ABSTRACT

We investigated the relationship between prostaglandin release and the coronary vasodilatation evoked by anoxia. Isolated rabbit hearts were perfused via the aorta with Krebs-Ringer's solution. The coronary effluent was bioassayed continuously in terms of prostaglandin E2 for prostaglandin-like substance which was present (at < 1 ng/ml) in 60 of 66 hearts. This basal release was abolished by the prostaglandin synthetase inhibitor, indomethacin (1-2 μg/ml), a result which adds further to the identity of the prostaglandin-like substance as a prostaglandin. Anoxia increased coronary flow sometimes by 100% and evoked prostaglandin release shortly thereafter. Abolition of prostaglandin synthesis by indomethacin pretreatment did not affect nor did infusion of exogenous prostaglandin mimic the anoxia-induced flow increment; thus, we conclude that prostaglandin release cannot account for the anoxia-induced vasodilator response. Furthermore, the failure of indomethacin to alter resting coronary blood flow suggests that a local prostaglandin release is not responsible for either the maintenance or the modulation of coronary flow in this preparation.

KEY WORDS prostaglandin synthetase inhibition reactive hyperemia indomethacin anoxia-induced vasodilatation coronary blood flow

It has been proposed that prostaglandins are mediators or modulators of the coronary vasodilatation that occurs in the hypoxic myocardium, for prostaglandin-like substances are released following coronary artery occlusion or systemic hypoxia in dog hearts in situ (1-3). The discovery that aspirin and other nonsteroid anti-inflammatory agents such as indomethacin and meclofenamate inhibit prostaglandin biosynthesis (4, 5) has provided a pharmacological tool to determine whether prostaglandin release, in general, serves any specific physiological functions. Thus, in support of their hypothesis, Alexander et al. (2) have found that indomethacin and meclofenamate reduce the vasodilatation elicited by coronary artery occlusion or by hypoxia. However, Owen et al. (6) have reported that in the dog indomethacin has no effect on either resting coronary blood flow or the reactive hyperemia that ensues on restoration of flow following coronary artery occlusion. A further consideration arises from the observation that aspirin fails to inhibit a prostaglandin synthetase isolated from canine myocardium (7) but almost completely abolishes prostaglandin production in a similar preparation from dog spleen (5, 7).

Whether prostaglandins participate in the coronary vascular response to oxygen lack in other species, especially in vitro, is also the subject of dispute. For example, Minkes et al. (8) have found that rabbit isolated hearts only occasionally release prostaglandin-like substances following at least 5-8 minutes of ischemia. However, we have shown that rabbit isolated hearts rendered anoxic for 6 minutes usually release prostaglandin-like substances into the coronary effluent in amounts sufficient to be detected by bioassay (9, 10). In guinea pig isolated hearts, neither indomethacin nor polyphloretin phosphate, a prostaglandin antagonist, inhibits the vasodilatation evoked by coronary artery occlusion or adenosine; yet SC 19220, another prostaglandin antagonist, blocks the reactive hyperemia as well as the vasodilatation.
tion induced by adenosine or prostaglandin E₂ (11).

In view of these conflicting results, even within species, we systematically analyzed the putative role of prostaglandins in the anoxia-induced vasodilator response. We used isolated rabbit hearts, which released prostaglandinlike substances in response to anoxia and in which indomethacin inhibited prostaglandin synthesis and release (10). We recorded flow changes in response to anoxia and measured continuously by bioassay any changes in the output of prostaglandinlike substances subsequent to anoxia or inhibition of prostaglandin biosynthesis by indomethacin.

