von Willebrand Factor for Aortic Valve Intervention

From Bench to Real-Time Bedside Assessment

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VWF (von Willebrand factor) is a circulating multimeric blood glycoprotein. VWF plays a major role in primary hemostasis by promoting the adhesion of platelets to subendothelial collagen at sites of vascular damage and thereby promoting platelet aggregation. VWF is synthesized in endothelial cells and megakaryocytes. The VWF units dimerize and are transported into the Golgi apparatus, where disulfide bonds are formed leading to formation of VWF multimers. This large subunit combination is required to support its hemostatic function.

VWF has the unique features to be circulating in an inactive coiled form, hiding binding domains for platelet receptors and subendothelial collagen. At the site of vascular injury, VWF binds to the exposed collagen and unfolds. Once VWF is unfolded, the VWF A1 domain is exposed allowing the binding of platelets via GP Ib (glycoprotein IB) receptor. After platelet activation, GP IIb/IIIa (glycoprotein IIb/IIIa) receptor becomes able to bind VWF C1 domain. The VWF conformation and activity is intimately related to shear conditions and blood flow. At high shear rate (beyond 10–15 pN), it becomes unfolded exposing binding sites but also the cleavage site in VWF A2 domain for ADAMTS13 (adisintegrin-like and metalloprotease thrombospondin) protease that conducts to its proteolysis. Overall, these environmental changes generate the modification of the conformation of VWF that conduct to its cleavage and a shift in the VWF size distribution to smaller VWF multimers with less hemostatic potential. This VWF conformation balance is described as a unique mechanoenzymatic process.[1]

Acquired deficiency of VWF is characterized by a loss of high-molecular-weight multimers which can be caused by cardiovascular disorders in which a large blood volume is exposed to high shear stress.[2–4]

Several groups, including us, described that a large majority of patients with severe aortic stenosis had structural and functional abnormalities of VWF. In our large cohort of 50 consecutive patients, 79% of patients had a loss of high-molecular-weight multimers.[5] We and others also reported that this VWF deficiency presented in aortic stenosis is corrected within days after the surgical replacement of the diseased valve.[6]

These observations confirmed the hypothesis that turbulent blood flow through the stenotic heart valve enhanced the shear stress-induced ADAMTS13 proteolysis and explained the VWF defect observed in patients.[7]

Transcatheter aortic valve intervention (TAVI) is currently the gold standard treatment for inoperable patients and is recommended for high-risk patients with severe aortic stenosis.[8] TAVI is a less-invasive alternative to open heart surgery procedure that consists to deliver via catheters a bioprosthetic valve within the stenotic aortic valve.

One remaining issue preventing the generalization of TAVI to lower risk patients is the higher rate of paravalvular regurgitation (PVR) compared with surgical replacement. PVR is one of the complications of this procedure that occur when the bioprosthesis valve incompletely seals the annulus of the native aortic valve allowing the flow to regurgitate into the left ventricle during diastole.[9]

Even if low rate (3.5%) of PVR has been achieved in clinical trial evaluating the last generation of valve, its deleterious clinical impact is still significant with moderate or greater PVR associated with a 2.4-fold increase of mortality at 1 year.[10]

Transesophageal echocardiography is the gold standard technique to assess the presence and the severity of PVR but requires an additional expert physician in valvular imaging during the procedure. Cineangiography is highly subjective, impacted by numerous technical factors inducing variability in grading, and is not recommended by the Valve Academic Research Consortium-2 but remains the most frequently used method of assessment.[11]

We and others have previously described that the VWF defect presented by patients with aortic stenosis was corrected within minutes after TAVI except when PVR occurs (maintained high shear stress from regurgitant flow).[12,13]

We recently reported that the VWF is a useful biomarker to detect and monitor PVR.[14] In our single-center study of 183 patients with transfemoral TAVI, we assessed VWF multimerization before, during, and at the end of the procedure and compared the biological results with transesophageal

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echocardiography evaluation. Patients with residual PVR after the procedure also had persistently high-molecular-weight multimer levels. Those with no PVR and those in whom the PVR was corrected with additional balloon inflation had a restoration of VWF multimer levels.

Thus, high-molecular-weight multimers discriminated patients with or without moderate or greater PVR with a negative predictive value of 98.7%. Because VWF multimers are not routinely measured in clinical practice, we included the point-of-care primary hemostasis testing PFA-100 (platelet function analyzer-100; Siemens Healthcare Diagnostics, Marburg, Germany), which is highly sensitive to high-molecular-weight multimer defect measuring a prolongation of the closure time of a membrane coated with ADP. Closure time of a membrane coated with ADP >180 seconds discriminated PVR with a negative predictive value of 98.6%. These results were replicated in a multicenter cohort of 201 patients. Moreover, persistent high-molecular-weight multimer abnormal (<0.8) at the end of the procedure was a strong predictor factor associated with a 3-fold increase in the risk of mortality at 1 year.

Whether this new method can be applied to all patients merits further assessment. Other causes of high-molecular-weight multimer defects, such as significant mitral regurgitation, could make difficult the interpretation of the test. On the contrary, we have provided reassuring data on the use of P2Y12 inhibitor by showing that the value of the closure time of a membrane coated with ADP was not affected by clopidogrel administration in a subgroup of 40 patients in our study.[14]

VWF appears as a valuable, noninvasive, and highly reproducible biomarker to assess PVR. Randomized clinical trials are now needed to address the incremental value of this biomarker in TAVI procedure and improve procedural and clinical outcomes.

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Disclosures

None.

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