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SOME DIRECT AND REFLEX CARDIOVASCULAR ACTIONS OF PROSTACYCLIN (PGI_2) AND PROSTAGLANDIN E_2 IN ANAESTHETIZED DOGS

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1 The aim of the study was to determine the mechanism of the hypotension and bradycardia produced by prostacyclin (PGI_2).

2 Haemodynamic studies were carried out in nineteen open-chest beagle dogs anaesthetized with chloralose. PGI_2 was infused intravenously or into the left atrium.

3 Infusions of PGI_2 either intravenously or into the left atrium equally reduced arterial pressure and total peripheral resistance but bradycardia was greater after infusion into the left atrium.

4 Comparison of effects of PGI_2 with those of prostaglandin E_2 (PGE_2) showed that although left atrial infusions both reduced aortic pressure and total peripheral resistance, PGE_2 always increased heart rate, cardiac output and maximum acceleration.

5 Similar effects were observed with sodium nitroprusside except that it always caused tachycardia and reduced stroke volume.

6 Atropine (0.05 or 1 mg/kg i.v.) reduced or reversed the bradycardia induced by PGI_2 but its hypotensive effects were reduced only after 1 mg/kg atropine. After vagotomy changes in cardiac output, stroke volume and maximum acceleration were increased, the hypotensive effects of PGI_2 were reduced and the bradycardia was reversed; effects induced by PGE_2 were not significantly altered.

7 The hypotension induced by prostacyclin is due to two components, a direct relaxation of vascular smooth muscle and a reflex, non-cholinergic vasodilatation. The bradycardia is reflex in nature and is partially mediated by the vagus pathway.

Introduction

It is now well established that prostacyclin (PGI_2) is the predominant cyclo-oxygenase metabolite of arachidonic acid synthesized by blood vessels *in vitro* (Moncada, Gryglewski, Bunting & Vane, 1976; Moncada & Vane, 1977). Furthermore, in the dog prostacyclin is the only active metabolite that can be detected on the arterial side of the circulation when arachidonic acid is infused intravenously (Dusting, Moncada, Mullane & Vane, 1978b; Mullane, Dusting, Salmon, Moncada & Vane, 1978). Indeed, the lungs release prostacyclin as a circulating hormone (Moncada, Korbut, Bunting & Vane, 1978; Gryglewski, Korbut & Ocetkiewicz, 1978; Dusting, Moncada & Vane, 1978c). Prostacyclin relaxes arterial vascular smooth muscle from several species *in vitro* (Bunting, Gryglewski, Moncada & Vane, 1976; Dusting, Moncada & Vane, 1977; Moncada & Vane, 1977) and is a powerful vasodilator agent *in vivo* causing hypotension in rats, rabbits (Armstrong, Lattimer, Moncada & Vane, 1978), cats (Lefer, Ogletree, Smith, Silver, Nicolaou, Barnette & Gasic, 1978) and dogs (Armstrong, Chapple, Dusting, Hughes, Moncada & Vane, 1977; Dusting, Chapple, Hughes, Moncada & Vane, 1978a; Dusting *et al.*, 1978c; Dusting, Moncada & Vane, 1978d; Fitzpatrick, Alter, Corey, Ramwell, Rose & Kot, 1978).

In chloralose-anaesthetized dogs, prostacyclin often induced bradycardia despite the reduction in systemic blood pressure (Armstrong *et al.*, 1977; Dusting *et al.*, 1978a; Chapple, Dusting, Hughes & Vane, 1978). A similar effect of prostaglandin E_2 (PGE_2), which also reduces blood pressure, has not been reported. Lefer and co-workers (1978) also noted that the tachycardia accompanying prostacyclin-induced hypotension in anaesthetized cats was transient and followed by bradycardia.

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Our present results show that a vagal reflex is induced by infusion of prostacyclin and this contributes to its hypotensive action. Some of this work has been presented in a communication to the Physiological Society (Chapple *et al.*, 1978).

Methods

Haemodynamic studies were carried out in nineteen beagle dogs of either sex, weighing 9.4 to 13.8 kg. Anaesthesia was induced with thiopentone sodium (25 mg/kg, i.v.) and maintained with chloralose (40 mg/kg, i.v.) after cannulation of a femoral vein for the administration of drugs. Further incremental doses of chloralose (5 to 10 mg/kg, i.v.) were given as required. A stiff polyethylene catheter was pushed down the left carotid artery into the aortic arch for recording aortic blood pressure (Statham P23dB transducer); heart rate was measured from the electrocardiogram (Lead II) and oesophageal temperature was monitored with a thermistor probe (Yellow Springs Instruments) and maintained in the range 37° to 39°C by means of a heated table. The chest was opened by splitting the sternum and the lungs ventilated with air using a Starling pump (rate 24 per min, tidal volume 150 to 250 ml). A cuffed electromagnetic flow sensor (10 to 14 mm) was placed around the root of the aorta to measure phasic aortic blood flow. In nine dogs the cervical vago-sympathetic trunk was divided bilaterally after control responses to prostaglandins had been obtained.

