JACC: Heart Failure
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 2, No. 2, 2014
ISSN 2213-1779/$36.00
http://dx.doi.org/10.1016/j.jchf.2013.10.008

Acquired von Willebrand Syndrome in Patients With a Centrifugal or Axial Continuous Flow Left Ventricular Assist Device

Anna L. Meyer, MD,* Doris Malehsa, MD,† Ulrich Budde, MD,‡ Christoph Bara, MD,† Axel Haverich, MD,† Martin Strueber, MD*

Leipzig, Hannover, and Hamburg, Germany

Objectives The aim of this study was to determine whether differences in continuous flow left ventricular assist devices (LVADs) may lead to differences in the von Willebrand profile and the occurrence of bleeding and thromboembolic events.

Background The HeartMate II (Thoratec Corp., Pleasanton, California) and HeartWare Ventricular Assist Device (HVAD) (HeartWare, Inc., Framingham, Massachusetts) systems are the most frequently implanted LVADs worldwide. In all patients with an axial-flow HeartMate II, acquired von Willebrand syndrome (AvWS) due to the loss of large molecular weight multimers was found. The large molecular weight multimers of the von Willebrand factor (vWF) play a key role in primary hemostasis through interactions with platelets.

Methods This was a retrospective study of the vWF profile and incidence of bleeding and thromboembolic events in 102 patients receiving the HeartMate II ($n = 51$) and HVAD ($n = 51$). Between January 2003 and December 2010, vWF testing was performed in 102 of 175 consecutive patients after LVAD implantation.

Results AvWS was found in all patients, demonstrated by a decrease in the high molecular weight multimers of vWF to $30 \pm 14\%$ in HeartMate II patients and $34 \pm 13\%$ in patients with an HVAD. Significant predictors of vWF antigen included age ($p = 0.011$), number of days on the device ($p = 0.035$), C-reactive protein ($p < 0.001$), and blood group ($p = 0.007$). Bleeding and thromboembolic event rates were similar. However, lower fractions of vWF antigen and high molecular weight multimers did not correlate with the rate of bleeding complications or thromboembolic events.

Conclusions AvWS developed in all patients after centrifugal or axial flow pump implantation. Different patterns of AvWS were seen between the devices as well as individually. However, the complication rates after implantation were similar. (J Am Coll Cardiol HF 2014;2:141–5) © 2014 by the American College of Cardiology Foundation

Implantation of left ventricular assist devices (LVADs) is an established therapy in patients with end-stage heart failure. The most common LVADs are the HeartMate II (HM II) (Thoratec Corp., Pleasanton, California) and the HeartWare Ventricular Assist Device (HVAD) (HeartWare, Inc., Framingham, Massachusetts). The HM II has been implanted in >10,000 patients. The pump has a maximal flow of 10 l/min, with a typical range of speed between 8,600 and 10,000 rpm.

The HVAD is a centrifugal flow left ventricular assist pump implanted in the pericardial space. More than 1,500 implantations have been performed worldwide. The HVAD also generates flows up to 10 l/min, but at speeds typically between 2,400 and 3,200 rpm.

See page 146

Bleeding complications are a major problem after LVAD implantation. In the initial study of the HVAD, bleeding complications were documented in 30% of patients in the first year of follow-up (1). Current data show bleeding events in 44% to 59% of patients after HM II implantation (2,3). A major bleeding complication is gastrointestinal bleeding, with an incidence reported between 19% and 40% (4,5). The cause of the frequent bleeding complications after LVAD implantation appears to be multifactorial. To date, the reasons for the differences between continuous flow

From the *Heart Center Leipzig University, Clinic for Heart Surgery, Leipzig, Germany; †Department of Cardiothoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany; and ‡AescuLabor Hamburg, Hamburg, Germany. Dr. Strueber was a primary investigator in the HeartMate II Pilot and the HeartWare HVAD trial and is an expert consultant for HeartWare, Inc., and a member of the European Advisory Board of Thoratec, Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 26, 2013; revised manuscript received October 11, 2013, accepted October 17, 2013.

