate followed by increasing atrial paced heart rates with increments of 10 beats min\(^{-1}\) between measurements to a maximum heart rate of 100 beats min\(^{-1}\) chosen to avoid angina pectoris or AV block. Pacing was discontinued and left ventricular pressure measurements made at a spontaneous heart rate until within 10% of control values.

Dopexamine (Fisons plc; England) was then administered by a slow intravenous infusion at 2 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) over 10 min. In two patients, including the one patient who had received a single dose of \(\beta\)-adrenoceptor blockers preceding the study, a significant response was not observed after 2 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) and so a second intravenous infusion at 4 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) over 10 min was immediately administered. Haemodynamic and left ventricular measurements were repeated every 60 s during the infusions.

A pulmonary arterial sample was withdrawn for dopexamine blood concentration measurement following the final set of measurements.

Analysis

Group data measurements following the final 10 min dopexamine infusion were compared in all patients. Measurements at the conclusion of this infusion were compared to the preceding pacing measurements obtained at the closest individually matched heart rate and to control. Measurement of aortic and pulmonary artery pressure were available in nine patients and right atrial pressure in eight patients. Minute to minute data were available in nine patients.

Statistics

Results are expressed as the mean ± s.e. mean. Group data from control, matched pacing, and final dopexamine infusion measurements were analyzed by a repeated measures analysis of variance. Variables found to vary significantly \((P < 0.05)\) were then compared by the method of least significant difference to determine the level of significance for each paired comparison (Snedecor & Cochran, 1967).

Results

Systemic haemodynamic changes with dopexamine infusion (Table 1)

Dopexamine infusion led to a marked increase in heart rate from 62 ± 4 to 86 ± 6 beats min\(^{-1}\) (± 39%, \(P < 0.001\)). Increases in heart rate occurred in an infusion duration related manner.

Figure 2 Individual changes in a) heart rate (HR) and b) \(V_{\text{max}}\) derived from total pressure during a 10 min infusion of dopexamine \((n = 9)\). Both variables increasingly rose with the duration of the infusion.
in all 10 patients (Figures 2 and 3). Systolic, diastolic, and mean aortic pressure remained unchanged with doxapamine. Mean pulmonary artery pressure increased and right atrial pressure remained unchanged. Cardiac index increased from $3.1 \pm 0.2$ to $5.0 \pm 0.5 \text{min}^{-1} \text{m}^{-2}$ (+61%, $P < 0.001$). Systemic vascular resistance decreased from $1347 \pm 120$ to $900 \pm 121 \text{dyn s cm}^{-5}$ (-33%, $P < 0.001$) and pulmonary vascular resistance remained unchanged.

**Left ventricular function changes with doxapamine infusion (Table 2)**

Before and following doxapamine infusion, left ventricular systolic pressure were without significant change. Left ventricular peak $+dP/dt$, peak measured $V_{CE}$, and $V_{max}$ all increased significantly. Peak $+dP/dt$ and $V_{max}$ increased progressively during the infusion and paralleled increases in heart rate (Figures 2 and 3).

Peak $-dP/dt$ decreased and the time constant for the first 40 ms of isovolumic relaxation, $T_1$, was reduced.

**Comparison between matched atrial pacing and doxapamine infusion (Tables 1 and 2)**

A close matching of heart rates during atrial pacing and subsequent doxapamine infusion was obtained with a pacing rate of $86 \pm 5$ beats min$^{-1}$ and a doxapamine rate of $86 \pm 6$ beats min$^{-1}$.

At this matched heart rate, there was no difference in aortic systolic pressure, however aortic diastolic and mean pressure were lower with doxapamine ($P < 0.001$ and $P < 0.01$, respectively). Mean pulmonary artery pressure was higher with doxapamine ($P < 0.01$) and right atrial pressure was unchanged. Cardiac index was $3.7 \pm 0.3 \text{min}^{-1} \text{m}^{-2}$ with pacing and $5.0 \pm 0.5 \text{ min}^{-1} \text{m}^{-2}$ with doxapamine ($P < 0.001$). Systemic vascular resistance was lower with doxapamine ($P < 0.001$) and pulmonary vascular resistance was without significant change.

