Acquired von Willebrand syndrome in patients with ventricular assist
device or total artificial heart

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Summary
Unexplained bleeding episodes are associated with ventricular assist
devices (VAD) and can occur in part due to acquired von Willebrand syn-
drome (AVWS). AVWS is characterised by loss of high molecular weight
(HMW) multimers of von Willebrand factor (VWF) and decreased ratios
of collagen binding capacity and ristocetin cofactor activity to VWF
antigen. Loss of multimers can occur as VWF is subjected to increased
shear stress, which occurs in presence of VADs. We studied 12 patients
who required mechanical support of their native heart for terminal car-
diac insufficiency. Nine patients underwent placement of a VAD, while
three underwent placement of a total artificial heart (TAH), which is
connected directly to heart and large cardiac vessels without cannulas.
Within one day of VAD implantation, four of five patients evaluated
demonstrated loss of HMW multimers and impaired VWF function.

AVWS was present within two weeks of implantation in eight of nine
patients, and in all seven tested patients after ≥3 months. Patients with
different VAD types developed varying severities of AVWS. After VAD ex-
plantation, HMW multimers were detectable and VWF function normal-
ised in all patients. AVWS was not observed in the TAH patients studied.
Our findings demonstrate that patients with an implanted VAD experi-
ence a rapid onset of AVWS that is quickly and completely reversed
after device explantation. In addition, TAH patients do not develop
AVWS. These results suggest that shear stress associated with exposure
of blood to VAD cannulas and tubes may contribute to the development
of AVWS.

Keywords
Acquired coagulation disorders, von Willebrand disease, surgery

Introduction
Unexplained bleeding episodes are associated with ventricular as-
sist devices (VAD) and can occur in part due to acquired von Wille-
brand syndrome (AVWS) (1–5). AVWS is a bleeding disorder
which is characterised by loss of high-molecular weight (HMW)
multimers of von Willebrand factor. HMW multimers are respon-
sible for platelet adhesion and aggregation. VWF binds by its A1
domain to the platelet receptor GPIb/IX. Platelets attach to injured
vessel walls or to foreign surfaces, become activated, and aggregate
(6). VWF mediates binding of platelets to the injured vessel wall by
also interacting with the collagen exposed at endothelial lesions.

VWF is stored in endothelial cells and megakaryocytes and is re-
leased from endothelial cells and platelets (reviewed by Sadler et al.
[7]). Upon secretion, the size of the VWF multimers is regulated by
the proteases ADAMTS13 (8–11) and thrombospondin-1 (12, 13).
Normal shear stress in flowing blood leads to unfolding of VWF
multimers, exposure of the A2 domain, and cleavage of VWF by
ADAMTS13 (14, 15). HMW multimers subjected to physiologic
shear conditions have a typical size of 20,000 kDa. Pathologic shear
stress due to vascular injury or to acceleration in VADs causes activ-
ation of VWF with exposure of the A1 domain and subsequent
VWF binding. Further unfolding of A2 domains results in down-
sizing of the HMW multimers by ADAMTS13 (16). The resultant
loss of VWF HMW multimers causes impaired VWF function and
platelet aggregation, as medium and small multimers do not me-
diate binding of platelets to denuded vessel walls as effectively as
the HMW multimers (3, 17).

Loss of HMW multimers can be visualised by multimeric analy-
sis (4). In addition, binding of VWF to the platelet receptor GPIb/
IX can be stimulated by ristocetin in vitro and is measured as ris-
tocetin-cofactor activity (VWF:RCo), while binding to collagen
(collagen binding capacity, VWF:CB) can be analysed in vitro as
well. Impaired VWF function is revealed by a decrease in the ratio
of these parameters to the absolute amount of VWF antigen
(VWF:RCo/VWF:Ag, VWF:CB/VWF:Ag) (18, 19). Hence, these
ratios provide surrogate markers for the loss of HMW multimers.

