Denton A. Cooley's 50th Anniversary in Medicine

Conversion from Chronic to Acute Coronary Heart Disease Syndromes

Role of Platelets and Platelet Products

James T. Willerson, MD

Vascular endothelial injury associated with arterial narrowing leads to platelet adhesion and aggregation at the site of endothelial injury and to the local accumulation of several mediators that promote platelet aggregation and vasoconstriction, including thromboxane A_2, serotonin, adenosine diphosphate, platelet activating factor, oxygen-derived free radicals, activated thrombin, and tissue factor. At the same sites of endothelial injury, there is a reduction in absolute or relative amounts of the endogenous inhibitors of platelet aggregation and vasoconstriction, including prostacyclin, endothelium-derived relaxing factor (nitric oxide), and tissue plasminogen activator; the loss of the effects of the endogenous inhibitors preventing platelet aggregation and vasoconstriction helps to create a prothrombotic and vasoconstrictive environment. Endothelial injury occurs as a result of atherosclerotic plaque fissuring or ulceration, flow shear stress, hypertension, diabetes mellitus, immune complex deposition, infection, and mechanical injury in the form of diagnostic and therapeutic catheterization. Endothelial injury and the accumulation of platelet- and other cell-derived mediators promotes neointimal proliferation in an exaggerated wound-healing response, resulting in further anatomic narrowing of an artery in the subsequent days and weeks. Future methods that may prove useful in protecting the individual with these vascular problems from acute myocardial infarction and its consequences are inhibition of multiple mediators of platelet aggregation and vasoconstriction, restoration of the presence of the normal endogenous inhibitors of platelet aggregation and vasoconstriction, and/or rapid therapeutic regeneration of the injured endothelium. ***(Tex Heart Inst J 1995;22:13-9)***

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Approximately 15 years ago, my colleagues and I suggested that during "the natural evolution of atherosclerotic plaques" and other forms of endothelial injury, platelets attach to the exposed subendothelium, releasing thromboxane A_2, which promotes further platelet aggregation and dynamic vasoconstriction that in turn lead to transient or permanent coronary artery thrombosis (Fig. 1).[1-4] We suggested that conversion from chronic stable to unstable angina was caused by this sequence of events.[1,5] Our initial studies testing this hypothesis demonstrated that patients with active rest angina had increases in transcardiac thromboxane concentration, as did several patients with recent unstable angina (Fig. 2).[1] However, patients with stable angina, those with valvular and myocardial diseases, and those with chest pain syndromes not caused by coronary heart disease had substantially lower transcardiac thromboxane values.[1] Subsequent studies from our laboratories and those of other investigators have demonstrated that several additional mediators, such as serotonin and platelet activating factor, accumulate across the human coronary bed as patients develop unstable angina.[6,7] Thrombin production increases at sites of endothelial injury,[8,9] causing further platelet aggregation and vasoconstriction, and mediating the conversion of fibrinogen to fibrin, in which platelets aggregate. Constantinides,[10] Davies and Thomas,[11] and Falk[12] have shown that atherosclerotic plaque fissuring and ulceration are often causes of endothelial injury leading to abrupt development of unstable angina and acute myocardial infarction. Thus, as human beings develop unstable angina, several products derived from platelets, endothelial cells, smooth muscle cells, and inflammatory cells accumulate, which leads to transient or permanent thrombosis initiated by platelet aggregation and dynamic vasoconstriction (Fig. 3).

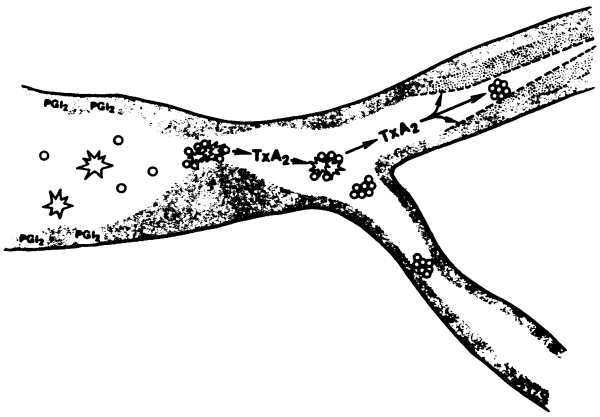

Fig. 1 *Shows the initial scheme proposed by the author's group suggesting that the "natural evolution of atherosclerotic plaques" is associated with exposure of the subendothelium, attachment and aggregation of platelets, and release of thromboxane A_2, causing further platelet aggregation and vasoconstriction as the fundamental mechanisms responsible for the conversion of coronary heart disease syndromes from chronic to acute.*

