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

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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.


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 veratrine 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-
Effects of Intracoronary Arachidonic Acid (AA), before beginning the experiments. Mg), PGI2 (3°C), and a 27-gauge needle was placed in each artery soaked sponges. After surgery, we waited 30 minutes kept moist with saline warmed to 37°C and with saline-gas analyzer (Radiometer, BMS3 MK2). The heart was just distal to the flow probe for drug injection. The animals were warmed with a water-circulating heating system around the descending thoracic aorta (435°C, 440°C, 445°C, some animals, a noncannulating flow probe was placed possible, for the placement of flow probes (408°C, 409°C, 410°C), and a 27-gauge needle was placed in each artery 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 manageable zone). Six tissue sections were also taken from areas perfused by the LAD and LCX. Five transverse tissue sections were taken from areas perfused by the LAD and LCX. The order of injections and 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 M, 9 μm) labeled with ¹²⁵I, ⁸⁵Sr, and ⁴⁶Sc, 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; Domenech 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...
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 (Fisher) was extended up in 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). 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, 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 LCA and the LAD are shown in Table 1. LCA injection of AA resulted in significant dose-related falls in arterial pressure (−9.0 to −27%), heart rate (−5.0 to −10%), 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 PGD₂, 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 administered into the LAD.

Nitroprusside caused large increases in coronary blood flow when injected into either the LCA (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>Control</th>
<th>∆</th>
<th>LCX injection</th>
<th>∆</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAP (mm Hg)</td>
<td>HR (beats/min)</td>
<td>LV dP/dt (mm Hg/sec)</td>
<td>CBF (ml/min)</td>
</tr>
<tr>
<td>MAP (control)</td>
<td>151 ± 7.0</td>
<td>181 ± 4.6</td>
<td>5867 ± 400</td>
<td>24.0 ± 6.0</td>
</tr>
<tr>
<td>MAP (injection)</td>
<td>157 ± 9.1</td>
<td>184 ± 5.9</td>
<td>5934 ± 553</td>
<td>36 ± 5.1</td>
</tr>
<tr>
<td></td>
<td>Arachidonic acid (200 µg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAP (control)</td>
<td>149 ± 5.8</td>
<td>178 ± 4.0</td>
<td>5200 ± 563</td>
</tr>
<tr>
<td>MAP (injection)</td>
<td>158 ± 7.8</td>
<td>183 ± 5.8</td>
<td>5966 ± 616</td>
<td>38 ± 6.0</td>
</tr>
<tr>
<td></td>
<td>Arachidonic acid (400 µg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAP (control)</td>
<td>147 ± 4.6</td>
<td>176 ± 5.0</td>
<td>5667 ± 425</td>
</tr>
<tr>
<td>MAP (injection)</td>
<td>154 ± 6.7</td>
<td>181 ± 5.8</td>
<td>6100 ± 787</td>
<td>37 ± 4.8</td>
</tr>
<tr>
<td></td>
<td>Arachidonic acid (800 µg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAP (control)</td>
<td>147 ± 4.6</td>
<td>176 ± 5.0</td>
<td>5667 ± 425</td>
</tr>
<tr>
<td>MAP (injection)</td>
<td>154 ± 6.7</td>
<td>181 ± 5.8</td>
<td>6100 ± 787</td>
<td>37 ± 4.8</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...
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.

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 20%, 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
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.

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-
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FIGURE 4. Summary of data following LCX injection of arachidonic acid (250 ng) 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)

Arachidonic Acid (250ugs)

FIGURE 5. Injection of AA (250 ng) 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.

Concomitant with the hypotension and reduction in heart rate, the intracoronary injection of AA results in a significant fall in LV dP/dt and an increase in aortic blood flow. The reduction in LV dP/dt may result from a change in afterload (Mahler et al., 1975; Braunwald, 1977) from a reduction in contractility via the release of acetylcholine from the vagus nerve (Randall and Armour, 1974), or from a fall in heart rate (Zucker and Cornish, 1981). Alternatively, LV dP/dt may fall because of a reduction in preload. This latter possibility is unlikely, since heart rate fell and stroke volume increased—probably because of an increase in preload—after the injection of AA or prostacyclin, in our study.

The correlation we observed between the doses of AA and the reduction in heart rate, arterial pressure, and LV dP/dt indicates that cardiac production of prostaglandins may lead to graded reflex changes in cardiovascular function. This is important if the activation of ventricular reflexes by intracardiac prostaglandin synthesis is involved in physiological regulation. The reductions in heart rate and arterial pressure that we observed after LCX injection of AA are qualitatively similar to those observed by other investigators after the injection of veratridine in anesthetized dogs (Frink et al., 1971; Donald and Shepherd, 1978, 1979; Thames et al., 1978; Walker et al., 1978) or in conscious dogs (Zucker and Cornish, 1981), during coronary occlusion in anesthetized (Thames et al., 1978) or conscious dogs (Petersen and Bishop, 1974), and during coronary arteriography in humans and dogs (Eckberg et al., 1974; Frink et al., 1975). Since the two receptor areas in the left ventricle are of approximately equal size and...
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, PGE$_2$ and PGI$_2$, also were studied. The slowing of the heart following the intracoronary injection of PGI$_2$ 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 E$_2$ had effects similar to PGI$_2$, although doses of PGE$_2$ that were 10 times higher than those of PGI$_2$ 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 PGE$_2$, but are in contrast to our previous work using pulmonary artery or intravenous injection of PGE$_2$ (Hintze et al., 1979). Since PGE$_2$ 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 PGE$_2$ 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 $\alpha$-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 (Cole-ridge 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 veratrine 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 $LV \frac{dp}{dt}$. 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.

We thank Kathleen Vagi for help in preparation of the manuscript and Arsenio Baez and Maret Panzenbeck for superb technical assistance. Prostacyclin (PGI$_2$) and prostaglandin E$_2$ were kindly supplied by Drs. Udo Axen and John Pike of the Upjohn Company, Kalamazoo, Michigan. This work was supported by a grant from the Whitehall Foundation.

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Received December 20, 1982; accepted for publication December 29, 1983.

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Index Terms: Arachidonic acid · PG1 · PGE2 · Renal blood flow · Microspheres · Left circumflex coronary artery · Left anterior descending coronary artery
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Circ Res. 1984;54:239-247
doi: 10.1161/01.RES.54.3.239

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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