Acquired von Willebrand Syndrome in Patients With an Axial Flow Left Ventricular Assist Device

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Background—Rotary blood pumps used as left ventricular assist devices (LVADs) allow for long-term support and may become suitable alternatives to heart transplantation. Effects of this technology on the coagulation system are not completely understood, leading to controversial anticoagulation protocols. Thus, we investigated the primary hemostasis in patients with chronic LVAD therapy.

Methods and Results—Twenty-six outpatients received axial flow LVAD (HeartMate II; Thoratec) for a median support time of 4.5 months. In a cross-sectional protocol, platelet aggregation in response to ADP and epinephrine, von Willebrand antigen (vWF:AG), and collagen-binding capacity (vWF:CB) were obtained. Von Willebrand factor (vWF) multimer analyses were performed, and patients were screened for bleeding events. This analysis was repeated after removal of the device for transplantation or recovery (n=12) and after a median of 15.5 months in ongoing patients (n=11). In all patients on devices, severe impairment of platelet aggregation as well as a loss of large vWF multimers were found. In 10 patients, a decreased vWF:CB/vWF:AG ratio was observed. Bleeding episodes occurred with an incidence of 0.17 per patient-year. After removal of the device, normal patterns of platelet aggregation, multimer analysis, and vWF:CB/vWF:AG ratio were recorded. In the second analysis of ongoing patients, impairment of platelet aggregation and loss of large vWF multimers were verified.

Conclusions—A diagnosis of von Willebrand syndrome type 2 was established in all patients after LVAD implantation, and bleeding events confirmed this finding. Reversibility of this condition was found after removal of the device. (Circ Heart Fail. 2010;3:675-681.)

Key Words: von Willebrand disease type 2 ▪ ventricle-assist device ▪ heart-assist device

Left ventricular assist devices (LVADs) have been successfully used as a bridge to heart transplantation in patients with high pulmonary vascular resistance and in deteriorating candidates waiting for a donor heart. Because of the scarcity of resources in cardiac transplantation, these devices also have been used as a chronic therapy in patients with heart failure unsuitable for transplantation. Initially, this approach was limited by the mechanical stability of first-generation pulsatile devices. However, the clinical introduction of second- and third-generation nonpulsatile devices suggests that these devices can be used as a long-term approach. Despite this, bleeding complications and thromboembolic events still remain the most serious adverse events of this therapy. Early experience with continuous flow device-related thrombosis and thromboembolic events led to a maximum tolerable regimen of antiplatelet and anticoagulation therapies. With further improvements in the devices, less-aggressive regimens were advised.

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Nevertheless, minor and major bleeding episodes are the leading adverse events. Although this axial flow pump is engineered to provide long-term stability and full cardiac support without hemolysis, it is not known whether this technology has an impact on the coagulation system itself. Fifty years ago, an association between gastrointestinal bleeding and aortic stenosis was reported. In 1992, it was postulated that acquired von Willebrand syndrome (vWS) plays a key role in the pathogenesis of bleeding complications in patients with severe aortic stenosis.

The von Willebrand factor (vWF) circulates in the blood as the largest soluble multimeric protein. It is cleaved by a metalloprotease (ADAMTS13), particularly under conditions of high shear stress. Specifically, structural changes can be induced by high shear stress in the von Willebrand molecule exposing the bond between amino acids 842 and 843 to the
specific von Willebrand protease (ADAMTS13). This results in acquired type 2 vWS, which is characterized by the loss of the largest von Willebrand multimers, which are most effective in platelet-mediated hemostasis. The incidence of bleeding events in patients with aortic stenosis within 6 months before valve replacement was 21%. It has also been shown that the severity of the stenosis, indicated by higher mean transvalvular gradients as well as higher wall shear stress, was negatively correlated with the percentages of the highest-molecular-weight multimers.

It has been speculated recently that this mechanism may impair patients with ventricular assist devices (VADs). The typical laboratory findings of an acquired vWS have been demonstrated in patients with different types of VADs (Thoratec biventricular assist device HeartMate II and other rotary blood pumps). To evaluate the prevalence of vWS with the use of a modern device, we analyzed outpatients on chronic support with the HeartMate II assist device and reported the hemostatic abnormalities and clinical consequences for this patient cohort. The analysis was repeated after removal of the device for transplantation or recovery as well as in the majority of ongoing patients.