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VADs cause increased shear stress due to acceleration in the pump as well as in the cannulas and blood-conducting tubes which connect the device to the heart and great vessels. In contrast, total artificial hearts (TAH) are connected directly to the remaining native heart and large cardiac vessels and do not contain cannulas and tubes.

We hypothesised that 1) AVWS in VAD patients would be reversible soon after explantation, and 2) patients with TAH would not suffer from AVWS. To test these hypotheses we studied nine VAD patients during support and after explantation of the VAD. In addition, we investigated three patients with TAH for parameters of AVWS.

### Materials and methods

#### Patients

Following approval by our local institutional ethics committee, 12 patients who underwent VAD implantation or TAH placement between June 2006 and March 2009 were studied. Patient characteristics are shown in Table 1. Nine patients (age 40.4 ± 15.5 years) who received a VAD and who subsequently underwent heart transplantation (n=7) or weaning (n=2) were analysed on the first day (n=5), within two weeks (7 ± 4 days, n=9) and after ≥3 months (115 ± 42 days, n=7) following VAD implantation and, again, after explantation (1–52 days, median 1.5 days, n=9). Two patients had a left-ventricular HeartMate II® (Thoratec Corporation, Pleasanton, CA, USA) and five patients needed biventricular support consisting of two Thoratec PVAD® (Paracorporeal VentrAssist Device). Two patients received a VentrAssist® (Ventracor Limited, Chatswood, Australia). VADs were implanted between June 2006 and August 2008.

In addition, we analysed three patients who received a total artificial heart (CardioWest®, SynCardia Systems Inc., Tucson, AZ, USA) between July 2007 and March 2009. Data was collected twice – at one week (7 ± 1 days) after implantation of the TAH and on day 20, 32 or 346 days after the implantation.

No patient had suffered from a bleeding disorder prior to device implantation.

#### Device characteristics and surgical procedures

The intracorporeal systems HeartMate II® and VentrAssist® were implanted as previously described (20, 21). Briefly, the inflow cannula were inserted into the left ventricular apex, and the outflow cannulas anastomosed to the ascending aorta. The HeartMate II® is an axial pump with a spinning rotor and no valves whereas the VentrAssist® is a centrifugal pump with a hydrodynamically suspended impeller. Typical operating speeds are 9,000 rpm and 2,000 rpm, respectively.

Standard surgical technique was used for paracorporeal Thoratec BVAD (biventricular assist device) implantation. The left-ventricular VAD was connected as described above, while the inflow cannula of the right-ventricular assist device was implanted into the right ventricular apex (n=4) or right atrium (n=1). The respective outflow graft was anastomosed to the main pulmonary artery. The biventricular system’s two pump chambers are driven by pneumatic power moving a membrane which expels the blood from the artificial ventricle. Mechanical tilting disc valves in the inflow and outflow ports ensure unidirectional blood flow through the device. Pumping frequency conforms to the patient’s physiological range. An appropriate drive pressure is chosen to empty the VAD completely with a systolic ejection time of 300 ms. Anticoagulation was started for all three systems following implantation with heparin with a target activated partial thromboplastin

