Artificial Organs

Influence of a Rotational Speed Modulation System Used With an Implantable Continuous-Flow Left Ventricular Assist Device on von Willebrand Factor Dynamics

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Abstract: We have developed a rotational speed (RS) modulation system for a continuous-flow left ventricular assist device (EVAHEART) that can change RS in synchronization with a patient's electrocardiogram. Although EVAHEART is considered not to cause significant acquired von Willebrand syndrome, there remains a concern that the repeated acceleration and deceleration of the impeller may degrade von Willebrand factor (vWF) multimers. Accordingly, we evaluated the influence of our RS modulation system on vWF dynamics. A simple mock circulation was used. The circulation was filled with whole bovine blood (650 mL), and the temperature was maintained at 37 ± 1°C. EVAHEART was operated using the electrocardiogram-synchronized RS modulation system with an RS variance of 500 rpm and a pulse frequency of 60 bpm (EVA-RSM; $n = 4$). The pumps were operated at a mean flow rate of 5.0 ± 0.2 L/min against a mean pressure head of 100 ± 3 mm Hg. The continuous-flow mode of EVAHEART (EVA-C; $n = 4$) and ROTAFLOW (ROTA; $n = 4$) was used as controls. Whole blood samples were collected at baseline and every 60 min for 6 h. Complete blood counts (CBCs), normalized indexes of hemolysis (NIH), vWF antigen (vWF:Ag), vWF ristocetin cofactor (vWF:Rco), the ratio of vWF:Rco to vWF:Ag (Rco/Ag), and high molecular weight multimers (HMWM) of vWF were evaluated. There were no significant changes in CBCs throughout the 6-h test period in any group. NIH levels of EVA-RSM, EVA-C, and ROTA were 0.0035 ± 0.0018, 0.0031 ± 0.0007, and 0.0022 ± 0.0011 g/100 L, respectively. Levels of vWF:Ag, vWF:Rco, and Rco/Ag did not change significantly during the test. Immunoblotting analysis of vWF multimers showed slight degradation of HMWM in all groups, but there were no significant differences between groups in the ratios of HMWM to low molecular weight multimers, calculated by densitometry. This study suggests that our RS modulation system used with EVAHEART does not have marked adverse influences on vWF dynamics. The low NIH and the absence of significant decreases in CBCs indicate that EVAHEART is hemocompatible, regardless of whether it is operated with the RS modulation system. **Key Words:** Left ventricular assist device—von Willebrand factor—Rotational speed modulation—EVAHEART.

Continuous-flow left ventricular assist devices (CF-LVADs) have improved the prognosis of patients with end-stage heart failure. The number of patients under CF-LVAD support is increasing, and continuous flow is widely applied, not only as a bridge to transplantation but also as a destination therapy. Continuous flow is not a physiological flow, and it can result in various adverse events, such as intracranial hemorrhage, gastrointestinal (GI) bleeding, epistaxis, development of aortic insufficiency, and impaired vascular reactivity.

Acquired von Willebrand disease (AVWD) is known as a frequent bleeding complication in patients under CF-LVAD support (1). According to recent studies, the disease is caused by degradation of

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high molecular weight multimers (HMWM) of von Willebrand factor (vWF). Although AVWD is not fully understood, shear stress and a metalloproteinase called ADAMTS-13 are thought to play important roles in its development.

EVAHEART (Sun Medical Technology Research Corporation, Nagano, Japan) is an implantable CF-LVAD that has been widely used as a bridge to transplant in Japan since its approval in 2010. The pump is designed to achieve low shear stress and provides wider clearance between the impeller and the housing (2). These features may contribute to fewer adverse effects on the blood and a lower rate of AVWD and GI bleeding (2–5). We developed a rotational speed (RS) modulation system for EVAHEART that can change the RS in synchronization with the cardiac cycle of the native heart. We have previously reported that this system can change the native heart load, alter arterial pulsatility, enhance myocardial perfusion, and may be able to prevent aortic insufficiency (6–8) without harmful effects on hemolysis (9). Although these properties can be beneficial to patients under CF-LVAD, there remains a concern that the repeated acceleration and deceleration of an impeller may affect vWF dynamics. This concern needs to be resolved before the system is applied in the clinical setting. We conducted this study to evaluate the influence of our RS modulation system on vWF dynamics when used with a CF-LVAD.

