PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 156, 393-395 (1977)

Cardiovascular Responses to PGD_2 in the Dog[1] (39943)

ALLAN D. ANGERIO, PETER W. RAMWELL, PETER A. KOT,[2] AND JOHN C. ROSE

Department of Physiology and Biophysics, Georgetown University Medical Center, Washington, D.C. 20007

The prostaglandins and their precursor fatty acids and intermediate endoperoxides exhibit a wide variety of cardiovascular effects. In the dog, the bisenoic prostaglandin precursor arachidonic acid (AA) has a profound depressor effect which can be completely blocked by pretreatment with aspirin or indomethacin (1). In the isolated canine lung lobe (2) and isolated hind limb (3) AA is directly vasoconstrictor. Myocardial contractile force in the dog is not directly affected by AA (4). On the other hand, prostaglandin E_2 (PGE_2) has a depressor effect and a direct positive inotropic effect in the dog (4). Prostaglandin D_2 (PGD_2) is another depressor product of AA metabolism, recently available in pure form. The purpose of this study was to compare the effects of PGD_2 and PGE_2 on systemic arterial blood pressure and myocardial contractile force in the intact dog and during left ventricular bypass.

Materials and methods. Mongrel dogs of either sex were anesthetized with sodium pentobarbital (30 mg/kg), intubated, and maintained on intermittent positive-pressure respiration with a Harvard respirator. A left thoracotomy was performed. In eight dogs the common carotid arteries were exposed bilaterally, and identified with loose ligatures for use in testing the efficacy of ganglionic blockade. A Walton-Brodie strain-gauge arch was sutured to the right ventricular wall for measurement of myocardial contractile force. In eight additional dogs, a small catheter was inserted into a branch of the left pulmonary artery for direct recording of pulmonary arterial pressure. In each dog, a femoral artery and vein were catheterized for direct measurement of systemic arterial pressure and for administration of test substances directly into the inferior vena cava.

PGD_2 and PGE_2 were dissolved in ethanol to provide 1 mg/ml solutions. These were diluted in saline to 20 μg/ml. Hexamethonium chloride (Schwarz/Mann) was prepared in aqueous solution in a concentration of 50 mg/ml.

Following observation of the initial cardiovascular responses to each of the prostaglandins, ganglionic blockade was induced with hexamethonium (2 mg/kg) in eight dogs and the test doses were repeated. Ganglionic blockade was tested by bilateral carotid artery occlusion for 30 sec to 1 min. Lack of blood pressure or heart rate response was taken as evidence of effective blockade.

To establish that effects on myocardial contractile force were not due to changes in pre- or afterload, the cardiovascular responses to the prostaglandins were studied in five dogs during bypass of the left ventricle, using a technique previously described (5). All pulmonary venous blood was diverted into a reservoir from which it was pumped into the descending thoracic aorta at steady controlled flow rates with an extracorporeal pump. Myocardial contractile force was measured simultaneously by suturing a Walton-Brodie strain-gauge arch to the left ventricular wall.

Results. Systemic arterial pressure. In animals with an intact circulation, administration of 5 μg/kg of PGD_2 intravenously decreased the mean systolic pressure 23.1 $\pm$ 4.7% (SE) and the mean diastolic pressure 25.7 $\pm$ 4.3%. The systemic depressor effect is illustrated in Fig. 1. Following ganglionic blockade the depressor response persisted,

[1] This work was supported by a Grant-in-Aid from the American Heart Association, Nation's Capital Affiliate.

[2] Address reprint requests to Dr. Peter A. Kot, Department of Physiology and Biophysics, Georgetown University Medical Center, 3900 Reservoir Road, N.W., Washington, D. C. 20007.

ISSN 0037-9727

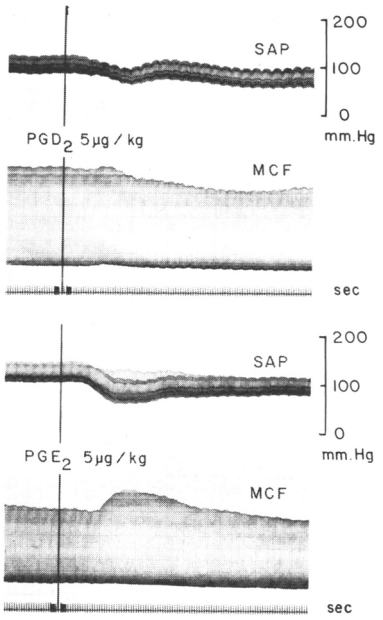

FIG. 1. These are traces of the effect of PGD_2 and PGE_2 on systemic arterial pressure (SAP) and myocardial contractile force (MCF) in the same dog. The point of intravenous administration of PGD_2 and PGE_2 is indicated by the dark vertical lines.

