Heart Disease, Aspirin, and Fish Oil

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The antithrombotic action of aspirin depends on inhibition of cyclooxygenase activity in platelets, thereby reducing thromboxane A₂ formation and consequently, their aggregability.

In 1978, two important concepts on eicosanoid formation were presented. The first was that the vascular wall could utilize endoperoxides released by adhering platelets for the formation of prostacyclin. The second proposed that eicosapentaenoic acid (EPA) from oily fish or fish oil could, through the formation of the active analogue of prostacyclin, prostaglandin I₂ but inactive thromboxane A₃, produce an antithrombotic state that protects against cardiovascular disease. Over the last decade, both concepts have been vigorously debated. The publication of Force et al³ in the current issue of Circulation adds important clarification, but at the same time exposes new substantial issues with respect to the dosage of aspirin as an antithrombotic agent.

The targets for aspirin or EPA are the blood platelets, and the aim is to make these aggregate less easily to form intra-arterial thrombi. The mechanisms by which the compounds produce their effects are entirely different. However, they both affect the balance between thromboxane A₂ released from platelets and prostacyclin made by the blood vessel walls.

Prostacyclin and Thromboxane Balance

Prostacyclin and thromboxane A₂ are both formed from the endoperoxide prostaglandin H₂, derived from arachidonic acid freed from the phospholipids of cell membranes. Thromboxane A₂ is an unstable (t₁/₂=30 seconds at 37°C) powerful vasoconstrictor agent and aggregator of platelets. Prostacyclin is also unstable (t₁/₂=3 minutes at 37°C) but it induces vasodilatation and inhibits platelet aggregation.⁵ Thromboxane A₂ and prostacyclin represent the opposite poles of a homeostatic mechanism for regulation of platelet aggregability in vivo.⁶

A number of cardiovascular thrombotic diseases have been associated with an imbalance in the prostacyclin-thromboxane system. Platelets from patients with arterial thrombosis, deep venous thrombosis, or recurrent venous thrombosis produce more thromboxane A₂ than normal and have a shortened survival time.⁷ Platelets from rabbits made atherosclerotic by a high fat diet⁸ or from patients who have survived myocardial infarction⁹–¹² or ischemic stroke¹³ are abnormally sensitive to aggregating agents and produce more thromboxane A₂ than controls. Patients with arteriosclerosis obliterans or diabetes mellitus had more thromboxane B₂ and less 6-oxo-prostaglandin F₁₅ (the immediate breakdown products of thromboxane A₂ and prostacyclin) in their plasma than control patients without these diseases.¹⁴

Aspirin in Coronary Artery Disease

The antiplatelet effect of aspirin is due to the irreversible inactivation of platelet cyclooxygenase. Cyclooxygenase must be continuously produced in endothelial cells because they recover their ability to synthesize prostacyclin within a few hours. However, the nonnucleated platelets cannot make fresh cyclooxygenase and thromboxane A₂ synthesis only recovers with the release of new platelets. The life of a platelet in the circulation is some 8–11 days. Thus, a treatment regime with aspirin every day or every two days will lead to a cumulative inhibition of thromboxane A₂ formation, allowing endothelial cells to produce prostacyclin by new enzyme synthesis.

Thromboxane synthesis can be largely prevented by administering one low dose (80–100 mg) of aspirin¹⁵ or by as little as 10 mg of aspirin taken daily for 3 weeks.¹⁶

The selective action of aspirin on platelets has been ascribed partly to regeneration of the endothelial cell cyclooxygenase and partly because platelets encounter orally administered aspirin in the systemic circulation before it is deacetylated in the liver and diluted by other venous blood. Thus, it is theoretically possible by treatment with low doses of aspirin to ablate thromboxane A₂ formation while allowing endothelial cells to produce prostacyclin by new enzyme generation.¹⁷

