Coronary Thrombosis
Effects of Blood Flow on the Mechanism of Thrombus Formation

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SUMMARY
The mechanism of arterial thrombosis, including coronary thrombosis, is different from that of thrombosis which occurs at sites of blood stasis such as deep venous thrombosis. Considering the onset of arterial thrombus formation, soluble coagulant factors may not play important roles for its onset since they are diluted by the effect of blood flow and cannot reach high enough concentrations to form insoluble fibrin. Platelets, which can stick to damaged vascular lumen even in the presence of shearing effects of blood flow, may play a crucial role in the onset of arterial thrombus formation. Thus, the mechanism of platelet thrombus formation should be assessed in the presence of blood flow. However, current dogma that fibrinogen binding to activated GP IIb/IIIa is the final common pathway for platelet thrombus formation was developed by using the function assay system of aggregometer, in which the effects of blood flow were not seriously considered. We are proposing in this review that plasma ligand protein of von Willebrand factor (vWF) and its interactions with platelet GP Ib and GP IIb/IIa, which become apparent only in assays systems under influence of high shear rates of flow condition such as flowchambers or cone-plate viscometers, are the key events leading to the onset of arterial thrombosis. A better understanding of the vWF-mediated mechanism of platelet thrombus formation is important for the development of better clinical tools to prevent ischemic heart disease as well as for a complete understanding of the mechanism of coronary thrombosis. (Jpn Heart J 1998; 39: 579-596)

Key words: Coronary thrombosis, Blood flow, Platelet, von Willebrand factor, Platelet glycoproteins

ARTERIAL thrombosis, including acute myocardial infarction and cerebral infarction, is one of the most important human health-related issues in industrialized countries. Current investigations have revealed that the rupture of atheroma and subsequent formation of occlusive thrombus in coronary artery is the crucial event leading to the onset of acute myocardial infarction. The issue we address in this review is why occlusive thrombus develops after atheroma
rupture even in the presence of rapid blood flow in coronary arteries generating high shear stress. Indeed, an old pathologist of Virchow proposed that blood stasis is one of the major risk factors for thrombosis, which is true in venous thrombosis including deep venous thrombosis.\textsuperscript{4,5} The mechanisms of thrombus formation at the site of blood stasis are well understood;\textsuperscript{4} activated coagulant factors are concentrated to form the final thrombotic material of fibrin, since dilution of activated coagulant factor by blood flow does not occur due to blood stasis. Anticoagulants such as heparin or warfarin are quite effective for preventing those thrombotic disorders occurring at the site of blood stasis.\textsuperscript{6-11} On the other hand, the mechanism of the onset of coronary thrombosis cannot be explained by the above mechanism because the ruptured atherome, the site where thrombus develops, is exposed to very strong blood flow.

Recently, most investigators believe that platelets, which can adhere to damaged vascular surfaces and may accumulate as aggregations even in the presence of blood flow, play a crucial role in arterial thrombosis occurring under the effect of blood flow.\textsuperscript{12,13} Several clinical studies have clearly demonstrated that anti-platelet agents are at least partly effective for preventing arterial thrombosis in acute coronary syndrome\textsuperscript{14-24} and in some types of cerebral infarction.\textsuperscript{25-27} Although platelets play a crucial role in thrombus formation under the effect of blood flow, most attention has focused on the mechanism of platelet thrombus formation rather than on the effects of blood flow. This review addresses the mechanism of coronary thrombus formation with specific attention to the effect of blood flow.