PGI_2 = prostaglandin I_2 (prostacyclin); TxA_2 = thromboxane A_2

(From: Hirsh PD, et al. Am J Med 1981;71:1009-26. Reproduced by permission of Exerpta Medica.)

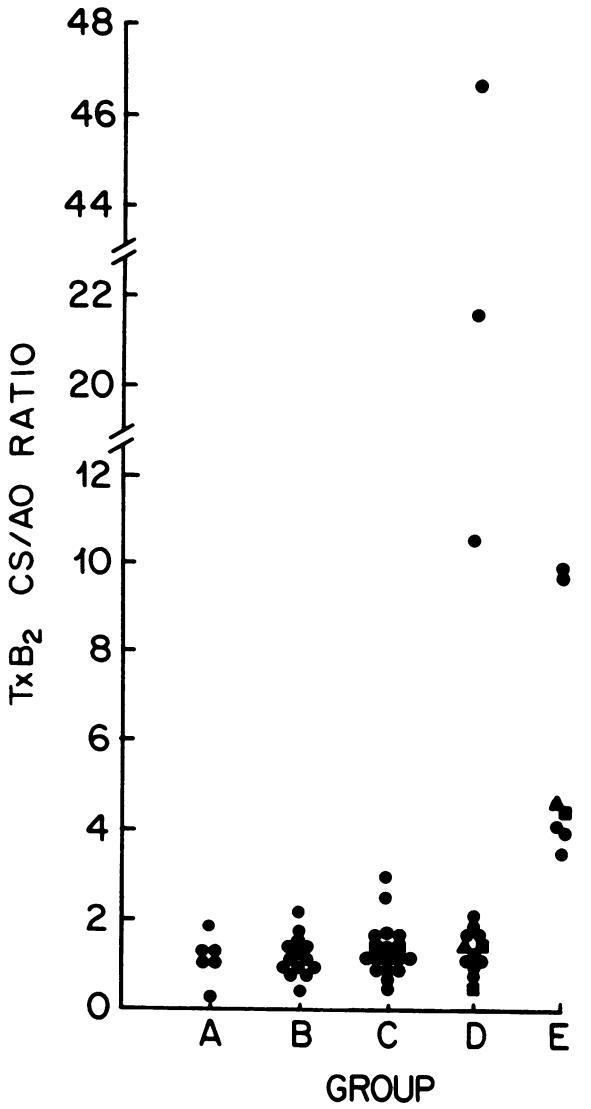

Fig. 2 *Note the increases in transcardiac thromboxane A_2 in patients with active unstable angina (group E) and in 3 patients with recent unstable angina (group D). In the 60 patients shown in this figure, thromboxane B_2, the inactive metabolite of thromboxane A_2, was measured by a sensitive and specific radioimmunoassay, and thromboxane A_2 concentrations were estimated from coronary sinus values. The increases in transcardiac thromboxane concentration were greater in patients with active unstable angina than in patients with stable angina (group C) and in patients with noncoronary chest pain syndromes and valvular and myocardial diseases (groups A and B). Each point represents the data from 1 patient. Squares identify patients who received a cyclooxygenase inhibitor within 5 days of study, and triangles patients with coronary arterial spasm.*

AO = aorta; CS = coronary sinus; TxB_2 = thromboxane B_2

(From: Hirsh PD, et al.[1] Reproduced by permission of the New England Journal of Medicine.*)*

