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The haemodynamic and myocardial effects of dopexamine: a new β_2-adrenoceptor and dopaminergic agonist

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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 α-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 β_2-adrenoceptor agonist with only very weak β_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 α_1- or α_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 β_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 β_1-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.

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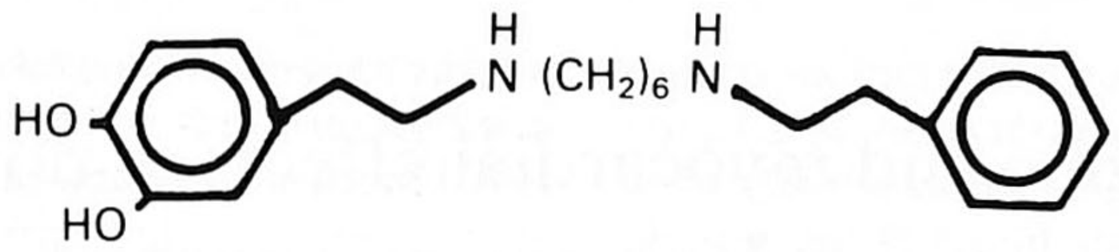
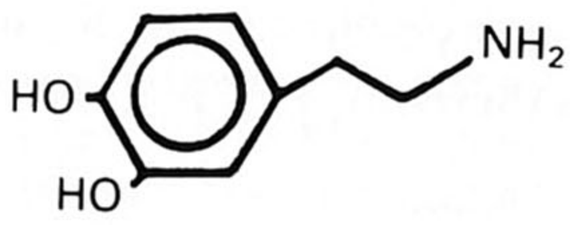


Dopexamine .2HCl



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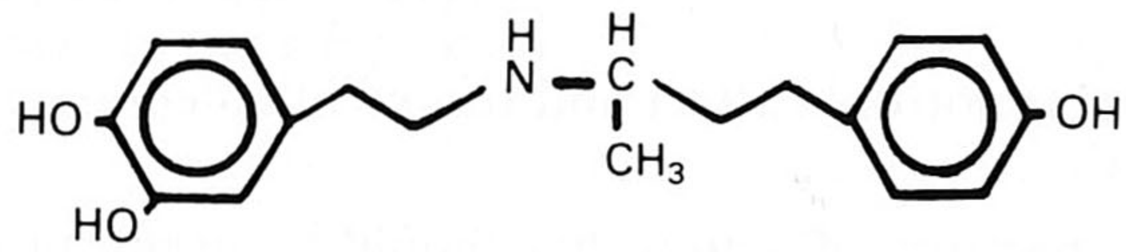

Dobutamine

Figure 1 Structural and chemical formulas of dopexamine and dopamine.

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^{-1}), 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 V_{CE}, s^{-1}), V_{max} (V_{CE} linearily extrapolated to 0 mm Hg), and T_1 (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, l min^{-1}) was determined by duplicate thermodilution measurements. Cardiac index (CI, l 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.l.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 μg kg^{-1} min^{-1} over 10 min. In two patients, including the one patient who had received a single dose of β-adrenoceptor blockers preceding the study, a significant response was not observed after 2 μg kg^{-1} min^{-1} and so a second intravenous infusion at 4 μg 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

