Synthesis of Prostaglandins and Thromboxane B₂ by Cholesterol-Fed Rabbits

Tao Wang, Pierre Falardeau, and William S. Powell

Alterations in the synthesis of thromboxane A₂ (TXA₂) and prostacyclin have been implicated in the development of atherosclerosis. We measured the amounts of the degradation products of these substances, TxB₂ and 6-oxo-prostaglandin F₁₅, (6-oxo-PGF₁₅), respectively, as well as PGE₂, that were synthesized by slices and the luminal surfaces of aortas from rabbits fed either a control diet or a diet supplemented with cholesterol and peanut oil. For these studies, we developed conditions that were designed to minimize the autoinactivation of cyclooxygenase during removal and preparation of the tissue. Pretreatment of aortas with a medium containing ibuprofen and EDTA resulted in an approximately twofold increase in 6-oxo-PGF₁₅ production upon subsequent incubation. Despite the increased lipid peroxidation associated with atherosclerotic lesions, we observed no changes in either aortic 6-oxo-PGF₁₅ production or in the levels of its major urinary metabolite, 2,3-dinor-6-oxo-PGF₁₅, after as long as 15 weeks of dietary supplementation with cholesterol and peanut oil. Similarly, synthesis of PGE₂ by aortic slices and the aortic lumen was the same in cholesterol-fed and control rabbits. In contrast to aortic 6-oxo-PGF₁₅ and PGE₂ synthesis, there was a dramatic 10-fold increase in TxB₂ released from slices of thoracic aorta after 15 weeks on the atherogenic diet. This was much greater than the approximately twofold increase in the synthesis of TxB₂ by the luminal surface of the thoracic aorta, suggesting that the primary site of TxB₂ synthesis in the aorta is in the inner part of the blood vessel. Slices of pulmonary artery released more TxB₂, 6-oxo-PGF₁₅, and PGE₂ than did slices from the aortic arch or the middle section of the thoracic aorta in control rabbits. However, the aortic arch was the major site of TxB₂ production in hypercholesterolemic rabbits. It is possible that aortic TXA₂ could contribute to the development of atherosclerosis due to its potent effects on platelets. (Arteriosclerosis and Thrombosis 1991;11:501–508)

Prostacyclin (prostaglandin I₂ [PGI₂]) and thromboxane A₂ (TXA₂) are important mediators of cardiovascular and platelet function. Because of its potent inhibitory effects on platelet activation, PGI₂ could diminish the accumulation of platelets at the site of atherosclerotic lesions and prevent or impede the progression of the disease. In addition to its effects on platelets, PGI₂ is a potent vasodilator and a systemic vasodepressor.¹ PGI₂ has a stimulatory effect on cholesteryl ester hydrolase in vascular smooth muscle cells, which could result in a reduction in the accumulation of cholesteryl esters at the site of the lesion.² PGI₂ has also been reported to inhibit the release of platelet-derived growth factor from platelets, as well as the release of growth factors from endothelial cells and macrophages.³ Because of these effects, sustained PGI₂ production by the vascular endothelium, its major site of synthesis, may be an important factor in preventing the onset of atherosclerosis. TXA₂, which is produced in large amounts by platelets⁴ but in very small amounts by normal blood vessels, is a potent stimulator of platelet aggregation and vasoconstrictor and could enhance the development of atherosclerosis.⁵ There is considerable controversy in the literature about the production of PGI₂ by atherosclerotic blood vessels, with several reports indicating considerably diminished production⁶–¹⁰ and others reporting unchanged¹¹ or enhanced¹²–¹⁵ production. The major objectives of the present study were to determine whether the atherosclerotic lesions induced by dietary supplementation with cholesterol in rabbits were accompanied by alterations in the synthesis of PGI₂, TXA₂, and PGE₂ by the aorta. We also wanted to ascertain whether this treatment caused changes in the production of PGI₂ and TXA₂ in vivo as assessed by measurement of the major urinary metabolites of these substances.

