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Haemodynamic profile of an inhibitor of phosphodiesterase III, adibendan (BM 14.478): comparison with nitroprusside and dobutamine in conscious dogs

A. Dorszewski, [1]B. Müller-Beckmann, L. Kling & G. Sponer

Medizinische Forschung, Herz-/Kreislaufpharmakologie, Boehringer Mannheim GmbH, Mannheim, FRG

1 This study was performed to investigate whether cardiac positive inotropic as well as peripheral vasodilator properties of adibendan contribute to its overall haemodynamic profile in conscious dogs.

2 Haemodynamic measurements were carried out in conscious chronically instrumented dogs after administration of adibendan, sodium nitroprusside or dobutamine.

3 The cardiovascular changes induced by adibendan (0.01 and 0.03 mg kg^{-1}) resembled those of dobutamine (1.0–4.0 μg kg^{-1} min^{-1}): left ventricular dP/dt_{60} (LV dP/dt_{60}), stroke volume (SV) and cardiac output (CO) increased to a similar extent, but mean arterial pressure (MAP) and heart rate (HR) remained unchanged.

4 In contrast to dobutamine, higher doses of adibendan (0.1–1.0 mg kg^{-1}) decreased MAP and LVEDP. These effects were of a similar magnitude to those observed following nitroprusside administration (0.5–12.5 μg kg^{-1} min^{-1}). In contrast to nitroprusside, adibendan still showed additional effects on LV dP/dt_{60} and CO.

5 From these results, it is concluded that both the peripheral vasodilator and the cardiac positive inotropic action of adibendan contribute to its overall haemodynamic profile.

Introduction

Adibendan (BM 14.478) is a benzimidazole derivative (Mertens *et al.*, 1987) with marked haemodynamic effects after acute i.v. and oral administration (Müller-Beckmann *et al.*, 1988a). Experiments *in vitro* have demonstrated positive inotropic and vasodilator properties (Müller-Beckmann *et al.*, 1988b) and have characterized the compound as a strong inhibitor of phosphodiesterase III (PDE-III = guanosine 3':5'-cyclic monophosphate (cyclic GMP)-inhibited PDE; Bethke *et al.*, 1988) and a calcium-sensitizing agent (Freund *et al.*, 1987; Gärtner *et al.*, 1987). Thus, the compound is related to amrinone (Farah & Alousi, 1978), enoximone (Dage *et al.*, 1982) and pimobendan (van Meel, 1985).

Because of their pronounced vasodilator properties these compounds have been classified as 'inodilators' (Opie, 1988). It is often claimed that their clinical efficacy is exclusively due to the peripheral action with a subsequent reflex increase in contractility (Firth *et al.*, 1984; Wilmshurst *et al.*, 1984; Franciosa, 1985; Miller *et al.*, 1987).

The aim of this study was to clarify whether the cardiac positive inotropic as well as the peripheral vasodilator properties of adibendan contribute to its overall haemodynamic profile. The cardiovascular effects of adibendan were compared with those of sodium nitroprusside, a pure vasodilator substance, and dobutamine, a strong positive inotropic drug, in an experimental model of conscious chronically instrumented dogs.

Methods

A left-side thoracotomy was carried out in mongrel dogs of either sex, weighing 25–34 kg, under aseptic conditions and general anaesthesia (halothane 0.5 vol%, 70% N_2O, 30% O_2). A Konigsberg manometer (model P5, Konigsberg Instruments, Pasadena, California, U.S.A.) was inserted through the apex of the heart into the left ventricle and an electromagnetic flowprobe (Speth, Dallenwil, Switzerland) was implanted around the aortic root. Finally, two polypropylene catheters (PP 120, e.d. 2 mm, i.d. 1 mm, Portex, Hythe, Kent) were placed in the abdominal aorta and in the inferior vena cava via the left femoral artery and vein, respectively. All implants were exteriorized between the shoulder blades and covered by a special suit.

Dogs were used in the experiments after a recovery period of at least 8 days. During the experiment they lay quietly in a cage. Arterial blood pressure (MAP) was recorded via a Statham P 23 db transducer, left ventricular pressure (LVP), left ventricular end-diastolic pressure (LVEDP) and cardiac output (CO; Hillers flowmeter, Hellige, Freiburg, F.R.G.) were measured. Heart rate (HR) was derived from the LVP signal by use of a pulse counter (MINO-Berlin, F.R.G.).

