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ORIGINAL RESEARCH - PRECLINICAL

Preservation of von Willebrand Factor Activity With the ModulHeart Device

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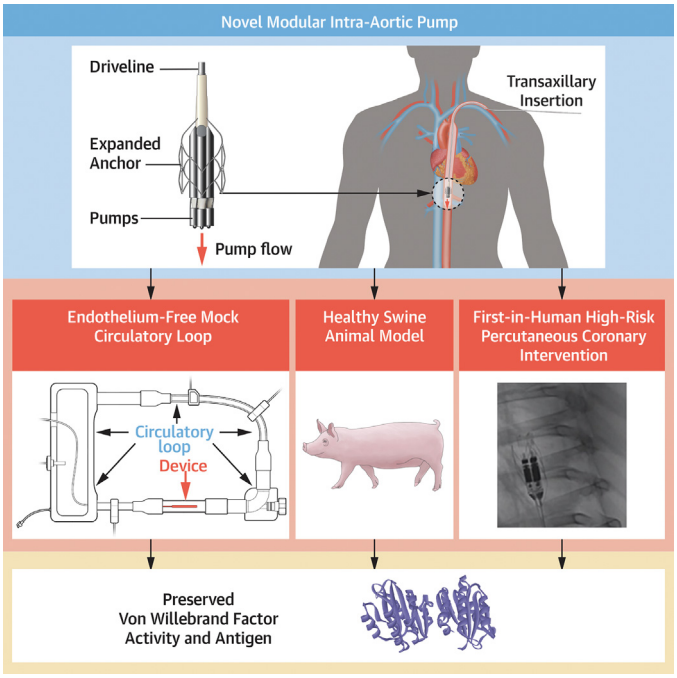
VISUAL ABSTRACT



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HIGHLIGHTS

- **vVWF destruction is common with currently available surgical and transcatheter heart pumps, and is associated with a significant increase in bleeding risk.**
- **ModulHeart (Puzzle Medical Devices Inc) is a novel percutaneous aortic flow entrainment device using 3 endovascular pumps assembled in parallel.**
- **In contrast to current single transcatheter pumps, baseline VWF activity was maintained with ModulHeart after 60 minutes in a mock circulatory loop.**
- **ModulHeart support resulted in preservation of VWF activity in vivo.**
- **VWF activity remained stable in patients undergoing protected high-risk percutaneous coronary intervention with the ModulHeart device.**

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ANOVA = analysis of variance

CBA:Ag = collagen binding activity:antigen

LVAD = left ventricular assist device

PCI = percutaneous coronary intervention

VWF = von Willebrand factor

SUMMARY

von Willebrand Factor (VWF) destruction is common with current heart pumps. This study evaluates VWF activity with ModulHeart, a novel device using 3 micropumps in parallel. In model 1, ModulHeart was compared with Impella devices in vitro. In model 2, 3 healthy swine received ModulHeart. Model 3 includes VWF data from patients who underwent protected percutaneous coronary intervention with ModulHeart. In models 1, 2, and 3, ModulHeart resulted in preservation of VWF, whereas there was a 27% and 19% reduction in VWF activity with the Impella CP and 5.0, respectively. ModulHeart features a unique design and demonstrated preservation of VWF activity. (J Am Coll Cardiol Basic Trans Science 2024;9:33–42)

Continuous-flow left ventricular assist devices (LVADs), both temporary and durable, alter von Willebrand factor (VWF) physiology by: 1) accelerating VWF proteolysis due to supraphysiologic shear stress; and 2) down-regulating release of VWF by the vascular bed due to loss of arterial pulsatility.[1-5] Clinically, this translates into a significant increase in bleeding risk, further aggravated by the need for anticoagulation to prevent pump thrombosis. In fact, gastrointestinal bleeding is the most frequent complication associated with durable LVADs.[6,7] Clinical management is challenging due to the lack of targeted therapy. There is strong evidence that pathologic VWF metabolism not only increases the risk of bleeding but also leads to gastrointestinal angiodysplasia.[1,3,4,7] Development of new-generation devices designed to minimize shear stress and preserve arterial pulsatility could lead to substantial improvement in patient outcomes and reduce the burden of LVAD therapy.[6,8]

The ModulHeart device (Puzzle Medical Devices Inc) is an intra-aortic flow-entrainment pump for cardiorenal support in acute and chronic heart failure. The device features a modular construct with the assembly of 3 microaxial endovascular pumps in parallel to provide a higher degree of flow at lower speeds compared with a single pump, resulting in lower blood element damage (**Figure 1A**). A self-expandable anchor secures the device in the abdominal aorta (**Figure 1B**). Recently, the ModulHeart device was evaluated in a first-in-human study in patients undergoing high-risk percutaneous coronary intervention (PCI).[9] ModulHeart resulted in improved hemodynamic and renal parameters with no signs of hemolysis or thrombosis.

The current study summarizes preclinical and clinical evaluation of VWF activity with the ModulHeart device. Specifically, we describe 3 experimental designs: 1) an in vitro mock circulatory loop where ModulHeart was compared with predicate devices; 2) an animal model to evaluate VWF activity in response to ModulHeart support in vivo; and 3) a clinical model to report VWF activity in patients who received ModulHeart therapy during high-risk PCI.

