

## CIRCULATORY EFFECTS OF PROSTAGLANDIN ENDOPEROXIDE ANALOGUES STUDIED IN THE DOG DURING LEFT VENTRICULAR BYPASS

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- 1 Intravenous administration of both the 9 $\alpha$ ,11 $\alpha$ -(epoxymethano) and 11 $\alpha$ ,9 $\alpha$ -(epoxymethano) analogues of prostaglandin H<sub>2</sub> (0.25  $\mu$ g/kg) produced a prominent rise in pulmonary arterial pressure and a moderate increase in systemic arterial pressure.
- 2 Direct administration of the endoperoxide analogues (1.25  $\mu$ g/kg) into the bypass reservoir produced a greater rise in systemic arterial pressure and less prominent rise in pulmonary arterial pressure.
- 3 An intravenous dose of prostaglandin F<sub>2a</sub> that was 20 times larger was needed to produce a comparable rise in pulmonary arterial pressure.
- 4 The pulmonary and systemic pressor responses produced by the endoperoxide analogues were due to a direct increase in the vascular resistance.

### Introduction

The incorporation of molecular oxygen into the polyenoic fatty acid arachidonic acid, yields a cascade of compounds possessing great biological activity. Some of the end products of this metabolic pathway are prostaglandins D<sub>2</sub>, E<sub>2</sub>, and F<sub>2a</sub> and the thromboxanes. The initial products of this reaction are prostaglandin endoperoxides (prostaglandins G<sub>2</sub> and H<sub>2</sub>). The naturally occurring endoperoxides are unstable, possess a short half-life (Hamberg, Svensson, Wakabayashi & Samuelsson, 1974) and produce complex systemic arterial pressure responses when administered intravenously in guinea-pigs (Hamberg, Hedqvist, Strandberg, Svensson & Samuelsson, 1975).

Recent studies in our laboratory show that three stable synthetic prostaglandin endoperoxide analogues are systemic pressor agents, potent pulmonary vasoconstrictors and exert a direct positive inotropic effect on the heart (Rose, Kot, Ramwell, Doykos & O'Neill, 1976). The systemic arterial pressure response to these analogues was characterized by a transient fall in pressure followed by a prolonged pressor response which lasted for 5 to 10 minutes. To separate the various components of this systemic vascular response, experiments were performed in dogs on left ventricular bypass so that the systemic responses could be studied independently of cardiac effects.

### Methods

Ten dogs of either sex, ranging in weight from 15 to 22 kg, were anaesthetized with intravenous sodium pentobarbitone (25 to 30 mg/kg). The animals were intubated with an endotracheal tube and ventilated with room air with a Harvard respirator.

A thoracotomy was performed in the fourth left intercostal space. To bypass the left ventricle, all pulmonary venous return was diverted into a reservoir from which it was pumped at a controlled flow rate into a T-tube inserted into the descending thoracic aorta. Additional details regarding the technique of left ventricular bypass have been described previously (Rose, Broida, Hufnagel, Gillespie, Rabile & Freis, 1955). Prior to initiating bypass, heparin (7 to 8 mg/kg) was administered intravenously.

A small branch of the left pulmonary artery and one femoral artery were catheterized with polyethylene catheters for measurement of pressure. One femoral vein was also catheterized for administration of test substances. In some animals central venous pressure was measured.

Two cyclic ether endoperoxide analogues and prostaglandin F<sub>2a</sub> were provided by the Upjohn Company (Bundy, 1975). The synthetic endoperoxides are: (15 S)-hydroxy-9 $\alpha$ ,11 $\alpha$ -(epoxymethano)prosta-5Z,13E-dienoic acid, referred to as 9 $\alpha$ ,11 $\alpha$ -(epoxymethano), and (15 S)-hydroxy-11 $\alpha$ ,9 $\alpha$ -(epoxy-

methano) prosta—5Z,13E-dienoic acid, referred to as 11 $\alpha$ ,9 $\alpha$ -(epoxymethano). They were dissolved in ethanol to provide 1 mg/ml stock solutions which were further diluted with 0.9% w/v NaCl solution (saline) to a final concentration of 20  $\mu$ g/ml.