Stroke volume was derived by electrical integration of the phasic aortic flow signal with a Beckman type 9873B integrating coupler which was reset through a relay by each R-wave of the electrocardiogram. A 'Philbrick/Nexus' operational amplifier manifold as described by Hughes (1971) was used to derive the following: (a) Cardiac output (less coronary flow) was computed by integrating the phasic aortic flow signal and resetting the operational amplifier every 4 s. (b) Maximum acceleration of blood from the left ventricle was derived by differentiating the phasic aortic flow signal. This variable was used as an index of myocardial contractility although it is sensitive to changes in after load (Chung, Chamberlain & Seed, 1974). (c) Total peripheral resistance (excluding coronary circulation) was obtained by dividing mean aortic pressure by mean aortic flow.

Recordings were made on a Beckman 8-channel type R Dynograph. Arterial blood–gas tensions were measured frequently (Corning 175 Automatic pH/Blood gas system): P_{O_2} was always above 100 mmHg and P_{CO_2} and pH were maintained in the range 25 to 40 mmHg and 7.3 to 7.5 pH units respectively.

An interval of at least 30 min was allowed between the completion of surgery and injection of drugs. Infusions were given for 3 min at 1 ml/min into a femoral vein and in nine dogs drugs were also administered through a fine catheter into the left atrium. Prostacyclin was also given via catheters inserted into the right carotid artery (2 dogs) and left circumflex artery (Dusting *et al.*, 1978a).

Eight other mongrel and beagle dogs were anaesthetized as above. Systemic arterial pressure was measured from a catheter in a femoral artery which, together with heart rate, were recorded on a Grass polygraph (Model 7D). Drugs were infused intravenously or through a catheter, introduced retrogradely through the right carotid artery, whose tip lay just above the aortic values.

Prostacyclin was obtained as the sodium salt (Johnson, Lincoln, Thompson, Nidy, Mizdak & Axen, 1977; Whittaker, 1977). Stock solutions were prepared daily at 1 mg/ml in 1 M Tris buffer (pH 8.4 at 5°C) and kept at 0°C. PGE_2 (Cambrian Chemicals) was stored as stock solutions of 1 mg/ml in ethanol at −20°C, which was evaporated before preparation of test solutions. Test solutions of the above substances were prepared in 0.05 mol/l Tris buffer (pH 7.5 at 5°C) and kept at 0°C; prostacyclin solutions were always prepared immediately before injection. Sodium nitroprusside (Sigma) was diluted in 0.9% w/v NaCl solution (saline) immediately before use and atropine sulphate in ampoules (Burroughs Wellcome) or as a powder (BDH) was used.

Table 1 Resting levels of cardiovascular variables in all control dogs

Hours after anaesthesia	*Number of dogs*	*Mean aortic pressure (mmHg)*	*Total peripheral resistance (dyn cm^{-5} s)*	*Heart rate (beats/min)*	*Cardiac output (ml/min)*	*Stroke volume (ml)*	*Maximum acceleration (g)*
0.5–1	15	112 ± 5.8	6693 ± 548	163 ± 6	1265 ± 109	8.8 ± 0.63	4.9 ± 0.76
3	15	116 ± 5.1	6540 ± 683	201* ± 7	1242 ± 173	7.2 ± 0.70	5.2 ± 0.74
5	11	100 ± 6.2	7055 ± 793	214* ± 9	978 ± 159	5.9* ± 0.72	3.9 ± 0.65

* Significantly different ($P < 0.05$, unpaired test) from values at 0.5 to 1 h.

Responses were compared by Student's t test of paired data, unless otherwise stated. A probability of 0.05 was taken as the minimum level of significance.

Results

Resting cardiovascular variables in control dogs

Chloralose-anaesthetized dogs maintained a stable control arterial pressure for at least 5 h despite frequent infusion of vasodilator prostaglandins (Table 1). However, in most dogs, heart rate and total peripheral resistance tended to increase (by 30 and 5% respectively) and cardiac output and stroke volume to decrease (by 24 and 33% respectively) during the same period. Changes induced by prostaglandins were therefore calculated as a percentage of the control values immediately before injection or infusion for each test.

Infusion of prostacyclin by the intravenous route

Haemodynamic effects of intravenous infusions of prostacyclin (0.05 to 0.5 μg kg^{-1} min^{-1}) are shown in Table 2. In all dogs aortic pressure and total peripheral resistance decreased in proportion to the rate of infusion. Cardiac output increased moderately in five out of seven dogs but was reduced in the others; tachycardia occurred in five dogs while bradycardia appeared in the other two. Effects on cardiac output and heart rate were not always dose-dependent and there was no obvious relationship between the resting levels of these variables and the direction of change induced by prostacyclin. Stroke volume and maximum acceleration generally increased. Higher rates of infusion (0.5 to 1.0 μg kg^{-1} min^{-1}) caused greater reductions in aortic pressure and total peripheral resistance but more divergent effects on the other variables.