Methods

New Zealand white rabbits (2.0-3.6 kg) were given heparin (1000 IU/kg, iv); they were then killed by a blow on the head and bled via the carotid arteries. The hearts were dissected out, and the coronary vessels were perfused via the aorta with a modified Krebs-Ringer's solution at 37°C, bubbled with a 95% O₂-5% CO₂ gas mixture. The Krebs-Ringer's solution (12) had the following millimolar composition: NaCl 150, KCl 4.7, CaCl₂ (anhydrous) 2.6, KH₂PO₄ 1.2, MgSO₄·7H₂O 1.2; NaHCO₃ 25, sodium pyruvate 4.9, sodium fumarate 5.4, and glucose 11.5. The coronary circulation was perfused from a Sigmamotor T6S peristaltic pump driven by a Servomex MC47 control unit equipped to operate at either constant pressure or constant flow. Initially, in the constant-flow mode, the pump rate was gradually increased until no further increase in ventricular pressure occurred. Perfusion pressure by this time had equilibrated between 70 and 120 mm Hg. Thereafter, the pump was adjusted to perfuse the heart at constant pressure. This situation was achieved via a negative feedback device (13) that received its signals from a pressure transducer which sensed perfusion pressure from a side arm on the perfusion pump. For example, a fall in coronary resistance was immediately corrected by a change in output of the pump. For example, a fall in coronary resistance evoked an increase in pump rate (i.e., an increase in flow). Perfusion pressure was thus kept constant throughout the experiment. Coronary flow was measured from the electrical output of a generator attached to the perfusion pump and displayed after amplification on a Beckman eight-channel dynograph. Calibration of the pen recording was achieved by measuring the flow at various pump speeds. The perfusion pressure signal was obtained from the feedback device, and left ventricular pressure was monitored directly from a pressure transducer connected to a small rubber balloon which had been inserted and secured into the left ventricle (14). Both pressure signals were suitably amplified and displayed on the dynograph.

Prostaglandinlike substances were detected in the coronary effluent by a modification of the blood-bathed organ technique (15, 16). Figure 1 illustrates the apparatus. There were two circuits, one for perfusing the heart and the other for superfusing the isolated assay tissues. Coronary effluent was withdrawn from a cannula inserted into the right ventricle (14) and initially flowed via gravity to waste. At the desired time, a portion of the coronary effluent (10 ml/min) was switched into the superfusion circuit, reoxygenated, and then used to superfuse the assay tissues. The tissues usually employed were the rat stomach strip, the chick rectum, and the rat colon (17). The initial resting load on the tissues was 2-3 g, and their contractions were detected by Harvard smooth muscle transducers and displayed on the recorder. The tissues were made insensitive to acetylcholine, histamine, 5-hydroxytryptamine, and catecholamines by continuously infusing a mixture of antagonists (18) into the superfusing fluid (Fig. 1) to give the following final concentration of the active bases: hyoscine hydrobromide 10⁻⁷ g/ml, mepyramine maleate 10⁻⁷ g/ml, methys- ergide maleate 2 x 10⁻⁷ g/ml, phenoxybenzamine hydrochloride 10⁻⁷ g/ml, and propranolol hydrochloride 2 x 10⁻⁸ g/ml. Indomethacin was similarly infused (except where indicated in the text) to give a final concentration of 1-2 µg/ml to inhibit prostaglandin biosynthesis within the tissues and to increase their sensitivity to exogenous prostaglandins (19). Prostaglandins were administered directly into the superfusing fluid (DIR in figure legends) or into the total coronary inflow (IA in figure legends).
To evoke maximal flow changes and to standardize experimental conditions, anoxia was the only vasodilator stimulus investigated. Anoxia was achieved by perfusing the heart with Krebs-Ringer’s solution which had been equilibrated for at least 1 hour with a 95% N₂-5% CO₂ gas mixture.

**DRUGS**

Prostaglandins E₁, E₂, and F₂α were freshly prepared by dissolving the powder in ethanol (5 mg/0.3 ml) and diluting this solution with Krebs-Ringer’s solution. Isopropynorepinephrine sulfate (Boots) was dissolved in 0.9% NaCl and used immediately; the dose refers to the base. Heparin (Boots) was used as supplied.

**Results**

**BASAL RELEASE OF PROSTAGLANDINLIKE SUBSTANCE**

Sixty-six rabbit hearts were perfused with oxygenated Krebs-Ringer’s solution; prostaglandinlike substance (PLS) was detected in the coronary effluent of 60 of them. PLS concentration was calculated in terms of prostaglandin E₂ (PGE₂) and varied from 0.1 to 1 ng/ml (mean ± SE 0.27 ± 0.03 ng/ml). Indomethacin (1–2 μg/ml), a potent prostaglandin synthetase inhibitor in all tissues studied to date (20), always abolished the basal release of PLS when it was infused through the heart, thereby adding to the identity of PLS as a prostaglandin.

