Ventricular Receptors Activated following Myocardial Prostaglandin Synthesis Initiate Reflex Hypotension, Reduction in Heart Rate, and Redistribution of Cardiac Output in the Dog

Thomas H. Hintze and Gabor Kaley
From the Department of Physiology, New York Medical College, Valhalla, New York

SUMMARY. Arachidonic acid (250 µg) injected into the left circumflex coronary artery of anesthetized dogs, with carotid arteries tied to reduce baroreflex-induced changes, caused a reduction in heart rate (—15 ± 1.6 beats/min), mean arterial pressure (—27 ± 3.4 mm Hg), and left ventricular dP/dt (—939 ± 138 mm Hg/sec). In contrast, injection of arachidonic acid into the left anterior descending coronary artery caused smaller changes in heart rate (—4.6 ± 1.6 beats/min), arterial pressure (—14 ± 2.8 mm Hg), and left ventricular dP/dt (—118 ± 131 mm Hg/sec). The hypotension following the injection of arachidonic acid results from an increase in perfusion of the kidney and skeletal muscle (as measured by radioactive microspheres), and is entirely reflex, since the changes in renal blood flow, as well as the reduction in heart rate and the hypotension, are eliminated by bilateral vagal section. Increasing the dose of arachidonic acid results in dose-related changes in heart rate, arterial pressure, and left ventricular dP/dt. Prostacyclin and prostaglandin E₂, the two principle coronary vasodilator metabolites of arachidonic acid, but not nitroprusside, cause a fall in blood pressure and heart rate, establishing that coronary vasodilation per se is not responsible for initiating the reflex fall in arterial pressure and heart rate. In two dogs with sinoaortic denervation, circumflex injection of arachidonic acid caused large reductions in heart rate (—21 ± 1.5 beats/min) and mean arterial pressure (—51 ± 3.5 mm Hg). In summary, the intracardiac production of prostaglandins causes activation of left ventricular receptors, particularly in the posterior wall of the heart, and results in a reflex reduction in heart rate and reflex hypotension which stems from vasodilation in kidney and skeletal muscle. (Circ Res 54: 239-247, 1984)

RECENT WORK from our laboratory has shown that the cardiopulmonary injection of prostacyclin (PGI₂) or arachidonic acid (AA) results in a vagal reflex bradycardia in the anesthetized (Hintze et al., 1978, 1979, 1982; Kaley et al., 1980) or in the conscious dog (Hintze et al., 1981). The reflex effects of PGI₂ are similar to other cardiac depressor reflexes (von Bezold and Hirt, 1867; Jarisch and Richter, 1939) that are caused by stimulation of ventricular receptors, located predominantly in the posterior wall of the heart (Frink and James, 1971; Walker et al., 1978). Activation of these reflexes results not only in a diminution of heart rate, but, also, in a reduction of arterial pressure resulting primarily from a redistribution of peripheral blood flow to skeletal muscle and kidney (Dawes, 1947; Dawes and Comroe, 1954; Mancia et al., 1973, 1975). In addition, the baroreflexes may modify these depressor reflexes, since Thames et al. (1978) and Walker et al. (1978) have shown that stimulation of cardiopulmonary reflexes by coronary occlusion or veratridine injection has a more pronounced effect on heart rate and peripheral resistance when the systemic baroreflexes are eliminated.

Unlike veratridine, which has little or no direct vasodilator activity in the dog (Dawes, 1947), the prostaglandins, especially PGI₂, are among the most potent, naturally occurring vasodilator substances (Armstrong et al., 1978; Moncada et al., 1978; Dusting et al., 1979), and have direct, as well as reflex, effects on peripheral blood vessels. Additionally, pulmonary c-fibers are stimulated by prostaglandins, leading to reflex cardiovascular changes (Coleridge et al., 1976). We have shown previously that both the increase in coronary flow and cardiac slowing to the injection of arachidonic acid are abolished by the administration of indomethacin (Hintze and Kaley, 1977; Hintze et al., 1979), and are thus due to the synthesis of prostaglandins. However, our previous studies, which describe the reflex effects of AA and PGI₂, established neither the magnitude nor reflex component of the hypotension produced by prostaglandins, nor which vascular beds were contributing to it. Furthermore, in previous studies, we did not attempt to locate the receptors responsible for initiating the reflex.

