9. Thrombosis and the Injurious Agent

"Unless proven otherwise, arterial thrombosis as now comprehended is primarily a misdirected or amplified form of primary hemostasis and is modulated by blood platelets."
AJ Marcus, [129]

Platelets, Injury Repair and Thrombosis

The adhesion, activation and aggregation of platelets that lead to the formation of intravascular thrombosis are generally considered a pathologic process, rather than a physiologic response to injury. The same hemostatic response, however, that occurs with injury to tissues outside the vascular system, with the platelet response and with the same structure as intravascular thrombus, is considered a normal, necessary physiologic response to injury. Although intravascular thrombosis may progress to produce pathologic disease states, this does not mean that the hemostatic responses taking place inside the vascular tree are pathologic. The basic, initial hemostatic responses of platelet activation to intravascular injury cannot, per se, be considered pathologic in nature (127). Fibrin and mural thrombus formation are beneficial and essential to the resolution of injury. They provide the scaffolding for in-growing fibroblasts and other elements essential to injury repair. For example, the basic hemostatic responses following PTCA injury are essential elements in the healing, repair, and stabilization of the PTCA site [68]. It is important to distinguish pathologic thrombosis from physiologic hemostasis within the vascular tree.

Platelet activation and aggregation are, broadly speaking, a physiologic defense whose primary purpose is to stop blood loss and to initiate the repair and resolution of injury. This response becomes pathologic only under certain circumstances [127,128]. Marcus [129] believes thrombosis is a misdirected or amplified form of primary hemostasis and is modulated by blood platelets. If this is correct, the ongoing and continuing hemostatic responses surrounding platelet activation, over and above what is required for injury repair, are pathologic and may lead to obstructing thombosis [129]. Specifically, thrombus formation reflects loss, failure, or inability of the thromboregulatory system to halt or control basic hemostatic responses, and can be interpreted as a pathologic breakdown of normal defense systems [129]. What causes this loss of thromboregulatory control, and what is the role of the IA in the pathogenesis of thrombosis?

Pathologic Hemostasis and Thrombosis

Figures 21A-F, is an example of apparently uncontrolled hemostatic responses that resulted in the formation of a large occlusive coronary thrombus. The thrombus is composed of large amounts of mature fibrin, with a superimposed platelet thrombus on the luminal surface (Figure 21D). The thrombus does not contain plaque contents, so it may have formed on a large endothelial surface erosion rather than on an ulcerated or ruptured plaque. Remnants of the fibrous cap are encased in the thrombus (Figure 21F). This thrombus could also have formed on the exposed surface of what was once a large and extensive false channel. It has continued to grow, presumably because of continued platelet activation, aggregation, and the formation of fibrin. Such a thrombotic response is far in excess of that needed to repair this injured artery.

