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Research Article

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Regulation of Postocclusive Hyperemia by

Endogenously Synthesized Prostaglandins in the Dog Heart

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INTRODUCTION

Prostaglandins are a group of ubiquitous vasoactive lipids which have been postulated to have an important regulatory role in the cardiovascular system (1). The

capacity of the canine heart to both synthesize and metabolize prostaglandins has been demonstrated (2). The recent observation that the adenine nucleotides ATP and ADP are potent releasers of a prostaglandin-like material from the rabbit heart (3) and earlier evidence that the adenine nucleoside adenosine may be an important mediator of coronary vascular resistance (4) suggest that prostaglandins and the adenine nucleotides and their derivatives may interact in the regulation of coronary blood flow. There is, in fact, some evidence to suggest that adenosine is not the sole mediator of the altered coronary blood flow in reactive hyperemia and hypoxia (5, 6). Therefore, experiments were designed to elucidate the role of endogenous prostaglandin synthesis in the regulation of coronary blood flow.

METHODS

Intact animals

Mongrel dogs of either sex were anesthetized with sodium pentobarbital, 30 mg/kg i.v. A transverse thoracotomy was made in the fourth intercostal space with the animals on positive pressure respiration. 100 U/kg heparin was administered initially and then 10 U/kg per h. A stainless steel Gregg cannula was inserted into the left subclavian artery, which had previousy been ligated distally. The cannula was passed across the aortic arch and into the left main coronary artery, where it was tied in place by a 4-0 silk suture passed around the artery during earlier dissection. This cannula was perfused with blood obtained from the femoral artery. The perfusion circuit consisted of $\frac{3}{16}$-in tubing and an electromagnetic flow probe (Carolina Medical Electronics, Inc., King, N. C.). All flow meters were calibrated by passing canine blood through them with a constant flow pump and timing the collection of blood. A cannula was then placed into the coronary sinus.

Heart-lung preparation

Mongrel dogs of either sex were anesthetized as above. This preparation has been described in detail previously (7). Briefly, the preparation consisted of dissection of the left main coronary artery, the descending aorta proximal to the

first intercostal artery, the left subclavian artery, the brachiocephalic artery, and superior and inferior vena cavae, and ligation of the azygous vein. Heparin, 100 U/kg, was administered intravenously and the brachiocephalic artery was cannulated with an 18 F aortic cannula. A wide-bore cannula was inserted into the right atrium through the atrial appendage. The aortic and right atrial cannulas were connected to the perfusion circuit as shown in Fig. 1. The blood was directed through tubing ($\frac{3}{8}$ in ID) from the aortic cannula to the "systemic" and coronary perfusion circuits. The systemic circuit consisted of an electromagnetic flowmeter, a plastic 1-liter reservoir placed 137 cm above the animal's heart, a heat exchanger maintained at 37°C by a circulating water bath, a bubble trap, and a resistance clamp. The input gas to the respirator was changed from room air to 21% O_2, 5% CO_2, and 74% N_2, obtained from a gas-mixing system (8). The aorta was occluded proximal to the first intercostal artery. The systemic flow was maintained at 1 liter/min by adjusting the resistance clamp. The circulation of the heart and lungs was completely isolated from the remainder of the animal. Once systemic perfusion was instituted, the left main coronary artery and coronary sinus were cannulated as described above. Mean aortic pressure (and thereby coronary perfusion pressure) was maintained at 85–92 mm Hg by the arterial reservoir.

