Br. J. Pharmac. (1976), **56**, 245–253

REFLEX BRADYCARDIA AND HYPOTENSION PRODUCED BY PROSTAGLANDIN $F_{2\alpha}$ IN THE CAT

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1 Intravenous administration of prostaglandin $F_{2\alpha}$ results in a dose-dependent increase in pulmonary arterial pressure, decrease in systemic arterial pressure and a delayed bradycardia. Pulmonary vasoconstriction was observed at doses as low as 0.1 and 0.3 μg/kg. The systemic depressor and heart rate lowering effects were observed at 1 μg/kg doses and above.

2 A moderate bradycardia was still observed after atropine blockade but was abolished following bilateral vagotomy. Neither of these procedures affected the pulmonary vascular response.

3 Injections of submaximal doses of prostaglandin $F_{2\alpha}$ (1–4 μg/kg) produced a greater and longer lasting bradycardia when injected into the left atrium than was observed following intravenous administration. In addition the latency of onset was much shorter following left atrial injection. These doses resulted in no change in heart rate and a minimal hypotension when injected into the brachiocephalic artery or into the aortic arch.

4 Small doses of prostaglandin $F_{2\alpha}$ administered at the level of the origin of the coronary arteries produced marked decreases in heart rate and blood pressure whereas no change occurred following injection of the same amount into the ascending aorta at more distal sites.

5 These results suggest that prostaglandin $F_{2\alpha}$ produces bradycardia and hypotension in the cat by activating 'receptors' located in the left heart or by acting on structures perfused by means of the coronary arteries.

Introduction

Prostaglandin $F_{2\alpha}$ is unique among the various prostaglandin sub-groups in that there are qualitative species variations with regard to its cardiovascular actions (Bergström, Carlson & Weeks, 1968; Nakano, 1973). In contrast to the uniformly depressant actions of the E and A prostaglandin subgroups, intravenous administration of prostaglandin $F_{2\alpha}$ results in a systemic pressor response in the dog and rat (Ducharme, Weeks & Montgomery, 1968) and a systemic depressor response in the cat and rabbit (Änggård & Bergström, 1963; Horton & Main, 1965). We have demonstrated that several haemodynamic parameters are responsible for the depressor action of prostaglandin $F_{2\alpha}$ in the cat (Koss & Nakano, 1973; Koss, Gray, Davison & Nakano, 1973a). These include: (1) direct, but transient, peripheral vasodilatation, (2) decreased cardiac output as a result of increased pulmonary arterial pressure and (3) marked delayed bradycardia.

The present study was undertaken to analyze further the prostaglandin $F_{2\alpha}$-induced bradycardia and hypotension in the cat. Following an analysis of the dose-response relationships, an attempt was made to determine what role afferent as well as efferent vagal mechanisms might play in this response. This was accomplished by observing haemodynamic changes induced by prostaglandin $F_{2\alpha}$ before and after atropine and before and after bilateral vagotomy. In addition, different injection sites were used to identify possible sites of action for this agent. Our results suggest that intravenous prostaglandin $F_{2\alpha}$ acts on structures perfused by means of the coronary arteries. A preliminary report of this study has been published (Koss, Rieger & Nakano, 1973b).

Methods

Thirty-seven adult cats of either sex were anaesthetized with chloralose (60–80 mg/kg) given intraperitoneally. A femoral artery and vein were cannulated in order to measure systemic arterial blood pressure and for the intravenous administration of drugs. Following cannulation of the trachea, positive pressure respiration was initiated with a Harvard respirator. The animals were placed on their right sides

and the left hemithorax was opened, usually between the fourth and ninth ribs. A branch of the pulmonary artery supplying either the left cardiac or left apical lobe was cannulated for direct measurement of pulmonary arterial pressure. We were careful during these procedures not to damage the vagal fibres near the heart. Pulmonary and systemic arterial pressures were recorded continuously by means of Statham P23BC and P23Dd pressure transducers. Heart rate was measured with a Grass tachograph (7P4D) and all responses were recorded continuously on a Grass polygraph (7B).

In the first group of cats (6) an attempt was made to determine the effects of increasing doses of prostaglandin $F_{2\alpha}$ on the three haemodynamic parameters measured. A total of five injections was administered intravenously to each animal starting at the lowest dose (0.1 μg/kg) and progressing sequentially in approximately three-fold steps to the highest dose (9.0 μg/kg).