MATERIALS AND METHODS

Animals

The calves were maintained in accordance with the guidelines of the Committee on Animal Studies at the National Cerebral and Cardiovascular Center; the Center's Animal Investigation Committee approved the study. The animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (Publication No. 86-23, revised 1996).

Whole bovine blood collection

After a 48-h fast and overnight abstinence from water, all animals were sedated with an intramuscular injection of ketamine hydrochloride (8–10 mg/kg). General anesthesia was induced and maintained by inhalation of isoflurane (1–3 vol%/100 mL in oxygen). The animals were placed in the left recumbent position. After heparinization (300 IU/Kg), whole bovine blood was collected from the right carotid artery. The blood was gravity-drained directly into a 3L bag primed with 225 mL of acid citrate dextrose solution (ACD-A solution, Terumo Corporation, Tokyo, Japan) to create a concentration of 7.5%.

Mock circulatory loop

We used simple mock circulatory loops. Each loop consists of polyvinyl chloride (PVC) tubing, a PVC reservoir, resistant clamp, pressure monitors, and a pump head. Each loop was filled with 650 mL of whole bovine blood collected as described above.

The temperature of the blood was maintained at $37 \pm 1°C$ by a water bath. An ultrasonic flow meter (Transonic TS401 with a 1/2-inch flow probe, Transonic Systems Inc., Ithaca, NY, USA) was attached to each outflow tube. The pressures derived from the inflow and outflow tubes were monitored with a polygraph system (RM-7000, Nihon Koden Corporation, Tokyo, Japan). Data were recorded using LabChart 5 software (AD Instruments, Bella Vista, NSW, Australia).

Experimental protocol and LVAD driving method

EVAHEART was driven with the electrocardiogram-synchronized RS modulation system. We have previously reported the details of our RS modulation controller. We defined the systolic and diastolic phases as 33 and 67% of the RR interval, respectively, according to the previously published protocol (6). Our controller can change the RS of each phase by detecting the R wave from an electrocardiogram. In the present study, we used co-pulse mode (increased RS during systole). Artificial R-waves were provided by a pulse generator (Medtronic 5330, Medtronic, Minneapolis, MN, USA). The pulse frequency was set at 60 bpm, and the amplitude of the RS was set at 250 rpm (=RS variance of 500 rpm), according to the previous protocols. The pumps were operated at a mean flow rate of 5.0 ± 0.2 L/min against a mean pressure head of 100 ± 3 mm Hg. Apart from the RS modulation mode (EVA-RSM; $n = 4$), the continuous mode (constant RS) of EVAHEART (EVA-C; $n = 4$) and ROTAFLOW (MAQUET GmbH & Co. KG, Rastatt, Germany) (ROTA; $n = 4$) were used as controls.

Whole blood samples were collected at baseline and every 60 min during the 6-h experimental period. Complete blood counts (CBCs), plasma-free hemoglobin (Pf Hgb), vWF antigen (vWF:Ag, normal value: 40–190 IU/dL), vWF ristocetin cofactor

TABLE 1. *Hemodynamic data for each driving setting*

	EVA-C	EVA-RSM	ROTA
Blood flow (L/min)	4.94 ± 0.02	4.89 ± 0.05	4.90 ± 0.03
Mean RS (rpm)	2356.99 ± 22.08	2294.94 ± 36.47	2054.06 ± 5.62
Pressure head (mm Hg)	101.48 ± 2.16	98.13 ± 2.73	101.62 ± 0.77