Prostaglandin measurements

Blood was withdrawn into heparinized glass tubes and centrifuged at 4°C. 3 ml plasma were added to glass extraction tubes, in which 600 cpm of chromatographically pure [³H]prostaglandin E_1 (New England Nuclear, Boston, Mass.), in ethyl alcohol had previously been dried under nitrogen. The plasma was mixed to ensure that the labeled prostaglandin was in solution, acidified to pH 3.5 with formic acid, and extracted twice with 5 ml of ethyl acetate. The ethyl acetate was evaporated to dryness with N_2. The extract was then chromatographed on silicic acid (SilicAR cc 4, 200–325 mesh, Mallinkrodt Chemical Works, St. Louis, Mo.), activated by heating overnight at 100°C. 0.5 g silicic acid in a solution of benzene : ethyl acetate, 60:40 (solution I) was applied to a glass chromatography column plugged with glass wool. The column was allowed to run dry and then washed with 5 ml of benzene : ethyl acetate : methanol, 60:40:2. The extract was dissolved in 0.2 ml of benzene : ethyl acetate : methanol 60:40:10. Next 0.6 ml of solution I was added to the extract and mixed and then the mixture was applied to the column. The extraction tube was then rinsed with 0.2 ml of solution I and this was added to the column. The column ran dry and then was eluted with 1 ml of benzene and subsequently with 0.3 ml of solution I. Prostaglandin A fraction was then eluted with 5.0 ml of solution I, and prostaglandin E was eluted with 11 ml of benzene : ethyl acetate : methanol, 60:40:3. The prostaglandin E fraction was evaporated under a N_2 stream. This chromatography system provided effective group separation of the prostaglandins, as previously reported in the similar systems (9, 10). All organic solvents were spectral grade (Fisher Scientific Co., Pittsburgh, Pa.).

The prostaglandin E was converted to prostaglandin B by modifications of a previously published procedure (11). 1 ml of 0.1 N methanolic KOH was added to the tube containing the prostaglandin E fraction, mixed for 45 s, and kept at room temperature for 45 min. The solution was then acidified with 100 µl of 88% formic acid to a pH of about 3.0, and 5 ml of chloroform were added and mixed. 2 ml
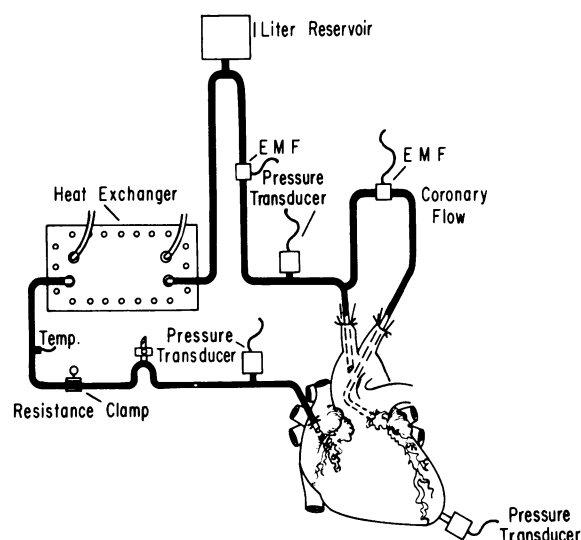

FIGURE 1 Heart-lung preparation perfusion circuit. Electromagnetic flow meters (EMF) monitor coronary blood flow and flow through the extracorporeal "systemic" circuit.

distilled water were then added and mixed. Thus any salts were extracted into the aqueous phase, and the methanol was partitioned between the chloroform and aqueous phases. The aqueous phase was removed and discarded and the chloroform was evaporated under N_2.

The antibody for the radioimmunoassay was made by coupling prostaglandin A_1 to bovine serum albumin with carbodiimide, injecting the conjugate, together with Freund's adjuvant, into sheep, and giving booster doses at monthly intervals for 3 mo. The resulting antibody, at a dilution sufficient to give 40% binding (final dilution of 1:75,000), gave a standard curve ranging from 2 to 0.08 ng of prostaglandin B_2. The log-logit plot of the dose of prostaglandin B_2 versus the fraction of tritiated prostaglandin B_1 bound gave a slope of -1.0. Scatchard plot analysis showed one binding site with an equilibrium constant of 2×10^9 liters/mol. 50% inhibition of binding for prostaglandin B_2, B_1, A_2, and A_1 occurred with 0.5, 0.09, 0.4, and 0.06 ng, respectively, of added material. On the other hand, the amount of prostaglandins E_2, E_1, and $F_{2\alpha}$ required to inhibit binding 50% was 12, 5.5, and greater than 100 ng, respectively.

