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Editorial

Subsequent Response of VWF and ADAMTS13 to Aortic Valve Replacement

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Normal hemostasis is maintained by well-balanced performance of many factors in plasma, blood cells, and vascular wall cells. von Willebrand factor (VWF) is one of the plasma proteins that is involved in platelet adhesion and aggregation[1]. VWF is synthesized in vascular endothelial cells and megakaryocytes, starting with a 350-kDa precursor. This polypeptide dimerizes in the endoplasmic reticulum through intermonomer disulfide bonds in the C-terminal regions, and the dimers are transported to the Golgi apparatus, where inter-dimer disulfide bonds in the N-terminal regions produce linear multimers[2]. In endothelial cells, the huge multimers of VWF are packaged into rod-shaped vesicles called Weibel−Palade bodies and are constantly secreted into the circulation or released in response to physiological and pathophysiological stimuli[3]. The largest circulating multimers have a mass of at least 20,000 kDa (>80 subunits). The large multimers have a higher activity in platelet aggregation than the smaller ones. In blood, VWF large multimers are cleaved by the plasma metalloprotease ADAMTS13, resulting in the decrease of highly active VWF multimers.

The ADAMTS13-catalyzed cleavage of VWF is dramatically facilitated by the conformational change of VWF to unfold the VWF A2 domain and expose the Tyr^{1605}-Met^{1606} scissile bond. Because of the cleavage, circulating VWF multimers are smaller than those initially secreted by endothelial cells or platelets. The VWF conformational change and subsequent cleavage occur when the multimers experience enough tensile force[4] (physiologically, when VWF multimers bind to cell surfaces or interact with platelets under conditions of high fluid shear stress). The balance in activity between VWF and ADAMTS13 is important for hemostasis. The functional deficiency of ADAMTS13 causes hyper-aggregation of platelets caused by the accumulation of unusually large VWF multimers, which can lead to thrombotic thrombocytopenic purpura (TTP)[5, 6]. The quantitative and qualitative deficiencies of VWF can lead to hemorrhagic disease, commonly called von Willebrand disease (VWD) for VWF genetic defect and acquired von Willebrand syndrome (AVWS) for nongenetic causes[6, 7].

Pathophysiologically, the conformational change-induced VWF cleavage is considered to occur under high shear stress conditions caused by aortic stenosis (AS)[8], extracorporeal membrane oxygenation (ECMO) implantation[9], ventricular assist devices (VAD) implantation[10] and so on. In patients with AS, symptoms of AVWS (loss of large VWF multimers and bleeding tendency) are corrected by aortic valve replacement (AVR). Yamashita *et al.*[11] in this issue tracked the data of VWF and ADAMTS13 in the plasma of nine AS patients treated with AVR. Although the data varied rather widely among the patients, it was evident that the ratio of VWF antigen to ADAMTS13 activity immediately and dramatically increased 1 day to 1 week after AVR, gradually decreased a few weeks later, and returned to preoperative levels after 1 year (**Fig. 1**). The authors also analyzed VWF multimer patterns in the plasma samples and revealed the association between AS severity and loss of large VWF multimers before AVR. In all patients, the levels of large multimers recovered to normal levels after AVR, and unusually large multimers (often observed in patients with TTP) were detected 1−3 weeks after AVR. In concordance with these findings, thrombus formation under high shear stress conditions was also increased compared with that before AVR (**Fig. 1**). The authors also found a recurrent deficiency of large VWF multimers 1 year after AVR in a patient with prosthesis size mismatch, suggesting that VWF multimer analysis is use-

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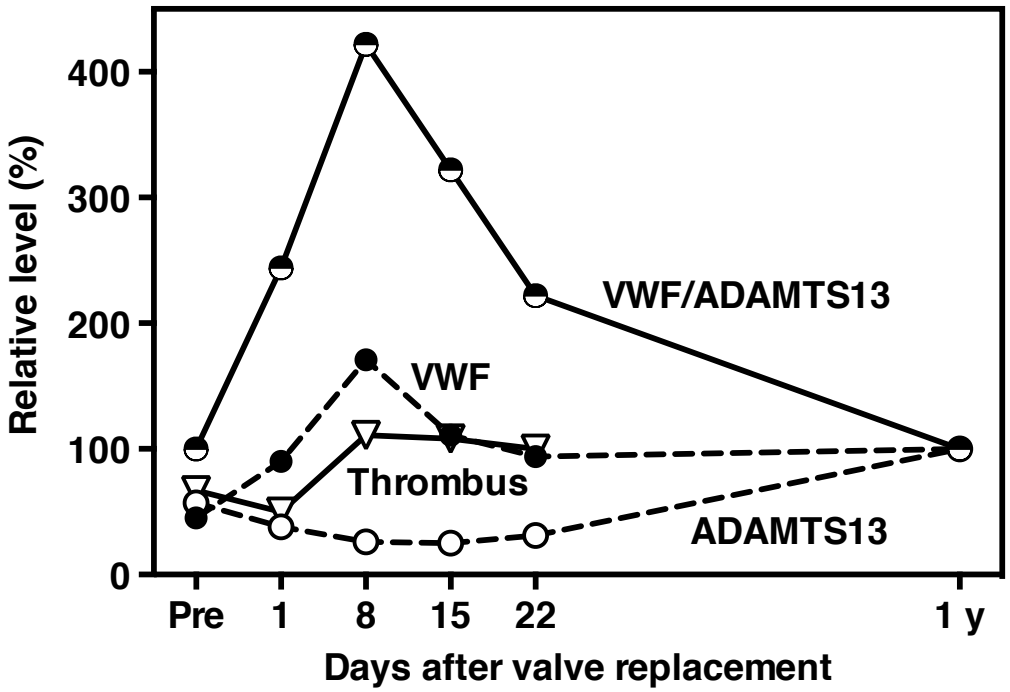

Fig. 1. Rapid increase of the VWF/ADAMTS13 ratio and thrombus formation after AVR in patients with AS. The graph was prepared using the data in Yamashita's paper[11] in this issue. Each value is plotted relative to that measured at 1 year (VWF, ADAMTS13, and VWF/ADAMTS13) or 22 days (thrombus) after AVR. VWF, plasma VWF antigen; ADAMTS13, plasma ADAMTS13 activity; thrombus, platelet thrombus formation under high shear stress conditions in a parallel plate flow chamber system.

ful as an index of successful treatment.

Can the measurement of VWF and ADAMTS13 be a good laboratory test to monitor clinical responses to AVR? There are some problems that need to be solved. First, because the number of patients analyzed in the study[11] was relatively small as the authors described, the findings and usefulness should be confirmed by observing more patients with AS in multiple hospitals. Second, the time-consuming, skill-requiring, and semi-objective assessment analysis of VWF multimer patterns should be improved. Recently, Tamura *et al.*[12] proposed the large VWF multimer index defined as the ratio of large multimers (≥22 subunits) in patients to those in controls. The index may be useful for the objective assessment of VWF multimers. However, the most desirable improvement is an easy-to-perform, rapid, and reproducible method of VWF multimer analysis as an alternative to the currently used method consisting of agarose gel electrophoresis and immunoblotting. A recently developed ELISA to quantitate proteolyzed VWF[13] may be useful for the diagnosis of AVWS in patients with AS and for monitoring the response to AVR.

Disclosures

The author declares that there are no conflicts of interest.

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