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**Preparation of Blood Vessels**

**Materials**

Cholesterol and propyl gallate were purchased from the Aldrich Chemical Co., Milwaukee, Wis. Ibuprofen, papaverine, and butylated hydroxyanisole were obtained from Sigma Chemical Company, St. Louis, Mo. Unlabeled arachidonic acid was purchased from NuChek Prep, Inc., Elysian, Minn., and purified just before use by chromatography on an open column of silicic acid to remove autooxidation products.

\[6 \cdot \text{OxO}[5,8,9,11,12,14,15-\text{H}]\text{PGF}_{1\alpha}, [5,6,8,11,12,14,15-\text{H}]\text{PGE}_{2},\]  
and [5,6,8,9,11,12,14,15-\text{H}]\text{TXB}_{2} were obtained from New England Nuclear, Lachine, Canada, whereas unlabeled \text{TXB}_{2}, \text{PGs}, and 2,3-dinor[18,18,19,19-\text{H}]\text{TXB}_{2} were kindly provided by J.E. Pike of The Upjohn Company, Kalamazoo, Mich. 2,3-Dinor-6-\text{oxo-PGF}_{1\alpha} and 2,3-dinor-6-\text{oxo}[8,10,10,12,14,15-\text{H}]\text{PGF}_{1\alpha} were prepared as described in the literature.\(^{16}\) Antisera to \text{PGE}_{2} and 6-\text{oxo-PGF}_{1\alpha} were purchased from Advanced Magnetics, Cambridge, Mass. and L. Levine, Brandeis University, respectively. F. Fitzpatrick kindly provided the antiserum to \text{TXB}_{2}.

**Animals and Diets**

Male New Zealand White rabbits (2–2.2 kg) were purchased from La Ferme Lapro Inc., Stukely-Sud, Canada. Rabbits (seven in each group) were fed a daily ration of either rabbit chow (60 g) or rabbit chow (53 g) supplemented with 0.5 g cholesterol, 6 g peanut oil (Planters, Ontario, Canada), 0.5 ml ethyl alcohol, and 0.5 g butylated hydroxyanisole as described in the literature.\(^{17}\) After 2, 8, or 15 weeks, the rabbits were placed in metabolic cages. Urine was collected on the second day the rabbits were in the cages and was processed for analysis of 2,3-dinor-6-\text{oxo-PGF}_{1\alpha} and 2,3-dinor-\text{oxo-TXB}_{2} as described below.

**Preparation of Blood Vessels**

Rabbits were injected with papaverine (4 mg/kg body wt) and heparin (200 units/kg body wt) to minimize the effects of vessel contraction and thrombin formation.\(^{18}\) Two minutes later, they were killed by inhalation of carbon dioxide. After the thoracic cavity was opened, the rabbit aorta was immediately perfused in situ with Ca\(^{2+}\)-free modified Krebs-Ringer-Tris medium containing ibuprofen and EDTA. The aorta was then removed and freed of adhering fatty tissue. Two sections (S\(_{1}\) and S\(_{2}\)) were cut into small slices and then incubated at 37°C for 30 minutes. The two remaining sections (T\(_{1}\) and T\(_{2}\)) were mounted in a template as described in "Methods."

An approximate estimate of the areas of the aorta covered by lesions was obtained independently by visual examination of the four sections from each aorta by two individuals, who estimated the percentage of the total area that was covered by lesions (to the nearest 10%). The areas of sections S\(_{1}\), T\(_{1}\), S\(_{2}\), and T\(_{2}\) covered by lesions were approximately 56%, 38%, 26%, and 14%, respectively, of the total surface area of that section after 8 weeks and 90%, 80%, 54%, and 50%, respectively, after 15 weeks.