Often, the basal output of PLS increased with time. For example, in the experiment illustrated in Figure 2, the assay tissues were first superfused with coronary effluent 25 minutes after starting perfusion of the heart with Krebs-Ringer’s solution. The concentration of PLS detected by the rat stomach strip was approximately 0.1 ng/ml. Coronary flow at this time was 33 ml/min. There-

1 Generously supplied by Upjohn.
2 Generously supplied by Merck, Sharp, and Dohme.

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**FIGURE 2**

Indomethacin (INDO) abolishes basal output of prostaglandinlike substance. The heart from a 2.1-kg rabbit was perfused at constant pressure (100 mm Hg). Each time the coronary effluent (CE) was used to superfuse the rat stomach strip (R.S.S.), it contracted. The second exposure to effluent produced a larger contraction of the rat stomach strip than did the first, indicating an increased release of PLS with time. Indomethacin (2 μg/ml) infused through the coronary circulation abolished the release of PLS within 15 minutes. Calibrating doses of prostaglandin E₂ (PGE₂) were infused directly to the assay tissues (DIR). Horizontal calibration = 10 minutes, and vertical calibrations = 10 cm and 150 mm Hg. In this experiment, the chick rectum and the rat colon were insensitive to the small PLS output, and the tracings are not shown.
Anoxia inhibits massage-induced release of PLS. The heart from a 2.2-kg rabbit was perfused at constant pressure (80 mm Hg). At the asterisks, the heart was gently massaged while coronary effluent (CE) superfused the rat stomach strip (R.S.S.); the first two of these stimuli released PLS, but the third, applied during anoxia (perfusion with a 95% N₂-5% CO₂ gas mixture [N₂]), did not. After discontinuing the anoxia, massage again released PLS. Indomethacin (INDO) infused into the coronary circulation during anoxia abolished both the basal and the massage-induced release of PLS, yet it had no effect on the vasodilatation produced by anoxia. Prostaglandin E₂ (PGE₂) was infused directly to the tissues (DIR). Horizontal calibration = 10 minutes, and vertical calibrations = 10 cm, 75 ml/min, and 150 mm Hg.

Therefore, the total output of PLS was ≈ 3.3 ng/min. When the assay tissues were superfused with fresh Krebs solution instead of with the coronary effluent, the rat stomach strip relaxed to its previous resting level. When coronary effluent was tested a second time approximately 20 minutes later, the concentration of PLS was approximately 0.25 ng/ml. This output gradually increased to almost 0.4 ng/ml, although coronary flow remained unchanged. When indomethacin was infused through the coronary circulation, it abolished PLS release within 15 minutes, also without a change in coronary flow. Thus, although PLS release often increased with time, it was not paralleled by a commensurate increase in coronary flow.

**EFFECTS OF ANOXIA**

When the hearts were made anoxic by perfusion with Krebs-Ringer's solution equilibrated with the nitrogen mixture, ventricular pressure decreased and coronary flow increased, sometimes by more than 100%. After short periods of anoxia (< 10 minutes), these changes were reversible by reoxygenation. There was no increased PLS output during anoxia, but several minutes after reoxygenation of the heart the assay tissues contracted, indicating PLS release (13 of 14 trials). The increased concentration of PLS detected after a period of anoxia (over and above the resting output) varied from 0.1 to 1 ng/ml (mean ± SE 0.38 ± 0.08 ng/ml). Furthermore, as with resting coronary flow and PLS output, there was no correlation between the PLS output after anoxia and the magnitude of the vasodilator response (correlation coefficient \( r = 0.21 \), 13 observations).

