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Editorial

Subsequent Response of VWF and ADAMTS13 to Aortic Valve Replacement

Koichi Kokame

Department of Molecular Pathogenesis, National Cerebral and Cardiovascular Center, Suita, Japan

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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 inter-monomer 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-

Address for correspondence: Koichi Kokame, Department of Molecular Pathogenesis, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan
E-mail: kame@ncvc.go.jp
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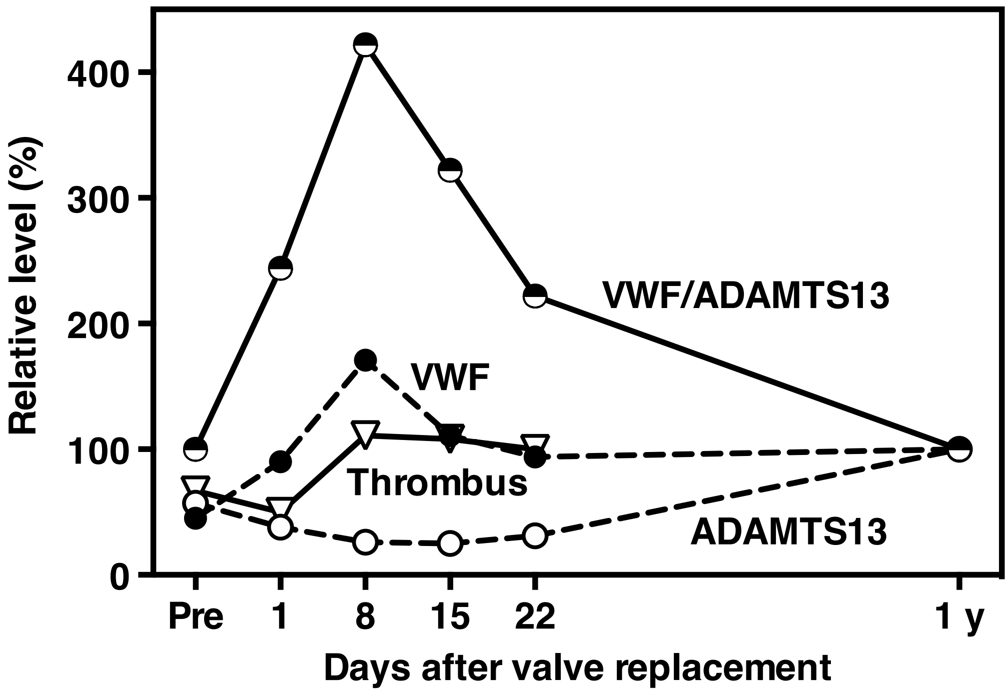

Fig. 1. Rapid increase of the VWF/ADAMTS13 ratio and thrombus formation after AVR in patients with AS. The graph was prepared using the data in Yamashita's paper[11] in this issue. Each value is plotted relative to that measured at 1 year (VWF, ADAMTS13, and VWF/ADAMTS13) or 22 days (thrombus) after 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.

References

1) Sadler JE: Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. Blood, 2008; 112: 11-18
2) Springer TA: von Willebrand factor, Jedi knight of the bloodstream. Blood, 2014; 124: 1412-1425
3) Lopes da Silva M and Cutler DF: Von Willebrand Factor multimerization and the polarity of secretory pathways in endothelial cells. Blood, 2016; [Epub ahead of print, DOI: 10.1182/blood-2015-10-677054]
4) Zhang X, Halvorsen K, Zhang CZ, Wong WP and Springer TA: Mechanoenzymatic cleavage of the ultralarge vascular protein von Willebrand factor. Science, 2009; 324: 1330-1334
5) Fujimura Y, Matsumoto M, Isonishi A, Yagi H, Kokame K, Soejima K, Murata M and Miyata T: Natural history of Upshaw-Schulman syndrome based on ADAMTS13 gene analysis in Japan. J Thromb Haemost, 2011; 9 Suppl 1: 283-301
6) Budde U and Schneppenheim R: Interactions of von Willebrand factor and ADAMTS13 in von Willebrand dis-

ease and thrombotic thrombocytopenic purpura. Hamostaseologie, 2014; 34: 215-225
7) Federici AB, Budde U, Castaman G, Rand JH and Tiede A: Current diagnostic and therapeutic approaches to patients with acquired von Willebrand syndrome: : a 2013 update. Semin Thromb Hemost, 2013; 39: 191-201
8) Casonato A, Sponga S, Pontara E, Cattini MG, Basso C, Thiene G, Cella G, Daidone V, Gerosa G and Pagnan A: von Willebrand factor abnormalities in aortic valve stenosis: Pathophysiology and impact on bleeding. Thromb Haemost, 2011; 106: 58-66
9) Kalbhenn J, Schmidt R, Nakamura L, Schelling J, Rosenfelder S and Zieger B: Early diagnosis of acquired von Willebrand Syndrome (AVWS) is elementary for clinical practice in patients treated with ECMO therapy. J Atheroscler Thromb, 2015; 22: 265-271
10) Nascimbene A, Neelamegham S, Frazier OH, Moake JL and Dong JF: Acquired von Willebrand syndrome associated with left ventricular assist device. Blood, 2016; [Epub ahead of print, DOI: 10.1182/blood-2015-10-636480]
11) Yamashita K, Yagi H, Hayakawa M, Abe T, Hayata Y, Yamaguchi N, Sugimoto M, Fujimura Y, Matsumoto M and Taniguchi S: Rapid restoration of thrombus formation and high-molecular-weight von Willebrand factor multimers in patients with severe aortic stenosis after valve replacement. J Atheroscler Thromb, 2016; 23: 1150-1158
12) Tamura T, Horiuchi H, Imai M, Tada T, Shiomi H, Kuroda M, Nishimura S, Takahashi Y, Yoshikawa Y, Tsujimura A, Amano M, Hayama Y, Imamura S, Onishi N, Tamaki Y, Enomoto S, Miyake M, Kondo H, Kaitani K, Izumi C, Kimura T and Nakagawa Y: Unexpectedly High Prevalence of Acquired von Willebrand Syndrome in Patients with Severe Aortic Stenosis as Evaluated with a Novel Large Multimer Index. J Atheroscler Thromb, 2015; 22: 1115-1123
13) Rauch A, Caron C, Vincent F, Jeanpierre E, Ternisien C, Boisseau P, Zawadzki C, Fressinaud E, Borel-Derlon A, Hermoire S, Paris C, Lavenu-Bombled C, Veyradier A, Ung A, Vincentelli A, van Belle E, Lenting PJ, Goudemand J and Susen S: A novel ELISA-based diagnosis of acquired von Willebrand disease with increased VWF proteolysis. Thromb Haemost, 2016; 115: 950-959