A standard curve from 2 to 0.08 ng prostaglandin B_2 was run with each assay. The radioimmunoassay was performed in a Tris buffer system (0.01 M Tris, 1.6×10^{-4} M Ca^{++}, 1.7×10^{-3} M Mg^{++}, 0.14 M NaCl, and 0.1 mg/100 ml gelatin) at pH 7.4. The volume was 0.5 ml. 1 ml of the Tris buffer was added to the tubes containing the converted prostaglandin E fraction and mixed for 1 min. 0.1 and 0.2 ml portions were then added to assay tubes and 0.3 ml was added to a counting vial for recovery. Approximately 6,000 cpm of [³H]prostaglandin B_1 (made from [³H]prostaglandin E_1 by the method outlined above) were added in 0.1 ml of the buffer and the assay was started by the addition of 0.2 ml of antibody (1:30,000). The mixture was incubated for at least 3 h at 4°C and bound and free prostaglandin were separated by adding 1 ml of dextran charcoal suspension (0.625 g of charcoal and 0.0625 g of dextran, radioimmunoassay grade, Schwarz/Mann Div., Becton, Dickinson & Co., Orangeburg, N. Y.) per 200 ml Tris buffer without gelatin) and centrifuging for 15 min at 1,000 g. The supernate was
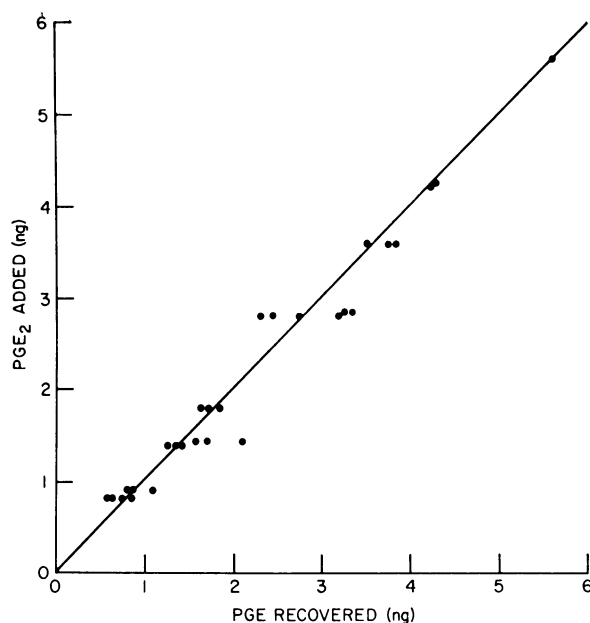
FIGURE 2 Recovery of prostaglandin E_2 added to plasma and carried through the entire assay procedure. The values were corrected for endogenous levels of prostaglandin E.

decanted into counting vials and counted on a Beckman liquid scintillation counter with Beckman Biosolve counting solution (Beckman Instruments, Inc., Fullerton, Calif.). Blank tubes (containing no antibody) were included with each assay and the counts in these tubes (usually about 120 cpm) were subtracted from the counts in all other tubes. The standard curve and the unknown samples were analyzed by a computer program (12). Duplicate samples varying by more than 15% were excluded and reassayed. The minimal detectable dose, as determined from the computer program, was 15-20 pg of prostaglandin B_2. The effective base line of the assay in plasma was 150-200 pg of prostaglandin E. The overall recovery averaged about 70%. The mean recovery of prostaglandin E_2 added to plasma and carried through the extraction and assay procedure was $104\pm19.8\%$ (SD) over the range from 0.8 to 5.6 ng. Fig. 2 demonstrates the individual points from five such experiments. Each value has been corrected for endogenous levels in the plasma. The slope of the regression line for these points does not differ significantly from 1. The value of the mean absolute error ($\sqrt{2/\pi}$ times the SD) of the value observed, compared to the amount of prostaglandin E_2 added, was 0.22 ng over the entire range.

Myocardial O_2 consumption (MVO_2)[1]

The arterial-venous (A-V) oxygen content difference across the coronary bed was continuously measured with a Guyton A-V O_2 difference analyzer (Oxford Instruments Inc., Annapolis, Md.). This instrument had been previously calibrated with canine blood with Van Slyke determination of blood O_2 content for the standardization. The output of

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[1] Abbreviations used in this paper: A-V, arterial-venous; MVO_2, myocardial oxygen consumption; Q_c, coronary blood flow.

this instrument provided an analog signal proportional to the difference of A-V O_2 content and was recorded.