Prostaglandin F<sub>2a</sub> solutions in ethanol (1 mg/ml) were evaporated to dryness under nitrogen, and the residue was dissolved with saline to a concentration of 100  $\mu$ g/ml.

Test substances were administered as bolus injections intravenously or were directly added to the pump reservoir. For intravenous injections the following dose levels were employed: 9 $\alpha$ ,11 $\alpha$ -(epoxymethano) and 11 $\alpha$ ,9 $\alpha$ -(epoxymethano) 0.25  $\mu$ g/kg, prostaglandin F<sub>2a</sub> 5  $\mu$ g/kg. When test substances were added directly to the reservoir the following dose levels were employed: 9 $\alpha$ ,11 $\alpha$ -(epoxymethano) and 11 $\alpha$ ,9 $\alpha$ -(epoxymethano) 1.25  $\mu$ g/kg, and prostaglandin F<sub>2a</sub> 10  $\mu$ g/kg. Sufficient time was allowed to elapse between administration of test substances to permit pressure levels to return to control values and this was usually 15 minutes.

## Results

### Systemic vascular responses

The changes in systemic arterial pressure produced by administration of the endoperoxide analogues and prostaglandin F<sub>2a</sub> are summarized in Table 1. The same intravenous dose of the endoperoxides (0.25  $\mu$ g/kg) which elicited a prominent rise in pulmonary arterial pressure had only moderate effects on systemic arterial pressure.

Direct administration of the endoperoxide analogues (1.25  $\mu$ g/kg) into the reservoir produced a greater rise in mean systemic arterial pressure than when administered intravenously.

Administration of the endoperoxide analogues by both routes induced a systemic pressor response that was characterized by a gradual and prolonged rise in pressure. This was not preceded by an initial transient fall in pressure nor a terminal depressor response (see Figure 1). No changes in central venous pressure were observed.

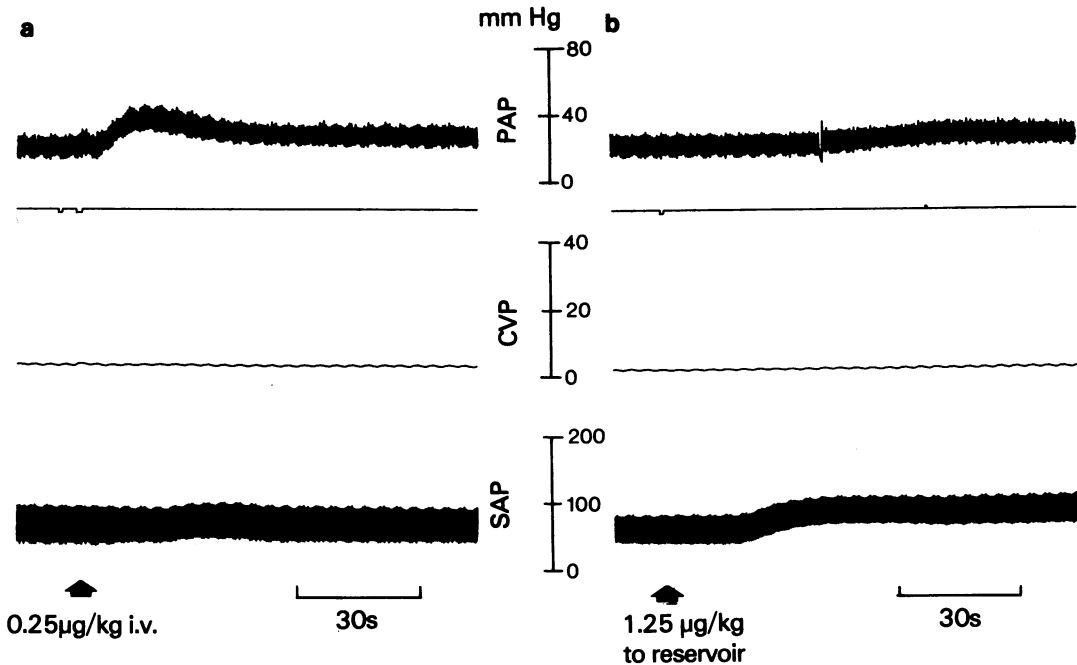
The increase in mean systemic arterial pressure was 17% following administration of 10  $\mu$ g/kg prostaglandin F<sub>2a</sub> into the reservoir. This was comparable to the rise observed when 5  $\mu$ g/kg of prostaglandin F<sub>2a</sub> was administered intravenously.

