EDITORIAL

Impact of transcatheter edge-to-edge valve repair on hemostasis in patients with severe mitral regurgitation: key findings from the Mitral Fibrin Study

Zsuzsa Bagoly[1,2,3], Linda Lóczi[1,2,3], István Szegedi[2,4]

1 Division of Clinical Laboratory Sciences, Department of Laboratory Medicine, Faculty of Medicine, Debrecen, Hungary
2 MTA-DE Lendület "Momentum" Hemostasis and Stroke Research Group, Debrecen, Hungary
3 MTA-DE Cerebrovascular Research Group, University of Debrecen, Debrecen, Hungary
4 Department of Neurology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

RELATED ARTICLE

by Siniarski et al

Correspondence to:
Zsuzsa Bagoly, MD, PhD, Division of Clinical Laboratory Sciences, Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen, 98 Nagyerdei krt., 4032 Debrecen, Hungary,
phone: +3652431956,
email: bagoly@med.unideb.hu
Received: July 15, 2024.
Accepted: July 16, 2024.
Published online: August 8, 2024
Pol Arch Intern Med. 2024; 134 (7-8): 16819
doi:10.20452/pamw.16819
Copyright by the Author(s), 2024

Mitral regurgitation (MR) is a prevalent and severe valvular heart disease, characterized by backflow of blood from the left ventricle into the left atrium during systole due to improper closure of the mitral valve.[1] Secondary MR is a condition where regurgitation of the mitral valve occurs due to changes in the left ventricle size and function rather than primary mitral valve pathology. This condition is closely linked to heart failure (HF), particularly HF with reduced ejection fraction (HFrEF), which leads to ventricular remodeling and dilation, resulting in regurgitation.[2]

The hemodynamic consequences of MR have a significant impact on the risk of thrombus formation and systemic embolization. On the one hand, MR is associated with a hypercoagulable state, as the increased hemodynamic stress leads to endothelial injury.[3] Damaged endothelium loses its anticoagulant properties and becomes prothrombotic, facilitating platelet adhesion, aggregation, and activation of the coagulation cascade.[4] On the other hand, a number of studies have indicated that significant MR jets may help reduce thromboembolic events, as a regurgitant jet creates a high-velocity, turbulent flow within the left atrium, which disrupts blood stasis, a critical factor for thrombus formation. This constant agitation of blood prevents settling of coagulation factors and thrombus formation.[5-7]

Mitral valve transcatheter edge-to-edge repair (TEER) is an innovative, minimally invasive procedure designed to treat MR. TEER provides an alternative to traditional open-heart surgery, particularly beneficial for patients at a high surgical risk. The intervention is currently recommended for symptomatic severe MR patients.[8] The effect of the TEER procedure on the left atrial hemodynamics indicates a possible impact on the coagulation system and, therefore, a risk of systemic embolization.

In a report from the Mitral Fibrin Study by Siniarski et al[9] published in this issue of *Polish Archives of Internal Medicine*, the authors aimed to understand the hemostatic alterations in severe MR and how TEER affects key coagulation and fibrinolytic parameters. As prior studies have suggested both protective and prothrombotic effects of MR,[5,6,10-12] a closer examination of fibrin clot properties and thrombin generation was pursued by the authors in HF patients undergoing TEER. The primary aim was to assess if MR reduction following TEER influenced specific clot phenotype characteristics in patients with HF, as this has not been previously investigated. The study enrolled 31 patients with severe MR scheduled for TEER. Blood samples were collected before the procedure (visit 1 [V1]) and at follow-up intervals after the procedure (V2 at 1–2 days after TEER and V3 at 6–8 weeks after TEER). Beyond routine laboratory examinations and fibrinogen concentration, key parameters investigating the prothrombotic fibrin clot phenotype were measured by the authors. A pressure-driven system was used to determine fibrin clot permeation (permeation coefficient, K_s), as described previously.[13] The fibrinolytic capacity of plasma samples was measured using the clot lysis time (CLT) assay, as recommended by the International Society on Thrombosis and Haemostasis, Fibrinogen and Factor XIII Scientific and Standardisation Subcommittee.[14] Thrombin generation kinetics was evaluated using the Calibrated Automated

Thrombogram assay (assessing peak thrombin level; endogenous thrombin potential).

The authors found that fibrinogen levels significantly decreased from V2 to V3 (1–2 days post-TEER vs a median of 50 days post-TEER). Additionally, K_s values showed a significant increase between these 2 visits (V2 vs V3). However, no significant differences were found in the other tested coagulation variables between V1 and V3. CLT was the only investigated hemostasis parameter that significantly correlated with a change in N-terminal pro–B-type natriuretic peptide (NT-proBNP) level between V2 and V1 ($r = 0.4$; $P = 0.049$). In a multivariable analysis, baseline CLT was found to be an independent predictor of early post-TEER NT-proBNP level change ($R^2 = 0.55$; $P = 0.02$), highlighting its significance as a potential key indicator of the hemodynamic response to TEER. For clinicians, the findings suggest that monitoring fibrinogen levels and perhaps other hemostasis parameters (eg, clot permeability, CLT), may be important in the future, when managing HF patients undergoing TEER. The ability to predict hemodynamic outcomes through CLT offers a practical tool for improving patient care and tailoring therapeutic strategies post-TEER. The potential value of determining fibrin clot properties has been shown in several prospective studies suggesting that clot permeability and CLT measurements may be useful in predicting cardiovascular events.[15] Although standardization of CLT had already been initiated,[14] results call for unified efforts toward further steps in the standardization of clot permeability and CLT, as a prerequisite of their use in the clinical practice in the future.