Methods

Patients

Within the past 5 years, 70 patients received an LVAD implantation using the HeartMate II LVAD (Thoratec; Pleasanton, Calif) at Hannover Medical School (Hannover, Germany). The cross-sectional study included all patients of our outpatient clinic after LVAD implantation at the point of data evaluation in summer 2008. This cohort included 2 female and 24 male patients (Table 1). The mean age was 43 years (range, 16 to 64 years). All patients were seen regularly, and complete follow-up was required to be included into this study. Informed consent was obtained from each patient, and the study was approved by the local ethics committee. Indication for LVAD implantation was heart failure despite maximum medical treatment, including catecholamine support. However, median sup-

Statistics

Statistical analyses were performed using SPSS version 16.0 (SPSS Inc; Chicago, Ill). Distribution of relevant variables was summarized using frequencies and medians and ranges, as appropriate. Bivariate correlation (Spearman ρ) was carried out to define correlations between time on the device and levels of vWF:AG and vWF:CB. All P values were obtained using 2-sided analyses. A P ≤ 0.05 was considered statistically significant for all analyses.

Blood Collection and Laboratory Assays

In patients with LVAD support, blood samples were collected during an outpatient visit. Platelet-related hemostasis was tested with a platelet function analyzer (PFA-100; Dade International; Miami, Fla) by determining closure times of epinephrine and ADP cartridges. Based on the work of Kratzer and Born, the analyzer is a high-shear-stress system for in vitro testing of platelet function that simulates primary hemostasis after injury to a small vessel. Platelet inhibition by aspirin can be distinguished from arachidonic acid-independent processes. Furthermore, this technique represents a highly sensitive way to screen patients for a von Willebrand defect (vWD). The closure time is measured by a capillary and a biologically active membrane coated with either collagen and epinephrine or collagen and ADP as an aspirin-independent test. The normal value is <160 seconds for the test with collagen and epinephrine and 121 seconds for collagen and ADP.

On the day of platelet function analysis (PFA), blood also was sampled for plasma vWF antigen (vWF:AG), for the functional analysis of vWF by measuring the vWF:AG:vWF collagen-binding capacity (vWF:CB) ratio, and for electrophoresis to determine the multimeric structure of plasma vWF. All samples were obtained from citrated blood and centrifuged at 4000 rpm for 5 minutes. The vWF:AG was measured using the vWF Antigen Assay (Gradiopore; Frenchs Forest, NSW, Australia) following the method described by Mazurier et al (normal value, 50% to 160%). The vWF:CB was measured by an ELISA using a collagen-binding assay as previously described by Brown and Bosak.

The ratio of vWF:CB and vWF:AG was calculated. A decreased ratio of ≤0.8 was considered a surrogate marker of acquired vWS. Sodium dodecyl sulfate-agarose discontinuous gel electrophoresis was carried out essentially as described (Figure 2). Briefly, medium (1.6%) and low-resolution (1.2%) gels (LGT agarose type VII; Sigma; Munich, Germany) were prepared. Electrophoresis was performed for 16 hours at 55 V. VWF multimers were transferred to nitrocellulose filters by electroblotting using transfer buffer solution (0.05 mol/L phosphate, pH 7.4 with 0.04 mol/L sodium dodecyl sulfate, without methanol). Visualization of the multimers was performed by videodensitometry. The filters were incubated twice for approximately 30 seconds in buffer solution (20 mmol/L Tris/HCl, 500 mmol/L NaCl, pH 7.5) and thereafter placed into a video-detection system (Fluorchem; Alpha Innotech Corp; San Leandro, Calif) consisting of a dark housing; a sensitive, cooled (~30°C) charge-coupled device camera; and software generating 12-bit computer graphics. The filters were overlaid with 5-mL solution containing 0.4 mg/mL luminol (Sigma-Aldrich Chemie; Steinheim, Germany), 0.01 mg/mL 4-iodophenol (Sigma-Aldrich Chemie), and 2.5 μL/mL 30% H2O2 (Perhydrol; Merck; Darmstadt, Germany) in Tris buffer solution (20 mmol/L Tris/HCl, 500 mmol/L NaCl, pH 7.5). Typical exposure times were between 30 and 60 seconds.

