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COMMENTARY

Bleeding in valvular heart disease: is von Willebrand factor the culprit?

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Valvular heart diseases affect 2.5% of the population, and their prevalence increases with age. They are associated with higher mortality and morbidity. Among them, mitral regurgitation (MR) is the second most common valvular heart disease in Europe [1].

A relationship between various cardiovascular diseases associated with flow disturbances and high shear stress, such as aortic stenosis (AS) [2] or the implantation of mechanical circulatory support for advanced heart failure [3], and von Willebrand factor (VWF) defects, characterized by the loss of high-molecular-weight multimers (HMWMs), has been extensively described [4]. The close relation of these VWF defects with blood flow abnormalities and their correction after aortic valve replacement is now well established, and in AS VWF, it has been proposed to monitor transcatheter aortic valve implantation procedures [5].

Although the association between bleeding, valvular heart disease, and VWF defects has been described, the direct relation between VWF defects and bleeding, particularly with bleeding associated with digestive track angiodysplasia, is much less certain and a causality has never been established.

VWF defects and bleeding have been well documented in AS but much less frequently in MR. A link between the loss of HMWM and MR has been suggested previously [6,7]. However, the association with bleeding events in this setting remains unclear and requires further investigation.

In the study published in *Research and Practice in Thrombosis and Haemostasis*, Takiguchi et al. [8] investigate the association between MR, VWF HMWM loss, and bleeding events and compare this association between MR and AS. This multicentric study included 84 patients presenting with moderate to severe MR, of whom 44 patients underwent surgery and 1 patient underwent percutaneous mitral valve replacement. Electrophoretic analysis of VWF multimers was performed with assessment of VWF large multimer index, designed as normal if >0.80. An assessment of VWF activity was also performed (VWF ristocetin cofactor [VWF:RCo], VWF antigen [VWF:Ag], and ratio of VWF:RCo to VWF:Ag). Bleeding history was reported for all patients.

The results show a loss of HMWM of VWF in patients with MR similar to those with AS. The VWF multimers normalize after mitral valve correction, up to 30 days after procedure. The authors demonstrate with a direct assessment of VWF multimers a more important alteration of VWF in organic MR compared with functional MR, as well as a similar alteration between severe and moderate MR. The authors report that bleeding is less frequent in patients with MR than in those with AS, affecting only 8% of patients. A quarter of the patients underwent gastrointestinal endoscopy (for anemia or suspected bleeding), and only 2 out of 31 patients presented with angiodysplasia.

Overall, this study confirms the relationship between MR and loss of HMWM and a recovery of the HMWM after management of this valvular heart disease. It also highlights, as previously described but after measuring VWF multimers for the first time, more significant alterations of VWF in organic etiology than in functional etiology, independently of left ventricular ejection fraction [9,10]. Indeed, functional MR is mostly associated with left ventricular ejection fraction alteration, suggesting that this difference may be explained by lower shear stress, contrary to what this study found. These data emphasize the importance of jet eccentricity in increasing shear forces.

The interesting point that is raised is the loss of HMWM associated with a lower bleeding tendency when compared with patients with AS, which questions the relevance of this defect without considering clinical events. It suggests that although VWF defect is a reliable marker of blood flow, its relation to bleeding in this setting is still unclear. It also highlights a multifactorial process since similar

