Cardiovascular Responses to PGI₂ (Prostacyclin) in the Dog

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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, PGI₂, PGE₂, and PGI₁ were administered in random order by bolus intravenous injections in approximately equidepressor doses to intact dogs. BP fell with each agent (AA, 300 µg/kg, -25%; PGD₂, 5 µg/kg, -26%; PGE₂, 5 µg/kg, -26%; PGI₁, 0.5 µg/kg, -26%). The vasodepressor action of PGI₁ 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%; PGI₁, -1%). Only PGE₂ had a significant effect on MCF (AA, +7%; PGD₂, +5%; PGE₂, +20%; PGI₁, -0.3%). At this dose, PGI₁ resembles AA in that it has little effect on either PAP or MCF. Of all known AA metabolites the response to PGI₁ most closely resembles that of exogenous AA in the dog.

ARACHIDONIC ACID (AA) produces a characteristic hypotensive response in several species.¹ The ability to block this response with prostaglandin (PG) synthetase inhibitors indicates that one or more of the vasoactive products of AA metabolism are responsible for this systemic hypotensive response, rather than AA itself. Studies of cardiac and hemodynamic responses to exogenous PGE₂, PGF₂α,²,³ and PGD₂,⁴,⁵ all of which are derived from the prostaglandin endoperoxides, PGG₂, and PGH₂, indicate that still other AA metabolites probably are involved in these responses. For example, prostacyclin (PGI₂, formerly known as PGX), a recently isolated product of AA metabolism, has been reported to relax arterial muscle strips⁶ and thus may be a depressor product like PGE₂ and PGD₂. Biosynthesis does not produce enough PGI₁ for in vivo studies. However, a convenient synthesis has been achieved.⁷

The objectives of this study were to establish the acute systemic effects of synthetic PGI₁ administered intravenously into the intact dog, to quantify the hemodynamic response to a range of administered doses and to compare the PGI₁ response to that produced by AA.

Methods

Seventeen mongrel dogs of either sex weighing 14–20 kg were anesthetized with sodium pentobarbital, 30 mg/medicine.gov. By guest on September 12, 2017 http://circres.ahajournals.org/ Downloaded from

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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 PG12 (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 PG12, (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 PG12. 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, PG12 (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 PG12 (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 PG1 induced little change. Only PGE2 induced a significant increase in MCF. The onset of AA response was more delayed when compared to PG1 and PGE2. The durations of action of AA and PG1 were comparable. However, the duration of action of PGE2 was shorter and that of PGD2 was substantially longer than that of AA or PG1 (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, PGF2α 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...
of the cardiovascular responses to equidepressor 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 MCF and AA produced only a variable pulmonary response.

PGL₁ 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 PGF₆α is the primary product of PGI₂ metabolism 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.

References


Table 1 Hemodynamic Changes Produced by Equidepressor Doses of PGI₂, AA, PGE₂, and PGD₂ in Intact Dogs

<table>
<thead>
<tr>
<th>Dose</th>
<th>μg/kg</th>
<th>n</th>
<th>Time to onset (sec)</th>
<th>BP (%)</th>
<th>PAP (%)</th>
<th>MCF (%)</th>
<th>Duration of action (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>300.0</td>
<td>13</td>
<td>15.0 ± 0.8</td>
<td>-25.0 ± 3.0</td>
<td>-0.7 ± 2.6</td>
<td>+7.5 ± 2.4</td>
<td>174.8 ± 18.3</td>
</tr>
<tr>
<td>PGE₂</td>
<td>5.0</td>
<td>5</td>
<td>7.8 ± 0.7</td>
<td>-23.4 ± 2.2</td>
<td>+20.1 ± 2.9</td>
<td>+20.1 ± 6.0</td>
<td>138.8 ± 26.9</td>
</tr>
<tr>
<td>PGD₂</td>
<td>5.0</td>
<td>6</td>
<td>12.3 ± 2.4</td>
<td>-25.6 ± 5.4</td>
<td>+66.4 ± 10.4</td>
<td>+4.6 ± 5.4</td>
<td>239.6 ± 44.8</td>
</tr>
<tr>
<td>PGI₁</td>
<td>0.5</td>
<td>11</td>
<td>8.6 ± 0.7</td>
<td>-26.2 ± 3.4</td>
<td>-1.4 ± 2.9</td>
<td>-0.3 ± 2.9</td>
<td>187.5 ± 17.7</td>
</tr>
</tbody>
</table>

Values in columns 4-8 are expressed as mean ± SE. n = number of responses; BP = systemic arterial pressure; PAP = pulmonary arterial pressure; MCF = myocardial contractile force.
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