### Table 1: Characteristics of VAD and TAH patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Diagnosis</th>
<th>Device</th>
<th>On device (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>DCM</td>
<td>HeartMate II</td>
<td>89</td>
<td>HTX</td>
</tr>
<tr>
<td>2.</td>
<td>DCM</td>
<td>Thoratec BVAD</td>
<td>114</td>
<td>HTX</td>
</tr>
<tr>
<td>3.</td>
<td>myocarditis</td>
<td>Thoratec BVAD</td>
<td>138</td>
<td>weaned</td>
</tr>
<tr>
<td>4.</td>
<td>ICM</td>
<td>HeartMate II</td>
<td>162</td>
<td>HTX</td>
</tr>
<tr>
<td>5.</td>
<td>DCM</td>
<td>Ventrassist</td>
<td>187</td>
<td>HTX</td>
</tr>
<tr>
<td>6.</td>
<td>myocarditis</td>
<td>Thoratec BVAD</td>
<td>227</td>
<td>weaned</td>
</tr>
<tr>
<td>7.</td>
<td>DCM due to myocarditis</td>
<td>Thoratec BVAD</td>
<td>316</td>
<td>HTX</td>
</tr>
<tr>
<td>8.</td>
<td>ICM</td>
<td>Ventrassist</td>
<td>321</td>
<td>HTX</td>
</tr>
<tr>
<td>9.</td>
<td>myocarditis and ICM</td>
<td>Thoratec BVAD</td>
<td>356</td>
<td>HTX</td>
</tr>
<tr>
<td>1.</td>
<td>Primary transplant failure</td>
<td>CardioWest TAH</td>
<td>29</td>
<td>HTX</td>
</tr>
<tr>
<td>2.</td>
<td>ICM</td>
<td>CardioWest TAH</td>
<td>85</td>
<td>living on device</td>
</tr>
<tr>
<td>3.</td>
<td>Primary transplant failure</td>
<td>CardioWest TAH</td>
<td>374</td>
<td>died on device</td>
</tr>
</tbody>
</table>
time (aPTT) of 60–80 seconds. Heparin was changed to phenprocoumon after removal of the chest drains and adequate oral intake. Target international normalised ratio (INR) for patients with HeartMate II® was 2.0 to 3.0, for the patients with VentrAssist® 2.8 to 3.2, and for the BVAD 3.0 to 3.5 according to the device-dependent risk for thrombosis. Platelet aggregation was inhibited by acetylsalicylic acid (ASA) 100 mg/day.

TAHs were anastomosed to the native atria and greater vessels. The device has four valves and is operated by pressurised air. Post-operative target INR was 3.0 to 3.5.

Seven VAD patients underwent heart transplantation with biatrial or bicaval anastomosis of the donor heart. Patients received heparin (4–5 IE/kg body weight/hour) and ASA 100 mg/day post-operatively. Two patients underwent BVAD explantation after successful weaning from the device which was achieved in a stepwise fashion over several weeks.

**Laboratory analysis**

Sodium citrate plasma was obtained by centrifugation at 1,500 g for 15 minutes at 20°C and analysed within 4 hours after drawing or stored at −80°C for a maximum of two weeks prior to analysis. VWF antigen (VWF:Ag; Siemens Healthcare Diagnostics, Eschborn, Germany) and ristocetin cofactor activity (VWF:RCO; Siemens Healthcare Diagnostics) were measured using the Analyzer Behring Coagulation System (BCS, Dade Behring, Marburg, Germany) according to standard protocols. Collagen type I (Nycomed Pharma, Unterschleissheim, Germany) was immobilised on a microtiter plate, and collagen binding capacity (VWF:CB) in plasma was determined photometrically using the ELISA technique. We calculated the ratios VWF:CB/VWF:Ag (normal: >0.7) and VWF:RCO/VWF:Ag (normal: >0.65).

VWF multimers were separated on SDS-agarose low resolution gels (1.0% agarose) and blotted on a PVDF membrane to assess the HMW multimers. High resolution gels (2.2% agarose) were performed to characterise triplet structure. VWF was detected using the appropriate primary and secondary antibodies (DAKO, Hamburg, Germany) and stained with 3,3’-diaminobenzidin/cobalt chloride (Bio-Rad, Munich, Germany). Standard human plasma (Siemens Healthcare Diagnostics) was used for control.

INR (Innovin®, Siemens Healthcare Diagnostics), aPTT (Paththromtin SL®, Siemens Healthcare Diagnostics), haemoglobin (HB), haematocrit (HKT), platelet counts, C-reactive protein (CRP) and factor VIII (FVIII)-activity were determined employing laboratory standard procedures. Values are reported as mean ± standard deviation.