The A-V O_2 difference was also continuously multiplied times the coronary blood flow (Q_c) by a four-quadrant analog multiplier (Intronics, Newton, Mass.) to provide a continuous online signal proportional to the MVO_2.

Blood gas analysis

Arterial pH and percentage of saturation were determined initially and at intervals through the experiment. Arterial pH was maintained between 7.35 and 7.45. Arterial saturation was maintained above 95%.

Myocardial lactate metabolism

Lactate measurements were performed on blood simultaneously withdrawn from the coronary arterial perfusion circuit and coronary sinus. The A-V lactate concentration times the coronary flow was taken as the lactate consumption or production of the heart. Lactate concentration was determined by the enzymatic reduction of NAD (rapid lactate, Calbiochem, San Diego, Calif.).

Experimental protocol

Reactive hyperemia. Reactive hyperemia was induced in five intact animals and six heart-lung preparations by occluding the left main coronary arterial perfusion circuit for 10, 15, and 20-s intervals. In some cases an additional 5-s interval of occlusion was used. 5 min was allowed for recovery between each occlusion, since we found that during this time basal Q_c stabilized and the amount of reactive hyperemia was reproducible after this 5-min period. Reactive hyperemia was defined as integral of the flow above basal flow, which occurred during the release of coronary occlusion. This value was obtained by electronically integrating Q_c after balancing the integrator (zero conditions) for basal flow conditions; i.e., zero integrator output for basal coronary flow. Also, the Q_c signal was conditioned by a half-wave rectifier so that only positive flow conditions would be integrated, since the fall to zero flow during occlusion would be spuriously integrated as a negative flow. Thus, the integrator output was the integral of the flow curve above base-line flow that occurred after occlusion.

Prostaglandin synthetase was inhibited by infusing the nonsteroidal anti-inflammatory agents indomethacin or meclofenamate. These chemically different agents have been shown to be potent inhibitors of prostaglandin synthetase in all tissues in which they have been tested (13), and were specifically shown to reduce canine coronary sinus immunoreactive prostaglandin E concentrations in preliminary experiments. Either compound was dissolved in 0.1 M sodium phosphate buffer (pH 7.4) at a concentration of 1 mg/ml and administered immediately. The indomethacin frequently required mild heating to enhance solubility. That indomethacin and meclofenamate were stable and maintained their pharmacologic activity under these conditions was manifested in their ability to decrease immunoreactive prostaglandin E concentrations. In the intact dogs either indomethacin or meclofenamate (50 mg) was infused into the coronary perfusion circuit at a rate of 2 mg/min. Since indomethacin is rapidly cleared in the dog ($t_\frac{1}{2}$ in dog plasma of about 10-20 min) by the liver and to a lesser extent the kidney (14), intracoronary infusion of the drugs was chosen because prostaglandin synthetase inhibition has been shown to be time-dependent in some tissues (15). In
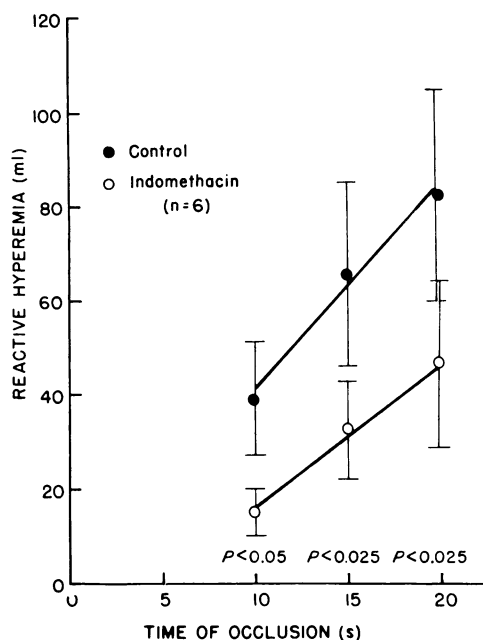
FIGURE 3 Reactive hyperemia before and after indomethacin. The results of three intact animals and three heart-lung preparations have been combined (see text for doses and methods of administration of indomethacin).
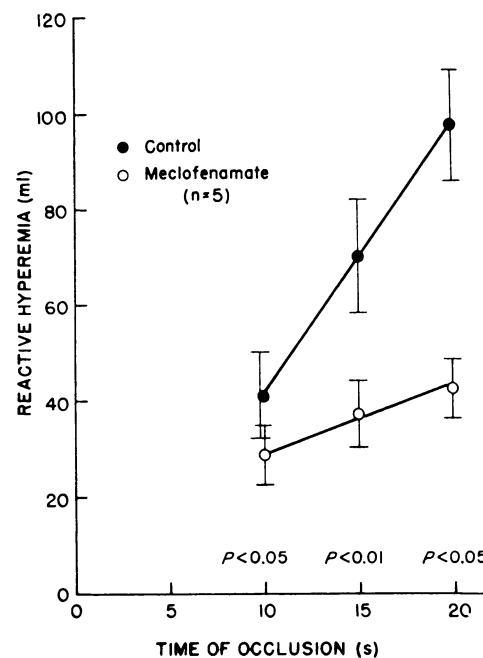

