Received: 21 June 2022 | Revised: 6 September 2022 | Accepted: 4 November 2022

DOI: 10.1111/aor.14456

Artificial Organs WILEY

REVIEW

Loss of pulsatility with continuous-flow left ventricular assist devices and the significance of the arterial endothelium in von-Willebrand factor production and degradation

Guruprasad A. Giridharan[1] | **Ian C. Berg**[2,3] | **Esraa Ismail**[4] | **Khanh T. Nguyen**[2,3] | **Jana Hecking**[2,3] | **James K. Kirklin**[5] | **Xuanhong Cheng**[4,6] | **Palaniappan Sethu**[2,3]

[1]Department of Bioengineering, J. B. Speed School of Engineering, University of Louisville, Louisville, Kentucky, USA

[2]Division of Cardiovascular Disease, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

[3]Department of Biomedical Engineering, School of Engineering and Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

[4]Department of Bioengineering, Lehigh University, Bethlehem, Pennsylvania, USA

[5]Division of Cardiothoracic Surgery, Department of Surgery, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

[6]Department of Materials Science and Engineering, Lehigh University, Bethlehem, Pennsylvania, USA

Correspondence
Palaniappan Sethu, Division of Cardiovascular Disease, University of Alabama at Birmingham, 1918 University Blvd, 290A MCLM, Birmingham, AL 35223, USA.
Email: psethu@uab.edu

Funding information
Foundation for the National Institutes of Health, Grant/Award Number: HL129948 and HL151663; National Science Foundation, Grant/Award Number: 2004475

Abstract

Background: Patients on continuous flow ventricular assist devices (CF-VADs) are at high risk for the development of Acquired von-Willebrand Syndrome (AVWS) and non-surgical bleeding. von Willebrand Factor (vWF) plays an essential role in maintaining hemostasis via platelet binding to the damaged endothelium to facilitate coagulation. In CF-VAD patients, degradation of vWF into low MW multimers that are inefficient in facilitating coagulation occurs and has been primarily attributed to the supraphysiological shear stress associated with the CF-VAD impeller.

Methods: In this review, we evaluate information from the literature regarding the unraveling behavior of surface-immobilized vWF under pulsatile and continuous flow pertaining to: (A) the process of arterial endothelial vWF production and release into circulation, (B) the critical shear stress required to unravel surface bound versus soluble vWF which leads to degradation, and (C) the role of pulsatility in on the production and degradation of vWF.

Results and Conclusion: Taken together, these data suggests that the loss of pulsatility and its impact on arterial endothelial cells plays an important role in

Abbreviations: ADAMTS13, A Disintegrin-like and Metalloprotease ThromboSpondin-13; ASYN, asynchronous flow modulation; AVWS, acquired von Willebrand syndrome; CF-VADs, continuous flow ventricular assist devices; ER, endoplasmic reticulum; GI, gastrointestinal; HF, heart failure; LVADs, left ventricular assist devices; MW, molecular weight; PF-VADs, pulsatile-flow ventricular assist devices; SYN, synchronous flow modulation; WPBs, weibel-palade bodies; vWF, von Willebrand Factor.

the production, release, unraveling, and proteolytic degradation of vWF into low MW multimers, contributing to the development of AVWS. Restoration of pulsatility can potentially mitigate this issue by preventing AVWS and minimizing the risk of non-surgical bleeding.

KEYWORDS
acquired von Willebrand syndrome, continuous flow, loss of pulsatility, von Willebrand Factor

1 | INTRODUCTION

Left Ventricular assist devices (LVADs) are standard therapy for patients with advanced heart failure (HF) refractory to medical therapy.[1] Categorized based on the type of flow, both pulsatile flow VADs (PF-VADs) and continuous flow VADs (CF-VADs) provide hemodynamic support and improve the quality of life and functional capacity of patients.[2,3] Clinically, CF-VAD implantations are preferred over PF-VADs owing to advantages in size, reliability, energy efficiency, and ease of implant. However, CF-VADs provide non-physiological stimuli that are associated with pump thrombosis (due to platelet activation as a result of supraphysiological shear[4,5]) and non-surgical bleeding, particularly in the gastrointestinal (GI) tract.[6,7] While still major challenges, hemolysis and pump thrombosis have been mitigated through pump designs that reduce the shear and residence times, proper positioning of the outflow cannula, and anticoagulant therapies.[5] Non-surgical bleeding remains a frequent complication in patients supported with CF-VADs.[8] Despite the fact that bleeding is a multifactorial event, evidence links GI bleeding and the development of acquired von Willebrand syndrome (AVWS), however, it is important to note that not all patients that develop AVWS experience non-surgical bleeding.[9,10] In AVWS, the large globular plasma glycoprotein vWF, which plays a critical role in facilitating coagulation through platelet adhesion, undergoes cleavage into low molecular weight (MW) multimers, which bind poorly to platelets and sub-endothelial collagen.[11] Quantitative evaluation of vWF multimers shows that CF-VAD patients often display a significant reduction in plasma vWF levels, and increased vWF degradation.[12] While decreased circulating high MW vWF multimers does not always lead to GI bleeding, patients experiencing GI bleeds have significantly lower levels of vWF.[9] The requisite anticoagulation therapy CF-VAD patients undergo complicates this pathophysiology. However, a clinical trial reported high levels of bleeding in CF-VAD patients not receiving systemic anticoagulation.[13] Despite the complex nature of this process, vWF degradation appears to play an important role in the development of non-surgical bleeding.

