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● ● ● PLATELETS AND THROMBOPOIESIS

Comment on Walton et al, page 2537

RBCs pin platelets against the (thrombus) wall

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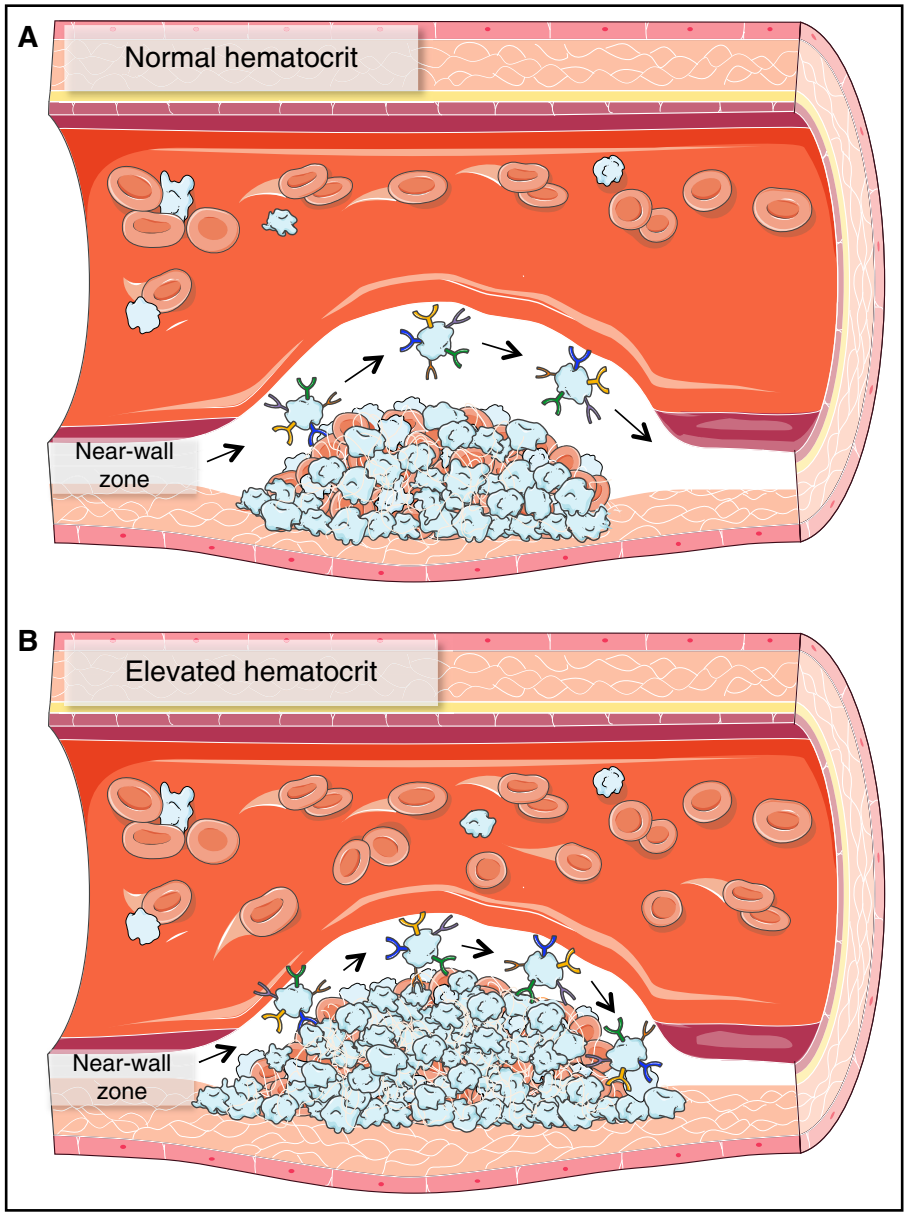
In this issue of *Blood*, Walton and colleagues reveal that elevated hematocrit enhances clot formation in vivo via increased platelet accumulation in a growing thrombus.[1] Although elevated hematocrit is an independent risk factor for cardiovascular disease, the specific contribution of an increased red blood cell (RBC) count to this etiology has remained elusive. This is largely due to complicating factors in diseases such as polycythemia vera (PV), where patients present with elevated hematocrit, but the specific role of RBCs in thrombotic risk is unclear. To circumvent these additional complications, Walton et al used a model where additional RBCs were infused into healthy mice and arterial clot formation was studied, thus isolating the contribution of the increased RBCs. Notably, the increased number of RBCs changed the hemodynamics of the blood around a growing thrombus, narrowing the near-wall, RBC-free zone (see figure). This narrowed zone created a locale where platelets spend significantly more time in contact with the growing thrombus, increasing the probability of their binding and incorporation into the clot. Thus, elevated hematocrit, perhaps unexpectedly, was shown to enhance thrombotic risk by increasing the number of platelets incorporated into the thrombus.