**Results**

Patients with VAD were analysed at three points: on the first day (n=5), within two weeks (7 ± 4 days, n=9) and after ≥3 months (115 ± 42 days, n=7) following VAD implantation and once after device explantation (1–52 days, median 1.5, n=9).

Over the time course of the study all nine VAD patients presented with acquired von Willebrand syndrome. Five of these nine patients were analysed already on the first day after implantation. In four of these five patients we detected missing HMW multimers and reduced values for VWF:CB/VWF:Ag ratio indicating AVWS. Furthermore, the ratio of VWF:RCO/VWF:Ag was decreased in two of these five patients (Fig. 1). HMW multimers were present in one patient who had a VentrAssist® device and who also maintained normal ratios of VWF:CB/VWF:Ag and VWF:RCO/VWF:Ag.
Two weeks after implantation, only one of the nine VAD patients did not show AVWS, while eight patients displayed missing HMW multimers and at least one pathologic functional VWF parameter: Seven of the nine patients showed reduced VWF:CB/VWF:Ag-ratios. VWF:RCo/VWF:Ag-ratio was investigated in seven of the nine patients, and five of them exhibited a reduced ratio (Fig. 1). Interestingly, the only patient without AVWS two weeks following VAD implantation had a VentrAssist® device, while the other patient with a VentrAssist® device who had shown no signs of AVWS on the first day after implantation (described above) had subsequently developed AVWS.

Laboratory studies from seven of nine patients on VAD were obtained again after a minimum of three months. All of these patients were tested for VWF:CB, and six were investigated for VWF:RCo and the presence of HMW multimers. Hence, two of these three parameters were available for each of the seven patients. At this time we detected AVWS in all patients studied. All patients revealed reduced VWF:CB/VWF:Ag and/or VWF:RCo/VWF:Ag ratios, respectively (Fig. 1), while HMW multimers were missing in all six tested patients (Fig. 2). Meanwhile both patients with a VentrAssist® device had developed AVWS.

Finally, all nine patients were analysed after VAD explantation. HMW multimers were detectable in all, and VWF function had returned to normal (Figs. 1 and 2). Notably, in four patients who were tested on the first day after explantation, analyses revealed that AVWS was no longer present.

Interestingly, we observed no AVWS at any time point in the patients with a total artificial heart (TAH). VWF multimeric analysis displayed regular HMW multimers (Fig. 2). VWF:CB/VWF:Ag ratio (0.76 ± 0.25 and 0.72 ± 0.12, respectively) and VWF:RCo/VWF:Ag-ratio (0.79 ± 0.15 and 0.77 ± 0.09) were normal at one week and ≥3 weeks after TAH implantation.

Major bleeding complications occurred in both HeartMate II® patients (haemothorax or gastrointestinal bleeding) and in four of the five BVAD patients (haemothorax or haemopericardium).

Table 2: Laboratory values of VAD patients. Data were assessed on the first day, within two weeks and at least three months after VAD implantation and again after explantation. VWF:Ag, von Willebrand factor antigen; VWF:CB, collagen binding capacity of VWF; VWF:RCo, ristocetin cofactor activity of VWF; FVIII:C, factor VIII activity; INR, international normalised ratio; aPTT, activated partial thromboplastin time; CPR, C-reactive protein; HB, haemoglobin; HKT, haematocrit.

