Plasminogen activator inhibitor type-1 (PAI-1) is the major physiological inhibitor of fibrinolysis. The fibrinolytic activity of plasma is influenced by the balance between PAI-1 and tissue-type plasminogen activator (t-PA). An increase in plasma PAI-1 concentration is associated with recurrent coronary events in the survivors of acute myocardial infarction (AMI). Elevated PAI-1 activity is associated with coronary microvascular dysfunction. Although PAI-1-deficient mice exhibit no apparent abnormalities, Iwaki et al. previously reported that PAI-1 deficiency in humans can cause a severe bleeding tendency and impairment of wound healing, suggesting an important role of PAI-1 in thrombosis and hemostasis in humans.

PAI-1 is also involved in tissue remodeling by inhibiting the activities of matrix metalloproteinases and urokinase-type plasminogen activators (uPAs). In experimental studies, Zaman et al. previously showed that the expression of PAI-1 in the heart exerts profibrotic effects. In blood vessels, an angiotensin-receptor blocker (ARB) also suppresses the expression of PAI-1. Enhanced PAI-1 expression may contribute to ventricular remodeling through the attenuation of extracellular matrix degradation.

In this issue of *The Journal of Atherosclerosis and Thrombosis*, Shimizu et al. have performed a clinical study to determine the relationship between PAI-1 produced in the myocardial infarct region and coronary and ventricular function in AMI patients. They measured PAI-1 activity and t-PA antigen level in plasma from the aortic root and interventricular vein in AMI patients with culprit left anterior descending coronary artery. Then, they estimated the release of PAI-1 and t-PA from the myocardium. There was a high transmyocardial gradient of PAI-1, suggesting the release of PAI-1 from the infarct region. Interestingly, the release of PAI-1 was associated with the endothelial dysfunction of the culprit coronary arteries and regional motion of the infarcted myocardium. Treatment with ARB suppressed PAI-1 production in the infarcted myocardium, suggesting that angiotensin II plays a critical role in PAI-1 production in the myocardium. One of the beneficial effects of ARBs on left ventricular function after AMI may involve the reduction of PAI-1 production in the heart.

Because we do not fully understand the underlying pathobiological mechanism, further investigation is necessary. The effects of angiotensin-converting enzyme (ACE)-inhibitor need to be investigated. Excessive inhibition of PAI-1 production may cause adverse effects such as bleeding because PAI-1 deficiency in humans has been reported to cause severe bleeding tendencies. Similarly, the excessive inhibition of PAI-1 may induce cardiac rupture due to excessive fibrinolysis. PAI-1 knockout mice exhibited increased inflammation and enhanced intramyocardial hemorrhage, suggesting that PAI-1 has some protective role against myocardial inflammation and ARBs may alter inflammation-related cytokine levels.

The work by Shimizu et al. suggested that the pharmacological inhibition of PAI-1 functions not only as an antithrombotic agent but also as an agent against pathobiological myocardial remodeling. As the case report of PAI-1 deficiency suggested, more research is necessary to carefully determine the physiological conditions where the pharmacological inhibition of PAI-1 can potentially become harmful.

**Disclosures**

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