### Pulmonary vascular response

The pulmonary arterial pressure responses following intravenous administration of the two endoperoxide analogues and prostaglandin F<sub>2a</sub> are summarized in Table 1. During left ventricular bypass, 0.25  $\mu$ g/kg of either analogue produced an equipressor response in the pulmonary circulation. Prostaglandin F<sub>2a</sub> was approximately one-twentieth as potent as the endoperoxide analogues. Figure 1 shows the pulmonary and systemic vascular effects of the 9 $\alpha$ ,11 $\alpha$ -(epoxymethano) analogue in the left ventricular bypass preparation. Following intravenous administration, the onset of the pulmonary pressor action of both endoperoxide analogues was rapid and the duration of the pressor response was generally longer than was observed with prostaglandin F<sub>2a</sub>. The mean percentage increase in pulmonary arterial

**Table 1** Effects of endoperoxide analogues and prostaglandin F<sub>2 $\alpha$</sub>  (PGF<sub>2 $\alpha$</sub> ) on mean systemic arterial pressure and on pulmonary arterial systolic and diastolic pressures in dogs during left ventricular bypass

Compound, route of administration and dose ( $\mu$ g/kg)	Number of experiments	% increase in mean systemic arterial pressure $\pm$ s.e.	Number of experiments	% increase in systolic and diastolic pressure $\pm$ s.e.
9 $\alpha$ ,11 $\alpha$ -(Expoxy-methano) i.v. 0.25	10	7 $\pm$ 6.5	10	51 $\pm$ 7.3 (systolic) 84 $\pm$ 15.3 (diastolic)
Reservoir 1.25	9	25 $\pm$ 6.6	9	19 $\pm$ 4.9 37 $\pm$ 7.6
11 $\alpha$ ,9 $\alpha$ -(Expoxy-methano) i.v. 0.25	12	9 $\pm$ 5.3	11	46 $\pm$ 7.1 91 $\pm$ 14.0
Reservoir 1.25	9	22 $\pm$ 5.6	9	22 $\pm$ 9.9 48 $\pm$ 18.0
PGF <sub>2<math>\alpha</math></sub> i.v. 5	7	18 $\pm$ 4.6	8	58 $\pm$ 11.7 112 $\pm$ 31.2
Reservoir 10	10	17 $\pm$ 3.9	10	11 $\pm$ 7.6 21 $\pm$ 13.8



**Figure 1** Two tracings, recorded in the same dog, show the changes in pulmonary arterial pressure (PAP), central venous pressure (CVP) and systemic arterial pressure (SAP) following (a) intravenous and (b) reservoir administration of the  $9\alpha,11\alpha$ -(epoxymethano) analogue during left ventricular bypass. The arrow at the lower left corner of each tracing indicates the point at which the analogue was administered.

diastolic pressure was nearly double the mean rise in pulmonary arterial systolic pressure.

When comparable doses of the endoperoxide analogues or prostaglandin  $F_{2\alpha}$  were administered directly into the pump reservoir, so that the substances passed through the systemic circulation before reaching the pulmonary circulation, either negligible or no pulmonary vascular effects were observed. This necessitated substantial increases in the dose levels of the endoperoxide analogues as well as prostaglandin  $F_{2\alpha}$  so that levels of pulmonary vascular responses shown in Table 1 could be achieved. The onset of elevation of pulmonary arterial pressure followed the onset of increase in systemic arterial pressure because of the delay in the drug reaching the pulmonary circulation.

