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EDITORIAL COMMENT

Exosome-Mediated Angiogenesis Underlies LVAD-Induced Bleeding in Patients With End-Stage Heart Failure*

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The von Willebrand factor (VWF), named after the Finnish physician who first described the hereditary disorder caused by its deficiency, is a large glycoprotein, synthesized in megakaryocytes and endothelial cells, that undergoes extensive post-translational processing.[1] The basic VWF monomer contains 2,050 amino acids; the multimeric structure of VWF, which can be exceptionally large (>20,000 kDa), makes the protein sensitive to changes in fluid flow and shear stress. Multimers of VWF are stored within the Weibel-Palade bodies in endothelial cells and α granules in megakaryocytes and platelets. High molecular weight VWF multimers are the most active functional forms of VWF because they provide multiple binding sites that can interact with platelets and vascular subendothelial structures at sites of endothelial injury, making them fundamental in primary hemostasis.

In addition to inherited von Willebrand disease, an acquired disorder has also been described, known as acquired von Willebrand syndrome (aVWS).[2] There are some conditions that generate high shear stress among the main causes of aVWS, which most likely elicit the unfolding and subsequent cleavage of VWF. Some examples of this include left ventricular assist devices (LVADs) and the use of extracorporeal membrane oxygenation. LVADs have been associated with increased bleeding risk, commonly attributed to hydrodynamic changes and shear stress induced by continuous flow across the device, which ultimately triggers an augmented VWF cleavage.[1,2] However, the exact mechanisms leading to aVWS in shear stress conditions are not fully understood.

In this issue of *JACC: Basic to Translational Science*, Yang et al[3] were able to identify shear-induced structural changes of VWF using both in vivo and in vitro experimental settings, by studying longitudinal samples from patients with New York Heart Association functional class IV heart failure who underwent LVAD treatment. They found that the plasma from these patients induced significant endothelial permeability, which was blocked by a VWF-blocking antibody. The augmented permeability was not observed when using purified VWF, nor when using plasma that did not contain extracellular vesicles (EVs). Moreover, plasma samples collected from LVAD-treated patients activated endothelial cells that expressed phosphatidylserine and released VWF.

Because increased permeability represents an early stage of angiogenesis, the investigators reasoned that EVs from patients with LVADs could carry angiogenic activity; they demonstrated that EVs from patients with LVADs contained vascular endothelial growth factor levels approximately 4-fold higher than the content found in normal plasma (**Figure 1**).

The investigators provided several lines of evidence that showed that the blood from patients with LVADs contain plasma-derived and EV-derived proangiogenic activities, and that the latter

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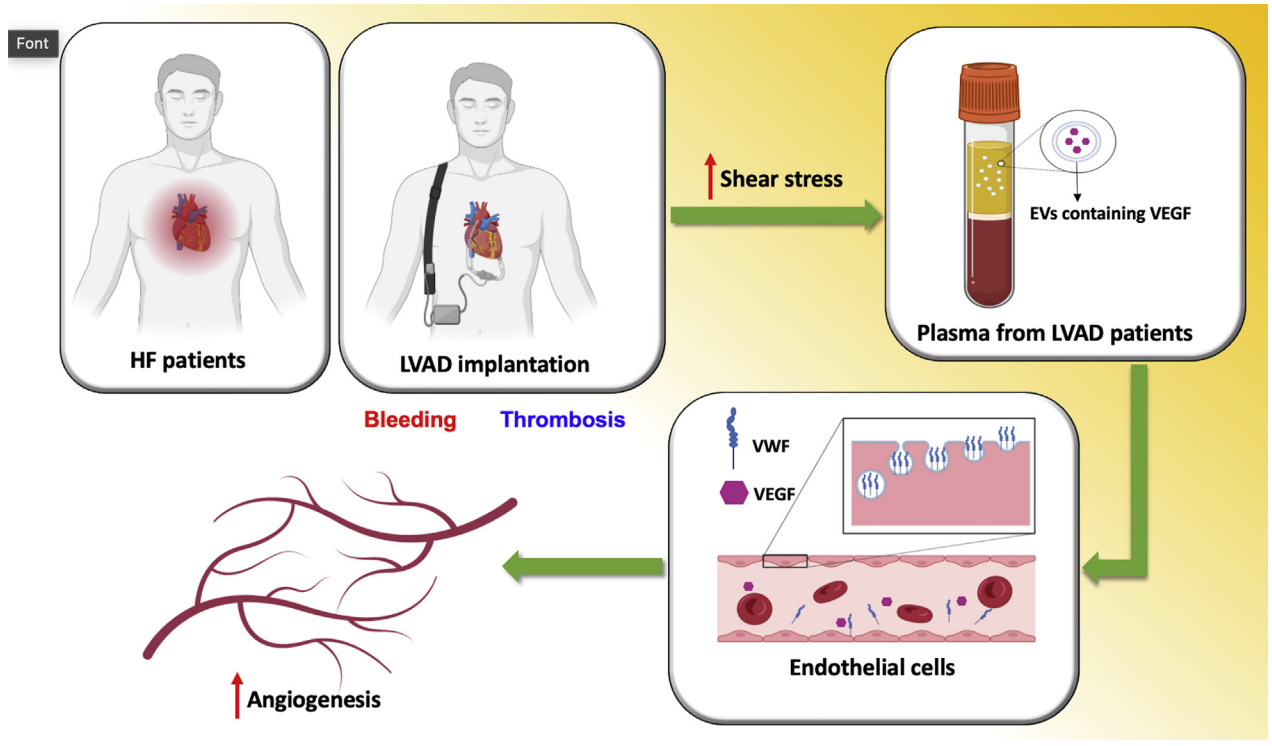
FIGURE 1 Schematic Representation of How Increased Angiogenesis Mediates LVAD-Induced Bleeding