vWF degradation into low MW multimers requires shear-mediated unraveling, resulting in the exposure of the scissile bond located within the A2 domain for proteolytic cleavage via metalloprotease A Disintegrin-like and Metalloprotease ThromboSpondin-13 (ADAMTS13).[14–16] Studies using mock flow loops and vortex mixers confirm that exposure of vWF to supraphysiological shear rates in the presence of ADAMTS13 (>10 000 s^{-1}) results in unraveling, proteolytic degradation, and breakdown of vWF into low MW multimers.[17] While considering shear stress, it is also important to consider the type of flow regime. High shear stress associated with the turbulence in the CF-VAD promotes vWF unraveling and degradation[18] whereas; high supraphysiological shear stress associated with CF-VADs using microfluidic devices where the flow is laminar did not result in excessive cleavage or decreased function of von Willebrand factor in the presence of ADAMTS13.[19] While AVWS development has primarily been considered in the context of these supraphysiological shear rates observed within the CF-VADs,[20] there are reasons to believe that the exposure to supraphysiological shear may not be the sole contributor. The short (30–200 milliseconds) residence time for vWF within the high shear stress areas of the CF-VAD, even when the flow is turbulent, may be insufficient for the unraveling of vWF required for degradation. Further, high supraphysiological shear within CF-VADs is limited to localized regions (<25% of CF-VAD volume)[21] and newer designs have reduced impeller shear rates and pump residence time.[22] Notably, such improvements to the Heartmate III device (Abbott Laboratories, Chicago, IL) resulted in an increased proportion of patients with intact high MW vWF multimers (from 9% to 25%). However, nearly 75% of Heartmate III patients still developed AVWS.[23]

Pulsatility is an intrinsic aspect of arterial circulation. Arterial endothelial cells transduce pulsatile pressure, shear, and stretch to maintain normal endothelial function, and changes in pulsatility affect arterial endothelial cell function.[24] Further, arterial endothelial cells produce and secrete vWF and represent the primary location of exposure of vWF to shear associated with blood flow.[25] Early LVAD design improvements focused on minimizing hemolysis and thrombosis, to improve patient safety and survival

with CF-VADs despite the loss of pulsatility. Frequent incidences of non-surgical bleeding with CF-VAD usage have renewed efforts to understand the consequences of loss of physiologic pulsatility and identification of mechanisms that possibly contribute to AVWS. Based on what we know from the process of arterial endothelial vWF production and release into circulation, theoretical and experimental studies establishing minimum shear thresholds for unraveling surface bound versus soluble vWF, the relationship between the level of pulsatility and vWF degradation,[26] and our recent study evaluating the unraveling behavior of surface-immobilized vWF under pulsatile and continuous flow[27]; *we postulate that the loss of pulsatility experienced by the arterial endothelium is highly significant in the context of vWF production, release, unraveling, and proteolytic degradation into low MW multimers*. A detailed discussion of each of these factors follows.

2 | PRODUCTION AND RELEASE OF ENDOTHELIAL vWF INTO CIRCULATION

vWF is a plasma glycoprotein, synthesized by endothelial cells, stored in Weibel-Palade bodies (WPBs) or by activated platelets, and released into circulation.[28] Endothelial cells ensure basal levels of vWF via constitutive, stimulation-independent secretion of vWF from WPBs (Figure 1, 1–6)

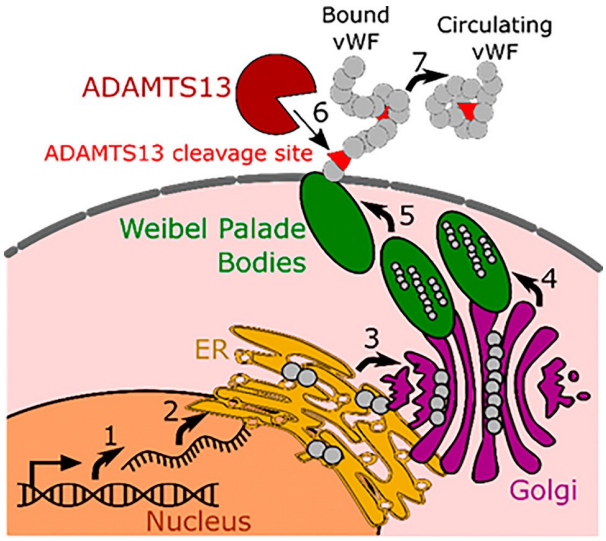

FIGURE 1 Schematic representation of high MW vWF production and secretion. Transcription (1) and translation (2) of vWF monomers occur in the nucleus. Dimerization (3) occurs in the endoplasmic reticulum (ER), followed by multimerization in the Golgi. vWF multimers are packaged into Weibel Palade bodies (4), from which vWF is secreted at the cell membrane (5). High MW VWF is cleaved from endothelial cells by ADAMTS-13 (6) leading to circulation (7).

and an increase in circulating vWF occurs in response to stimuli like a vascular injury.[29] Newly released vWF from WPBs is in the form of ultra-large multimers, which remain anchored to the endothelial surface and unravels under shear stress until being proteolytically released by ADAMTS13 (Figure 1 6–7).[14–16] While ADAMTS13 can bind to globular vWF, it cannot cleave it, as the scissile bond located on the A2 domain and other potential cleavage sites are hidden in its folded, globular form. Therefore fluid shear stress from blood flow is an important mediator of arterial homeostasis and maintenance of basal vWF levels. Change from normal pulsatile flow to continuous flow or "static" no-flow conditions results in a sharp decrease in vWF release from endothelial cells.[26,30] While it is not entirely clear if pulsatile flow increases transcriptionally regulated production of vWF, the pulsatile stretch may enhance the release of vWF stored in WPBs.[31]

In normal physiology, binding and proteolytic cleavage of vWF by ADAMTS13 occurs at three distinct locations: **(1) Surface of the arterial endothelium**: the endothelial cells that make up the arterial vessel walls are an important source of vWF. vWF secreted from WPBs that are produced within the arterial endothelial cells remains anchored to the arterial endothelium and requires proteolytic cleavage for release as ultra-large vWF molecules into circulation, **(2) In the bloodstream**: Globular vWF molecules in free circulation or transiting through the CF-VAD may unravel under elevated shear, exposing binding sites and the scissile bond resulting in cleavage, and **(3) Sites of vascular injury**: following rupture of any vessel within the body, large vWF multimers present in the bloodstream bind to activated platelets and sub-endothelial collagen beneath the damaged endothelial layer and unravel in response to shear from blood flow. Unraveling exposes both the A2 domain and additional binding exosites and cleavage locations, resulting in the degradation of vWF into smaller fibrils with significantly reduced adhesive potential to prevent whole vessel occlusion.