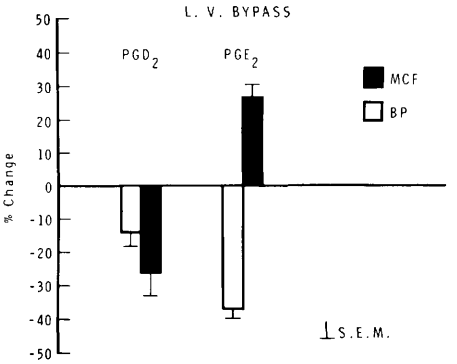

FIG. 2. This summarizes the effects of PGD_2 (four dogs) and PGE_2 (five dogs) on systemic arterial pressure (BP) and myocardial contractile force (MCF) during left ventricular bypass.

the mean systolic pressure decreasing 23.1 ± 2.8% and the mean diastolic pressure decreasing 24.5 ± 3.5%.

Pulmonary arterial (PA) pressure. Administration of 5 μg/kg of PGD_2 produced a 70.5 ± 12.2% rise in mean systolic pressure and a 115.4 ± 12.8% rise in mean diastolic pressure.

Myocardial contractile force (MCF). Before blockade all dogs injected with 5 μg/kg of PGD_2 exhibited a decrease in MCF averaging 22.0 ± 2.0% (Fig. 1). After ganglionic blockade the decrease in MCF was 28.0 ± 8.0%. In one dog there was an increase in MCF.

Left ventricular bypass. In four dogs the negative inotropic response to PGD_2 persisted, decreasing the MCF 26.3 ± 7.3%. In one dog there was an increase in MCF. In all instances PGD_2 produced a depressor response averaging 14.4 ± 3.8% (Fig. 2).

Comparative studies with PGE_2. In intact dogs PGE_2 decreased both the mean systolic (S) and diastolic (D) pressures before (S = −27.4 ± 2.8%; D = −24.6 ± 3.6%) as well as after ganglionic blockade (S = −18.7 ± 5.7%; D = −27.7 ± 6.0%) and its direct positive inotropic effect (Fig. 1) persisted after ganglionic blockade. In dogs on a left ventricular bypass circuit, PGE_2 increased MCF 26.5 ± 4.9% (Fig. 2).

Discussion. The hemodynamic action of PGD_2 appears to be species specific. Jones reported that PGD_2 in the sheep is a highly active pressor agent (6). Fletcher and Ramwell demonstrated in the baboon that PGD_2 is vasoactive and has a direct positive inotropic effect on the heart (7). Wasserman *et al.* have recently demonstrated that PGD_2 is depressor in the dog but that its systemic hypotensive action is less potent than that of PGE_2. PGD_2 also produced an increase in pulmonary arterial pressure and an increase in left ventricular *dp/dt*, which they suggested was reflexly mediated consequent to the decreased systemic arterial pressure (8). Our findings also indicate that PGD_2 has a systemic vasodepressor action. The bypass procedure demonstrates that the depressor effect of PGD_2 is exerted through peripheral vasodilatation.

Our findings indicate that, unlike the endoperoxide intermediates and other prostanoate products of arachidonic acid metabolism, PGD_2 has a negative inotropic effect on the heart. This negative inotropic effect was not modified by ganglionic blockade, indicating that autonomic reflexes are not involved. Changes in pre- or afterload were also considered as possible explanations for

the decrease in MCF. The left ventricular bypass experiments, in which ventricular volume remained constant, were designed to eliminate changes in pre- and afterload. In four dogs the direct negative inotropic effect persisted. In one dog there was an increase in MCF. These observations indicate that the negative inotropic effect of PGD_2 is a direct effect on the myocardium.

Summary. The cardiac and peripheral vascular effects of PGD_2 and PGE_2 were investigated in dogs with an intact circulation and during left ventricular bypass. PGE_2 had a positive inotropic effect, whereas PGD_2 produced a negative inotropic effect on the heart that was independent of reflex effects or changes in ventricular preload or afterload. Both PGE_2 and PGD_2 produced a systemic depressor response which was due to the direct peripheral vasodilating action of these compounds.

1. Rose, J. C., Johnson, M., Ramwell, P., and Kot, P. A., Proc. Soc. Exp. Biol. Med. **147,** 652 (1974).
2. Wicks, T. C., Rose, J. C., Johnson, M., Ramwell, P., and Kot, P. A., Circ. Res. **38,** 167 (1976).
3. Fitzpatrick, T. M., Rose, J. C., Kot, P. A., Johnson, M., and Ramwell, P. W., Fed. Proc. **34,** 353 (1975).
4. Kot, P. A., Johnson, M., Ramwell, P. W., and Rose, J. C., Proc. Soc. Exp. Biol. Med. **149,** 953 (1975).
5. Rose, J. C., Broida, H. P., and Hufnagel, C. A., J. Appl. Physiol. **7,** 580 (1955).
6. Jones, R. L., Brit. J. Pharmacol. **53,** 464P (1975).
7. Fletcher, J. R., and Ramwell, P. W., Clin. Res. **25,** 270A (1977).
8. Wasserman, M. A., DuCharme, D. W., Griffin, R. L., DeGraff, G. L., and Robinson, F. G., Prostaglandins **13,** 255 (1977).

Received May 23, 1977. P.S.E.B.M. 1977, Vol. 156.