



# Pathologic von Willebrand factor degradation is a major contributor to left ventricular assist device-associated bleeding: pathophysiology and evolving clinical management

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## Introduction

Non-surgical bleeding is the most frequent adverse event in patients with a continuous-flow left ventricular assist device (CF-LVAD). Bleeding is a major source of morbidity and an obstacle to improving outcomes, reducing costs, and expanding the public health impact of LVAD therapy. Mounting evidence demonstrates that the acquired von Willebrand factor (VWF) deficiency caused by CF-LVAD support is an important contributor to bleeding.

## Epidemiology

Thirty to seventy-five percent of LVAD patients experience episodic bleeding (1-4). Twenty to forty percent of patients bleed from the alimentary tract, most commonly from angiodysplasia (3,4). Gastrointestinal bleeding is the number one cause of hospital readmission for ambulatory LVAD patients. This is in part because all CF-LVAD patients acquire VWF deficiency (1-5). Within minutes of LVAD support, pathologic VWF degradation occurs. Within 24 hours, VWF deficiency plateaus and remains until LVAD support is discontinued.

## Normal VWF physiology

VWF, a multimeric plasma clotting protein, initiates primary hemostasis. Shear stress closely regulates VWF activation for thrombogenesis (6). Normal intravascular shear stress is approximately 2 to 8 Pa. VWF activation

occurs above 10 Pa. During activation, shear stress unravels inactive, globular VWF into an active, elongated conformation, which exposes binding sites for collagen and platelets to generate thrombus. Importantly, high-molecular-weight VWF multimers are most functional for clotting. However, unraveled, active high-molecular-weight VWF multimers are also sensitive to enzymatic cleavage by ADAMTS-13, the VWF-specific protease. ADAMTS-13 degrades active high-molecular-weight VWF multimers into low-molecular-weight VWF multimers and VWF fragments that are ineffective in clotting.

## LVAD-induced VWF degradation

CF-LVADs generate shear stress that exceeds physiologic values by two orders of magnitude (6). Inside CF-LVADs, an impeller spins at thousands of revolutions per minute (RPM) to propel blood forward. Shear stress of up to 1,500 Pa is produced. As a result, supraphysiologic LVAD shear stress causes pathologic VWF degradation by two biophysical mechanisms (2): (I) major mechanism—mechanoenzymatic degradation: LVAD shear stress activates VWF and exposes ADAMTS-13 cleavage sites for enzymatic degradation. (II) Minor mechanism—non-enzymatic degradation: shear stress alone (independent of ADAMTS-13) tears VWF multimers into smaller multimers. In parallel, LVAD shear stress activates platelets, which partially degranulate and release stores of ultra-high-molecular-weight VWF multimers (7), an important VWF reserve. Consequently, in

patients with an LVAD, platelet VWF is partially depleted when needed for primary hemostasis.

### Relationships between VWF deficiency and bleeding

A causal relationship between absence of high-molecular-weight VWF multimers and bleeding is well established. Non-LVAD patients with type IIA (congenital) and type IIB (acquired) von Willebrand Syndrome bleed because functional VWF multimers are absent. Patients often present with gastrointestinal bleeding from angiodysplasia (3,4). Similarly, in patients with Heyde's syndrome, elevated shear stress through a stenotic aortic valve causes degradation of high-molecular-weight VWF multimers and bleeding from angiodysplasia. Mechanisms of VWF degradation in Heyde's syndrome and LVAD patients are nearly identical (1-4).

Likewise, laboratory derangements and clinical presentation of LVAD patients are similar to patients with type II von Willebrand's disease and Heyde's syndrome. Patients exhibit absence of high-molecular-weight VWF multimers, reduced VWF: collagen binding and Ristocetin-induced platelet aggregation, and prolonged bleeding times that are independent of INR and antiplatelet therapy. Not surprisingly, a dose-response relationship exists. LVAD patients with the least high-molecular-weight VWF multimers and lowest VWF function are most likely to bleed (8).