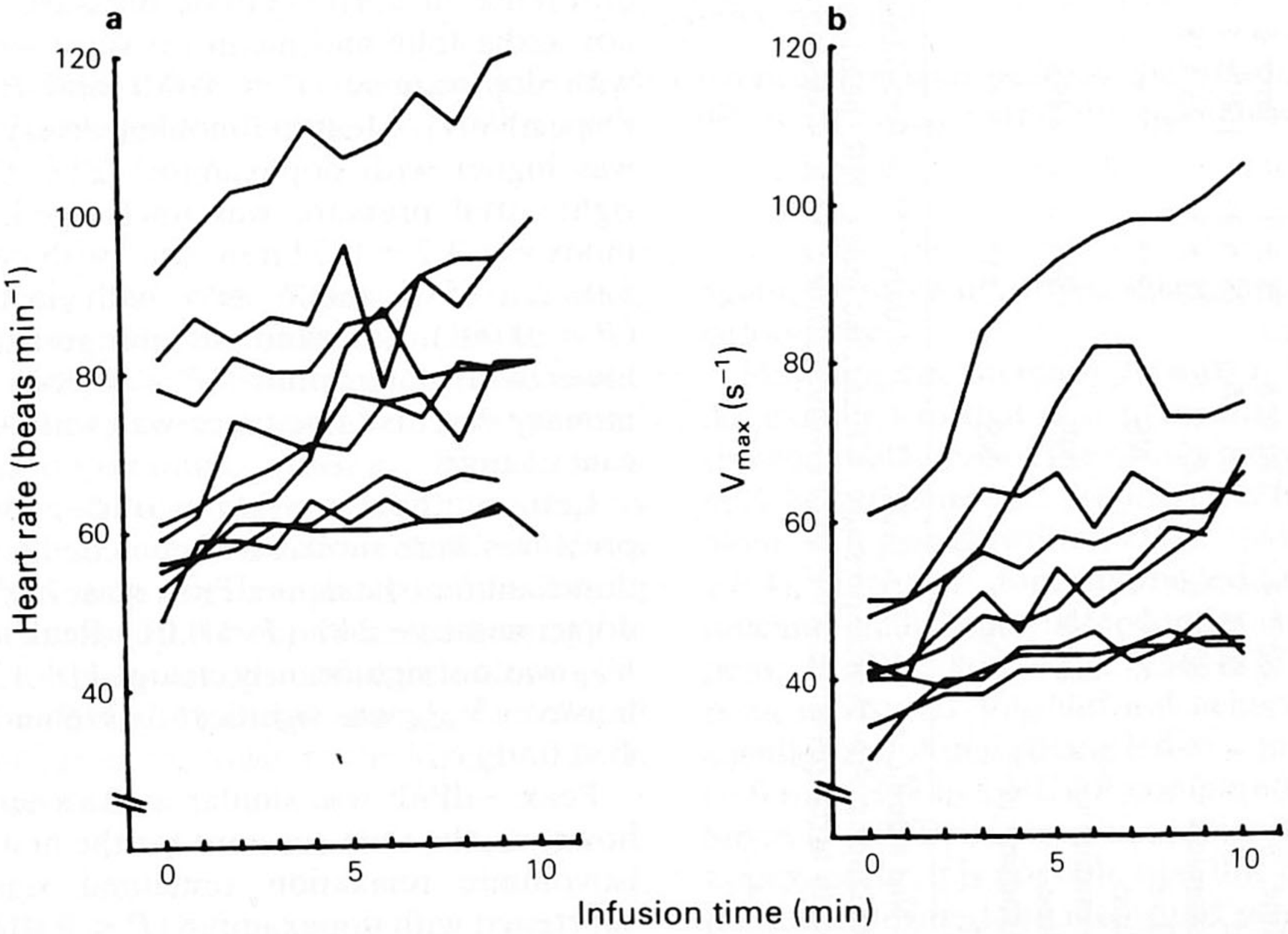

Figure 2 Individual changes in a) heart rate (HR) and b) V_{max} derived from total pressure during a 10 min infusion of dopexamine ($n = 9$). Both variables increasingly rose with the duration of the infusion.