**Incubation of Slices of Blood Vessels**

The aortic arch (S\(_{1}\)), the middle section of the thoracic aorta (S\(_{2}\)), and the PA were cut into small slices (about 3 mm\(^{2}\)). To remove the EDTA, ibuprofen, and papaverine, the slices were washed five times at 0°C with Krebs-Ringer-Tris medium containing 127 mM NaCl, 5 mM KCl, 1.27 mM MgSO\(_{4}\), 1.27 mM KH\(_{2}\)PO\(_{4}\), 2.7 mM CaCl\(_{2}\), 5.5 mM glucose, and 15 mM Tris HCl, pH 7.4 (medium B). The slices were then incubated for 30 minutes at 37°C in the absence of exogenous fatty acid substrate.

**Incubation of Luminal Surfaces of Aortas With Arachidonic Acid by the Template Method**

Sections T\(_{1}\) and T\(_{2}\) of the aorta were placed vertically between two Lucite blocks, one of which contained a small incubation chamber (height, 27 mm; diameter, 10 mm), which allowed the medium to come in contact with only the luminal surface of the aorta. The chamber extended below the aorta, which was mounted on the side, to permit stirring with a magnetic stirring bar during the incubation.\(^{18}\) The luminal surface (30 mm\(^{2}\)) of the aorta was incubated at 37°C for 5 minutes with medium A and then washed for five periods of 5 minutes each with medium B. The aorta was then incubated for 10 minutes at 37°C in the presence of arachidonic acid (25 μM).
Measurement of Prostanoids

The amounts of 6-oxo-PGF$_{1\alpha}$, PGE$_2$, and TXB$_2$ in the incubation media from slices and the luminal surfaces of aortas were measured by radioimmunoassay. Urinary levels of 2,3-dinor-6-oxo-PGF$_{1\alpha}$ and 2,3-dinor-TXB$_2$ were measured as described previously by negative-ion chemical-ionization gas chromatography–mass spectrometry using 2,3-dinor-6-oxo[8,10,10-^3H]PGF$_{1\alpha}$ and 2,3-dinor[18,18,19,19]TXB$_2$ as internal standards. These analyses were performed using a Hewlett-Packard Model 5895 mass spectrometer.

Measurement of Low Density Lipoprotein and Total Cholesterol in Aortas

On the morning of the day when the rabbits were to be killed, blood (14 ml) was withdrawn from the ear vein into two tubes, each of which contained potassium sorbate (0.014 mg) as well as tripotassium dihydrogen phosphate (0.014 mg). Blood was centrifuged at 5000 g for 15 minutes. The plasma from each tube was then separated, pipetted into the two tubes, each of which contained potassium sorbate (0.014 mg) as well as tripotassium dihydrogen phosphate (0.014 mg). The plasma was then centrifuged at 5000 g for 15 minutes. The supernatant from these tubes was then used for measurement of low density lipoprotein and total cholesterol.

Statistical Analysis

The statistical significance of differences between groups was determined as described in the legends to the figures. All statistical analyses were performed using SYSTAT (version 4.2, Intelligent Software, Evanston, Ill.) for personal computers.

Results

We evaluated prostanoid synthesis by the rabbit aorta with two different methods. The template procedure was used to measure prostanoids synthesized primarily by the cells of the aortic lumen. Since the basal release of prostanoids was quite low under these conditions, exogenous arachidonic acid was added to the medium. To investigate the synthesis of prostanoids by other vascular cells, we also measured the amounts of these products synthesized from endogenous substrates by slices of the aorta and PA.

Effects of Preincubation With Ibuprofen and EDTA on Synthesis of 6-oxo-PGF$_{1\alpha}$

The production of prostanoids by the aorta could be diminished by partial autoactivation of cyclooxygenase caused by a rapid burst of arachidonic acid released during preparation of the tissue. We attempted to minimize this problem by perfusing the aorta in situ with medium containing EDTA and the reversible cyclooxygenase inhibitor ibuprofen (10 μM). Tissue sections were then prepared in the same medium and mounted in a template as described above. After the tissue sections were washed several times with calcium-containing medium to remove the ibuprofen and EDTA, the aortic lumen was incubated with arachidonic acid (25 μM). Pretreatment of aortas with ibuprofen/EDTA resulted in a decrease in the basal release of 6-oxo-PGF$_{1\alpha}$ by the aortic lumen and an approximately twofold increase in the amount of this substance synthesized from exogenous arachidonic acid (25 μM) added after 40 minutes (Figure 2B). The initial burst in the release of 6-oxo-PGF$_{1\alpha}$ in the first 10 minutes, which was much greater in nonpretreated aortas, was presum-
ably due to stimulation caused by mounting the tissue in the template.