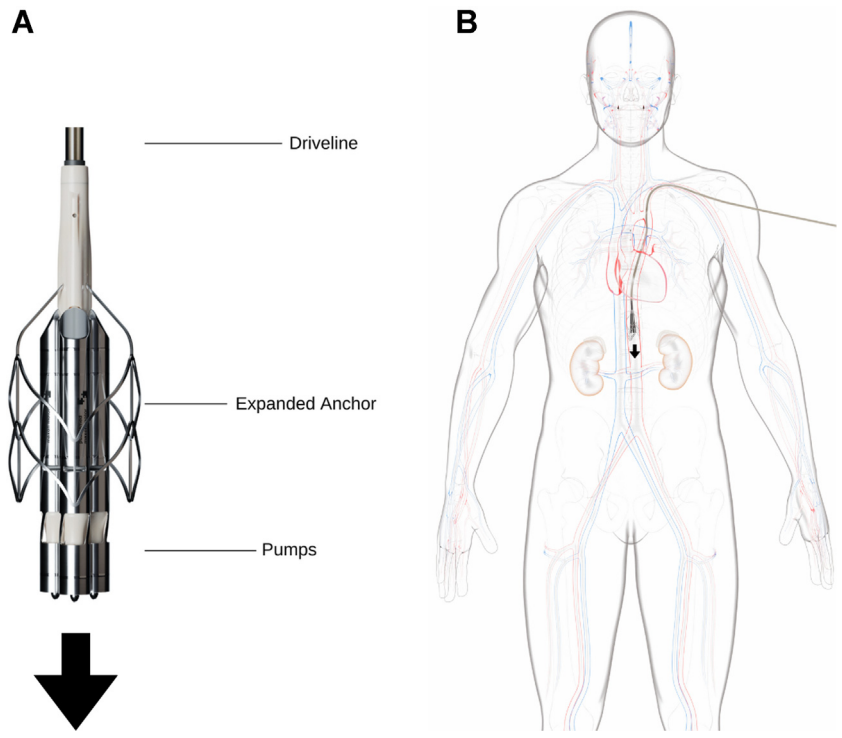
METHODS

The 3-part study design is presented in **Figure 2**. In model 1, the ModulHeart device was inserted into an endothelial-free mock circulatory loop and operated for 60 minutes. In this model, the ModulHeart device was compared with the Impella CP and Impella 5.0 (Abiomed) at matching flow rates. In model 2, 3 healthy swine received the ModulHeart device; blood samples were drawn after 60 minutes of pump support at a constant speed of 14,000 rpm. In model 3, we studied VWF activity in patients who underwent protected high-risk PCI with ModulHeart. The device was set at a constant speed of 14,000 rpm, and blood samples were drawn preprocedure, postprocedure, and at 24 hours.

The in vivo study (model 2) was performed at the AccelLAB center (Charles River Laboratories Inc) and was approved by the AccelLAB Animal Care and Use Committee. The first-in-human study (model 3) was performed at the Sanatorio Italiano, Asuncion, Paraguay. The study was approved by the Paraguay National Board of Health Bioethics Committee, and each patient provided informed consent.

MODEL 1: VWF ACTIVITY IN A MOCK CIRCULATORY LOOP. In model 1, we evaluated VWF activity in an endothelium-free, nonpulsatile circulatory loop. Four custom circulatory loops were built featuring a 22-mm diameter tube to simulate intra-aortic pump positioning (**Figure 3**). The loops were immersed in a 37°C water bath. Fresh frozen plasma (Sierra Medical) from 4 healthy calves was pooled and divided into 12, 350-mL aliquots (4 conditions, n = 3). One loop was fitted with the Impella CP, 1 was fitted with the Impella 5.0, 1 was fitted with the ModulHeart device,

FIGURE 1 **ModulHeart Device**



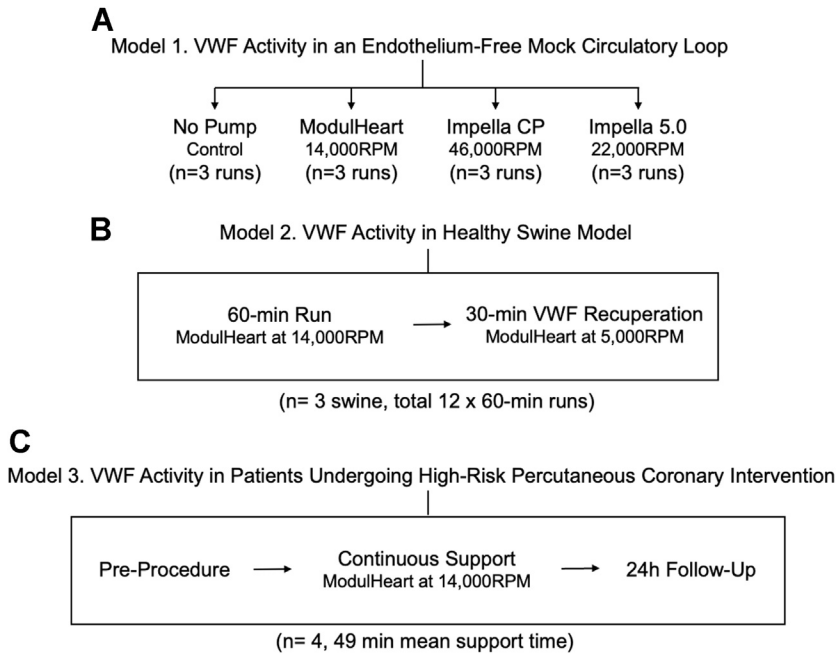
(A) The ModulHeart device in its assembled configuration with the 3 pumps anchored in parallel within a self-expandable anchor (expanded). (B) The ModulHeart device implanted transaxillary and positioned in the proximal abdominal aorta. The arrows indicate the direction of pump outflow.

