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EDITORIAL COMMENT

Are 3 Aorta Pumps Better Than 1 Transaortic to Preserve Von Willebrand Factor?*

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Mechanical circulatory support (MCS) use is increasing for patients with end-stage heart failure refractory to medical therapy or to facilitate interventional procedure at high risk of hemodynamic instability such as complex percutaneous coronary intervention (PCI).

Patients undergoing MCS are exposed to a high risk of bleeding complications related to their comorbidities, their heart failure condition, and the large-bore vascular access required for implantation or the anticoagulant treatment. Their bleeding risk is also high because of the impact of the pump on the circulating hemostatic factors. All MCS have in common to generate high-shear stress forces on bloodstream and most of them use continuous flow (CF) technology that damp the arterial pulsatility.[1] Von Willebrand factor (VWF) is one of the key primary hemostasis molecules directly impacted by MCS. VWF is a multimeric protein that has the unique ability to feel the bloodstream (shear stress) forces that cause its elongation and expose its cleavage sites to circulating metalloprotease a disintegrin and metalloprotease with thrombospondin type I repeats-13. It results in the loss of the most potent hemostatic-wise high-molecular-weight multimers (HMWM), that is, the acquired von Willebrand disease. Along the degradation of HMWM, it has been shown that the loss of pulsatility seems to mitigate the endothelial release of newly produced HMWM[2] and add to the negative impact of the pump.

Overall, bleeding is the most frequent adverse event associated with CF-MCS and its reduction is an unmet need.[3]

In the study published in this issue of *JACC: Basic to Translational Science*, Georges et al[4] present the results of a novel device (Modulheart) designed to address those limitations of CF-MCS.

The ModulHeart is made to provide circulatory support while generating low shear stress and preserving arterial pulsatility. It is not transvalvular (like Impella devices), but is inserted in the descending aorta and anchored through a self-expandable nitinol scaffold. Inside this latter are 3 microaxial pumps assembled in parallel, allowing a low rotating speed for each (compared with Impella devices) while producing a cumulative high flow rate. Given this aortic position, the ModulHeart does not impact per se the native arterial pulsatility of the left ventricle toward the vessels of the upper part of the body. Altogether those features suggest that the Modulheart is an innovative device that could preserve VWF (**Figure 1**).

Georges et al sought to demonstrate that through a remarkable 3-step translational study: in vitro experiments, in vivo animal modeling, and clinical use of the MCS for high-risk PCI.

First, they used a mock circulatory device (endothelium free) to compare the time course of VWF activity to Impella devices: Impella model CP (high flow rate and high-shear stress) and Impella 5.0 (very high flow rate and high shear stress). They observed a complete VWF activity preservation at 60 minutes, whereas VWF activity decreased of 20% to 30% with Impella pumps. Then, they implanted ModulHeart in 3 swine and they only observed a slight decrease in VWF activity during 60 minutes of support. Finally, those results were corroborated in the first-in-human

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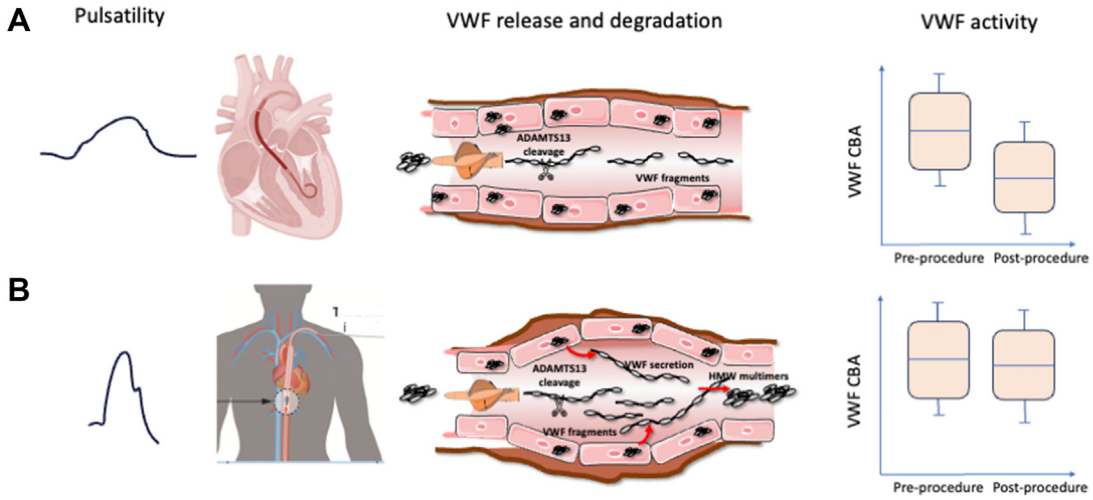
FIGURE 1 Proposed Physiopathology of the Impact of 2 Different Types of Mechanical Circulatory Supports on VWF Activity