Pretreatment with ibuprofen/EDTA had a relatively small effect on the amount of 6-oxo-PGF$_{1a}$ initially synthesized from endogenous substrates by slices of aorta (Figure 2A). However, the synthesis of this substance by nonpretreated aortas virtually ceased after incubation for 20 minutes, whereas it continued almost linearly with time up to 40 minutes after pretreatment with ibuprofen/EDTA (Figure 2A). It should be noted that in the experiment using the template, depicted in Figure 2B, the medium was changed every 10 minutes, whereas in the experiment performed on aortic slices, the values are the cumulative amounts of released 6-oxo-PGF$_{1a}$ measured in aliquots removed from the incubation mixture every 10 minutes.

**Biosynthesis of Prostaglandins and Thromboxane B$_2$ by Blood Vessels From Hypercholesterolemic Rabbits**

The amounts of 6-oxo-PGF$_{1a}$, TXB$_2$, and PGE$_2$ formed from endogenous substrates by slices of aortic arch (S$_1$) from rabbits fed cholesterol and peanut oil for different periods of time are shown in Figure 3 (panels A, C, and E). Figure 3 (panels B, D, and F) also shows the amounts of these substances synthesized from exogenous arachidonic acid (25 μM)
the luminal surface of the thoracic aorta (T₁) as evaluated by the template technique. In both cases, aortas were prepared in medium containing ibuprofen and EDTA as described above. We also examined the synthesis of these three prostanoids by different parts of the aorta and by the PA as shown in Figures 4A, 4C, and 4E (slices) and 4B, 4D, and 4F (luminal surface).

**Synthesis of 6-oxo-PGF₁α**

The amounts of 6-oxo-PGF₁α (i.e., PGI₂) synthesized by slices of the aortic arch (Figure 3A) and by luminal surfaces of aorta (Figure 3B) were almost the same for control and hypercholesterolemic rabbits at all time points investigated. Neither were there any differences between the control and cholesterol-fed groups in the ability of slices (Figure 4A) or the lumen (Figure 4B) from the lower part of the aorta (S₂ and T₂) to synthesize this product. Although slices of PA released about four times as much 6-oxo-PGF₁α compared with slices from the aortic arch, there were no differences between the two groups of animals.

**Synthesis of Thromboxane B₂**

In contrast to the results with 6-oxo-PGF₁α, the release of TXB₂ by slices of aortic arch (S₁) from the group fed cholesterol and peanut oil was significantly greater than from the control group \((p<0.01)\). This difference was the most dramatic after 15 weeks, when aortas from the experimental group produced

![Figure 4](image-url)  
**Figure 4.** Bar graphs showing synthesis of 6-oxo-prostaglandin F₁α (6-oxoPGF₁α), thromboxane B₂ (TXB₂), and prostaglandin E₂ (PGE₂) by different areas of aorta and pulmonary artery from rabbits fed either control (○) or (PA) cholesterol-supplemented (●) diets for 15 weeks. Amounts of 6-oxoPGF₁α (panels A and B), TXB₂ (panels C and D), and PGE₂ (panels E and F) synthesized by slices (ng/g tissue/30 min) and luminal surfaces of aortas (ng/cm²/10 min) were determined as described in the legend to Figure 3. All values are mean±SEM (n=7). Statistical significance of differences between two groups was calculated by Student’s t test. *p<0.05, **p<0.01. Regions of aortas used in these experiments (S₁ and S₂ for slices and T₁ and T₂ for template procedure) are shown in Figure 1.