and the fourth loop contained no pump (negative control). Flow was measured using a clamp-on flow probe (Transonic) to achieve equivalent flow rates with each device. The ModulHeart was operated with each of the 3 pumps running at 14,000 rpm; the Impella CP and Impella 5.0 were set at 46,000 rpm and 22,000 rpm, respectively. All loops were run simultaneously, and plasma samples were drawn from the loop reservoir at baseline (before pump start), and at 15, 30, and 60 minutes of pump operation.

MODEL 2: VWF IN A HEALTHY SWINE MODEL. In model 2, 3 healthy swine 90 to 120 kg were screened for femoral arteries >7 mm in diameter and descending aorta >20 mm using computed tomography angiography. Animals were anesthetized and received heparin to achieve an activated clotting time >250 seconds. Right femoral artery access was achieved via surgical cutdown. The ModulHeart device was delivered via a 22-F delivery sheath in the descending aorta above the renal arteries. The device was set at a constant speed of 14,000 rpm for 60 minutes. Blood samples were drawn at baseline (before pump start), and at 5, 15, 30, 45, and 60 minutes of support. Multiple (3 to 5) 60-minute runs were performed in each animal, for a total of 12 runs. A 30-minute recovery period with the pump at idle (5,000 rpm) was allowed for VWF to regenerate between each 60-minute run. The recovery period was shorter than what was previously described (60 minutes) because the device was expected to generate a lower level of blood damage than predicate devices.[2] At the end of the procedure, the device was removed, and the animals were terminated.

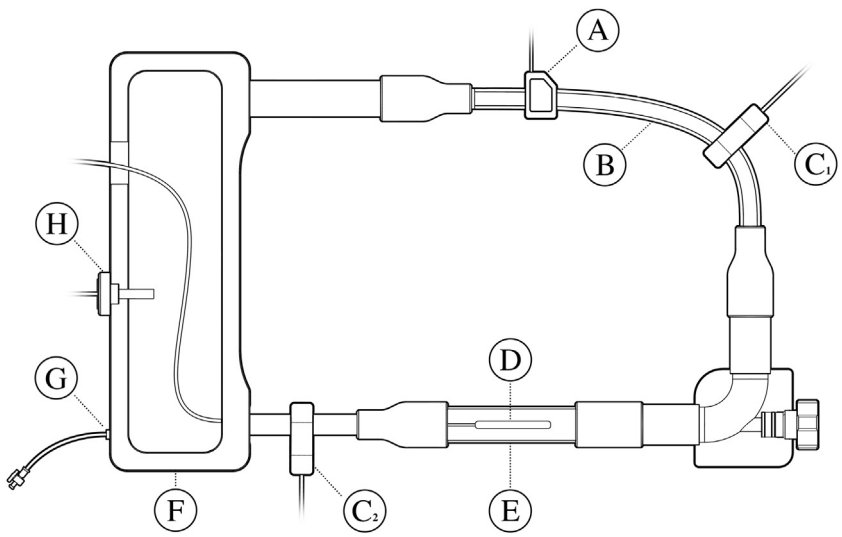
MODEL 3: VWF ACTIVITY IN PATIENTS UNDERGOING HIGH-RISK PCI. The first-in-human experience with the ModulHeart device is detailed elsewhere.[9] Briefly, 4 high-risk PCI patients received the ModulHeart device for a mean duration of 49 ± 8 minutes. The ModulHeart was set at 14,000 rpm. Blood samples were harvested preprocedure, immediately postprocedure (after pump removal), and at 24 hours. No device malfunction, or procedural or device-related adverse events were recorded. All 4 patients were alive at 30 days.

FIGURE 2 Study Design



(A) Model 1: von Willebrand factor (VWF) activity over pump support time (60 minutes) was evaluated in an endothelium-free mock circulatory loop. The ModulHeart device was compared to a no pump control, and 2 Impella devices (CP and 5.0). (B) Model 2: VWF activity was assessed in an in vivo swine model during multiple 60-minute cycles with the ModulHeart device at 14,000 rpm. (C) Model 3: VWF was evaluated in 4 patients undergoing high-risk percutaneous coronary intervention.