\textbf{VENOUS THROMBOSIS AND ARTERIAL THROMBOSIS}

Although we use the term thrombus to describe both arterial thrombus as occurs in coronary thrombosis and venous thrombus as seen in deep vein thrombosis, there are essential differences between the two\textsuperscript{28} as shown in the Table. Venous thrombosis occurs at sites of blood stasis, the coagulant cascade leading to fibrin formation plays a crucial role in onset, and anticoagulant agents such as heparin or warfarin are effective preventive\textsuperscript{+11} agents. Angioscopic and autopsy examinations revealed that venous thrombi are rich in erythrocytes, making them red in color.\textsuperscript{29} In contrast, arterial thrombosis occurs under the effect of blood flow, platelets rather than coagulant factors play a crucial role in onset,\textsuperscript{30} and antiplatelet agents such as aspirin are at least partly effective for prevention.\textsuperscript{14-24} Clinical studies have revealed that anticoagulant agents are also partly effective for preventing arterial thrombosis in certain situations,\textsuperscript{16,31} probably because coagulant cascades, especially the one dependent on tissue factor pathway,\textsuperscript{32,33} also play some role after initiation of formation of complete occlu-
Table. Venous Thrombosis and Arterial Thrombosis

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<th>Venous thrombosis</th>
<th>Arterial thrombosis</th>
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<tr>
<td>Site where occurs</td>
<td>blood stasis</td>
<td>blood flow present</td>
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<td>Color</td>
<td>red</td>
<td>white</td>
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<tr>
<td>Major component</td>
<td>fibrin</td>
<td>platelets</td>
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<tr>
<td>Effective treatment</td>
<td>anticoagulant (heparin, warfarin)</td>
<td>antiplatelet agents (aspirin, ticlopidine)</td>
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sive platelet thrombus and blood stasis. Another possibility is that activation of coagulant cascades can be induced on the activated platelet surface even under the effect of blood flow\(^34\) and that this activation may be inhibited by anticoagulants.

The mechanism of venous thrombus formation is well understood.\(^4\) Currently available preventive agents such as heparin are strong enough to control venous thrombosis almost completely.\(^4,35\) However, the mechanism of arterial thrombosis remains to be elucidated.\(^12,28\) Since our understanding of this mechanism remains poor, the clinical efficacy of currently available antiplatelet agents such as aspirin to prevent arterial thrombosis is unsatisfactory.\(^14\) Recently, strong antiplatelet agents which directly inhibit the platelet receptor glycoprotein (GP) IIb/IIIa have been developed and clinical studies have suggested a superior effect of these agents for the prevention of arterial thrombosis,\(^19-24\) though the exact antithrombotic mechanism of these agents is not completely understood. One of the most popular in vitro assay systems for dissecting the mechanism of platelet thrombus formation and the effects of antiplatelet agents is the conventional aggregometer,\(^36\) in which platelets are activated by the addition of chemical stimulants such as ADP and activated platelet aggregation is determined by changes in light transmittance. The results of assays performed with a conventional aggregometer represent the clinical characteristics of bleeding disorders such as thromboaesthesia well.\(^37\) Thus most investigators have applied the results obtained from them to explaining the mechanism of arterial thrombosis\(^38,39\) without any clear evidence to suggest that platelet aggregation occurring in a conventional aggregometer represents the mechanism of platelet thrombus formation occurring in vivo in the presence of blood flow. Understanding the mechanism of platelet thrombus formation under flow is crucial to clarify the mechanism of coronary thrombus formation.

**Principal Rheology and Methodological Considerations**

Before considering the effect of blood flow on arterial thrombus formation, the basic physical concept of rheology will be briefly discussed. As shown in
Figure 1. Blood flowing in vasculature generate parabolic velocity profile as shown in this figure. Local velocity gradients produce a shear rate, which can be converted to shear stress or shear force. Maximum shear stress can be generated between the vascular wall and liquid layer, which is defined as wall shear stress. Each portion of the liquid layer is also subjected to shear stress (dotted lines). Wall shear stress can influence endothelial cells fixed on vascular wall. Liquid shear stress may be applied also to cell components in the blood stream such as platelets, leukocytes and erythrocytes.

Figure 1. Steady Newtonian flow (blood flow may be considered as Newtonian flow at least under arterial flow levels) through a cylinder generates a parabolic velocity profile. Since blood flow can be defined as an infinite number of infinitesimal laminae sliding across one another and resistant to a certain level of viscosity, each layer moving at different speeds exerts shear forces on the next layer. Those shear forces can be defined as shear stress, which is defined as force per unit area between laminae. Shear stress has a linear relationship with shear rate, which is defined as the local velocity gradient, and therefore flowing liquid in the cylinder should be subjected to maximum shear stress in the cylinder wall and to zero shear stress in the center of flow as shown in Figure 1. Maximum shear stress between the wall and the liquid is often specified as wall shear stress, which is known to have at least some effects on the progression of atherosclerosis, platelet adhesion to vascular wall, regulation of biochemical function of endothelial cells, and the onset of atheroma rupture. Thus, shear stress caused by rapid and abundant coronary arterial blood flow has crucial effects on coronary thrombosis.