3 | SHEAR STRESS: SURFACE-BOUND VERSUS GLOBULAR vWF IN BULK FLOW

Vessel shear stress varies as a function of the radial distance from the center of the vessel, with surface-immobilized molecules experiencing significantly greater shear than molecules suspended in the fluid. Simulation and experimental studies confirm that vWF can unfold in response to shear both in solution and when immobilized on substrates. However, the shear threshold for the unraveling of surface-bound versus soluble vWF may differ significantly (Figure 2). Molecular simulations suggest that the critical

shear rate threshold for unraveling of vWF in solution (unbound) can be ~50-fold greater than for vWF immobilized to a surface.[32] Experimental studies using fluorescence microscopy,[33] small-angle neutron scattering (SANS),[34] and fluorescence spectroscopy[35] confirm that the critical shear rate for vWF unraveling was >5000 s^{-1} in solution.

The critical shear rates for the unraveling of surface-bound vWF have been experimentally measured in the range of 1000 to 3500 s^{-1} based on the method of immobilization.[36,37] Dong et al. showed that newly released vWF from endothelial cells undergo elongation and string formation at significantly lower shear rates (<500 s^{-1}) than vWF molecules immobilized with different chemistries.[15] This study also found that under flow conditions, endothelial-bound vWF was cleaved and released within seconds to minutes in the presence of normal plasma (~100% ADAMTS-13 activity) in contrast to plasma from patients with thrombotic thrombocytopenic purpura (TTP) (~0% to 10% ADAMTS-13 activity) that resulted in endothelial bound strings of vWF. These results demonstrate that vWF unraveling occurs at significantly lower shear rates for endothelial-bound vWF compared to surface-bound vWF and vWF in the bulk flow.

4 | UNRAVELING BEHAVIOR OF SURFACE IMMOBILIZED vWF UNDER CONTINUOUS AND PULSATILE FLOW

Normal pulsatile flow as seen in arterial vessels is associated with higher peak shear stress but also provides a period of zero/low shear. Continuous flow is associated with constant shear stress albeit at a lower magnitude than the peak seen with pulsatile flow. In vitro, the unraveling of vWF has been almost exclusively studied under conditions of continuous flow. Our group was the first to evaluate the unraveling behavior of vWF molecules immobilized using avidin-biotin chemistry under conditions of pulsatile flow. Our results demonstrated that the unraveling lengths of vWF are significantly reduced under conditions of pulsatile flow than with continuous flow. Increasing the magnitude of pulsatility up to physiological levels reduces the unraveling lengths of vWF molecules, and the frequency of pulsatility (20–60 cycles/min) does not have a major effect on the maximum or minimum unraveling lengths.[27] These direct vWF molecular observations suggest that vWF conformation changes related to recoiling are on the order of approximately 1 s. Despite the higher peak shear stress, the pulsatile flow does not result in a significant unraveling of surface-bound vWF, which minimizes exposure of the scissile bond within the A2 domain for proteolytic cleavage by ADAMTS13. Conversely, with continuous flow, the constant exposure to shear stress causes extensive and sustained unraveling of vWF leading to greater unraveling lengths, potentially increasing exposure of the scissile bond within the A2 domain for ADAMTS13 mediated proteolytic degradation of vWF into low MW multimers (Figure 3).

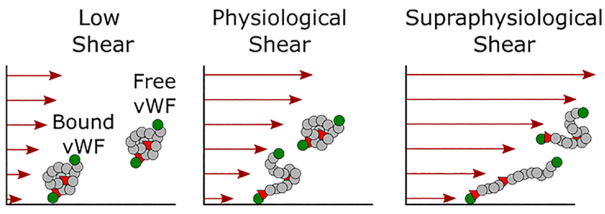

FIGURE 2 Shear-mediated unraveling behavior of surface-bound and free vWF under low, physiological, and supraphysiological flow.

5 | SIGNIFICANCE OF THE ARTERIAL ENDOTHELIUM IN vWF PRODUCTION AND DEGRADATION

In summary, data from published studies by others and our recent work strongly indicate that the arterial endothelium is a critical location where vWF degradation occurs and is a major contributor to the development of AVWS. Specific evidence includes the following 6 observations: (1) Newly released ultra large endothelial vWF is bound to the endothelium prior to release in circulation and requires ADAMTS13 for cleavage from the endothelial surface and release into circulation; this event precedes interaction of vWF in circulation with the CF-VAD

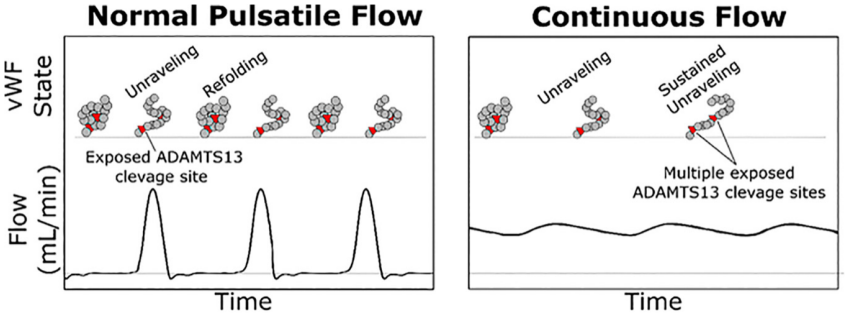

FIGURE 3 Unraveling and recoiling of surface-bound vWF under pulsatile and the continued unraveling of vWF under continuous flow.

