Effects of Prostaglandins $F_{2\alpha}$ and E_2 on the Bovine Circulation[1] (36609)

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(Introduced by G. E. Cartwright)

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The cardiovascular effects of the prostaglandins have been extensively studied in recent years. Though species differences exist, Prostaglandin F (PGF) generally acts as a vasoconstrictor on vascular smooth muscle, whereas PGE and PGA act as vasodilators (1, 2). The effects of PGF and PGE upon the bovine circulation are not known. Since a characteristic feature of this species is a high degree of pulmonary vasomotor reactivity under a variety of situations, a study was undertaken to determine the hemodynamic effects of $PGF_{2\alpha}$ and PGE_2. The results of these experiments form the basis for this report.

Methods. Studies were carried out in 18 Hereford normal calves (av wt 103 kg) obtained randomly at auction. Each calf was studied lying on its side without premedication or general anesthesia. The external jugular vein, common carotid artery, and a branch of the femoral artery and vein were surgically exposed under local lidocaine anesthesia. A No. 8 Cournand catheter was introduced in to the external jugular vein and under fluoroscopic guidance was advanced to the pulmonary artery (PA). Another No. 8 Cournand catheter was introduced into the common carotid artery and advanced to the left ventricle (LV). A Teflon cannula (18 gauge), 15 cm in length, was inserted into a branch of the femoral artery (FA), and advanced proximally. These catheters and cannulas were connected to P23Db pressure transducers.

Following placement of catheters each animal was given heparin (200 mg) intravenously to prevent formation of blood clots in catheters and cannula. Cardiac output (CO) was measured by the dye-dilution technique. Indocyanine green dye (5.0–7.5 mg) was injected into the PA and sampled from the FA through a densitometer (Gilson Medical Electronics, Middleton, WI) using a constant rate withdrawal pump (Harvard Apparatus Co., Millis, MA). Pressures, the electrocardiogram, and the dye curves were recorded on an oscillographic recorder (Minneapolis Honeywell, Denver, CO). Analysis of arterial blood for pH, CO_2 tension, and O_2 tension was carried out using the Astrup apparatus.

Cardiac output, PA, LV and FA pressures were measured during a control period with the animal breathing spontaneously. A 0.5–5 ml aliquot of a solution containing either $PGF_{2\alpha}$ (10 mg diluted in 0.1 ml ethyl acohol and 100 ml normal saline) or PGE_2 (10 mg diluted in 0.1 ml ethyl alcohol and 100 ml normal saline) was injected into the femoral vein while PA, FA, or LV pressures were being recorded continuously. Average dose per injection was 2.1 μg/kg for $PGF_{2\alpha}$ and 1.9 μg/kg for PGE_2. Cardiac output determination was carried out and arterial blood samples obtained for gas analysis at peak response to the PG. In 10 calves comparable doses of $PGF_{2\alpha}$ and PGE_2 were injected into the central aorta. Pressure and flow measurements were made as before.

Results. The results of a typical experiment are shown in Fig. 1A and B. Injection of 100 μg $PGF_{2\alpha}$ into the PA resulted in an increase in PA pressure and a fall in CO with either no change or a transient decrease in FA pressure. Injection of 100 μg PGE_2 into the PA resulted in a fall in FA pressure with

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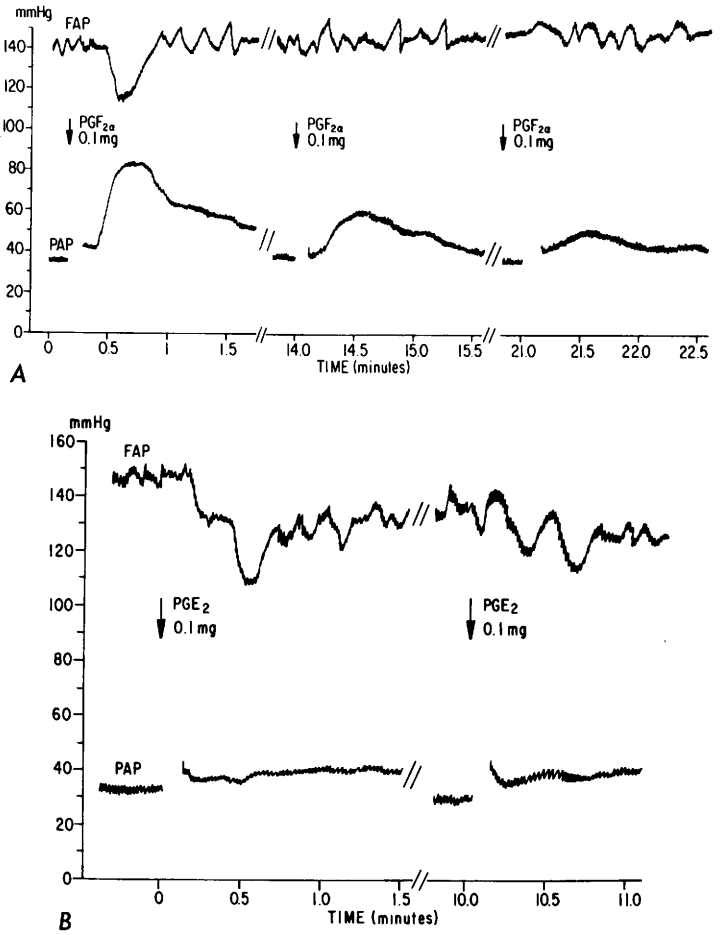