In the present study, in order to locate the receptors responsible for the depressor reflex to prostaglandin and to eliminate the effects of circulating prostaglandins, we used local intracoronary injec-
tions of AA in amounts which—when injected intravenously or into the aorta—did not cause changes in heart rate and blood pressure. In addition, to avoid competition between the systemic baroreflexes activated by hypotension and cardiopulmonary reflexes stimulated by prostaglandin, the experiments were done in dogs with carotid arteries ligated bilaterally in the neck throughout the experiments or in dogs with sinoaortic denervation. Under these conditions, the purposes of our study were (1) to investigate the changes in cardiovascular function caused by the intracoronary injection of AA and two of its principal vasodilator metabolites. PGI₂ and PGE₂, (2) to delineate the location of the receptors responsible for the reflex bradycardia by injection of AA into either the circumflex or the left anterior descending coronary artery, and (3) to describe the reflex redistribution of peripheral blood flow during the activation of ventricular reflexes by prostaglandin generation in the heart.

Methods

All of the dogs used in this study (n = 38) were males weighing between 20 and 30 kg (mean: 24 kg). All dogs were anesthetized with a mixture of Dial-urethane (Ciba) and Nembutal (Abbott), as previously reported (Hintze and Kaley, 1977). Cannulas (PE 240) were placed in the right femoral artery and vein for blood sampling and supplemental anesthesia, and in the brachial artery for the recording of arterial blood pressure (p=1000B Narco). The carotid arteries were ligated bilaterally in the neck. Special care was taken during dissection of the vagus nerve to avoid stretching or cutting the nerve during isolation of the carotid arteries.

The dog then was placed on its right side, intubated, and ventilated to keep PO₂ near 100 mm Hg, PCO₂ near 40 mm Hg, and pH near 7.38, by adjusting the respiratory speed, the expiratory resistance and supplementing room air with bottled oxygen. An incision was made in the 5th left intercostal space, the lungs were retracted and, in some animals, a noncannulating flow probe was placed around the descending thoracic aorta (435C, 440C, 445C, Carolina Medical Electronics) to measure aortic blood flow. A pericardial cradle was formed, and a cannula (PE 240) was placed in the apex of the left ventricle via a stab wound and purse string suture. The cannula was attached to a pressure transducer (Statham P23Db). The left circumflex (LCX) and the left anterior descending (LAD) coronary arteries were dissected free, as close to their origin as possible, for the placement of flow probes (408C, 409C, 410C), and a 27-gauge needle was placed in each artery just distal to the flow probe for drug injection. The animals were warmed with a water-circulating heating system (Thermorite), and blood gases were checked with a blood gas analyzer (Radiometer, BMS3 MK2). The heart was kept moist with saline warmed to 37°C and with saline-soaked sponges. After surgery, we waited 30 minutes before beginning the experiments.

Effects of Intracoronary Arachidonic Acid (AA), Prostaglandins, and Nitroprusside on Cardiovascular Function

In these experiments (n = 6), AA (200, 400, and 800 μg), PGI₂ (3 μg), PGE₂ (30 μg), and nitroprusside (300 μg) were injected into the LCX and LAD coronary arteries. The order of drug injections was randomized. However, in the case of AA, the smallest dose was given first, followed by increasing doses. We waited a minimum of 5 minutes after all parameters returned to control before giving another injection. Under these conditions, we observed no tachyphylaxis to any of the drugs used. In these dogs, recordings were made of systemic arterial pressure, heart rate, left ventricular pressure, LV dp/dt, and blood flow in the LAD and LCX coronary arteries. In six additional dogs 250, 500, 1000, and 2000 μg doses of AA were injected into the LAD and LCX coronary arteries. Arterial pressure, heart rate, LAD, and LCX blood flows were recorded.