The study by Siniarski et al[9] is of considerable importance, as it is the first to investigate thrombin generation and fibrin clot properties in the context of TEER in HF patients. The findings may contribute to better understanding of the coagulation changes associated with TEER, and highlight the importance of CLT as a predictive marker for hemodynamic outcomes. Nevertheless, results of this study should be interpreted in the context of its limitations and strengths. The work provides valuable insights, but also underscores the need for additional investigations to fully understand the implications of TEER on the coagulation and fibrinolytic system. Limitations of the study include a small sample size, exclusion of certain patient populations, and exclusion of certain hematologic parameters from the final statistical analysis. Additionally, the follow-up period was relatively short, and long-term effects of TEER on coagulation parameters remain unclear at this stage. Future studies should consider larger patient cohorts and longer follow-up periods to validate these findings and explore additional hemostasis parameters and markers of endothelial damage.

To conclude, the study by Siniarski et al[9] provided the first steps to clarify previous contradictory findings on the effect of MR on thromboembolic risk and provided novel insights into the interplay between MR and the coagulation system.[9] It is obvious, however, that the complex relationship between MR and the thromboembolic risk in HF requires further research. Efforts to understand the long-term impact of TEER on the coagulation system will surely be appreciated, and future results will likely help optimize patient outcomes and refine procedural techniques.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author(s) are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

ACKNOWLEDGEMENTS ZB is supported by the MTA-DE Lendület "Momentum" Hemostasis and Stroke Research Group of the Hungarian Academy of Sciences, the Lendület and OTKA Bridging Fund of the University of Debrecen. LL is supported by ÚNKP-23-4-I-DE-239 and the MTA-DE Cerebrovascular Research Group, University of Debrecen, Debrecen, Hungary.

CONFLICT OF INTEREST None declared.

OPEN ACCESS This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited, distributed under the same license, and used for noncommercial purposes only.

HOW TO CITE Bagoly Z, Lóczi L, Szegedi I. Impact of transcatheter edge-to-edge valve repair on hemostasis in patients with severe mitral regurgitation: key findings from the Mitral Fibrin Study. Pol Arch Intern Med. 2024; 134: 16819. doi:10.20452/pamw.16819

REFERENCES

1 Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. Lancet. 2009; 373: 1382-1394.

2 Chehab O, Roberts-Thomson R, Ng Yin Ling C, et al. Secondary mitral regurgitation: pathophysiology, proportionality and prognosis. Heart. 2020; 106: 716-723.

3 Drera A, Rodella L, Brangi E, et al. Endothelial dysfunction in heart failure: what is its role? J Clin Med. 2024; 13: 2534.

4 van Hinsbergh VW. Endothelium-role in regulation of coagulation and inflammation. Semin Immunopathol. 2012; 34: 93-106.

5 Blackshear JL, Pearce LA, Asinger RW, et al. Mitral regurgitation associated with reduced thromboembolic events in high-risk patients with nonrheumatic atrial fibrillation. Stroke Prevention in Atrial Fibrillation Investigators. Am J Cardiol. 1993; 72: 840-843.

6 Cevik C, Otahbachi M, Nugent K, Ozkan M. Mitral regurgitation reduces systemic coagulation activity in patients with rheumatic heart disease. J Heart Valve Dis. 2009; 18: 278-283.

7 Van Laer SL, Verreyen S, Winkler KM, et al. Effect of mitral regurgitation on thrombotic risk in patients with nonrheumatic atrial fibrillation: a new CHA(2)DS(2)-VASc score risk modifier? Am J Cardiol. 2021; 145: 69-76.

8 Hausleiter J, Stocker TJ, Adamo M, et al. Mitral valve transcatheter edge-to-edge repair. EuroIntervention. 2023; 18: 957-976.

9 Siniarski A, Stepien K, Golinska-Grzybala K, et al. Thrombin generation, fibrin clot permeation and lysis in patients with severe mitral regurgitation undergoing transcatheter edge-to-edge mitral valve repair: Mitral Fibrin Study. Pol Arch Intern Med. 2024: 134: 16755.

10 Movsowitz C, Movsowitz HD, Jacobs LE, et al. Significant mitral regurgitation is protective against left atrial spontaneous echo contrast and thrombus as assessed by transesophageal echocardiography. J Am Soc Echocardiogr. 1993; 6: 107-114.

11 Kranidis A, Koulouris S, Filippatos G, et al. Mitral regurgitation protects from left atrial thrombogenesis in patients with mitral valve disease and atrial fibrillation. Pacing Clin Electrophysiol. 2000; 23: 1863-1866.

12 Okhota S, Melnikov I, Avtaeva Y, et al. Shear stress-induced activation of von Willebrand factor and cardiovascular pathology. Int J Mol Sci. 2020; 21: 7804.

13 Natorska J, Corral J, de la Morena-Barrio ME, et al. Antithrombin deficiency is associated with prothrombotic plasma fibrin clot phenotype. Thromb Haemost. 2023; 123: 880-891.

14 Pieters M, Philippou H, Undas A, et al. An international study on the feasibility of a standardized combined plasma clot turbidity and lysis assay: communication from the SSC of the ISTH. J Thromb Haemost. 2018; 16: 1007-1012.

15 Zabczyk M, Ariens RAS, Undas A. Fibrin clot properties in cardiovascular disease: from basic mechanisms to clinical practice. Cardiovasc Res. 2023; 119: 94-111.