Infusion of prostacyclin by other routes

Into the left atrium The effects of injection or infusion of prostacyclin into the left atrium were compared with intravenous administration in six dogs. Intravenous doses (0.5 to 1 μg/kg or 0.25 to 0.5 μg kg^{-1} min^{-1}) which reduced total peripheral resistance by more than 40% did not have a significantly ($P > 0.05$) different effect on total peripheral resistance or arterial pressure when given into the left atrium (Figure 1). However, at these doses bradycardia occurred in all dogs and was more pronounced after left atrial administration in five out of six dogs (Figure 1), the difference in heart rate effects being highly significant ($P < 0.01$). Cardiac output tended to decrease with intra-atrial administration more than it did with intravenous infusions (Figure 1). In the other dog prostacyclin caused bradycardia and reduced cardiac output by either route at these doses. In all dogs there was less difference in the effects of prostacyclin given by the two routes at lower doses.

Into the aortic root In a separate group of dogs in which only aortic pressure and heart rate were measured, prostacyclin was infused for 3 to 15 min via a stiff catheter whose tip was located just above the aortic valves (Dusting *et al.*, 1978c). At higher doses (0.4 to 1.0 μg kg^{-1} min^{-1}, 6 dogs) the effects on aortic pressure were not significantly different whether the intravenous or intra-aortic route was used. Bradycardia, which occurred in all dogs but was often preceded by transient tachycardia, was similar or greater after intra-aortic administration. In two beagle dogs intra-aortic infusion at low rates (0.025 to 0.1 μg kg^{-1} min^{-1}) caused bradycardia (up to 26 beats/min) and hypotension (up to 50 mmHg) but intravenous infusion at the same rates had much weaker effects on both parameters. In all these dogs the route of administration made no difference to the amount of prostacyclin bioassayed in arterial blood as observed previously (see Dusting *et al.*, 1978c).

Into the carotid artery Injection of prostacyclin (1 μg/kg) into the right carotid artery in one dog caused tachycardia only, whereas intravenous injection of the same dose caused a smaller tachycardia followed by bradycardia. Cardiac output increased by both routes. In another dog, intra-carotid injection of prostacyclin (0.2 to 0.5 μg/kg) caused a weaker bradycardia but greater increase in cardiac output than intravenous injection. In both dogs the decrease in aortic pressure and total peripheral resistance were smaller when prostacyclin was given by the carotid route.

Injection into the coronary circulation Injection of subhypotensive doses (0.05 to 0.5 μg) of prostacyclin into the left circumflex artery did not affect heart rate (Dusting *et al.*, 1978a). Higher doses (1 to 30 μg) which reduced aortic pressure caused either tachycardia or bradycardia but the effects were similar when the same doses were injected intravenously.

Comparison of effects of prostacyclin with those of prostaglandin E_2

Since the lungs inactivate more than 90% of PGE_2 in a single passage (Ferreira & Vane, 1967) it was more convenient to compare the cardiovascular effects of PGE_2 and prostacyclin by infusion into the left atrium. PGE_2 also reduced aortic pressure and total peripheral resistance but peak effects generally occurred faster than they did with prostacyclin infusion (Figure 2) and aortic pressure tended to recover

Table 2 Effects of intravenous infusions of prostacyclin. Maximum changes occurring during 3 min infusions expressed as % of resting values

Infusion rate ($\mu g\ kg^{-1}\ min^{-1}$)	*Mean aortic pressure*				*Total peripheral resistance*				*Heart rate*				*Cardiac output*				*Stroke volume*			
	0.05	0.10	0.25	0.50	0.05	0.10	0.25	0.50	0.05	0.10	0.25	0.50	0.05	0.10	0.25	0.50	0.05	0.10	0.25	0.50
Dog 1	—	−4	—	−25	—	−12	—	−36	—	4	—	18	—	24	—	33	—	5	—	10
Dog 2	—	−14	−26	−50	—	−14	−30	−62	—	2	5	3	—	2	12	57	—	3	11	43
Dog 3	−7	−35	−66	—	−7	−44	−73	—	0	−6	−10	—	0	31	125	—	—	27	135	—
Dog 4	0	−4	−14	−26	−4	−9	−28	−48	0	1	7	7	10	10	37	71	8	12	24	40
Dog 5		−33	−46	—	—	−20	−32	—	—	−8	−17	—	—	−32	−44	—	—	—	—	—
Dog 6		−11	−24	—	—	−19	−26	—	—	2	8	—	—	13	−13	—	—	−11	−11	—
Dog 7	—	−22	−43	—	—	−34	−54	—	—	6	9	—	—	26	26	—	—	15	27	—
Mean	−4	−18	−37	−34	−6	−22	−41	−49	0	0	0	9	5	11	24	54	—	9	37	31
s.e. mean	—	5	8	10	—	5	8	9	—	2	5	5	—	9	26	14	—	6	28	13