Effects of Intracoronary Arachidonic Acid on Peripheral Blood Flows

Dogs (n = 15) were prepared in a fashion similar to that described above; however, a flow probe was placed on the aorta (n = 5), and a cannula was placed in the left atrial appendage (n = 15) for the injection of radioactive microspheres. In these dogs, the right femoral artery cannula was attached to a calibrated syringe pump (Harvard) for blood sampling during microsphere injection for derivation of blood flows. The minimum threshold dose of AA (mean = 250 μg; n = 15) for producing changes in heart rate and blood pressure when injected into the LAD was determined in each dog. The doses varied from dog to dog: 400 μg were injected into four dogs and 200 μg into 11 dogs. These doses were then increased into the LCX and LAD, and at the maximum fall in arterial pressure, approximately 2.0 X 10⁶ microspheres were injected into the left atrium to measure the peripheral distribution of blood flow. Microspheres (3 μm, 9 μm) labeled with ¹²⁵I, ⁸⁵Sr, and ⁴⁵Sc, were sonicated for at least 30 minutes before injection, in a solution containing Tween 80. Microspheres were injected both during control conditions and after AA injection into the LAD and LCX. The order of injections and isotopes was randomized. Systemic arterial pressure, heart rate, aortic flow, left ventricular pressure, LV dp/dt, and coronary blood flow were recorded continuously.

Reference blood samples were taken from the femoral artery at constant rate (10 ml/min) starting 30 seconds before and continuing for 90 seconds after microsphere injection. At the end of the experiment, the dogs were killed with an injection of potassium chloride, and the heart and peripheral organs were removed. The heart was separated into right and left ventricular free walls and septum. Six sections were taken from the right ventricular free wall and from the septum. Three transverse tissue sections were taken from areas perfused by the LAD and the LCX, and from the area between (termed the intermediate zone). Six tissue sections were also taken from the left kidney cortex and from the gracilis muscle. All tissue samples weighed between 1.0 and 2.0 g and were counted in a γ spectrophotometer (Searle Analytic model 1185) with the energy windows set to separate the isotope used. Blood flows were calculated by standard methods (Rudolph and Heymann, 1967; Dometnech et al., 1969; Heymann et al., 1977).

Vagal Reflex Actions of Intracoronary Arachidonic Acid

Dogs (n = 9) were prepared in essentially the same way as described above, except that only LCX injection of AA were injected into the LCX and LAD coronary arteries.
was given. A left flank incision was made just below the last rib, and the renal artery was isolated as close to the aorta as possible for the placement of an electromagnetic flow probe (410C, 412C Carolina Medical Electronics). In addition, the vagi were isolated in the neck for subsequent ligation and section. Arachidonic acid (250 µg) was injected into the LCX, before and after bilateral vagal section. Recordings were made of arterial pressure, heart rate, mean and phasic coronary blood flow, and mean and phasic renal blood flow.

### Effects of Intracoronary Arachidonic Acid in Dogs with Sinoaortic Denervation

In two dogs, prepared as described above, the carotid sinuses were stripped bilaterally in the neck and painted with a 1% phenol solution. The chest was then opened, and the aortic arch was stripped and painted with phenol. A flow probe was placed around the ascending thoracic aorta, a solid state pressure gauge (Konigsberg Instruments) was placed in the apex of the left ventricle, and a catheter side (sounding thoracic aorta) of the descending thoracic aorta for arterial pressure measurement. A needle was placed in the LCX for injection of AA (250 µg). One hour later, experiments were begun. AA was injected, while recordings were made of arterial pressure, heart rate, left ventricular pressure, LV dp/dt, and aortic blood flow (cardiac output-coronary blood flow). As a check of the completeness of sinoaortic denervation, nitroglycerin (5 µg/kg) was injected. Arachidonic acid was injected twice into each dog.

All indices were recorded on a direct-writing oscillograph (Narco), and blood flow was measured with matched electromagnetic flowmeters (Carolina Medical Instruments model 501). Flow probes were calibrated and the electronic zero reference was checked in situ in each animal at the end of the experiments. Heart rate was derived from the systemic arterial or left ventricular pressure pulse interval electronically (Narco Biotach). The frequency response of the catheter manometer recorder system was 30 Hz. The first derivative of changes in LV pressure, LV dp/dt, was calculated electronically (Narco differentiator) and used as an index of changes in cardiac contractility (Braunwald, 1977; Mahler et al., 1975). Blood flow in the aorta was recorded and used as an index of changes in cardiac output.