The contractility was measured as dP/dt_{60}, i.e., the derivative of LVP at a LV pressure of 60 mmHg (physiodifferentiator, Hugo Sachs, Hugstetten, F.R.G.). Peak negative dP/dt (dP/dt_{min}) was used as a measure of left ventricular relaxation. All parameters were recorded continuously on a universal amplifier 47/Varioscript 8008 (Schwarzer, Munich, F.R.G.).

Because the flow probes were not calibrated, the control values were taken as 100%. Total peripheral arterial resistance (TPR) was calculated according to Ohm's law. The control value of TPR was taken as 100% and the changes obtained after drug administration calculated relative to this value. Stroke volume (SV) was calculated as a ratio of CO and HR in percent, control value was expressed as 100%.

Three series of experiments were performed, with adibendan, nitroprusside, and dobutamine. Control values were taken after the baseline was constant for at least 30 min and calculated as the mean of two independent measures within 10 min before drug administration. The stability of the haemodynamic parameters during the experiments was achieved in previous investigations from our laboratories (Sponer *et al.*, 1987; Müller-Beckmann *et al.*, 1988a).

Drugs used

For intravenous administration 60.0 mg adibendan was dissolved in 1.0 ml dimethylformamide and 1.0 ml 1 N lactic acid.

[1] Author for correspondence at: Clinical Research, Boehringer Mannheim GmbH, Sandhofer Strasse 116, 6800 Mannheim 31, F.R.G.

This solution was further diluted with distilled water. Adibendan was injected intravenously every 15 min in increasing doses. The cumulative doses were 0.01, 0.03, 0.1, 0.3, 1.0 mg kg^{-1} adibendan. Parameters were determined 14 to 15 min after each injection. Sodium nitroprusside (Nipruss) 60.0 mg was prepared as a solution with 27 mg sodium citrate and diluted with isotonic saline. Dobutamine (Dobutrex) 100 mg was dissolved and diluted with isotonic saline. Both drugs were administered as a continuous i.v. infusion over 10 min. Data were obtained at the end of each infusion period. Doses administered were 0.5, 1.0, 2.5, 5.0, 12.5 μg kg^{-1} min^{-1} sodium nitroprusside and 1.0, 2.0, 4.0, 8.0, 20.0 μg kg^{-1} min^{-1} dobutamine.

Statistics

Results are presented as arithmetic means and the standard error of the means (s.e.mean). Significant effects were calculated by Student's t test for paired observations. Significance was assumed at a level of $P < 0.05$.

Results

Haemodynamic effects of adibendan (Table 1)

Intravenous injections of adibendan at doses between 0.01 and 0.03 mg kg^{-1} caused no relevant change of MAP or HR (control values: 106 ± 3 mmHg and 66 ± 3 b.p.m.). At higher doses, MAP fell to 76 ± 2 mmHg and HR increased up to 125 ± 9 b.p.m. (1.0 mg kg^{-1}). However, LVEDP decreased continuously over the entire dose-range (7.1 ± 1.1 mmHg, control value; 3.7 ± 1.1 mmHg, 0.03 mg kg^{-1}; −1.0 ± 1.3 mmHg, 1.0 mg kg^{-1}).

Adibendan induced a dose-dependent rise of dP/dt_{60} (2200 ± 130 mmHg s^{-1}, control value; 3310 ± 170 mmHg s^{-1}, 0.03 mg kg^{-1}; 4130 ± 220 mmHg s^{-1}, 1.0 mg kg^{-1}). Changes in dP/dt_{min} were only significantly different from the control values at 0.03 mg kg^{-1}.

CO increased from 100% (control value) to 120 ± 5% at 0.03 mg kg^{-1} and finally to 157 ± 8% (1.0 mg kg^{-1}). In contrast, SV only increased at doses of 0.01 and 0.03 mg kg^{-1} from 100% (control value) to 115 ± 3%. At doses in excess of 0.3 mg kg^{-1} SV fell below the control value. TPR decreased continuously from 100% (control value) to 79 ± 4% at 0.03 mg kg^{-1} and finally to 47 ± 3% after administration of 1.0 mg kg^{-1}.

Haemodynamic effects of nitroprusside (Table 2)

Nitroprusside lowered MAP from 104 ± 3 mmHg (control value) to 65 ± 3 mmHg and increased HR from 75 ± 3 b.p.m. (control value) to 116 ± 4 b.p.m. when infused intravenously at doses between 0.5 and 12.5 μg kg^{-1} min^{-1}. LVEDP was reduced from 6.7 ± 1.2 mmHg (control value) to 0.9 ± 1.5 mmHg (12.5 μg kg^{-1} min^{-1}).

