Regional Variability of Prostacyclin Biosynthesis

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To investigate the regional variability in arterial and venous endothelial prostacyclin (PGI₂) biosynthesis, we obtained 1-cm segments of carotid arteries, external jugular veins, femoral arteries and veins, iliac arteries and veins, inferior vena cavae (IVC), and aortas from 17 dogs. Vessel luminal PGI₂ production was measured in the basal state by radioimmunoassay of 6-keto-prostaglandin F₁α (6-keto-PGF₁α). A total of 90 arterial specimens (57, 19, and 14 segments, respectively, of femoral/carotid arteries, iliac arteries, and aorta) and 41 venous specimens (15, 10, and 16 segments, respectively, of femoral/jugular veins, iliac veins, and IVC) were analyzed. Overall, arterial endothelial 6-keto-PGF₁α was higher than venous (5.1±0.5 ng/ml vs. 4.8±0.7 ng/ml, p<0.0004); 6-keto-PGF₁α levels were greater in the arteries than in their corresponding veins (femoral/carotid arteries (6.3±0.4 ng/ml) vs. femoral/jugular vein (2.1±0.4 ng/ml), p<0.0002; iliac arteries (9.3±1.0 ng/ml) vs. iliac veins (4.8±0.9 ng/ml), p<0.005; aorta (14.0±1.6 ng/ml) vs. IVC (7.5±1.4 ng/ml), p<0.008). Within each type and vessel group, 6-keto-PGF₁α levels were higher in the more centrally located vessels [arterial group: analysis of variance (ANOVA), F=23.9, p=0.0001 (aorta>iliac, p<0.015; iliac>femoral/carotid, p<0.0008; aorta>femoral/carotid, p<0.0002); venous group: ANOVA, F=15.3, p=0.0001 (IVC>iliac, p<0.17, NS; iliac>femoral/jugular, p<0.005; IVC>femoral/jugular, p<0.002)]. PGI₂ biosynthesis is greater in arterial endothelium than venous endothelium; it is also greater in the arteries than in their corresponding veins. Within the arterial and venous systems, there is regional variability in PGI₂ production with greater activity in the more proximal or centrally located vessels, possibly in response to hemodynamic differences, such as greater mean flow velocity and shear stress.

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The antithrombotic and vasomotor properties of intact endothelium in vivo are dependent in part on endogenous biosynthesis and release of prostacyclin (PGI₂). This major product of arachidonic acid metabolism in animal and human blood vessels is produced primarily by the endothelium, with its synthesis progressively decreasing (abluminal gradient) toward the adventitial surface. In conjunction with thromboxane, PGI₂ has a distinct role in platelet-vessel wall interaction, regulation of blood flow, and hemostatic and fibrinolytic response to injury and disease. Additionally, its cytoprotective nature on a cellular, as well as a tissue, level has been described.

Endothelial biosynthesis of PGI₂ can be induced or blunted by various interventions. Pharmacologic and chemical agents that stimulate its production include arachidonate, thrombin, calcium ionophore A23187, tryptase, ciprofibrate, histamine, bradykinin, nitroglycerin, angiotensin II, high density lipoprotein, leukotriene C₄, interleukin-1, and interleukin-1β. Conversely, PGI₂ formation can be suppressed or abolished by indomethacin, aspirin, tranilcyromine, 15-hydroperoxyarachidonic acid, linoleic acid, low density lipoprotein, glycolipidoids, calcium channel blockers, and cigarette smoke condensate. Physiologic alterations, such as disordered blood flow, mechanical stress, high blood pressure, stasis, and low oxygen tension, or morphologic changes can result in enhanced vascular PGI₂ production. Mechanical trauma and endothelial injury due to excision, ex vivo storage, and surgical preparation of vein segments before grafting may acutely impair the capacity of the venous endothelium to generate PGI₂, while the chronic response to venoarterial grafting is increased production.

Vessels vary in their ability to synthesize PGI₂. Arterial endothelium produces significantly greater amounts than venous endothelium, a difference that may partially account for the higher patency rates of internal mammary artery compared to reversed saphenous vein grafts as coronary artery bypass conduits. Skidgel and Printz postulated a segmental variability of PGI₂ production in the same vessel; however, their study did not assess endogenous luminal production since it was based on addition of exogenous substance prostaglandin H₂ (PGH₂) to vascular homogenates and rings. To date, regional anatomic variability in arterial and venous endothelial PGI₂ biosynthesis from endogenous precursors has not been completely evaluated. Therefore, we investigated this regional variability in the unstimulated state to establish a baseline for further research on the regulation of PGI₂ biosynthesis.