In subsamples of 6 patients, the activity of vWF-cleaving protease ADAMTS13 and the antigen level were analyzed by a modified fluorescence resonance energy transfer assay (Technozym ADAMTS-13; Technoclone GmbH; Vienna, Austria).

Screening for Bleeding Events

Each patient’s bleeding history was evaluated at every outpatient visit using a standard screening questionnaire. All bleeding episodes during the outpatient follow-up were summarized.
Table 1. Patient Characteristics and Results of the von Willebrand Diagnostics

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<th>vWF: CB, %</th>
<th>vWF:CB/vWF:AG Ratio</th>
<th>Loss of Largest vWF MM, % vs Pool</th>
<th>High-Molecular-Weight MM, % vs Pool</th>
<th>PFA C-EPI, s</th>
<th>PFA C-ADP, s</th>
<th>Platelet, 1000/μL</th>
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BTT indicates bridge to transplantation; C-ADP, collagen and ADP; C-EPI, collagen and epinephrine; CHD, coronary heart disease; CRP, C-reactive protein; DCM, dilated cardiomyopathy; DT, destination therapy; Hct, hematocrit; MM, multimers.

*Selected patients for Table 2.
Results

In the first analysis with all patients being on the LVAD, the PFA revealed pathological high closure times (>250 seconds) in all samples using both epinephrine and ADP cartridges, independent of any patient-dependent factor such as sex, diagnosis, and time on the LVAD (Table 1). The vWF:CB ranged from 64% to 372% (median, 134%). There also was a significant decrease in vWF:CB with respect to time on the device (correlation coefficient, 0.51; P < 0.007).

In 10 patients, a decreased vWF:CB/vWF:AG ratio was determined. In all samples, a loss of the large multimers was found. A quantitative examination by densitometry was done in 54% (Table 1). Normal values of vWF-cleaving protease ADAMTS13 activity (median, 89%; range, 65% to 121%) and antigen (median, 0.98 μg/mL; range, 0.61 to 1.67 μg/mL) were reported.

The total follow-up period was 48 patient-years (median, 28 months; range, 4 to 53 months). During this time, there were no single hemorrhagic or ischemic cerebrovascular events. One patient died due to mesenteric ischemia 4 months after implantation of the LVAD, and 1 died due to sepsis after 40 months. In 1 patient, a pump thrombosis occurred after phenprocoumon was terminated for gastrointestinal bleeding. The patient was referred to our center and received a heart transplantation because of the high urgency of the case. In a second patient, a pump thrombosis was suspected due to signs of hemolysis. This condition resolved after temporary anticoagulation therapy with lepirudin.

All bleeding events occurring after discharge of the patient from LVAD implantation are summarized in Table 3. The median follow-up time of bleeding onset in outpatients was 6 months (range, 1 to 19 months). At the time of any bleeding event, vWF:CB and vWF:AG were determined.
event, no patient was thrombocytopenic. In all but 1 patient, INR was within range. For patient no. 1 with gastrointestinal bleeding, the last INR before signs of bleeding was 2.90. At emergency admission, a lower INR of 1.53 was noted. In total, 8 bleeding episodes were recorded within 48 patient-years, leading to a calculated incidence of 0.17 (95% CI, 0.03 to 0.31) per patient-year. These bleeding events ranged from epistaxis to life-threatening gastrointestinal bleeding. In the 3 patients with gastrointestinal bleeding, endoscopic examination revealed the source to be distal of the duodenum in the small bowel.