In the second series of experiments (10 cats), the effect of intravenous prostaglandin $F_{2\alpha}$ was observed before and after administration of atropine sulphate (1.5–2 mg/kg). At the onset of each experiment, the dose of prostaglandin $F_{2\alpha}$ producing the maximal change in all variables was established. This was within the range of 6–12 μg/kg. The effectiveness of the atropine blockade was established in each experiment by the absence of cardiovascular responses following intravenous acetylcholine chloride (5–10 μg).

In the third group of experiments (9 cats) the responses to maximally effective intravenous doses of prostaglandin $F_{2\alpha}$ (6–12 μg/kg) were observed before and after bilateral vagotomy. Both vagi were isolated at the cervical level prior to the control injections of prostaglandin $F_{2\alpha}$. At least two responses were obtained in each experiment before vagotomy and only those cats with reproducible responses were used.

The final series of experiments (12 cats) was designed to determine the principle site of action of prostaglandin $F_{2\alpha}$. Doses necessary to produce a moderate or submaximal change in heart rate and blood pressure were used (1–4 μg/kg). Intra-arterial injections were made by means of polyethylene catheters, the tips of which were placed at several sites. Injections were made into (1) the left atrium, (2) the brachiocephalic artery, (3) the ascending aorta at the origin of the coronary arteries, (4) the ascending aorta distal to the exit of the coronaries and (5) the aortic arch and descending aorta. The left atrial injections were made by means of a catheter placed in the left atrial appendage. The other sites were reached by means of a catheter in a femoral artery. In order to place the catheter at the exit of the coronary arteries it was first threaded into the left ventricle and then slowly withdrawn until the characteristic left ventricular pressure wave was either intermittent or absent. In the two cases where this was possible the location of this catheter was confirmed post-mortem. The positioning at the other sites was by direct palpation in the open chest animal.

Crystalline powder prostaglandin $F_{2\alpha}$ (tromethamine salt) used in these experiments was supplied by Dr J.E. Pike, Upjohn Company, Kalamazoo, Michigan. A stock solution (1 mg/ml) was prepared with distilled water and stored at −10°C. Fresh solutions (10 or 100 μg/ml) were prepared shortly before the experiments by diluting the stock solution with 0.9% w/v NaCl solution (saline). After the prostaglandin solution was placed in the cannula it was flushed in with 2 ml of saline for 2–3 seconds. As multiple injections were made, a recovery period of at least 15 min was used. The total number of injections generally varied between three and five in each experiment. As shown previously (Koss & Nakano, 1973; Koss, *et al.*, 1973a) there is no apparent tachyphylaxis at these dose levels when at least 15 min elapses between injections.

Results

Intravenous injections of prostaglandin $F_{2\alpha}$ caused dose-related changes in pulmonary arterial pressure, systemic arterial blood pressure and heart rate. As shown in Figure 1, doses as low as 0.1 and 0.3 μg/kg resulted in a constriction of the pulmonary vasculature while having little or no effect on systemic blood pressure and heart rate. Larger doses of prostaglandin $F_{2\alpha}$ (above 1.0 μg/kg) produced a fall in systemic arterial blood pressure and a delayed bradycardia. The onset of the systemic depressor action varied between 6–15 seconds. At 9 μg/kg the mean onset was 8.4 ± 1.7 s and the maximal effect was seen in 49.8 ± 6.0 s, $n=6$. In contrast, the onset of the bradycardia was more delayed with a mean onset for the 9 μg/kg dose occurring in 27.8 ± 6.0 s and reaching its peak effect in 66.4 ± 9.7 s in these same preparations. Table 1 summarizes the dose-related haemodynamic effects of prostaglandin $F_{2\alpha}$ in six experiments. Occasionally a transient hypertension lasting between 5–15 s was observed following the injection. It is not known whether this is a drug effect or merely a result of the bolus injection.