impeller.[14–16] (2) The critical shear rate for unraveling of newly released endothelial-bound vWF is <500 s^{-1}, which is significantly lower than shear rates at which globular soluble vWF unravels.[15] (3) Continuous flow results in greater unraveling of surface-bound vWF compared to pulsatile flow. An increase in the magnitude of pulsatile flow to normal pulsatility results in decreased vWF unraveling lengths which suggests that vWF at the endothelial surface undergoes extensive and sustained unraveling under minimally pulsatile flow, exposing additional ADAMTS13 binding sites.[27] (4) Recent studies with mock flow loops and swine models show a dose-response relationship between the degree of pulsatility and vWF; both high MW multimers and vWF collagen-binding activity were boosted with increased levels of pulsatility (but with similar average shear stress), with a strong direct correlation between pulse pressure and high MW multimers.[26] (5) In vitro studies suggest that endothelial production and/or release of vWF is suppressed under continuous flow, and basal levels of vWF are restored following return to normal pulsatile flow.[26] (6) Published studies and our patient data show that circulating vWF levels decrease by >40% in patients 1–3 months following CF-VAD placement.

These observations strongly suggest that the loss or marked decrease in pulsatility associated with CF-VAD support directly affects both the degradation of newly released ultra-large vWF from endothelial cells and the production/release of endothelial vWF. Specifically, newly released ultra-large vWF attached to the surface of the arterial endothelial cells undergoes only partial unraveling and refolding with the normal pulsatile flow and is released following cleavage by ADAMTS13 as high MW multimers into circulation. The partial unraveling behavior potentially protects the scissile bond within the vWF A2 domain, preserving vWF in its high MW form. However, under continuous flow associated with CF-VAD support, endothelial-bound vWF undergoes extensive unraveling, exposing the scissile bond within the vWF A2 domain and potentially additional cleavage sites for ADAMTS13 to facilitate proteolytic degradation into low MW vWF multimers released into circulation and are inefficient in preventing bleeding (Figure 4). Additionally, the change from pulsatile to continuous flow either directly or indirectly has an inhibitory effect on the endothelial release of vWF, which can be restored to basal levels following the reintroduction of pulsatility. Based on published results that suggest that a pulse pressure < 35 mm Hg is a major risk factor for the development of non-surgical bleeding,[38] we suspect that restoration pulse pressure ≥ 35 mm Hg is essential.

6 | IMPLICATIONS FOR CURRENT CF-VADs AND THE DESIGN OF THE NEXT GENERATION OF CF-VADs

CF-VADs continuously unload the native ventricle and significantly diminish arterial pressure pulsatility. Flow modulation is a potential option to reintroduce pulsatility and has been proposed both in literature[39–42] and introduced into clinical practice to augment pulsatility (Lavare cycle in HeartWare HVAD),[43,44] facilitate the opening of the aortic valve (intermittent low speed in Jarvik 2000)[45] or to improve washing (intrinsic pulsatility mechanism with Heartmate 3, (i.e.) 1 pulse every 2 s when operating above 4000 rpm).[46] While Heartmate 3, currently the only FDA-approved CF-VAD, is capable of intermittent speed modulation to provide artificial pulsatility[47,48] the intermittent speed reduction is not representative of physiological pulsatility and clinical studies show limited

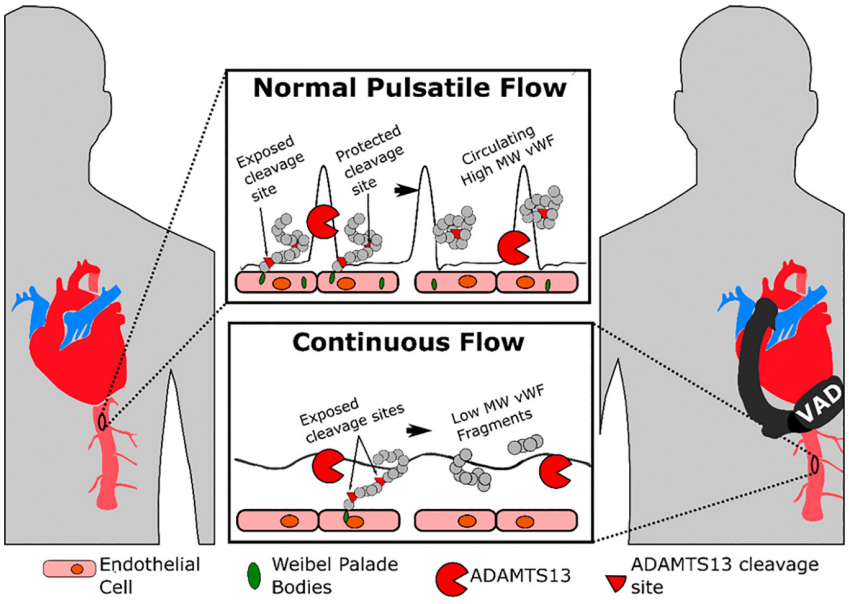

FIGURE 4 Proposed mechanism of AVWS development: Endothelial vWF requires cleavage by ADAMTS13 for vWF release into the circulation. Under pulsatile flow, the unraveling is limited, resulting in the release of high MW vWF whereas under continuous flow, sustained, unraveling results in exposure of the scissile bond in the A2 domain resulting in ADAMTS13 mediated proteolytic degradation into low MW multimers.