FIGURE 3 Custom Mock Circulatory Loop Set-Up



Four identical mock circulatory loops were built to simulate intra-aortic placement of circulatory support devices. Loops were fitted with the ModulHeart device, Impella CP, Impella 5.0, and 1 loop received no device (negative control). All devices were run simultaneously at matching flow rates. Shown in the loop diagram are (A) clamp-on flow meter, (B) 9.5-mm tubing, (C_1 and C_2) flow restriction clamps, (D) device being tested, (E) 22-mm tubing, (F) loop reservoir, (G) sampling port, and (H) temperature sensor.

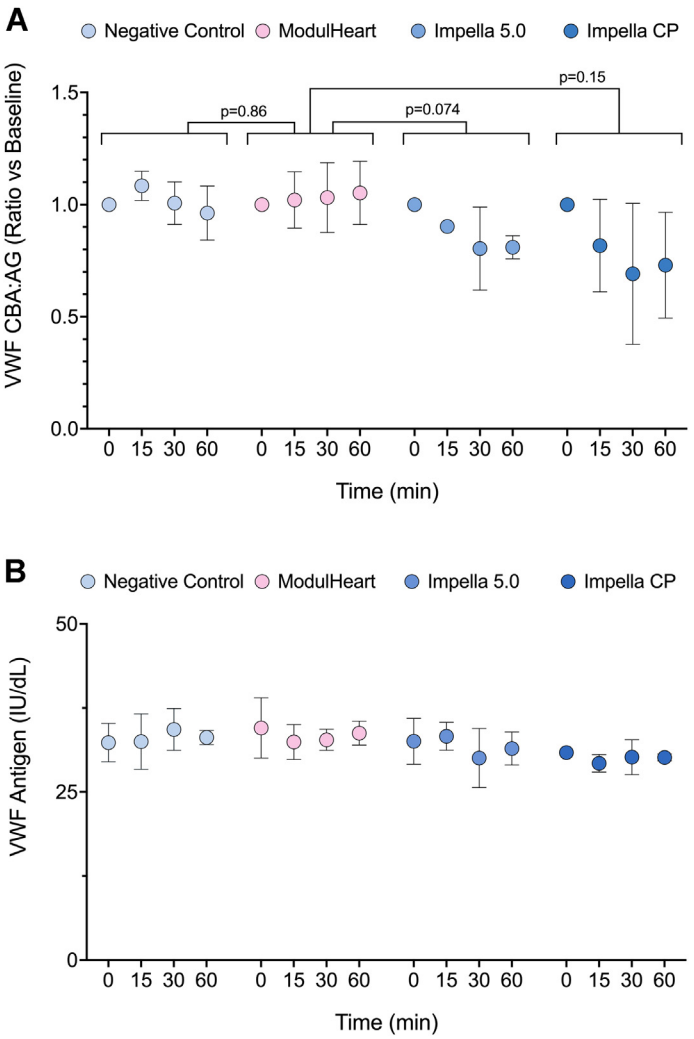
VWF ANALYSIS. VWF degradation is detectable after only 30 minutes of exposure to supraphysiological shear stress.[2] We chose a 60-minute time course to evaluate VWF activity in all models. Blood samples were centrifuged at 3,000 ×*g* for 15 minutes to obtain platelet-poor plasma, aliquoted, and stored at −80°C. VWF antigen levels and collagen binding activity were assessed by enzyme-linked immunosorbent assay using commercially available kits (Diapharma). Individual samples were analyzed as triplicates.

STATISTICAL ANALYSIS. VWF activity is presented as the antigen on collagen binding activity ratio (CBA:Ag) and compared with baseline (VWF CBA:Ag ratio vs baseline). All results are expressed as mean ± SD, unless stated otherwise. Distribution was evaluated using the Shapiro-Wilk or Kolmogorov-Smirnov tests. Paired analyses were performed using the paired Student *t*-test or Wilcoxon signed rank test, as appropriate. Multiple time comparisons were performed using repeated measures 1-way analysis of variance (ANOVA). In model 1, devices were compared using repeated measures 2-way ANOVA with time and device as factors. Data were analyzed using Prism (GraphPad Software). All measures were tested at a significance level of 0.05. There were no missing values.