To understand the relationship between the shearing effect of blood flow and the mechanism of platelet thrombus formation, special equipment to demon-
The mechanism of coronary thrombosis is crucial and requires the demonstration of thrombus formation under controlled shearing conditions. There are several well-established methods for this purpose. The simplest one is the forcing of blood through small holes or a column of glass beads. Thrombus formed under the effect of blood flow can be detected by their ability to inhibit or block blood flow.\(^6\) Although this method is simple and is suitable for clinical screening, it does not facilitate accurate quantitative determinations. To apply stable and homogeneous shear stress on a sample, a cone-and-plate viscometer is the method of choice (Figure 2). As far as the sample could be considered to act like Newtonian flow, the cone-and-plate viscometer can apply the same shear...
rate (the same liquid shear stress) to any part of the sample. The shear rate can be easily controlled by changing the cone-rotation speed. Several investigators have modified the viscometer to measure the extent of platelet aggregation, intracellular calcium ion concentration, soluble ligands binding to platelet, or to visualize thrombus formation by microscopy.

Another popular tool to dissect the mechanism of thrombus formation under the effect of blood flow is a parallel-plate flow chamber also shown in Figure 2. In this system, wall shear rates are determined by volumetric flow rate (Q: cm³/sec), width of the plate (W: cm) and the distance between the plate (2B: cm), as follows.

\[
\text{shear stress} = \frac{3Q}{2WB^2}
\]

Wall shear stress can be easily controlled by changing the flow rate in this system. The recent development of a Hele-Shaw type flow chamber has allowed us to control shear stress without changing flow rate. Thrombus formation in the flow chamber can be detected by serial pictures from an inverted microscope, fluorescent labeling of platelets detected by a fluorescence microscope or by piezo-electric methods. The parallel plate flow chamber is the suitable choice to detect cell-surface interactions such as platelet-collagen coated surface interactions mimicking in vivo platelet interactions with damaged coronary arterial surfaces under controlled flow conditions. Most investigators in this field have studied the mechanism of thrombus formation under the effect of blood flow using either cone-plate viscometer or parallel plate flow chambers.

**Platelet Thrombus Formation Under Flow**

Based on the theory that Badimon et al. proposed in 1988, the cause of acute myocardial infarction is the rupture of atheroma, i.e. the exposure of thrombogenic material such as collagen to flowing blood. Thus, flowing platelet adhesion to damaged vascular lumen is the initial step in the formation of occlusive thrombi. Several investigators have tried to reproduce this initial step in parallel-plate flow chambers coated with collagen. Unlike the mechanism of platelet thrombus formation proposed previously, flowing platelets can firmly attach to a collagen-coated surface even without chemical activation. Studies with functional blocking monoclonal antibodies clearly suggested that the plasma protein of von Willebrand factor (vWF) and its interaction with the platelet receptor protein of GP Ib/IX and GP IIb/IIIa complex is crucial to make stable platelet thrombi resistant to the shearing effect of blood flow. The formation of stable platelet thrombi is illustrated in Figure 3 and is considered to be the following; 1) soluble vWF is attached to the collagen-coated surface probably
Figure 3. Mechanism of platelet thrombus formation occurring under blood flow is summarized in the figure. Once endothelial damage occurs and thrombogenic subendothelial matrix such as collagen is exposed to the blood stream, the soluble plasma protein of von Willebrand factor (vWF) was immobilized onto the collagen surface through collagen binding site of vWF. Flowing inactivated platelets interact with immobilized vWF through its interacting site for GP Ib/IX complex. The characteristics of the vWF interaction with GP Ib/IX complex are transient but very strong. Flowing inactivated platelets trapped by immobilized vWF through GP Ib/IX complex are activated, and then can attach in a stable manner on to vWF through both GP Ib and activated GP IIb/IIIa. The same mechanism of platelet activation and immobilization occurs in vWF immobilized on platelet surface and a platelet thrombus grows to an occlusive thrombus.