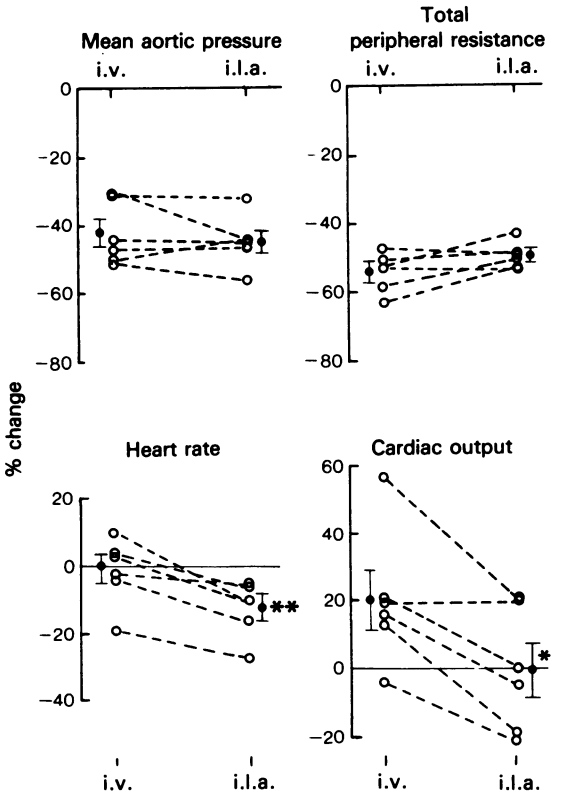

Figure 1 Comparison of effects of prostacyclin infused either intravenously (i.v.) or into the left atrium (i.l.a.). Results in six anaesthetized dogs are shown together with the mean (●) and standard error (vertical bars). Asterisks denote differences between i.v. and i.l.a. infusions significant at the 5% (*) and 1% (**) levels.

with prolonged infusion of PGE_2. In contrast to prostacyclin, PGE_2 infusion (0.1 to 0.25 μg kg^{-1} min^{-1}) always increased heart rate and cardiac output (Figures 2, 3). In three dogs prostacyclin (0.1 to 0.2 μg kg^{-1} or 0.25 μg kg^{-1} min^{-1}) was slightly more potent than PGE_2 in reducing total peripheral resistance but in three others it was less potent or there was no potency difference (one dog is not shown in Figure 3). There was no significant difference in the peak hypotensive effect of equal doses of prostacyclin and PGE_2. However, PGE_2 caused a greater tachycardia than prostacyclin in five out of six dogs and PGE_2-induced increases in cardiac output and maximum acceleration which were significantly greater ($P < 0.01$) than prostacyclin-induced responses: PGE_2 increased stroke volume more than prostacyclin in all these dogs (Figure 3). In the other dog injection of both prostacyclin and PGE_2 (0.1 and 0.2 μg/kg) caused bradycardia and markedly reduced maximum acceleration, stroke volume and cardiac output.

Haemodynamic actions of sodium nitroprusside

Intravenous sodium nitroprusside reduced aortic pressure and total peripheral resistance, but unlike prostacyclin, it always caused tachycardia and reduced stroke volume (Table 3A). In six dogs doses of nitroprusside (5 to 10 μg kg^{-1} min^{-1}) which reduced aortic pressure by more than 20 mmHg caused a significantly ($P < 0.01$) greater tachycardia than doses of prostacyclin which reduced aortic pressure by a similar amount (Table 3B).

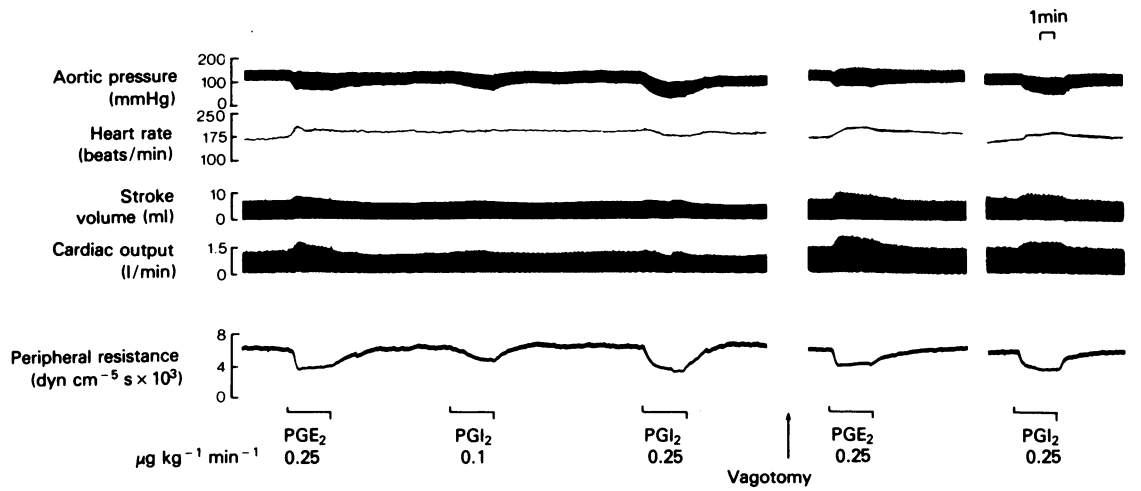

Figure 2 Records from an open-chest dog anaesthetized with chloralose showing the effects of left atrial infusions of prostacyclin (PGI_2) and prostaglandin E_2 (PGE_2) before and after vagotomy.