JACC: Heart Failure Vol. 2, No. 2, 2014
April 2014:141–5

Abbreviations and Acronyms

AvWS = acquired von Willebrand syndrome
CRP = C-reactive protein
HM II = HeartMate II
HVAD = HeartWare Ventricular Assist Device
LVAD = left ventricular assist device
vWF = von Willebrand factor
vWF:AG = von Willebrand factor antigen
vWF:CB = von Willebrand factor collagen binding

devices in contrast to pulsatile flow devices are not resolved, particularly regarding the relationship between continuous flow devices and arteriovenous malformations as a source of bleeding. Another important factor is the discovery of the loss of the high molecular weight multimers of the von Willebrand factor (vWF) in patients after ventricular assist device implantation. Acquired von Willebrand syndrome (AvWS) is detected in almost all patients after HM II implantation, but comparable data after HVAD implantation have not yet been reported (6–8).

The vWF is a multimeric protein with a size of >20,000 kD. The highest molecular weight multimers play a major role in primary hemostasis by binding to the glycoprotein 1b-V-IX and 2b/3a receptors of platelets and collagen form a clot and close a leakage in the vascular endothelium (9). Large multimers of vWF are cleaved by a metalloprotease (ADAMTS 13), particularly under conditions of high shear stress, which results in an AvWS (10). Vincentelli et al. (11) showed a higher incidence of bleeding events in patients with aortic stenosis. The severity of the stenosis, indicated by higher mean transvalvular gradients and higher vascular wall shear stress, was negatively correlated with the percents of highest molecular weight multimers. The different designs and resultant flow patterns of axial and centrifugal pumps could result in different shear stresses and hence lead to different results in an AvWS profile.

The examination of any differences between these devices is necessary for optimal anticoagulation management, and it can potentially play a role in future decisions between these pumps.

We describe here an analysis of the prevalence of AvWS in axial and centrifugal flow pumps, as well as bleeding and thromboembolic events in these patients. The goal of this study was to determine whether AvWS also develops in HVAD recipients and whether there are differences in the vWF profile between the HM II and HVAD that may contribute to bleeding risk.

Methods

In this retrospective study, the results of von Willebrand testing were available for 102 of 175 patients after LVAD implantation with an HM II (n = 51) and an HVAD (n = 51) between January 2003 and December 2010. Testing of vWF was not available for 73 patients due to transplantation, death, or explantation of the pumps. Blood samples were taken post-implantation during routine outpatient visits, with a mean time to testing of 213 ± 217 days after HM II and 182 ± 118 days after HVAD implantation. Samples of citrated blood were sent directly to a certified laboratory.

Demographic data were collected, and bleeding and thromboembolic events were followed from the day of implantation for a minimal of 180 days post-implantation.

Laboratory testing. AvWS was diagnosed by analyzing vWF antigen (vWF:AG). The vWF collagen binding (vWF:CB) activity, a functional test to measure the biological activity, was performed to determine the ratio of vWF:CB to vWF:AG. The ratio provides a quantification of the functional capability of vWF. A normal value of >0.8 represents a normal collagen binding activity of >80%.

Electrophoresis of vWF was performed to determine the multimeric structure of plasma vWF (6). By measuring the intensity of the banding, a quantitative analysis of the high, medium and low molecular weight multimers was completed (6). The samples were compared with plasma from a normal control group.

Platelet function–related hemostasis was measured using the PFA-100 Analyzer (Dade-Behring, Marburg, Germany), which measures the closure time at high sheer for platelets to seal a membrane aperture coated with collagen and either epinephrine or adenosine diphosphate. Patients with von Willebrand syndrome have increased closure times of >200 s.

Anticoagulation regimen. After implantation of the HM II or HVAD system, a continuous infusion of heparin was initiated after 24 h, when the chest tube drainage was <50 ml/h. After removal of drains and implantation of an implantable cardioverter-defibrillator, phenprocoumon (Roche, Grenzach-Wyhlen, Germany) was administered orally with a target international normalized ratio of 2.5 ± 0.5. In patients with an HVAD, clopidogrel (75 mg 3 times a week) was added to phenprocoumon for platelet inhibition beginning on postoperative day 3.