In the same dose range, dP/dt_{60} increased from 2100 ± 150 mmHg s^{-1} (control value) to 2750 ± 280 mmHg s^{-1} (12.5 μg kg^{-1} min^{-1}) and dP/dt_{min} decreased from 1850 ± 70 mmHg s^{-1} to 1250 ± 60 mmHg s^{-1}.

Nitroprusside caused an increase of CO from 100% (control value) up to 124 ± 6% (12.5 μg kg^{-1} min^{-1}). SV and TPR fell from 100% (control value) to 82 ± 4% and 51 ± 2% (12.5 μg kg^{-1} min^{-1}), respectively.

Haemodynamic effects of dobutamine (Table 3)

Intravenous infusion of dobutamine at doses between 1.0 and 4.0 μg kg^{-1} min^{-1} did not markedly affect MAP and HR (control values: 108 ± 4 mmHg; 69 ± 3 b.p.m.) while at higher doses MAP fell to 99 ± 4 mmHg and HR increased to 114 ± 2 b.p.m. (20.0 μg kg^{-1} min^{-1}). A significant change of LVEDP was observed only at the highest dose, from 8.9 ± 0.9 mmHg (control value) to 6.4 ± 0.8 mmHg (20.0 μg kg^{-1} min^{-1}).

Dobutamine produced a dose-dependent increase of dP/dt_{60} (2380 ± 140 mmHg s^{-1}, control value; 2970 ± 160 mmHg s^{-1}, 4.0 μg kg^{-1} min^{-1}; 4860 ± 100 mmHg s^{-1},

Table 1 Cardiovascular effects of intravenous adibendan in conscious dogs

		Adibendan (mg kg^{-1})					
		C	0.01	0.03	0.10	0.30	1.00
MAP	(mmHg)	106 ± 3	103 ± 3†	100 ± 4†	89 ± 4#	78 ± 1#	76 ± 2#
LVEDP	(mmHg)	7.1 ± 1.1	5.4 ± 1.1*	3.7 ± 1.1#	0.9 ± 1.2#	−0.4 ± 1.4#	−1.0 ± 1.3#
dP/dt_{60}	(mmHg s^{-1})	2200 ± 130	2710 ± 140#	3310 ± 170#	3940 ± 210#	4120 ± 240#	4130 ± 220#
dP/dt_{min}	(mmHg s^{-1})	1950 ± 90	2110 ± 110	2200 ± 150	2060 ± 150	2010 ± 170	1970 ± 220
HR	(b.p.m.)	66 ± 3	66 ± 2	69 ± 4	92 ± 7*	110 ± 7#	125 ± 9#
CO	(%)	100	108 ± 3†	120 ± 2*	143 ± 7#	147 ± 7#	157 ± 8#
SV	(%)	100	108 ± 2*	115 ± 3*	105 ± 6	90 ± 5	86 ± 6
TPR	(%)	100	90 ± 2*	79 ± 4#	60 ± 4#	51 ± 3#	47 ± 3#

Results are expressed as mean ± s.e.mean (n = 11). Different from control (C): † $P < 0.05$, * $P < 0.01$, # $P < 0.001$. MAP, arterial blood pressure, LVEDP, left ventricular end-diastolic pressure, dP/dt_{60}, derivative of LVP at a LV pressure of 60 mmHg; dP/dt_{min}, peak negative dP/dt; HR, heart rate; CO, cardiac output; SV, stroke volume; TPR, total peripheral arterial resistance.

Table 2 Cardiovascular effects of intravenous sodium nitroprusside in conscious dogs

		Nitroprusside (μg kg^{-1} min^{-1})					
		C	0.5	1.0	2.5	5.0	12.5
MAP	(mmHg)	104 ± 3	98 ± 3*	91 ± 3#	81 ± 3#	77 ± 3#	65 ± 3#
LVEDP	(mmHg)	6.7 ± 1.2	5.7 ± 1.2*	4.3 ± 1.2#	3.4 ± 0.9#	2.5 ± 0.9#	0.9 ± 1.5#
dP/dt_{60}	(mmHg s^{-1})	2100 ± 150	2210 ± 180*	2250 ± 170*	2350 ± 200*	2460 ± 250*	2750 ± 280†
dP/dt_{min}	(mmHg s^{-1})	1850 ± 70	1830 ± 70	1740 ± 50†	1620 ± 70*	1570 ± 90#	1250 ± 60#
HR	(b.p.m.)	75 ± 3	78 ± 4†	79 ± 3	94 ± 6*	108 ± 5#	116 ± 4#
CO	(%)	100	105 ± 3	109 ± 4†	120 ± 5*	128 ± 5#	124 ± 6*
SV	(%)	100	101 ± 3	102 ± 2	96 ± 5	88 ± 4*	82 ± 4*
TPR	(%)	100	91 ± 4†	82 ± 2#	66 ± 3#	58 ± 2#	51 ± 2#