Table 1 Haemodynamics during baseline, matched pacing, and dopexamine

	HR (*beats min*$^{-1}$)	Ao_{sys} (*mm Hg*)	Ao_{dias} (*mm Hg*)	*Ao* (*mm Hg*)	*PA* + (*mm Hg*)	*RA* ++ (*mm Hg*)	*CI* (*l min*$^{-1}$ *m*$^{-2}$)	*SVI* (*ml m*$^{-2}$)	*SWI* (*g m m*$^{-2}$)	*SVR* (*dyns cm*$^{-5}$)	*PVR* (*dyn cm*$^{-5}$)
Baseline	62 ± 4	130 ± 8	72 ± 3	96 ± 5	14 ± 1	5 ± 1	3.1 ± 0.2	50 ± 2	53 ± 3	1347 ± 120	198 ± 14
Paced	86 ± 5	126 ± 6	78 ± 3	100 ± 4	13 ± 1	4 ± 1	3.7 ± 0.3	42 ± 3	51 ± 2	1229 ± 146	168 ± 15
Dopexamine	86 ± 6	127 ± 7	71 ± 3	95 ± 5	17 ± 7	4 ± 1	5.0 ± 0.5	57 ± 4	62 ± 3	900 ± 121	161 ± 19
Paced *vs* Baseline	***	NS	***	*	NS	NS	*	**	NS	NS	NS
Dopexamine *vs* Baseline	***	NS	NS	NS	*	NS	***	**	*	***	NS
Dopexamine *vs* Paced	NS	NS	***	**	**	NS	***	***	**	***	NS

NS = Not significant, * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$ + In nine patients + + In eight patients.
Abbreviations: Ao: Aortic pressure; CI: cardiac index; HR: heart rate; PA: pulmonary artery pressure; PVR: total pulmonary vascular resistance; RA: right atrial pressure; SVI: stroke volume index; SVR: systemic vascular resistance; SWI: stroke work index.

in all 10 patients (Figures 2 and 3). Systolic, diastolic, and mean aortic pressure remained unchanged with dopexamine. Mean pulmonary artery pressure increased and right atrial pressure remained unchanged. Cardiac index increased from 3.1 ± 0.2 to 5.0 ± 0.5 l min^{-1} m^{-2} (+ 61%, $P < 0.001$). Systemic vascular resistance decreased from 1347 ± 120 to 900 ± 121 dyn s cm^{-5} (−33%, $P < 0.001$) and pulmonary vascular resistance remained unchanged.

Left ventricular function changes with dopexamine infusion (Table 2)

Before and following dopexamine 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 dopexamine infusion (Tables 1 and 2).

A close matching of heart rates during atrial pacing and subsequent dopexamine infusion was obtained with a pacing rate of 86 ± 5 beats min^{-1} and a dopexamine rate of 86 ± 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 dopexamine ($P < 0.001$ and $P < 0.01$, respectively). Mean pulmonary artery pressure was higher with dopexamine ($P < 0.01$) and right atrial pressure was unchanged. Cardiac index was 3.7 ± 0.3 l min^{-1} m^{-2} with pacing and 5.0 ± 0.5 l min^{-1} m^{-2} with dopexamine ($P < 0.001$). Systemic vascular resistance was lower with dopexamine ($P < 0.001$) and pulmonary vascular resistance was without significant change.

Left ventricular systolic and end-diastolic pressures were similar with matched pacing and dopexamine. Peak +dP/dt was higher with dopexamine (+ 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 dopexamine ($P < 0.01$).

Figure 4 summarizes the present changes from control in haemodynamic parameters at matched