The prevalence of primary erythrocytosis in the United States has been reported to be 44 to 57 per 100 000.[2] The natural history of PV is complicated by thromboembolic events; patients with myeloproliferative disorders suffer from both arterial and venous thrombosis, which accounts for 40% of the mortality associated with these disorders.[3] However, the etiology of this high thrombotic rate has remained unclear. Recent advances attributed the thrombotic risk to blood hyperviscosity, as well as platelet and leukocyte dysfunction.[4,5] However, one of the paradoxical findings in this disorder is that an elevation in platelet count is not correlated with the risk of thrombosis; to date, no study has demonstrated a correlation between the absolute platelet number or platelet functionality and the risk of thrombosis in PV or other myeloproliferative disorders. In the European Collaboration on Low-Dose Aspirin in Polycythemia Vera study, platelet count thresholds could not predict the risk of thrombosis, making this parameter unlikely to be useful for risk stratification.[6] Instead, elevated hematocrit and leukocytosis have been linked to platelet activation via cathepsin G and CD62P (P-selectin).[7] In addition, the cytoreduction-PV trial clearly demonstrated that the risk of thrombosis in PV was highly correlated with elevated hematocrit.[8] In this multicenter trial, patients with a high hematocrit carried a four times higher thrombotic risk than those in the lower hematocrit group.[8] The importance of these parameters is best emphasized by the fact that the cornerstone of treatment for PV is to use therapeutic phlebotomy to keep the hematocrit at a level <45%.[8] In the article by Walton et al, a novel mechanism by which elevated hematocrit can lead to increased thrombosis risk has now been elucidated. The heightened hematocrit, which is the cornerstone of PV, results in redistribution of the blood cells within the circulatory bed. The RBCs push the platelets closer to the vessel wall, increasing the probability of adhesion and activation via von Willebrand factor and collagen, ultimately resulting in thrombotic manifestations. This novel finding is consistent with the etiology of thrombosis in PV, where an elevated platelet count does not explain thrombotic risk, and may finally provide an explanation for the mechanism of thrombosis in these patients.

Arterial clots are dependent on platelets for their propagation; therefore, the article by Walton et al clearly establishes a mode by which elevated hematocrit increases the risk of arterial thrombotic events. However, patients with an elevated hematocrit can present with both arterial and venous thrombosis.[3,5,9] Therefore, what remains to be understood is whether similar principles apply to the formation of venous thrombi, which are not platelet-dependent but instead largely RBC- and fibrin-rich. Although the increased risk of venous thrombosis has also been tied to elevated hematocrit, it has been proposed that



Schematic showing the mechanism of enhanced thrombosis in patients with elevated hematocrit. Increased RBCs narrow the near-wall RBC depleted zone around a growing thrombus. This narrowing traps platelets, allowing them to spend significantly more time in this zone, enhancing the probability that they will be incorporated into the clot. (A) Normal hematocrit and (B) elevated hematocrit. This figure was created with images adapted from Servier Medical Art by Servier. Original images are licensed under a Creative Commons Attribution 3.0 Unported License.

the mechanism of thrombosis may be due to qualitative changes in the RBCs themselves, increasing their adhesiveness to the endothelial wall.[9,10] The implications of this study by Walton et al on venous events are indeed intriguing and warrant further study to parse apart the similar and disparate aberrant mechanisms that contribute to venous vs arterial thrombus formation in patients with an elevated hematocrit. Notably, this study has important implications for how we treat all patients with an elevated hematocrit, in both PV and other pathological manifestations, and clearly establishes the importance of decreasing the hematocrit as the cornerstone of therapy to reduce thrombotic risk.

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