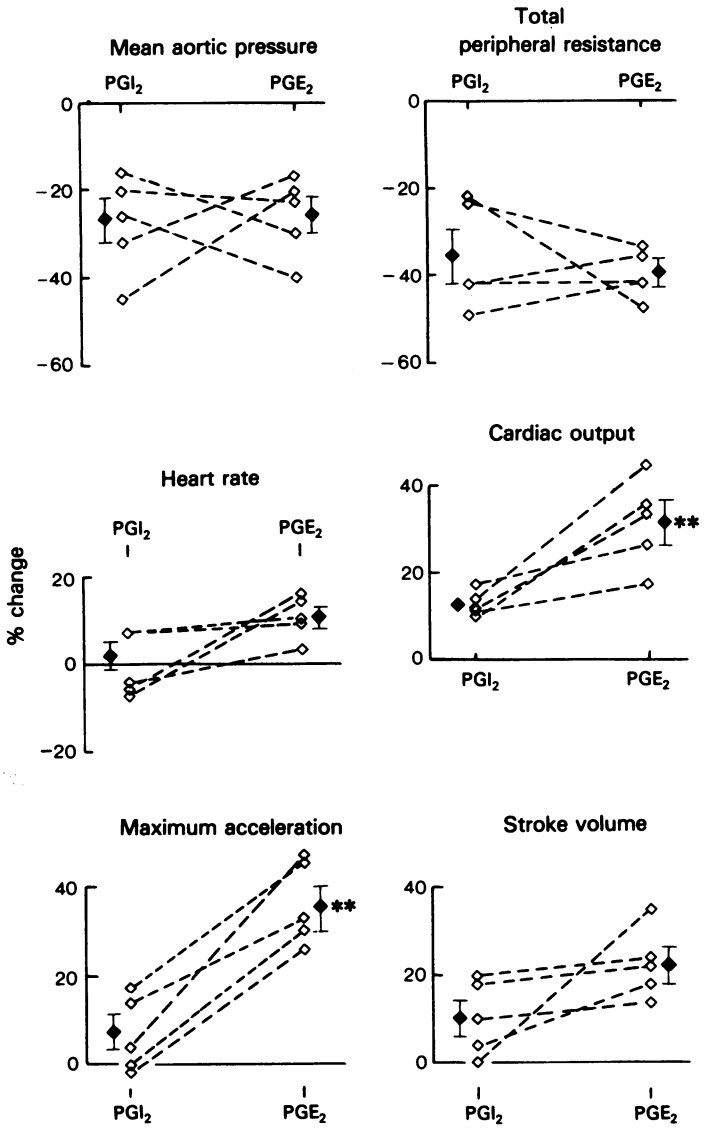

Figure 3 Comparison of effects of prostacyclin (PGI_2) and prostaglandin E_2 (PGE_2) infused into the left atrium. Results in five anaesthetized dogs are shown together with the mean (◆) and standard error (vertical bar). Asterisks denote differences between PGI_2 and PGE_2 significant at the 5% (*) and 1% (**) levels.

Effect of atropine on haemodynamic actions of prostacyclin

Resting aortic pressure, heart rate and cardiac output increased slightly in two out of three dogs 15 min after intravenous atropine (0.6 mg $\simeq$ 0.05 mg/kg) but in the other there was little change (Table 4a). Total peripheral resistance did not change significantly. This dose of atropine was sufficient to abolish the bradycardia induced by intravenous doses of acetylcholine, 750 to 1000 μg.

In a further four dogs, resting aortic pressure and peripheral resistance were significantly reduced 15 min after intravenous atropine 1 mg/kg (Table 4b); increases in heart rate, cardiac output and maximum acceleration were minimal. This dose of atropine not only abolished the bradycardia induced by intravenous doses of acetylcholine (750 to 1000 μg) but also

reduced the hypotensive response to acetylcholine. After intravenous doses of either 0.05 or 1 mg/kg atropine, the bradycardia induced by infusing prostacyclin into the left atrium was either reduced or reversed to a slight tachycardia (Tables 5a and b). However the hypotensive effects of prostacyclin were significantly reduced only after 1 mg/kg atropine (Table 5b) but changes in total peripheral resistance, cardiac output and maximum acceleration were not significantly affected by either dose of atropine (Tables 5a and b).

Effects of cervical vagotomy on haemodynamic actions of prostacyclin and prostaglandin E_2

Resting cardiovascular variables The mean changes in resting cardiovascular variables following bilateral cervical vagotomy are shown in Table 6. After transient fluctuations on dividing the vagi, aortic pressure, total peripheral resistance, cardiac output and maximum acceleration were not significantly altered 15 min after vagotomy but resting heart rate declined slightly in six out of nine dogs.

