It is a common understanding that the rupture of an atheroma in the coronary arteries is the initial event in the onset of arterial thrombosis resulting in myocardial infarction.1 Ex vivo perfusion experiments using human blood have clearly demonstrated that platelet accumulation occurs immediately when the subendothelial matrix, such as collagen, is exposed to the blood stream.2 However, initiation of platelet thrombus formation after endothelial disruption resulting in exposure of the subendothelial matrix does not directly represent the onset of symptomatic atherothrombotic diseases, such as myocardial infarction, which were caused by thrombotic arterial occlusion. For example, coronary intervention, while causing damage to the endothelium, does not, in most cases, result in any symptomatic myocardial ischemia. Moreover, recent advances in clinical imaging techniques, such as intracoronary ultrasonography, have revealed a much higher incidence of atheroma rupture than of symptomatic atherothrombotic coronary artery diseases, including myocardial infarction and unstable angina pectoris.3,4

These observations suggest the contribution of propagating factors for thrombus growth, besides exposure of the subendothelial matrix due to endothelial disruption, in the onset of symptomatic arterial thrombotic diseases.

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In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Yamashita et al have elegantly demonstrated in experimental studies the importance of 2 factors in the formation of arterial occlusive thrombi, namely increased vascular wall thrombogenicity induced by the accumulation of tissue factor and reduction of the total arterial blood flow by increased vascular resistance.5 The former explains the difference between the onset of myocardial infarction induced by the rupture of an inflamed tissue factor–rich atheromatous plaque1 and the asymptomatic limited-size thrombus formation initiated by coronary intervention. Blood flow reduction, induced either by local blood flow disturbance after rupture of an atheroma or by increased microvascular resistance6,7 also plays an important role in the propagation of arterial thrombi. In addition, embolization of microvessels by platelet-rich thrombi,8 as well as the microvessel contraction induced by bioactive substances released from activated platelets9 such as thromboxane A2, may play some roles in the reduction of arterial blood flow.

von Willebrand factor, along with its putative platelet receptor GP Ibα, plays a crucial role in the initiation of platelet thrombus formation (Figure).10 Then the stimulation of various platelet surface receptors, including integrin αIIbβ3 (GP IIb/IIIa),11 αIβ (vitronectin receptor),12 and catecholamine receptor,13 as well as ADP receptors (P2Y12 and P2Y1)14–16 and others, were involved in the growth of platelet thrombi. Even with those stimulations, platelet thrombi could not grow large enough to cause arterial occlusion by themselves without contribution of fibrin formation. Tissue factor, which is known to initiate coagulation cascade,1 plays a role in fibrin formation around platelet thrombi to cause so called stable mixed thrombi. These contributing effects of tissue factor have been clearly demonstrated by Falati et al with the use of intravital microscopy.17 There still is the discussion on the origin of tissue factor incorporated in the arterial occlusive thrombi. Those present in the vascular wall may play an important role as demonstrated by Yamashita et al,9 although tissue factor in circulating blood, either in a soluble form or in association with membrane microparticle, may also be involved.18

Until now, the beneficial effects of antithrombotic therapy were supposed to be mediated only by their inhibitory effects on the initiation and growth of thrombi at the site of occlusive thrombus as formation takes place. The experimental results reported by Yamashita et al may suggest other possible mechanisms of actions of antiplatelet drugs in the prevention of occlusive thrombus formation, such as the role of aspirin in reducing the vasoconstriction mediated by the inhibition of thromboxane A2 production,19 the role of anti-GP IIb/IIIa in the prevention of distal embolization,6,20 or the effects of clopidogrel in the prevention of release of vasoactive substances from activated platelets.21 According to the experimental results published by Yamashita et al, it might be reasonable to suppose that the inhibition of the accumulation of thrombogenic substances in the vascular wall, as well as the preservation of microvessel function, may be the new targets for the prevention of symptomatic arterial thrombotic diseases.

Acknowledgments

This work was supported in part by a Grant-in-Aid for Scientific Research in Japan (13670744, 15590771), the Tokai University School of Medicine, Project Research 2004, a grant from the Vehicle Racing Commemorative Foundation, and the Grant for Advanced Medicine Supported by the Ministry of Health, Labor, and Welfare (H15-MP-012).
Mechanism of thrombus initiation and thrombus propagation. Endothelial damage induced by any cause, such as atheroma rupture, erosion, or vascular interventional treatment, initiates platelet accumulation and thrombus formation; however, most of the thrombi do not grow large enough to cause clinical symptoms. The size of the thrombus is augmented when the blood flow velocity is also reduced because of increased vascular resistance. Distal embolization, along with microvascular contraction caused by bioactive materials released from activated platelets, such as thromboxane A2, may play important roles in increasing the vascular resistance. Accumulation of tissue factor in the vascular wall, mostly originating from the inflammatory cells migrated into the vascular wall, along with the fibrin deposition initiated by it, also enhances the propagation of thrombi. Blood flow reduction by small vessel embolization and increased vascular wall thrombogenicity mediated by tissue factor accumulation are presumed to play crucial roles in the formation of arterial occlusive thrombi causing symptomatic diseases.

References


Propagation of Arterial Thrombi: Local and Remote Contributory Factors
Shinya Goto

Arterioscler Thromb Vasc Biol. 2004;24:2207-2208
doi: 10.1161/01.ATV.0000149144.86175.03
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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