Modification of Fatty Acid Precursors by Fish Oils

The main eicosanoid precursor in humans, arachidonic acid, is obtained from the meat of farm animals or by chain elongation of the linoleic acid in vegetables. EPA (C₂₀:₅ω₃) is a polyunsaturated fatty acid like arachidonic acid (C₂₀:₄ω₆) but has a higher
degree of unsaturation. There is now considerable evidence that eating fish or taking fish oils containing EPA protects against cardiovascular disease. The fatty acid available for prostaglandin biosynthesis in Greenland Eskimos is mainly EPA, unlike that in caucasians, which is mainly arachidonic acid. These differences may explain why Eskimos have a low incidence of acute myocardial infarction, low blood cholesterol levels, and an increased tendency to bleed. This prolonged bleeding time is related to a reduction in ex vivo platelet aggregability.

In vivo, EPA is incorporated into platelet phospholipids, to some extent replacing arachidonic acid. Thus, following phospholipase A2 activation, EPA as well as arachidonic acid can be released. As both acids are substrates for cyclooxygenase, there will be some trienoic prostaglandins generated from EPA. These have important differences in biological activity, in that prostaglandin I2 is equipotent to prostacyclin (prostaglandin I2), in preventing platelet aggregation, but thromboxane A2 is much less active than thromboxane A2 in causing platelets to clump. Thus, when EPA is available as a precursor, platelets are less prone to aggregate without substantial reduction of endothelial thromboresistance. Therefore, people who eat more fish or take fish oil containing EPA have a shift in their eicosanoid formation towards the antithrombotic side. This shift is the simplest scientific explanation for decreased heart attacks in fish eaters.

In a recent study of more than 2,000 patients who had had heart attacks, there was a 30% decrease in recurrence among those who ate at least two meals a week that consisted of fatty fish or who took an equivalent amount of fish oil. There is also convincing epidemiological evidence that the risk factors for heart disease are decreased by eating fish or taking fish oil. Clearly, a high intake of n-3 fatty acids (for example, EPA) in populations with a moderate-to-low consumption of dietary saturated fatty acids is associated with a low incidence of coronary heart disease.

Overall then, the present evidence suggests that it is well worth while continuing to study the effects of EPA in humans.

Conclusions

In their ingenious study on patients with coronary artery disease, Force et al have combined the administration of fish oil with that of aspirin in order to dissect the interactions between platelets and vessel walls using measurements of urinary metabolites as indicators of eicosanoid formation. In confirmation of others, they showed that fish oil alone halved thromboxane A2 production by platelets whereas aspirin in any dose (50 mg–1,300 mg/day) virtually abolished it. Fish oil slightly reduced the formation of prostacyclin, but this was compensated for by an increase in prostaglandin I2 formation. Low-dose aspirin (50 mg/d) substantially reduced prostacyclin production in the patients receiving fish oil, but higher doses of aspirin had no further effect. Importantly, aspirin in any dose did not affect prostaglandin I2 formation. This suggests that in these patients taking fish oil, aspirin had little or no effect on the cycloxygenase of endothelial cells. Instead, the fall in prostacyclin production was because of a reduction in the transfer of the endoperoxide prostaglandin H2 from platelets.

There are three important conclusions from this study. First, the aspirin-induced decrease in prostacyclin production may be unavoidable, for it arises not from cyclooxygenase inhibition in endothelial cells but from a reduction of endoperoxide formation by platelets, an inherent feature of the beneficial action of aspirin. Second, aspirin does not interfere with the possible benefits of fish oil ingestion; indeed the two regimes may be additive. Third, the rationale for using a low dose of aspirin in order to spare the endothelium is questioned by these results. Specifically, the authors suggest that it is more important to suppress thromboxane A2 production by platelets by more than 99% with 100–325 mg aspirin daily than by 95% with the smaller doses. The beneficial effects of 325 mg of aspirin in preventing myocardial infarction have been so clearly demonstrated that to take the dosage regime much lower may be counter productive.

References


**KEY WORDS** • arachidonic acid • eicosapentaenoic acid • cyclooxygenase • thromboxane • Editorial Comments
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