Effect of atropine blockade

The responses to intravenous prostaglandin $F_{2\alpha}$ (6–12 μg/kg) were observed before and after blockade of efferent vagal mechanisms with atropine sulphate (1.5–2 mg/kg). This dose range produced maximal changes in the three parameters measured. As shown in Figure 2c, the increase in pulmonary arterial pressure was not altered following atropine whereas the bradycardia and hypotension were reduced. Initial blood pressure and heart rate levels in all of the experiments were similar to those in Figure 2 (a and b). The prostaglandin $F_{2\alpha}$-induced decrease in mean systemic arterial pressure averaged 56 ± 6 mmHg before and 30 ± 4 mmHg after atropine blockade

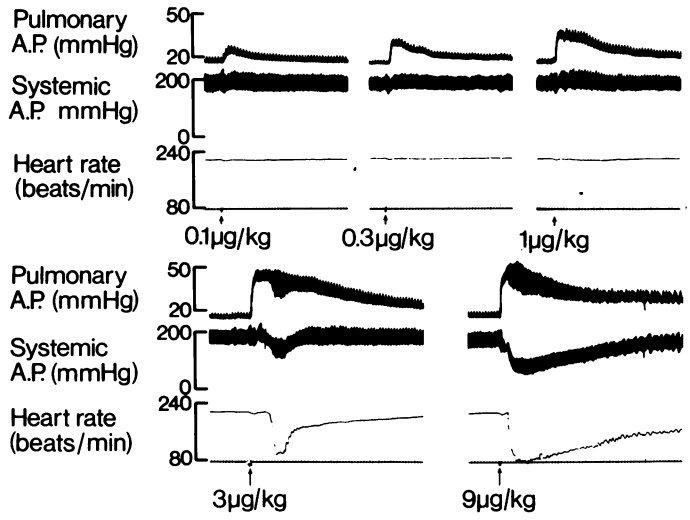

Figure 1 Effects of intravenous administration of prostaglandin $F_{2\alpha}$ (0.1 to 9 μg/kg) on pulmonary arterial pressure, systemic arterial pressure and heart rate in cat anaesthetized with chloralose. Doses were injected sequentially from the smallest to the largest at no less than 15 min intervals. Each time mark equals 5 seconds. Upper panels represent 4 min and lower panels represent 6 minutes.

($P < 0.01$, $n = 10$). The decrease in heart rate averaged 48 ± 7 beats/min before and 10 ± 2 beats/min after atropine ($P < 0.01$, $n = 10$). A residual bradycardia and prolonged depressor response was observed in all of the atropine-treated preparations.

Effect of bilateral vagotomy

In another group of cats, the responses to intravenous prostaglandin $F_{2\alpha}$ were observed before and after vagotomy eliminated both the afferent and efferent

Table 1 Effect of prostaglandin $F_{2\alpha}$ on pulmonary arterial pressure, mean systemic arterial pressure and heart rate

	0.1 μg/kg	*0.3 μg/kg*	*1.0 μg/kg*	*3.0 μg/kg*	*9.0 μg/kg*
Pulmonary arterial pressure (mmHg)					
Initial level	18.5 ± 1.8	17.5 ± 1.2	17.8 ± 1.1	16.8 ± 1.0	17.8 ± 0.7
Response	+9.2 ± 1.2	+16.5 ± 2.8	+21.8 ± 3.4	+28.3 ± 3.0	+30.2 ± 2.1
Duration (min)	2.5 ± 0.6	3.2 ± 0.7	4.2 ± 0.3	6.0 ± 0.7	7.5 ± 1.4
Mean systemic arterial pressure (mmHg)					
Initial level	158.0 ± 8.9	159.3 ± 7.0	155.3 ± 7.4	150.8 ± 9.6	150.8 ± 5.6
Response	+1.7 ± 2.8	−0.8 ± 2.3	−16.6 ± 8.6	−38.8 ± 10.2	−51.8 ± 10.1
Duration (min)	–	–	1.4 ± 0.2	3.3 ± 1.0	4.8 ± 1.0
Heart rate (beats/min)					
Initial level	195.4 ± 8.7	194.0 ± 7.4	192.0 ± 8.2	194.5 ± 8.1	199.0 ± 9.1
Response	−1.3 ± 0.6	+0.8 ± 0.8	−12.1 ± 6.0	−60.3 ± 16.9	−69.8 ± 18.6
Duration (min)	–	–	5.5 ± 0.9	7.6 ± 1.6	10.2 ± 2.7

Values are means ± s.e. of six experiments. All responses statistically significant ($P < 0.05$) except mean systemic arterial pressure and heart rate at 0.1 and 0.3 μg/kg.