RESULTS

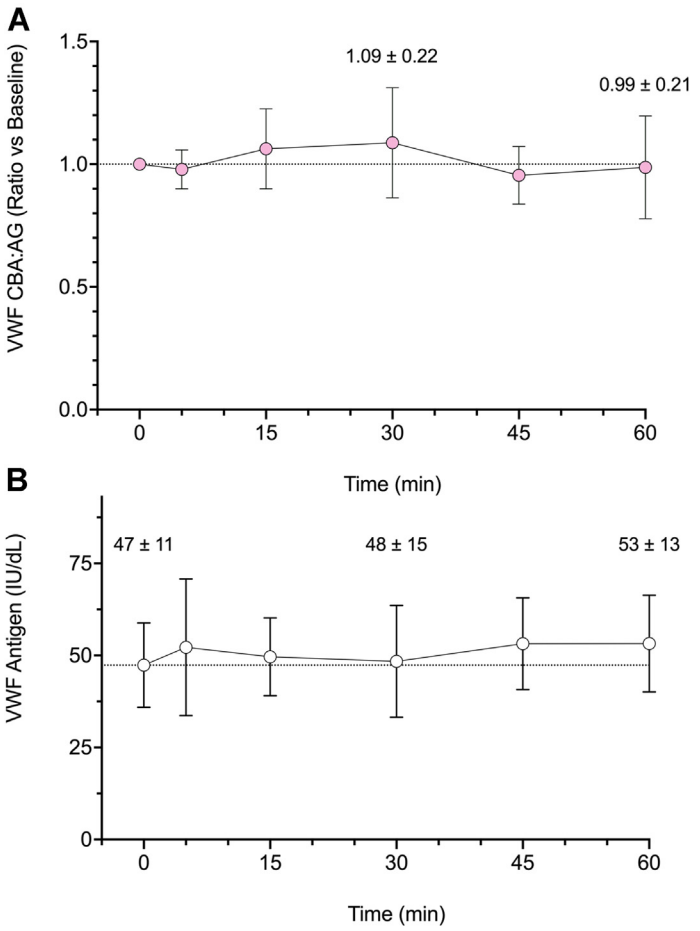
MODEL 1: VWF ACTIVITY IN A MOCK CIRCULATORY LOOP. In the negative control loop (loop with no pump), there was no change in VWF activity over time (mean VWF CBA:Ag ratio vs baseline of 1.08 ± 0.07, 1.01 ± 0.10, and 0.96 ± 0.12 at 15, 30, and 60 minutes, respectively; repeated measures 1-way ANOVA $P = 0.23$) (Figure 4A). Similar to the negative control loop, VWF activity remained stable over time with the ModulHeart device at 14,000 RPM (VWF CBA:Ag ratio to baseline of 1.02 ± 0.12, 1.03 ± 0.156, and 1.05 ± 0.14 at 15, 30, and 60 minutes, respectively; repeated measures 1-way ANOVA $P = 0.79$). There was no significant difference between VWF activity with the ModulHeart device compared with the no pump control (repeated measures 2-way ANOVA $P = 0.86$). VWF activity decreased rapidly (after 15 minutes) with both Impella devices. In the Impella CP loop, VWF CBA:Ag ratio to baseline was reduced to 0.82 ± 0.21, 0.69 ± 0.31, and 0.73 ± 0.24 at 15, 30, and 60 minutes, respectively (repeated measures 1-way ANOVA $P = 0.22$). The Impella 5.0 also resulted in reduction of VWF activity over time (VWF CBA:Ag ratio to baseline 0.90 ± 0.03, 0.80 ± 0.19, and 0.81 ± 0.05 at 15, 30, and 60 minutes, respectively; repeated measures 1-way ANOVA $P = 0.17$). The difference in time course of the VWF activity between devices did not reach statistical significance (repeated measures 2-way ANOVA ModulHeart vs Impella CP, $P = 0.15$; ModulHeart vs Impella 5.0, $P = 0.074$; Impella CP vs 5.0, $P = 0.57$). There was no significant

FIGURE 4 VWF Parameters Measured in an Endothelium-Free Continuous-Flow Circulatory Loop



(A) There was no significant difference between von Willebrand factor (VWF) activity with the ModulHeart device compared with the no pump control ($P = 0.86$; repeated measures 2-way analysis of variance with time and groups as factors). VWF activity was 1.05 ± 0.14 vs baseline levels after 60 minutes of ModulHeart operation at 14,000 RPM. There was a 27% loss in VWF activity with the Impella CP and 19% loss with the Impella 5.0 at 60 minutes. Level of change in VWF activity over time between the devices did not reach statistical difference. (B) VWF antigen levels remained stable over time in each experimental setup (repeated measures 1-way analysis of variance $P = 0.49$, $P = 0.46$, $P = 0.17$, and $P = 0.51$ for negative control, ModulHeart, Impella 5.0, and Impella CP, respectively). Results are presented as mean ± SD.
CBA:Ag = collagen binding activity:antigen.

FIGURE 5 Change in VWF Parameters in Swine Under ModulHeart Support



(A) There was no change in VWF activity after 60 minutes of ModulHeart support at 14,000 RPM in 3 healthy swine (repeated measures 1-way analysis of variance $P = 0.13$). (B) VWF antigen levels were preserved over time (repeated measures 1-way ANOVA $P = 0.40$). Results are presented as mean ± SD. Abbreviations as in Figure 4.

variation in VWF antigen levels over time in the negative control loop (mean of 32 ± 3 IU/dL at baseline vs 33 ± 1 IU/dL after 60 minutes) or the 3 experimental loops (baseline vs 60 minutes: 35 ± 4 vs 34 ± 2 IU/dL, 33 ± 3 vs 31 ± 2 IU/dL, and 31 ± 1 vs 30 ± 1 IU/dL for ModulHeart, Impella 5.0, and Impella CP, respectively) (Figure 4B).