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VARIABILITY OF PG\textsubscript{I2} BIOSYNTHESIS

Fann et al.

Methods

Seventeen adult male and female mongrel dogs (weighing 18 to 35 kg) were studied. The animals were anesthetized with intravenous sodium pentobarbital (25 mg/kg), were endotracheally intubated, and were placed on controlled mechanical ventilation (Harvard Apparatus, Mills, MA). Through neck and bilateral groin incisions, we gently dissected and removed 1-cm segments of the carotid arteries, external jugular veins, femoral arteries, and femoral veins. A midline laparotomy was then performed followed by dissection and removal of 1-cm segments of abdominal aorta, inferior vena cava (IVC), iliac arteries, and iliac veins. Care was taken to avoid sampling vessels at branching points. The specimens were rinsed immediately with heparinized (1 IU/ml) saline at room temperature, were opened longitudinally, and were placed into a custom-designed incubation chamber apparatus described in previous reports.\textsuperscript{4,42,43} The apparatus exposed 36 mm\textsuperscript{2} of the flow surface of the vessel for assay. The upper and lower plates were apposed to avoid leakage of the fluid from the chambers. A 300-\textmu l aliquot of Tris-\textsuperscript{\textit{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{NaCl buffer (pH 8.6, 37°C) was placed into the incubation well for exactly 2 minutes, after which the fluid was pipetted into a polypropylene tube and frozen immediately at -70°C for subsequent analysis. All vessel specimens were treated in the same fashion with a maximum of 10 minutes elapseding from the time of vessel harvest to completion of sample freezing.

Vessel luminal PG\textsubscript{I2} production was measured in the basal state by radioimmunoassay for 6-keto-PGF\textsubscript{I2}, (6-keto-prostaglandin F\textsubscript{I2}, the stable metabolite of PG\textsubscript{I2}) in duplicate with the use of tritiated 6-keto-PGF\textsubscript{I2}, tracer and rabbit anti-6-keto-PGF\textsubscript{I2}, antiserum (New England Nuclear, Boston, MA). Standard curves were constructed for each assay with known amounts of 6-keto-PGF\textsubscript{I2} (500, 250, 100, 50, 25, and 10 pg/100 \textmu l). Values of 6-keto-PGF\textsubscript{I2} are expressed as ng/ml of incubation fluid.

All animals received care in compliance with "Principles of Laboratory Animals Care" formulated by the National Society of Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Science and published by the National Institutes of Health (NIH publication 80-23, revised 1985).

All continuous data are expressed as mean\pm one standard error of the mean (SEM). The difference between the overall mean arterial and venous levels of 6-keto-PGF\textsubscript{I2} and the differences between the mean 6-keto-PGF\textsubscript{I2} in arteries and their anatomically corresponding veins were compared using Student's \textit{t} test for unpaired data. Analysis of variance (ANOVA) was used to detect differences among the mean 6-keto-PGF\textsubscript{I2} levels in each group (arterial or venous); if a significant difference was noted, Student's \textit{t} test for unpaired data with the Bonferroni correction was performed. A two-tailed \textit{p} value less than 0.05 (i.e., <0.017 adjusted for three multiple comparisons) was considered to be statistically significant.

Results

A total of 90 arterial and 41 venous segments were analyzed. Fifty-seven, 19, and 14 segments, respectively, of femoral/carotid artery, iliac artery, and aorta were studied. There were 15, 10, and 16 segments, respectively, of femoral/jugular vein, iliac vein, and IVC available for analysis. Overall, the mean arterial endothelial level of 6-keto-PGF\textsubscript{I2} was significantly greater than the mean venous level (8.1±0.5 ng/ml vs. 4.9±0.7 ng/ml, \textit{p}<0.0004).

Accounting for the respective anatomic regions, the luminal levels of 6-keto-PGF\textsubscript{I2} in the arteries were greater than those in their corresponding veins (femoral/carotid arteries (6.3±0.4 ng/ml) vs. femoral/jugular veins (2.1±0.4 ng/ml), \textit{p}<0.0002; iliac arteries (9.3±1.0 ng/ml) vs. iliac veins (4.8±0.9 ng/ml), \textit{p}<0.005; aorta (14.0±1.6 ng/ml) vs. IVC (7.5±1.4 ng/ml), \textit{p}<0.006) (Figure 1). Within the arterial group, the 6-keto-PGF\textsubscript{I2} levels were significantly higher in the proximal, i.e., more centrally located vessels than those in the periphery (ANOVA, \textit{F}=23.9, \textit{p}=0.0001; femoral/carotid vs. iliac, \textit{p}<0.0008; iliac vs. aorta, \textit{p}<0.015; femoral/carotid vs. aorta, \textit{p}=0.0002) (Figure 2). A similar trend was noted in the venous group although the difference in 6-keto-PGF\textsubscript{I2} levels between iliac vein and IVC did not achieve statistical significance (ANOVA, \textit{F}=15.3, \textit{p}=0.0001; femoral/jugular vs. iliac, \textit{p}>0.005; iliac vs. IVC, \textit{p}<0.17, NS; femoral/jugular vs. IVC, \textit{p}<0.002) (Figure 3).

