Prostacyclin, High Density Lipoproteins, and Myocardial Ischemia

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Ever since the discovery of prostacyclin (originally termed PGX by Moncada et al but later designated PGI₂), there has been considerable interest in its role in cardiovascular homeostasis. Despite the fact that PGI₂ is not cleared by the lung in contrast to virtually all other prostaglandins, its circulating concentration is very low.²,³ This low circulating PGI₂ level is in part due to its instability in aqueous media at physiological pH, its rapid rate of metabolism, and its uptake by target tissues. The half-life of prostacyclin in blood is generally acknowledged to be about 3 minutes.⁴ Despite its short half-life, prostacyclin has been accorded a prominent role in vascular homeostasis because it has potent biological effects that act as a defensive humoral agent opposing the untoward effects of thromboxane A₂ (TXA₂). In this connection, 10 nM prostacyclin can totally block the marked degree of platelet aggregation induced by 0.5 mM arachidonic acid.⁵ In so doing, PGI₂ blocks the formation of TXA₂ by more than 80%.⁶

An important piece of the puzzle related to the effectiveness of PGI₂ was recently discovered by Yui et al,⁷ who identified the hitherto-unknown “prostacyclin stabilizing factor” (PSF) as apolipoprotein (apo) A-1, a major protein constituent of high density lipoprotein (HDL) particles present in blood. This research group has just extended their work in an article in this issue of Circulation⁸ by showing that the apo A-1 level, and thus prostacyclin stabilization, is markedly lower in patients experiencing unstable angina and the acute phase of myocardial infarction and to a lesser extent in patients experiencing angina pectoris and the later phases of myocardial infarction. The authors claim that reduced apo A-1 and lower PGI₂ stabilization “may play an important role in the pathogenesis of atherosclerosis and thrombus formation during an acute coronary event.” Although the data are from a relatively small patient population, these findings are of great potential for determining the protective role of HDL and PGI₂ in the pathogenesis of coronary artery disease, particularly in patients with atherosclerosis or acute myocardial infarction.

Examine some of the mechanisms by which HDL and PGI₂ protect in acute myocardial infarction and atherogenesis. HDL may protect in acute myocardial ischemia by a variety of mechanisms, including 1) transport of free cholesterol from the blood to the liver where it is esterified by lecithin cholesterol acyl transferase (LCAT). The apo A-1 component of HDL promotes activation of LCAT. The net effect is the removal of free cholesterol from the circulation, leaving less cholesterol to be deposited inside the walls of blood vessels; 2) preservation of endothelial cell function including the release of endothelium-derived relaxing factor (EDRF), a substance produced by endothelial cells that is an important contributor to vasodilation, inhibition of platelet aggregation, and prevention of neutrophil adherence.⁹ Both cholesterol deposits in blood vessels and low density lipoprotein (LDL), particularly in its oxidized form, inhibit the release of EDRF. HDL tends to oppose these EDRF-inhibitory effects of LDL and free cholesterol; 3) HDL promotes the release of PGI₂ from endothelial cells,¹⁰ and as shown by Aoyama et al in this issue of Circulation, HDL stabilizes circulating PGI₂.

This latter effect of HDL in stabilizing PGI₂ is very important because prostacyclin has a variety of actions that are important protective mechanisms during angina, acute myocardial ischemia, and the development of myocardial infarction. In this connection, exogenously administered PGI₂ has been shown to preserve myocardial integrity in acute myocardial ischemia in a variety of species. Since the pioneering paper of Ogletree et al a decade ago showing cardioprotection in cats with acute myocardial ischemia, the beneficial effects of PGI₂ in myocardial ischemia have been confirmed in dogs,¹³,¹⁴ rabbits,¹⁵ rats,¹⁶ and humans.¹⁷ Thus, the findings that HDL exerts effects that enhance both the release and the stabilization of PGI₂ is of considerable potential significance, particularly since reduced apo
A-1 levels were found by Aoyama et al7 in patients experiencing angina or myocardial ischemia.