FIGURE 4 Reactive hyperemia before and after meclofenamate. The results of three intact animals and three heart-lung preparations have been combined (see text for doses and methods of administration of meclofenamate).

the heart-lung preparation 15 mg (25 mg in one animal) of either drug was injected into the systemic circuit. From 20 to 30 min after administration of the drug, reactive hyperemia was again induced.

Reactive hyperemia and prostaglandin production. In an additional five heart-lung preparations, prostaglandin production was measured by simultaneously sampling arterial and coronary sinus blood for prostaglandin determinations in the basal state and during reactive hyperemia. Three separate 20-s occlusions were performed at 5-min intervals. The arterial and coronary sinus blood was withdrawn for 30 s immediately after the release of the occlusion. Thus, prostaglandin output by the heart, during this period, was calculated as the coronary sinus prostaglandin concentrations minus the arterial concentration times the average flow during the 30-s period (obtained by integration). Indomethacin (7 mg) was then administered to the perfusion circuit (resultant concentration approximately 3.5 μg/ml) and 30 min later the procedures were repeated.

Statistics

The data were analyzed by a paired t test (16). A P of less than 0.05 was considered significant.

RESULTS

Reactive hyperemia

Coronary flow. After the release of occlusions of the left main coronary artery in both intact dogs and canine heart-lung preparations, there was an increase in coronary flow above base-line flow. The integral of the flow above base line, reactive hyperemia, was directly

proportional to the duration of occlusion (Figs. 3 and 4). Reactive hyperemia was significantly reduced in five animals after meclofenamate and in six animals after indomethacin administration (Figs. 3 and 4). The responses of the intact animals and heart-lung preparations were not significantly different and have been combined in these figures. The apparent differences in
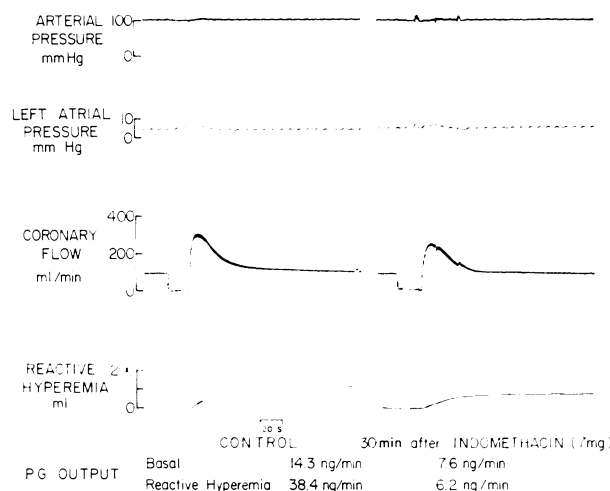

FIGURE 5 Effects of indomethacin on reactive hyperemia in a canine heart-lung preparation. Indomethacin (7 mg) decreased prostaglandin synthesis and reactive hyperemia.

