Acquired von Willebrand syndrome in paediatric patients during mechanical circulatory support

Rouven Kubickia,*, Brigitte Stillerb, Johannes Krollb, Matthias Siepeb, Friedhelm Beyersdorf, Christoph Benkb, René Höhna, Jochen Grohmanna, Thilo Fleck and Barbara Zieger

a Department of Congenital Heart Disease and Pediatric Cardiology, University Heart Center Freiburg-Bad Krozingen, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

b Department of Cardiovascular Surgery, University Heart Center Freiburg-Bad Krozingen, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

c Department of Pediatrics and Adolescent Medicine, Division of Pediatric Hematology and Oncology, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

* Corresponding author. Department of Congenital Heart Disease and Pediatric Cardiology, University Heart Center, Freiburg-Bad Krozingen, Mathildenstrasse 1, 79106 Freiburg, Germany. Tel: +49-761-27043230; fax: +49-761-27044680; e-mail: rouven.kubicki@universitaets-herzzentrum.de (R. Kubicki).

Received 23 July 2018; received in revised form 15 October 2018; accepted 1 November 2018

Abstract

OBJECTIVES: Bleeding signs can become life-threatening complications in patients on mechanical circulatory support (MCS). Clinical phenotyping and comprehensive analyses of the cause of bleeding are, therefore, essential, especially when risk-stratifying patients during MCS workup. We conducted coagulation analyses and determined von Willebrand factor (VWF) parameters in a paediatric cohort on temporary extracorporeal life support, extracorporeal membrane oxygenation or long-term ventricular assist device support.

METHODS: We carried out an observational single-centre study including 30 children with MCS (extracorporeal life support, n = 13; extracorporeal membrane oxygenation, n = 5; and ventricular assist device, n = 12). We also assessed the acquired von Willebrand parameters of each study participant: collagen binding capacity (VWF:CB), the ratio of collagen-binding capacity to VWF antigen (VWF:CB/VWF:Ag) and high-molecular-weight VWF multimers. We also documented bleeding events, transfusion requirement, haemolysis parameters and surgical interventions.

© The Author(s) 2018. Published by Oxford University Press on behalf of the European Association for Cardio-Thoracic Surgery. All rights reserved.
RESULTS: All children developed AVWS (acquired von Willebrand syndrome) during MCS, usually during the early postoperative course. They presented no AVWS after device explantation. We detected a loss of high-molecular-weight VWF multimers, decreased VWF:CB/VWF:Ag ratios and reduced VWF:CB levels. Twenty of the 30 patients experienced bleeding complications; approximately 53% of them required surgical revision. There were no deaths due to bleeding during support.

CONCLUSIONS: The AVWS prevalence in paediatric patients on MCS is 100% regardless of the types of devices tested in this study. The bleeding propensity of AVWS patients widely varies.

Keywords: Mechanical circulatory support • Paediatrics • Bleeding • Acquired von Willebrand syndrome • Haemostasis

INTRODUCTION

Rapid, recent progress in mechanical circulatory support (MCS) technology and management strategies has extended survival and improved the quality of life of patients experiencing advanced respiratory or heart failure [1, 2]. Extracorporeal circulatory life support (ECLS) and extracorporeal membrane oxygenation (ECMO) play an important role in modern temporary bridging concepts for critically ill children. At the same time, the demand for ventricular assist devices (VADs) for long-term support is rising due to the scarcity of donor organs for transplantation [3].

MCS remains the last resort that is not initiated until all conservative treatment options to save a patient’s life have failed. Typical major complications in patients on MCS are life-threatening bleeding episodes that contribute to significant morbidity and are more frequent than thromboembolic events [4]. These disorders are caused by complex interactions between blood components with the foreign surfaces, changes in haemodynamics and rheology and the concomitant need for anticoagulation therapy [5]. In that context, analysing clinical and biochemical data plays a central role to diagnose acquired von Willebrand syndrome (AVWS), which may be the major cause of bleeding in these patients [6, 7]. AVWS is characterized by the loss of high-molecular-weight (HMW) multimers of von Willebrand factor (VWF), which can be shear stress induced, ultimately impairing VWF’s function [8, 9]. Therefore, in patients with AVWS collagen-binding capacity (VWF:CB), levels are reduced and ratios of collagen-binding capacity to antigen (VWF:CB/VWF:Ag) decreased [9, 10].

Interestingly, AVWS is characterized by significant variation in the severity of bleeding propensity among patients during MCS [10, 11]. Detailed clinical and biochemical phenotyping is essential to risk-stratifying patients during MCS workup. We thus determined VWF parameters in a paediatric cohort undergoing temporary ECLS, ECMO or long-term VAD support.

PATIENTS AND METHODS

An observational single-centre study was conducted to analyse AVWS in patients aged 1–19 years undergoing MCS for a cardiac and/or pulmonary indication between 2008 and 2017. The cohort was divided into 2 groups: patients on ECLS/ECMO and patients on VAD support. Our local ethics committee approved the study protocol. Children on whom we had no analyses of HMW VWF multimers and those with a bleeding disorder prior to MCS were excluded.

Data collection

Baseline demographics comprised age, gender, body surface area, patients’ diagnosis, outcome, indication for MCS, duration of MCS support and the device used for MCS.

