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# Central autonomic effects of prostaglandin $F_{2\alpha}$ on the cardiovascular system of the dog

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## Summary

1. Prostaglandin $F_{2\alpha}$ infused into the vertebral artery of the anaesthetized greyhound in doses which had no effect when given intravenously ((8–64 ng/kg)/min) caused an increase in blood pressure and heart rate.

2. This response was not significantly altered by $\beta$-adrenoceptor blockade with propranolol (10 mg i.v.) or by cervical cord section at $C_{4\text{-}6}$.

3. The tachycardia was abolished and the pressor response greatly reduced by vagotomy or atropine (250 $\mu$g/kg i.v.).

4. The pressor response which remained after vagotomy was abolished by subsequent sympathetic blockade with bethanidine (2–3 mg/kg i.v.) or bretylium (10 mg/kg i.v.).

5. In contrast to the effects of propranolol or cervical cord section bethanidine (4–5 mg/kg i.v.) or bretylium (10 mg/kg i.v.) significantly reduced blood pressure and heart rate responses to intravertebral prostaglandin $F_{2\alpha}$. This result suggests that bethanidine and bretylium have some central actions.

6. It is concluded that the cardiovascular effects of intravertebral infusions of prostaglandin $F_{2\alpha}$ are mediated by the autonomic nervous system and that the preferential pathway is withdrawal of vagal tone to the heart.

## Introduction

The discovery that prostaglandins occur in the brain (Samuelsson, 1964 ; Horton & Main, 1966 ; Holmes & Horton, 1967) and in superfusates of cat cerebral and cerebellar cortex (Coceani & Wolfe, 1965) has led to the suggestion that they may have a fundamental role in nerve physiology, perhaps as neurotransmitters (Horton, 1969).

The possibility of a centrally mediated cardiovascular role for prostaglandin $E_1$ was first suggested by Kaplan, Grega, Sherman & Buckley (1969) and in a previous paper (Lavery, Lowe & Scroop, 1970) we showed that some prostaglandins have cardiovascular effects when infused into the vertebral artery of anaesthetized greyhounds in doses which have no effect when given into the carotid artery or intravenously. Prostaglandin $F_{2\alpha}$ had the most striking effect ; an infusion at 400 ng/min into the vertebral artery caused an increase in blood pressure, tachycardia and increased cardiac output. Peripheral resistance remained essentially unchanged and central venous pressure fell. At least a hundred times this dose had to be given

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to obtain any response to intravenous or intracarotid infusion of $PGF_{2\alpha}$. $PGF_{1\alpha}$ had similar effects, but was only one-tenth as potent, and $PGE_1$ caused tachycardia only.

Because $PGF_{2\alpha}$ produces its central cardiovascular effects at low concentration and has been found in brain homogenates, we have studied the efferent pathways involved in the response to intravertebral infusions of this compound.

## Methods

Greyhounds weighing between 20 and 30 kg were premedicated with morphine (2 mg/kg), anaesthetized with chloralose (120–140 mg/kg) and artificially ventilated. Intravascular pressures (1 mmHg≡1·333 mbar) and heart rate were recorded and drugs were infused into one vertebral artery, the opposite vessel being ligated, exactly as in the previous work (Lavery *et al.*, 1970). For statistical analysis the heart rate and blood pressure responses were regarded as the integral. A line was drawn by eye through control levels 5 min before the infusion was begun and after the recorded response had returned to this level. The area above this line was measured by planimetry.

Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) was prepared as before (Lavery *et al.*, 1970). Other drugs used were atropine sulphate, bethanidine sulphate (Burroughs Wellcome), bretylium tosylate (Burroughs Wellcome), α-chloralose (B.D.H.), isoprenaline hydrochloride (Burroughs Wellcome), morphine sulphate and propranolol (I.C.I.). Doses are expressed in terms of the active bases.