### Pathologic VWF metabolism may contribute to angiodysplasia

CF-LVAD patients develop nasal mucosal vascular proliferation and gastrointestinal arteriovenous malformations (1,3,4). Emerging evidence suggests this is a distinct form of angiodysplasia (3,4), which begs the question, does abnormal VWF metabolism somehow alter angiogenesis and cause angiodysplasia? Interestingly, VWF is an early regulator of angiogenesis. In fact, VWF interacts with at least twenty molecular partners involved in angiogenesis, vascular inflammation, endothelial life cycle, smooth muscle proliferation, and arterial remodeling (1,3,9). Indeed, normal angiogenesis requires normal levels of VWF multimers. In contrast, absence of VWF multimers and high levels of VWF fragments may alter angiogenesis

and cause angiodysplasia in multiple human diseases (1,3,4,9). As a result, in CF-LVAD patients, pathologic VWF degradation is likely a strong contributor to the high incidence of gastrointestinal angiodysplasia and bleeding (3).

### Management

Consensus guidelines do not exist to manage LVAD-associated bleeding. Blood transfusion may be lifesaving, but sensitizes bridge-to-transplant candidates. Reduced anticoagulation and cessation of antiplatelet therapy prevent recurrent bleeding but increase risk of LVAD thrombosis. Endoscopic intervention for gastrointestinal bleeding addresses sources of bleeding but does not address underlying pathophysiology. Likewise, pharmacotherapy with Octreotide, Arginine Vasopressin, Danazol, synthetic Estrogens, and Wilfactin have demonstrated limited success in managing LVAD bleeding, likely because pathophysiologic mechanisms of VWF degradation and angiodysplasia are not specifically targeted (3).

Targeted therapies designed to preserve VWF multimers (10) or to correct angiogenic imbalance (3) may have clinical utility. As an example, ADAMTS-13 inhibition is a potential strategy to reduce pathologic VWF degradation during high shear stress. However, this strategy must be approached with caution. Accumulation of activated, pro-thrombotic VWF multimers has potential to cause thrombosis (11). Alternatively, thalidomide, a potent anti-angiogenesis agent, may prevent recurrent bleeding from angiodysplasia in LVAD patients.

Reduction of LVAD RPM has been proposed as an adjunctive therapy for LVAD-associated bleeding. However, clinical and experimental data demonstrate that RPM reduction does not reduce shear stress sufficiently to preserve VWF multimers and is inappropriate bleeding management (12). In contrast, pulsatile blood flow may protect against LVAD-associated bleeding (13). Pulsatile stretch is an important trigger for endothelium to secrete VWF multimers and replenish plasma VWF (14). Pulsatile flow through the aortic valve also maintains a normal flow path in parallel with the LVAD pathway, which may reduce total blood exposure to supraphysiologic shear stress through the LVAD (12).

Ultimately, LVADs designed with reduced shear stress and pulsatile flow may reduce bleeding (6). Specific LVAD design features (impeller shape/orientation, RPM range,

flow-gap size, internal geometry, blood transient time, flow algorithm) influence shear stress. As such, next-generation LVADs designed to minimize shear stress and preserve VWF multimers should reduce bleeding.

### Toward standardized testing of VWF degradation during mechanical circulatory support

Multiple qualitative, semi-quantitative, and quantitative techniques to evaluate the severity of VWF deficiency in LVAD patients have been reported (5). However, a standard methodology has not been established as has been for hemolysis. As a result, interpretation of different metrics of VWF multimer degradation across preclinical and clinical studies is limited. Therefore, a consensus practice to quantify and report VWF multimers and industry standards for LVAD-associated VWF degradation is needed to standardize comparisons across patients, devices, studies, and clinical outcomes (5).

### Conclusions

CF-LVADs cause pathologic VWF degradation, acquired VWF deficiency, gastrointestinal angiodysplasia, and recurrent bleeding. Management strategies are evolving. Targeted therapies designed to preserve VWF multimers or to correct angiogenic imbalance may have clinical utility. Next-generation LVADs designed with lower shear stress and pulsatile flow will prevent abnormal VWF metabolism and reduce LVAD-associated bleeding. Standardized testing and accepted thresholds for VWF degradation in LVAD patients are needed.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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