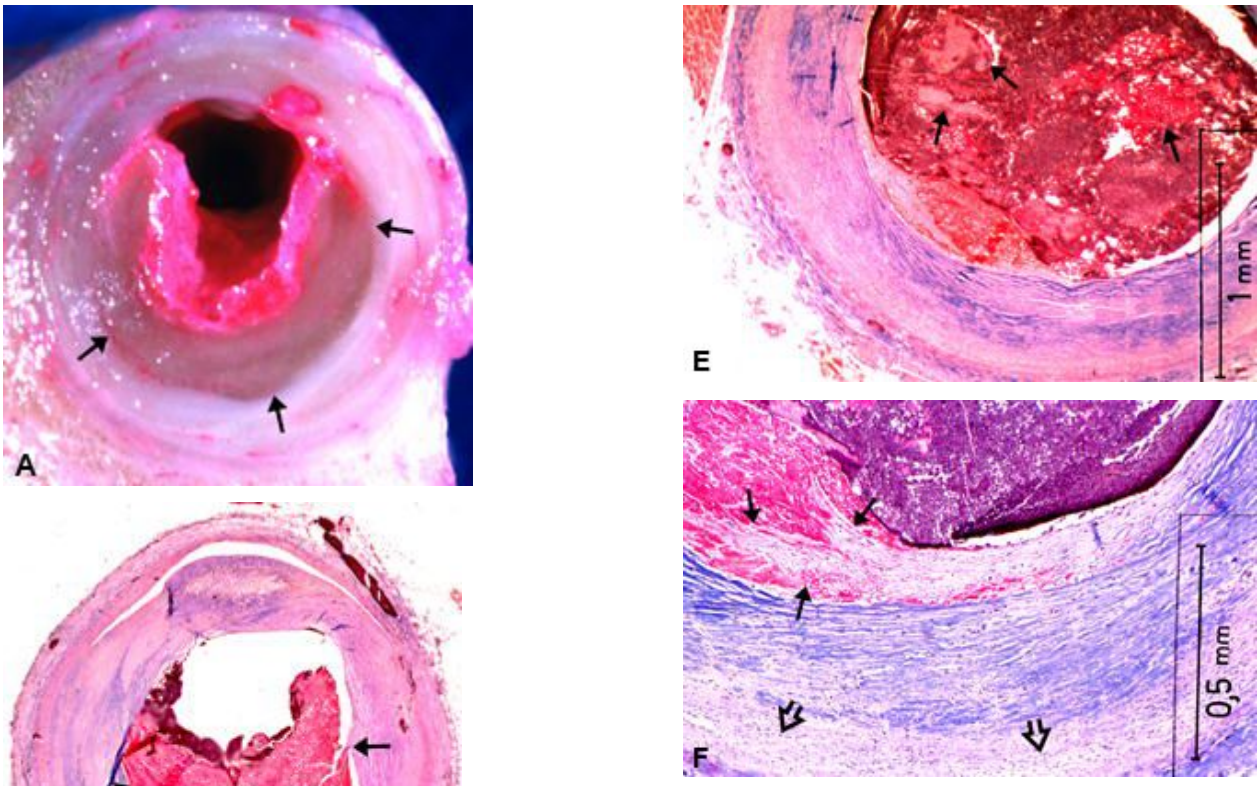

Figure 21: **A**–**F** are sections taken from three contiguous segments of the proximal LAD coronary artery of a 34-year-old male who died SCD outside the hospital. **A** & **B** are from the proximal segment, **C** & **D** from the middle segment, and **E** & **F** from the distal segment. Gross (**A**) and microscopic (**B**) are views of a large, circumferential, but incompletely organized mural thrombus (arrows) producing severe luminal stenosis. Magnification x15. Low- (**C**) and high-power (**D**) views of the mural thrombus showing the surface is covered with a platelet thrombus, indicating the thrombus (arrows) is actively growing. Low- (**E**) and high-power (**F**) views of the distal end of the thrombus showing many platelet fibrin microemboli (arrows) and a great reduction in the size of the thrombus. In **F**, a remnant of the fibrous cap has been incorporated into the thrombus (solid arrows). A marked infiltration of T cells (open arrows) into the deep area of the intima is also present. **B - F**, All MSB stain.

Thromboregulatory Control

The failure to modulate and control platelet activation and pathologic thrombus formation may be due in part to an imbalance in the concentration of thrombolytic and thrombogenic factors in circulating blood. The ratio of active Tissue Plasminogen Activator (TPA) to active Plasminogen Activator Inhibitor (PAI-1) is 1:8 in healthy male subjects, but

in men with atherothrombotic disease, the ratio is 1:50 [130], indicating that these patients suffer from a systemic abnormality of the thromboregulatory system, resulting in a prothrombotic state. The cause of this imbalance is not clear. It appears to be due, at least in part, to increased production of PAI-1 by one or more of the following mechanisms:

First, as recent studies show, increased production of PAI-1 by endothelial cells and vascular SMCs that have been stimulated by various growth factors, including fibroblast growth factor and platelet derived growth factor, are produced by macrophages or lipid-laden foam cells [131–133].

Second, studies show a marked increase in Angiotensin Converting Enzyme (ACE) activity in the endothelium and other intimal vascular cells, especially lipid-laden macrophages within atherosclerotic plaques [134]. This increased ACE activity results in increased conversion of Angiotensin I into Angiotensin II. Angiotensin II has been shown to be a strong stimulus of the increased production of PAI-1 [134,135]. The increase in ACE activity within the plaque , producing an increased amount of PAI-I, may disturb the thromboregulatory balance within the plaque and attenuate inherent thrombolytic mechanisms [134].

Third, Angiogtensin II is also involved in platelet activation and aggregation and could contribute to the continued and excessive platelet responses involved in thrombus formation, increasing the thrombogenic potential [134,135].

The increase in PAI-1 and the failure of the thrombo-regulatory system can be traced to the lipid-laden macrophages and foam cells within the atherosclerotic plaque. These are the same SMC and lipid-laden macrophages formed in response to the IA that are responsible for many of the atherosclerotic lesions described in previous chapters. The creation or development of a prothrombotic state in patients with active disease appears to be another example of subversion of normal regulatory and defensive responses by the IA. In other words, the IA, directly or indirectly, is the cause of and actively promotes thrombus formation as a component of active, progressive atherosclerotic disease (136). What other mechanisms related to the activity of the IA alter or affect the thromboregulatory system and promote thrombus formation?