Discussion

In agreement with previous reports,\textsuperscript{42-45} the results of this study indicate that endogenous endothelial PG\textsubscript{I2} production is generally greater in arteries than in veins. As a corollary, PG\textsubscript{I2} biosynthesis is greater in arteries than in the respective (anatomically corresponding) veins. Finally, there is a consistent regional variability in PG\textsubscript{I2} formation with...
ARTERIOSCLEROSIS VOL 9, NO 3, MAY/JUNE 1989

Figure 2. Depiction of 6-keto-prostaglandin F\(_{1\alpha}\) (6-keto-PGF\(_{1\alpha}\)) production (ng/ml) by various arteries. Regional variability of prostacyclin (PGI\(_2\)) production is illustrated by significantly greater production in aorta compared with the femoral/carotid and iliac arteries. Likewise, the iliac artery generated more PGI\(_2\) than did the femoral/carotid artery. Values indicate group means ± SEM; p values from unpaired t tests with the Bonferroni correction.

Figure 3. Depiction of 6-keto-prostaglandin F\(_{1\alpha}\) (6-keto-PGF\(_{1\alpha}\)) production (ng/ml) by various veins. The inferior vena cava (IVC) and the iliac vein generated significantly more prostacyclin (PGI\(_2\)) than did the femoral/jugular vein. The IVC produced more PGI\(_2\) than did the iliac vein, although the difference was not statistically significant. The values indicate group means ± SEM; p values from unpaired t tests with the Bonferroni correction.

significantly higher levels in the proximal, or more centrally located, vessels compared to those in the periphery.

All layers of the vascular wall are capable of synthesizing PGI\(_2\), however, the intima produces a disproportionately high amount, generating about 40% of the total endogenous PGI\(_2\) while representing only 5% of the arterial tissue.\(^3\) Because PGI\(_2\) formed by the deeper layers of the media normally does not reach the luminal surface, endothelial tissue is responsible for nearly all PGI\(_2\) at this critical interface of platelet-vessel wall interaction.\(^4\) The usual source of substrate for PGI\(_2\) production appears to be intracellular pools of esterified latty acid within the endothelium; upon synthesis, it is released immediately from the cells, so that synthesis is synonymous with release.\(^4\) Skidgel and Printz\(^24\) reported that rat arteries generated greater quantities of PGI\(_2\) than did veins and further postulated a segmental distribution of PGI\(_2\) synthetase activity in blood vessels. Because their study evaluated the utilization of an exogenous substrate PGH\(_{2}\) by homogenates of vessels from various regions, it is possible that these observed regional differences reflected nonendothelial, as opposed to endothelial, PGI\(_2\) production, since the contribution from the various layers could not be differentiated. In addition, tissue homogenization is traumatic and may affect utilization of exogenous precursors in PGI\(_2\) synthesis, thereby possibly precluding an accurate assessment of prostaglandin metabolism in the normal state. Although intact vascular rings were also assessed by Skidgel and Printz, sampling was limited to the aorta and vena cava of only two rats, and the tissue was processed with the cut edges of the specimens (nonendothelial tissue) exposed during analysis; moreover, precise appreciation of tissue (i.e., unstimulated) endogenous endothelial PGI\(_2\) production and its regional variability was not possible. In this study, we systemically evaluated specimens from various regions of the arterial and venous vasculature by using a specific radioimmunoassay for the stable hydrolysis product 6-keto-PGF\(_{1\alpha}\), as described by Eldor et al.,\(^4\) and we confined the area of analysis to the luminal surface of these vessels to achieve a better understanding of the role of PGI\(_2\) on the endothelial surface, i.e., the site of platelet-vessel wall interaction in the normal physiologic state.