## Results

In all experiments $PGF_{2\alpha}$ was infused into the vertebral artery in doses which had no effect when given intravenously ((8–64 ng/kg)/min). The cardiovascular effects of intravertebral infusion may therefore have been due entirely to an action on structures within the distribution of the vertebral artery. It seemed likely that the site of action was the brain and that the cardiovascular effects were mediated by the autonomic nerves. We have attempted to determine which pathways are used by studying the effects of β-adrenoceptor blockade, vagotomy and cervical cord section on the response.

### *Effects of propranolol*

Propranolol (10 mg intravenously) caused no significant change of blood pressure or heart rate, nor did it alter the response to intravertebral infusion of $PGF_{2\alpha}$ although in all dogs it abolished the response to intravenous injection of isoprenaline (2 μg). Figure 1 illustrates a single experiment and Table 1 summarizes the results in seven dogs. These results suggested that the tachycardia due to intravertebral infusion of $PGF_{2\alpha}$ was not due to activation of sympathetic nerves to the heart and was likely to be due to inhibition of parasympathetic tone. To verify this we studied the effects of cutting the vagi and of atropine.

### *Effects of vagotomy or atropine*

On sectioning the vagi the arterial pressure and heart rate increased, but in all dogs the heart rate was capable of further increase, as shown by the effects of carotid occlusion. After vagotomy, intravertebral $PGF_{2\alpha}$ caused no tachycardia

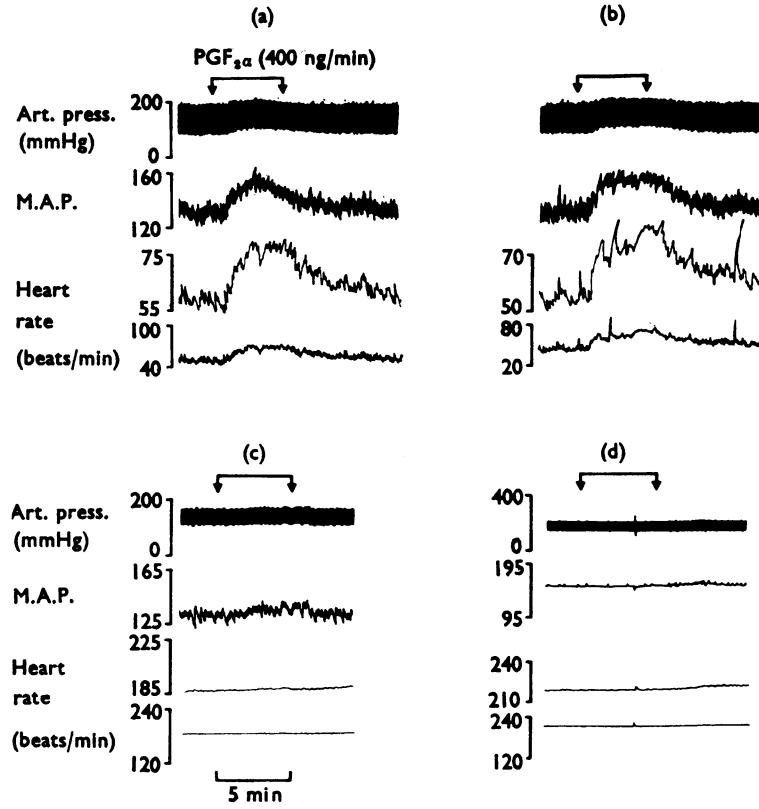


FIG. 1. Effect of infusion of prostaglandin $F_{2\alpha}$ (400 ng/min for 5 min) into the vertebral artery in the chloralose anaesthetized greyhound. Pulsatile arterial pressure (Art. press.), mean arterial pressure (M.A.P.) and heart rate (at two different gain factors) are illustrated. The response in the intact dog (a) is shown and then the sequential effects of (b) propranolol, (c) vagotomy and (d) bethanidine.