Experimental Animal Studies

Following the demonstration that thromboxane A_2 accumulates across the human coronary bed in patients as they develop unstable angina, we used an animal model developed originally by Folts and coworkers[13] to determine whether thromboxane A_2 plays a causal role when endothelial injury and coronary artery narrowing coexist and intravascular thrombosis occurs. We found in canine models (and later in rabbits, goats, pigs, and nonhuman primates) that mechanical obstruction from platelets and vasoconstriction contributes to the development of coronary artery thrombosis that often follows spontaneous reductions in coronary blood flow known as "cyclic flow variations."[3-5,13,14] We also found that there are several mediators of intravascular thrombosis, including thromboxane A_2, serotonin, adenosine diphosphate (ADP), activated thrombin, platelet activating factor, and free radicals, that accumulate at sites of endothelial injury and arterial narrowing[15-22] (Fig. 3). Each of these substances contributes to in vivo platelet aggregation, and thromboxane A_2, serotonin, thrombin, and platelet activating factor cause dynamic coronary artery vasoconstriction. Other investigators have shown that exposure to tissue factor contributes to coronary artery thrombosis in similar experimental models.[23]

Further studies using the Folts model have demonstrated that reductions in the effects of endogenous endothelial inhibitors of platelet aggregation and vasoconstriction—prostacyclin, tissue plasminogen activator, and endothelium-derived relaxing factor (nitric oxide [NO])—contribute to transient platelet aggregation, vasoconstriction, and thrombus development following endothelial injury, especially

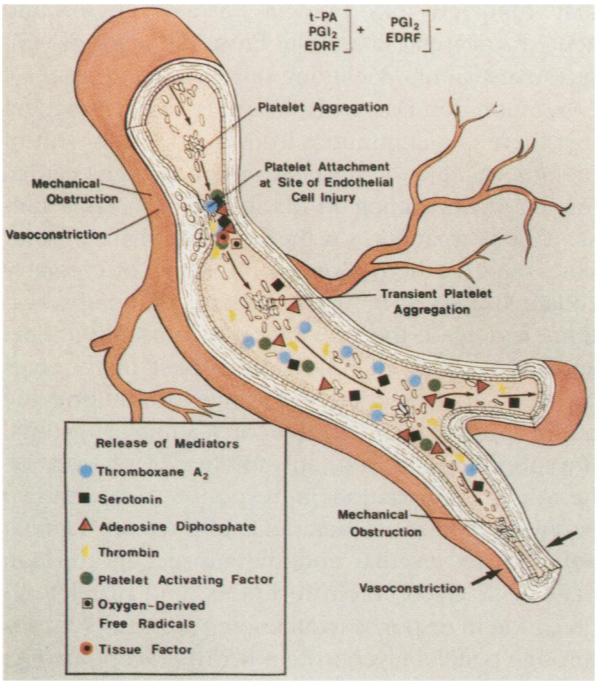

Fig. 3 *This figure provides a more comprehensive representation of mediators that promote platelet aggregation and dynamic vasoconstriction at sites of endothelial injury and vascular narrowing. The list is considerably longer than just thromboxane A_2 and includes serotonin, activated thrombin, adenosine diphosphate (ADP), tissue factor, free radicals, and platelet activating factor.*

EDRF = endothelium-derived relaxing factor; PGI_2 = prostaglandin I_2 (prostacyclin); t-PA = tissue plasminogen activator

(From: Willerson JT, Cohn JN, Masseri A. Angina pectoris. In: Willerson JT, Cohn JN, eds. Cardiovascular medicine. New York: Churchill Livingstone, 1995:335. Reproduced by permission of Churchill Livingstone.)

when arterial narrowing is present.[24,25] Figure 3 provides a more comprehensive list of the mediators causing vasoconstriction and thrombosis following endothelial injury with coexistent coronary artery narrowing. In experimental studies, promoting the release of endothelium-derived relaxing factor (NO) by L-arginine administration eliminates cyclic flow variations in canine coronary arteries with endothelial injury and stenosis when cyclic flows have been initiated by the administration of an inhibitor of nitric oxide synthase, N^{O} monomethyl-L-arginine (LNMMA).[24] Local restoration of prostacyclin synthesis through gene therapy in porcine carotid arteries with endothelial injury prevents thrombosis when the endothelial injury has been caused by angioplasty.[26,27]