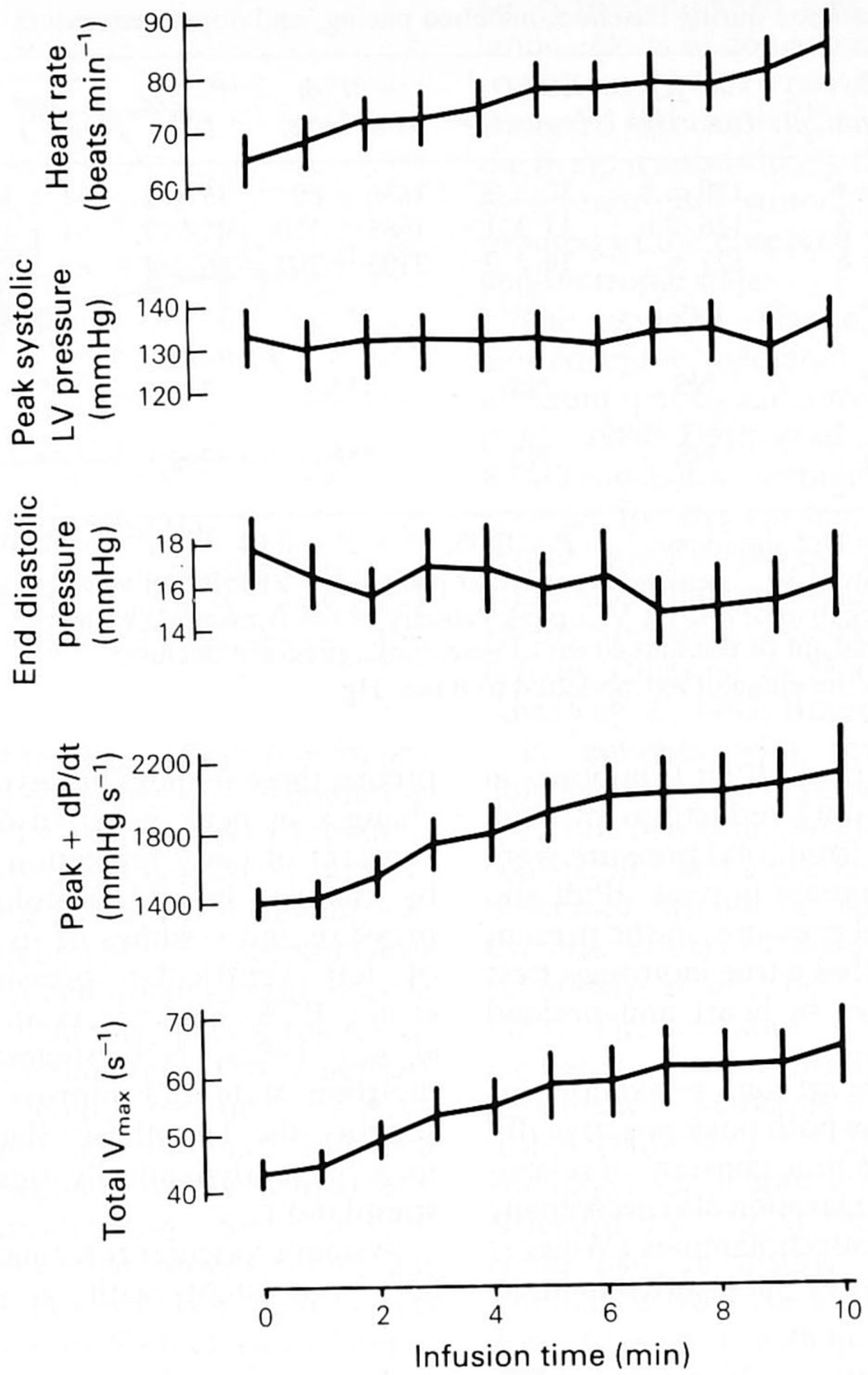

Figure 3 Group changes in heart rate, peak systolic left ventricular pressure peak systolic pressure, left ventricular end-diastolic pressure (LVEDP), peak + dP/dt, and V_{max} during 10 min infusion of dopexamine ($n = 9$).

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 V_{max}. The 12% increase in peak measured V_{CE} 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

	HR (*beats min*$^{-1}$)	LV_{sys} (*mm Hg*)	*LVEDP* (*mm Hg*)	+ *dP/dt* (*mm Hg s*)	*Pk* V_{ce} (s^{-1})	V_{max} (s^{-1})	−*dP/dt* (*mm Hg* s^{-1})	T_1 (*ms*)
Baseline	62 ± 4	130 ± 8	17 ± 2	1436 ± 80	33 ± 2	44 ± 3	1607 ± 74	54 ± 3
Paced	86 ± 5	126 ± 6	11 ± 1	1568 ± 110	41 ± 3	51 ± 4	1709 ± 87	46 ± 4
Dopexamine	86 ± 6	127 ± 7	14 ± 2	2105 ± 207	46 ± 4	63 ± 5	1856 ± 117	39 ± 2
Paced *vs* Baseline	***	NS	*	*	*	NS	NS	**
Dopexamine *vs* Baseline	***	NS	NS	***	***	***	**	***
Dopexamine *vs* Paced	NS	NS	NS	***	NS	**	NS	**

