Acquired type 2A von Willebrand syndrome caused by aortic valve disease corrects during valve surgery

C. Solomon1,2*, U. Budde4, S. Schneppenheim4, E. Czaja2, C. Hagl3, H. Schoechl5, M. von Depka6 and N. Rahe-Meyer2

1 Department of Anaesthesiology and Intensive Care, Salzburger Landeskliniken SALK, Salzburg, Austria
2 Department of Anaesthesiology and Intensive Care Medicine and 3 Department of Cardiac, Thoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany
4 Department of Haemostasis, Aesculabor, Hamburg, Germany
5 Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria
6 Haemophilia Department, Werlhof Institute, Hannover, Germany

* Corresponding author. E-mail: solomon.cristina@googlemail.com

Editor’s key points

• Aortic valvular disease can cause an acquired type 2A von Willebrand syndrome due to reduced high molecular weight multimers (HMWM) of von Willebrand factor, but its impact on perioperative haemostasis is unknown.

• In this prospective observational study of 17 patients undergoing aortic valve (AV) surgery, reduced HMWM present before operation normalized by the end of cardiopulmonary bypass (CPB).

• Bleeding after CPB is unlikely to be related to persistent type 2A von Willebrand syndrome in patients undergoing AV surgery.

Background. Aortic valve (AV) defects can destroy high molecular weight multimers (HMWM) of von Willebrand factor (VWF), leading to acquired von Willebrand syndrome (aVWS) type IIA. This syndrome is considered a cause for increased perioperative bleeding in AV surgery. If diagnosed before operation, administration of VWF/FVIII concentrates is recommended. However, there is currently no evidence that the VWF HMWM defect persists during surgery long enough to require haemostatic therapy. We hypothesized that the preoperative VWF HMWM defect corrects already during cardiopulmonary bypass (CPB) before any haemostatic therapy.

Methods. This prospective observational study enrolled 17 patients undergoing AV surgery, either isolated or associated with mitral valve or aorta surgery, and also 10 patients undergoing coronary artery bypass surgery (CABG) for comparison. VWF HMWM, VWF antigen (VWF:Ag) concentration, and collagen-binding capacity (VWF:CB) were measured before operation, directly after weaning from CPB, and on the first postoperative day.

Results. In 12 of the 17 subjects undergoing AV surgery (71%), VWF HMWM were abnormally absent before operation. At the end of CPB, VWF HMWM were normal in 15 of AV subjects (88%), and was normal in 16 subjects on the first postoperative day. VWF:Ag and VWF:CB were within or above the normal range at all three times. Two out of 10 subjects undergoing CABG (20%) had preoperative deficits of VWF HMWM that normalized after operation.

Conclusions. Preoperative VWF HMWM defects corrected at the end of CPB in the absence of haemostatic therapy in most patients undergoing AV surgery. Diffuse bleeding occurring after CPB is unlikely to be related to persisting type 2A von Willebrand syndrome; other causes of coagulopathy should be suspected. Administration of VWF/FVIII concentrates appears unnecessary in this setting.

Keywords: coagulation; surgery, cardiovascular

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Acquired deficiency of the high molecular weight multimers (HMWM) of von Willebrand factor (VWF) and manifest bleeding signs have been described in aortic valve (AV) disorders. The HMWM deficiency occurs through multiple mechanisms: blood flow disturbances induce high shear stress that affects the endothelium, activates platelets, and changes the shape of VWF molecules from a coil to an elongated filament. Unfolding the VWF molecule exposes ADAMTS-13 cleavage sites, resulting in degradation and loss of VWF HMWM. Lack of VWF HMWM has been reported to increase bleeding tendency. In contrast, some researchers have described a pronounced discrepancy between bleeding symptoms and the prevalence of VWF abnormalities in patients with AV defects. In cardiac surgery performed with cardiopulmonary bypass (CPB), the clinical decision for haemostatic therapy can only be made after neutralization of heparin and weaning from CPB, and should be made as fast as possible.
In patients undergoing AV surgery, one would expect the persistence of the VWF HMWM defect to be an important cause of bleeding after CPB. However, unlike for the deficit in fibrinogen concentration/fibrin quality or in platelet activity, this assumption cannot be verified in real time in the perioperative setting because there is currently no rapid test for VWF HMWM. Electrophoretic multimer analysis can identify a VWF HMWM defect before operation, but this method is too time-consuming and complex for intraoperative application. Collection of plasma samples and analysis at later time points in specialized laboratories is the only procedure currently available.