(vWF:Rco, normal value: 40–170 IU/dL), the ratio of vWF:Rco to vWF:Ag (Rco/Ag, normal value: > 0.65), and vWF multimer analysis were evaluated. vWF:Ag was measured using an immuno-turbimetric method (STA Liatest vWF, Diagnostica Stago, Asnières sur Seine, France). vWF:Rco was measured using a vWF:Rco assay (Siemens BC Von Willebrand Reagent, Siemens, Margerg, Germany). vWF multimers were analyzed via 1% agarose-SDS gel electrophoresis and immunoblotting. The blots were incubated with polyclonal rabbit antihuman vWF primary antibody (Dako, Capinteria, CA, USA) and IRDye 800CW anti-rabbit secondary antibody (LI-COR Biosciences, Lincoln, NE, USA). Relative levels of vWF degradation fragments were quantified using densitometry. ImageJ software (National Institutes of Health, Bethesda, MD, USA) was used to measure the luminescent intensity of vWF multimer bands. The cutoff values were defined as five bands for low molecular weight multimers (LMWM), 6–10 bands for medium molecular weight multimers (MMWM), and >10 bands for HMWM, in accordance with a previous report (10). The normalized index of hemolysis (NIH) was calculated according to American Society for Testing Materials standards using the following equation (11): NIH (g/100 L) = ΔPf Hgb $\times$ V $\times$ (100 - Hct)/100 $\times$ 100/(Q $\times$ T), where V(L) is the priming volume of the circulation, Hct (%) is the hematocrit of the blood sample, Q (L/min) is the blood flow rate, and T (min) is the time of pump operation.

Statistical analysis

All numerical data are presented as mean ± standard deviation. Comparisons between groups were performed by using repeated-measures analysis of variance followed by Tukey's multiple comparisons test. All analyses were two-sided, and a P value <0.05 was considered to be statistically significant. We used R software (R Foundation for Statistical Computing, Vienna, Austria) for all statistical analysis.

RESULTS

Table 1 shows the hemodynamic data during pump operation. There were no significant differences between driving modes. To achieve test conditions, the mean RS of EVA-RSM was set at 2356.99 ± 22.08 rpm and that of EVA-C was set at 2294.94 ± 36.47 rpm, which are higher than the clinical settings (usually about 1800–1900 rpm).

Table 2 shows the CBCs during pump operation. CBCs did not decrease significantly during the 6-h evaluation under any of the driving conditions ($P > 0.05$). NIH levels of EVA-RSM, EVA-C, and ROTA were 0.0035 ± 0.0018, 0.0031 ± 0.0007, and 0.0022 ± 0.0011 g/100 L, respectively. There was no significant difference between NIH levels ($P = 0.743$). These results imply that none of the pump driving settings had adverse effects on blood cells or hemoglobins.

Table 3 shows the levels of vWF:Ag, vWF:Rco, and Rco/Ag. These levels did not change significantly

TABLE 2. *Levels of complete blood counts*

	Time (hour)	EVA-C	EVA-RSM	ROTA
WBC	0	6.15 ± 0.35	6.18 ± 0.22	6.04 ± 0.31
(10^3 cells/μL)	3	5.89 ± 0.44	6.08 ± 0.33	5.89 ± 0.29
	6	6.06 ± 0.36	5.84 ± 0.30	6.29 ± 0.72
	P value (ANOVA)	0.81	0.412	0.729
RBC	0	6.62 ± 0.37	6.55 ± 0.27	6.62 ± 0.28
(10^6 cells/μL)	3	6.51 ± 0.34	6.54 ± 0.17	6.43 ± 0.12
	6	6.56 ± 0.31	6.52 ± 0.21	6.27 ± 0.25
	P value (ANOVA)	0.953	0.989	0.329
Platelets	0	447.50 ± 27.57	449.00 ± 7.07	445.00 ± 29.69
(10^3 cells/μL)	3	441.50 ± 28.99	430.50 ± 37.47	435.50 ± 31.82
	6	443.75 ± 35.35	437.00 ± 39.59	437.75 ± 43.84
	P value (ANOVA)	0.973	0.848	0.96

WBC, white blood cell; RBC, red blood cell; ANOVA, analysis of variance.