Whether occurring in the blood or on the endothelial cell surface, the mechanisms of the potential enhanced stabilization of PG12 are both complex and important in the preservation of myocardial function. Although prostacyclin is a coronary vasodilator, most of the studies showing cardioprotection with PG12 were conducted at infusion rates of PG12 that produced threshold or nondetectable decreases in blood pressure and presumably only minor changes in coronary blood flow. Large shifts in blood pressure or large coronary flow redistributions could result in a coronary steal; however, low infusion rates of PG12 (i.e., those that protect in ischemia) do not produce a steal.18 At concentrations that do not vasodilate, prostacyclin is a potent inhibitor of platelet aggregation1,5 and can even disaggregate clumps of aggregated platelets.4 Perhaps even more important in myocardial ischemia, PG12 is a potent membrane-stabilizing agent of both plasma membranes and lysosomal membranes.5,19 This effect may be related to preservation of myocardial cell membrane phospholipids during acute myocardial ischemia.16 In addition, PG12 counteracts the proischemic effects of TXA2, the proaggregatory, vasoconstrictor, and cytolytic eicosanoid produced largely by activated platelets.20 Because PG12 inhibits TXA2 formation in human platelets5 and exerts a profile of effects opposing the proischemic effects of TXA2, this action of PG12 may be important in the pathogenesis of myocardial ischemia. Moreover, PG12 acts synergistically with EDRF to inhibit platelet aggregation and exert other cytoprotective effects so that lower concentrations of PG12 are more effective in the presence of an intact endothelium that releases EDRF, presently thought to be nitric oxide.21

All of the above cited actions of PG12 are acute effects occurring over seconds and minutes. Prostacyclin also exerts chronic effects on cholesterol metabolism that may be potentially important in preventing myocardial ischemia. First, it inhibits platelet mitogen release (e.g., platelet-derived growth factor [PDGF]),22 thus retarding one of the initial steps in atherogenesis. Second, PG12 reduces cholesterol esters present in foam cells during atherogenesis and facilitates the transport of cholesterol to the liver via HDL.23,24 These important chronic effects of PG12 occurring over a long time-span can be a major factor in retarding atherosclerosis, which clearly can be a precipitating factor in angina and myocardial ischemia.

While the above matrix of effects of PG12 is impressive, there remain several unanswered questions so the findings of Aoyama et al,7 must be viewed with caution. First, are there corresponding changes in TXA2 concentration or TXA2 sensitivity in the coronary microvasculature during angina and myocardial ischemia? PG12 is one portion of the cyclooxygenase pathway of arachidonic acid metabolism; TXA2 is another important component. Considerable evidence exists that the PG12-to-TXA2 ratio is a critical factor in coronary artery disease and related phenomena. Thus, the relation between apo A-1 and TXA2 production, metabolism, receptor density and sensitivity may be particularly important because cholesterol has been shown to increase TXB2 production in human platelets.25 Second, how relevant are the PG12-stabilizing effects in the presence of endothelial injury with or without atherosclerosis? Is enough PG12 produced by damaged endothelium or in atherosclerosis to be stabilized? Is synergy between EDRF and PG12 essential for an effective concentration of PG12? Third, there is clear evidence that PG12 does not normally circulate at concentrations that exert biological effects.2,3 Is the circulating PG12 an “overflow mechanism”? Does PG12 exert a coating effect on the endothelium, contributing to its “antithrombotic surface” without actually circulating? Finally, does the finding by Aoyama et al7 obtained in Japanese adults apply to other populations (e.g., Western society) on a different diet? Is this a universal finding, or is it a regional one? Additional investigation will undoubtedly be addressed to answer these questions. Nevertheless, at this time, another important piece of the eicosanoid puzzle relating to cardiovascular disease appears to have been provided by the work of Aoyama and coworkers.7

References

1. Moncada S, Gryglewski RJ, Bunting S, Vane JR: A lipid peroxide inhibits the enzyme in blood vessel microsomes that generates from prostaglandin endoperoxides the substance (prostaglandin X) which prevents platelet aggregation. Prostaglandins 1976;12:715–733