We next examined the temporal relationship between anoxia and PLS release, since PLS always appeared following but not during anoxia. The sensitivity of the assay tissues to prostaglandins and to other agonists is reduced by inadequate oxygenation of the bathing fluid (18); it was for this reason that the effluent was always reoxygenated before it was used to superfuse the tissues. That the assay tissue sensitivity did not vary during cardiac anoxia was confirmed by infusing prostaglandins. Thus, the failure to detect an increase in PLS output during cardiac anoxia was not an artifact of the assay method.

Prostaglandin biosynthesis, which can be equated with release since tissues do not store prostaglandins (19), requires molecular oxygen (21, 22). Thus, the lack of PLS output during cardiac anoxia could have been due to
the nonavailability of oxygen. The experiment illustrated in Figure 3 tested this possibility. Since mechanical manipulation consistently releases PLS in the isolated heart (10), we examined the efficacy of this stimulus before, during, and after anoxia. Shortly after each of the first two mechanical stimuli in Figure 3, PLS appeared in the coronary effluent, but it did not appear when massage was applied during anoxia. As in previous experiments, PLS appeared only after anoxia (which in this experiment lasted 15 minutes), and massage once more increased further the output of PLS. Both the massage-induced and the anoxia-induced release of PLS were abolished by indomethacin (2 μg/ml).

EFFECTS OF INDOMETHACIN ON CORONARY FLOW

In 25 experiments, indomethacin (1–2 μg/ml) was infused into the coronary circulation after 0.5–1 hour of perfusion; there was no change in resting coronary flow. Furthermore, an infusion of indomethacin during the anoxia-induced increase in coronary flow also had no effect on the elevated flow rate (Fig. 3). However, in those experiments in which several periods of anoxia were applied, indomethacin infused before an anoxic interval abolished the PLS output and sometimes apparently reduced the increase in coronary flow as well. In the experiment illustrated in Figure 4, for instance, the first and second periods of anoxia increased coronary flow by 32 and 29 ml/min, respectively; shortly after each stimulus the rat stomach strip (and the chick rectum) contracted, the second stimulus evoking a slightly greater output of PLS than the first. Fifteen minutes after starting an infusion of indomethacin (2 μg/ml) through the heart, anoxia increased coronary flow by only 10 ml/min and there was no increased PLS release after reoxygenation. However, even without indomethacin treatment, the second or third period of anoxia sometimes induced a smaller increase in coronary flow than that seen before; this phenomenon can be seen in Figure 3. For this

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

**FIGURE 4**

Effect of indomethacin (INDO) on anoxia-induced release of PLS and increase in coronary flow. The heart from a 2.0-kg rabbit was perfused at constant pressure (115 mm Hg). Anoxia 6 minutes in duration was produced by perfusing the heart with Krebs-Ringer's solution equilibrated with a 95% N₂, 5% CO₂ gas mixture (N₂). The first two periods of anoxia increased coronary flow by 32 and 29 ml/min, respectively. Shortly after anoxia was terminated, the rat stomach strip (R.S.S.) contracted. Indomethacin, infused through the heart before the third anoxic period, abolished the basal as well as the anoxia-induced release of PLS. There was also a reduction in the coronary vasodilator response during this exposure to anoxia. Prostaglandin E₂ (PGE₂) was infused directly to the assay tissues (DIR). Prostaglandin E₁ (PGE₁) infused through the heart (IA) after the coronary effluent (CE) no longer superfused the assay tissues did not cause vasodilatation. Horizontal calibration = 10 minutes, and vertical calibrations = 5 cm, 105 ml/min, and 150 mm Hg.
Anoxia increases coronary flow in the indomethacin-treated heart. The heart from a 3.6-kg rabbit pretreated with indomethacin (2 mg/kg) was perfused at constant pressure (90 mm Hg) with Krebs-Ringer’s solution containing indomethacin (2 μg/ml). PLS was not present in the coronary effluent (CE) nor was it released after anoxia (which increased coronary flow from 46 to 67 ml/min). Initially, prostaglandin E₂ (PGE₂) (1000 ng/min) infused through the heart (IA) produced a modest increase in coronary flow (6 ml/min); this same dose before and during the second anoxic interval did not appreciably alter this flow increment. Prostaglandin E₁ (PGE₁) was infused directly to the tissues (DIR). R.S.S. = rat stomach strip. N₂ = perfusion of the heart with a 95% N₂-5% CO₂ gas mixture. Horizontal calibration = 10 minutes, and vertical calibrations = 5 cm, 70 ml/min, and 150 mm Hg.