Prostaglandins and Coronary Blood Flow **1177**

TABLE I

Effects of Indomethacin on Prostaglandin Production and Reactive Hyperemia

Basal						Reactive hyperemia					
Coronary flow		[PG] difference*		PG output‡		Peak coronary flow		Reactive hyperemia§		PG output‖	
Cont	After I¶	Cont	After I	Cont	After I	Cont	After I	Cont	After I	Cont	After I
ml/min		*ng/ml*		*ng/min*		*ml/min*		*ml*		*ng/min*	
145	100	0.09	0.07	13.1	7	365	273	81	53	22.7	8.4
115	90	0.33	0.02	38	1.8	340	243	101	59	55.6	0
145	110	0.10	0.09	14.5	9.9	332	303	125	65	30.4	13.5
110	135	0.12	0.07	13.2	9.5	290	266	123	76	29.3	7.7
95	95	0.15	0.08	14.3	7.6	318	252	103	71	38.4	6.2
122±9.9	106±8	0.16±0.04	0.07±0.01	18.6±4.9	7.2±1.4	329±12	267±10	107±8	65±4	35.3±5.6	7.2±2
NS		NS		NS		$P < 0.025$		$P < 0.005$		$P < 0.025$	

* PG concentration difference: coronary sinus − arterial.
‡ PG output calculated as PG concentration differences × coronary flow.
§ Reactive hyperemia, integral of coronary flow (above base line) after occlusion release (see text).
‖ PG output, calculated as [PG] difference of blood collected during the 30 s after the occlusion release × average flow during the same time period.
¶ 7 mg indomethacin administered to entire circuit, the volume of which was 2 liters (approximately 3.5 μg/ml).

the slopes of the lines describing the relationship between reactive hyperemia and the duration of occlusion after indomethacin and meclofenamate are not statistically significant ($P > 0.1$).

The original tracings of physiologic data obtained from a heart-lung preparation are shown in Fig. 5. Reactive hyperemia after a 20-s occlusion of the coronary perfusion circuit was decreased after indomethacin (7 mg). Systemic arterial pressure, left atrial pressure, systemic flow, heart rate, and basal coronary blood flow were unaffected by indomethacin but reactive hyperemia was significantly reduced after indomethacin.

Reactive hyperemia was repeatedly induced in two heart-lung preparations and one intact animal over 150 min without any pharmacologic interventions, and was found to be stable and reproducible.

Prostaglandin production. In five heart-lung preparations, prostaglandin production by the heart averaged

FIGURE 6 Adenosine dose response curve before (○) and after (△) indomethacin administration in three dogs.

18.6±4.9 ng/min in the basal state. Blood collected in the 30 s immediately after the release of a 20-s occlusion demonstrated a significant rise in the production of prostaglandin E-like material to 35.3±5.6 ng/min ($P < 0.025$). The cardiac production of prostaglandin E-like material in nanograms per minute was calculated from the concentration difference (coronary sinus minus arterial in nanograms per milliliter) times the coronary flow (milliliters per minute). Basal cardiac production was calculated from the basal coronary flow times the concentration difference in the basal state. For the prostaglandin output during reactive hyperemia, arterial and coronary sinus blood were collected for 30 s immediately after occlusion release. The product of the average coronary flow during the 30-s collection period and the concentration difference during the collection period was determined. In the basal state there was no significant reduction of coronary flow 30 min after 7 mg of indomethacin. After indomethacin the difference in prostaglandin concentration across the coronary bed fell in each preparation and the average A-V difference decreased from 0.16±0.04 to 0.07±0.01 ng/ml. Also, after indomethacin, prostaglandin production fell in each animal and the average decreased from 18.7±4.8 to 7.2±1.4 ng/min. However, neither of these values reached statistical significance (Table I). It should be noted that basal prostaglandin concentrations were determined from samples drawn 30 min after indomethacin administration. During the next 20 min, each of the five preparations had further decrease in the concentration of coronary sinus immunoreactive prostaglandin E, to levels approaching arterial levels. After indomethacin there was no significant increase in prostaglandin output in response to the 20-s coronary artery occlusion (basal 7.2±1.4 ng/min, during reactive hyperemia 7.2±2 ng/
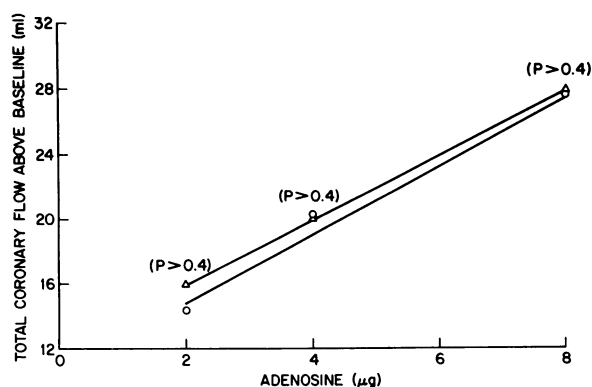
min) and both the peak flow and total amount of reactive hyperemia were significantly reduced (Table I).

