ABSTRACT
The effects of intravenous prostaglandin A₁ (PGA₁) on systemic and coronary hemodynamics were studied in 13 intact, conscious dogs after recovery from operation for implantation of Doppler ultrasonic flow probes on the ascending aorta and left circumflex coronary artery. Graded doses of PGA₁ (0.01 to 1.0 μg/kg) caused arterial pressure and total systemic resistance to decrease progressively and heart rate and cardiac output to increase progressively. At the maximum dose administered (1.0 μg/kg), arterial pressure and systemic resistance decreased by averages of 30% and 51% below control, respectively, and heart rate and cardiac output rose 64% and 47%, respectively. After beta-receptor blockade with propranolol, PGA₁ still caused a similar increase in cardiac output. In spite of arterial hypotension, PGA₁ produced a progressive increase in coronary flow, with a peak increase of 74% above control with 1.0 μg/kg and a corresponding graded decrease in coronary resistance, with a decrease of 61% below control with 1.0 μg/kg. Marked increases occurred in systolic as well as diastolic coronary flow. The coronary vasodilation was not abolished by preventing the PGA₁-induced tachycardia with electrical pacing, by beta-receptor blockade, or by combined blockade of beta receptors and cholinergic nerve fibers. While arterial Po₂ remained constant, coronary sinus Po₂ rose when coronary flow was increased by PGA₁. Thus PGA₁ is both a primary and secondary coronary vasodilator which increases cardiac output and decreases total systemic resistance.

KEY WORDS: blood pressure, coronary flow, cardiac output, cholinergic blockade, beta-receptor blockade, heart rate.

Since the discovery of the potent effects of the prostaglandins on vascular smooth muscle by Goldblatt (1) and von Euler (2), a large family of prostaglandins has been found to be ubiquitous in mammalian tissues and to have diverse physiologic effects on numerous organs. In contrast to the numerous actions of the prostaglandin E (PGE) and prostaglandin F (PGF) compounds, which have effects on tissues and metabolic processes other than the cardiovascular system, the effects of prostaglandin A (PGA) compounds are relatively specific for the cardiovascular system (3-19). Furthermore, the PGA compounds are not substantially metabolized in the lungs as are the other prostaglandins (20, 21) and therefore could act as hormonal factors in the regulation of arterial pressure and regional blood flow. Thus, from the standpoints of both cardiovascular physiology and therapeutics, the PGA compounds are clearly the prostaglandins of greatest interest.

Although direct intraarterial infusion of PGA₁ in anesthetized dogs has been shown to increase blood flow in the carotid, mesenteric, renal, and femoral arterial beds, only small
increases were observed in coronary flow (13, 22). Furthermore, it is not clear whether coronary flow increases when systemic hypotension occurs in response to the intravenous administration of PGA1 and whether PGA1-induced elevations in coronary flow reflect a primary effect on the coronary vascular bed or are secondary to increased metabolic requirements of the myocardium caused by tachycardia and reflex sympathetic stimulation of the heart (23).

From the information available on the effects of PGA1 on systemic hemodynamics in the anesthetized dog, it appears that this compound causes only small increases in cardiac output, even when given in large doses (12). Furthermore, it is not clear whether PGA1 is capable of increasing cardiac output independent of reflexly induced sympathetic activity and myocardial catecholamine stores. To gain a clearer understanding of the effects of PGA1 in the normal intact circulatory system, we studied the effects of intravenously administered PGA1 on systemic and coronary hemodynamics in the conscious, healthy dog, an experimental model which provides a normal, physiologic milieu in which cardiovascular control mechanisms are intact, in which the effects of anesthesia and recent surgery are absent, and in which the side effects of PGA1 can be observed.

**Methods**

During operations carried out under sterile conditions and pentobarbital sodium anesthesia (25 mg/kg), Doppler ultrasonic blood flow transducers were implanted around the base of the aorta, or left circumflex coronary artery, or both, in 13 dogs of mixed breed, weighing between 21 and 30 kg. In four of these dogs, catheters were placed in the coronary sinus by the method of Rayford et al. (24) for chronic studies and in another four dogs, epicardial pacemaker electrodes were sutured to the right ventricle. In one additional dog, an electromagnetic flowmeter transducer was placed around the left circumflex coronary artery.