<table>
<thead>
<tr>
<th>VAD</th>
<th>day 1</th>
<th>≤2weeks</th>
<th>≥3 months</th>
<th>VAD off</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>normal</td>
<td></td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>VWF:Ag</td>
<td>0.6–1.5 U/ml</td>
<td>2.3</td>
<td>0.7</td>
<td>5</td>
</tr>
<tr>
<td>VWF:CB</td>
<td>0.6–1.5 U/ml</td>
<td>1.5</td>
<td>0.8</td>
<td>5</td>
</tr>
<tr>
<td>VWF:RCo</td>
<td>0.5–1.8 U/ml</td>
<td>1.8</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>FVIII:C</td>
<td>0.7–1.6 U/ml</td>
<td>0.6</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>INR</td>
<td>0.85–1.15</td>
<td>1.0</td>
<td>0.1</td>
<td>5</td>
</tr>
<tr>
<td>aPTT</td>
<td>23–36 seconds</td>
<td>35.4</td>
<td>2.6</td>
<td>5</td>
</tr>
<tr>
<td>Platelets</td>
<td>140–400 x 1000/μl</td>
<td>150.2</td>
<td>74.0</td>
<td>5</td>
</tr>
<tr>
<td>CRP</td>
<td>&lt;5 mg/l</td>
<td>117.3</td>
<td>77.8</td>
<td>5</td>
</tr>
<tr>
<td>HB</td>
<td>12–18 g/dl</td>
<td>9.9</td>
<td>0.9</td>
<td>5</td>
</tr>
<tr>
<td>HKT</td>
<td>37–52%</td>
<td>28.9</td>
<td>2.1</td>
<td>5</td>
</tr>
</tbody>
</table>

Figure 2: Representative image of VWF multimeric analysis of a VAD patient three months after implantation (A) and on the first day after heart transplantation (HTX), that is, after explantation (B), and of a patient three weeks after TAH implantation (C). Standard human plasma (SHP) is blotted as control. Loss of HMW multimers during VAD support is indicated by missing bands in the upper part of the gel (arrow).

However, no bleeding was observed in the two patients with the VentrAssist® device. One TAH patient developed a haemothorax that required surgical evacuation 30 days after implantation. At that time the patient’s platelet count was 138,000/μl and aPTT was 67 seconds.

All patients in this study suffered from moderate anaemia regardless of the duration or type of mechanical assistance (Tables 2 and 3). We also noted increased CRP within the first two weeks after implantation and following explantation. However, CRP returned to normal in three of seven patients during long-term sup-
Discussion

Bleeding in patients with VAD or TAH can result from several causes including therapeutic anticoagulation, consumptive coagulation, liver insufficiency, and AVWS. Most patients present more than one reason. While AVWS has previously been reported in VAD patients (1–5), our study demonstrates that it is readily detectable shortly after device implantation, in keeping with the single-case report by Velik-Salchner et al. (5). Moreover, we found that it quickly resolved following VAD removal. In contrast to patients with an implanted VAD, our patients with a total artificial heart (TAH) did not develop AVWS.

VAD and TAH systems follow different principles of mechanical circulatory support. VADs are connected to the chambers of the native heart and major arteries by inflow and outflow cannulas. Extracorporeal systems (like the Thoratec BVAD assessed in this study) also contain rather long blood-conducting tubes. TAHs, however, replace the native heart and are connected immediately to the remaining atria and large cardiac vessels. Thus, they do not require cannulas and blood-transporting tubes. In addition, their inlet and outlet dimensions correspond to normal human anatomy. Of note, TAH patients receive an anticoagulation regimen similar to that of the VAD patients.

The role of increased shear stress in AVWS has previously been demonstrated in other cardiac diseases. Vincentelli et al. (22) calculated the shear stress at aortic stenoses in vitro and demonstrated an association between elevations in shear stress and the loss of HMW multimers. In addition, AVWS has been shown to resolve in affected patients with aortic stenosis following valve replacement (23). While data allowing us to clinically calculate shear stress in VADs are not easily or reliably accessible, a number of investigations of blood flow in different types of VADs using various theoretical methods have been published. They all report increased shear stress, turbulence and high velocity in the inflow and outflow cannulas of VADs (24–27). These observations are consistent with our findings of loss of HMW multimers in VAD patients, and support our hypothesis that device-related increases in shear stress may play an important role in the development of AVWS in patients with VADs. Although our analysis is hampered by small cohort size, our generally consistent finding of an acute development of AVWS following implantation as well as its rapid and complete reversal after VAD explantation, similar to its disappearance following aortic valve replacement (27), provide further evidence to support this mechanism of action.