benefit in preventing non-surgical bleeding.[23] In addition to Heartmate 3, there are two other pumps, the CorWave LVAD, which relies on a proprietary 'wave membrane' technology, and the EVAHEART®2 CF-VAD, which uses a hydraulically levitated "open vane" impeller. Restoration of near-physiological levels of pulsatility is possible with the Heartmate 3 and the EVAHEART®2 via rapid changes in pump speed[49–51] and the CorWave Membrane LVAD with changes in the frequency of actuation of the membrane.[52] Unlike the native ventricle which can generate peak flows of 30–40 L/min, these devices are limited to peak flow rates of ~10 L/min which limits the level of pulsatility that can be restored. Therefore, pulsatility can be restored in two ways: **(1) Synchronous Flow Modulation (SYN)**: where changes in pump speed are accomplished in synchrony with native myocardial contractions.[53–55] The only variable that can be modulated is the pulse pressure. These devices (Heartmate 3) are limited to peak flow rates of ~10 L/min, which limits the pulse pressure that can be generated with synchronous flow modulation to ≤20 mm Hg.[56] Pulsatile devices in development like the VentriFlo and NuPulseCV iVAS generally produce higher levels of arterial pulsatility than CF-VADs at native heart rates (>60 bpm) and are capable of faster displacement, which can be used to enhance arterial pressure pulsatility and reduce vWF degradation. **(2) Asynchronous Flow Modulation (ASYN)**: where changes in pump speed are accomplished independent of the native heart rate.[57,58] Both pulse pressure and frequency can be modulated to achieve desired levels of pulsatility. Asynchronous modulation at lower VAD flow modulation rates (≤25 bpm) can generate near physiological pulse pressures (~40 mm Hg) even with peak flow rates of 10 L/min.[56] While all three CF-VADs can restore some level of pulsatility, given their peak flow rate limitations, it is unclear as to the levels of pulse pressure and pulse frequency that need to be restored to prevent vWF dysregulation.

Current flow modulation approaches like the Lavare cycle augment pulsatility but is sporadic with prolonged periods of diminished pulsatility that can potentially cause vWF degradation and affect the physiologic release of vWF from endothelial cells. Restoration of normal levels of pulse pressures (>35 mm Hg) on a consistent basis can only be accomplished at lower pulse frequencies (≤25 bpm). A recent publication (Previous AO publication) demonstrated that pulsatility delivered at lower pulse frequencies (20 bpm) did not adversely affect vWF unraveling (similar vWF lengths) compared to normal frequencies. Flow modulation with CF-VADs can cause increases in peak shear rates but previous studies have not demonstrated differences in time-averaged hemolysis or cf_LVAD-induced vWF degradation[42,59] compared to constant pump speed operation. Thus, flow modulation approaches that consistently provide physiologic levels of pulsatility may not only minimize vWF destruction but also maintain physiologic release. Additionally, Lavare cycle and flow modulation with HeartMate 3 have been demonstrated to increase ventricular intracavity washing and washout of the aortic root,[43,60] potentially reducing thrombisis risk. Flow modulation to produce physiologic levels of pulsatility can not only further augment intraventricular and aortic washout, but has the potential to improve intrapump washing. However, blood pumps need to be designed to avoid areas of blood stasis, especially during low flow rates during flow modulation. Studies evaluating the effects of various combinations of pulse pressure and pulse frequency on vWF production and degradation can potentially provide important insights into minimal levels of pulsatility required and optimal pulsatility profiles that can minimize surface-bound vWF degradation and restore basal vWF production.

7 | CONCLUSIONS

In summary, current literature on endothelial vWF production and release suggests a critical role for the arterial endothelium, especially following the loss of pulsatility, in the development of AVWS. Further studies are necessary to elucidate the exact mechanisms through which the complete or partial loss of pulsatility affects various events associated with the production and degradation of vWF. Knowledge gained from these studies will provide insights that can help identify critical levels of pulsatility (pulse pressure, pulse frequency) necessary to maintain normal levels of vWF production and minimize degradation of endothelial-bound vWF. These findings can potentially inform viable strategies to reintroduce pulsatility using current CF-VADs and guide the development of the next-generation VADs to prevent AVWS, which is a major contributing factor to the development of non-surgical bleeding.

AUTHOR CONTRIBUTIONS

All authors contributed to compiling information for this review and writing, editing, and proofreading. Specifically, PS, GAG, and XC were responsible for defining the focus of this article, JKK provided a clinical perspective, ICB generated all of the figures for the review, and EI and KTN contributed to writing and editing.

ACKNOWLEDGMENTS

The authors would like to acknowledge funding support from the National Institute of Health (Grant # R01HL151663) and the National Science Foundation (Grant # 2004475). Ian C. Berg was supported by a T32 training grant from the National Institute of Health (Grant # T32HL129948).

CONFLICT OF INTEREST

None declared.

ORCID

Guruprasad A. Giridharan https://orcid.org/0000-0003-3263-9354
Ian C. Berg https://orcid.org/0000-0003-2302-7006
Esraa Ismail https://orcid.org/0000-0001-8020-6997
Khanh T. Nguyen https://orcid.org/0000-0003-1233-7527
Jana Hecking https://orcid.org/0000-0003-1919-7766
James K. Kirklin https://orcid.org/0000-0002-7861-3267
Xuanhong Cheng https://orcid.org/0000-0002-6331-8572
Palaniappan Sethu https://orcid.org/0000-0002-5794-2037