Results are expressed as mean ± s.e.mean (n = 11). Different from control (C): † $P < 0.05$; * $P < 0.01$; # $P < 0.001$. For abbreviations see footnote to Table 1.

Table 3 Cardiovascular effects of dobutamine in conscious dogs

		Dobutamine ($\mu g\,kg^{-1}\,min^{-1}$)					
		C	1.0	2.0	4.0	8.0	20.0
MAP	(mmHg)	108 ± 4	107 ± 3	104 ± 5	110 ± 5	106 ± 4	99 ± 4*
LVEDP	(mmHg)	8.9 ± 0.9	9.3 ± 1.0	9.7 ± 1.4	10.4 ± 0.8	8.2 ± 1.0	6.4 ± 0.8†
dP/dt_{60}	($mmHg\,s^{-1}$)	2380 ± 140	2490 ± 160†	2640 ± 180#	2970 ± 160#	3660 ± 160#	4860 ± 100#
dP/dt_{min}	($mmHg\,s^{-1}$)	2160 ± 100	2150 ± 120	2130 ± 80	2320 ± 110*	2510 ± 190†	2940 ± 320†
HR	(b.p.m.)	69 ± 3	67 ± 4	67 ± 3	69 ± 3	82 ± 2*	114 ± 2#
CO	(%)	100	103 ± 3	110 ± 6	122 ± 7†	162 ± 9#	226 ± 12#
SV	(%)	100	107 ± 2†	112 ± 2*	118 ± 3#	134 ± 4#	134 ± 6#
TPR	(%)	100	96 ± 3	90 ± 4	85 ± 6†	62 ± 4#	42 ± 3#

Results are expressed as mean ± s.e.mean ($n = 10$). Different from control (C): † $P < 0.05$, * $P < 0.01$, # $P < 0.001$. For abbreviations see footnote to Table 1.

$20.0\,\mu g\,kg^{-1}\,min^{-1}$) and a slight increase of dP/dt_{min} ($2160 \pm 100\,mmHg\,s^{-1}$, control value; $2320 \pm 110\,mmHg\,s^{-1}$, $4.0\,\mu g\,kg^{-1}\,min^{-1}$; $2940 \pm 320\,mmHg\,s^{-1}$, $20\,\mu g\,kg^{-1}\,min^{-1}$).

CO and SV (control values: 100%) rose to 122 ± 7% and 118 ± 3% at $4.0\,\mu g\,kg^{-1}\,min^{-1}$, respectively, and finally increased to 226 ± 12% and 135 ± 6%, respectively, after administration of $20.0\,\mu g\,kg^{-1}\,min^{-1}$. TPR was dose-dependently diminished from 100% (control value) to 42 ± 3% ($20\,\mu g\,kg^{-1}\,min^{-1}$).

Discussion

In accordance with the literature, the direct dilator effects of nitroprusside, on arterial and venous vessels, induced pronounced decreases in TPR, MAP and LVEDP (Rowe & Henderson, 1974; Brodie *et al.*, 1977; Pagani *et al.*, 1978; Dinerman *et al.*, 1988). Because no direct positive inotropic or chronotropic properties of nitroprusside have been found in several experimental models, the increase in HR and contractility under intact haemodynamic conditions is in general attributed to sympathetic reflex responses and parasympatholysis (Chatterjee *et al.*, 1973; Pagani *et al.*, 1978; Pennington *et al.*, 1979; Macho & Vatner, 1981; Dumont *et al.*, 1983). The reduced rate of left ventricular relaxation, observed in the present study, is probably due to its correlation with the magnitude of peak aortic systolic pressure (Weisfeldt *et al.*, 1974; Brodie *et al.*, 1977).