There are several important points to emphasize in the above hypothesis. First, fibrinogen, which is thought to play a major role in platelet thrombus formation, only plays a limited role in platelet thrombus formation under flow. Platelets also adhere to fibrinogen-coated surfaces such as the vWF-coated surface, but only under relatively low shear rates. The interaction between fibrinogen and GP IIb/IIIa cannot produce enough power to support platelet thrombus formation under relatively high shear rates. This fact is also true even after full activation of platelets. Second, the concurrent interactions of
GP Ib and GP IIb/IIIa with vWF are crucial. Functional blocking antibodies, which either block vWF interaction with GP Ib or GP IIb/IIIa inhibited platelet thrombus formation under flow.\(^{28,89,90}\) Third, vWF interaction with GP Ib and GP IIb/IIIa is not really dependent on shear rates.\(^{28,76}\) The same mechanism of interaction can be induced even under relatively low shear rates although the number of platelets transported adjacent to the collagen-coated surface is not that high under low-shearing conditions. These mechanisms described above are not concordant with the previously proposed mechanism. But we believe this is not a methodological artifact since the same mechanisms of platelet thrombus formation can also be demonstrated in a cone-plate viscometer.

Platelet-platelet interactions rather than platelet-surface interactions can be demonstrated in a cone-plate viscometer.\(^{28,90}\) Platelet aggregation occurring in a viscometer is called shear-induced platelet aggregation. The mechanism of shear-induced platelet aggregation is similar to that which occurs as platelet attachment to a collagen-coated surface under flow conditions, i.e. vWF and its interaction with platelet receptors GP Ib and GP IIb/IIIa is crucial.\(^{28,90}\) Similar to platelet attachment to immobilized plasma ligand, fibrinogen interaction with GP IIb/IIIa only weakly supports platelet aggregation under relatively low shear rates and could not support platelet aggregation under high shear situations, even after full activation of platelets by chemical stimulants.\(^{89,90}\) This means that the conventional aggregometer, which can demonstrate platelet aggregation mediated through fibrinogen binding to activated GP IIb/IIIa may be an in vitro artifact, and that the same mechanism of aggregation will not occur in the presence of blood flow. Our observation that platelet aggregation supported by fibrinogen binding to activated GP IIb/IIIa can be easily dissociated under the effect of high shear stress supports that idea.\(^{89}\)

**What does the Blood Flow Do?**

In explaining the mechanism of vWF-mediated platelet thrombus formation, the most important question is “why is the vWF-mediated platelet thrombus formation only apparent under flow conditions?”. Most investigators including ourselves first supposed that rheological shear (stress or force) could physically change the protein conformation of ligand molecules or platelet receptors, and then allow them to interact with each other probably by exposing the hidden binding sites by physical force (Figure 4: upper panel). However, after developing an accurate assay system to detect platelet thrombus formation on collagen-coated surfaces\(^{50}\) or soluble ligand protein binding to platelets under shear,\(^{76}\) the above hypothesis no longer appears to be helpful in understanding the real mechanism. There are several important points to consider when examining this
Figure 4. Summary of proposed mechanism of interaction between von Willebrand factor (vWF) and platelet receptors. Previously, most investigators supposed that shear stress directly applied to platelet receptor protein may change the conformation of the receptor and allow open ligand binding sites as shown in the upper panel. Although some investigators still believe that the protein conformation may change under flow, recent quantitative studies described in the body of the text suggest that the main effect of shearing is simply to permit cell-cell interaction. The details of the mechanism are described in the text.
mechanism. In a cone-plate viscometer, soluble vWF only binds to part of the platelet population, even though homogeneous shear stress should be applied to any part of the sample in a cone-plate viscometer. This fact as well as the fact that the number of vWF molecules bound to platelets varies greatly from platelet to platelet, strongly suggested that the interaction between ligand and receptor is not directly influenced by shear stress. Second, unlike ristocetin or α-thrombin-induced vWF binding to platelets, vWF interaction with platelets occurring under the effect of shearing always requires two platelet receptors and the corresponding binding sites of vWF. In other words, even if vWF binding to GP Ib could be induced by shear stress, it will always be transient and could not be demonstrated by the current methods of detection of ligand binding to platelet receptors. Third, unlike ristocetin- or platelet activator such as α-thrombin-induced vWF binding, shear-induced vWF binding to platelets is significantly decreased when the platelet count of the suspension is decreased. Indeed, no aggregation or vWF binding could be induced under platelet counts less than 50,000/μl. This observation strongly suggested that platelet-platelet interactions induced by flow rather than by the direct physical effect of shear stress on proteins play a crucial role in not only platelet aggregation but also in soluble ligand interactions with platelet receptors.