We have previously described varying extents of haemolysis in patients with different devices (28). Haemolysis was most pronounced in BVAD patients, less severe with the HeartMate II® and only mild in patients with a VentrAssist®. Similarly, we have found in the current study that the extent and time course of AVWS differed among patients who had different types of VAD devices implanted. All patients with the axial intracorporeal HeartMate II® and with the pneumatic paracorporeal BVAD had early onset, persistent AVWS at all time-points examined. On the other hand, both patients with the centrifugal intracorporeal VentrAssist® displayed changing patterns of AVWS after VAD implantation. However, ultimately both developed AVWS. In keeping with this difference between devices, Malehsa et al. (29) have described in a single-case report the development of AVWS in a patient after switch from a HeartMate XVE® (an intracorporeal pulsatile pump) to a HeartMate II®. Here again it appears that different operating modes, surfaces and tube lengths of VAD systems may be producing varying degrees of shear stress and a variable risk of side effects.

We also observed that all of our patients with VAD or TAH displayed normal or increased levels of VWF antigen. We believe that this can be explained by the presence of a chronic inflammatory state in patients who are supported by a VAD or TAH (30). Increased values of VWF:Ag are part of an acute phase reaction, which is further demonstrated in our patients by the occurrence of increased CRP values. However, while total VWF antigen was in-

### Table 3: Laboratory values of TAH patients after one and at least three weeks following implantation.

<table>
<thead>
<tr>
<th></th>
<th>1 week</th>
<th>≥20 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>VWF:Ag</td>
<td>0.6–1.5 U/ml</td>
<td>3.4</td>
</tr>
<tr>
<td>VWF:CB</td>
<td>0.6–1.5 U/ml</td>
<td>2.6</td>
</tr>
<tr>
<td>VWF:RCo</td>
<td>0.5–1.8 U/ml</td>
<td>3.2</td>
</tr>
<tr>
<td>VWF:HC</td>
<td>0.7–1.6 U/ml</td>
<td>2.3</td>
</tr>
<tr>
<td>INR</td>
<td>0.85–1.15</td>
<td>1.2</td>
</tr>
<tr>
<td>aPTT</td>
<td>23–36 seconds</td>
<td>52.7</td>
</tr>
<tr>
<td>Platelets</td>
<td>140–400 x 1000 /μl</td>
<td>92.0</td>
</tr>
<tr>
<td>CRP</td>
<td>&lt;5</td>
<td>83.0</td>
</tr>
<tr>
<td>HB</td>
<td>12–18 g/dl</td>
<td>8.8</td>
</tr>
<tr>
<td>HKT</td>
<td>37–52%</td>
<td>27.4</td>
</tr>
</tbody>
</table>
increased the ratios of VWF:CB/VWF:Ag and of VWF:RCo/VWF:Ag were decreased, indicating the loss of the HMW multimers and impaired functional activity of the protein. This finding is consistent with the impaired platelet aggregation in VAD patients, independent of anticogulation therapy, that has been reported by others (2, 3).

In conclusion, we have identified the development of AVWS in patients following implantation of a VAD with a subsequent resolution following device explantation. AVWS was not observed in patients with a TAH. These findings suggest that the canulas and tubes that connect the VAD to the native circulation may be contributing to the development of AVWS as a result of an increase in shear stress. Other causative factors may include different types of surfaces of pumps and tubes that have not been previously evaluated. These results should spur efforts to re-design VADs so that they minimise the presence of surfaces that result in unphysiologically high and detrimental shear stress.

Disclosures
Both patients with a VentAssist® ventricular assist device were included in the BRACE study (“Better Results and Cost Effectiveness”) sponsored by Ventracor Limited, Chatswood, Australia. The study presented here is supported partially by CLS Behring, Hattersheim am Main, Germany.

Acknowledgement
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References