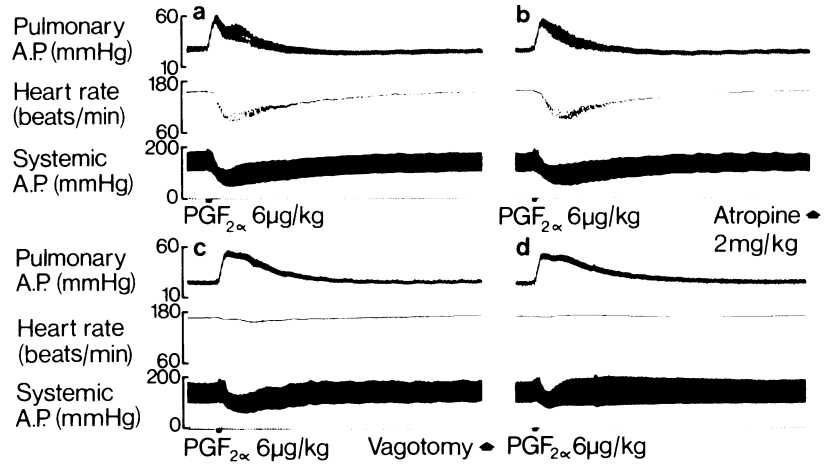

Figure 2 Effect of intravenous administration of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) on pulmonary arterial pressure, heart rate and systemic arterial pressure. (a) and (b) are control responses. Atropine (2 mg/kg) was administered between panels (b) and (c). Both vagi were sectioned prior to response seen in panel (d). Each panel represents 9 minutes. Time mark at 5 s intervals.

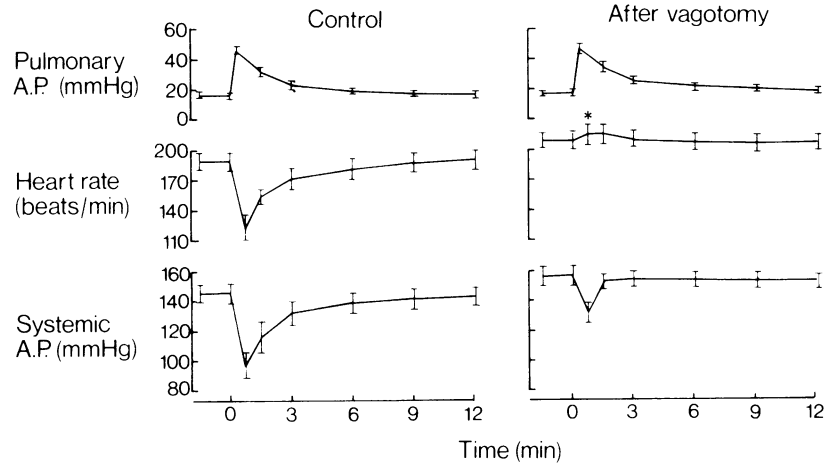

Figure 3 Composite representation of haemodynamic responses to maximally effective doses of prostaglandin $F_{2\alpha}$ (6–12 μg/kg, i.v.) before (left) and after bilateral vagotomy (right). Vertical bars represent ± s.e. ($n=9$). All peak responses are significant ($P<0.01$) with the exception of the tachycardia following vagotomy * ($P<0.20$, NS).

vagal mechanisms. A typical response is shown in Figure 2d (in this case one of the previously atropine-treated animals was used). The composite responses of nine cats (not previously treated with atropine) are shown in Figure 3. As with atropine, bilateral vagotomy did not alter the increase in pulmonary arterial pressure. The prostaglandin $F_{2\alpha}$-induced bradycardia was abolished following vagotomy with most of these preparations exhibiting some degree of tachycardia ($P<0.20$, NS). As shown in Figure 3, vagotomy greatly reduced the magnitude of the depressor response and shortened the time of recovery to control levels. The blood pressure returned to basal levels in about 1.5–3 min in all of the vagotomized preparations.