![Figure 5](image-url)  
**Figure 5.** Scatterplot showing correlation between cholesterol content (mg/g tissue) and thromboxane B₂ (TXB₂) production (ng/g tissue/30 min) in slices of aortas from hypercholesterolemic rabbits. Rabbits were fed a diet supplemented with cholesterol and peanut oil for either 8 (○) or 15 (●) weeks. Slices of aortic arch (S₁) were incubated at 37°C for 30 minutes. TXB₂ content was then measured in aliquots of the incubation medium by radioimmunoassay, whereas aortic total cholesterol was measured by gas chromatography as described in “Methods.” Correlation coefficient \((r)\) for the relation between cholesterol content and TXB₂ production was computed using Pearson product–moment correlations.
we measured the amounts of their principal urinary metabolites, 2,3-dinor-6-oxo-PGF1α and 2,3-dinor-TXB2, in rabbits fed control diets or diets enriched in cholesterol and peanut oil (Figure 6). There were no significant differences in the amounts of urinary 2,3-dinor-6-oxo-PGF1α between hypercholesterolemic rabbits and controls after 2, 8, and 15 weeks (Figure 6A). Somewhat unexpectedly, the levels of 2,3-dinor-TXB2 in urine were the same for controls and cholesterol-fed rabbits after 15 weeks (Figure 6B).

Discussion

The major metabolite of arachidonic acid released by both slices and luminal surfaces of rabbit aorta was PGI2, which was measured as its stable degradation product, 6-oxo-PGF1α. The amounts of 6-oxo-PGF1α synthesized by blood vessels from hypercholesterolemic and control rabbits were virtually identical, irrespective of the length of time on the diet and whether we measured its synthesis by tissue slices or the aortic lumen. This was also true for both the upper and lower sections of the thoracic aorta, despite the fact that the upper section (S2) was almost completely covered with lesions.

These results are not in accord with a number of reports in the literature on vascular PGI2 synthesis in hypercholesterolemic rabbits. The synthesis of PGI2 by slices of aorta, measured using a bioassay, was reported to be reduced by about 80% in rabbits fed a diet supplemented with cholesterol for 4 weeks.6 PGI2 synthesis remained at this level for up to 13 weeks but subsequently increased, so that it was only about 35% lower than in controls after 22 weeks on the diet.6 Similar results were recently reported by another group that used radioimmunoassay to measure 6-oxo-PGF1α production by aortic slices from rabbits fed a cholesterol-supplemented diet for 9 weeks followed by a normal diet for an additional 5 weeks.7 In a slightly different model, diet-induced hypercholesterolemia was shown to prevent the recovery of PGI2 synthesis by rabbit aortas after removal of the endothelium with a balloon catheter.24 Human atherosclerotic arteries were found to synthesize less PGI2 than similar control arteries.8 Cul-
tured smooth muscle cells from cholesterol-fed rabbits were reported to produce less PGI₂ from exogenous arachidonic acid compared with corresponding cells from control rabbits. Cholesterol enrichment of normal rabbit arterial smooth muscle cells has also recently been shown to result in a reduction in the synthesis of 6-oxo-PGF₁α.

In contrast to the above studies, a number of other groups have reported modest increases in PGI₂ synthesis by homogenates and slices of aortas from cholesterol-fed rabbits as well as by aortic slices from cholesterol-fed rabbits whose aortas had been subjected to de-endothelialization.

The reason for the discrepancy between our results and those described above is not clear, but the experimental protocol we used was somewhat different from those used in the above studies, most of which used only tissue slices. In our study, we attempted to minimize autoinactivation of cyclooxygenase caused by manipulation of the aorta before incubation by pretreatment with ibuprofen and EDTA. Thus, our results should more accurately reflect the ability of the aorta to synthesize PGI₂ in vivo.