Table 3 (A) Haemodynamic effects of intravenous prostacyclin (PGI_2) and sodium nitroprusside (NP)

	Dose injected ($\mu g/kg$)		*Rate of infusion* ($\mu g\ kg^{-1}\ min^{-1}$)		*Maximum change as % of resting level*									
					Mean aortic pressure		*Total peripheral resistance*		*Heart rate*		*Cardiac output*		*Stroke volume*	
	PGI_2	NP	PGI_2	NP	PGI_2	NP	PGI_2	NP	PGI_2	NP	PGI_2	NP	PGI_2	NP
Dog 1			0.10	—	−35	—	−44	—	−6	—	31	—	27	—
			0.25	5	−66	−58	−73	−45	−10	4	125	6	135	5
Dog 2			0.50	10	−9	−20	−14	−23	7	10	50	17	27	−21
Dog 3	0.10	0.75	—	—	−43	−23	−33	−14	−6	2	−14	−13	−10	−13
	0.50	1.0	—	—	−46	−48	−51	−35	−19	2	−28	−20	−16	−23
Dog 4	0.15	1.5	—	—	−5	−10	−16	−9	1	2	7	7	0	−8
	0.72	3.6	—	—	−35	−16	−37	−17	−3	2	10	10	19	−11

(B) Effect on heart rate of equihypotensive doses of prostacyclin (PGI_2) and sodium nitroprusside (NP)

Dog number		1	2	3	4	5	6	*Mean*	*s.e. mean*
Decrease in mean aortic pressure (mmHg)	PGI_2	22	12	22	82	38	25	34	11
	NP	21	43	20	75	27	18	36	10
Change in heart rate (beats/min)	PGI_2	−25	−20	15	−20	−12	5	−10	7
	NP	15	10	45	8	5	5	15*	7

* Significantly different $P < 0.001$ from PGI_2

Table 4 Effects of atropine on cardiovascular variables: values were measured 15 min before (B) and 15 min after (A) intravenous injection of atropine: (a) 0.6 mg (≃0.05 mg/kg), (b) 1 mg/kg

		Mean aortic pressure (*mmHg*)		*Total peripheral resistance* ($dyn\ cm^{-5}\ s$)		*Heart rate* (*beats/min*)		*Cardiac output* (*ml/min*)		*Maximum acceleration* (*g*)	
		B	A	B	A	B	A	B	A	B	A
(a)	Mean (3 dogs)	101	107	8100	8400	210	210	1145	1210	4.5	4.6
	s.e. mean	20.8	23.0	3458	3924	22.0	19.8	359	359	1.45	1.62
(b)	Mean (4 dogs)	103	80**	6600	4800*	188	195	1300	1320	5.8	5.9
	s.e. mean	14.6	14.3	1600	1400	19.5	28.2	479	396	1.12	0.96

* $P < 0.05$; ** $P < 0.01$.

Intravenous and intra-atrial prostacyclin The bradycardia induced by infusion of prostacyclin into the femoral vein or into the left atrium was reversed to tachycardia after vagotomy and the hypotensive effect of prostacyclin was reduced (Figure 2). In contrast to atropine, vagotomy also reduced the vasodilator effect of prostacyclin as indicated by the change in total peripheral resistance (Fig. 4). Prostacyclin generally caused a more pronounced increase in stroke volume and maximum acceleration after vagotomy (Figures 2 and 4). The mean effects of vagotomy on prostacyclin-induced haemodynamic changes are shown in Figure 5. Whether given by the intravenous or intra-atrial routes, prostacyclin (0.5 to 1.0 μg kg^{-1} or 0.25 to 0.5 μg kg^{-1} min^{-1}) reduced aortic pressure and total peripheral resistance significantly less ($P < 0.01$) after vagotomy. Cardiac output responses induced by intra-atrial PGI_2 were significantly increased ($P < 0.01$) after vagotomy; this effect was associated with tachycardia, increased stroke volume and maximum acceleration (Figure 5).

Intra-atrial prostaglandin E_2 Although the tachycardia induced by PGE_2 (0.2 to 0.5 μg kg^{-1} or 0.25 to 0.5 μg kg^{-1} min^{-1} administered through the left atrium) was slightly greater after vagotomy (Figure 2), in contrast to prostacyclin the effects on aortic pressure, total peripheral resistance and cardiac output were not significantly altered by vagotomy (Figure 5).