TABLE 1. *Effect of propranolol* (10 *mg i.v.*) *on the increase in blood pressure and heart rate during infusions of prostaglandin* $F_{2\alpha}$ (200–1600 *ng/min/for* 5 *min*) *into the vertebral artery of the dog* (*seven experiments*)

| | Integral blood pressure response (mmHg × min) | Integral heart rate response (beats) |
|---|---|---|
| Before propranolol (mean ± S.E.) | 80·63 ± 12·28 | 93·80 ± 14·75 |
| After propranolol (mean ± S.E.) | 94·69 ± 10·46 | 87·77 ± 23·29 |
| Mean difference | +14·06 | −6·03 |
| Significance | Not significant | Not significant |

TABLE 2. *Effect of vagotomy on the increase in blood pressure and heart rate during infusions of prostaglandin* $F_{2\alpha}$ (400–800 *ng/min for* 5 *min*) *into the vertebral artery of the dog* (*five experiments*)

| | Integral blood pressure response (mmHg × min) | Integral heart rate response (beats) |
|---|---|---|
| Before vagotomy (mean ± S.E.) | 127·9 ± 19·92 | 218·6 ± 58·63 |
| After vagotomy (mean ± S.E.) | 11·4 ± 7·6 | 0 ± 0 |
| Mean difference | −116·5 | −218·6 |
| Significance | $P < 0·001$ | $P < 0·001$ |

and produced a much smaller pressor response than before. Figure 1 illustrates an experiment in which after propranolol had failed to alter the response to $PGF_{2\alpha}$ subsequent vagotomy abolished the tachycardia response and greatly reduced the pressor response. Table 2 summarizes results from five experiments in which the vagi were cut without prior administration of propranolol, demonstrating that a small residual pressor effect of $PGF_{2\alpha}$ without tachycardia persists after vagotomy.

To verify that these effects of vagotomy were due to interruption of the efferent rather than afferent pathways we studied the effect of atropine in three dogs. In order to achieve complete and sustained atropinization, 250 $\mu$g/kg were injected intravenously and then a continuous infusion of 100 $\mu$g/min was maintained. The atropine caused a pressor response and tachycardia ; it also abolished the tachycardia