For patients with acquired von Willebrand syndrome (aVWS), prophylactic perioperative administration of VWF/FVIII concentrates has been recommended, even in the absence of preoperative spontaneous bleeding symptoms. However, there are no reports on the perioperative evolution of VWF HMWM, particularly at the end of CPB, in patients undergoing corrective AV surgery.

Our hypothesis was that the preoperative VWF HMWM defect is corrected during CPB before any haemostatic therapy, and that consequently it has little or no influence on perioperative bleeding and transfusion in AV surgery.

**Methods**

**Study design**

This study represents an analysis of plasma samples in a cohort of consecutive patients undergoing cardiac surgery with CPB. Samples were collected during a 2 week period in October 2006. Inclusion criteria were age above 18, elective surgery, and no preoperative coumarins. Patients with congenital bleeding disturbances were excluded from the study. Bleeding history was recorded using the model proposed by Koscielny and colleagues. The study was approved by the local Ethics Committee and all patients gave informed consent. Changes in VWF HMWM represented the primary study outcome.

**Study subjects**

From a total of 70 patients undergoing cardiac surgery with CPB during the study period, 17 patients undergoing AV surgery were included in the study (AV surgery group). Five patients underwent isolated AV surgery, four patients combined AV and mitral valve surgery, three patients AV and ascending aorta surgery, and five patients AV, ascending aorta, and aortic arch surgery. Selected CABG patients were also included for comparison: those with the lowest transfusion and postoperative drainage volume (n=4, low transfusion CABG subgroup) and those with the highest transfusion (n=6, high transfusion CABG subgroup). Thus, 10 out of 37 patients undergoing CABG were included in the study.

**Perioperative procedures**

General anaesthesia was induced with etomidate, fentanyl, and cisatracurium. After initial anticoagulation with pig mucosal heparin (400 IU kg⁻¹), additional doses were administered to maintain activated clotting time >480 s (ACT Plus; Medtronic, Minneapolis, MN, USA). One million kallikrein inhibiting units (KIU) of aprotinin were administered before CPB and 1 million KIU were added to the CPB prime. Heparin was neutralized with protamine sulphate, 1 mg protamine per 100 units of total heparin, immediately after weaning from CPB. Activated clotting time <150 s indicated reversal of the effects of heparin. Arterial blood gas was monitored according to α-stat and haemacritic was maintained above 25% intraoperatively and above 28% after operation by red blood cell transfusion. If diffuse microvascular bleeding was observed after weaning from CPB and neutralization of heparin, fresh-frozen plasma (FFP) and platelet concentrates were administered according to clinic standards: 1–2 units of apheresis platelet concentrates were used as a first-line therapy in the case of recent intake of platelet aggregation inhibitors; otherwise, FFP in an amount of 10–15 ml kg⁻¹ bodyweight was applied as a first-line haemostatic therapy. Intraoperative haemostatic transfusion was considered sufficient when the bleeding clinically observed on the mediastinal operation field was reduced to a secure level. Haemostatic therapy at the intensive care unit (ICU) was performed according to chest tube drainage volume: for bleeding >200 ml in two consecutive half-hours, transfusion of 2 units of FFP or 2 units of FFP and 1 unit of platelet concentrate was administered.

**Blood samples**

Blood was collected in 3.8% citrate and EDTA (both Sarstedt collection vials, Sarstedt, Germany) before induction of anaesthesia (T1), after weaning from CPB (T2), and on the first postoperative day in the ICU (T3) according to the local protocol of coagulation monitoring. Citrated blood samples were centrifuged at 3000g for 15 min to obtain platelet-poor plasma, which was stored at −70°C until analysis.

**Coagulation tests**

The VWF multimer pattern was assessed using low-resolution (1.2%) low-gelling temperature agarose gel electrophoresis, Western blot with luminescence video imaging, and subsequent quantitative characterization by densitometric analysis. VWF HMWM were defined as band 11 or greater of that found in normal human plasma. The VWF HMWM content was expressed as a percentage of that found in normal human plasma.