reason, it was impossible to test adequately within a single experiment the effects of indomethacin on the anoxia-induced increase in coronary flow. To overcome this difficulty, anoxia was produced in hearts from rabbits which had been pretreated (30–60 minutes before killing) with either indomethacin (2–10 mg/kg, iv) or indomethacin solvent alone. The hearts from indomethacin-treated rabbits were always perfused continuously with Krebs-Ringer’s solution containing indomethacin (2–5 μg/ml); these hearts did not release PLS into the coronary effluent (Fig. 5), although those treated with solvent alone did. Comparison of the experiments illustrated in Figures 4 and 5 shows that the resting coronary flow all as the first anoxia-induced flow increments were similar. Table 1 summarizes the results of this series of 14 experiments and shows further that there was no significant difference between the two groups. In addition, there was no significant difference between their respective perfusion pressures (unpaired t-test, P > 0.1). Figure 5 also illustrates that prostaglandin E₁ (PGE₁), a coronary vasodilator in the rabbit (23), failed to duplicate or even approximate the magnitude of the anoxia-induced vasodilation. The concentration used (> 20 ng/ml) was more than ten times that of PLS usually detected after anoxia. In the same experiment, PGE₁ infused for 4 minutes before and during the anoxia did not potentiate the flow increment in this indomethacin-treated heart. In three other experiments with or without indomethacin, infusions of PGE₁ or PGE₂ in concentrations ranging from 1 to 20 ng/ml did not cause any appreciable increase in coronary flow (see Fig. 4).

In each of two experiments, a 30-second infusion of isopropylnorepinephrine (1 μg/ml) increased coronary flow by approximately 60%, a similar increment to that produced by anoxia. This result, together with the fact that anoxia always increased coronary flow, showed that the coronary vasculature was

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<td><strong>Effect of Indomethacin on Blood Flow and Perfusion Pressure</strong></td>
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<th>Perfusion pressure (mm Hg)</th>
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<tr>
<td></td>
<td>N</td>
<td>Resting</td>
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<tr>
<td>Control</td>
<td>7</td>
<td>93.6 ± 7.8</td>
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<tr>
<td>Indomethacin</td>
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<td>81.4 ± 8.4</td>
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Indomethacin (2-10 mg/kg) was injected intravenously at least 30 minutes before the rabbit was killed; in addition, indomethacin-treated hearts were perfused with Krebs-Ringer’s solution containing indomethacin (2–5 μg/ml). N = number of rabbits in each group. Statistical significance (P < 0.05) was determined by Student’s t-test for unpaired data (29); NS = not significant.
not maximally dilated. That the anoxia-induced flow increase probably did not arise passively due to the fall in ventricular pressure is reinforced by the facts that (1) the increase in coronary flow usually preceded the fall in ventricular pressure and (2) ventilatory pressure could fall without a substantial flow increase (e.g., third exposure to anoxia in Fig. 4).

REMOVAL OF PROSTAGLANDINS BY THE HEART

Nakano and Prancan (24) have found that homogenates of rat heart do not appreciably metabolize added PGE\(_2\). To determine whether rabbit isolated hearts removed or metabolized prostaglandins infused through their vascular bed, infusions of PGE\(_2\) were made into the aortic cannula while the assay tissues were being superfused with coronary effluent. The resulting contractions of the assay tissues were calibrated by infusing prostaglandins into the total coronary effluent. In three hearts, less than 5% of the PGE\(_2\) disappeared; in one other heart, 25% was removed.

Discussion

Piper and Vane (25) have suggested that the prevailing factor which induces prostaglandin release from tissues is a disturbance of cellular membranes. Traumatic stimuli, such as mechanical manipulation and gaseous emboli, release prostaglandins from rabbit isolated hearts (10), and it is possible that anoxia also causes prostaglandin release by inducing changes in the cell membrane. Occasionally, rabbit isolated hearts, like the cat isolated spleen (26), release more prostaglandins as the experiment progresses. This increased prostaglandin release might be linked to a gradual deterioration of the preparation (Fig. 2), perhaps resulting from slight edema.