### Statistical Evaluation and Drug Preparation

Data points were taken at the maximum fall in arterial pressure for all injections. Since each animal served as its own control, a paired Student's t-test was used to show changes which were significantly different from control. The responses before and after bilateral vagal section and the differences in the peripheral distribution of blood flow (microspheres) during LAD and LCX injection of AA were compared by Student’s paired t-test. For microsphere blood flows, the calculated blood flows per gram of tissue sample, taken from each organ or from the same area of the heart, were averaged in each dog and then averaged for all the dogs studied.

Prostacyclin was prepared fresh in 100 mm Tris, pH 9.2, and diluted just prior to use in Tris, pH 7.3. Prostaglandin E₂ was prepared in sodium carbonate (100 mm) and either stored in the cold at a concentration of 1.0 mg/ml or used after dilution with saline. Sodium nitroprusside (Fisher) was made up in distilled water and stored in the cold and dark, or diluted in saline and injected. Arachidonic acid (Nucheck) was prepared as the sodium salt in preweighed vials by the addition of sodium carbonate (100 mm), stirred in the cold and dark, under nitrogen. All vehicles were tested daily and found to have no effects. In addition, the microsphere diluent also was found to have no effect in our anesthetized dogs (Millard et al., 1977).

### Results

**Effects of Intracoronary Arachidonic Acid, Prostaglandins, and Nitroprusside on Cardiovascular Function**

The effects of injection of increasing doses of AA into the LCX and the LAD are shown in Table 1. LCX injection of AA resulted in significant dose-related falls in arterial pressure (~9.0 to ~27%), heart rate (~5.0 to ~16%), and LV dp/dt (~15 to ~34%), while injection into the LAD resulted in lesser effects at each comparable dose. Injection into either artery caused a significant increase in peak coronary blood flow in that artery (Table 1). No significant change in flow occurred in the LAD during LCX injection, or in LCX flow during LAD injections.

Because the conversion of AA leads to diverse enzymatic products, the two primary coronary vasodilator prostaglandins, PGE₂ and PGL₂, were injected into the LAD and LCX, and these effects were compared with those of AA and nitroprusside. Results of LCX injection are shown in Figure 1. Both prostaglandins increased flow by at least 200% in the artery in which they were injected. Prostacyclin, like AA, caused falls in heart rate (~6.0%), arterial pressure (~10%), and LV dp/dt (~14%). After injection of PGI₂, there was a 18.7 ± 1.3 and 12.7 ± 1.0 second delay before heart rate and blood pressure began to fall; a return to preinjection values occurred in 323 ± 26 and 262 ± 20 seconds, respectively. Prostaglandin E₂, at a dose 10 times higher than PGI₂, caused falls in heart rate (~3.2%) and arterial pressure (~25%), and had no effect on LV dp/dt. After injection of PGE₂, there was a 19.3 ± 1.3 and 10.6 ± 1.0 second delay in the responses. Both heart rate and blood pressure returned to control in 270 ± 40 and 288 ± 20 seconds, respectively. Injection of PGI₂ or PGE₂ had no statistically significant effects on heart rate, arterial pressure, and LV dp/dt, when administrated into the LAD.

Nitroprusside caused large increases in coronary blood flow when injected into either the LCX (274%) or the LAD (200%) coronary artery, accompanied by a reduction in arterial pressure (~11%), and — unlike the prostaglandins and AA — caused a tachycardia and a small increase in LV dp/dt (10%). In striking contrast to the prostaglandins and AA, nitroprusside caused an increase in flow—not only in the injected artery—but in the other coronary artery, as well (+35%).

So that we might examine the full range of activity of prostaglandins produced in the heart, larger doses of AA (up to 2000 µg) were given to additional dogs.
TABLE 1
Cardiovascular Actions of Arachidonic Acid Injected into the Left Circumflex (LCX) and Left Anterior Descending (LAD) Coronary Arteries of Dogs