Response to adenosine

To determine if indomethacin had a nonspecific depressant effect on coronary vascular reactivity in general and to the vasodilator response to adenosine in specific, adenosine was injected into the coronary perfusion circuit both before and after these drugs were administered. There were no significant effects on the adenosine dose-response curve in three heart-lung preparations after indomethacin. Fig. 6 represents the response curve of the three preparations before and after indomethacin.

Lactate metabolism

In five of the heart-lung preparations, to determine if prostaglandin synthetase blockade interfered with aerobic metabolism, left ventricular lactate consumption was measured by simultaneously determining lactate concentrations in the arterial and coronary sinus blood and the left main coronary flow. In two of the preparations lactate consumption was determined before and after indomethacin, in two preparations before and after meclofenamate, and in one preparation no drug was given. In all preparations there was a slight time-dependent increase in lactate extraction, which did not exceed 18% in any preparation. Lactate extraction averaged 9.8 ± 0.8 mg/min during the control period and 1 h after administration of drugs in four preparations was 11.0 ± 1 mg/min.

MVO_2

In the five heart-lung preparations and two intact dogs in which oxygen consumption was measured, there was no change in MVO_2 during the experimental procedures. MVO_2 averaged 13 ± 2.5 ml/min before prostaglandin synthetase inhibition and 12.5 ± 3.0 ml/min after inhibition.

DISCUSSION

These data suggest that prostaglandin synthesis is necessary for the normal modulation of blood flow in response to brief periods of ischemia in the canine heart.

Although coronary blood flow is related to the metabolic requirements of the heart (17, 18), not all of the factors involved in regulating coronary blood flow are known (18). The flow debt incurred during brief occlusion of a coronary artery is repaid up to two-fold and the coronary A-VO_2 difference actually decreases while flow is still increased during the later stages of reactive hyperemia, thus leading to the overpayment of the calculated O_2 debt in occlusions of 15 s or longer (19). These findings suggest that other factors in ad-dition to cardiac metabolic products are involved in the regulation of coronary blood flow.

Endogenous prostaglandin synthesis is thought to be of possible importance in the regulation of blood flow in the kidney (20), lung (21), skin (22), and possibly other organs. Relatively little is known about the physiologic role of prostaglandins in the heart. Prostaglandin synthetase activity has been demonstrated in canine heart as has prostaglandin dehydrogenase, an important enzyme in prostaglandin metabolism (2). Furthermore, prostaglandin receptors are present in the canine heart, since infused prostaglandin E results in an increase in coronary blood flow and in contractility (23).

A possible role for prostaglandins in the regulation of coronary blood flow has been suggested recently. Prolonged occlusion (10 min) of a coronary artery in the isolated perfused rabbit heart results in the release of prostaglandin-like material about 50% of the time in an amount measurable by bioassay (3). In addition, the adenine nucleotides ATP and ADP, but not adenosine, were consistent releasers of prostaglandin E-like material. These findings suggest a possible interrelationship between myocardial metabolism and purine nucleotides, on the one hand, and prostaglandin synthesis and release, on the other.