Bleeding event. Any type of intracerebral bleeding or bleeding that resulted in death was documented. Postoperative bleeding was defined as any bleeding during hospital stay after implantation requiring reoperation. Gastrointestinal bleeding was defined as confirmed by endoscopy or requiring treatment with a transfusion of packed red blood cells. Epistaxis was included if it required hospital stay and a transfusion of packed red blood cells, packing, or cauterization. Other bleeding, such as hematuria, was documented if a packed red blood cell transfusion or an intervention was necessary.

Statistical analysis. All statistical analyses were performed with the use of SPSS version 17.0 (SPSS Inc., Chicago, Illinois). The differences between HM II and HVAD were tested using a 2-sample *t* test when the assumption of normalcy was met; otherwise, the Mann-Whitney *U* test was used. Correlations were performed using the Pearson or the Spearman rho test. All statistical comparisons were 2 sided. Statistical significance was accepted at $p < 0.05$. Biochemical and hemodynamic data are presented as mean ± SD or median and range when appropriate.

Table 1 Characteristics of Patients With HeartMate II (N = 51) or HVAD (N = 51) Left Ventricular Assist Devices

Parameter	HeartMate II (Group 1)	HeartWare (Group 2)	p Value
N	51	51	
Age, yrs	50.9 ± 13.2	49.6 ± 15.0	0.644
Sex, female	8	16	0.219
Etiology			0.182
DCM	51	69	
ICM	47	29	
Myocarditis	2	2	
No. of days on device	852 ± 576	664 ± 287	0.410
Initial discharge at POD, days*	49 ± 39	41 ± 30	0.199
Current status			0.005
Ongoing	43	76	
Transplanted	29	8	
Explanted	8	4	
Dead	20	10	
Cause of death			0.647
Multiorgan failure	6	6	
Sepsis	4	4	
Cerebrovascular accident	4	2	
Right heart failure	2	0	
Other	4	0	

Values are % or mean ± SD. *Initial discharge at POD means POD between operation day and day of first (initial) discharge.
DCM = dilated cardiomyopathy; ICM = ischemic cardiomyopathy; POD = post-operative day.

Table 2 Characteristics of von Willebrand Factor, Bleeding, and Thromboembolic Events

	HeartMate II (N = 51)	HeartWare (N = 51)	p Value
Parameter			
Speed, rpm	9,741 ± 333	2,892 ± 17	0.000
CRP at testing, mg/l	22 ± 47	17 ± 44	0.540
Blood type			0.933
0	19	20	
A	23	20	
B	5	5	
AB	4	6	
Testing on POD, days	219 ± 220	182 ± 118	0.296
vWF:AG	194 ± 74	160 ± 58	0.010
vWF:CB	140 ± 65	113 ± 57	0.028
vWF:AG/vWF:CB	0.7 ± 0.2	0.7 ± 0.2	0.553
Large MM/N	30 ± 14	34 ± 13	0.090
Medium MM/N	103 ± 21	106 ± 14	0.396
Small MM/N	153 ± 34	146 ± 28	0.332
Loss of largest MM	All	All	
Complications			
Follow-up, yrs	118.9	92.7	
Thromboembolic events			
Thrombus formation in LVAD	4	14	0.081
Transient ischemic attack	4	4	0.647
Cerebral ischemia	6	6	1.000
Mesenterial ischemia*	2	0	0.315
Bleeding events			
Re-exploration	35	22	0.124
Gastrointestinal bleeding	18	6	0.065
Epistaxis	8	4	0.400
Cerebral bleeding	2	4	0.558
Others	6	6	1.000

Values mean ± SD or %. *Pathogen finding.
CRP = C-reactive protein; LVAD = left ventricular assist devices; MM = multimers; MM/N = multimers/normal plasma; POD = post-operative day; rpm = revolutions per minute; vWF:AG = von Willebrand factor antigen; vWF:CB = von Willebrand factor collagen binding.