Different injection sites

The previous results with atropine and vagotomy suggested that both afferent and efferent vagal

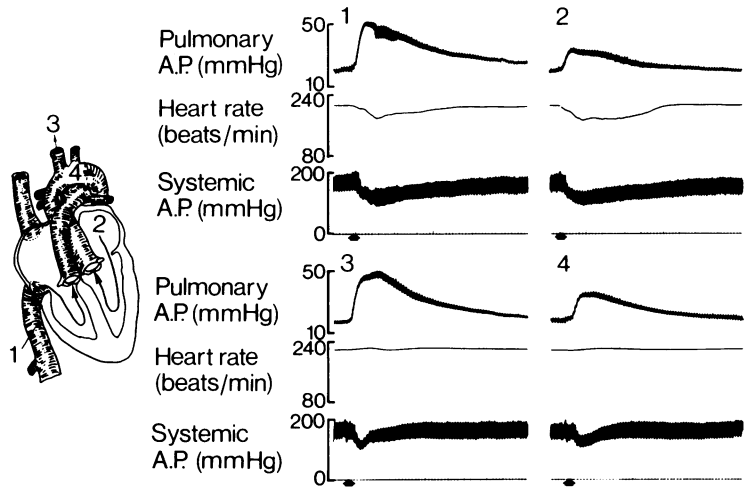

Figure 4 Cardiovascular actions of prostaglandin $F_{2\alpha}$ (4 μg/kg) injected (1) intravenously, (2) into the left atrium, (3) into the brachiocephalic artery and (4) into the aortic arch. Numbers on drawing at left (1–4) correspond to responses seen in panels on right (1–4). Each panel represents 5 minutes.

mechanisms might contribute to the bradycardia and hypotension associated with intravenous injections of prostaglandin $F_{2\alpha}$. With this in mind, an attempt was made to ascertain the loci or regions responsible for the bradycardia and hypotension produced by this agent. This was done by injection of submaximal doses (1–4 μg/kg) of prostaglandin $F_{2\alpha}$ at several locations. Depending on the sensitivity of the animal, these doses produced a moderate, submaximal bradycardia and systemic hypotension following intravenous injection.

Figure 4 illustrates the differential effects of prostaglandin $F_{2\alpha}$ administration in a typical experiment. Intravenous injection of prostaglandin $F_{2\alpha}$ (4 μg/kg) resulted in marked pulmonary constriction associated with a moderate bradycardia and hypotension (Figure 4–1). The same amount injected directly into the left atrium (Figure 4–2) resulted in less pulmonary constriction and a somewhat more extensive bradycardia. Injection into the brachiocephalic artery (Figure 4–3) or into the aortic arch at the level of the left subclavian artery (Figure 4–4) resulted in no change in heart rate and only a minimal depressor response which recovered rapidly. The constriction of the pulmonary vasculature was greater following brachiocephalic injection than was observed after administration into the aortic arch. This is probably due to the fact that prostaglandins are broken down by enzymes in the kidney and spleen but are not inactivated to any significant degree in the brain (Änggård, 1971; Nakano, Prancan & Moore, 1972).

Table 2 summarizes the haemodynamic responses to submaximal doses of prostaglandin $F_{2\alpha}$ following injection at these different sites in eight experiments. Note that the onset of bradycardia is much sooner after injection into the left atrium than after intravenous administration. In addition the magnitude and duration of the heart rate responses were greater following left atrial injections. The record shown in Figure 5 demonstrates these differences. In this example, 1 μg/kg administered intravenously resulted in the typical prostaglandin $F_{2\alpha}$-induced pulmonary arterial constriction, hypotension and bradycardia. The latency to onset was 38 s with the maximal bradycardia of 44 beats/min occurring in 70 seconds. The total duration of the response was 6.8 minutes. In contrast, the same dose (1 μg/kg) injected into the left atrium resulted in little or no pulmonary vasoconstriction. The heart rate slowed by 92 beats/min with a latency of onset of only 7 seconds. In this example the maximal effect was seen in 34 s and the duration of the response was 8.2 minutes.