Left ventricular systolic and end-diastolic pressures were similar with matched pacing and doxapamine. Peak $+dP/dt$ was higher with doxapamine (+34%, $P < 0.01$). Peak measured $V_{CE}$ was not significantly changed (+12%, NS), however $V_{max}$ was significantly higher (+24%, $P < 0.01$).

Peak $-dP/dt$ was similar at matched pacing, however, the time constant for the first 40 ms of isovolumic relaxation remained significantly shortened with doxapamine ($P < 0.01$).

Figure 4 summarizes the present changes from control in haemodynamic parameters at matched
atrial pacing and with dopexamine infusion. Figure 5 compares the changes in stroke work index vs changes in left ventricular end-diastolic pressure during control, matched atrial pacing, and with dopexamine infusion. Blood levels were obtained from seven of the ten subjects after 10 min at each infusion level. Blood levels after 10 min at 2 µg kg⁻¹ ranged from 52 to 186 ng ml⁻¹. The two subjects who received 4 µg kg⁻¹ in addition to the lower dose increased blood concentrations from 186 and 88 ng ml⁻¹ to 263 and 188 ng ml⁻¹ from the lower to the higher infusion rate, respectively.

Discussion

These observations support the concept that dopexamine acts as a positive chronotropic agent, positive inotropic agent, and peripheral vasodilator.

Matching the increase in heart rate following dopexamine to that of a preceding pacing rate showed that some of the drug's inotropic effects may be attributed to the increase in heart rate alone (Treppe-Bowditch effect) (Mahler et al., 1974). However, dopexamine led to further significant heart rate-independent increases in peak + dP/dt and Vmax. The 12% increase in peak measured VCe did not achieve statistical significance. Atrial pacing led to a small decrease (~6 mm Hg) in LVEDP compared to control. Since LVEDP did not change significantly with dopexamine, it is possible that this higher filling pressure elevated the measured peak + dP/dt.

Quinones et al. examined the effects of acute increases in preload and found an increase in isovolumic systolic indexes derived from deve-
Table 2  Left ventricular function during baseline, matched pacing, and dopexamine

<table>
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<th>HR (beats min⁻¹)</th>
<th>LVsys (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>+ dP/dt (mm Hg s⁻¹)</th>
<th>Pk Vce (s⁻¹)</th>
<th>Vmax (s⁻¹)</th>
<th>−dP/dt (mm Hg s⁻¹)</th>
<th>T1 (ms)</th>
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<tr>
<td>Baseline</td>
<td>62 ± 4</td>
<td>130 ± 8</td>
<td>17 ± 2</td>
<td>1436 ± 80</td>
<td>33 ± 2</td>
<td>44 ± 3</td>
<td>1607 ± 74</td>
<td>54 ± 3</td>
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<td>Paced</td>
<td>86 ± 5</td>
<td>126 ± 6</td>
<td>11 ± 1</td>
<td>1568 ± 110</td>
<td>41 ± 3</td>
<td>51 ± 4</td>
<td>1709 ± 87</td>
<td>46 ± 4</td>
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<tr>
<td>Dopexamine</td>
<td>86 ± 6</td>
<td>127 ± 7</td>
<td>14 ± 2</td>
<td>2105 ± 207</td>
<td>46 ± 4</td>
<td>63 ± 5</td>
<td>1856 ± 117</td>
<td>39 ± 2</td>
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<tr>
<td>Paced vs Baseline</td>
<td>***</td>
<td>NS</td>
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<td>Dopexamine vs Baseline</td>
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NS = Not significant * = P < 0.05, ** = P < 0.01, *** = P < 0.001

Abbreviations: HR: heart rate; LVsys: peak left ventricular pressure; LVEDP: left ventricular end-diastolic pressure; ± dP/dt: peak positive or negative dP/dt; Pk Vce: peak velocity of the contractile element; T1: the exponential time constant of the first 40 ms of isovolumic pressure decline; Vmax: velocity of the contractile element extrapolated to 0 mm Hg.

higher pressure and in peak dP/dt (Quinones et al., 1976). However, only reductions in peak Vce and Vmax derived from total pressure were found. The marked increase in peak dP/dt and Vmax derived from total pressure, in the present study, strongly implies that a true inotropic effect independent of changes in heart and preload occurred.