Discussion

Bradycardia accompanying hypotension induced by prostacyclin has been previously observed in anesthetized dogs (Armstrong *et al.*, 1977; Dusting *et al.*, 1978a; Hintze, Kaley, Martin & Messina, 1978) and only transient, weak tachycardia accompanied prostacyclin infusion in anaesthetized cats (Lefer *et al.*, 1978). In contrast, the hypotension induced by PGE_2 always causes tachycardia, which presumably is mediated by baroreceptors (Malik & McGiff, 1976). Although there is no clear difference in the overall systemic vasodilator effects of these two prostaglandins as assessed by total peripheral resistance, PGE_2 has a more pronounced effect on cardiac output and myocardial contractility (as indicated by maximum acceleration of aortic blood flow). This finding confirms the direct positive inotropic effect of PGE_2 on the heart which has been previously demonstrated in dogs either using d*p*/d*t max* (Jones, Kane & Ungar, 1974) or the Walton-Brodie strain gauge arch (Kot, Johnson, Ramwell & Rose, 1975) as an index of myocardial contractility. Stroke volume is also increased more by PGE_2 than by prostacyclin which may be due to the difference in contractility or a greater venodilator effect of prostacyclin leading to less cardiac filling. These observations indicate that in equi-hypotensive doses prostacyclin reduces cardiac work more than PGE_2. Intravenous doses of prosta-

Table 5 Effects of prostacyclin (PGI_2) infused into the left atrium, before (B) and after (A) intravenous injection of atropine: (a) 0.6 mg (≃0.05 mg/kg), (b) 1 mg/kg, shown as % change

		Mean aortic pressure		*Total peripheral resistance*		*Heart rate*		*Cardiac output*		*Maximum Acceleration*	
		B	A	B	A	B	A	B	A	B	A
(a)	Mean (3 dogs)	−43	−47	−51	−62	−14	+7	+11	+25	+15	+35
	s.e. mean	7.3	9.6	5.8	5.7	8.3	2.0	7.3	8.9	20.6	13.3
(b)	Mean (4 dogs)	−59	−40**	−46	−41	−14	−1	−40	−24	−37	−24
	s.e. mean	8.0	8.3	7.7	3.7	6.8	0.8	4.1	6.2	3.5	9.6

** $P < 0.01$.

Table 6 Effect of vagotomy on cardiovascular variables in nine dogs; values were measured 15 min before (B) and 15 min after (A) bilateral division of cervical vago-sympathetic trunk

	Mean aortic pressure (mmHg)		*Total peripheral resistance (dyn cm^{-5} s)*		*Heart rate (beats/min)*		*Cardiac output (ml/min)*		*Maximum acceleration (g)*	
	B	A	B	A	B	A	B	A	B	A
Mean	101	105	7172	7386	215	208	1123	1148	3.5	3.7
s.e. mean	9.2	12.1	1314	1501	7.7	7.3	179	170	0.80	0.98

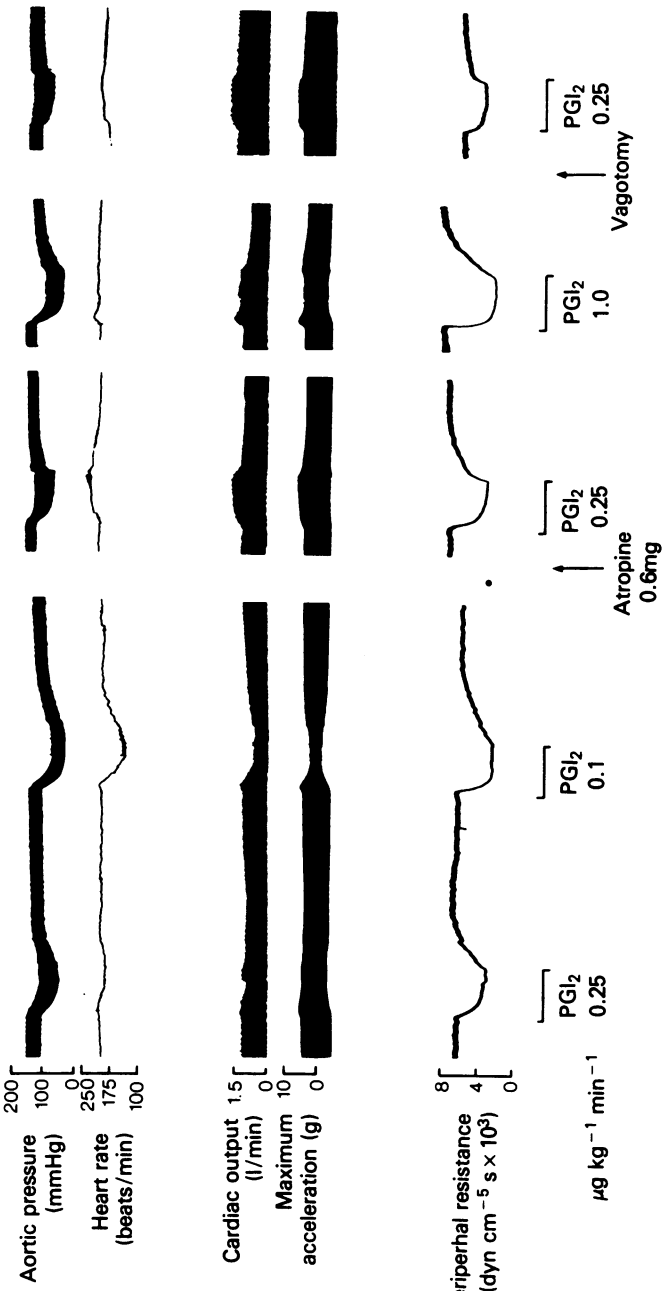

Figure 4 Record from an open-chest dog anaesthetized with chloralose showing effects of prostacyclin (PGI_2) infused into the left atrium before and after atropine 0.6 mg intravenously and after vagotomy.