Therapeutic Strategies Derived from Experimental and Human Studies

It has become clear that interfering with any single mediator of platelet aggregation and vasoconstriction does not provide complete protection against the development of intravascular thrombosis and vasoconstriction, especially when the stimulus for thrombosis is strong, such as occurs with deep arterial injury and with increased local concentrations of catecholamines.[18,28] Single inhibitors, such as a thromboxane A_2 synthesis inhibitor or receptor antagonist or aspirin, eliminate cyclic flow variations in experimental studies; but increases in systemic catecholamine concentrations restore the cyclic flows.[28] On the other hand, a combination of inhibitors of the various mediators shown in Figure 3 generally eliminates cyclic flow variations experimentally, even when systemic catecholamine concentrations are markedly increased.[18,29,30] Catecholamine promotion of platelet aggregation is an important concern, since patients with unstable angina and myocardial infarcts generally have marked increases in plasma catecholamines. Therefore, simultaneous inhibition of multiple mediators that promote platelet aggregation and vasoconstriction is important in experimental animal models, in order to provide comprehensive protection when endothelial injury and arterial narrowing coexist. I suspect the same is true in human beings with unstable angina and acute myocardial infarction.

Transient Platelet Aggregation Promoting Neointimal Proliferation ("Restenosis Lesions") after Endothelial Injury

In canine and porcine models, mechanical endothelial injury induced by an external constrictor limiting arterial flow causes cyclic flow variations associated with transient platelet aggregation and dislodgement and vasoconstriction. During 7 to 21 days of follow-up, these animals develop varying degrees of neointimal proliferation associated with the accumulation of smooth muscle cells and monocytes/macrophages.[31] In the canine model, there is a near linear relationship between the frequency and severity of cyclic flow variations and the severity of neointimal proliferation following mechanical arterial injury[31] (Fig. 4). The administration of inhibitors of multiple mediators of platelet aggregation and cyclic flow variations markedly reduces the severity of neointimal proliferation.[31] The administration of antagonists for thromboxane A_2 and serotonin[31] in combination with an inhibitor of ADP markedly reduces the severity of neointimal proliferation, especially when given prior to angioplasty injury of a canine coronary artery.[32] These data emphasize the importance of platelets and platelet-derived products in a continuum from the development of transient and permanent arterial thrombosis with associated vasoconstriction to the development of the fibroproliferation that characterizes "restenosis lesions" after mechanical injury to the endothelium.

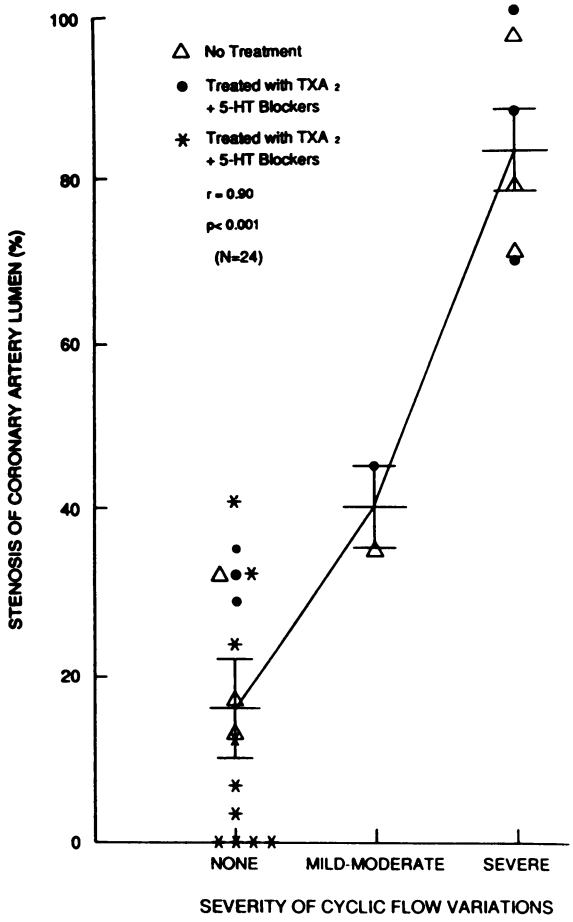

Fig. 4 *This figure shows a near linear relationship between the frequency and severity of platelet aggregation and dislodgement and the severity of neointimal proliferation at sites of mechanical injury to the canine coronary endothelium. Cyclic flow variations serve as a surrogate for platelet aggregation and dislodgement.*

5-HT = serotonin; TXA_2 = thromboxane A_2

(From: Willerson et al.[31] Reproduced by permission of the National Academy of Sciences.)