Finally, at matched heart rate, relaxation was improved as assessed by both peak negative dP/dt and a decrease in the time constant of relaxation. Improvements in relaxation also accompany the administration of catecholamines (Weiss et al., 1976; Karliner et al., 1977). Caution in interpreting those findings however, is necessary since changes in peak negative dP/dt and the time constant of early relaxation may be influenced by changes in end-diastolic and end-systolic pressure and volumes or in the offset pressure of left ventricular pressure decay (Weiss et al., 1976; Karliner et al., 1977; Thompson et al., 1982). Nevertheless the increase in inotropic state and improvement in relaxation support the hypothesis that dopexamine led to a haemodynamically significant myocardial stimulation.

Systemic vascular resistance was decreased by 33% consistent with a significant arterial

Figure 4  Percent change from control with matched pacing (□) and dopexamine (■) in heart rate (HR), stroke volume index (SVI), cardiac index (CI), left ventricular systolic (LVsys) and end-diastolic (LVEDP) pressures, peak + dP/dt, and Vmax (n = 10).
vasodilator effect of the drug. Both $\beta_2$-adrenoceptor and dopaminergic receptor stimulation must be considered. Two subclasses of dopaminergic receptors have been proposed in man: $DA_1$ and $DA_2$ (Goldberg & Kohli, 1979; Kebabian & Calne, 1979). Stimulation of $DA_1$ receptors may account for the direct end organ smooth muscle vascular relaxation including specific renal vascular vasodilation. Stimulation of $DA_2$ receptors located at the presynaptic terminals of postganglionic sympathetic nerves, may lead to a diminution in local release of the sympathetic neurotransmitter noradrenaline. Since, in vitro studies have shown that dopexamine has approximately equal $DA_1$ and $DA_2$ activity, it is likely that stimulation of both classes of dopaminergic receptors occurred in addition to $\beta_2$-adrenoceptor stimulation to account for the observed decrease in systemic vascular resistance.

The effect of dopexamine on venous tone in this study is uncertain. There was no changes in measured right atrial pressure, however, marked increases in cardiac output (venous return) could have maintained central venous pressure despite a decrease in venous tone. Direct assessment of venous tone (e.g. by forearm vascular capacitance) would be required to assess the relative venous versus arterial vasodilating effects of dopexamine.

Although it is not possible to ascribe all of the observed myocardial changes to direct effects of the drug, it seems likely that direct dopexamine $\beta_2$-adrenoceptor stimulation of the heart contributed to the observed increases in heart rate and inotropic state.

The reported relative roles of $\beta_1$- and $\beta_2$-adrenoceptor mediated effects is variable in different species and uncertain in man (Hedberg et al., 1980; Heitz et al., 1983). The effects of $\beta_2$-adrenoceptor stimulation in humans may account for the cardiac effects of $\beta_2$-adrenoceptor specific drugs such as pirbuterol or salbutamol that have also been ascribed to these agents’ possible nonspecific $\beta_1$-adrenoceptor activity (Sharma & Goodwin, 1978; Canepa-Anson et al., 1982; Bourdillon et al., 1980).

In patients with severe cardiac failure, dopexamine would appear to offer a favourable spectrum of action. An increase in heart rate and contractility and a decrease in systemic vascular resistance would be similar to the haemodynamic effects of dobutamine administration (Goldberg et al., 1977; Leier & Unverferth, 1983). The activation of dopaminergic receptor mediated renal vasodilation would benefit patients with markedly compromised renal perfusion (Goldberg, 1972). Compared with the administration of both dobutamine and dopamine (Richard et al., 1983), the effects of dopexamine could still be distinct since $\alpha$-adrenoceptor stimulation would be avoided by any therapeutic dose. In patients with heart failure, increases in heart rate could be offset by a reduction in preexisting increased sympathetic tone accompanying systemic hemodynamic improvement.

Further clinical experience will be necessary to assess the effects of dopexamine in patients with heart failure and to rigorously assess its clinical efficacy compared to that of dobutamine, dopamine, or a pure vasodilator such as nitroprusside.

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References


Figure 5 Change from control in left ventricular end-diastolic pressure (LVEDP) and stroke work index (SWI) with matched pacing and dopexamine ($n = 10$).


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