<table>
<thead>
<tr>
<th></th>
<th>LAD injection</th>
<th></th>
<th>LCX injection</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Control</td>
<td>Control</td>
<td>Control</td>
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<tr>
<td>Arachidonic acid (200 µg)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MAP</td>
<td>151 ± 7.0</td>
<td>157 ± 9.1</td>
<td>157 ± 9.1</td>
<td>-14 ± 2.8*</td>
</tr>
<tr>
<td>HR</td>
<td>181 ± 4.6</td>
<td>184 ± 5.9</td>
<td>184 ± 5.9</td>
<td>-9.0 ± 1.7*</td>
</tr>
<tr>
<td>LV dP/dt</td>
<td>5867 ± 400</td>
<td>-67 ± 183†</td>
<td>5934 ± 553</td>
<td>-767 ± 120*</td>
</tr>
<tr>
<td>CBF</td>
<td>24.0 ± 6.0</td>
<td>+80 ± 4.5*</td>
<td>36 ± 5.1</td>
<td>+103 ± 18.8*</td>
</tr>
<tr>
<td>Arachidonic acid (400 µg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>149 ± 5.8</td>
<td>158 ± 7.8</td>
<td>183 ± 5.8</td>
<td>-30 ± 7.2*</td>
</tr>
<tr>
<td>HR</td>
<td>178 ± 4.0</td>
<td>184 ± 5.9</td>
<td>183 ± 5.8</td>
<td>-11 ± 1.3*</td>
</tr>
<tr>
<td>LV dP/dt</td>
<td>5200 ± 563</td>
<td>-117 ± 323†</td>
<td>5966 ± 616</td>
<td>-1100 ± 317*</td>
</tr>
<tr>
<td>CBF</td>
<td>22 ± 2.0</td>
<td>+85 ± 13*</td>
<td>38 ± 6.0</td>
<td>99 ± 23*</td>
</tr>
<tr>
<td>Arachidonic acid (800 µg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>147 ± 4.6</td>
<td>154 ± 6.7</td>
<td>181 ± 5.8</td>
<td>-41 ± 7.9*</td>
</tr>
<tr>
<td>HR</td>
<td>176 ± 5.0</td>
<td>-11 ± 4.3†</td>
<td>184 ± 5.8</td>
<td>-18 ± 2.6*</td>
</tr>
<tr>
<td>LV dP/dt</td>
<td>5667 ± 425</td>
<td>-818 ± 200†</td>
<td>6100 ± 787</td>
<td>-1783 ± 344*</td>
</tr>
<tr>
<td>CBF</td>
<td>24 ± 6.0</td>
<td>95 ± 9.0*</td>
<td>37 ± 4.8</td>
<td>109 ± 12.5*</td>
</tr>
</tbody>
</table>

Values are the mean ± standard error of the mean (SEM). MAP: mean arterial pressure (mm Hg); HR: heart rate (beats/min); LV dP/dt (mm Hg/sec); CBF: coronary blood flow (ml/min); n = 6. ∆ = change from control. * Different from control, P < 0.05. † Different from LCX injection, P < 0.05.

At doses less than 1000 µg, injection of AA into the LCX coronary artery caused a greater reduction in heart rate, arterial pressure, and LV dP/dt than similar injections into the LAD. In contrast, at doses of 1000 and 2000 µg, the response to LCX and LAD injections were similar. Doses of AA less than 1000 µg had no effect on arterial pressure or heart rate when administered into the pulmonary artery (Hintze et al., 1979).

Effects of Intracoronary Arachidonic Acid on Peripheral Blood Flows

Control cardiovascular function and the changes which result from injection of AA into the LCX and the LAD of a separate group of dogs, used to measure the distribution of cardiac output by radioactive microspheres, are shown in Table 2 and Figure 2. In addition to a large decrease in LV dP/dt (−21%), aortic flow increased significantly (17%), upon LCX injection. This was due entirely to an increase in stroke volume from 10.3 to 13.0 ml that was accompanied by a fall in total peripheral resistance from 0.0869 to 0.0629 mm Hg/ml per min.

In these dogs, there was a delay after the injection of AA of 28 ± 2.2 seconds before heart rate and...
arterial pressure began to fall. Both heart rate and arterial pressure returned to control in 385 ± 33 seconds. Control blood flow, as measured by microspheres, in the LCX, intermediate zone, LAD, right ventricle, and septum were 1.19 ± 0.09, 1.20 ± 0.06, 1.19 ± 0.06, 0.76 ± 0.05, and 1.35 ± 0.09 ml/min per g, respectively. Injection of AA into the LCX coronary artery increased flow by 267% in the area perfused by the LCX, by 229% in the intermediate zone, and caused no change in flow in the area perfused by the LAD. In addition, flow in the right ventricular free wall and in the intraventricular septum increased (15% and 18%, respectively). On the other hand, injection of AA into the LAD caused flow to increase by 282% in the area perfused by the LAD coronary artery, by 141% in the intermediate zone, and caused no change in flow in the area perfused by the LCX. Flow in the right ventricle and the intraventricular septum increased (50% and 20%, respectively).