In more recent studies, it has become apparent that thromboxane A_2, serotonin, and ADP are mitogens that amplify the endothelial and smooth muscle growth effects of one another.[33,34] Rapid anatomic progression of the severity of arterial narrowing after endothelial injury may occur as a consequence of platelet aggregation, leading to thrombosis, vasoconstriction, and the accumulation of platelet-derived growth factors. Almost certainly, this same sequence of events occurs in at least some patients with unstable angina and acute myocardial infarction.

Prevention of Unstable Angina and Myocardial Infarction in Human Beings

The elucidation of the biology of vascular injury leading to thrombosis and vasoconstriction will allow the development of more protective therapies that ultimately may prevent unstable angina and acute myocardial infarction. From the work of various investigators, including our group and those of Constantinides, Davies, Falk, and Fuster, it is evident that there is a continuum from the development of endothelial injury to unstable angina and myocardial infarction, depending on whether thrombosis is transient or permanent, on the location of the thrombosis, and on the presence or absence of coronary collateral vessels.[1-24,28-41] On the basis of the observations reviewed, the prevention of unstable angina and myocardial infarction (and most likely cerebrovascular accidents) will require inhibiting the multiple mediators capable of leading to arterial thrombosis. Therefore, an inhibitor of platelet adhesion or aggregation in response to all known agonists should be therapeutically useful. Platelet adhesion to vascular endothelium occurs through platelet Ib glycoprotein receptors, and platelet aggregation in response to all known mediators occurs through platelet glycoprotein IIb/IIIa receptors (Fig. 5).

Prevention of Arterial Thrombosis and Its Consequences in Human Beings

Dr. Barry Coller has developed a monoclonal antibody against the platelet glycoprotein IIb/IIIa recep-

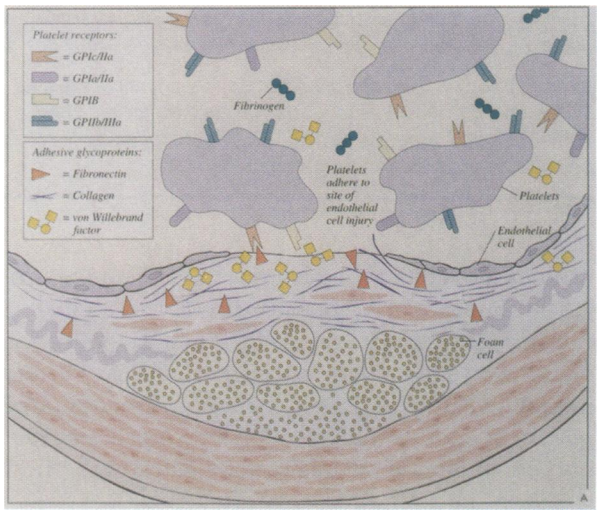

Fig. 5 *This figure demonstrates schematically the mechanisms involved in platelet adherence and aggregation at sites of endothelial injury. Platelet glycoprotein IIb/IIIa receptors are involved in platelet aggregation, and platelet glycoprotein Ib receptors are involved in platelet adhesion to the damaged endothelium.*

GPIc/IIa = glycoprotein Ic/IIa; GPIa/IIa = glycoprotein Ia/IIa; GPIB = glycoprotein Ib; GPIIb/IIIa = glycoprotein IIb/IIIa

(From: Willerson JT. Medical treatment of coronary heart disease. In: Willerson JT, Baim DS, Cooley DA, Frazier OH, Grundy SM, Kaplan NM, et al, eds. Treatment of heart diseases. New York: Gower, 1992:1.38-1.60. Reproduced by permission.)