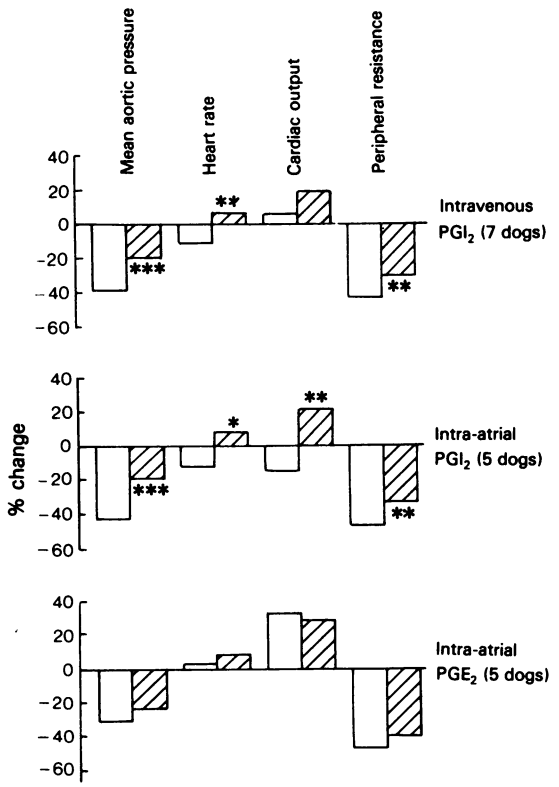

Figure 5 Comparison of effects of prostacyclin (PGI_2) infused intravenously or into the left atrium and prostaglandin E_2 (PGE_2) into the left atrium, before (open columns) and after vagotomy (hatched columns) in anaesthetized open-chest dogs. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

cyclin produced increases in phasic aortic flow and cardiac output and also increases in phasic coronary flow and mean coronary flow but these were not dose related (Dusting *et al.*, 1978).

Prostacyclin, unlike PGE_2 (Ferreira & Vane, 1967), is not inactivated during its passage through the lungs (Dusting *et al.*, 1978c). Therefore, the systemic hypotensive and vasodilator effects of prostacyclin are similar whether it is infused intravenously or into the arterial side of the circulation. However, in one complete passage around the circulation approximately 50% of prostacyclin is inactivated in other vascular beds (Dusting *et al.*, 1978c). Therefore the concentration of prostacyclin reaching the pulmonary circulation is lower when it is infused into the aorta or left atrium than when it is infused into the right atrium or intravenously. Coleridge, Coleridge, Ginzel, Baker, Banzett & Morrison (1976) have observed stimulation of 'irritant' receptors and afferent C-fibres in lungs by $PGF_{2\alpha}$ and PGE_2 and greater effects were observed after injection into the right rather than left atrium. In contrast, prostacyclin causes a greater bradycardia when administered into the left atrium. Clearly although prostacyclin dilates the pulmonary circulation (Mullane *et al.*, 1978), the bradycardia does not result from stimulation of receptive areas in the lungs. Furthermore, since little or no bradycardia resulted from injection of prostacyclin into the carotid or coronary circulation, it is unlikely that receptive areas in the carotid sinus or left ventricle initiate this response. Stimulation of mechano-receptors in the left ventricle can also initiate afferent C-fibre activity Thorén, Donald & Shepherd, 1976), such as occurs during haemorrhage. We did not measure ventricular pressures in this study but nitroprusside, which reduces cardiac filling pressure, causes tachycardia. Therefore it also seems unlikely that reduced cardiac filling in the face of systemic hypotension can account for the bradycardia induced by prostacyclin.

Nevertheless, it is clear that the bradycardia induced by prostacyclin is a reflex response mediated at least partially by parasympathetic fibres innervating the heart since atropine reduces or abolishes the bradycardia. However, the afferent arc is also subserved by vagal fibres as vagotomy reduces the hypotensive effects of prostacyclin to a greater extent than atropine 1 mg/kg intravenously. Therefore the hypotension induced by prostacyclin has at least two components: direct relaxation of vascular smooth muscle and reflex, non-cholinergic vasodilatation. Reflex stimulation by prostacyclin also attenuates the increase in cardiac output which would otherwise accompany vasodilatation, perhaps by affecting myocardial contractility as well as heart rate. Furthermore, it is clear that PGE_2 does not cause the reflex effects associated with prostacyclin and this accounts, in large part, for the difference in the haemodynamic actions of the two prostaglandins.

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