MODEL 2: VWF ACTIVITY IN HEALTHY SWINE MODEL. In all 3 animals, the device was successfully implanted at a satisfactory location above the renal arteries with no detectable movement between time of delivery and retrieval. No procedural or device-related adverse events were recorded. VWF activity was stable between each new 60-minute cycle start (repeated measures 1-way ANOVA $P = 0.17$). ModulHeart at 14,000 RPM did not result in a significant change in VWF activity over time compared with baseline (Figure 5A). VWF CBA:Ag ratio vs baseline was 0.98 ± 0.08, 1.06 ± 0.16, 1.09 ± 0.22, 0.96 ± 0.12, and 0.99 ± 0.21 at 5, 15, 30, 45, and 60 minutes, respectively (repeated measures 1-way ANOVA $P = 0.13$). VWF antigen also remained stable over time (47 ± 11, 48 ± 15, and 53 ± 13 IU/dL at baseline, 30 minutes, and 60 minutes, respectively; repeated measures 1-way ANOVA $P = 0.40$) (Figure 5B).

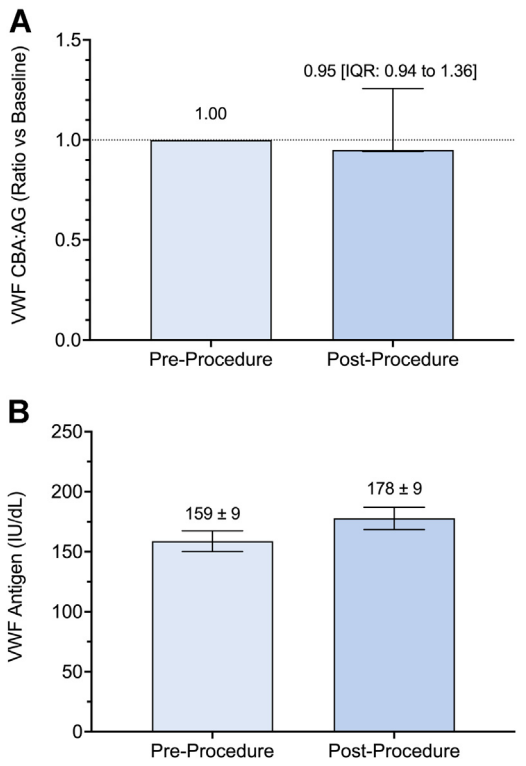
MODEL 3: VWF ACTIVITY IN PATIENTS UNDERGOING HIGH-RISK PCI. ModulHeart was successfully implanted in 4 patients undergoing high-risk PCI. Mean duration of support was 49 ± 8 minutes (range 46 to 58 minutes). ModulHeart did not result in a reduction of VWF activity at the end of the procedure compared with baseline (median VWF CBA:Ag ratio vs baseline 0.95 [IQR: 0.94-1.36], Wilcoxon signed rank test $P = 0.88$) (Figure 6A). Levels of VWF antigen were also preserved postprocedure compared with baseline (mean of 159 ± 9 IU/dL vs 178 ± 9 IU/dL; paired t-test $P = 0.08$) (Figure 6B).

DISCUSSION

The present study evaluated VWF activity with the ModulHeart device in 3 experimental models: an in vitro mock circulatory loop (model 1), a healthy swine model (model 2), and first-in-human implantations in high-risk PCI patients (model 3). The key findings of these studies are as follows: 1) compared with single microaxial pumps, ModulHeart demonstrated intrinsic preservation of VWF activity in an endothelium-free mock circulatory loop; 2) VWF activity was preserved throughout ModulHeart support in vivo; and 3) the unique modular pump design resulted in normal VWF activity in patients who received the ModulHeart device.

ModulHeart DEVICE KEY CHARACTERISTICS. ModulHeart is a unique modular device consisting of 3 individual endovascular pumps delivered in series and assembled in parallel inside a self-expandable anchor. Due to the combination of multiple pumps in parallel, the device can generate greater flows at lower speeds compared with single transcatheter pumps. With each pump running at 14,000 rpm, the device can generate 4 L/min of flow and up to 10 L/min with each pump set at 25,000 rpm. Each microaxial pump is driven by an independent implantable motor, which is fully enclosed into a titanium housing and magnetically coupled to the impeller. No purge solution is required. The pumps are docked into a large cell-sized self-expandable nitinol anchor to ensure stability and allowing for

FIGURE 6 VWF in Patients Undergoing High-Risk PCI With ModulHeart Support



(A) Postprocedure von Willebrand factor (VWF) activity remained unchanged compared with preprocedure levels (Wilcoxon signed-rank test $P = 0.88$). (B) There was no significant variation in VWF antigen levels postprocedure (paired t-test $P = 0.078$). Results are presented as mean ± SD. PCI = percutaneous coronary intervention.

uninterrupted support during patient ambulation. Additionally, compared with transvalvular devices, implantation of the ModulHeart device in the abdominal aorta conceptually nullifies the risks of thromboembolic strokes and potentially enables the device to be used in patients with severely calcified/stenotic aortic valves, mechanical aortic valves, or left ventricle thrombus or patients with significant aortic insufficiency. Other advantages of the ModulHeart device include percutaneous delivery and removal, and an axillary driveline that allows for patient ambulation.