tors that prevents platelet binding to fibrinogen and aggregation in response to all known agonists.[35-38] Recently, a pivotal clinical trial has indicated that the administration of this antibody to high-risk patients for 12 hours after coronary artery angioplasty reduces the frequency of myocardial infarction and the need for a subsequent revascularization procedure[37] (Fig. 6). Follow-up of these patients for the next 6 months demonstrated a 23% reduction in the need for an additional revascularization procedure in patients receiving short-term infusion of the antibody following angioplasty[38] (Fig. 7). Administration of the antibody was associated with an increased risk of bleeding, especially at groin puncture sites, and with a higher need for transfusion.[38] However, it seems likely that more careful attention to the groin puncture site will reduce the excess bleeding. There was no increased intracranial bleeding in the patients treated with the antibody.[38] Other inhibitors of the platelet glycoprotein IIb/IIIa receptors have been developed, including synthetic peptides and small molecular weight inhibitors, some of which are now in clinical trials in patients undergoing angioplasty and in those with unstable angina. At present, inhibitors of thrombin, tissue factor, and platelet glycoprotein Ib receptors are being evaluated in experimental trials.

Summary

Considerable progress has been made in the elucidation of the biology of arterial injury leading to the development of thrombosis, vasoconstriction, and neointimal proliferation. There is a continuum from endothelial injury with arterial narrowing to the development of unstable angina and myocardial infarction. Insights into the mechanisms of this process have led to the development of more protective interventions, especially ones that inhibit the multiple mediators of platelet aggregation and vasoconstriction, including inhibitors of the platelet glycoprotein IIb/IIIa receptors. Ultimately, greater protection against the abrupt development of arterial thrombosis may also be provided by gene therapy that hastens the reestablishment of a relatively normal endothelium and/or restores the presence of endogenous endothelial inhibitors of platelet aggregation, vasoconstriction, and neointimal proliferation.

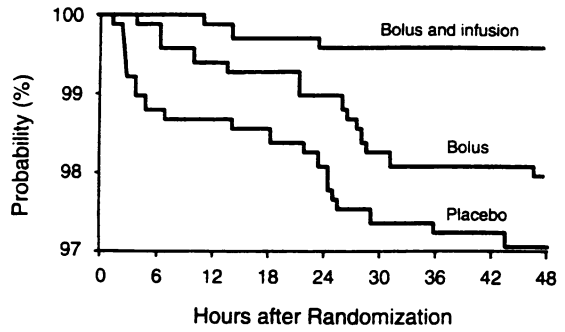

Fig. 6 *Shows probability of no urgent repeated percutaneous revascularization procedures in the 3 treatment groups. Note reduction in the need for a 2nd interventional procedure in high-risk patients undergoing coronary artery angioplasty who were treated with a bolus administration and several-hour infusion of the monoclonal antibody to the platelet glycoprotein IIb/IIIa receptors. This study involved nearly 2,100 patients in a multicenter evaluation of the ability of this antibody to reduce the frequency of thrombotic events after percutaneous transluminal coronary angioplasty. The y axis is truncated at 97 percent to demonstrate the differences in this end point, which occurred with low frequency.*

(From: EPIC Investigators.[37] Reproduced by permission of the EPIC Investigators and the New England Journal of Medicine.*)*

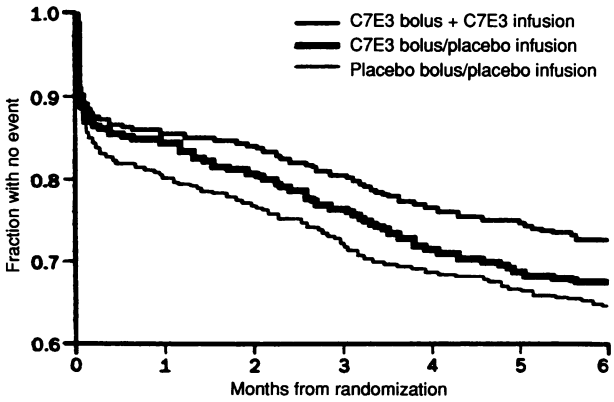

Fig. 7 *In the 6 months following initial coronary artery angioplasty, there is a 23% reduction in the need for a 2nd interventional procedure in patients who received a bolus and several-hour infusion of the monoclonal antibody to platelet glycoprotein IIb/IIIa receptors at the time of the original angioplasty.*

7E3 = monoclonal antibody against the platelet glycoprotein IIb/IIIa receptor

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