NS = Not significant * = $P < 0.05$, ** = $P < 0.01$, *** $P = < 0.001$

Abbreviations: HR: heart rate; LV_{sys}: peak left ventricular pressure; LVEDP: left ventricular end-diastolic pressure; ± dP/dt: peak positive or negative dP/dt; Pk V_{ce}: peak velocity of the contractile element; T_1: the exponential time constant of the first 40 ms of isovolumic pressure decline; V_{max}: volocity of the contractile element extrapolated to 0 mm Hg.

loped pressure and in peak dP/dt (Quinones *et al.*, 1976). However, only reductions in peak V_{CE} and V_{max} derived from total pressure were found. The marked increase in peak dP/dt and V_{max} 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

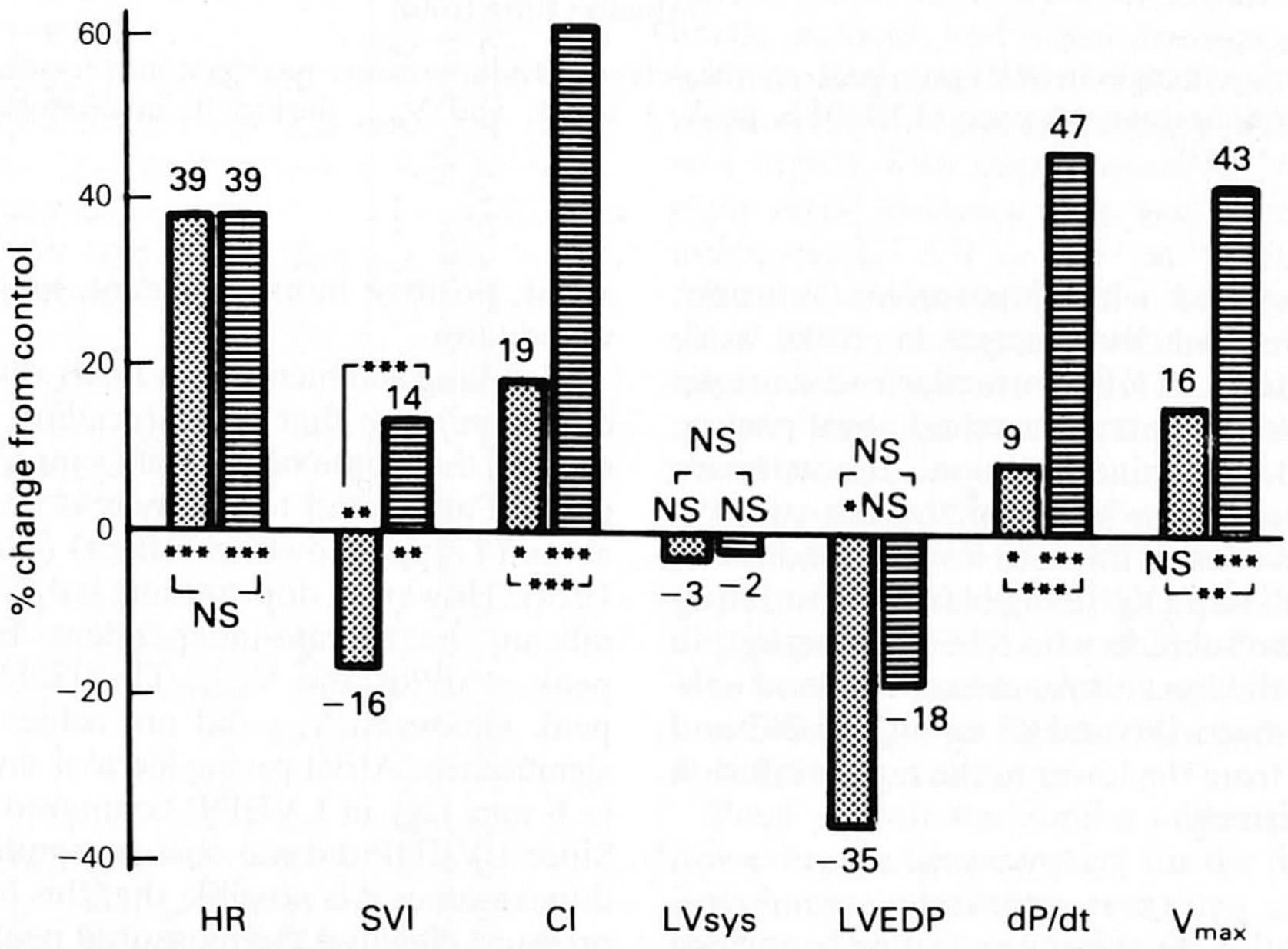

Figure 4 Percent change from control with matched pacing (⚄) and dopexamine (▤) in heart rate (HR), stroke volume index (SVI), cardiac index (CI), left ventricular systolic (LV_{sys}) and end-diastolic (LVEDP) pressures, peak + dP/dt, and V_{max} ($n = 10$).