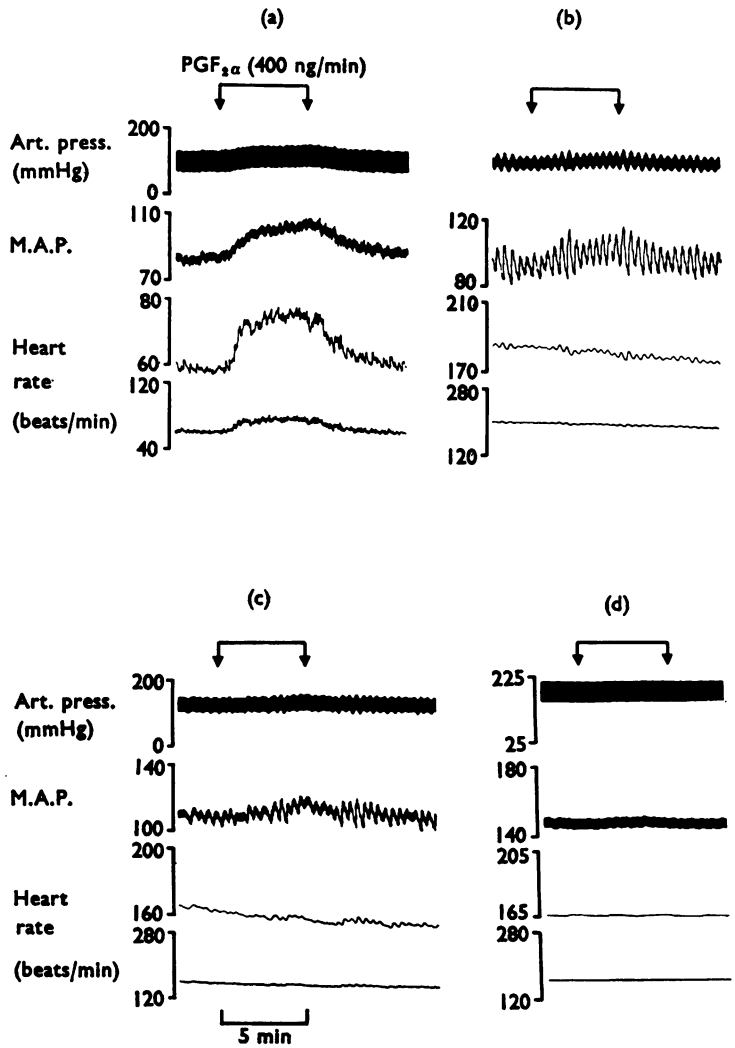


FIG. 2. Effect of infusion of prostaglandin $F_{2\alpha}$ (400 ng/min for 5 min) into the vertebral artery. Pulsatile arterial pressure (Art. press.), mean arterial pressure (M.A.P.) and heart rate (at two different gain factors) are illustrated. The response in the intact dog (a) is shown and then the sequential effects of (b) atropine, (c) vagotomy and (d) bretylium.

response to $PGF_{2\alpha}$ and reduced the pressor response. Figure 2 illustrates a sample experiment also showing that subsequent vagotomy does not significantly modify the response further.

It seemed likely that this residual pressor response was due to activation of adrenergic nerves to the peripheral vessels. To verify this we studied the effect of bethanidine and bretylium on this residual pressor response in those dogs in which it still occurred after vagotomy. In all such animals the response was abolished by bethanidine or bretylium (see Figs. 1 & 2).

The foregoing results indicated that the tachycardia due to intravertebral $PGF_{2\alpha}$ was not due to activation of sympathetic nerves to the heart but to inhibition of vagal tone. Since the pressor response in the intact dog is due entirely to an increase of cardiac output, with no increase of peripheral resistance (Lavery *et al.*, 1970) it seems that the pressor response is also due primarily to inhibition of vagal tone. If this deduction is correct, and if the site of action of $PGF_{2\alpha}$ is in the brain rather than in the spinal cord, then the response to intravertebral $PGF_{2\alpha}$ would persist after section of the cervical cord.