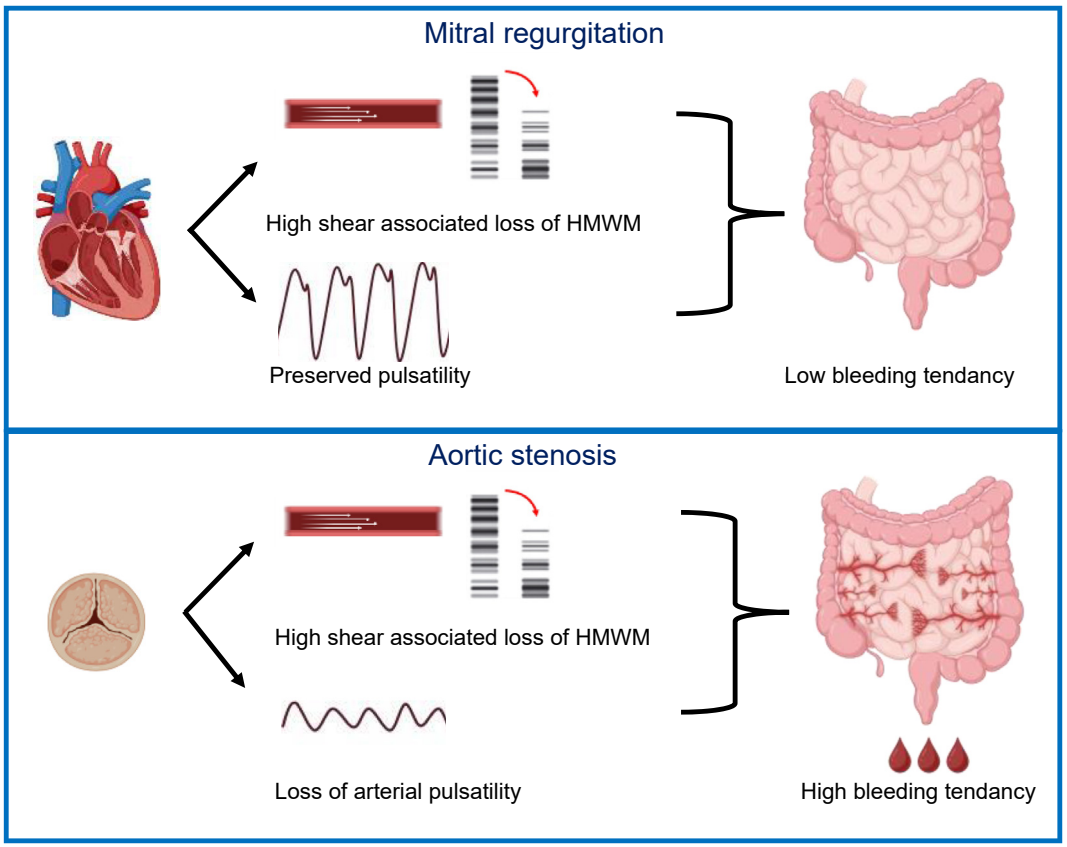

FIGURE Proposed physiopathology of the impact of different valvular heart diseases on gastrointestinal bleeding. HMWM, high-molecular-weight multimer.

VWF HMWM defects do not lead to similar bleeding events or development of angiodysplasia.

Before drawing any conclusion with this finding, the differences between the 2 populations must be underlined, such as patients with AS being older, more exposed to antithrombotic treatments, and therefore at higher hemorrhagic risk, and this could explain part of the difference. Patients with severe AS also have a longer disease history, usually several years, while patients with severe organic MR are usually proposed a valve replacement within months of the diagnosis. The longer exposure to VWF defect in patients with AS could facilitate the development of angiodysplasia and also partly explain the higher bleeding rate. Another explanation may be the impact of flow conditions and pulsatility on bleeding events, which has been previously demonstrated. Indeed, patients with mechanical circulatory support had more bleeding events when pulsatility was lower [11]. It is suggested that a decrease in pulsatility, by itself, could lead to an increase in proangiogenic factors and lead to development of angiodysplasias [12]. AS is associated with altered pulsatility and lower cardiac output, in contrast to what is observed in MR (Figure).

Almost all interventions performed were surgical, with only one percutaneous mitral valve replacement. The study therefore does not explore the course of VWF multimers in that case, which is of major interest given the constant rise of percutaneous procedures in an aging population. Echocardiographic assessment in such a procedure is challenging, and the use of VWF as a dynamic marker could help in refining periprocedural evaluation, as previously demonstrated in the case of percutaneous management of AS by percutaneous valve replacement, which leads to restoration of HMWM within minutes [5].

Finally, using the VWF:RCo-to-VWF:Ag ratio as a screening test to detect VWF multimer defects, as proposed and as also explored before for AS by the authors [13], does not seem appropriate given the low sensitivity. The PFA-100 (Siemens Healthineers) (platelet function analyzer) is an alternative for testing VWF activity that is highly sensitive and specific, allows rapid diagnosis, and seems to be more appropriate [14].