ModulHeart is intended to provide cardiorenal support in heart failure patients by mechanically augmenting renal blood flow and improving cardiac function mainly via a reduction in left ventricular afterload. The device was successfully used to support patients undergoing high-risk percutaneous coronary intervention[9] and is currently being investigated as an adjunct treatment to improve decongestion in patients with acute decompensated heart failure refractory to diuretic therapy. Importantly, future studies will evaluate the feasibility of chronic support with the device for indications such as bridge-to-transplant and destination therapy. Key conceptual design advantages over conventional durable LVADs include the potential for a reduction in stroke risk (pump outflow downstream of carotid arteries) and gastrointestinal bleeding (preservation of VWF and native pulsatility), percutaneous implantation and explanation, and avoidance of sternotomy in patients awaiting a heart transplant. However, the exact patient population who will benefit from cardiorenal support with the ModulHeart device remains to be determined, and patient selection for future studies should take into consideration advantages set forth in this section and intrinsic design limitations (ie, indirect left ventricular unloading).

INTRINSIC CAPACITY TO PRESERVE VWF ACTIVITY. We first investigated the time course of VWF activity in a custom endothelium-free continuous-flow mock circulatory loop. Because there is no potential for new VWF multimer release in this experimental set up (absence of vascular bed), the model evaluates the device's intrinsic capacity to preserve or degrade existing VWF multimers, and VWF antigen levels are expected to remain stable.[2] VWF antigen levels remained stable in all circulatory loops; however, compared with the Impella CP and Impella 5.0 devices, ModulHeart demonstrated complete VWF activity preservation over time similar to the control with no pump (0% loss after 60 minutes). The greatest decrease in VWF activity was found with the Impella CP (~30% loss after 60 minutes) followed by the Impella 5.0 (~20% loss after 60 minutes). These results are in line with prior investigations that had previously demonstrated even stronger reduction in VWF activity with the Impella devices in a mock circulatory loop (>50% after 60 minutes or less).[2,10] Compared with other blood elements, VWF is particularly susceptible to scalar shear stress. It has been proposed that accelerated proteolysis of VWF multimers by the enzyme ADAMTS-13 occurs at scalar shear stress levels of <5 Pa.[11] VWF multimers elongate in response to shear stress, exposing cleavage sites to the metalloprotease ADAMTS-13, resulting in acquired von Willebrand disease.[1,4] By comparison, platelet activation occurs at scalar shear stress levels of >50 Pa, and the threshold for hemolysis is approximately 150 Pa.[1,12] VWF preservation with the ModulHeart device most likely results from lower

rotational speeds due to its unique configuration with 3 pumps assembled in parallel. As pump speed is decreased, scalar shear stress on fluid passing through the pump also decreases.[2,13] Although all devices were set at an equivalent flow rate, the greatest loss in VWF activity was observed with the Impella CP, which was set at the highest speed (46,000 rpm), followed by the Impella 5.0, which had an intermediate speed (22,000 rpm). The ModulHeart device had the lowest speed (14,000 rpm) and resulted in no loss of VWF activity. Of note, this relation between pump speed and scalar shear stress requires pumps of similar diameter and geometry. Scalar shear stress also increases with pump radius because of an increase in tangential force at the tip of the blade. Therefore, pathologic VWF degradation is also observed both clinically and in vitro with durable LVAD running at relatively low rpm (3,000 to 9,000 rpm).[1,10,11,13-16]

IN VIVO PRESERVATION OF VWF ACTIVITY. We further investigated VWF activity in 3 healthy swine undergoing ModulHeart implantation. In all cases, the ModulHeart device ran uneventfully. There were no significant changes in VWF antigen level or CBA:Ag ratio during the 60 minutes of support with ModulHeart compared with baseline (99% of baseline VWF CBA:Ag ratio at 60 minutes). Although there was no direct comparison to predicate devices in this experimental setup, the Impella 5.0 was used in a similar swine model by Vincent et al.[2] The group studied the effect of arterial pulsatility on VWF activity using different configurations of Impella devices in transvalvular and aortic position. Significant reductions in VWF activity after 30 minutes were seen in all Impella conditions, and loss of arterial pulsatility was found to be associated with significant decline in VWF activity and antigen.[2] Potential mechanism for stability of VWF activity with the ModulHeart device include: 1) intrinsic pump characteristics resulting in lower shear stress; and 2) preservation of arterial pulsatility due to its intra-aortic position (indirect left ventricular unloading).