A more specific localization is illustrated in Figure 6. In this example, prostaglandin $F_{2\alpha}$ (6 μg total dose = 1.8 μg/kg) was injected into the ascending aorta with the tip of the catheter just distal to the aortic valve (Figure 6a). This injection at the level of the exit of the coronary arteries resulted in a pronounced bradycardia associated with prolonged hypotension but only a minimal pulmonary arterial constriction. Administration of the same dose into the aortic arch (Figure 6b) produced no change in heart rate or systemic blood pressure. Control injections of saline were without effect at either site. In 3 additional experiments the results were consistent with the example shown in Figure 6. In two of these, the injection was made at the level of the aortic arch first, followed by injection at the level of the coronary arteries. Administration of pro-

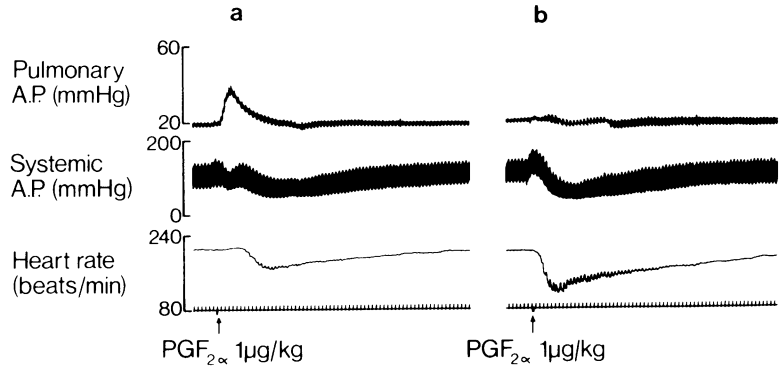

Figure 5 Comparison of the haemodynamic effects of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 1 μg/kg) injected intravenously (a) and into the left atrium (b). Note the shorter latency and greater magnitude of the bradycardia following the left atrial injection. Time mark is at 5 s intervals. Each panel represents 6 minutes.

staglandin $F_{2\alpha}$ (1–2 μg/kg) at the level of the coronary arteries resulted in a bradycardia of 52.2 ± 5.8 beats/min in these four experiments. The mean latency was 13.5 ± 4.1 s and the average duration was 7.7 ± 2.1 minutes. In three of these experiments the hypotension resulting from prostalglandin $F_{2\alpha}$ injected near the coronary arteries occurred concomitantly with the bradycardia. The average decrease in blood pressure was 40.0 ± 4.2 mmHg with a latency of 11.3 ± 2.7 s and a duration of 7.6 ± 2.2 minutes. The fourth cat had no change in blood pressure even though the heart rate decreased 46 beats/min (onset latency in this animal was 24 seconds). The same doses administered at the level of the aortic arch resulted in no change in blood pressure or heart rate in any of these experiments.

Table 2 Effect of prostaglandin $F_{2\alpha}$ (1–4 μg/kg) at different injection sites

	Intravenous	*Left atrium*	*Brachiocephalic artery*	*Aortic arch*
Pulmonary arterial pressure (mmHg)				
Initial level	18.1 ± 0.6	17.6 ± 0.5	16.3 ± 0.5	16.8 ± 0.5
Response	+24.3 ± 3.0	+11.6 ± 2.5	+17.0 ± 5.3	+11.3 ± 3.2
Onset (s)	5.4 ± 0.3	11.8 ± 1.6	10.4 ± 1.4	12.4 ± 4.1
Maximum (s)	25.4 ± 2.2	38.0 ± 6.7	31.5 ± 5.5	31.3 ± 2.7
Duration (min)	5.2 ± 0.7	4.5 ± 0.7	3.5 ± 1.2	3.5 ± 0.6
Mean systemic arterial pressure (mmHg)				
Initial level	149.0 ± 8.8	136.6 ± 7.8	135.5 ± 14.2	133.5 ± 11.2
Response	−37.6 ± 9.6	−38.8 ± 11.4	−11.8 ± 13.9	−0.4 ± 7.7
Onset (s)	11.2 ± 2.1	14.8 ± 2.1	–	–
Maximum (s)	54.5 ± 9.3	50.6 ± 6.2	–	–
Duration (min)	5.4 ± 1.4	6.1 ± 0.6	–	–
Heart rate (beats/min)				
Initial level	193.8 ± 9.1	192.6 ± 8.8	211.0 ± 5.5	200.3 ± 11.6
Response	−37.0 ± 8.9	−81.1 ± 10.8	0 ± 1.6	−4.3 ± 2.5
Onset (s)	34.4 ± 5.8	8.8 ± 2.3	–	–
Maximum (s)	65.8 ± 10.0	46.6 ± 4.3	–	–
Duration (min)	5.6 ± 1.1	8.1 ± 1.1	–	–

Values represent means ± s.e. of eight experiments. $n = 3$ at 1 μg/kg; 1 at 2 μg/kg; 1 at 3 μg/kg; 3 at 4 μg/kg.