Postulated explanations and mechanisms for higher PGI\(_2\) production in arterial compared to venous tissue include a variety of mechanical and biochemical factors, such as greater hemodynamic stress associated with higher blood flow and pressure, differences in oxygen content and tension, increased endothelial turnover rate, and enzyme induction.\(^32,24,38-42,49-52\) It is known that PGI\(_2\) production in vascular tissue\(^35\) and endothelial cell cultures\(^51,52\) is increased by mechanical and pulsatile shear stress, with the dependence on shear rate being more marked in the presence of platelets.\(^50\) Additionally, arteries from spontaneously hypertensive rats have an enhanced capacity (compared to normal tissue) to convert arachidonic acid to PG\(_{1\alpha}\), presumably as a consequence of greater mechanical stress. To clarify the effects of blood pressure and flow on PGI\(_2\) production, Eldor et al.\(^4\) analyzed canine venous segments transplanted for 6 weeks into the arterial circulation and noted no significant difference in spontaneous and arachidonatesimulated PGI\(_2\) synthesis between arterialized venous autografts and control veins.\(^4\) Conversely, our group and others demonstrated that interposition of venous grafts into the arterial position in canine\(^42,43\) and rat\(^44\) models for an extended period, for example, 10 to 12 weeks, resulted in increased graft luminal production of PGI\(_2\) equalling the level of normal arteries. This finding is consistent with the concept that higher flows, pressures, and shear stress in the arterial circulation\(^32,50\) contribute to enhanced PGI\(_2\) production. We subsequently noted that this time-dependent biochemical "arterialization" was incomplete,
since no significant response to substrate enhancement with arachidonic acid occurred in canine venoarterial autografts. Interestingly, studies focused on the effects of aging on PGI₂ formation revealed no difference between young and mature porcine aortic intimal strips in the basal state, but in the presence of exogenous arachidonic acid, young intimal strips possessed a twofold greater ability to produce PGI₂ than did mature tissues. Therefore, endothelial changes associated with arterialization and the decreased capacity for PGI₂ formation after substrate enhancement may be comparable to those associated with maturation or aging.

Venous endothelium is morphologically distinct from arterial endothelium, but it is unknown whether this represents different cell types or structural (and/or biochemical) phenotypic modulation of endothelial cell function with concomitant activation of PGI₂ synthetic pathways as a result of increased blood flow. The nature of this activation, which occurred during the "sprouting" phase of cultured endothelial cell growth, has yet to be elucidated. But if this in vitro sprouting occurs in vivo, then it may represent a physiologic mechanism that lends a degree of protection from the deleterious effects of platelet aggregation and release. The adaptation of venoarterial graft endothelium, therefore, may reflect a normal chronic cellular response to the arterial environment, thereby inhibiting platelet adhesion and platelet-endothelial interaction.

Oxygen tension and ischemia are possible regulators of PGI₂ synthesis. It has been speculated that exposure to higher oxygen content or tension in the arterial system may account for greater PGI₂ production in arteries compared to veins. Experimental evidence, however, has been to the contrary. Venous stasis and ischemia have been shown to cause an initial increase in PGI₂ formation, with subsequent exhaustion of this effect after several similar interventions. Studies in healthy subjects indicated an increase in urinary excretion of PGI₂ metabolites during heavy leg exercise without altering urinary excretion of thromboxane A₂ metabolites, implying that augmentation of PGI₂ production may be an independent process. The excretion of PGI₂ metabolites increased more than sevenfold during the hour of exertion and decreased to pre-exercise level after 3 to 4 hours. Exercise-induced alterations in blood pressure and cardiac output, both of which may contribute to the observed findings, however, were not assessed. In addition, the generation of 6-keto-PGF₁α was significantly higher when arterial tissue was subjected to a high nitrogen/oxygen environment. Thus, reduction in oxygen supply may be a trigger to increased PGI₂ production, but the influence of other concomitant metabolic alterations, such as changes in pH and accumulation of acidic metabolites, remains to be elucidated.

The proposed mechanisms—hemodynamic stress, blood flow, endothelial turnover, and enzyme induction—accounting for differences in PGI₂ synthesis between the arterial and venous endothelium may also be relevant in understanding the regional variability of PGI₂ production. Oxygen content and ischemia may possibly influence PGI₂ synthesis, but this effect was negli-

ble in this study since they did not vary in the arterial or venous regions from which the segments were obtained. Investigating PGI₂ production at different sites of aortic wall in healthy rabbits and in rabbits with atherosclerosis, Voss et al. found that, contrary to previous studies, plaque-containing regions generated higher amounts of PGI₂ than did normal areas. Because the areas with the most severe atherosclerotic changes were also assumed to be subject to the greatest hemodynamic stress along the aorta, the balance of these two opposing factors on PGI₂ synthesis might result in the net increase observed. In normal animals, the highest PGI₂-synthesizing capacity was found in the aortic arch and near the ostia of the major abdominal arteries; when regions surrounding the ostia were examined, there was a trend, though not statistically significant, toward greater PGI₂ formation in the distal as opposed to the proximal side. In addition, endothelium in areas of artificial arterial stenoses (with resultant disordered blood flow and turbulence) increased PGI₂ output that was stenosis-size dependent; that is, the greater the degree of stenosis, the greater the increase in its synthesis. These findings may be the consequence of higher wall shear stress.