TABLE 3. *Levels of vWF:Ag, vWF:Rco, and Rco/Ag*

	Time (hour)	EVA-C	EVA-RSM	ROTA	*P* value (ANOVA)
vWF:Ag	0	58.25 ± 24.17	60.00 ± 23.98	59.50 ± 23.21	0.994
(IU/dL)	3	56.50 ± 20.07	58.25 ± 21.23	57.25 ± 21.93	0.993
	6	59.00 ± 19.64	57.50 ± 19.87	57.75 ± 20.84	0.994
	P value (ANOVA)	0.986	0.986	0.989	—
vWF:Rco	0	161.75 ± 83.66	161.50 ± 81.80	166.00 ± 84.73	0.996
(IU/dL)	3	138.25 ± 81.11	148.25 ± 84.03	145.50 ± 82.21	0.984
	6	152.50 ± 87.21	149.50 ± 98.64	147.25 ± 94.13	0.997
	P value (ANOVA)	0.924	0.973	0.935	—
Rco/Ag	0	2.69 ± 0.44	2.60 ± 0.34	2.68 ± 0.43	0.936
	3	2.29 ± 0.78	2.42 ± 0.66	2.40 ± 0.57	0.965
	6	2.42 ± 0.68	2.37 ± 0.90	2.34 ± 0.84	0.991
	P value (ANOVA)	0.688	0.882	0.738	—

ANOVA, analysis of variance.

throughout the 6-h pump operation ($P > 0.05$). When compared with each pump driving setting at the same pump-driving time, these values did not differ significantly ($P > 0.05$).

Figure 1A shows the results of electrophoresis. A slight decrease in HMWM of vWF was seen under all three pump driving conditions. The ratios of HMWM, medium molecular weight multimer (MMWM), and low molecular weight multimer (LMWM) calculated using densitometry (Table 4) showed gradual decreases in the ratios of HMWM (Fig. 1B) and increases in the ratios of LMWM during the 6-h evaluation, although the changes were statistically non-significant ($P > 0.05$). There were no significant differences in these ratios between any of the pump driving settings when compared at the same driving time ($P > 0.05$).

DISCUSSION

Improvement in the prognosis of patients with end-stage heart failure as a result of CF-LVAD has led to an increase in the number of patients treated with these devices. Nonetheless, there are concerns about complications associated with continuous flow and decreased pulsatility, such as GI bleeding, hemorrhagic stroke, increased vascular impedance, progression of aortic valve insufficiency, and the development of AVWD.

AVWD is a complication of CF-LVAD that is associated with bleeding complications, even in patients who are under appropriate anticoagulation therapy. Shear stress forces vWF to unfold and activate ADAMTS-13. Activated ADAMTS-13 cleaves HMWM of vWF, while shear stress derived from the assist device itself degrades vWF. Implantable CF-LVADs are smaller in size than pulsatile LVADs. Such smaller size pumps, especially axial flow pumps, require a high RS to establish sufficient blood flow, resulting in high shear stress. In contrast, a pulsatile LVAD has a low tendency to cause AVWD (12). All kinds of rotary pumps, including implantable centrifugal pumps, extracorporeal centrifugal pumps, and short-term support devices, can

TABLE 4. *Ratios of high molecular weight multimers (HMWM), medium molecular weight multimers (MMWM), and low molecular weight multimers (LMWM)*

	Time (hour)	EVA-C	EVA-RSM	ROTA	*P* value (ANOVA)
HMWM	0	21.54 ± 10.25	25.30 ± 10.07	24.08 ± 12.38	0.99
	1	19.65 ± 8.70	21.50 ± 7.32	21.99 ± 10.18	0.891
	2	18.53 ± 10.83	19.87 ± 7.66	20.43 ± 10.79	0.945
	6	16.28 ± 10.95	16.34 ± 9.36	16.61 ± 10.93	0.973
	P value (ANOVA)	0.378	0.301	0.329	—
MMWM	0	39.16 ± 3.17	39.42 ± 3.11	35.35 ± 4.36	0.98
	1	40.45 ± 1.77	39.37 ± 2.78	38.74 ± 3.20	0.795
	2	40.68 ± 2.94	41.49 ± 2.21	39.87 ± 3.64	0.932
	6	40.72 ± 3.24	39.83 ± 2.58	38.28 ± 2.71	0.976
	P value (ANOVA)	0.796	0.919	0.801	—
LMWM	0	39.3 ± 8.09	35.29 ± 7.44	40.57 ± 12.98	0.906
	1	30.91 ± 7.42	39.14 ± 4.58	39.27 ± 6.99	0.682
	2	40.79 ± 8.47	38.63 ± 5.62	39.71 ± 7.16	0.961
	6	43.00 ± 8.57	43.83 ± 8.29	45.12 ± 9.33	0.887
	P value (ANOVA)	0.596	0.694	0.768	—

ANOVA, analysis of variance.

