SUMMARY Arachidonic acid (AA) produces characteristic hemodynamic changes in the canine circulation. These responses are blocked by prostaglandin (PG) synthetase inhibitors, indicating that AA and its nonprostanoic metabolites are not vasoactive. The hemodynamic effects of the cyclic endoperoxides, thromboxanes, and PGD₂, PGE₂, and PGF₁α, differ from those produced by AA. PGI₂, a newly identified product of AA, is reported to relax arterial strips. However, its cardiac and systemic effects are unknown. In 12 open-chest, anesthetized dogs, PGI₂ (0.25–5.0 μg/kg) produced a dose-related decrease in systemic arterial pressure (BP) and myocardial contractile force (MCF). In five left ventricular bypass preparations, PGI₂ produced only a slight decrease in MCF at all doses, whereas the BP decreases were parallel to those in the intact preparation. AA, PGD₂, PGE₂, and PGI₂ were administered in random order by bolus intravenous injections in approximately equidelpressor doses to intact dogs. BP fell with each agent (AA, 300 μg/kg, -25%; PGD₂, 5 μg/kg, -26%; PGE₂, 5 μg/kg, -26% PGI₂, 0.5 μg/kg, -26%). The vasodepressor action of PGI₂ was approximately 10 times greater than that of PGD₂ and PGE₂. Pulmonary arterial pressure (PAP) rose significantly with PGD₂ and PGE₂ (AA, -1%; PGD₂, +66%; PGE₂, +20%; PGI₂, -1%). Only PGE₂ had a significant effect on MCF (AA, +7%; PGI₂, +5%; PGE₂, +20%; PGI₂, -0.3%). At this dose, PGI₂ resembles AA in that it has little effect on either PAP or MCF. Of all known AA metabolites the response to PGI₂ most closely resembles that of exogenous AA in the dog.

Methods

Seventeen mongrel dogs of either sex weighing 14–20 kg were anesthetized with sodium pentobarbital, 30 mg/kg, iv, intubated with a cuffed endotracheal tube, and ventilated with ambient air by a positive pressure respirator. Airway pressure (AP), which is an index of airway resistance, was measured via a needle inserted into the endotracheal tube and connected to a strain gauge. The right femoral artery and vein were catheterized to record systemic arterial pressure (BP) and for intravenous administration of test substances, respectively. A thoracotomy was performed at the 4th left intercostal space. An indwelling catheter was inserted into a branch of the left pulmonary artery and attached to a strain gauge to measure PAF. In the intact dogs, a Walton-Brodie strain gauge arch was sutured to the right ventricular wall for measurement of MCF.

In the left ventricular bypass preparation, 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. The strain gauge arch was sutured to the left ventricular wall in this preparation. Additional details regarding the left ventricular bypass have been described previously.8 Before the bypass was initiated, heparin (8 mg/kg) was administered intravenously.

The sodium salt of arachidonic acid (5,8,11,14-eicosatetraenoic acid, >99% pure from porcine liver; Sigma and NuChek) was prepared by dissolving in sodium carbonate (100 mM) during constant stirring under nitrogen, in the absence of light. PGE₂ and PGD₂ were generously provided by the Upjohn Co. Solutions of each prostaglandin in ethanol (1 mg/ml) were evaporated to dryness under nitrogen. The residues were dissolved in normal saline to a final concentration of 100 μg/ml. PGI₂, 9-deoxy-6,9α-epoxyΔ²-PGF₁α, was synthesized as previously indicated.7 Samples were prepared in Tris buffer (pH 9) and then diluted to 100 μg/ml before use; 15-
hydroperoxy arachidonic acid was prepared by the method of Hamberg and Samuelsson. It was obtained as an oil which was suspended in phosphate buffer to 30 mg/ml with a sonicator. Hexamethonium (2 mg/kg), a ganglionic blocking agent, was administered to one dog.

Prostaglandins were administered in random order by intravenous bolus injection (0.35-1.0 ml). Before administration of each test substance, AP, BP, MCF, and PAP were allowed to return to control values.

Results

In 12 dogs with an intact circulation, the typical cardiovascular responses to PGI₂ (2 μg/kg) were characterized by a significant drop in both systolic and diastolic BP and by little or no change in either AP, PAP, or MCF (Fig. 1). Varied doses of PGI₂, (0.25-5.0 μg/kg) were administered. The changes in the PAP responses were variable; mean percentage change remained close to the control values at all doses employed. Mean variations in heart rate (-1.3 to +4.0%) were negligible during the maximal vasodepressor responses at all dose levels of PGI₂. As shown in Figure 2, there was a dose-dependent decrease in both MCF and BP. MCF was slightly elevated at the lower doses and significantly decreased at the upper doses. Administration of Tris buffer vehicle in the same volumes produced no change in any of the recorded parameters.

