von Willebrand factor-mediated platelet adhesion is critical for deep vein thrombosis in mouse models.

Deep vein thrombosis (DVT) and its complication, pulmonary embolism, are frequent causes of disability and mortality. Although blood flow disturbance is considered an important triggering factor, the mechanism of DVT initiation remains elusive. Here we show that 48-hour flow restriction in the inferior vena cava (IVC) results in the development of thrombi structurally similar to human deep vein thrombi. von Willebrand factor (VWF)-deficient mice were protected from thrombosis induced by complete (stasis) or partial (stenosis) flow restriction in the IVC. Mice with half normal VWF levels were also protected in the stenosis model. Besides promoting platelet adhesion, VWF carries Factor VIII. Repeated infusions of recombinant Factor VIII did not rescue thrombosis in VWF(-/-) mice, indicating that impaired coagulation was not the primary reason for the absence of DVT in VWF(-/-) mice. Infusion of GPG-290, a mutant glycoprotein Ibα-immunoglobulin chimera that specifically inhibits interaction of the VWF A1 domain with platelets, prevented thrombosis in wild-type mice. Intravital microscopy showed that platelet and leukocyte recruitment in the early stages of DVT was dramatically higher in wild-type than in VWF(-/-) IVC. Our results demonstrate a pathogenetic role for VWF-platelet interaction in flow disturbance-induced venous thrombosis.