In the normal arterial system, wall tension, mean arterial pressure, and mean flow velocity are higher in the aorta than in the peripheral large and medium-sized arteries. The endothelium is subjected to only a small fraction of the radial stress produced by blood pressure, which is borne mostly by elastic and collagen in the vessel wall; wall shear stress, however, is borne entirely by the endothelial layer. Because mean flow velocity and transmission of energy from the flowing blood to the vessel wall are greater in the aorta compared to smaller arteries, the shear stress on the aortic endothelium is higher than that on endothelial cells of the peripheral arteries. In this study, the finding that endothelial PGI₂ production is significantly greater in the aorta than in iliac and femoral arteries may be the result of higher mean flow velocity and resultant shear stress.

Similar segmental physiologic differences exist in the venous vasculature. The wall tension, mean flow velocity, and shear stress are normally greater in the IVC than in smaller peripheral veins (including the iliac and femoral veins); mean blood pressure, however, is less in centrally located veins than in those in the periphery. As in the arterial system, physiologic variations in mean flow velocity and shear stress may thus account for greater PGI₂ production by the IVC compared to the peripheral veins. Hence, regional variability—more centrally located vessels generating greater amounts of PGI₂—may be due to regional hemodynamic differences.

Another endothelial biosynthetic product, which may be identical to nitric oxide, is endothelium-derived relaxing factor (EDRF). Although their mechanisms are different (e.g., PGI₂ acts via adenylate cyclase, whereas EDRF acts via guanylate cyclase), EDRF has features distinctly similar to PGI₂, including a short half-life (6 seconds vs. 2 to 3 minutes for PGI₂) and potent vasodilatory and antithrombotic properties. In addition, EDRF synthesis and release are stimulated by moderate hypoxia, a variety of pharmacologic agents, and
increased flow.\textsuperscript{7,8} Recently, it has been shown that EDRF production is greater in artery compared to vein in humans.\textsuperscript{9} In view of the regional heterogeneity observed in our canine study, the question of whether EDRF production has a similar regional distribution must be investigated.

Some limitations of this study should be addressed. The intent of this investigation was to evaluate PGI\textsubscript{2} production in various segments of the arterial and venous vasculature in the normal unstimulated state. It can be hypothesized that this regional variability of basal PGI\textsubscript{2} is also present when the various segments are provided with enough substrate (e.g., arachidonic acid) enhancement; however, this question was not addressed in this experiment. Additionally, blood pressure, velocity, flow, and wall shear stress were not directly measured or calculated in the various regions of the vasculature from which the specimens were obtained; interpretations of the findings, therefore, are based on existing hemodynamic inferences. In summary, arterial endothelial PGI\textsubscript{2} production is generally greater than that in venous endothelium; specifically, PGI\textsubscript{2} synthesis is greater in the arteries than in their anatomically corresponding veins. Within the arterial and venous systems, there exists regional variability in PGI\textsubscript{2} production with greater activity in the more centrally located vessels, possibly in response to greater mean flow velocity and shear stress. The findings in this study are of particular relevance to future investigations of PGI\textsubscript{2} biosynthesis in various regions of the vasculature.