REFERENCES

1. McLarty A. Mechanical circulatory support and the role of LVADs in heart failure therapy. Clin Med Insights Cardiol. 2015;9:1–5. https://doi.org/10.4137/CMC.s19694
2. Thohan V, Stetson SJ, Nagueh SF, Rivas-Gotz C, Koerner MM, Lafuente JA, et al. Cellular and hemodynamics responses of failing myocardium to continuous flow mechanical circulatory support using the DeBakey-Noon left ventricular assist device: a comparative analysis with pulsatile-type devices. J Heart Lung Transplant. 2005;24:566–75. https://doi.org/10.1016/j.healun.2004.02.017
3. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361:2241–51. https://doi.org/10.1056/NEJMoa0909938
4. Chen Z, Jena SK, Giridharan GA, Koenig SC, Slaughter MS, Griffith BP, et al. Flow features and device-induced blood trauma in CF-VADs under a pulsatile blood flow condition: a CFD comparative study. Int J Numer Method Biomed Eng. 2018;34:e2924. https://doi.org/10.1002/cnm.2924
5. Fraser KH, Zhang T, Taskin ME, Griffith BP, Wu ZJ. A quantitative comparison of mechanical blood damage parameters in rotary ventricular assist devices: shear stress, exposure time and hemolysis index. J Biomech Eng. 2012;134:081002. https://doi.org/10.1115/1.4007092
6. Chen Z, Sun A, Wang H, Fan Y, Deng X. Non-physiological shear stress-induced blood damage in ventricular assist device. Med Novel Technol Devices. 2019;3:100024. https://doi.org/10.1016/j.medntd.2019.100024
7. Cushing K, Kushnir V. Gastrointestinal bleeding following LVAD placement from top to bottom. Dig Dis Sci. 2016;61:1440–7. https://doi.org/10.1007/s10620-016-4123-4
8. Eckman PM, John R. Bleeding and thrombosis in patients with continuous-flow ventricular assist devices. Circulation. 2012;125:3038–47. https://doi.org/10.1161/circulationaha.111.040246
9. Crow S, Chen D, Milano C, Thomas W, Joyce L, Piacentino V 3rd, et al. Acquired von Willebrand syndrome in continuous-flow ventricular assist device recipients. Ann Thorac Surg. 2010;90:1263–9; discussion 1269. https://doi.org/10.1016/j.athoracsur.2010.04.099
10. Uriel N, Pak SW, Jorde UP, Jude B, Susen S, Vincentelli A, et al. Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during Long-term support and at the time of transplantation. J Am Coll Cardiol. 2010;56:1207–13. https://doi.org/10.1016/j.jacc.2010.05.016
11. Franchini M, Mannucci PM. Acquired von Willebrand syndrome: focused for hematologists. Haematologica. 2020;105:2032–7. https://doi.org/10.3324/haematol.2020.255117
12. Bartoli CR. Pathologic von Willebrand factor degradation is a major contributor to left ventricular assist device-associated bleeding: pathophysiology and evolving clinical management. Ann Cardiothorac Surg. 2021;10:389–92.
13. Katz JN, Adamson RM, John R, Tatooles A, Sundareswaran K, Kallel F, et al. Safety of reduced anti-thrombotic strategies in HeartMate II patients: a one-year analysis of the US-TRACE study. J Heart Lung Transplant. 2015;34:1542–8. https://doi.org/10.1016/j.healun.2015.06.018
14. Dong JF, Moake JL, Bernardo A, Fujikawa K, Ball C, Nolasco L, et al. ADAMTS-13 metalloprotease interacts with the endothelial cell-derived ultra-large von Willebrand factor. J Biol Chem. 2003;278:29633–9. https://doi.org/10.1074/jbc.M301385200
15. Dong JF, Moake JL, Nolasco L, Bernardo A, Arceneaux W, Shrimpton CN, et al. ADAMTS-13 rapidly cleaves newly secreted ultralarge von Willebrand factor multimers on the endothelial surface under flowing conditions. Blood. 2002;100:4033–9. https://doi.org/10.1182/blood-2002-05-1401
16. Jin S, Skipwith CG, Shang D, Nagaswami C, Weisel JW, Zheng XL. Proteolytic cleavage of endothelial cell-bound Von Willebrand factor polymers by ADAMTS13 in the absence of flow shear stress. Blood. 2008;112:3913. https://doi.org/10.1182/blood.V112.11.3913.3913
17. Bartoli CR, Kang J, Restle DJ, Zhang DM, Shabahang C, Acker MA, et al. Inhibition of ADAMTS-13 by doxycycline reduces von Willebrand factor degradation during supraphysiological shear stress: therapeutic implications for left ventricular assist device-associated bleeding. JACC Heart Fail. 2015;3:860–9. https://doi.org/10.1016/j.jchf.2015.06.016
18. Bortot M, Ashworth K, Sharifi A, Walker F, Crawford NC, Neeves KB, et al. Turbulent flow promotes cleavage of VWF (von Willebrand factor) by ADAMTS13 (A Disintegrin and metalloproteinase with a Thrombospondin Type-1 motif, member 13). Arterioscler Thromb Vasc Biol. 2019;39:1831–42. https://doi.org/10.1161/ATVBAHA.119.312814
19. Bortot M, Sharifi A, Ashworth K, Walker F, Cox A, Ruegg K, et al. Pathologic shear and elongation rates do not cause cleavage of Von Willebrand factor by ADAMTS13 in a purified system. Cell Mol Bioeng. 2020;13:379–90. https://doi.org/10.1007/s12195-020-00631-2
20. Bartoli CR, Restle DJ, Zhang DM, Acker MA, Atluri P. Pathologic von Willebrand factor degradation with a left ventricular assist device occurs via two distinct mechanisms: mechanical demolition and enzymatic cleavage. J Thorac Cardiovasc Surg. 2015;149:281–9. https://doi.org/10.1016/j.jtcvs.2014.09.031
21. Berk ZBK, Zhang J, Chen Z, Tran D, Griffith BP, Wu ZJ. Evaluation of in vitro hemolysis and platelet activation of a newly developed maglev LVAD and two clinically used LVADs