The changes in peripheral blood flow during LCX and LAD injection of AA are shown in Figure 3. The flow increase in the kidney cortex and in the gracilis muscle are significantly greater after LCX injection of AA than after LAD injection (P < 0.05).

### Vagal Reflex Actions of Intracoronary Arachidonic Acid

LCX coronary artery injections of AA (250 µg) before bilateral vagal section caused a significant reduction in heart rate and arterial pressure, and a large increase in flow in the renal artery (Fig. 4). The effects of LCX injection of AA on arterial pressure, heart rate, and renal blood flow were eliminated by bilateral vagal section (Fig. 4). The increase in flow in the LCX was unaffected by vagotomy, indicating that this is a consequence of cardiac prostaglandin production. Renal vascular resistance fell by 26% from 0.66 mm Hg/ml per min before vagotomy, and did not change after bilateral vagal section, following the LCX injection of AA.

### Effects of Intracoronary Arachidonic Acid in Dogs with Sinoaortic Denervation

In two dogs, LCX injection of AA (250 µg) caused a 22 and 19 beats/min fall in heart rate from 164 beats/min, a 47 and 54 mm Hg fall in arterial pressure from 118 mm Hg, a 443 and 703 ml/min increase in cardiac output from 2580 ml/min, a 288 and 1006 mm Hg/sec fall in LV dP/dt from 3340

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### Table 2

<table>
<thead>
<tr>
<th></th>
<th>LAD injection</th>
<th>LCX injection</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Δ</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>145 ± 6</td>
<td>-13.8*</td>
</tr>
<tr>
<td>SEM</td>
<td>2.8</td>
<td>6</td>
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<tr>
<td>n</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Heart rate</td>
<td>168 ± 7</td>
<td>-4.6*</td>
</tr>
<tr>
<td>SEM</td>
<td>1.6</td>
<td>6</td>
</tr>
<tr>
<td>n</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Systolic ventricular pressure</td>
<td>157 ± 9</td>
<td>-10.6*</td>
</tr>
<tr>
<td>SEM</td>
<td>2.8</td>
<td>8</td>
</tr>
<tr>
<td>n</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>LV dP/dt</td>
<td>4395 ± 164</td>
<td>-118</td>
</tr>
<tr>
<td>SEM</td>
<td>131</td>
<td>138</td>
</tr>
<tr>
<td>n</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>LCX flow</td>
<td>42.1 ± 4.6</td>
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</tr>
<tr>
<td>SEM</td>
<td>1.3</td>
<td>9.6</td>
</tr>
<tr>
<td>n</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>LAD flow</td>
<td>40.5 ± 9.0</td>
<td>+64.0*</td>
</tr>
<tr>
<td>SEM</td>
<td>10.7</td>
<td>2.5</td>
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<tr>
<td>n</td>
<td>8</td>
<td>4</td>
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<tr>
<td>Aortic blood flow</td>
<td>1965 ± 270</td>
<td>+100*</td>
</tr>
<tr>
<td>SEM</td>
<td>27</td>
<td>64</td>
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<tr>
<td>n</td>
<td>5</td>
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</table>

Values are the mean ± standard error of the mean (SEM), n = the number of animals. Δ: change from control. Mean arterial and systolic ventricular pressures in mm Hg; Heart rate in beats/min; LV dP/dt in mmHg/sec; LCX flow, LAD flow, and aortic blood flow in ml/min.

* Significantly different from control, P < 0.01.
† Significantly different from LAD injection, P < 0.01.
**FIGURE 2.** The injection of arachidonic acid (AA, 200 μg) into the left anterior descending coronary artery (LAD) in left panel, had little or no effect on mean arterial blood pressure (BP), heart rate (HR), circumflex coronary blood flow (LCX), left ventricular dP/dt, and left ventricular systolic pressure (VP). In contrast, injection into the LCX coronary artery of 200 μg of arachidonic acid (right panel) caused a fall in BP, HR, LV dP/dt, and LV systolic pressure. Injection of AA into either artery caused large increases in coronary flow only in the artery in which the injection was made. Ms represents the point at which radioactive microspheres were injected. This is a recording from a single dog. Length of horizontal bar equals 1 minute.