Except for the animals with coronary sinus catheters, the experiments were started 2 to 4 weeks after operation. In the four dogs with the coronary sinus catheters, experiments were conducted 1 week after operation, before the time of expected clotting of these catheters. At the time of initiation of the experiments, all dogs were vigorous and apparently fully recovered from operation, with resting heart rates below 100/min and a distinct sinus arrhythmia. During the control state and after graded doses of PGA1, continuous measurements were made of arterial pressure and coronary flow in normal sinus rhythm in seven dogs, with the right ventricle stimulated electrically with an external pacemaker at a frequency of 180 beats/min in four dogs, after beta-receptor blockade with propranolol in seven dogs, and after combined blockade of beta receptors with propranolol and of cholinergic nerve fibers with atropine in seven dogs. Measurements of arterial pressure and cardiac output were made in six dogs prior to and in five dogs after beta-receptor blockade. In four dogs, samples of arterial and coronary sinus blood were simultaneously withdrawn for determination of PO2 and pH during the control period and at the time of the peak increase in coronary blood flow following administration of PGA1. Determinations of PO2 and pH were made by a blood gas analyzer (Instrument Laboratory, model 113).

The PGA1 used in this study was a crystalline preparation which was dissolved in ethanol, stored at 0°C and diluted with sterile, distilled water just before the experiments were begun. PGA1 was administered intravenously in doses of 0.01, 0.1 and 1.0 μg/kg. Higher doses were poorly tolerated, resulting in excitement, which interfered with accurate observation of the hemodynamic responses to the drug. Beta-receptor blockade was produced with 1.0 to 2.0 mg/kg propranolol and the adequacy of the blockade tested by demonstrating that the intravenous administration of 1 μg/kg isoproterenol caused negligible changes in heart rate and blood pressure. Cholinergic nerve fibers were blocked with 0.1 to 0.4 mg/kg of atropine; adequacy of blockade was tested by demonstrating that 0.1 mg acetylcholine caused negligible changes in heart rate and blood pressure.

Arterial pressure was continuously sampled by a catheter placed in the central aorta through the femoral artery under local anesthesia and measured with a Statham P23Db strain gauge manometer. Aortic flow (cardiac output) and coronary blood flow were measured by the Doppler ultrasonic flowmeter (25, 26). Blood flow velocity was derived from the Doppler equation as previously described (25). Zero flow was repeatedly determined electrically, and the accuracy of the electrical zero was confirmed terminally by comparing electrical zero with

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1Medtronic, Inc., Minneapolis, Minnesota.
2Supplied by Upjohn Company, Kalamazoo, Michigan.
mechanical occlusive zero. A recent study demonstrated consistently and repeatedly in peripheral arteries that the Doppler flowmeter has a stable zero flow and that only a negligible discrepancy exists between electrical and occlusive zero flow (26). Other experiments in our laboratory have demonstrated the linear relationship between blood flow velocity and volume flow as long as the diameter of the vessel within the transducer does not change, and volume flow calibrations by timed collections of blood verified the linear relationship between blood flow velocity and volume flow in the present study. Postmortem examination of these dogs demonstrated adherence of the vessel wall to the transducer shell by a firm fibrous shell minimizing changes in the caliber of the vessel with alterations of arterial pressure. The internal cross-sectional area of the blood vessel was measured at autopsy, and blood flow rate was calculated as the product of the cross-sectional area and blood flow velocity. The cross-sectional area of the blood vessel at autopsy can be expected to vary from that during life, suggesting caution in interpreting the absolute values for volume flow. However, any deviation is constant in the control period and during response to PGA.

Since the demodulation circuit of the Doppler flowmeter does not define the direction of flow, reverse flow is recorded as a positive wave. To obviate this possible error, the negative flow wave occurring at the base of the aorta just before closure of the aortic valve and recorded as a small positive wave was considered as negative (reverse flow) in calculating mean cardiac output and stroke volume. Reverse flow was negligible in the coronary bed both at rest and during the response to the administration of PGA in the doses used in this study. The absence of negative coronary flow in response to PGA was confirmed by measuring left circumflex coronary flow with a gated square wave electromagnetic flowmeter in one additional conscious dog. No reverse flow was observed during the response to intravenously administered PGA, even with sufficient PGA to lower mean systemic arterial pressure to 60 mm Hg.