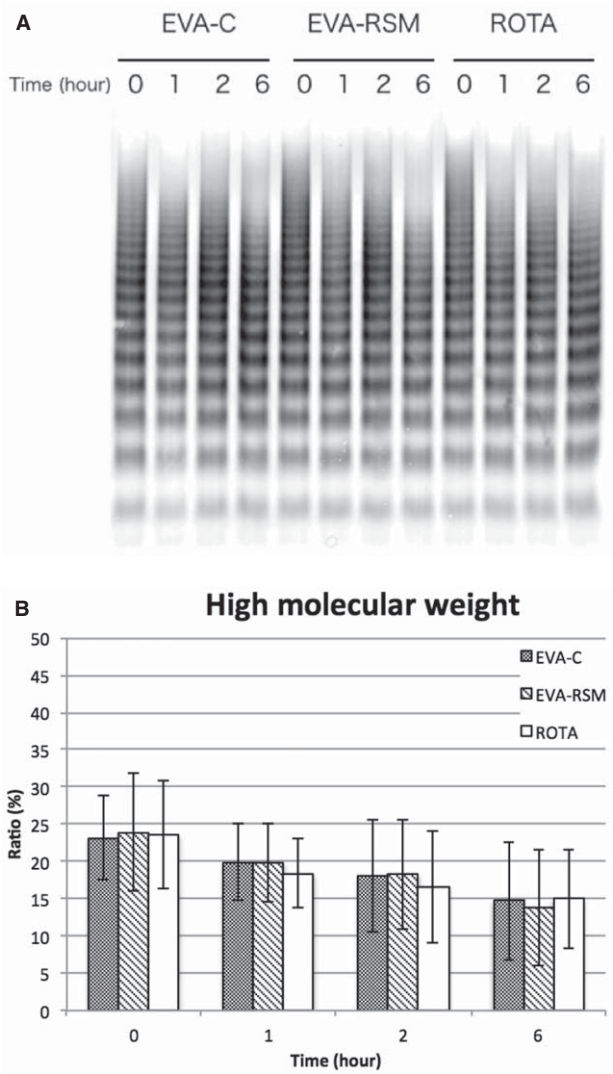

FIG. 1. (A) An example of agarose gel electrophoresis with immunoblotting demonstrated slight degradation of high molecular weight multimers. (B) Ratios of high molecular weight multimers (HMWM) calculated by densitometry analysis. Although statistically insignificant, ratios of HMWM decreased in all the groups.

cause AVWD, even though there are some differences in severity (13–16). Each device has different properties with respect to AVWD. Pumps and their driving settings need to be not only hemocompatible (free from blood cell destruction), but also less susceptible to AVWD. Furthermore, clinicians should pay attention to the differences. AVWD can occur in the very early postoperative period (13) and may be associated with nonsurgical bleeding events in the early period (17,18). Some in vitro studies showed similar results, in which degradation of HMWM occurred shortly after the pumps were started (19).

Although the need for pulsatility in patients under LVAD support is controversial, there have been some reports of harmful effects from CF-LVADs, especially when used for long periods. CF-LVADs have many favorable factors, such as the smaller pump size and long durability. CF-LVADs that can provide pulsatile flow offer the benefits of both CF-LVAD and a pulsatile pump. We have previously demonstrated that our RS modulation system used with EVAHEART can alter heart load, aortic pulsatility, and coronary flow. Kishimoto et al. reported the probability of prevention of aortic insufficiency with a modified RS modulation (8), and Arakawa et al. showed prevention of leftward shift of the interventricular septum followed by preservation of right heart function (20). The continuous-flow driving mode of EVAHEART itself can provide some pulsatility, because of the large inflow and outflow conduits (inner diameter of 16 mm) and flat slope pressure–flow curve (2). In addition to the above-mentioned pulsatility, low shear stress derived from the continuous-flow driving mode may contribute to lower rate of AVWD and GI bleeding. Despite these proven beneficial effects, there remain concerns about the influence of the RS modulation system on vWF dynamics that need to be resolved before the system can be applied in a clinical setting. Kishimoto et al. showed that our RS modulation system did not have adverse effects on hemolysis (9). The present study also showed similar results, even though the pumps were operated for a longer duration (6 h vs. 4 h). Repeated acceleration and deceleration of RS can cause a higher shear stress than in the continuous-flow driving mode, which could exacerbate AVWD. As mentioned above, degradation of HMWM plays an important role in the development of AVWD (21). However, that is not the only factor associated with bleeding complications. Not all patients with lower amounts of HMWM have such complications (1,22,23). Other factors are thought to be regional hypoxia, vascular dilation, and arteriovenous malformation caused by continuous blood flow or reduced pulse pressure. Thus, pulsatility itself could have beneficial effects by preventing hemorrhagic events. In this study, RS modulation was not found to have any adverse effects on vWF dynamics—a major step toward the application of the system for clinical use.