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References

1. Moncada S, Gryglewski RJ, Bunting S, Vane JR. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. Nature 1976;263:663–665
2. Bunting S, Gryglewski RJ, Moncada S, Vane JR. Arterial walls generate from prostaglandin endoperoxides a substance (prostaglandin X) which relaxes strips of mesenteric and cellars arteries and inhibits platelet aggregation. Prostaglandins 1976;12:897–913
3. Moncada S, Herman AG, Higgs EA, Vane JR. Differential formation of prostacyclin (PGX) or PGI\textsubscript{2} by layers of arterial wall. An explanation for the antithrombotic properties of vascular endothelium. Thromb Res 1977;11:323–344
4. Eldor A, Falcone DJ, Heijer DP, Minick CR, Weisber MB. Recovery of prostacyclin production by de-endothelialized rabbit aorta: Critical role of neonatal smooth muscle cells. J Clin Invest 1981;67:735–741
5. Eldor A, Falcone DJ, Heijer DP, Minick CR, Weisber BB. Recovery of prostacyclin production by de-endothelialized rabbit aorta: Critical role of neonatal smooth muscle cells. J Clin Invest 1981;67:735–741
6. Moncada S, Higgs EA, Vane JR. Human arterial and venous tissues generate prostacyclin (prostaglandin XI), a potent inhibitor of platelet aggregation. Lancet 1977;1:19–20
7. Moncada S. Prostacyclin/thromboxane-mediated mechanisms in platelet-vascular wall interactions. Adv Prostaglandin Thromboxane Leukotriene Res 1985;15:507–512
8. Gryglewski RJ, Moncada S. Secretory function of vascular endothelium. Adv Prostaglandin Thromboxane Leukotriene Res 1987;17:397–404
9. Gorog P, Kovacs IB. Prostacyclin is a more potent stimulator of thrombocytosis than inhibitor of hemostasis. Haemostasis 1986;16:337–345
10. Weisber BB, Ley CW, Jaffe EA. Stimulation of endothelial cell prostacyclin production by thromboxane and the ionophore A 23187. J Clin Invest 1978;62:923–930
11. Marcus AJ, Weisber BB, Jaffe EA, Broekman J. Synthesis of prostacyclin from platelet-derived endoperoxides by cultured human endothelial cells. J Clin Invest 1980;66:976–986
12. Fry GL, Czervionke RL, Hoak JC, Smith JB, Haycraft DL. Platelet adherence to cultured vascular cells: Influence of prostacyclin (PGI\textsubscript{2}). Blood 1980;55:271–275
13. Czervionke RL, Smith JB, Hoak JC, Fry GL, Haycraft DL. Use of radioligand assay to study thrombin-induced release of PGI\textsubscript{2} from cultured endothelium. Thromb Res 1978;14:781–796
14. Blass KE, Block Hu, Forster W, Ponicka K. Dipyridamole: A potent stimulator of prostacyclin (PGI\textsubscript{2}) biosynthesis. Br J Pharmacol 1980;68:71–73
15. Moncada S, Kurbut R. Dipyridamole and other phosphodiesterase inhibitors act as antithrombotic agents by potentiating endogenous prostacyclin. Lancet 1978;1:1288–1289
16. Hong SL. Effect of bradykinin and thrombin on prostacyclin synthesis in endothelial cells from calf and pig aorta and human umbilical cord vein. Thromb Res 1980;15:787–795
17. Levin R, Jaffe EA, Weiskler BB, Tack-Goldman K. Nitroglycerin stimulates synthesis of prostacyclin in cultured human endothelial cells. J Clin Invest 1981;67:762–768
18. Rossii V, Breviario F, Gliuzzi P, Dejana E, Mentovani A. Prostacyclin synthesis induced in vascular cells by interleukin-1. Science 1985;229:174–178
19. Nolan RD, Dusting GJ, Martin TJ. Phospholipase Inhibition and the mechanism of agonist-induced prostacyclin release from rat mesenteric vasculature. Biochem Pharmacol 1981;30:2121–2125
20. Fiescher LN, Tall AR, Witte LD, Cannon PJ. Effects of high density lipoprotein and the apoprotein of high density lipoprotein on prostacyclin synthesis by endothelial cells. Adv Prostaglandin Thromboxane Leukotriene Res 1983;11:475–480
21. Bittz J, Forster W. Influence of human low density and high density lipoprotein cholesterol on the in vivo prostaglandin I\textsubscript{2} synthesis activity. Biochim Biophys Acta 1990;520:352–355
22. Boeniger NL, Force LE, Becherer PR. Histamine stimulates prostacycin synthesis in cultured human umbilical vein endothelial cells. Biochem Biophys Res Commun 1980;92:1435–1440