(A) Transvalvular pump generating low pulsatility and high shear conditions induces a proteolytic cleavage of von Willebrand factor (VWF) and a decrease in VWF activity, which is not compensated by the endothelial release of new VWF. (B) ModulHeart aorta devices with 3 low-speed rotating pumps mitigating VWF proteolytic cleavage. Its aorta position is not impacting the left ventricle and arterial pulsatility and preserving the release of new VWF from endothelial Weibel Palade bodies (WPBs), which preserves VWF activity. ADAMTS13 = a disintegrin and metalloprotease with thrombospondin type I repeats-13; CBA = collagen-binding activity.

experiences of the pump implantation for high-risk PCI (n = 4), where VWF baseline activity remained nearly unchanged during approximately 50 minutes.

Those exploratory results are promising, but several limitations should be highlighted. The first and foremost is the absence of multimers quantification. Electrophoresis analysis of VWF multimers is the gold standard and the only one allowing to demonstrate the preservation of HMWM. Unfortunately, the authors were not able to performed this analysis and they only measured the VWF collagen-binding assay, which is a surrogate marker of VWF activity that is less sensitive that HMWM electrophoretic quantification, especially in swine models.

This study does not explain mechanisms for the seemingly preservation of VWF activity. Whether this phenomenon is mainly driven by preservation of pulsatility (and release of new endothelial VWF) or by shear stress reduction (reduction of VWF degradation) is unknown. The swine model and first-in-human study were performed in animals and patients with preserved left ventricular function. We can assume that, in cardiogenic shock conditions, the device location in the descending aorta still exposes the majority of the vascular bed (abdominal and lower limbs) to a CF and a subsequent reduction of pulsatility.

The acute setting (60 minutes in vitro and 50 minutes in the first-in-human study) of the blood samples analyses also prevent to extrapolate those results to clinical practice. We cannot exclude that this new MCS device only decreased the speed of HMWM degradation. Indeed, it has been previously observed that time-dependent decrease in VWF collagen-binding activity under other CF-MCS[5] is relevant after 180 minutes. A head-to-head comparison with Impella devices in a similar swine model and in high-risk PCI would have been necessary to demonstrate the incremental value of ModulHeart.

The authors tested the device at low rotating speed. However, they previously reported that ModulHeart at 14,000 rpm increased cardiac output only by <5% in calves and by 25% in patients with mean normal left ventricular function.

Altogether, those points raise questions on the clinical relevance of this type of aortic pump. Whether it is able to provide enough assistance at low rotating speed (14,000 rpm) for patients in cardiogenic shock remain to be demonstrated. This device certainly provides partial support that could be

enough for high-risk PCI, but VWF degradation and acquired von Willebrand disease are not really a concern in this setting.

Overall, the authors who are also innovators and inventors of the pump, should be strongly encouraged and congratulated to leading a such elegant study. More research is needed to demonstrate that this new MCS provide a better hemocompatibility profile than others devices and play as a game changer in the landscape of MCS devices.

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