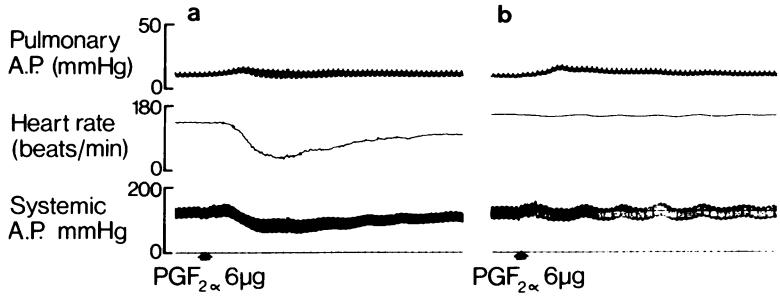

Figure 6 Effects of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 6 µg total dose = 1.8 µg/kg) injected at the level of the origin of the coronary arteries (a) and into the ascending aorta distal to the exit of the coronary arteries (b). Note that the pronounced bradycardia and hypotension is observed only when this agent is able to enter the coronary circulation. Each panel represents 3.5 minutes.

Discussion

The cardiovascular responses to prostaglandin $F_{2\alpha}$ are obviously extremely complex and appear to be composed of a variety of direct and reflex effects. In recent investigations (Koss & Nakano, 1973; Koss *et al.*, 1973a,b) we have shown that direct vasodilatation is the primary factor responsible for the depressor action of prostaglandin E_1 in the cat. In contrast, the direct vasodilator response following intra-arterial injection of prostaglandin $F_{2\alpha}$ was not only variable from one preparation to another but was much more transient than the overall hypotensive response following systemic administration. It was apparent in these previous studies that the depressor action of prostaglandin $F_{2\alpha}$ is due to a combination of haemodynamic factors other than direct vasodilatation. These factors include both a decrease in cardiac output resulting from pulmonary vascular constriction and an extensive delayed bradycardia which is abolished following vagotomy. The present experiments suggest that the hypotension and bradycardia produced by prostaglandin $F_{2\alpha}$ in the cat is mediated, at least in part, by reflex mechanisms. A moderate but consistent decrease in heart rate associated with the systemic depressor response was observed after atropine but not following vagotomy. This observation supports the contention that afferent as well as efferent vagal mechanisms are involved in this response.

In their original investigation concerning the cardiovascular actions of prostaglandins, Änggård & Bergström (1963) observed that intravenous injection of prostaglandin $F_{2\alpha}$ results in a decrease in the systemic blood pressure of the cat. They concluded that this overall effect might be partially caused by an increase in pulmonary vascular resistance and cardiac slowing, and only to a minor extent to a direct vascular action. In addition, they reported that the bradycardia was delayed in onset (10–30 s) and could be abolished by vagotomy. Several years later, Horton & Main (1965) observed that both prostaglandin E_1 and $F_{2\alpha}$ increased blood flow through skeletal muscle and lowered arterial blood pressure in the cat. In these studies prostaglandin $F_{2\alpha}$ was found to be about one-tenth as active as E_1.

Änggård & Bergström (1963) suggested that the vagal activation induced by prostaglandin $F_{2\alpha}$ might be related to reflex effects elicited from pressure receptors in the lungs or from the right side of the heart. Earlier workers have described reflex hypotension and bradycardia due to increased pulmonary arterial pressure or to increased venous pressure activating receptors in the right heart (Aviado, Li, Kalow, Schmidt, Turnball, Peskin, Hess & Weiss, 1951; Dawes & Comroe, 1954). The present results do not support this hypothesis as injection of prostaglandin $F_{2\alpha}$ into the ascending aorta at the level of the origin of the coronary arteries continued to elicit an extensive bradycardia and hypotension without the concomitant increase in pulmonary arterial pressure. The observation that the reflex effects of prostaglandin $F_{2\alpha}$ were greater after injection into the left side of the heart than after intravenous administration, suggests that right atrial or right ventricular receptors are not primarily responsible for the reflex actions of this agent.