Additional tests included determination of VWF antigen (VWF:Ag) and VWF collagen-binding capacity (VWF:CB) based on ELISA analyses. The collagen-binding capacity assesses the affinity of the HMWM of VWF for collagen. Equine type I collagen fibrils (95% collagen type I and 5% collagen type III) were used in accordance with European Pharmacopoeia recommendations (expert group 6B). The VWF:CB/VWF:Ag ratio was also calculated because it...
potentially offers information on VWF function even when absolute levels are elevated.8

Other analyses of the blood samples obtained perioperatively included activated partial thromboplastin time, prothrombin time, fibrinogen concentration, platelet count, and haematocrit, performed in the clinic’s central laboratory.

Statistical analysis

The distribution of data was evaluated using the Kolmogorov–Smirnov test. The data were considerably skewed; therefore, analyses were performed using non-parametric methods and the data were presented as median (minimum, maximum). Differences between time points were assessed using the Wilcoxon test. A \( P \)-value of <0.05 was considered significant. The data were analysed using SigmaPlot 11.0 (Systat Software Inc., Chicago, IL, USA) and MedCalc (MedCalc Software, Mariakerke, Belgium). The study was considered exploratory; therefore, sample size was not calculated \textit{a priori}.

Results

Patient characteristic and surgery data

The patient characteristic and clinical data are listed in Table 1. None of the patients included in the study had been diagnosed with aVWS before operation. The bleeding history was positive in only one patient who belonged to the high transfusion CABG subgroup. This patient reported spontaneous muco-cutaneous bleeding that accompanied long-term intake of aspirin. One patient in the low transfusion CABG subgroup reported taking aspirin within 2 days before surgery. One patient in the high transfusion CABG subgroup reported taking clopidogrel, but no aspirin, within the same time frame. None of the CABG patients had taken oral anticoagulants during the immediate preoperative period. None of the patients undergoing AV surgery had taken platelet inhibiting agents or oral anticoagulants before operation.

Changes in von Willebrand HMWM

The perioperative evolution of VWF parameters is presented in Table 2. The qualitative pattern of VWF HMWM and corresponding quantitative densitometric analysis from one subject undergoing isolated AV surgery are illustrated in Figure 1. In 12 of the 17 subjects undergoing AV surgery (71%), VWF HMWM were abnormally absent before operation (Table 2). At the end of CPB, VWF HMWM were normal in 88% of AV subjects—all of them except two: one subject who also showed absence of VWF HMWM before operation and on the first postoperative day (Table 2), and one subject who showed normal VWF HMWM at these time points. Two out of the 10 subjects undergoing CABG (20%) had preoperative deficits of VWF HMWM. These defects persisted until the end of CPB in one patient, but the postoperative analysis showed normal distribution of VWF HMWM in all subjects.

Changes in other VWF parameters

The VWF:Ag concentration was within or above the normal range of 50–160% at all times in both the AV surgery and CABG groups (Fig. 2). For the AV surgery subjects, mean preoperative and end-of-CPB values for VWF:Ag were comparable (\( P = 0.79 \)), but mean postoperative values were significantly higher than the preoperative and end-of-CPB values (\( P = 0.001 \) and 0.0017, respectively). For the CABG subjects, first postoperative day values were significantly higher than those at the end of CPB (\( P = 0.027 \)).

Also VWF:CB was normal (50–250%) or higher than normal at all times (Fig. 2). The absolute values for VWF:CB in the AV group on the first day after operation were significantly higher than those observed before operation (\( P = 0.0007 \)) and at the end of CPB (\( P = 0.0009 \)). There were no significant differences in VWF:CB between time points in CABG subjects.

Among AV surgery patients, the preoperative VWF:CB/ VWF:Ag ratio was normal (0.8–2) in 82%, and slightly decreased in 18%. The corresponding percentages in the CABG group were 90% and 10%, respectively. No abnormal values were observed after this time point (data not shown).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>AV surgery (n = 17)</th>
<th>Low transfusion CABG (n = 4)</th>
<th>High transfusion CABG (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59 (27, 74)</td>
<td>68 (53, 71)</td>
<td>67 (57, 78)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>95 (59, 128)</td>
<td>73 (66, 79)</td>
<td>84 (73, 105)</td>
</tr>
<tr>
<td>Male</td>
<td>11</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Obesity (body mass index &gt;30 kg m(^{-2}))</td>
<td>7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Smoking</td>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>13</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>153 (44, 354)</td>
<td>72 (70, 87)</td>
<td>67 (52, 160)</td>
</tr>
<tr>
<td>Aortic clamp time (min)</td>
<td>90 (30, 210)</td>
<td>45 (33, 48)</td>
<td>43 (26, 110)</td>
</tr>
<tr>
<td>Lowest temperature on CPB (°C)</td>
<td>32.6 (28, 35.5)</td>
<td>34.6 (34, 34.9)</td>
<td>34.3 (34.2, 36.1)</td>
</tr>
</tbody>
</table>
not associated with spontaneous bleeding tendency. This before operation abnormal VWF HMWM distribution was such as muco-cutaneous bleeding.16 In the present study, been associated with signs of primary haemostasis disorders circulation. 