In the present study, the quantitative values of vWF and its activity did not change significantly during the 6-h pump operation, even under RS modulation conditions. Signs of slight degradation of HMWM in all the groups were apparent on electrophoresis, but this could have been exacerbated by the closed in vitro loop without a supply of vWF derived from vascular endothelial cells or platelets. Sujith et al. showed that vWF degradation occurred quickly

(within 120 min) in mock circulatory loops (4). The results of our study are consistent with that finding. Considering that there were no significant differences in the ratios of HMWM, MMWM, and LMWM between the various centrifugal pump modes, RS modulation used for EVAHEART does not appear to have significant adverse effects on vWF dynamics. The mean RS in this study was higher than in clinical settings: The mean RS of EVAHEART was set at approximately 2300 rpm in both the EVA-RSM and EVA-C groups. Yamene et al. showed that the maximum shear rates of EVAHEART were about 15 000/s and about 14 000/s at flow rates of 6 L/min and 4 L/min, respectively, when operated with RS of 2300 rpm (24). Theoretically, the shear rate could not be higher in clinical settings than in this study. Although vWF multimers are thought to begin to unfold at shear rates of 1000/s and more (24), the critical shear rate and cutoff values are not precisely known. Given the results of the present study, a shear stress of about 15 000/s may not have marked adverse effects on vWF degradation. In contrast, Selgrade et al. showed that the maximum shear rate of HeartMate III, a smaller centrifugal pump than EVAHEART, was higher, reaching more than 20 000/s at 4 L/min (25). An axial pump may provide a higher shear rate than HeartMate III, although quantitative values are unclear because of the lack of published data. The changes in shear rates during RS modulation have not been clearly determined, but a 500-rpm variance in the RS did not have worse effects on vWF dynamics than the continuous mode. The amplitude of RS modulation was set at 250 rpm, based on previous studies showing that an RS variance of 500 rpm was enough to provide sufficient pulsatility (7). In addition, there is a risk of retrograde blood flow in the pump at low RS, because of the large inlet and outlet diameters of EVAHEART.

Levels of NIH and CBCs in RS modulation were comparable to those in the continuous mode and ROTAFLOW. EVAHEART remained hemocompatible, even while being driven by the RS modulation system.

Limitations of the study

This study has several limitations. We used a simple mock circulation, which is not an adequate substitute for animal models and clinical settings. Moreover, there was no supply of vWF derived from the body, such as vascular endothelial cells and platelets. This would result in overestimation of vWF degradation. Bovine blood could be different from human as regards vWF metabolism, ADAMTS 13 activity, etc. This study was conducted for only 6 h, which was relatively short to observe chronic complications. Even though HMWM of vWF is thought to be degraded in the short term, a longer duration test should be conducted to confirm the effects. Quantitative values of shear rates during RS modulation should be obtained by computational fluid dynamics.

CONCLUSIONS

This study indicates that our rotational speed modulation system, used with EVAHEART under conditions of synchronization with the cardiac cycle of the native heart, does not have a marked adverse influence on von Willebrand factor dynamics. The low NIH levels and the absence of significant decreases in complete blood counts show that EVAHEART is hemocompatible, regardless of whether it is operated with the RS modulation system.

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