Extracellular vesicles (EVs) enriched in vascular endothelial growth factor (VEGF) trigger angiogenesis that underlies left ventricular assist device (LVAD)–induced alterations in hemostasis in patients with end-stage heart failure (HF). Some images were created using Biorender. VWF = von Willebrand factor.

promotes aberrant angiogenesis and is primarily derived from EVs from platelets activated by VWF under high shear stress. Hence, this work adds another piece to the rapidly growing field of EVs and exosomes in cardiovascular medicine.

VWF multimers in patients with LVADs are oxidized and undergo conformational changes to expose the A1 domain and to bind platelets. Thus, following LVAD implantation, endothelial cells undergo persistent exocytosis of VWF and are subjected to even more stress at the time of severe bleeding or thrombosis. Furthermore, plasma VWF in patients with LVADs is hyperadhesive; however, it loses large multimers and forms fibrillary structures under high shear stress.

In summary, VWF does not seem to promote angiogenesis directly, but most likely serves as a coupling factor that tethers platelet EVs to endothelial cells. In this manner, vascular endothelial growth factor becomes locally concentrated for angiogenesis and can induce VWF release from endothelial cells, thus enhancing endothelial permeability and promoting the formation of immature leaky vessels.

The most important limitation of the study was its small sample size (26 patients and 10 control subjects); thus, the study was not powered to associate VWF changes with clinical events.

Another limitation was that because of a limited plasma volume, the investigators were unable to map the specific amino acids involved in forming intermultimer disulfide bonds or being oxidized.

LVADs are mechanical circulatory devices used in patients with cardiogenic shock or end-stage heart failure. They are assuming a greater role in the care of patients with heart failure, not only as a bridging tool to heart transplantation, but also as a permanent therapy for end-stage heart failure. Bleeding remains the most frequent complication in these patients, occurring in up to 60% of patients with LVADs.[4]

Defining excessive cleavage by the loss of large VWF multimers in plasma may perhaps be inaccurate because large and hyperadhesive VWF multimers bind to platelets and are thus selectively and

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disproportionally removed from plasma. This artificially amplifies the amount of cleaved soluble VWF.

Interestingly, patients who have received angiotensin-converting enzyme inhibitors or angiotensin receptor blockage after LVAD implantation have significantly fewer bleeding events,[5] which strongly suggests that aberrant angiogenesis is a causal factor for LVAD-induced bleeding, in line with the findings of Yang et al.[3]

Further studies are needed to clarify how to better manage hemostatic complications in patients with LVADs, especially in the attempt to tackle VWF-mediated platelet activation and EV-driven angiogenesis.

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