23. Hall ER, Papp AC, Seifert WE, Wu KK. Stimulation of endothelial cell prostacycin formation by interleukin-2. Lymphokine Res 1985;5:57–66
24. Cramer EB, Polage L, Pawlowski NA, Cohn ZA, Scott WA. Leukotriene C4 promotes prostacyclin synthesis by human endothelial cells. Proc Natl Acad Sci USA 1983;80:4109–4113
25. Jaffe EA, Weiskler BB. Recovery of endothelial cell prostacyclin production after inhibition by low doses of aspirin. J Clin Invest 1978/63:352–358
26. Kelton JG, Hirsh J, Carter CJ, Buchanan MR. Thrombogenic effect of high-dose aspirin in rabbits. J Clin Invest 1978;62:892–895
27. Weiskler BB, Marous AJ, Jaffe EA. Synthesis of prostaglandin I\textsubscript{2} (prostaglandin) by cultured human and bovine endothelial cells. Proc Natl Acad Sci USA 1977;74:3922–3926
28. Spector AA, Hoak JC, Fry GL, Denning GM, Stoll LL, Smith JB. In vitro inhibition of prostacyclin production by cultured human endothelial cells. J Clin Invest 1980;65:1003–1012
29. Van de Velde VJS, van der Bosche BM, But H, Herman AG. Modulation of prostacyclin bioactivity by calcium entry blockers and extracellular calcium. Biochem Pharmacol 1986;35:253–256
30. Lewis GD, Campbell WB, Johnsen AR. Inhibition of prostaglandin synthesis by glycoproteins in human endothelial cells. Endocrinology 1986;119:52–59
31. Jermy JT, Mikhailidis DP, Dandona P. Cigarette smoke extracts, but not nicotine, inhibit prostaglandin (PGI\textsubscript{2}) synthesis in human, rabbit and rat vascular tissue. Prostaglandins Leukotrienes Med 1985;19:261–270
31. Reinders JH, Brinkman HJM, van Mourik JA, deGroot PG. Cigarette smoke impairs endothelial cell prostacyclin production. Arteriosclerosis 1986;15:15–23.
32. Ovarford PG, Relly LM, Lusby RJ, et al. Prostacyclin production in regions of arterial stenosis. Surgery 1985; 98:484–490.
33. Pace-Asclier CR, Cannara MC, Rangaraj G, Nicolosi KC. Enhanced formation of PGI2, a potent hypotensive substance, by aortic rings and homogenates of the spontaneously hypertensive rat. Prostaglandins 1978;15:1005–1012.
34. Petry JJ, Burstein S, Chang WHJ, Wortham K, Sedor C, Hunter SA. Prostacyclin production by vein grafts in the arterial circulation: A study in rats. Prostaglandins Leuko-\[t\]mesins Med 1982;2:511–516.
35. Chyman RI, Maureen F, Kooper MA, Wiener F, Heymann MA, Rudolph AM. Formation of prostacyclin (PGI2) by the ducus arteriosus of fetal lambs at different stages of gestation. Prostaglandins 1978;16:633–642.
36. Skrdal RA, Prinzi MP. PGI2 production by rat blood vessels. Diminished prostacyclin formation in vessels compared to arteries. Prostaglandins 1978;16:61–16.
37. Smerly GGN, Poggea GML, Gallant G. Release of prostacyclin into the bloodstream and its exhalation in humans after local blood flow changes (ischemia and venous stasis). Thromb Res 1980;17:197–208.
38. Dasing R, Landagberg G, Pietsch R, Schoof H, Kramer J. Prostacyclin biosynthesis by human arterial tissue in vitro: Dependence on oxygen tension. Adv Prostaglandin Throm-\[b\]ox Leukotriene Res 1987;17:405–408.
39. Bush HL, Hong SI, Deykin D, Nambaeth DC. Effect of surgical trauma on prostacyclin production by vein grafts. Surg Forum 1982;33:463–465.
40. Bush HL, McCabe ME, Nambaeth DC. Functional injury of vein graft endothelium. Arch Surg 1984;119:770–774.
41. Angelini GD, Breckenridge IM, Paslje JV, Williams HM, Henderson AH, Newby AC. Preparation of human saphenous vein for coronary artery bypass grafting: Impairment of capacity to produce prostacyclin. Cardiovasc Res 1987; 21:28–33.
42. Henderson VJ, Cohen RG, Mitchell RS, Kosek JC, Miller DC. Biochemical (functional) adaptation “arterialized” vein grafts. Ann Surg 1986;203:339–345.
43. Cahill PD, Brown BA, Henden CE, Kosek JC, Miller DC. Incomplete biochemical adaptation of vein grafts to the arterial environment in forms of prostacyclin production. J Vasc Surg 1987:3:496–503.
44. Eldor A, Hoover EL, Pett SB, Gay WB, Alonzo DR, Weiskler BB. Prostacyclin production by arterialized autogenous venous grafts in dogs. Prostaglandins 1981; 22:485–498.