Results

Patient characteristics are shown in Table 1. There were no significant differences between the 2 groups, with the exception of a higher rate of transplantation in patients in the HM II group. The total follow-up period was 118.9 patient-years in HM II patients and 92.7 patient-years for HVAD patients. The median LVAD support time for patients with the HM II was 852 ± 576 days (range, 24 to 2,823 days) versus 664 ± 287 days (range, 73 to 1,422 days) in those with the HVAD system (p = 0.41). The mean pump speed of the HM II and HVAD in patients on the day of von Willebrand testing was 9,712 ± 300 (range, 9,000 to 10,200) rpm and 2,892 ± 17 (range, 2,400 to 3,200) rpm in the HM II and HVAD, respectively.

The analysis of vWF showed a decrease in the high molecular weight multimers of 30 ± 14% in the HM II group (range, 2% to 64%) and of 34 ± 13% (range, 11% to 63%) in the HVAD group compared with normal plasma levels. In contrast, the medium and low molecular weight multimers were increased compared with the normal plasma, but significant differences between HM II and HVAD were not detected (Table 2). The mean vWF:AG and vWF:CB were significantly higher in patients with the HM II compared with the HVAD (194 ± 74% vs. 160 ± 58%, p = 0.010 and 140 ± 65% vs. 113 ± 57%, p = 0.028, respectively). However, the mean ratio (vWF:AG/vWF:CB) did not differ.

The analysis of a correlation between age, speed, C-reactive protein (CRP), or blood type, and the percent of the vWF:AG and vWF:CB ratios and high molecular weight multimers of vWF revealed a significantly higher percent of vWF:AG (p = 0.011) and vWF:CB (p = 0.005) in older patients compared with younger patients. The analysis of time on support revealed lower vWF:AG (p = 0.035) and vWF:CB (p = 0.024), in patients supported for a longer versus a shorter time period. Also, a higher CRP correlated with a higher vWF:AG (p < 0.001).

Differences due to the speed were only seen in patients with an HVAD. HVAD patients demonstrated a lower percent of high molecular weight multimers at higher speeds, with a correlation coefficient of −0.343 (p = 0.015) (Fig. 1). The correlation between speed and the percent of high molecular weight multimers was not significant in HM II patients.

Another factor found to have an influence on the vWF profile was blood type. The analysis revealed lower vWF:AG and vWF:CB in patients with blood type O (O: 149 ± 50, A: 193 ± 81, B: 209 ± 51, AB: 182 ± 51 [p = 0.007] and O: 108 ± 55, A: 136 ± 63, B: 139 ± 55, AB: 146 ± 86

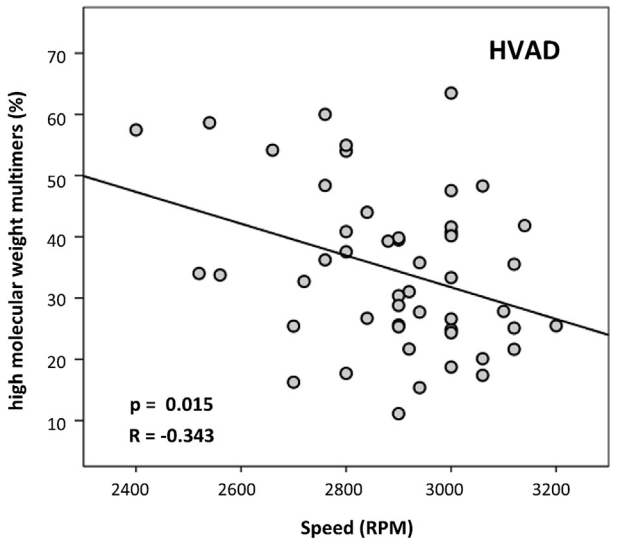

Figure 1 **HVAD Pump Speed Versus High Molecular Weight Multimers**

Correlation between the HeartWare Ventricular Assist Device (HVAD) pump speed and the percent of high molecular weight multimers of von Willebrand factor.