with human blood. Artif Organs. 2019;43:870–9. https://doi.org/10.1111/aor.13471
22. Kang J, Zhang DM, Restle DJ, Kallel F, Acker MA, Atluri P, et al. Reduced continuous-flow left ventricular assist device speed does not decrease von Willebrand factor degradation. J Thorac Cardiovasc Surg. 2016;151:1747–1754.e1741. https://doi.org/10.1016/j.jtcvs.2016.01.031
23. Geisen U, Brehm K, Trummer G, Beyersdorf F, Berchtold-Herz M, Heilmann C, et al. Improved values for acquired Von Willebrand syndrome and better clinical outcome in patients with Heartmate III compared to Heartmate II. Blood. 2016;128:2582–2.
24. McEniery CM, Wallace S, Mackenzie IS, McDonnell B, Yasmin E, Newby DE, et al. Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans. Hypertension. 2006;48:602–8. https://doi.org/10.1161/01.HYP.0000239206.64270.5f
25. Turner NA, Nolasco L, Ruggeri ZM, Moake JL. Endothelial cell ADAMTS-13 and VWF: production, release, and VWF string cleavage. Blood. 2009;114:5102–11. https://doi.org/10.1182/blood-2009-07-231597
26. Vincent F, Rauch A, Loobuyck V, Robin E, Nix C, Vincentelli A, et al. Arterial pulsatility and circulating von Willebrand factor in patients on mechanical circulatory support. J Am Coll Cardiol. 2018;71:2106–18. https://doi.org/10.1016/j.jacc.2018.02.075
27. Wang Y, Nguyen KT, Ismail E, Donoghue L, Giridharan GA, Sethu P, et al. Effect of pulsatility on shear-induced extensional behavior of Von Willebrand factor. Artif Organs. 2021;46:887–98. https://doi.org/10.1111/aor.14133
28. Lenting PJ, Christophe OD, von Denis CV. Willebrand fac-tor biosynthesis, secretion, and clearance: connecting the far ends. Blood. 2015;125:2019–28. https://doi.org/10.1182/blood -2014-06-528406
29. Rusu L, Minshall R. Endothelial Dysfunction—Old Concepts and New Challenges. London, United Kingdom. InTech; 2018.
30. Galbusera M, Zoja C, Donadelli R, Paris S, Morigi M, Benigni A, et al. Fluid shear stress modulates von Willebrand factor release from human vascular endothelium. Blood. 1997;90:1558–64.
31. Xiong Y, Hu Z, Han X, Jiang B, Zhang R, Zhang X, et al. Hypertensive stretch regulates endothelial exocytosis of Weibel-Palade bodies through VEGF receptor 2 signaling pathways. Cell Res. 2013;23:820–34. https://doi.org/10.1038/cr.2013.56
32. Schwarzl R, Netz RR. Hydrodynamic shear effects on grafted and non-grafted collapsed polymers. Polymers. 2018;10:926.
33. Schneider SW, Nuschele S, Wixforth A, Gorzelanny C, Alexander-Katz A, Netz RR, et al. Shear-induced unfolding triggers adhesion of von Willebrand factor fibers. Proc Natl Acad Sci U S A. 2007;104:7899–903. https://doi.org/10.1073/pnas.0608422104
34. Singh I, Themistou E, Porcar L, Neelamegham S. Fluid shear induces conformation change in human blood protein von Willebrand factor in solution. Biophys J. 2009;96:2313–20. https://doi.org/10.1016/j.bpj.2008.12.3900
35. Themistou E, Singh I, Shang C, Balu-Iyer SV, Alexandridis P, Neelamegham S. Application of fluorescence spectroscopy to quantify shear-induced protein conformation change. Biophys J. 2009;97:2567–76. https://doi.org/10.1016/j.bpj.2009.08.023
36. Siedlecki CA, Lestini BJ, Kottke-Marchant KK, Eppell SJ, Wilson DL, Marchant RE. Shear-dependent changes in the three-dimensional structure of human von Willebrand factor. Blood. 1996;88:2939–50.
37. Wang Y, Morabito M, Zhang XF, Webb E III, Oztekin A, Cheng X. Shear-induced extensional response behaviors of tethered von Willebrand factor. Biophys J. 2019;116:2092–102. https://doi.org/10.1016/j.bpj.2019.04.025
38. Joly JM, el-Dabh A, Kirklin JK, Marshell R, Smith MG, Acharya D, et al. High right atrial pressure and low pulse pressure predict gastrointestinal bleeding in patients with left ventricular assist device. J Card Fail. 2018;24:487–93. https://doi.org/10.1016/j.cardfail.2018.03.003
39. Ising M, Warren S, Sobieski MA, Slaughter MS, Koenig SC, Giridharan GA. Flow modulation algorithms for continuous flow left ventricular assist devices to increase vascular pulsatility: a computer simulation study. Cardiovasc Eng Technol. 2011;2:90–100. https://doi.org/10.1007/s13239-011-0042-x
40. Soucy KG, Giridharan GA, Choi Y, Sobieski MA, Monreal G, Cheng A, et al. Rotary pump speed modulation for generating pulsatile flow and phasic left ventricular volume unloading in a bovine model of chronic ischemic heart failure. J Heart Lung Transplant. 2015;34:122–31. https://doi.org/10.1016/j.healun.2014.09.017
41. Naito N, Nishimura T, Iizuka K, Takewa Y, Umeki A, Ando M, et al. Rotational speed modulation used with continuous-flow left ventricular assist device provides good pulsatility. Interact Cardiovasc Thorac Surg. 2017;26:119–23. https://doi.org/10.1093/icvts/ivx236
42. Naito N, Mizuno T, Nishimura T, Kishimoto S, Takewa Y, Eura Y, et al. Influence of a rotational speed modulation system used with an implantable continuous-flow left ventricular assist device on von Willebrand factor dynamics. Artif Organs. 2016;40:877–83. https://doi.org/10.1111/aor.12666
43. Kumar J, Elhassan A, Dimitrova G, Essandoh M. The Lavare cycle: a novel pulsatile feature of the HVAD continuous-flow left ventricular assist device. J Cardiothorac Vasc Anesth. 2019;33:1170–1. https://doi.org/10.1053/j.jvca.2018.11.029
44. Saeed D, Maxhera B, Sadat N, Petrov G, Albert A, Lichtenberg A. Gastrointestinal bleeding in patients with HeartWare ventricular assist device: does the activation of the Lavare cycle make a difference? ASAIO J. 2018;64:126–8.
45. Kohno H, Matsumiya G, Sawa Y, Fukushima N, Saiki Y, Shiose A, et al. Can the intermittent low-speed function of left ventricular assist device prevent aortic insufficiency? J Artif Organs. 2021;24:191–8. https://doi.org/10.1007/s10047-020-01234-4
46. Bourque K, Cotter C, Dague C, Harjes D, Dur O, Duhamel J, et al. Design rationale and preclinical evaluation of the HeartMate 3 left ventricular assist system for hemocompatibility. ASAIO J. 2016;62:375–83.
47. Bourque K, Dague C, Farrar D, Harms K, Tamez D, Cohn W, et al. In vivo assessment of a rotary left ventricular assist device-induced artificial pulse in the proximal and distal aorta. Artif Organs. 2006;30:638–42. https://doi.org/10.1111/j.1525-1594.2006.00276.x
48. Pirbodaghi T, Cotter C, Bourque K. Power consumption of rotary blood pumps: pulsatile versus constant-speed mode. Artif Organs. 2014;38:1024–8. https://doi.org/10.1111/aor.12323
49. Pirbodaghi T, Axiak S, Weber A, Gempp T, Vandenberghe S. Pulsatile control of rotary blood pumps: does the modulation waveform matter? J Thorac Cardiovasc Surg. 2012;144:970–7. https://doi.org/10.1016/j.jtcvs.2012.02.015
50. Pirbodaghi T, Weber A, Axiak S, Carrel T, Vandenberghe S. Asymmetric speed modulation of a rotary blood pump affects