During dobutamine infusion, the predominant effects observed can be explained by direct stimulation of cardiac β_1-adrenoceptors and the subsequent intracellular increase of adenosine 3′:5′ cyclic monophosphate (cyclic AMP) (Katz, 1983; Sonnenblick *et al.*, 1979). There was a marked increase in contractility, ventricular relaxation and increases in SV and CO.

The chronotropic efficacy of dobutamine was more pronounced at higher doses. As previously described (Vatner *et al.*, 1974; Hinds & Hawthorne, 1975; Tuttle & Mills, 1975) the effects of dobutamine on pre- and afterload were small. The marked fall in TPR can be explained by reflex vasodilatation in skeletal muscle (Liang & Hood, 1979) and by an additional direct β_2-adrenoceptor-mediated dilator effect at high concentrations (Robie *et al.*, 1974; Vatner *et al.*, 1974).

In these experiments, adibendan and nitroprusside showed similar arterio- and venodilating properties, as illustrated by the decrease of MAP, TPR and LVEDP (Figure 1). The reduction in LVEDP may also have been caused by enhanced myocardial relaxation or improved pump function (Ludmer *et al.*, 1986). However, in the present study, neither adibendan nor nitroprusside improved ventricular relaxation, as measured by dP/dt_{min}. In addition, given the marked rise of CO with dobutamine and the concurrent minimal change of LVEDP, improved pump function also seems unlikely to explain the marked fall of LVEDP associated with adibendan and nitroprusside administration. Adibendan, like nitro-

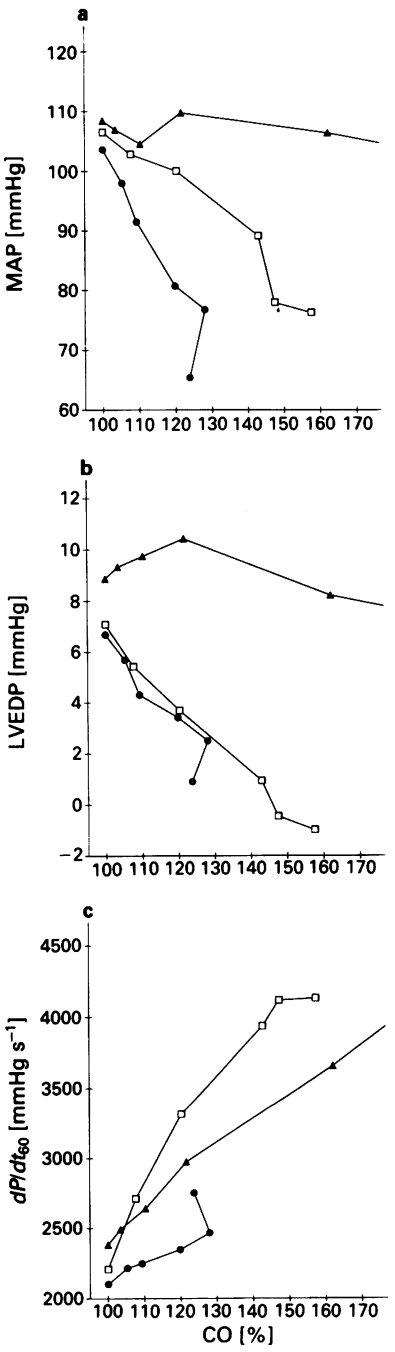

Figure 1 Effects of adibendan (□) ($n = 11$), nitroprusside (●) ($n = 11$) and dobutamine (▲) ($n = 10$) on mean arterial blood pressure (MAP), left ventricular end-diastolic pressure (LVEDP) and dP/dt_{60} in relation to the cardiac output (CO).

prusside might stimulate reflex mechanisms to increase cardiac contractility. However, since adibendan produced a greater increase in contractility and CO than nitroprusside and increased SV, at low doses, an additional direct positive inotropic effect seems likely.

In fact, the haemodynamic profile of adibendan at low doses (0.01 and 0.03 mg kg^{-1}) resembles the effects of dobutamine at a dose-range between 1.0 and 4.0 μg kg^{-1} min^{-1} (Figure 2). LV dP/dt_{60}, SV and CO increased to a similar extent, TPR fell slightly, but MAP and HR remained unchanged. The main difference was the marked decrease of LVEDP observed after adibendan administration, this is probably due to a direct venodilator effect as discussed above.