In the subject with isolated-AV surgery [6 (0, 16) units] and high transfusion in the patients with AV, ascending aorta, and aortic arch surgery [15 (8, 67) units]. Subjects in the low transfusion CABG subgroup received no transfusion of allogeneic blood products and had a mean 24 h postoperative drainage volume of 55 ml. Subjects in the high transfusion CABG subgroup received 11 (6, 18) units and had a high 24 h postoperative drainage volume of 1110 (900, 1800) ml.

**Perioperative bleeding parameters**

In the 17 subjects undergoing AV surgery, total transfusion after CPB and during the first day at ICU varied according to the complexity of the operation, with lowest transfusion in the subjects with isolated-AV surgery [6 (0, 16) units] and highest transfusion in the patients with AV, ascending aorta, and aortic arch surgery [15 (8, 67) units]. Subjects in the low transfusion CABG subgroup received no transfusion of allogeneic blood products and had a mean 24 h postoperative drainage volume of 55 ml. Subjects in the high transfusion CABG subgroup received 11 (6, 18) units and had a high 24 h postoperative drainage volume of 1110 (900, 1800) ml.

**Discussion**

The present study confirmed that a large percentage of patients with AV defects present with non-symptomatic aVWS type II A, characterized by a deficit of HMWM. We show that normal VWF HMWM distribution was restored intraoperatively in patients undergoing AV surgery (isolated or combined with mitral valve or aortic surgery). This effect was observed immediately after weaning from CPB, before any haemostatic therapy, and persisted during the first postoperative day. These findings suggest that the preoperative VWF HMWM defect is corrected early enough to not represent a cause of bleeding after weaning from extracorporeal circulation.

The lack of VWF HMWM in patients with AV defects has been associated with signs of primary haemostasis disorders such as muco-cutaneous bleeding.1 6 In the present study, before operation abnormal VWF HMWM distribution was not associated with spontaneous bleeding tendency. This observation is in agreement with the apparent discrepancy between the low frequency of bleeding symptoms and the high prevalence of haemostatic abnormalities described by Sucker and colleagues6 in this setting.

A number of previous studies have described a preoperative abnormality in VWF HMWM distribution pattern in patients undergoing AV surgery. A normalized pattern was subsequently reported on the first postoperative day, and the normal pattern was maintained for 7 days,1 1,6 and 6 months,1 16 except in patients with a prosthesis mismatch.6 The earliest time point for the investigation of VWF HMWM distribution reported in the literature is 3 h after surgery.1 None of these studies investigated VWF HMWM distribution intraoperatively, immediately after weaning from CPB, although this is the time when bleeding status is assessed, haemostatic therapy is chosen and most blood products and coagulation factor concentrates are administered.

Surgical correction of the AV defect, resulting in decreased mechanical stress on de novo secreted VWF HMWM, has been suggested as an explanation for the normalization of VWF HMWM distribution observed late after operation.6 In contrast, our data support the hypothesis that vascular and cardiac surgery activate endothelial cells,17 18 triggering the release of intact VWF HMWM from the endothelial pool during an acute intraoperative inflammatory reaction. As long as normal VWF HMWM endothelial pools are available (i.e. in the absence of hereditary VWF HMWM defects; in the absence of severe, prolonged bleeding causing a generalized haemostatic deficit), release of normal VWF HMWM during CPB can be expected. Comparable correction of VWF HMWM was also described in a randomized study investigating the effects of desmopressin on postoperative bleeding.19 In that study, VWF HMWM were absent before operation in a mixed collective of patients with aortic, mitral valve disease, or both and increased significantly within minutes after weaning from CPB regardless of desmopressin administration. A second mechanism of HMWM normalization might involve a change in the activity of ADAMTS-13 after cardiac surgery, leading to a change in the percentage of degraded VWF HMWM molecules. However, results are conflicting (i.e. an increase of 10%).20