The absence of a reduction in PGI₂ synthesis in hypercholesterolemic rabbits was confirmed by measurement of its urinary metabolite, 2,3-dinor-6-oxo-PGF₁α, the levels of which were the same in the control and experimental groups. To our knowledge, this is the first report on the urinary levels of this substance in hypercholesterolemic rabbits. In vivo production of PGI₂ has been reported to be higher in atherosclerotic humans than in healthy control subjects on the basis of measurement of urinary 2,3-dinor-6-oxo-PGF₁α. This may be due to an increase in platelet–vessel wall interactions in atherosclerotic subjects, as suggested by the substantial increases in the excretion of 2,3-dinor-TXB₂ in these individuals.

In contrast, there was no evidence for increased platelet production of TXB₂ in vivo in the hypercholesterolemic rabbit model used in this study, as indicated by the urinary levels of 2,3-dinor-TXB₂ (Figure 6B).

The most dramatic change in prostanoid synthesis observed in our study was in TXB₂ formation, which was about 10 times higher in slices from the aortic arch (S₁) of hypercholesterolemic rabbits compared with controls after 15 weeks (Figure 3B). There was also a large increase in the release of TXB₂ by slices from the lower part of the thoracic aorta (S₂), but the difference was less than that in the aortic arch (Figure 4B). The amount of released TXB₂ appeared to be correlated with the degree of coverage by aortic lesions. More than 90% of the aortic arch of rabbits fed a cholesterol-supplemented diet for 15 weeks was covered with lesions, whereas about 53% of the lower part of the aortas (S₂) was covered. Similarly, about 56% of the aortic arch of cholesterol-fed rabbits was covered with lesions after 8 weeks. The relation between aortic TXB₂ production and atherosclerotic lesions was further supported by the strong correlation between aortic cholesterol content and TXB₂ release (Figure 5). Although TXB₂ synthesis by slices of PA from control rabbits was about three times higher than by the aortic arch, we did not detect the high levels of TXB₂ synthesis reported earlier for this tissue. TXB₂ release by the PA appeared to be elevated in hypercholesterolemic rabbits, but the difference was not significant.

In contrast to aortic slices, the differences between TXB₂ formation by the luminal surface of aortas from control and hypercholesterolemic rabbits were relatively modest, suggesting that the major site of increased TXB₂ synthesis in aortas from hypercholesterolemic rabbits is not the endothelium, but rather the underlying cells. Atherosclerotic lesions from hypercholesterolemic rabbits are known to contain foam cells derived from both smooth muscle cells and macrophages. Both intravascular macrophages and rabbit circulating monocytes have been reported to synthesize substantial amounts of TXB₂. Thus, either macrophages or macrophage-derived foam cells could be a likely source of the TXB₂ synthesized by aortas from atherosclerotic rabbits.

Modest increases (30–200% above control values) in the production of TXB₂ by whole aortas or aortic slices from hypercholesterolemic rabbits have recently been reported in the literature. Production of TXB₂ from exogenous arachidonic acid by slices of de-endothelialized aortas from hypercholesterolemic rabbits was also recently reported to be about 70% higher after 30 minutes than in controls. Production of TXB₂ by different regions of the aorta or by the luminal surface was not reported in the above studies.

An inhibitor of thromboxane synthase has been shown to reduce the area of the aorta covered by atherosclerotic lesions in cholesterol-fed rabbits. The large increase in TXB₂ synthesis by the aortic arch that we observed raises the possibility that aortic TXA₂ could be involved in the development of atherosclerosis due to its potent effects on platelets. However, it must be kept in mind that TXA₂ production by blood vessels, even in atherosclerosis, would be much less than by platelets, the major site of its production. We did not observe any significant differences in the excretion of the urinary TXA₂ metabolite, 2,3-dinor-TXB₂, between control and cholesterol-fed rabbits, suggesting that in this model there are not large alterations in TXA₂ production by platelets in vivo. This is in contrast to human studies in which the in vivo production of TXA₂ was shown to be considerably elevated in atherosclerotic patients.

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