Mean arterial pressure and mean coronary and aortic flows were derived using RC electronic filters with a 2-second time constant. Systemic vascular and left circumflex coronary mean resistance was calculated as the quotient of the mean arterial pressure and mean aortic and left circumflex coronary flows. Late diastolic coronary resistance, determined in seven dogs, was calculated as the quotient of the late diastolic thoracic aortic pressure and late diastolic coronary flow.

Late diastolic resistance was calculated at the point on the diastolic coronary flow waveform just before the decrease in coronary flow associated with isometric contraction. Heart rate was monitored continuously by a cardiotachometer (Beckman type 9857 B) triggered by the electrical signal from the aortic pressure pulse. All data were recorded on a multichannel magnetic tape recorder and played back on a multichannel oscillograph.

Results

Systemic Circulation.—With increasing dosage of PGA, there was progressive decrease in arterial pressure and total systemic resistance, while heart rate and cardiac output increased progressively (Fig. 1). With 1.0 μg/kg of PGA arterial pressure decreased by an average of 30 ± 5% (SE); cardiac output increased by an average of 47 ± 3%; total systemic resistance decreased by an average of 51 ± 4%; heart rate increased by an average of

![FIGURE 1](http://circres.ahajournals.org/)

Average changes (±SE) produced by three graded doses of PGA. Control values are indicated for each of these parameters; n = number of animals.
Effects of 1 µg/kg PGA₁ on Systemic Hemodynamics before and after Beta-Receptor Blockade

**TABLE 1**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Control</th>
<th>PGA₁</th>
<th>Control</th>
<th>PGA₁</th>
<th>Control</th>
<th>PGA₁</th>
<th>Control</th>
<th>PGA₁</th>
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<tbody>
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<td>AP (mm Hg)</td>
<td>116</td>
<td>57</td>
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<td>88</td>
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<tr>
<td></td>
<td>CO (L/min)</td>
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<td>2.7</td>
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<td>3.3</td>
<td>4.8</td>
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<tr>
<td></td>
<td>SV (L/min)</td>
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<td>35</td>
<td>33</td>
<td>40</td>
<td>30</td>
<td>29</td>
<td>27</td>
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<td>29</td>
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<td>TPR (mm Hg/ml/min)</td>
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<td>0.020</td>
<td>0.027</td>
<td>0.015</td>
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<td>0.040</td>
<td>0.019</td>
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<tr>
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<td>138</td>
<td>82</td>
<td>160</td>
<td>78</td>
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<tr>
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</tr>
<tr>
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<td>SV (L/min)</td>
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<td>28</td>
<td>46</td>
</tr>
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<td>TPR (mm Hg/ml/min)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>HR (beats/min)</td>
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<td>83</td>
<td>78</td>
<td>78</td>
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<td>78</td>
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</tr>
</tbody>
</table>

**NSR, preblockade**

**NSR, beta-receptor blockade**

AP = arterial pressure; CO = cardiac output; NSR = normal sinus rhythm; SV = stroke volume; TPR = total peripheral resistance; HR = heart rate.
TABLE 2
Effects of 1 µg/kg PGA1 on Coronary Hemodynamics in Normal Sinus Rhythm, Paced at 180/min, after Beta-Receptor Blockade and Combined Blockade of Beta Receptors and Cholinergic Nerve Fibers