45. Johnson AR. Human pulmonary endothelial cells in culture: Activities of cells from arteries and cells from veins. J Clin Invest 1980;65:841–850.
46. Chalkouni A, Crawford FW, Kochel PJ, Glaoner LS, Halluska PV. Human internal mammary artery produces more prostacyclin than saphenous vein. J Thorac Cardiovasc Surg 1986;92:88–91.
47. Subramanlen VA, Hernandez Y, Tack-Goldman K, Grabowski EF, Weiskler BB. Prostacyclin production by internal mammary artery as a factor in coronary artery bypass grafts. Surgery 1985;98:378–382.
48. Weiskler BB, Eldor A, Falcone D, Levin RL, Jaffe EA, Minnick CR. Prostaglandins and vascular endothelium. In: Herman AG, Vanhoutte PM, Denolin H, Goossena A, eds. Cardiovascular pharmacology of the prostaglandins. New York: Raven Press, 1982:137–148.
49. Voss R, ten Hoor F, Matthies FR. Prostacyclin production and atherosclerosis of the rabbit aorta. Adv Prostaglandin Thrombox Leukotriene Res 1985;11:469–474.
50. Grabowski EF, Weiskler BB, Jaffe EA, Tack-Goldman K, Gerston SL. Platelet augment prostaglandin (PGI2) production by cultured endothelial cells exposed to flowing blood. Circulation 1984;70(suppl II):II-57.
51. Frangos JA, Eskin SG, Mincione LV, Ives CL. Flow effects on prostacyclin production by cultured human endothelial cells. Science 1985;227:1477–1479.
52. Sumpl BE, Barnes AJ. Prostacyclin synthetic activity in cultured endothelial cells undergoing cyclic mechanical deformation. Surgery 1988;104:383–389.
53. Kent RS, Keithel BB, Shand DG, Whorton AR. The ability of vascular tissue to produce prostacyclin decreases with age. Prostaglandins 1981;21:463–490.
54. Fonkaleru EW, Sanchoz M, Zerubavel R. Morphological evaluation of canine autogenous vein grafts in the arterial circulation. Surgery 1987;94:253–264.
55. Hahn GL, Polgar PR. Prostacyclin production in phenotypically distinct cultured bovine pulmonary artery endothelium. Atherosclerosis 1984;5:143–150.
56. Edler A, Fitzgerald A, Sevastik B, Wernmalm A. Leg exercise increases prostacyclin synthesis without activating platelets in both healthy and atherosclerotic humans. Adv Prostaglandin Thrombox Leukotriene Res 1987;17:447–449.
57. Green K, Vesterqvist O. In vivo synthesis of thromboxane and prostacyclin in man in health and disease. Data from GC-MS measurements of major urinary metabolites. Adv Prostaglandin Thrombox Leukotriene Res 1988;18:309–324.
58. Dembinska-Kiec A, Gryglewski T, Zmuda A, Gryglewski RJ. The generation of prostacyclin by arteries and by the coronary vascular bed in reduced experimental atherosclerotic rabbits. Prostaglandins 1977;14:1025–1034.
59. Lernou J, Rigaud M, Daret D, Demond J, Durand J, Bricaud H. Prostacyclin production by cultured smooth muscle cells form atherosclerotic rabbit aorta. Nature 1980; 285:467–468.
60. Popovic R, Winton M, Ferry A, Sintzinger H. Prostacyclin formation around blood vessel and connective tissue. Prostaglandins Leukotrienes Med 1987;25:53–63.
61. Burton AC. Physiology and biophysics of the circulation, ed. 2. Chicago: Yearbook Medical Publishers, 1972:51–114.
62. Cargo CG, Pedley TJ, Schrotter RC, Seed WA. The mechanics of the circulation, Oxford: Oxford University Press, 1978; 243–348.
63. Lamann JB. Going with the flow. Nature 1988;331:481–482.
64. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373–376.
65. Palmer RMJ, Ferrage AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 1987;327:542–546.
66. Vanhoutte PM. The end of the quest. Nature 1987; 327:459–460.
67. Azuma H, Ishikawa M, Sekizaki S. Endothelium-dependent inhibition of platelet aggregation. Br J Pharmacol 1986; 89:411–415.
68. Rubanyi GM, Romero JC, Vanhoutte PM. Flow-induced release of endothelium-derived relaxing factor. Am J Physiol 1986;250:H145–H149.
69. Luscher TF, Dierich D, Siebenmann R, et al. Difference between endothelium-dependent relaxation in arterial and venous coronary bypass graft. N Engl J Med 1988; 319:462–467.

Index Terms: prostaglandins • prostacyclin • 6-keto-PGF1α • prostaglandin X • endothelium