To date, 10 successful heart transplantations were performed in 10 patients of this cohort. In 2 patients, the device was explanted for myocardial recovery. Blood samples were taken in a median of 14.5 months (range, 2 to 34 months) after device removal (Table 2). Gel electrophoresis displayed all fractions of multimers of the vWF in all patients. Quantitative analysis of multimers was done in 9 patients. In these patients, the percentage of high-molecular-weight multimers was normal (median, 27.8%; range, 20.1% to 34.1%, versus median, 26.6%; range, 22.1% to 33.2%, in normal pool plasma). The vWF:CB/vWF:AG ratio was within the normal range in 10 patients but reduced in 1 patient and borderline in another patient.

Platelet function testing was done in 11 patients. The test with ADP was within normal range in all but 1 patient, who suffered from a severe pulmonary infection at the time of investigation.

Except for 2 patients, the remaining 12 are still receiving therapy with the LVAD. A second PFA and vWF diagnostics were carried out in 11 of these patients 15.5 months (median) after the first blood sampling. In the repeat analysis, the largest vWF multimers were still absent. The vWF:CB/vWF:AG ratio was decreased in all but 1 case, and the PFA revealed prolonged clotting times for all samples.

### Discussion

An acquired loss of large vWF monomers by definition leads to the diagnosis of vWS. These monomers were missing in all samples taken from our patients on LVAD support. Because data before implantation of the device are missing, it is an inherent limitation of this study that the acquisition of vWS is not directly provable. However, after the removal of the device in all 12 patients, restoration of a normal vWF monomer pattern was found. This indirect evidence supports our hypothesis that a vWS not only is present in all patients being supported with the HeartMate II axial flow device, but also is an acquired form that resolves after removal of the

### Table 3. Bleeding Complications and Thromboembolic Events After LVAD Implantation

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Months After Implantation</th>
<th>Type of Bleeding</th>
<th>Thromboembolic Event</th>
<th>INR</th>
<th>Platelets, 1000/μL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>Gastrointestinal</td>
<td></td>
<td>2.90/1.53</td>
<td>287</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>…</td>
<td>Suspected device thrombosis</td>
<td>2.23</td>
<td>229</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>Hematuria</td>
<td>…</td>
<td>2.16</td>
<td>311</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>Gastrointestinal</td>
<td>…</td>
<td>2.17</td>
<td>153</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>Epistaxis</td>
<td>…</td>
<td>3.46</td>
<td>327</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>Epistaxis</td>
<td>…</td>
<td>2.09</td>
<td>213</td>
</tr>
<tr>
<td>21</td>
<td>7</td>
<td>Gingiva</td>
<td>…</td>
<td>2.82</td>
<td>198</td>
</tr>
<tr>
<td>22</td>
<td>19</td>
<td>Gingiva</td>
<td>…</td>
<td>1.97</td>
<td>133</td>
</tr>
<tr>
<td>23</td>
<td>1</td>
<td>Gastrointestinal</td>
<td>…</td>
<td>2.35</td>
<td>354</td>
</tr>
<tr>
<td>2</td>
<td>…</td>
<td>Gastrointestinal</td>
<td>Device thrombosis</td>
<td>2.25</td>
<td>371</td>
</tr>
</tbody>
</table>
device. The vWF:CB/vWF:AG ratio used as a surrogate marker for acquired vWS was pathological in 10 out of 26 patients in the first analysis and in 10 out of 11 patients in the repeat analysis 15.5 months later. We chose a threshold of <0.8 for the ratio because it showed a sensitivity of 80% for the detection of vWS. At a threshold of <0.7, used by other investigators, sensitivity was only 46%. The vWF:CB/vWF:AG ratio has been shown to perform at least equal to the measurement of ristocetin cofactor activity as long as suitable collagens are used. The vWF:CB/vWF:AG ratio used here was the preferred method because of a higher level of precision. However, a limitation of this approach is that other abnormalities in addition to the presence or absence of large multimers were not detected in our analysis.