PRESERVATION OF VWF AND IMPLICATIONS FOR MECHANICAL CIRCULATORY SUPPORT IN HEART FAILURE. Similar to what was observed in the preclinical evaluation of the device, normal VWF activity and antigen levels were preserved in patients who received ModulHeart support during high-risk PCI. VWF metabolism is closely regulated by rheologic conditions of the blood, and loss of VWF activity is observed after only 5 minutes of mechanical circulatory support.[2] In this first-in-human experiment, patients received ModulHeart therapy for ~50 minutes with no signs of significant reduction in VWF activity (median of 95% baseline levels [IQR: 94%-136%]). These findings suggest that intra-aortic fluid entrainment with the ModulHeart does not lead to pathologic VWF metabolism, which is associated with a high risk of bleeding and angiodysplasia.[3,7]

Current-generation durable LVADs are associated with 0.25 gastrointestinal bleeding events/patient-year (>3× the odds with pulsatile devices).[7,17] Because there is no targeted treatment for LVAD-induced coagulopathy, clinical management is challenging.[5] Additionally, repeated transfusions may limit patient eligibility for transplantation. Invasive evaluation can be useful in some cases, but angiodysplasia is often a diffuse along the gastrointestinal tract. As a result, 40% of patients have repeat episodes, and bleeding location remains unknown in ~20% of cases.[7] Other management strategies include withdrawal of antiplatelet therapy, reduction of anticoagulation targets, or even temporary discontinuation of anticoagulation; however, this conceptually increases the risk of thromboembolic complications. Experience with agents such as octreotide and thalidomide remain anecdotal,[1,7] but other novel strategies such as monoclonal antibodies against the enzyme ADAMTS13 are being developed.[18]

The best strategy to reduce the incidence of bleeding complications may be to prevent pathologic degradation of VWF by designing new-generation devices that minimize shear stress. ModulHeart features a unique modular design with 3 endovascular pumps inserted percutaneously in series and assembled in parallel. This allows generation of greater flow at lower speeds compared with single microaxial pumps. The device also preserves native pulsatility (a trigger for release of VWF by the vascular bed) due to its intra-aortic positioning.[2] Importantly, these findings suggest that ModulHeart may lead to a reduction in bleeding events in heart failure patients.

STUDY LIMITATIONS AND FUTURE DIRECTIONS. In this acute study, we demonstrated stability of VWF activity with the ModulHeart device; however, some limitations of the current study should be acknowledged. First, the current studies were performed with the initial 22-F transfemoral version of the device. There may be small variations with the upcoming <16-F transaxillary device. Second, although loss of VWF activity can be seen within a few (5) minutes after initiation of mechanical circulatory support,[2] longer-term evaluation is required to

determine whether VWF metabolism remains normal during long-term support with ModulHeart. Third, we did not perform VWF multimeric structure analysis using electrophoresis and immunoblotting. Instead, we report antigen and collagen binding assay results, which have been extensively used to evaluate high shear stress-induced VWF syndrome, are more sensitive than other techniques, more easily performed and reproduced, and importantly, enable quantitative assessment of VWF quantity and activity.[1,2,10,19,20] In our in vitro model, loss of VWF activity despite VWF antigen stability with the Impella device was detected as previously described,[2,10,21] whereas activity and antigen levels remained stable with the ModulHeart device. In the event of a decrease in VWF activity with the ModulHeart device, an electrophoretic pattern could have confirmed the loss of high-molecular weight multimers, as a type 2a pattern (low level of high-molecular-weight multimers) is expected in the LVAD patient.[1,2] However, VWF activity with ModulHeart support remained stable compared with baseline in all 3 experimental models. Consequently, although our results do not provide unequivocal proof that high-molecular-weight multimers are preserved, they do support stability of VWF activity during acute ModulHeart support, which remains an important and clinically relevant finding.

CONCLUSIONS

The unique modular design of the ModulHeart device demonstrated a lack of intrinsic VWF degradation in a mock circulatory loop and preservation of normal VWF activity both in vivo (animal) and clinically (human). These findings are important and may lead to improved safety and efficacy of short- and longer-term mechanical circulatory support among patients with advanced heart failure.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The current study was supported by Puzzle Medical Devices Inc. Dr Georges has equity in Puzzle Medical Devices Inc. Mr Trudeau has equity in and is an employee of Puzzle Medical Devices Inc. Dr Potvin has been a consultant for Puzzle Medical Devices Inc. Dr Généreux has been a consultant for Abbott Vascular, Abiomed, BioTrace Medical, Boston Scientific, CARANX Medical, Cardiovascular System Inc., Edwards Lifesciences, GE Healthcare, iRhythm Technologies, Medtronic, Opsens, Pi-Cardia, Puzzle Medical, Saranas, Shockwave, Siemens, Soundbite Medical Inc., Teleflex, and 4C Medical; has received speaker fees from Abbott Vascular, Abiomed, BioTrace Medical, Edwards Lifesciences, Medtronic, and Shockwave; has served as a principal investigator for trials funded by Cardiovascular System Inc., Edwards Lifesciences, and 4C Medical; has been a proctor for and received research funding from Edwards Lifesciences; and holds equity in Pi-Cardia, Puzzle Medical, Saranas, and Soundbite Medical Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A novel percutaneous aortic flow entrainment device using 3 endovascular pumps assembled in parallel, with each pump running at a lower speed than would a single-pump device, resulted in preservation of von Willebrand factor activity in vitro, in vivo, and in human clinical use.

TRANSLATIONAL OUTLOOK: Whether a novel modular heart pump design with improved preservation of von Willebrand factor activity may reduce the risk of bleeding and improve outcomes in heart failure patients requiring acute and chronic mechanical circulatory support remains to be determined.

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