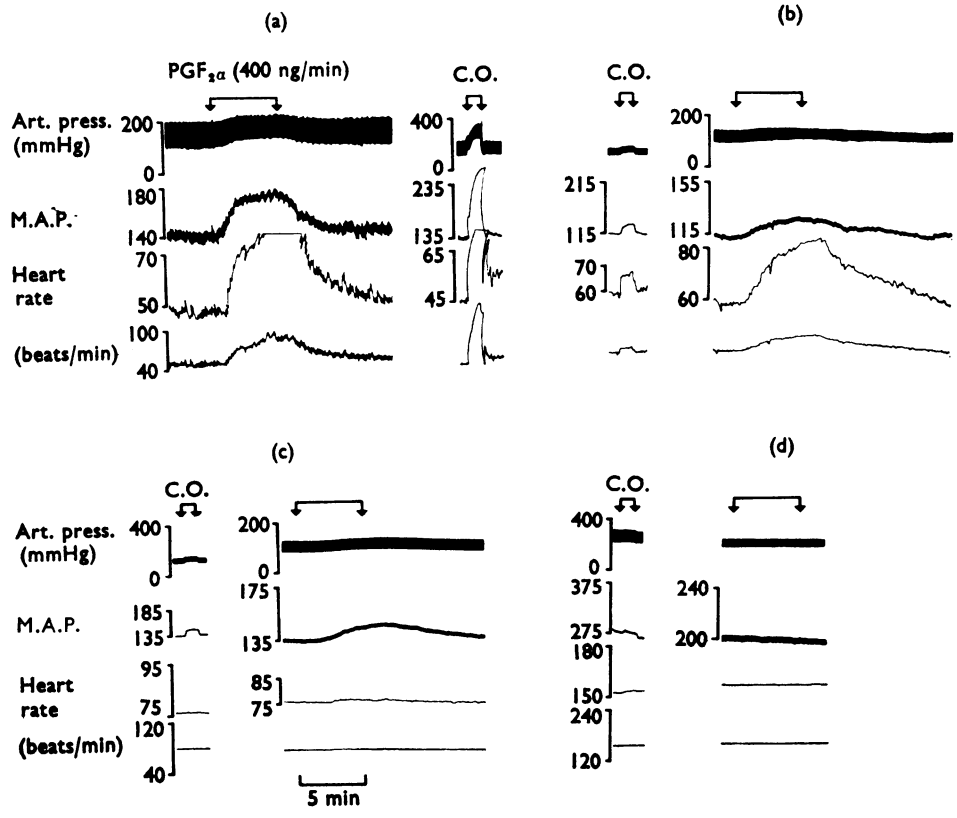


FIG. 3. Effect of infusion of prostaglandin $F_{2\alpha}$ (400 ng/min for 5 min) into the vertebral artery. Pulsatile arterial pressure (Art. press.), mean arterial pressure (M.A.P.) heart rate at two different gains and the effect of bilateral carotid artery occlusion (C.O.) are illustrated. The response in the intact dog (a) is shown and then the sequential effects of (b) cervical cord section at $C_5$ (c) vagotomy and (d) bethanidine. Control intravenous infusions at the same rate had no effect at any stage.

### *Effect of cervical cord section*

In six dogs the cervical cord was transected at $C_{4-5}$ above the level of the sympathetic outflow. This procedure caused a fall of blood pressure and a tachycardia, but immediately afterwards the response to $PGF_{2\alpha}$ was still present, although sometimes reduced. However, in those dogs in which the response was reduced, it gradually increased over the next 2 h and this later response did not differ significantly from that in the normal animal. To verify that the response was still mediated by the vagus nerve, both vagi were subsequently cut in six dogs and the infusion of $PGF_{2\alpha}$ repeated. The tachycardia was abolished but a smaller pressor response remained in four of the six dogs. A single experiment is shown in Fig. 3 and the results of six experiments are summarized in Table 3.

These results confirmed that in the animal with intact vagi the predominant effect of intravertebral $PGF_{2\alpha}$ was to cause inhibition of vagal tone to the heart and that the sympathetic pathway played no part in causing tachycardia, and little part in the pressor response. We therefore thought that sympathetic post ganglionic blockade with bretylium or bethanidine would not significantly affect the response to $PGF_{2\alpha}$.

### *Effect of bethanidine or bretylium*

Contrary to our expectations, bethanidine (4–5 mg/kg intravenously) significantly reduced the blood pressure and heart rate response to intravertebral $PGF_{2\alpha}$ infusions. This dose of bethanidine was effective in producing sympathetic blockade in that the response to carotid occlusion was abolished by subsequent vagotomy. Table 4 summarizes the results in seven dogs treated with bethanidine. Similar results were obtained with bretylium (10 mg/kg intravenously) in four animals. Subsequent vagotomy abolished the remaining blood pressure and heart rate responses in animals treated with bethanidine or bretylium.

TABLE 3. *Effect of cervical cord section at $C_{4-6}$ on the increase in blood pressure and heart rate during infusions of prostaglandin $F_{2\alpha}$ (400–800 ng/min for 5 min) into the vertebral artery of the dog (five experiments)*

| | Integral blood pressure response (mmHg × min) | Integral heart rate response (beats) |
|---|---|---|
| Before cord section (mean ± S.E.) | 110·0 ± 14·88 | 190·0 ± 39·68 |
| After cord section (mean ± S.E.) | 73·80 ± 11·50 | 144·6 ± 39·71 |
| Mean difference | −36·20 | −45·4 |
| Significance | Not significant | Not significant |