Based on these observations, we proposed a model to explain the mechanism of platelet thrombus formation and platelet-soluble ligand interactions occurring under blood flow (Figures 3 and 4). Once non-activated flowing platelets come close to surfaces covered by immobilized vWF and collagen, platelets interact with that vWF through GP Ib leading to activation. The activated platelet is then stabilized on the vWF surface through concurrent GP Ib and GP IIb/IIIa binding to vWF. Other non-activated flowing platelets may then interact with the vWF immobilized on the platelet surface. A similar interaction may also occur between soluble vWF and platelets. If platelet-platelet interactions, which can only be induced in the presence of blood flow, occur during vWF interaction with GP Ib, the concurrent signal can lead to activation of platelets. The soluble vWF can then be stabilized on the platelet surface by interacting concurrently with both GP Ib and GP IIb/IIIa.

**CLINICAL CONSIDERATIONS OF vWF-MEDIATED PLATELET THROMBUS FORMATION**

vWF-mediated platelet thrombi formed under blood flow have several distinct features as compared to platelet thrombi formed after activation of platelets by chemical agonists. Morphologically, shear-induced vWF-mediated platelet aggregates are relatively smaller in size, and the extent of aggregation and the
amount of secretion are relatively low. In congenital bleeding disorders, vWF-mediated platelet thrombi did not occur in patients congenitally lacking vWF, GP Ib/IX complex or GP IIb-IIIa complex, but occurred normally in all patients lacking fibrinogen. Patients with high affinity mutations of either vWF or GP Ibα showed enhanced platelet aggregation. There are only a few reports suggesting a relationship between vWF-mediated platelet thrombus formation and thrombotic disorders. Platelet-rich plasma obtained from patients with cerebral infarction suggested that shear-induced platelet aggregation was augmented only in patients with thrombotic etiology, and not in embolic etiology. Another report suggested that normal platelet aggregation was enhanced by the addition of plasma obtained from acute myocardial infarction probably because the vWF concentration was about two times higher in myocardial infarction plasma. Humoral factors such as epinephrine are known to selectively enhance vWF-mediated platelet thrombus formation which might also relate to the fact that acute coronary syndrome tends to occur in the early morning when sympathetic tone is known to be augmented. The fact that vWF-mediated platelet thrombus formation was augmented after treadmill exercise testing also supports the idea that sympathetic stimulation may have at least some role in enhancing platelet thrombus formation.