ventricular unloading. Eur J Cardiothorac Surg. 2013;43:383–8. https://doi.org/10.1093/ejcts/ezs299
51. Saito S, Yamazaki K, Nishinaka T, Ichihara Y, Ono M, Kyo S, et al. Post-approval study of a highly pulsed, low-shear-rate, continuous-flow, left ventricular assist device, EVAHEART: a Japanese multicenter study using J-MACS. J Heart Lung Transplant. 2014;33:599–608. https://doi.org/10.1016/j.healun.2014.02.015
52. Botterbusch C, Barabino N, Cornat F, Jem N, Pruvost R, Marino D, et al. Progress in the development of the pulsatile CorWave LVAD. J Heart Lung Transplant. 2021;40:S104. https://doi.org/10.1016/j.healun.2021.01.338
53. Cox LG, Loerakker S, Rutten MC, de Mol BA, van de Vosse FN. A mathematical model to evaluate control strategies for mechanical circulatory support. Artif Organs. 2009;33:593–603. https://doi.org/10.1111/j.1525-1594.2009.00755.x
54. Letsou GV, Pate TD, Gohean JR, Kurusz M, Longoria RG, Kaiser L, et al. Improved left ventricular unloading and circulatory support with synchronized pulsatile left ventricular assistance compared with continuous-flow left ventricular assistance in an acute porcine left ventricular failure model. J Thorac Cardiovasc Surg. 2010;140:1181–8. https://doi.org/10.1016/j.jtcvs.2010.03.043
55. Shi Y, Lawford PV, Hose DR. Numerical modeling of hemodynamics with pulsatile impeller pump support. Ann Biomed Eng. 2010;38:2621–34. https://doi.org/10.1007/s10439-010-0001-y
56. Ising MS, Sobieski MA, Slaughter MS, Koenig SC, Giridharan GA. Feasibility of pump speed modulation for restoring vascular Pulsatility with rotary blood pumps. ASAIO J. 2015;61:526–32. https://doi.org/10.1097/mat.0000000000000262
57. Bearnson GB, Olsen DB, Khanwilkar PS, Long JW, Allaire PE, Maslen EH. Pulsatile operation of a centrifugal ventricular assist device with magnetic bearings. ASAIO J (American Society for Artificial Internal Organs: 1992). 1996;42:M620–4.
58. Qian KX. Pulsatile impeller heart: a viable alternative to a problematic diaphragm heart. Med Eng Phys. 1996;18:57–66.
59. Chen Z, Jena SK, Giridharan GA, Sobieski MA, Koenig SC, Slaughter MS, et al. Shear stress and blood trauma under constant and pulse-modulated speed CF-VAD operations: CFD analysis of the HVAD. Med Biol Eng Comput. 2019;57:807–18. https://doi.org/10.1007/s11517-018-1922-0
60. Ortiz S, Vu V, Montes R, May-Newman K. Left ventricular flow dynamics with the HeartMate3 left ventricular assist device: effect of inflow cannula position and speed modulation. ASAIO J. 2021;67:1301–11. https://doi.org/10.1097/mat.0000000000001523

How to cite this article: Giridharan GA, Berg IC, Ismail E, Nguyen KT, Hecking J, Kirklin JK, et al. Loss of pulsatility with continuous-flow left ventricular assist devices and the significance of the arterial endothelium in von-Willebrand factor production and degradation. Artif. Organs. 2023;47:640–648. https://doi.org/10.1111/aor.14456