TABLE 4. *Effect of bethanidine (4–5 mg/kg i.v.) on the increase in blood pressure and heart rate during vertebral artery infusions of prostaglandin $F_{2\alpha}$ (400–1600 ng/min for 5 min) in the dog (seven experiments)*

| | Integral blood pressure response (mmHg × min) | Integral heart rate response (beats) |
|---|---|---|
| Before bethanidine (mean ± S.E.) | 108·6 ± 14·01 | 111·4 ± 27·89 |
| After bethanidine (mean ± S.E.) | 51·86 ± 12·15 | 21·57 ± 10·12 |
| Mean difference | −56·71 | −89·86 |
| Significance | $P < 0·001$ | $P < 0·02$ |

**Discussion**

The experiments described here show that the cardiovascular effects of intravertebral infusions of $PGF_{2\alpha}$ are mediated by the autonomic nervous system.

The tachycardia is not due to excitation of sympathetic nerves to the heart because it was unaffected by cervical cord section or by propranolol. We find that the dose of propranolol used (10 mg) almost abolishes the tachycardia response to carotid occlusion in vagotomized dogs and is therefore effective in blocking the effects of stimulating cardiac sympathetic nerves. If the tachycardia response to $PGF_{2\alpha}$ is not due to activation of sympathetic nerves to the heart, it must be due to inhibition of vagal tone and this was confirmed by experiments in which changes of parasympathetic tone to the heart were prevented by vagotomy or by atropine. $PGF_{2\alpha}$ then produced no changes in heart rate.

The mechanism of the pressor response is less certain, but might be entirely due to changes of parasympathetic tone to the heart with resulting changes of heart rate and cardiac output. Contrary to previous findings in both cats and dogs we find that abolition of vagal tone by vagotomy or atropine causes a striking and sustained increase of arterial pressure. The major difference in our experiments is that we use morphine—chloralose anaesthesia which does not cause a rise of heart rate and does not depress cardiovascular reflexes to the extent that pentobarbitone does (Shabetai, Fowler & Hurlburt, 1963); there is therefore a normal amount of vagal tone at rest, and vagal section may result in a threefold increase in heart rate. In the sodium pentobarbitone anaesthetized dog, the resting heart rate is usually above 100, there is little vagal tone and vagal section does not cause much pressor response.

Although the tachycardia in response to $PGF_{2\alpha}$ is due entirely, and the pressor response predominantly to inhibition of vagal tone, it is apparent that $PGF_{2\alpha}$ can activate adrenergic nerves because after vagotomy a residual pressor response remained, which was abolished by subsequent administration of bethanidine or bretylium.

An unexpected feature of our results was the finding that in the animal with intact vagi, either bethanidine or bretylium greatly reduced both the tachycardia and the pressor response to $PGF_{2\alpha}$. We conclude that this reduction is not due to a peripheral action of the two drugs, because neither propranolol nor cervical cord section have this effect. The most likely explanation is that both bethanidine and bretylium have some central actions, perhaps interfering with conduction in central adrenergic pathways involved in the response to $PGF_{2\alpha}$. The view that these drugs have central actions is reinforced by other experiments in which we have found that they antagonize the central effects of clonidine (to be published).

The precise site of action of $PGF_{2\alpha}$ in the brain has not been fully defined although it clearly lies within the territory of distribution of the vertebral artery and its main site of action in the central nervous system is above $C_4$. It appears that prostaglandins are unevenly distributed in the central nervous system (Holmes & Horton, 1968) and it is possible that they have a specific function in the area where they are most highly concentrated. It has been suggested that prostaglandins may act as chemical transmitters of nerve impulses. Avanzino, Bradley & Wolstencroft (1966) applied very small amounts ($<10$ pmol) of prostaglandins to brain stem neurones of decerebrate cats and observed selective excitatory or inhibitory actions. There is also substantial evidence that on nerve stimulation, prostaglandins are

released in association with chemical transmitters (Davies, Horton & Witherington, 1967) indicating that prostaglandins may act as modulators of nerve transmission. Thus it is possible that prostaglandin $F_{2\alpha}$ may act as a chemical transmitter or modulator of transmission at cardioregulatory and vasomotor centres in the hind brain.

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