The clinical events of spontaneous bleeding were also similar to the findings in patients with acquired vWS due to aortic stenosis. Mucosal bleeding predominates; however, in some patients, more severe gastrointestinal bleeding occurs. The similarity to patients with acquired vWS and aortic stenosis may be explained by the fact that blood is exposed to high shear stress either by the aortic stenosis or by the LVAD. Cessation of life-threatening gastrointestinal bleeding episodes have been found after removal of the source of high shear stress, the aortic stenosis, or the LVAD. Geisen et al reported nonsurgical bleeding in patients with VADs in association with acquired vWS, and Steinlechner et al reported the loss of large vWF multimers in 12 patients with rotary blood pumps other than HeartMate II. These findings indicate that acquired vWS is present in patients with differently designed rotary blood pumps and not related to a particular design. Steinlechner et al also described platelet dysfunction unrelated to the vWF. Other studies emphasized the potential role of a leukocyte-platelet interaction.

Impaired platelet aggregation also was described by Klovaite et al in a cohort of 12 patients being supported by the HeartMate II assist device. This group also found the absence of large vWF monomers in patients on support and restitution after heart transplantation and concluded that implantation of a HeartMate II LVAD is associated with impaired platelet aggregation and induction of an acquired vWS type 2.

The effects on primary hemostasis increase the risk for bleeding events, especially in combination with anticoagulation and platelet inhibitors. Individual confounding patient factors may be an underlying cause of the actual bleeding, such as mucosal defects, angiodysplasias, injuries, and infection. To determine these factors, large longitudinal studies are required, but despite this, the findings of the present investigation may have implications for patient treatment and care management. Dental procedures or other surgical interventions should be performed with the knowledge that a coagulation disorder is present in addition to anticoagulation treatment. Therefore, special care in terms of local bleeding control, antifibrinolytic therapy, and substitution of coagulation factor concentrate are recommended. As a consequence, we consider our outpatients as a high-risk group with respect to potential bleeding complications when all surgical interventions are performed.

In life-threatening bleeding episodes or planned surgical (dental) interventions, supplementation with factor VIII/vWF concentrate may be necessary. With the improvements made in designing LVADs mechanically stable enough to provide support for many years and the demographic changes in the western population, it can be expected that these devices will be used not only as a bridge to transplantation, but also as an alternative to heart transplantation. Although hemolysis avoidance has already been achieved in the design of modern rotary blood pumps, future efforts must address the challenges of long-term support, including the impact of the devices on inflammation, platelet function, and the coagulation system.

Because pump thromboses still occur in some patients after LVAD implantation, a result of the withdrawal of anticoagulation medication, the activation of platelets, or both in patients with various types of VADs, most centers choose an anticoagulation regime consisting of warfarin or phenprocoumon and a platelet inhibitor. However, a more adapted anticoagulation in LVAD therapy is warranted because of results and changes of the coagulation system.

Disclosures
Dr Slaughter has received research/grant support from Thoratec Corporation. Dr Strueber was a primary investigator in the HeartMate II pilot trial and the HeartWare HVAD trial and a member of the European advisory board of Thoratec. Drs Meyer, Malehsa, Bara, Budd, and Haverich have no conflicts to disclosure.

References


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**CLINICAL PERSPECTIVE**

Rotary blood pumps replaced pulsatile displacement pumps in long-term left ventricular support. Their mechanical stability combined with miniaturization of the pump was favorable compared to the first-generation pulsatile devices. However, with prolongation of support times, bleeding episodes became a limitation of this therapy. In addition to epistaxis, gastrointestinal bleeding from the small bowel was seen in these patients at an incidence not known in patients with pulsatile devices. The finding of acquired von Willebrand syndrome (vWS) in all of our patients being supported with the HeartMate II axial flow device may contribute to the pathophysiological understanding of this clinical problem. In addition to intended anticoagulation and platelet inhibition, primary hemostasis is impaired by acquired vWS. Although there is no consensus yet on how to treat patients with bleeding episodes, it is helpful to know that in the case of gastrointestinal bleeding the source is likely to be found in the small intestine and that treatment of acquired vWS may be required.

Recommendations for anticoagulation for patients with the HeartMate II device were revised several times in the past to lower international normalized ratio levels to prevent bleeding. Patients should be advised that epistaxis and potential gastrointestinal bleeding are associated with long-term ventricular support. Physicians are encouraged to check for vWS also in patients with implanted rotary blood pumps other than the HeartMate II.
Acquired von Willebrand Syndrome in Patients With an Axial Flow Left Ventricular Assist Device
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