<table>
<thead>
<tr>
<th>Dog</th>
<th>NSR, preblockade</th>
<th>Paced (180/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AP (mm Hg)</td>
<td>CF (ml/min)</td>
</tr>
<tr>
<td>3</td>
<td>88</td>
<td>54</td>
</tr>
<tr>
<td>PGA1</td>
<td>69</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>108</td>
<td>41</td>
</tr>
<tr>
<td>PGA1</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
<td>35</td>
</tr>
<tr>
<td>PGA1</td>
<td>70</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>88</td>
<td>54</td>
</tr>
<tr>
<td>PGA1</td>
<td>85</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>116</td>
<td>41</td>
</tr>
<tr>
<td>PGA1</td>
<td>72</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>102</td>
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<td>PGA1</td>
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<td>9</td>
<td>106</td>
<td>44</td>
</tr>
<tr>
<td>PGA1</td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td>100</td>
<td>44</td>
</tr>
<tr>
<td><strong>SE</strong></td>
<td>±5</td>
<td>±4</td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td>PGA1</td>
<td>69</td>
</tr>
<tr>
<td><strong>SE</strong></td>
<td>±5</td>
<td>±6</td>
</tr>
</tbody>
</table>

CF = coronary flow; CR = coronary resistance; all other abbreviations as in Table 1.

Effects of 1 ng/kg PGA1 on Coronary Hemodynamics in Normal Sinus Rhythm, Paced at 180/min, after Beta-Receptor Blockade and Combined Blockade of Beta Receptors and Cholinergic Nerve Fibers

64 ± 13%; and stroke volume decreased by an average of 13 ± 4% (Table 1). Each of these variables returned to control levels after 15 to 20 minutes. All of these changes were statistically significant (P < 0.001).

After beta-receptor blockade, 1.0 µg/kg PGA1 produced a 27 ± 7% decrease in arterial pressure (P < 0.001), a 52 ± 6% decrease in total systemic resistance (P < 0.001), and a 39 ± 7% increase in heart rate (P < 0.001), a 52 ± 7% increase in cardiac output (P < 0.001), a 9 ± 3% increase in stroke volume (P < 0.05). Both before and after beta-receptor blockade, comparable alterations of arterial pressure, cardiac output, and total systemic resistance occurred; however, after blockade there was less increase in heart rate and a slight increase in stroke volume, rather than a decrease as observed prior to blockade.

Coronary Circulation.—With increasing dosage of PGA1 there was a progressive increase in mean left circumflex coronary blood flow and a progressive decrease in mean left circumflex coronary resistance (Fig. 1). At the time of the peak response to 1 µg/kg of PGA1, coronary flow increased by an average of 74 ± 14% (Table 2). In addition to

FIGURE 2
Mean values (7 dogs) during control and during the peak response to 1 µg/kg PGA1.
the increase in diastolic coronary flow (33 ± 2 ml/min to 53 ± 5 ml/min), there was a large increase in systolic coronary flow (11 ± 1 ml/min to 25 ± 2 ml/min) (Fig. 2). During the control period, the systolic component averaged 23 ± 1% of total coronary flow while during the peak response to 1 μg/kg of PGA₁, the systolic component was 32 ± 2% of total coronary flow. During the peak response to 1 μg/kg, coronary resistance decreased an average of 61 ± 2% below control and late diastolic coronary resistance decreased an average of 58 ± 3% (Fig. 2). All of these changes were statistically significant (P < 0.001).

When the heart was maintained constant by electrical stimulation at 180 beats/min 1.0 μg/kg of PGA₁ resulted in an arterial pressure decrease averaging 28 ± 6%; coronary flow increased 39 ± 15%; and coronary resistance decreased 54 ± 3% (Table 2). All of these changes were statistically significant (P < 0.001). The decrease in arterial pressure was comparable to that seen in the unpaced state, but the increase in coronary flow and decrease in coronary resistance (Fig. 3) were of lesser magnitude.

In response to PGA₁ administration after beta-receptor blockade, arterial pressure decreased by an average of 29 ± 5%, coronary blood flow increased 38 ± 2%, coronary resistance decreased 54 ± 3%, and heart rate increased 39 ± 7% (Table 2). All of these changes were statistically significant (P <
0.001). After beta-receptor blockade the alterations in heart rate and coronary blood flow were not as great as before blockade. There was no statistically significant difference between the decreases in coronary resistance induced by PGA₁ before and after beta-receptor blockade (P > 0.1 < 0.2).