Luminal Stenosis and Thrombosis

Chapters 3, 4, and 5 showed the direct relationship between active atherosclerotic disease, caused by the IA, and the development of luminal stenosis. Luminal stenosis is an essential element required for thrombus formation, primarily by causing shear forces that activate platelets and thus promote thrombosis [121,137,138]. However, luminal stenosis and associated platelet activation alone do not necessarily lead to pathologic thrombosis, and many severely stenotic lesions remain relatively unchanged and stable for many years [139]. Luminal stenosis is not synonymous with thrombosis, but the activation of platelets may have implications for other acute lesions, such as UPs [57], within the coronary tree. Although luminal stenosis is essential, other factors must be present for thrombi to form.

Wall Injury and Thrombosis

Breach of endothelial integrity will activate platelets and provide the substrate for thrombus formation. The IA, by producing active, expanding, atherosclerotic disease that affects the overlying endothelium, is responsible, directly or indirectly, for producing the pathologic substrate necessary for thrombus formation. Data show that virtually all surface erosions or UPs are associated with adventitial inflam-

matory cell infiltrates, an objective sign of active, injurious atherosclerotic disease [57]. We believe that excessive, pathologic thrombosis is caused by and promoted by the IA by altering hemostatic factors, producing luminal stenosis and injuring or eroding the endothelium, Virchow's Triad [130].

Evolutionary Purpose

If thrombosis is a component, not necessarily a complication, of active atherosclerotic disease, what is the evolutionary purpose of thrombus formation? Why should the IA subvert or alter the thromboregulatory system to promote thrombosis? Is thrombosis just one of many features of active atherosclerosis, or does thrombus formation benefit the IA in some way? Does thrombus supply lipid or some other energy source for the replication, growth, and expansion of the IA, as we postulated in Chapter 4? Apolipoprotein (a) (Lp(a)), closely resembles plasminogen. It is found in thrombus and may have evolved to play a role in wound healing by delivering cholesterol and other lipids to sites of fibrin deposition where membrane synthesis is required. Lipoprotein (a),(Lp(a)), due to its similarity to plasminogen, may also interfere with plasmin generation and inhibit thrombolysis [140]. We speculate that thrombus provides a more readily available supply of lipids or other elements necessary for the IA to survive than does plaque tissue.

Clinical Implications

If thrombosis is a component, not a complication, of active atherosclerotic disease, what difference does this make in management of the patient with active coronary disease, and what is gained by making this distinction? If thrombosis is a component, then it is an expected development or event, and all patients with active atherosclerotic disease should receive antithrombotic, antiplatelet therapy, ACE inhibitors, or other drugs to reduce or prevent thrombus development beyond that required for tissue repair. Patient management should aim to reestablish thromboregulatory balance, prevent further injury or breach of the endothelium, and prevent the development of luminal stenosis [129].

However, if thrombosis is a complication of active atherosclerosis, then it is a pathologic event that must be prevented. As noted above, we do not wish to prevent thrombosis, per se, we want to prevent excessive throm bosis that leads to obstruction of coronary flow. Treating thrombosis as a pathologic condition or eliminating it may also prevent or eliminate desirable hemostatic responses necessary to repair the injured artery. Eliminating all hemostatic responses may lead to further pathologic conditions and problems, such as cerebrovascular accidents and acute coronary events [141]. If thrombosis is approached as a component of active disease that will eventually happen, then management will be aimed at preventing excess growth of thrombus rather than preventing all thrombus formation.

The essence here is to identify the patient with active disease. Identifying patients with active disease will aid greatly in risk stratification and will focus on measures to avoid or prevent excessive thrombus formation. The use of C Reactive Protein and Fibrinogen, acute phase reactants, may be useful in identifying the patient with active atherosclerotic disease, but these tests do not identify the location of the active disease whether intra- or extra-cardiac [142]. Not only do we need to know the presence or absence of active disease, we also need to develop some way to measure the degree of activity, and to locate the most active sites. Specific identification of the most active sites would allow specific treatments or interventions to be planned under controlled conditions designed to prevent excessive thrombus formation. For example, if it were possible to identify and quantify the activity of "vulnerable" plaques [143] it might be

possible to focus treatments, medical or interventional, designed to stabilize or remove such plaques, particularly if they were causing significant, >80%, luminal stenosis. Recent studies of thermal heterogeneity, using infra red technology have been able to identify “hot” plaques -those with active inflammatory disease. These studies may be very useful in the future [65,71].

In Review

Pathologic thrombosis is due to uncontrolled hemostatic responses, modulated by platelet activation over and above what is required for injury repair. An imbalance in TPA/PAI-1 ratio develops as a result of breakdown of normal defense systems, leading to a hypercoagulable state in patients with coronary atherosclerosis. Thrombosis is actively promoted by the activity of the IA. It is a component, not a complication, of active, inflammatory, atherosclerotic disease. The recognition that thrombosis is a component of active atherosclerotic disease alters our view of the pathogenesis of thrombosis, and of our approach to the treatment and prevention of ACD.