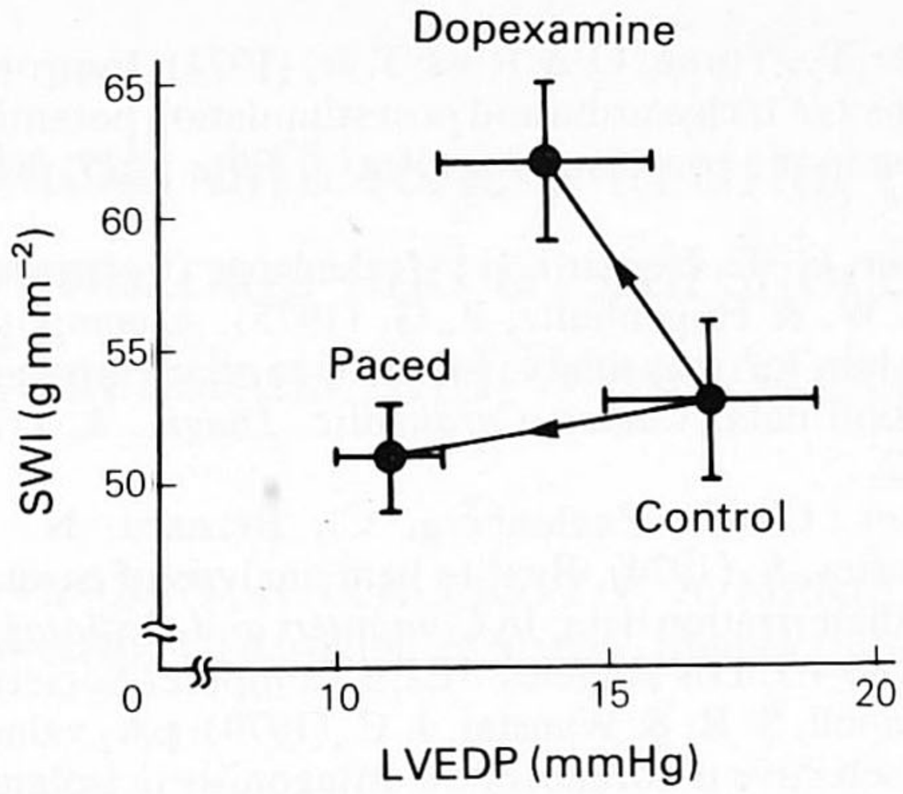

Figure 5 Change from control in left ventricular end-diastolic pressure (LVEDP) and stroke work index (SWI) with matched pacing and dopexamine ($n = 10$).

vasodilator effect of the drug. Both β_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 β_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 β_2-adrenoceptor stimulation of the heart contributed to the observed increases in heart rate and inotropic state.

The reported relative roles of β_1- and β_2-adrenoceptor mediated effects is variable in different species and uncertain in man (Hedberg *et al.*, 1980; Heitz *et al.*, 1983). The effects of β_2-adrenoceptor stimulation in humans may account for the cardiac effects of β_2-adrenoceptor specific drugs such as pirbuterol or salbutamol that have also been ascribed to these agents' possible nonspecific β_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 α-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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