Although prostaglandins were released following anoxia, we do not think that they mediate the accompanying increase in coronary flow. Sometimes, within a single experiment, indomethacin appeared to reduce the increase in flow induced by anoxia, but so did multiple exposures to anoxia even in the absence of indomethacin (see especially Fig. 4). To overcome these difficulties, anoxia was produced in hearts from rabbits pretreated with indomethacin or indomethacin solvent alone; there was no difference in the anoxia-induced vasodilator response, showing that prostaglandin biosynthesis and release did not mediate the vasodilatation. The failure of exogenously administered PGE\(_2\) or PGE\(_3\) to mimic the flow increment also supports this finding.

Since several mammalian organs such as the lung avidly inactivate prostaglandins (17), the rabbit heart could have released more prostaglandins than appeared in the effluent. This possibility was shown to be unlikely, for rabbit isolated hearts removed only 5-25% of the biological activity of PGE\(_2\) infused through the coronary bed. It also seems unlikely that prostaglandins play a permissive or facilitatory role in the genesis of anoxia-induced vasodilatation, since PGE\(_2\), infused prior to and during anoxia in indomethacin-treated hearts, merely added to and not potentiate, the anoxia-induced flow increment.

A second possibility exists, namely, that a prostaglandin maintains the vascular tone of this preparation and that abolition of prostaglandin synthesis by oxygen deficiency then causes vasodilatation. Certainly, the intramural generation of prostaglandins contributes to the maintenance of tone in some isolated smooth muscle preparations (19). This possibility can also be excluded, however, since indomethacin abolished prostaglandin synthesis but failed to increase resting coronary blood flow.

The rabbit isolated heart has a relatively high coronary flow, which may be due to a vasodilator substance which is continuously released because of the conditions of the experiment. The lack of effect of indomethacin on the resting coronary flow in this preparation shows that any such vasodilator substance is not prostaglandin.

With this preparation, we have shown the following. (1) Sufficient oxygen is available for basal synthesis of PLS. (2) The heart has the capacity to increase coronary flow in response to anoxia and infusions of isopropylnorepinephrine. (3) Indomethacin, although it abolishes basal and anoxia-induced PLS output, does not alter either resting coronary flow or the anoxia-induced flow increment. (4) Exogenous PGE\(_2\) or PGE\(_3\), in concentrations which lead to amounts in the coronary effluent at least ten times greater...
than the amount of PLS normally detected, do not mimic or affect the anoxia-induced vasodilatation. (5) Rabbit hearts do not appreciably metabolize exogenous prostaglandins.

From these results we conclude that the anoxia-induced release of PLS from rabbit isolated hearts is related to the trauma imposed by the stimulus and is not responsible for the coronary dilator response which accompanies the anoxia.

One further point should be made. Generation of prostaglandins requires oxygen (21, 22) so the lack of PLS output during anoxia in our experiments is easily understood. Likewise, the failure of indomethacin to alter the anoxia-induced vasodilator response when it is infused during such a vascular adjustment (when prostaglandin synthesis cannot proceed) is equally clear. It might be argued that a less extreme stimulus would have allowed prostaglandin generation, which might have caused a further increase in flow over and above that found with anoxia. Against this argument is the fact that the burst of PLS release which followed anoxia was not associated with any postanoxia increase in flow. Furthermore, it is well established (27) that the degree of hyperemia is directly related to the degree of cardiac hypoxia. However, our experiments do not exclude such a possibility, which might imply two mechanisms of vasodilatation during cardiac hypoxia. One would depend on prostaglandin generation and the other, presumably the one we have studied in the rabbit isolated heart, on a nonprostaglandin mechanism, such as adenosine release, as proposed by Berne and his colleagues (27, 28). If two mechanisms do exist, their relative importance may vary from species to species and with the type of preparation studied; such variation may account for the present dissimilar results (2, 6).

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