In response to 1.0 μg/kg of PGA₁ after combined blockade of beta receptors and cholinergic nerve fibers, arterial pressure decreased 36 ± 6% (P < 0.001), coronary blood flow changed little, increasing by only 9 ± 1% (P > 0.2); coronary resistance decreased 42 ± 5% (P < 0.001) and heart rate did not change significantly (P > 0.2) (Table 2). Compared to the response to PGA₁ prior to the combined blockades, in addition to the abolition of the tachycardia, the increase in coronary flow and decrease in coronary resistance (Fig. 3) were reduced.

During the time of the peak coronary flow produced by 1.0 μg/kg of PGA₁, there was a rise in coronary sinus Po₂, while arterial Po₂ and pH remained constant in each of the four dogs in which these variables were measured (Fig. 4).

**Discussion**

In this study, PGA₁ in doses which were well tolerated by the conscious, unsedated dog caused profound decreases in arterial pressure and total systemic resistance while heart rate and cardiac output increased. In spite of the decline in systemic arterial pressure, this compound also markedly increased coronary blood flow with augmentation of both systolic and diastolic flows, resulting in marked reductions in coronary vascular resistance. This coronary dilatation was still evident when heart rate was maintained constant during electrical stimulation at 180/min, after beta-receptor blockade alone or combined with blockade of cholinergic nerve fibers.

Studies in laboratory animals (9, 13, 14, 27-29) and in man (17, 30-33) have demonstrated potent effects of prostaglandins on central and peripheral hemodynamics through what is believed to be an action on adenyl cyclase, which is not yet fully characterized. The prostaglandin A and E compounds have been shown in experimental animals to cause a lowering of arterial pressure and an associated tachycardia, whereas the prostaglandin F compounds elevate arterial pressure and have a negligible effect on heart rate. All three groups of compounds increase cardiac output and myocardial contractile force in the anesthetized dog, with the E compounds exerting the greatest effect (12). In the present study, the coronary vascular dilatation, tachycardia, and augmented cardiac output induced by PGA₁ in the conscious, resting dog are directionally similar but quantitatively much greater than those observed for either PGA₁ or PGE₁ in the anesthetized dog (12, 13, 22). Nakano and McCurdy (12) found a more profound vasodilatation and a greater increase in cardiac output with PGE₁ than with PGA₁ in the anesthetized, open-chest dog; however, Weeks et al. (9), working with unanesthetized dogs, found PGA₁ to be the more potent vasodilator. Although we have not studied PGE₁ in the unanesthetized animal, it is clear
that PGA decreased arterial pressure and increased cardiac output to a greater magnitude in the conscious dog than either PGA or PGE in the anesthetized dog.

After beta-receptor blockade, PGA caused an even greater relative increase in cardiac output than during control, indicating that the ability of PGA to increase cardiac output is independent of direct or reflex sympathetic nervous activity. The relatively greater increase in cardiac output after beta-receptor blockade may have been due to the direct effect of PGA on hearts depressed by this large dose of propranolol, as indicated by the lower control cardiac output after beta-receptor blockade. Three possible mechanisms may have contributed in varying degrees to the increase in cardiac output after beta-receptor blockade: (1) a decreased afterload, (2) a direct positive inotropic effect of PGA, and (3) tachycardia due to reflex withdrawal of vagal influence on the sinoatrial node. The relative contribution of each of these mechanisms has not yet been elucidated.

Previous studies in anesthetized dogs using direct intraarterial infusions of PGA compounds demonstrated large increases in brachial, femoral, carotid, and renal flows but only a small increase in coronary flow (13, 22). Contrary to these earlier reports, PGA administered intravenously in this study caused profound increases in coronary blood flow in the resting, unanesthetized dog. To elucidate the relative importance of the direct vasodilating effect of PGA and the indirect vasodilating effect due to increased metabolic requirements consequent to the increased heart rate and reflex sympathetic stimulation of the heart, the effect of 1 ug/kg of PGA on coronary resistance was determined when heart rate was controlled by stimulating at a rate above that induced by this dose of PGA (180/min) and after beta-receptor blockade alone or combined with blockade of cholinergic nerve fibers. During each of these states, PGA still caused substantial coronary vasodilation but less than was observed when sinus rhythm was normal before blockade (Fig. 4). When the effects of reflexly induced sympathetic activity were blocked and heart rate remained constant after combined beta-receptor and cholinergic nerve fiber blockades, the oxygen requirements of the myocardium should have decreased in response to PGA since arterial pressure decreased markedly, although this could possibly have been offset, in part, by a direct inotropic effect. Under these conditions PGA still caused a 42% decrease in coronary resistance, indicating that to a major extent the coronary vasodilation caused by PGA is a direct vascular effect and not due primarily to increased metabolic requirements of the myocardium. This interpretation is strongly supported by the observed rise in coronary sinus Po2 at the time of peak coronary flow in all four dogs in which this was measured. In this regard, Smith et al. (28) demonstrated that the vasoactivity of another prostaglandin, PGE, on the femoral bed is not mediated by adrenergic, cholinergic, histamine-releasing, or serotonin-releasing mechanisms and have concluded that it is a direct action on arteriolar smooth muscle. Similarly, PGE and PGA, by direct action on vascular smooth muscle in vitro, have been shown to cause relaxation of isolated arterial strips taken from small peripheral arteries (35).