## Discussion

Our interest in the cardiovascular actions of the endoperoxides stems from previous studies with their fatty acid precursor arachidonic acid, which consistently produced a systemic depressor response, pulmonary vasoconstriction and a variable effect on myocardial contractile force in dogs (Rose, Johnson,

Ramwell & Kot, 1974; Kot, Johnson, Ramwell & Rose, 1975; Wicks, Rose, Johnson, Ramwell & Kot, 1976). These haemodynamic changes were completely blocked by pretreatment of the animal with aspirin or indomethacin suggesting that arachidonic acid itself is not vasoactive and that one or more compounds generated from arachidonic acid via the cyclo-oxygenase pathway are responsible for the observed haemodynamic changes. Our attention was directed to the endoperoxides since they are the first of the intermediate compounds formed from arachidonic acid and have been shown to be potent vasoactive compounds (Needleman, Minkes & Raz, 1976). The naturally occurring endoperoxides, prostaglandins  $G_2$  and  $H_2$  are highly unstable compounds with a biological half-life of approximately 5 min (Hamberg *et al.*, 1975). They produce a 'triphasic' blood pressure response when administered intravenously in guinea-pigs. Initially, there was a transient fall in systemic arterial pressure, which was followed by a rise in arterial pressure of short duration and finally a prolonged depressor response. Hamberg *et al.* (1975) concluded that the initial decline and subsequent increase in systemic arterial pressure could be explained on the basis of pulmonary and systemic vasoconstriction respectively. The prolonged

reduction of systemic arterial pressure was attributed to prostaglandin  $E_2$ , which was thought to be generated during the degradation of the endoperoxides.

In intact dogs, systemic administration of these stable endoperoxide analogues produced pulmonary and systemic pressor responses and an increase in myocardial contractile force (Rose *et al.*, 1976). These cardiovascular actions were not blocked by pretreatment of the animals with indomethacin. The systemic arterial pressure response to the analogues was characterized by a transient initial fall in blood pressure followed by a gradual moderate increase in pressure. However, unlike prostaglandins  $G_2$  and  $H_2$ , no terminal depressor response was observed with the analogues. The pulmonary arterial vasoconstriction was intense.

Because of the complex nature of the systemic arterial pressure response, the systemic and pulmonary vascular effects of the endoperoxide analogues were studied in the dog during left ventricular bypass. The results show quite clearly that the two analogues are potent pulmonary vasoconstrictor agents, as previously demonstrated (Kadowitz, Spannhake & Hyman, 1976; Rose *et al.*, 1976). This pulmonary pressor response was due to a direct action of the endoperoxides on pulmonary vascular smooth muscle, with both intrapulmonary arteries and veins appearing to participate in the response (McNamara, Gruetter, Hyman & Kadowitz, 1976). The pulmonary pressor activity of the endoperoxide analogues was greater than that of prostaglandin  $F_{2a}$  and the order of potency was approximately 20:1 at the doses used in these studies.

In the bypass preparation, the analogues increased systemic arterial pressure indicating an increase in systemic vascular resistance since blood flow was maintained constant. A transient initial decrease in systemic arterial pressure was not observed in the bypass animals. This finding is consistent with the interpretation that the transient early decrease in systemic arterial pressure observed in the intact circulation is the result of reduced cardiac output. This decrease in cardiac output results from intense pulmonary vasoconstriction temporarily restricting pulmonary venous return to the left side of the heart. Instead of a terminal depressor response, there was a gradual return of systemic arterial pressure to control levels. Since the analogues do not convert to prostaglandin  $E_2$ , Hamberg *et al.* (1975) may be correct in assuming that the terminal depressor response observed with prostaglandins  $G_2$  and  $H_2$  is, indeed, due to prostaglandin  $E_2$  generation.

These studies demonstrate that the haemodynamic changes induced by the endoperoxide analogues are qualitatively different from those produced by arachidonic acid. This suggests two possibilities: (i) the endoperoxide intermediates are not the primary cause of the haemodynamic changes observed with systemic administration of arachidonic acid and (ii) the cardiovascular responses induced by arachidonic acid may represent the combined actions of several compounds generated in the biosynthetic pathway from arachidonic acid to the prostaglandins.

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