To conclude, it remains unclear why similar alterations of VWF in MR and AS lead to difference in clinical bleeding events and angiodysplasia occurrence; the major difference between the 2 populations must be taken into account. Furthermore, it is still unclear if percutaneous interventions such as mitral valve transcatheter clip repair or replacement can improve VWF function similarly to surgical interventions. More research is needed to clarify these current questions.

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S.B. and F.V. wrote the manuscript, and S.S. critically reviewed the manuscript.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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REFERENCES

[1] Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease: developed by the Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Rev Esp Cardiol (Engl Ed)*. 2022;75:524. https://doi.org/10.1016/j.rec.2022.05.006

[2] Vincentelli A, Susen S, Le Tourneau T, Six I, Fabre O, Juthier F, et al. Acquired von Willebrand syndrome in aortic stenosis. *N Engl J Med*. 2003;349:343–9.

[3] Uriel N, Pak SW, Jorde UP, Jude B, Susen S, Vincentelli A, et al. Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. *J Am Coll Cardiol*. 2010;56:1207–13.

[4] Van Belle E, Vincent F, Rauch A, Casari C, Jeanpierre E, Loobuyck V, et al. von Willebrand factor and management of heart valve disease: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2019;73:1078–88.

[5] Van Belle E, Rauch A, Vincentelli A, Jeanpierre E, Legendre P, Juthier F, et al. Von Willebrand factor as a biological sensor of blood flow to monitor percutaneous aortic valve interventions. *Circ Res*. 2015;116:1193–201.

[6] Blackshear JL, Wysokinska EM, Safford RE, Thomas CS, Shapiro BP, Ung S, et al. Shear stress-associated acquired von Willebrand syndrome in patients with mitral regurgitation. *J Thromb Haemost*. 2014;12:1966–74.

[7] Pappalardo F, Della Valle P, Maj G, Franco A, Lattuada A, Landoni G, et al. Perioperative evaluation of primary hemostasis in patients undergoing mitral valve repair. *HSR Proc Intensive Care Cardiovasc Anesth*. 2010;2:119–27.

[8] Takiguchi H, Miura M, Shirai SI, Soga Y, Hanyu M, Sakaguchi G, et al. Mitral regurgitation is associated with similar loss of von Willebrand factor large multimers but lower frequency of anemia compared with aortic stenosis. *Res Pract Thromb Haemost*. 2024;8:102431. https://doi.org/10.1016/j.rpth.2024.102431

[9] Meindl C, Paulus M, Koller T, Rogalski D, Hamerle M, Schach C, et al. Acquired von Willebrand syndrome and factor VIII in patients with moderate to severe mitral regurgitation undergoing transcatheter mitral valve repair. *Clin Cardiol*. 2021;44:261–6.

[10] Matsushita K, Marchandot B, Kibler M, Trimaille A, Hess S, Grunebaum L, et al. Discrepancy in von Willebrand abnormalities between degenerative and functional mitral regurgitation. *Am J Cardiol*. 2021;149:157–9.

[11] Wever-Pinzon O, Selzman CH, Drakos SG, Saidi A, Stoddard GJ, Gilbert EM, et al. Pulsatility and the risk of nonsurgical bleeding in patients supported with the continuous-flow left ventricular assist device HeartMate II. *Circ Heart Fail*. 2013;6:517–26.

[12] Starke RD, Ferraro F, Paschalaki KE, Dryden NH, McKinnon TAJ, Sutton RE, et al. Endothelial von Willebrand factor regulates angiogenesis. *Blood*. 2011;117:1071–80.

[13] Okubo N, Sugawara S, Fujiwara T, Sakatsume K, Doman T, Yamashita M, et al. von Willebrand factor ristocetin co-factor activity to von Willebrand factor antigen level ratio for diagnosis of acquired von Willebrand syndrome caused by aortic stenosis. *Res Pract Thromb Haemost*. 2024;8:102284. https://doi.org/10.1016/j.rpth.2023.102284

[14] Fressinaud E, Veyradier A, Truchaud F, Martin I, Boyer-Neumann C, Trossaert M, et al. Screening for von Willebrand disease with a new analyzer using high shear stress: a study of 60 cases. *Blood*. 1998;91:1325–31.