The systolic component of left circumflex coronary flow in the resting dogs in this study (23 ± 1%) is greater than that in the anesthetized dog but comparable to that previously reported in the resting, unanesthetized dog in which coronary flow was measured with electromagnetic flowmeters (36, 37). The increase in systolic coronary flow caused by 1.0 ug/kg of PGA was remarkable and of the magnitude seen after administration of ephedrine and release of coronary occlusion (36, 38).

The absence of profound increases in coronary flow in previous studies in anesthetized open-chest dogs may have been due to the relatively dilated coronary arterial bed in these dogs in which control coronary flow was already elevated due to the tachycardia induced by anesthesia and thoracotomy (13). Furthermore, the operative manipulations
required for installation of the instruments for flow measurement used in these earlier acute studies could be expected to cause marked alterations in basal coronary arterial tone and to interfere with vasoactive responses to subsequent drug infusions.

After beta-receptor blockade, the tachycardia in response to PGA₁ persisted, as indicated by an increase in heart rate averaging 39% following administration of 1.0 μg/kg of PGA₁. An important contribution made by the withdrawal of vagal activity to the tachycardia in response to prostaglandin has not been observed in studies in anesthetized animals in which prior treatment with propranolol, reserpine, or ganglionic blocking agents abolished the tachycardia produced by large doses of prostaglandins (27, 39). This observation may be indicative of a basic difference in the mechanism of the baroreceptor reflex-induced tachycardia in conscious and anesthetized animals which results from reductions in resting vagal tone in the anesthetized state (40). In the studies on anesthetized animals referred to above, pentobarbital sodium, an agent known to depress vagal activity (41) was used to produce anesthesia. The resting heart rates in excess of 140/min in the anesthetized animals compared to the control rates of 72/min in this study also indicates a difference in the resting tone of the two components of the autonomic nervous system in unanesthetized and anesthetized animals. Total prevention of cardiac acceleration with PGA₁ after combined beta-receptor and cholinergic nerve fiber blockade in the conscious dog is consistent with the findings in the isolated heart (29) and anesthetized dog (12, 27) that prostaglandins are devoid of positive chronotropic activity.

The actions of PGA₁ observed in this investigation prompt speculation on several clinical situations in which PGA₁ could be of therapeutic efficacy. Since PGA₁ increases cardiac output and causes peripheral vasodilatation, it could be of value in various states of circulatory shock, particularly those associated with marked peripheral vasoconstriction as seen in some patients with septicemia and in the low cardiac output state occasionally encountered after prolonged cardiopulmonary bypass. The observation that PGA₁ can increase cardiac output independent of catecholamine stores and can induce natriuresis and diuresis (31, 42, 43) suggests its usefulness in congestive heart failure. It also appears to be an ideal parenteral antihypertensive agent, since it can profoundly lower arterial pressure while renal blood flow and urine output are well maintained (33, 43).

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CORONARY DILATATION WITH PROSTAGLANDIN A1

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Books Received

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CHARLES B. HIGGINS, STEPHEN F. VATNER, DEAN FRANKLIN, THOMAS PATRICK, EUGENE BRAUNWALD, DANIEL P. MCKOWN and DAVID HENDRICK

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