mm Hg/sec, a 48% and 61% fall in total peripheral resistance from 0.046 mm Hg/ml per min, and a 37% and 40% increase in stroke volume from 15.8 ml (Fig. 5). In these dogs, after intravenous injection of a relatively low dose (5 μg/kg) of nitroglycerin, arterial pressure fell by 30 and 28 mm Hg, while heart rate increased by only 6 and 8 beats/min. LV dP/dt did not increase, but actually fell by 230 and 268 mm Hg/sec. Despite the apparent elimination of the baroreflexes, arachidonic acid caused heart rate to fall, indicating that cardiac vagal afferents were still intact.

**FIGURE 3.** Following LAD (open bars) and LCX (closed bars) injection of arachidonic acid blood flow increased, as measured with radioactive microspheres, in the gracilis muscle and left kidney cortex. The control flow in the gracilis muscle was 0.057 ± 0.004 ml/min per g and in the kidney cortex 4.61 ± 0.30 ml/min per g. The increase in flow following LCX injection was significantly greater (P < 0.05) than during LAD injection (n = 15). * Different from control (P < 0.05).

**Discussion**

The bradycardia which results from the injection of PGI₂ has been described previously by us (Hintze et al., 1978, 1979, 1981, 1982; Kaley et al., 1980), and by others (Chappie et al., 1978, 1980; Jentzer et al., 1979; Chiba and Malik, 1980; Dusting and Vane, 1980). However, until now, the location of the receptors which are activated was open to question. Our data conclusively show that the local intracardiac synthesis of prostaglandins, whether it be PGI₂ or PGE₂, a combination of these, or perhaps other products of the AA metabolism, activates receptors in the heart, located predominantly—although not exclusively—in the posterior wall of the left ventri-
Figure 4. Summary of data following LCX injection of arachidonic acid (250 ug) before (open bars) and after (solid bars) bilateral vagal section. The effects on mean arterial pressure (BP), heart rate (HR), and renal blood flow (RBF) were eliminated by vagotomy. The effects on circumflex coronary blood flow (CBF) were unchanged (ns), since this increase in blood flow is a direct effect of intracoronary prostaglandin synthesis. • Different after vagal section (P < 0.05) (n = 9).

LV Pressure (mmHg)  
LV dP/dt (mmHg/sec)  
Arterial Pressure (mmHg)  
Heart Rate (b/min)  
Aortic Flow (ml/min)  
Aortic Flow (ml/min)  
Arachidonic Acid (250ug)  

Figure 5. Injection of AA (250 ug) in a dog with sinoaortic denervation resulted in a fall in LV systolic pressure, LV dP/dt, arterial pressure, and heart rate, and an increase in aortic blood flow.
receive equal blood flow (Thames et al., 1978), the number of receptors or the potential for prostaglandin synthesis in the area perfused by the LCX must also be greater.

Because the injection of AA leads to the intracoronary synthesis of prostaglandins (Hintze and Kaley, 1977) which is abolished by indomethacin, the effects of the two primary vasodilator products of AA metabolism in the heart, PGE2 and PGI2, also were studied. The slowing of the heart following the intracoronary injection of PGI2 was similar in magnitude to that observed after the intracoronary injection of a dose of AA that was 100 times larger. This is consistent with a 1–3% conversion of injected AA to prostaglandins in the coronary circulation (Needleman and Kaley, 1978).

Prostaglandin E2 had effects similar to PGI2, although doses of PGE2 that were 10 times higher than those of PGI2 had to be injected to obtain approximately equivalent reductions in heart rate. These effects are in agreement with recent work by Baker et al. (1979b), who employed left atrial injection of PGE2 but are in contrast to our previous work using pulmonary artery or intravenous injection of PGE2 (Hintze et al., 1979). Since PGE2 is degraded by the lungs, the systemic injection of even very large doses of it may not lead to local concentrations sufficient to activate those cardiac receptors which are responsible for reducing heart rate in the dog. In a similar fashion, injection of PGE2 into the coronary arteries in the course of other studies (Armstrong et al., 1978; Dusting and Vane, 1979; Chapple et al., 1980; Chiba and Malik, 1980) did not lead to bradycardia.