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**Table 2** Perioperative changes in VWF parameters. Data are shown as median (minimum, maximum) or number of subjects. T1 = before operation; T2 = end of cardiopulmonary bypass; T3 = first postoperative day. *At this time point, samples were obtained from only four of the five patients (the fifth patient had died after surgery). VWF:Ag normal range 50–160%; VWF:CB normal range 20–250%; VWF:CB/VWF:Ag normal range 0.8–2. VWF, von Willebrand factor; HMWM, high molecular weight multimers; VWF:Ag, von Willebrand factor antigen; VWF:CB, von Willebrand collagen-binding capacity; AV, aortic valve; Low CABG, low transfusion coronary artery bypass grafting; High CABG, high transfusion coronary artery bypass grafting.

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Subjects with normal VWF HMWM</th>
<th>VWF:Ag (%)</th>
<th>VWF:CB (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
</tr>
<tr>
<td>AV surgery (n=17)</td>
<td>5</td>
<td>15</td>
<td>15*</td>
</tr>
<tr>
<td>Low CABG (n=4)</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>High CABG (n=6)</td>
<td>5</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

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**Standard laboratory analyses**

In all groups, decreases in haemoglobin, haematocrit, fibrinogen plasma concentration, and platelet count were observed at the end of CPB, followed by partial or complete recovery on the first postoperative day. There was no statistically significant difference in preoperative platelet count between subjects undergoing AV surgery or CABG.
or an estimated decrease of 40%)\textsuperscript{21} and could be influenced by the method used to measure ADAMTS-13 activity.

The correction of VWF HMWM distribution could depend on the severity of the trauma: the more severe or prolonged the trauma, the higher the amount of normal VWF HMWM released from endothelial pools. The VWF HMWM-dependent postoperative bleeding risk could be considerably lower in patients with AV defects undergoing corrective cardiac surgery than in those with AV defects undergoing less traumatic surgical interventions. A prospective comparison between AV patients undergoing surgery of different extent might confirm this possibility. Furthermore, measurements of VWF HMWM during minor and major surgery in AV patients with preoperative spontaneous bleeding might further support our hypothesis.

The CABG patients were included to allow comparison of the VWF parameters among AV patients with a group of patients undergoing low-risk cardiac surgery performed on...
CPB. Surprisingly, a VWF HMWM defect was observed in two patients undergoing CABG. The defect was corrected by the end of CPB in one patient and during the first postoperative day in the other patient. More common types of vascular pathology than AV defects could cause VWF HMWM destruction. Post-CPB acute normalization of VWF HMWM might occur via the same acute inflammatory response mechanism as in AV patients. This hypothesis requires further investigation.

The current haemostatic therapy for aVWS is under debate. There have been no reports of prospective investigations of either VWF status at the end of CPB or the efficacy of the recommended therapy in preventing or correcting bleeding. The administration of VWF/FVIII concentrates is recommended for hereditary VW disease type 2A,22 23 and this recommendation has also been extended to the therapy of the bleeding episodes in aVWS accompanied by the destruction of VWF HMWM, although patients with associated aortic stenosis or other cardiac valve disorders respond infrequently to this therapy.24 Furthermore, it is assumed that patients with aVWS 2A are more prone to bleeding under CPB. On the basis of this assumption, extended laboratory investigation and prophylactic administration of concentrates before surgery are recommended, even in the absence of bleeding symptoms.11 This therapeutic approach has only been described in a case report of a patient with AV stenosis and spontaneous bleeding: VWF/FVIII concentrate was administered as prophylaxis before operation and intraoperatively using the same therapeutic protocol as for patients with hereditary VW disease undergoing corrective valve surgery.25 VWF HMWM were investigated only before operation and on the seventh postoperative day, when the multimer pattern had normalized.

Current guidelines for the management of aVWS recommend administration of VWF/FVIII concentrate immediately before surgery among patients who demonstrate transient improvement in VWF activity with a test dose (rec-
istasis. Clin Appl Thor... 10: 195–204