Comment on Panova-Noeva, page 251

Genetic and nongenetic determinants of mean platelet volume

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In this issue of *Blood*, Panova-Noeva et al identify genetic and nongenetic determinants of mean platelet volume (MPV) that substantially differ between males and females. Analysis of cumulative mortality also showed that increased MPV is independently associated with mortality.[1]

Platelets are small subcellular elements produced from bone marrow megakaryocytes.[2] The typical diameter of these unique corpuscular elements is between 1.6 and 3.9 μm, and their normal volume usually ranges between 7 and 11 fL.[2,3] The dichotomous but complementary role of platelets in physiological and pathological hemostasis is now well established. After vessel cell injury, activated platelets participate in the generation of the first hemostatic plug by means of their adhesive and cohesive functions, thus creating an immediate barrier to arrest bleeding (ie, primary hemostasis). However, the platelet clot is a highly unstable defense because it requires stabilization by a fibrin network that originates from the subsequent activation of blood coagulation (ie, secondary hemostasis). The initiation of blood coagulation is mainly sustained by the release of tissue factor from injured endothelial cells, but the further amplification of the coagulation cascade up to the generation of insoluble fibrin requires a sequential and coordinated series of enzymatic reactions involving many coagulation factors.[2] The conversion of each zymogen to its relative active serine protease typically occurs on the platelet membrane where the exposure of phospholipidic surfaces enormously amplifies the catalytic conversion of clotting factors into their active counterparts.

The initial physiological response toward the development of hemostatic plugs or blood clots encompasses a change in platelet shape from discoid to spherical, an extrusion of pseudopods, and a volume modification.[4] Importantly, platelet activation is associated with a rapid intracellular reorganization of actin and microtubule components of the cytoskeleton, which produces a considerable enhancement of the platelet surface area mirrored by a parallel increase in the MPV.[5] Several lines of evidence accumulated over the past decade suggest that a significant association exists between MPV and human diseases, especially cardiovascular disorders. Briefly, larger platelets overexpress surface activation markers and seem to be metabolically and enzymatically more active, thus establishing a prothrombotic milieu that increases the risk of thrombosis. Unfortunately, it is not clear which comes first, the chicken or the egg. Are larger platelets the cause of the thrombosis? Or has the thrombotic process directly contributed to triggering platelet activation and increase of MPV? It is now undeniable that the assessment of platelet size should be regarded as a valuable tool for diagnosis and therapeutic monitoring of a wide spectrum of arterial and venous disorders.[6]

The recent study by Panova-Noeva et al provides novel and important insights regarding platelet biology and its relationship with thrombosis. Higher MPV values were found to be significantly associated with a number of genetic polymorphisms and clinical factors, including age, smoking, hypertension, and glucose levels in men, and oral contraceptives and menstruation in women. Seven single nucleotide polymorphisms (SNPs) in women and four SNPs in men were also found to be significant determinants of larger platelet size. Even more interestingly, multivariable linear regression analysis revealed that the combination of these clinical and genetic determinants explained up to 20% of total MPV variance in both sexes. Notably, a substantially higher mortality rate was also observed in individuals with MPV above the upper limit of the reference range (ie, >10.1 fL) during a median follow-up period of 5.0 years. Overall, each 1-fL increase in MPV was independently associated with a 16% higher risk of death.

Indeed, the findings of the study by Panova-Noeva et al represent a major breakthrough in unraveling the key role played by platelets in the pathogenesis of occlusive thrombotic disorders and further support the use of antiplatelet agents for prevention and treatment of both arterial and venous thrombosis.[7] The significant associations that have been observed between MPV and advanced age, smoking, hypertension, diabetes, and use of oral contraceptives unveil the existence of a previously unidentified and apparently gender-dependent interplay between platelet biology and inherited or acquired cardiovascular or thrombotic risk factors, which may ultimately contribute to generation of a prothrombotic state in certain patients, thus increasing their individual risk of mortality, especially for cardiovascular diseases. Taken together, these results also provide further support for the routine measurement of MPV in clinical practice. At variance with other predictive or diagnostic biomarkers, and despite the current lack of standardization of this index of platelet size, the MPV is now automatically estimated by the vast majority of commercial hematologic analyzers,[8] thus providing an inexpensive, easy, fast, and reliable parameter to help stratify risk for cardiovascular diseases and death in the general population as well as in selected categories of patients. Interesting evidence is also emerging in other branches of science and medicine wherein platelet size is seemingly associated with fitness and human performance, thus expanding the pleiotropic activity of platelets far beyond the boundaries of hemostasis.[9]

In conclusion, the study by Panova-Noeva et al opens new avenues in our understanding of platelet biology and underpins the key contribution of simple and often underestimated laboratory parameters to care pathways in a world with limited resources, only recently recovering from an unprecedented economic crisis.[10]

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REFERENCES

1. Panova-Noeva M, Schulz A, Hermanns MI, et al. Sex-specific differences in genetic and nongenetic determinants of mean platelet volume: results from the Gutenberg Health Study. *Blood*. 2016;127(2):251-259.

2. Lippi G, Franchini M. Platelets and immunity: the interplay of mean platelet volume in health and disease. *Expert Rev Hematol*. 2015;8(5):555-557.

3. Noris P, Biino G, Pecci A, et al. Platelet diameters in inherited thrombocytopenias: analysis of 376 patients with all known disorders. *Blood*. 2014;124(6):e4-e10.

4. Kamath S, Blann AD, Lip GY. Platelet activation: assessment and quantification. *Eur Heart J*. 2001;22(17): 1561-1571.

5. Aslan JE, Itakura A, Gertz JM, McCarty OJ. Platelet shape change and spreading. *Methods Mol Biol*. 2012;788: 91-100.

6. Lippi G. Red blood cell distribution width and mean platelet volume: Surrogate markers for, or treatment targets in, dyslipidemia? *Clin Biochem*. 2015;48(9): 555-556.

7. Mekaj YH, Daci FT, Mekaj AY. New insights into the mechanisms of action of aspirin and its use in the prevention and treatment of arterial and venous thromboembolism. *Ther Clin Risk Manag*. 2015;11: 1449-1456.

8. Lippi G, Pavesi F, Pipitone S. Evaluation of mean platelet volume with four hematological analyzers: harmonization is still an unresolved issue. *Blood Coagul Fibrinolysis*. 2015;26(2): 235-237.

9. Lippi G, Salvagno GL, Danese E, et al. Mean platelet volume (MPV) predicts middle distance running performance. *PLoS One*. 2014;9(11): e112892.

10. Appleby J, Helderman JK, Gregory S. The global financial crisis, health and health care. *Health Econ Policy Law*. 2015;10(1):1-6.

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