The reflex hypotension following the intracardiac production of prostaglandins is mediated by a decrease in resistance in skeletal muscle and kidney, a finding that is in essential agreement with those obtained after the injection of a veratridine (Walker et al., 1978) and those seen during the study of the interaction of ventricular reflexes and systemic arterial baroreflexes (Mancia et al., 1973, 1975, 1976; Chen, 1979). The effects of intracoronary AA injection are entirely reflex, since they are eliminated by bilateral vagal section. The increase in peripheral blood flow probably is mediated by withdrawal of α-adrenergic tone (Mancia et al., 1973) caused by a decrease in sympathetic fiber discharge (Thames, 1979). Although controversial, especially in anesthetized dogs, it is possible that a portion of the reflex hypotension may be mediated by stimulation of peripheral cholinergic vasodilator mechanisms (Zucker and Cornish, 1981). The vasodilation in renal and skeletal muscle is consistent with the increase in aortic flow we observed.

The precise type of ventricular receptors (Coleridge et al., 1964) that are activated during the intracoronary production of prostaglandins in our experiments is open to speculation. However, recent work by Baker et al. (1979a, 1979b) and Roberts et al. (1980) using direct c-fiber recordings indicates that prostaglandins stimulate chemosensitive endings and not mechanoreceptors.

Other investigators have shown that coronary injections of bradykinin (Neto et al., 1974; Kaley et al., 1980), veratrine (Dawes and Comroe, 1954), or veratridine in anesthetized (Walker et al., 1978; Kaley et al., 1980), or conscious dogs (Zucker and Cornish, 1981) result in a vagal reflex slowing of the heart. The reduction in cardiac rate induced by bradykinin or veratridine is not blocked by the inhibition of prostaglandin synthesis (Kaley et al., 1980). Similarly, the bradycardia that is frequently seen after coronary occlusion in anesthetized dogs is not eliminated by indomethacin (Hintze and Kaley, unpublished observations). In this regard, it is important to note that the activation of ventricular reflexes may occur primarily during pathological situations, such as myocardial ischemia and infarction in patients, when cardiac prostaglandin synthesis is enhanced (Berger et al., 1976).

In summary, the intracoronary synthesis of prostaglandins which results from the administration of AA causes a vagal reflex hypotension, and reduction in heart rate, in the dog. The hypotension results from vasodilation in skeletal muscle and kidney. Furthermore, the slowing of the heart and the hypotension are accompanied by an increase in aortic flow and a reduction in LV dP/dt. The receptors responsible for this effect are located primarily, although not exclusively, in the posterior wall of the left ventricle. This is the first evidence that the production of a naturally occurring substance in the coronary circulation of dogs can cause a systemic cardiovascular depressor reflex.

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Address for reprints: Dr. Gabor Kaley, Professor and Chairman, Department of Physiology, New York Medical College, Valhalla, New York 10595.

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Prostaglandins Stimulate Ventricular Reflexes

Hintze and Kaley

Prostaglandins have been shown to exert a variety of physiological effects. In the heart, prostaglandins (PG) have been implicated in the regulation of cardiovascular function. This has been particularly evident in the study of the Bezold-Jarisch reflex, a cardiovascular response elicited by stimulation of the heart. PGs have been shown to mediate reflex bradycardia, with PGD2, PGE2, and PGF2α being particularly active. However, the role of these PGs in the reflex is not fully understood, and the mechanism by which they elicit the reflex remains a topic of ongoing research.

PGs have been shown to affect other aspects of cardiovascular function, including blood pressure and coronary vasomotor effects. PGD2 has been shown to cause hypotension and bradycardia, while PGI2 has been shown to increase heart rate. Studies have also suggested that the reflex actions of arachidonic acid metabolites, such as PGE2, are mediated by PGs.

The role of PGs in mediating reflex bradycardia has been studied in both anesthetized and conscious animals. In anesthetized dogs, PGs have been shown to increase heart rate and decrease blood pressure. In conscious animals, PGs have been shown to elicit reflex bradycardia, with PGI2 being particularly active.

Additional References:
Ventricular receptors activated following myocardial prostaglandin synthesis initiate reflex hypotension, reduction in heart rate, and redistribution of cardiac output in the dog.

T H Hintze and G Kaley

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