Higher doses of adibendan produced different haemodynamic changes. Instead of a further increase, SV decreased. This reduction might be caused by a lowered preload (Veit *et al.*, 1985; Müller-Beckmann *et al.*, 1988a). Contractility continued to increase, but was no longer accompanied by a corresponding increase of CO, as was the case with dobutamine (Figure 1). The reduction in MAP certainly contributed to a reflex increase of HR and to a further decrease of SV.

All three drugs increased the HR to a similar extent. This can be explained for dobutamine by its direct chronotropic effects and for nitroprusside by reflex chronotropy. Both mechanisms could account for the chronotropic activity of a PDE-III inhibitor. There was a similar ratio of increase of HR to decrease of MAP for adibendan and nitroprusside, indicating that the positive chronotropy observed after adibendan administration is mediated via reflex mechanisms (Figure 3). This would be in agreement with results obtained in atrial preparations *in vitro* which demonstrated only small positive chronotropic responses to adibendan (Bethke *et al.*, 1988; Müller-Beckmann *et al.*, 1988b).

No evidence for an improvement in ventricular relaxation, as may be expected following PDE inhibition, was observed after adibendan administration. As discussed for sodium nitroprusside the dependency of dP/dt_{min} on peak systolic aortic pressure may have disguised any change. In addition, the known Ca^{2+}-sensitizing action of adibendan (Freund *et al.*, 1987; Gärtner *et al.*, 1987) might have contributed to a slowing of ventricular relaxation.

In conclusion, both the cardiac inotropic and the peripheral vasodilator effects of adibendan contribute clearly to its overall haemodynamic profile.

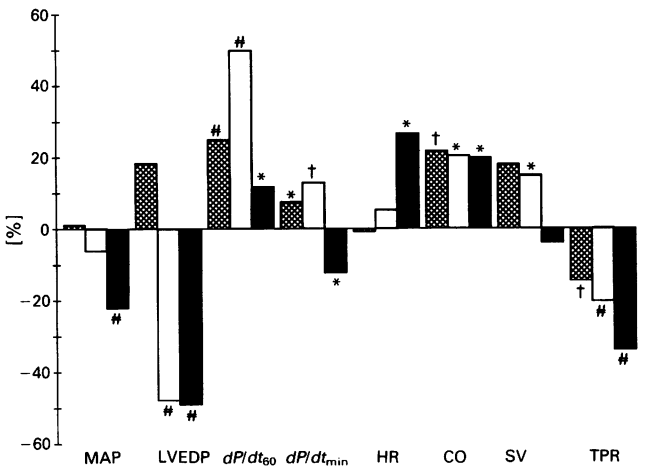

Figure 2 Cardiovascular effects of adibendan (open columns, 0.03 mg kg^{-1}), nitroprusside (solid columns, 2.5 μg kg^{-1} min^{-1}) and dobutamine (cross hatched columns, 4.0 μg kg^{-1} min^{-1}) are compared at doses which increase cardiac output by approximately 20%. Data presented as percentage change; † $P < 0.05$, * $P < 0.01$, # $P < 0.001$. For abbreviations, see footnote to Table 1.

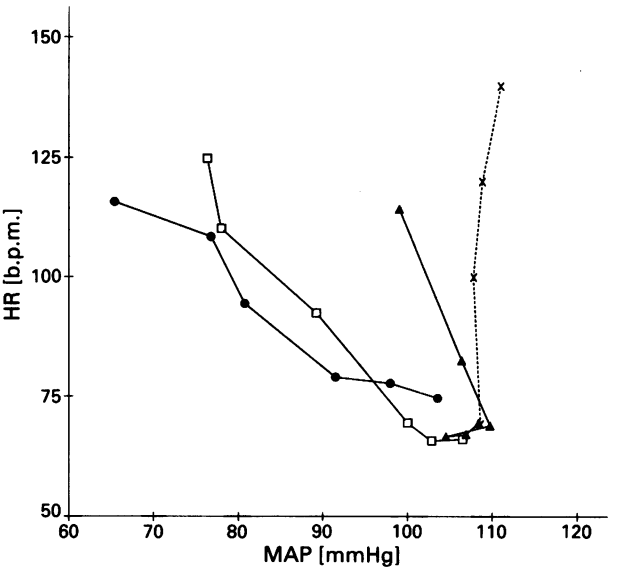

Figure 3 The relationship between heart rate (HR) and mean arterial blood pressure (MAP) is shown for adibendan (□) ($n = 11$), nitroprusside (●) ($n = 11$) and dobutamine (▲) ($n = 10$) as well as external pacing (×) ($n = 10$) in the same dogs.

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