FIG. 1A. Typical response to sequential injections of 0.1 mg prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) into the pulmonary artery. PAP = pulmonary artery pressure. FAP = femoral artery pressure. (B) Typical response to sequential injections of 0.1 mg prostaglandin E_2 (PGE_2) into the pulmonary artery.

no change in CO and either no change or slight increase in PA pressure.

Hemodynamic and blood gas data representing the effects of $PGF_{2\alpha}$ in 27 separate experiments on 18 calves and the effects of PGE_2 in 29 separate experiments on 17 calves are summarized in Table I. Injection of $PGF_{2\alpha}$ into the PA resulted in a significant increase in PA pressure and fall in CO whereas FA pressure, LV end diastolic pressure, heart rate (HR), blood gases and pH were not significantly altered. Average values for onset, peak, and duration of response were 23, 75 and 344 sec, respectively. Injection of PGE_2 into the PA resulted in a significant decrease in FA pressure, increase in HR and a small but significant increase in PA pressure, whereas LV end diastolic pressure CO, blood gases and pH were not significantly altered. Average values for onset, peak and duration of response were 12, 46, and 396 sec, respectively.

The effect of each injection of $PGF_{2\alpha}$ on the PA pressure and of each injection of PGE_2 on the FA pressure is shown in Fig. 2A and B. PA pressure increased significantly (5 mm Hg or greater) in 16 of 29 calves given $PGF_{2\alpha}$ where FA pressure fell by at least 5 mm Hg or more in all but 1 of 27 calves given PGE_2.

In 9 calves $PGF_{2\alpha}$ and PGE_2 (dose comparable to the PA injections) were injected

TABLE I. Summary of Mean ($\bar{x}$) Hemodynamic and Blood Gas Data ± 1 Standard Error (SE) During the Control Period and at the Peak Response to Either Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) or E_2 (PGE_2).[a]

	Control			Peak			
	n	$\bar{x}$	SE	n	$\bar{x}$	SE	p
			PGE_2				
PAP	27	26	1.5	27	28	2.3	<.05
FAP	27	138	2.9	27	116	3.0	<.01
LVedp	12	7	1.5	12	6	1.8	NS
HR	25	84	4.2	25	98	5.7	<.01
CO	14	104	7.6	14	105	7.4	NS
P_{O_2}	10	58	2.8	9	57	2.9	NS
P_{CO_2}	9	37	1.8	8	38	2.7	NS
pH	9	7.36	0.02	8	7.37	0.01	NS
			$PGF_{2\alpha}$				
PAP	29	26	1.5	29	37	3.5	<.01
FAP	29	139	2.2	29	140	3.0	NS
LVedp	13	8	0.9	13	8	0.9	NS
HR	28	79	3.1	28	80	2.7	NS
CO	21	120	7.5	21	108	6.3	<.01
P_{O_2}	14	61	2.5	14	58	2.4	NS
P_{CO_2}	13	36	1.5	13	35	1.4	NS
pH	13	7.36	0.01	13	7.38	0.01	NS

[a] PAP = pulmonary artery pressure (mm Hg); FAP = femoral artery pressure (mm Hg); LVedp = left ventricular end diastolic pressure (mm Hg); HR = heart rate; CO = cardiac output (liters/min/kg); $\bar{P}_{O_2}$ = partial pressure of oxygen (mm Hg); P_{CO_2} = partial pressure of carbon dioxide (mm Hg); n = number of observations; NS = not significant.

into the ascending aorta. The hemodynamic response to PGF_2 was similar to that following PA injections. However, PGE_2, in addition to inducing a fall in FA pressure evoked a small but signficant rise in PA pressure from a mean of 18 to 24 mm Hg ($p < .01$). There was no corresponding change in LV end diastolic pressure or CO.

In those calves in which several successive injections of $PGF_{2\alpha}$ or PGE_2 were made tachyphylaxis was observed (Fig. 1).