In five ventricular bypass preparations, PGI₂ (0.5, 2.0 and 5.0 μg/kg) produced a slight but consistent decrease in MCF. In contrast, one dog developed an increased MCF at all dose levels; after ganglionic blockage with hexamethonium, similar reductions in MCF were noted. Although less pronounced, the changes in BP observed in the bypass preparation were parallel to the response in the intact dog (Fig. 2). There were no changes in PAP or AP in this dose range.

The effects of equidepressor doses of AA (300 μg/kg), PGE₂ (5 μg/kg), and PGD₂ (5 μg/kg) were compared to PGI₂ (0.5 μg/kg). The results of this comparison are presented in Table 1. PGD₂ produced the most significant increase in PAP, followed by PGE₂, whereas AA and PGI₂ induced little change. Only PGE₂ induced a significant increase in MCF. The onset of AA response was more delayed when compared to PGI₂ and PGE₂. The durations of action of AA and PGI₂ were comparable. However, the duration of action of PGE₂ was shorter and that of PGD₂ was substantially longer than that of AA or PGI₂ (Table 1).

In three dogs, the administration of 15-hydroperoxy AA (300 μg/kg) had no inhibitory effect on the systemic hypotensive response to an immediate administration of AA (300 μg/kg).

Discussion

The systemic hypotensive response produced by AA was reported as early as 1959 by Jaques, yet the mechanisms and site of action have not been identified. Inhibition of the vascular response to AA by nonsteroidal antiinflammatory drugs shows that AA itself or the products of the nonprostanoate pathways have little cardiovascular activity. Consequently, attention has been directed to the prostanoic products of AA metabolism to explain this hypotensive response.

Endoperoxide intermediates, PGG₂ and PGH₂, known to be contractors of vascular smooth muscle strips, produce triphasic alterations in BP when administered intravenously to the guinea pig. The terminal hypotensive phase has been attributed to a potent vasodepressor metabolite of these endoperoxides. Thromboxane A₂, a major component of rabbit aorta-contracting substance and a product of endoperoxide metabolism, contracts all isolated blood vessel preparations. Similarly, PGF₅ulant administered intravenously produces a hypertensive response. The known prostanoic metabolites of AA that consistently produce a systemic hypotensive response in the dog are PGD₂ and PGE₂. However, a comparison

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**Figure 1** Effects of prostacyclin (PGI₂, 2 μg/kg) on airway pressure (AP), pulmonary arterial pressure (PAP), systemic arterial pressure (BP), and myocardial contractile force (MCF) in the intact dog. Arrow indicates point of intravenous injection.

**Figure 2** Percentage change in myocardial contractile force (MCF) and systemic arterial pressure (BP) as a function of the log dose of PGI₂. Solid lines represent results in the intact dog; dashed lines represent results in the left ventricular bypass preparation; vertical lines show SE.
of the cardiovascular responses to equi depressor doses of AA, PGD₂, and PGE₂ has demonstrated significant differences in their modes of action. PGE₂, unlike AA, consistently produced a direct increase in MCF. Moreover, PGD₂ and PGE₂ increased PAP and AA produced only a variable pulmonary response.

PGE₁ is a newly discovered substance formed by the endothelial microsomal enzymes from the endoperoxide intermediate (s) that induces relaxation of arterial muscle strips and inhibition of platelet aggregation. Moreover, 6-keto PGF₆, is the primary product of PGI₂ metabolites and has been identified as the principal metabolite when coronary arteries are incubated with AA. In the study described here, the vasodepressor action of PGI₂ was approximately 10 times greater than that of PGE₂ and PGD₂. The time to onset of action of PGI₂ was similar to that of PGE₂, and probably represents the transit time from point of injection to the site of action in the systemic arterioles, whereas the delayed onset of action of AA suggests a delay for the enzymatic conversion to a vasoactive product(s).

PGI₂ resembles AA in that it does not increase PAP, as does PGE₂ and PGD₂. Furthermore, at lower doses of PGI₂ there was no apparent effect on MCF, unlike the positive inotropic effect of PGE₂.

The decreased MCF observed at higher doses of PGI₂ could be related to alterations in preload or afterload, or to a negative inotropic effect. In the left ventricular bypass preparation, PGI₂ produced only a slight decrease in MCF that was not dose dependent. Therefore, MCF changes in the intact dog must be due at least in part to variations in preload or afterload.

Inhibitors of PGI₂ synthetase would be useful to clarify this point further: 15-hydroperoxy AA, administered in a dose that inhibits the production of PGI₂ in vitro, produced no inhibition in this in vivo preparation. However, the presence of glutathione peroxidase, as suggested by Bunting et al., may reduce the hydroperoxide to a less potent inhibitor of PGI₂ synthetase. This could explain the lack of inhibition in this preparation.

These data suggest that the response to exogenous AA is probably due to a combination of vasoactive products; however, of all known AA metabolites, PGI₂ may be the one mainly responsible for this systemic hypotension.

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