[p = 0.015], respectively). However, the percent of patients with blood type O was equivalent in both patient cohorts.

During the follow-up period, pump thromboses were found in 7 patients with an HVAD and in 2 patients with an HM II. In all patients, the pump had to be exchanged. The rates of transient ischemic attack as well as ischemic cerebrovascular accident were statistically similar between the 2 groups. Additionally, no significant differences were seen in the comparison of patients with a bleeding event. Gastrointestinal bleeding and epistaxis exhibited the same incidence and long-term outcomes among HM II and HVAD cohorts. The rates (as events per patient year) of a thromboembolic or bleeding event were 0.29 and 0.07 in HM II and 0.23 and 0.07 in patients with a HVAD, respectively.

Analysis of the early post-operative period showed no significant differences in the rates of re-exploration due to tamponade or bleeding in patients with the HM II compared with the HVAD (35% vs. 22%, p = 0.124).

The analysis of a potential influence of vWF:AG or vWF:CB ratios or the decreased high molecular weight multimers of vWF on a tendency for bleeding and thrombosis revealed no significant differences, with all comparisons having a p value >0.05.

The PFA-100 analysis demonstrated no significant differences between the HM II and the HVAD, and all patients had closure times >200 s.

Discussion

AvWS after LVAD implantation was first described in patients with axial continuous flow pumps and was shown to be reversible after explantation of the device (8). We detected the same phenomenon in patients with a centrifugal pump. The smaller contact surface to the blood in the HVAD pumps and the lower speed seemed to be without an effect. Unfortunately, specific tests for shear stress or calculated shear stress in patients with the HVAD and the HMII are not yet available in the literature (12). Zhang et al. (13) showed that shear stress in a centrifugal pump is approximately proportional to the rotational speed. This could explain the lower percent of high molecular weight multimers at higher pump speeds in patients with HVAD pumps (p = 0.015), but not the lack of influence of speed on the vWF pattern in patients with HM II pumps.

Differences in the vWF profile between the HM II and the HVAD, similar to the higher values of vWF:AG in the HM II, group must be distinguished from influences by sex, age, blood type, infection/sepsis, or malignant disease (14,15). Our studies confirm an influence on vWF by age, CRP, and blood type. However, analysis of the blood samples in most patients were completed 1 year after ventricular assist device implantation; therefore, any influence due to the postoperative healing process could be excluded, although acute infections were not documented. The comparison of patient parameters including age, CRP, sex, blood type, and days on device showed no significant differences between the 2 LVAD groups.

The most interesting question was whether there was an influence or definitive cause of the bleeding complications after LVAD implantation. Bleeding is a major adverse event after LVAD implantation (1,3,16). An event rate of 1.44 events/patient-year was described for HM II patients in the post–U.S. Food and Drug Administration approval study (2). Data from the HVAD bridge to transplantation pivotal trial reveal an event rate of 0.62 events/patient-year (17). In our analysis, the post-operative bleeding complications were similar in both groups, and the vWF profiles did not discriminate between patients with and without bleeding and thromboembolic events.

Moreover, the more intense anticoagulation used in the HVAD patients by adding a platelet inhibitor was not reflected in a higher rate of bleeding events in this group. Also, recent design changes to the inflow cannula of the HVAD may have affected the anticoagulation management and coagulation system response. The titanium inflow cannula was sintered to stimulate the growth of a pseudoneointima (18) to prevent clotting at the surface of the cannula and consequent potential thromboembolic events. Patients with these newer sintered pumps were not included in this study.

Study limitations. Limitations include the retrospective data collection and the single-center design. The impact of the varying day of testing for vWF in the patient samples was not assessed. Testing on the same post-operative day in all patients could exclude this variable, which could potentially influence the results of the von Willebrand test (14).

Conclusions

An acquired von Willebrand syndrome is present in both HVAD and HM II patients. The degree decrease in large molecular weight multimers of vWF was similar among patients with both devices. In HVAD patients, lower speed may have resulted in less loss of large multimers. Speed does not appear to affect vWF profile in HM II patients. The vWF antigen and collagen binding results (vWF:AG, vWF:CB) appear to change with time on device. The von Willebrand profile does not correlate with the incidence of bleeding or thrombembolic complications.