Discussion. The results of these studies indicate that in the bovine $PGF_{2\alpha}$ may cause significant pulmonary hypertension with little or no effect on the systemic circulation. These data are in accord with those of other studies in which $PGF_{2\alpha}$ has been shown to produce pulmonary hypertension in dogs and cats (2, 3). Pulmonary hypertension in the bovine following the administration of PGF_2 appears to result from active pulmonary vasoconstriction rather than passive distension of vessels in that CO falls and LA pressure remains constant. Hypoxia and/or acidosis do not seem to be involved in this response since P_{O_2}, P_{CO_2} and pH remained normal during the period of pulmonary hypertension. The mechanism of the pulmonary vasoconstriction is unknown.

PGE_2 produced a fall in systemic arterial pressure when given into the PA. This effect is consistent with that observed by others in different species (1, 2, 4–6), and probably results from arteriolar dilatation since CO was not affected. The mechanism whereby PGE_2 mediates this effect is unknown. The slight increase in PA pressure in some animals in the absence of an increase in CO suggests pulmonary vasoconstriction as well. Increased venous return to the heart with a corresponding increase in CO and PAP has been observed in the dog (7, 8). While our

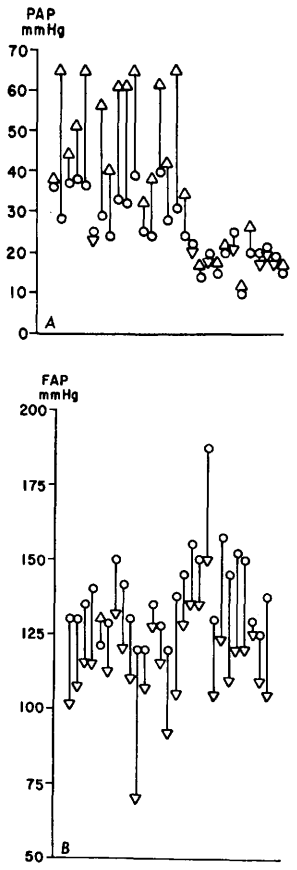

FIG. 2A. Individual effect of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), average dose 2.1 μg/kg, on pulmonary artery pressure (PAP). (○) Control PAP; (△) PAP at peak response to $PGF_{2\alpha}$. (B) Individual effect of prostaglandin E_2 (PGE_2), average dose 1.9 μg/kg, on femoral artery pressure (FAP). (○) Control FAP; (△) FAP at peak response to PGE_2.

data do not indicate a change in CO after PGE_2, the effect may have been transient and not detectable by the dye method. Increased LV diastolic pressure was not observed.

It should be emphasized that the foregoing analysis as it relates to vascular resistance is based upon the assumption that CO was accurately estimated during the hemodynamic changes induced by the prostaglandins. Valid determination of CO by the dye dilution method requires steady state conditions. Insofar as possible this requirement was met. However, it is obvious that changes in CO during transient pressure changes may not be accounted for by a method that takes 15–30 sec to perform. Thus it is quite possible that changes in vascular resistance other than those indicated by the available data may have occurred.

Significant degradation of $PGF_{2\alpha}$ and PGE_2 by the lungs did not appear to occur in our preparation in that the pulmonary vasomotor response to $PGF_{2\alpha}$ and the systemic response to PGE_2 were indistinguishable following PA or aortic root injections.

It is significant that 9 of 29 calves failed to develop pulmonary hypertension when given $PGF_{2\alpha}$. This is consistent with earlier observations in the bovine of a propensity for increased pulmonary vasomotor reactivity in some, but not all calves (9). The frequency and etiology of this trait is not known. An alternate possibility to explain different responses from one calf to the next is that of variability in the potency of $PGF_{2\alpha}$. While 2 different lots of $PGF_{2\alpha}$ were used each elicited a pulmonary pressor response in some calves. Further, this variability in vasomotor reactivity apparently does not apply to peripheral vessels since systemic vasomotor tone was uniformly affected by PGE in all but one calf.

Thus it would appear from these data that the effects of $PGF_{2\alpha}$ and PGE_2 in the bovine conform to those observed in other species. The mechanisms whereby these vasomotor changes occur, however, are unknown.

Summary. The effects of $PGF_{2\alpha}$ and PGE_2 on the pulmonary and systemic circulations were studied in unanesthetized calves. $PGF_{2\alpha}$, average dose 2.1 μg/kg, injected into the pulmonary artery resulted in a significant increase in PA pressure and fall in CO whereas FA pressure, LV end diastolic pressure, HR, blood gases and pH were not significantly altered. PGE_2, average dose 1.9 μg/kg, injected into the pulmonary artery resulted in a significant decrease in FA pressure, increase in HR and a small but significant increase in PA pressure whereas LV end diastolic pressure, CO, blood gases and pH were not significantly altered. Thus, this study indicates that in the bovine $PGF_{2\alpha}$ causes pulmonary vasoconstriction and PGE_2 causes systemic vasodilatation.

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