The present data clearly demonstrate that the nonsteroidal anti-inflammatory agents indomethacin and meclofenamate result in a diminution of reactive hyperemia, associated with a decrease in cardiac immunoreactive prostaglandin E production. Although there are difficulties associated with the radioimmunoassay of prostaglandin E, as recently discussed (10), the apparent specificity of the present assay suggests that the immunoreactive material does, in fact, represent prostaglandin E. The use of an effective chromatography system coupled with an antibody of relatively high specificity makes it unlikely that the assay system is measuring biologically active material other than prostaglandin E.

Several lines of evidence suggest that the decrease in reactive hyperemia is the result of the inhibition of prostaglandin synthetase by indomethacin and meclofenamate, and not a nonspecific inhibition of ion transport or of other enzymes that has been demonstrated at high concentrations of these agents in other tissues. First, indomethacin at a concentration of 10^{-4} M has been shown to have no effect on calcium uptake by guinea pig aortic microsomes (24). Furthermore, indomethacin (5.6×10^{-5} M) has no significant effect on calcium uptake by the electrically stimulated guinea pig aorta (25). Finally, indomethacin (5×10^{-4} M) has no effect on the calcium, sodium, or potassium fluxes of guinea pig heart muscle (26). The apparent concentration of indomethacin in the heart-lung preparation in the

present studies was either 2.8×10^{-5} M or 1.1×10^{-5} M but the effective concentration may have been considerably lower, since over 90% of indomethacin in canine plasma is protein bound (27). Thus, it seems unlikely that the present results could be explained by nonspecific alteration of ion transport in heart or blood vessels. Second, although indomethacin has been shown to inhibit phosphodiesterase in toad bladder (20% inhibition at 2.8×10^{-5} M) (28), meclofenamate does not inhibit phosphodiesterase at a concentration of 2.8×10^{-5} M (R. W. Alexander and V. Manganiello, unpublished observations) and thus inhibition of phosphodiesterase is not likely to be the common mechanism of action on reactive hyperemia. Third, MVO_2 was not appreciably changed by the drugs. Finally, that the dose-response curve of infused adenosine was unaltered by indomethacin proves that coronary vascular reactivity is not nonspecifically altered by the nonsteroidal anti-inflammatory agents and suggests that factors in addition to adenosine are involved in mediating reactive hyperemia.

The methylxanthines attenuate or abolish the coronary vasodilator response to infused adenosine (5, 29). Although it has not been proved, it has been speculated that the inhibition of the adenosine response is a result of the phosphodiesterase inhibition by the methylxanthines (30). Thus, the failure of indomethacin to inhibit the adenosine response in the present studies provides further evidence that indomethacin is not exerting its effect on reactive hyperemia through phosphodiesterase inhibition.

Although prostaglandins of the E series are potent vasodilators and are continuously produced by the heart in the dog heart-lung preparation, the failure of prostaglandin synthetase inhibition to consistently decrease basal coronary blood flow suggests that continuous prostaglandin production is not necessary for the maintenance of basal flow. This view is consistent with the conclusions of a recently published report (31). On the other hand, the consistent increase in prostaglandin production during reactive hyperemia suggests that prostaglandin might be involved in modulating this response. The consistent decrease in postocclusive reactive hyperemia after prostaglandin synthetase inhibition supports this conclusion. A preliminary report has been published that also suggests that prostaglandins are released from the dog heart during reactive hyperemia (32). Another laboratory (33), however, has failed to demonstrate any effect of indomethacin on reactive hyperemia. These investigators examined only peak-flow hyperemic responses. In the present study, whereas peak-flow responses after 20-s occlusions were significantly reduced by indomethacin, peak-flow responses after shorter occlusions were not significantly reduced. However, in-

domethacin and meclofenamate significantly reduced integrated flow after occlusion release for occlusions of all durations (Figs. 3 and 4). That reactive hyperemia is not abolished after prostaglandin synthetase inhibition suggests that factors in addition to prostaglandin E are involved in modulating this response.

The possibility that prostaglandin E modulates coronary vascular response to hypoxia or to myocardial infarction awaits further investigation. Similarly, the precise relationship between prostaglandin E and other putative determinants of coronary blood flow, such as adenosine, remains to be elucidated.

ACKNOWLEDGMENTS

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