Reprint requests and correspondence: Dr. Martin Strueber, Heart Center Leipzig University, Clinic for Heart Surgery, Struempellstrasse 39, 04289 Leipzig, Germany. E-mail: martin.strueber@med.uni-leipzig.de.

REFERENCES

1. Wieselthaler GM, O Driscoll G, Jansz P, Khaghani A, Strueber M, HVAD Clinical Investigators. Initial clinical experience with a novel left ventricular assist device with a magnetically levitated rotor in a multi-institutional trial. J Heart Lung Transplant 2010;29:1218–25.
2. Starling RC, Naka Y, Boyle AJ, et al. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). J Am Coll Cardiol 2011;57:1890–8.
3. Lahpor J, Khaghani A, Hetzer R, et al. European results with a continuous-flow ventricular assist device for advanced heart-failure patients. Eur J Cardiothorac Surg 2010;37:357–61.
4. Demirozu ZT, Radovancevic R, Hochman LF, et al. Arteriovenous malformation and gastrointestinal bleeding in patients with the HeartMate II left ventricular assist device. J Heart Lung Transplant 2011;30:849–53.
5. Stern DR, Kazam J, Edwards P, et al. Increased incidence of gastrointestinal bleeding following implantation of the HeartMate II LVAD. J Card Surg 2010;25:352–6.
6. Meyer AL, Malehsa D, Bara C, et al. Acquired von Willebrand syndrome in patients with an axial flow left ventricular assist device. Circ Heart Fail 2010;3:675–81.
7. Crow S, Chen D, Milano C, et al. Acquired von Willebrand syndrome in continuous-flow ventricular assist device recipients. Ann Thorac Surg 2010;90:1263–9; discussion 1269.
8. Geisen U, Heilmann C, Beyersdorf F, et al. Non-surgical bleeding in patients with ventricular assist devices could be explained by acquired von Willebrand disease. Eur J Cardiothorac Surg 2008;33:679–84.
9. Pareti FI, Lattuada A, Bressi C, et al. Proteolysis of von Willebrand factor and shear stress-induced platelet aggregation in patients with aortic valve stenosis. Circulation 2000;102:1290–5.
10. Tsai HM, Sussman II, Nagel RL. Shear stress enhances the proteolysis of von Willebrand factor in normal plasma. Blood 1994;83:2171–9.
11. Vincentelli A, Susen S, Le Tourneau T, et al. Acquired von Willebrand syndrome in aortic stenosis. N Engl J Med 2003;349:343–9.
12. Mizunuma H, Nakajima R. Experimental study on shear stress distributions in a centrifugal blood pump. Artif Organs 2007;31:550–9.
13. Zhang T, Taskin ME, Fang HB, et al. Study of flow-induced hemolysis using novel Couette-type blood-shearing devices. Artif Organs 2011;35:1180–6.
14. Bockmeyer CL, Reuken PA, Simon TP, et al. ADAMTS13 activity is decreased in a septic porcine model. Significance for glomerular thrombus deposition. Thromb Haemost 2011;105:145–53.
15. Gill JC, Endres-Brooks J, Bauer PJ, Marks WJ Jr., Montgomery RR. The effect of ABO blood group on the diagnosis of von Willebrand disease. Blood 1987;69:1691–5.
16. Strueber M, O'Driscoll G, Jansz P, Khaghani A, Levy WC, Wieselthaler GM. Multicenter evaluation of an intrapericardial left ventricular assist system. J Am Coll Cardiol 2011;57:1375–82.
17. Aaronson KD, Slaughter MS, Miller LW, et al. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. Circulation 2012;125:3191–200.
18. Zapanta CM, Griffith JW, Hess GD, et al. Microtextured materials for circulatory support devices: preliminary studies. ASAIO J 2006;52:17–23.

Key Words: bleeding ■ HeartMate II ■ HeartWare ■ LVAD ■ von Willebrand syndrome.