Efficacy of antiplatelet agents on platelet aggregation is characteristic of vWF-mediated platelet thrombus formation. The most widely used anti-platelet agent, aspirin, at least at lower concentrations, had weak effects on shear-induced vWF-mediated platelet aggregation although it strongly inhibited arachidonic acid-induced platelet aggregation. Some reports have suggested that higher concentrations of aspirin inhibited shear-induced platelet reaction, however, this effect is probably not directly related to its effect on cyclo-oxygenase inhibition. This limited effect of aspirin on the formation of the frame-work of platelet thrombi does not indicate that aspirin is not effective for thrombus formation occurring under blood flow. Aspirin may inhibit activation of a coagulant cascade on the platelet surface, or may inhibit the release reaction subsequent to vWF-mediated platelet activation. Still, there remains the possibility that agents which directly block vWF-mediated thrombus formation may be stronger anti-platelet agents than aspirin. In fact, tichlopidine, which is known to inhibit shear-induced vWF-mediated platelet aggregation, is a more potent antiplatelet agent for the prevention of acute myocardial infarction. These effects probably depend on increased c-AMP levels in platelets. Drugs known to inhibit calcium entry non-specifically could also inhibit shear-induced platelet aggregation, although receptor-operated calcium channel blockers such as verapamil had no effects on shear-induced platelet aggregation. Shear-induced platelet aggregation seems to be independent from the cyclooxygenase pathway but depends on
the c-AMP levels and intracellular calcium ion concentration of the platelets.

There is disagreement about the effect of anti-coagulant agents on vWF-mediated platelet thrombus formation. Some investigators have suggested that the extent of aggregation in platelet-rich plasma was less with hirudin and more with non-fractionated heparin than PRP anticoagulated by citrate; while others suggested that there were no differences among them. In the former report, the extent of aggregation was measured under shear by detecting LASER transmittance, whereas in the latter report, the extent of aggregation was calculated by measuring the single platelet count before and just after shearing stopped. Different results may depend on differences in methodology. In fact the effect of heparin is rather complicated. It is well known that heparin can augment the potential of anti-thrombin III and shows strong anticoagulant effects. The A1 domain of vWF which includes the GP Ib-binding domain also has a binding site for heparin. Thus, modification of the A1 domain by heparin binding may either increase or decrease its binding affinity to GP Ib. The fact that heparin can prevent acute myocardial infarction in patients with unstable angina pectoris suggests that heparin may inhibit platelet thrombus formation in vivo. Careful study should be made to clarify these questions.

THERAPEUTIC CONSIDERATIONS

Since vWF-mediated platelet thrombi play a crucial role in the onset of coronary thrombosis, the target of antithrombotic therapy should be vWF-mediated platelet thrombus formation. Ideally, a safe and effective anti-platelet agent should have two opposite characteristics; it should inhibit thrombus formation but not cause bleeding. The vWF interaction with GP Ib may possibly be a target of choice because it occurs mainly under the effect of blood flow. Several investigators have suggested that monoclonal antibodies against either vWF or the GP Ibα binding site of vWF, or chemical materials known to inhibit the vWF interaction with GP Ibα effectively prevent thrombus formation in vivo. In addition, clinical observations suggest that the bleeding tendency is less severe in patients lacking vWF or GP Ibα than in patients lacking GP IIb-IIIa. These observations provide sufficient reason for us to continue our effort to understand the exact mechanism of vWF-mediated high shear-induced platelet activation and thrombus formation.

A recently developed direct inhibitor of platelet GP IIb/IIIa, anti-GP IIb-IIIa 7E3, has proven to be a very strong and effective agent to prevent coronary thrombosis. Unlike other direct inhibitors of GP IIb/IIIa such as RGD peptides, 7E3 can inhibit not only platelet aggregation or ligand binding to activated platelet but also vWF-mediated platelet activation. Based on the mechanism of
platelet thrombus formation described in this review, its in vivo anti-thrombotic effect is probably mainly due to its inhibitory effects on vWF binding to GP IIb/IIIa, rather than its inhibitory effects on fibrinogen binding. The answer to whether vWF or fibrinogen plays a crucial role in in vivo coronary thrombosis will only be obtained after specific tools that inhibit the vWF interaction with GP Ib or GP IIb/IIIa become clinically available.

CONCLUSION

The mechanism of coronary thrombus formation should be investigated with serious consideration given to the effects of blood flow. Platelets play a crucial role in thrombus formation under blood flow. The mechanism of platelet thrombus formation is also different under flow, i.e. vWF and its concurrent interaction with GP Ib and GP IIb/IIIa is crucial. A better understanding of the mechanism of vWF-mediated platelet thrombus formation is crucial not only for a complete understanding of coronary thrombosis but also for the development of better clinical tools to prevent ischemic heart disease.

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