In previous experiments we were unable to demonstrate any direct brainstem action following direct injection of prostaglandin $F_{2\alpha}$ into the left vertebral artery (Koss *et al.*, 1973a). In the present study, doses of prostaglandin $F_{2\alpha}$ producing a moderate vagal activation when injected intravenously, were ineffective when injected into the brachiocephalic artery or into the aorta distal to the origin of the coronary arteries. These results suggest that this agent does not exert a major action on structures distal to the cardiopulmonary region. At these low dosage levels, prostaglandin $F_{2\alpha}$ does not appear to produce cardiovascular effects by acting directly on the carotid bodies,

nodose ganglia or various mid- and forebrain structures. McQueen & Belmonte (1974) have recently reported that prostaglandin $F_{2\alpha}$ has no direct action upon carotid baroreceptors or chemoreceptors in the cat.

It is of interest that brachiocephalic injection results in pulmonary arterial constriction of almost the same magnitude as seen following intravenous administration. On the other hand, the pulmonary vascular response is reduced following injection of the same dose into the left heart or into the descending aorta. These results are consistent with the observation that prostaglandins are rapidly metabolized by enzymes concentrated in the kidney, lungs and spleen (Änggård, 1971) and are not inactivated to any significant degree following passage through the brain (Nakano *et al.*, 1972).

Following the original observations by von Bezold & Hirt in 1867, a large number of cardiovascular reflexes have been shown to be the result of activation of structures or receptors within the heart and lungs. Comprehensive reviews of these varied responses have been presented by Dawes & Comroe (1954) and more recently by Paintal (1973). As mentioned previously, it is unlikely that prostaglandin $F_{2\alpha}$ exerts its primary action in the lungs, either by the increase in vascular resistance or by a direct action on pulmonary chemoreceptors.

In the cat, the aortic bodies received their blood supply, at least in part, via the coronary arteries (Coleridge, Coleridge & Howe, 1967). However, chemical activation of the aortic bodies would be expected to produce the opposite effects of those observed in the present experiments. It has been demonstrated that, in both dogs and cats, chemical activation of the aortic bodies usually results in a rise in blood pressure and heart rate whereas activation of the carotid bodies results in bradycardia and hypotension (Comroe, 1939; Dawes & Comroe, 1954; Comroe &Mortimer, 1964; MacLeod & Scott, 1964; Daly & Ungar, 1966).

As early as 1915, Cramer demonstrated conclusively that small doses of veratrum viride activate vagal afferents and that both reflex bradycardia and reflex peripheral vasodilatation contribute to the overall hypotensive response. Subsequent investigators demonstrated that the reflex decrease in blood pressure and heart rate following injection of small doses of veratridine is due primarily to an action upon receptors in the heart (Dawes, 1947; Aviado, Pontius & Schmidt, 1949). More recent observations indicate that receptors in the cardiopulmonary region exert a continuous restraint on sympathetic outflow by means of afferent vagal fibres (Mancia, Donald & Shepherd, 1973). These studies suggest that a concomitant inhibition of sympathetic outflow may be a frequent result of pronounced afferent vagal activation.

One possible explanation for the action of prostaglandin $F_{2\alpha}$ is that this agent induces a coronary chemoreflex mechanism by virtue of its action on receptors perfused by the coronary circulation or by acting on structures located in the left heart. A similar action is not seen in the dog in that prostaglandin $F_{2\alpha}$ produces an overall pressor response (Nakano & Cole, 1969). 5-Hydroxytryptamine and phenyldiguanide also produce different cardiovascular responses in the dog and cat (Dawes & Comroe, 1954). However, if this mechanism is responsible for the action of prostaglandin $F_{2\alpha}$ it is more selective in that only the cardiac receptors appear to be activated by prostaglandin $F_{2\alpha}$. Both 5-hydroxytryptamine and phenyldiguanide produce a characteristic triad of reflex apnoea, bradycardia and hypotension by acting on many receptors including those in the lungs and nodose ganglia as well as in the heart (Jacobs & Comroe, 1971). It is not known whether larger doses of prostaglandin $F_{2\alpha}$ might also activate these other receptors.

This investigation was supported by grants from the Oklahoma Heart Association and the Tulsa Chapter of the American Heart Association.

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(Received March 11, 1975. Revised October 6, 1975.)