When Flow Goes Slow, von Willebrand Factor Can Bind Red Blood Cells

Scott L. Diamond

“Stasis, hypercoagulability, vessel wall injury”: If you repeat Virchow’s triad to yourself a few times, it almost sounds like the definition of clotting rather than the cause of clotting. Still, Virchow’s triad is a remarkable predictor of where clotting initiates, specifically during venous thrombosis in the valve pocket. In the body, blood is typically clotting under flow conditions unless it has pooled outside of a broken vessel. Within vessels, the prevailing flow dictates the cellular collision frequency, the collision interaction time, as well as the forces on adhering or aggregating cells. However, when venous flows becomes pathologically slow at $<100\ s^{-1}$ wall shear rate (or $<1\ \text{dyne/cm}^2$ wall shear stress), the collision rate drops, while the interaction times for adhesive bonding increase, and the forces on those bonds also decrease. Unusual adhesion bonding events may reveal themselves at pathologically low flows that would never exist in physiological venous or arterial flows. Also, at low flow, red blood cells (RBC) can form rouleaux to dramatically increase blood viscosity.

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Apart from hemoglobinopathies and malaria, RBCs were generally considered passive bystanders during thrombosis. Arterial clots often lack RBC, while venous clots were thought to merely entrap the RBC during fibrin polymerization. The passive entrapment of RBC during venous thrombosis was called into question when healthy RBC were shown to bond to activated neutrophils, activated platelets, and clotted plasma at low shear rates. More recently, the role of FXIIIα-mediated cross-linking of fibrin was shown to be essential for RBC retention during clot retraction. In this issue, Smeets et al used pathologically low flows to visualize a new bonding interaction between RBCs and VWF (von Willebrand factor). In thrombosis and hemostasis, VWF is an extremely well-studied polymeric protein known for capture of flowing platelets via glycoprotein Iba.

Smeets et al found that VWF immobilized on a surface led to capture of RBC at 0.75 dyne/cm², an adhesion not seen with albumin or other matrix proteins, such as collagen, fibronectin, fibrinogen, or fibrin. This adhesion was even more abundant on VWF at extremely low shear stresses (0.125–0.5 dyne/cm²) that remained nonpermissive for RBC adhesion to collagen.

References

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