Comprehensive analysis for diagnosing AVWS included quantification of VWF:Ag, VWF:CB and the separation of HMW VWF multimers and was done as described previously [10]. The ratio of collagen-binding capacity to antigen (VWF:CB/VWF:Ag) was calculated. Normal value ranges were VWF:Ag 0.6–1.5 U/ml, VWF:CB 0.6–1.5 U/ml and VWF:CB/VWF:Ag >0.7. AVWS was diagnosed when HMW VWF multimers were missing and the ratio of VWF:CB/VWF:Ag was <0.7. Each patient underwent AVWS diagnostics once during MCS. Whenever feasible, blood samples were also collected before implantation and after device explantation.

Each study participant’s bleeding events, the need for transfusions and bleeding episodes requiring surgical intervention were evaluated. A bleeding event was defined as episodes of suspected internal or external bleeding that resulted in either resurgery or haemoglobin depletion requiring red blood cell transfusion.

Haemolysis-related parameters [total haemoglobin and lactate dehydrogenase (LDH)] were measured in all patients. Data from blood samples were routinely obtained during MCS on days 3, 14, 30, 60 and 90 after VAD implantation and similarly on days 3 and 14 after ECLS/ECMO implantation.

Device characteristics and surgical procedures

The ECLS circuit setup included diagonal (Deltastream® DP2 or DP3, MEDOS Medizintechnik AG, Stolberg, Germany) or a centrifugal (Revolution LivaNova Deutschland GmbH, Munich, Germany) pump and a plasma tight polymethylpentene hollow fibre oxygenator HILITE 800LT for flow rates up to 0.8 l/min or a HILITE 2400LT oxygenator for flow rates between 0.8 l/min and 2.4 l/min (MEDOS Medizintechnik AG). The extracorporeal circuit is coated with Rheoparin® (MEDOS Medizintechnik AG) to minimize thrombogenicity. Thin-walled polyurethane arterial cannulae with inner diameters from 8 Fr to 16 Fr depending on the patient’s weight and venous cannulae with bevelled metal multi-port tips in paediatric sizes from 12 Fr to 20 Fr were used. In patients on ECLS, direct aortic (arterial inflow) and transhilar atrial (venous drain) cannulation was usually preferred, while femoral cannulation (inflow via the arteria femoralis and venous drain via the femoral vein) was reserved for older children and adolescents. Patients on ECMO underwent cannulation of the jugular vein (a double-lumen cannula).

Most end-stage heart failure patients received a Berlin Heart EXCOR (BHE, Berlin Heart GmbH, Berlin, Germany) as a left ventricular assist device (LVAD). Furthermore, 3 intracorporeal LVADs (HeartMate II® and HeartMate 3®, Thoratec Corporation, Pleasanton, CA, USA; HeartWare®, Framingham, MA, USA) and 1 Thoratec PVAD® (Pleasanton) as LVAD support were implanted. All VADs were implanted via routine median sternotomy (Fig. 1).

None of our patients underwent tandem support (additional ECLS/ECMO during VAD support).
were observed, the pump was replaced.

detect any early formation of small thrombi. If larger thrombi
BHE pumps were subjected to transillumination twice daily to
stored using anti-Xa levels with target of 0.8–1.2 IU/ml. Target INR
(vitamin K antagonist). Low-molecular-weight heparin was moni-
time lasting 60–80 s. For long-term therapy, patients were
unfractionated heparin titrated to a target partial thromboplastin
platelet count >100 000/mm$^3$.

Anticoagulation for all 4 LVAD systems was started with
unfractionated heparin titrated to an activating clotting time be-
tween 160 s and 180 s. Fibrinogen was maintained at >200 mg/dl,
antithrombin III >70%, haemoglobin level >10 mg/dl and the

Anticoagulation with extracorporeal life support, extracorporeal membrane oxygenation and
ventricular assist devices

During ECLS/ECMO support, patients were anticoagulated with
unfractionated heparin titrated to an activating clotting time bet-

### Statistical analysis

Due to the relatively small number of patients in our study co-
hort, our analysis is predominantly descriptive. Categorical varia-
bles are presented as absolute numbers and percentages. Continuous data were summarized as mean ± standard deviation (SD) and median (range). The non-parametric Mann–Whitney U-test and the Wilcoxon signed-rank test were used to assess statistical significance. No correction was performed for multiple testing. All statistical tests were 2-sided, and $P$-values <0.05 were considered statistically significant. The results are shown as box-and-whiskers plots. The freedom-from-bleeding-complication analysis was done using the Kaplan–Meier graphs. Data were analysed using SPSS 23.0 (SPSS, Inc., Washington, DC, USA).

### RESULTS

A total of 30 patients were included: 18 children required ECLS or ECMO support and 12 children underwent VAD support. Table 1 illustrates patients’ basic characteristics including MCS-related data and outcome.

von Willebrand factor parameters and acquired von Willebrand syndrome

VWF was analysed prior to MCS support in 4 patients (ECLS $n=3$; VAD $n=1$) and revealed no evidence of AVWS. One child presented elevated levels of VWF:Ag and VWF:CB with a normal VWF:CB/VWF:Ag ratio (Table 1, the ECLS/ECMO group: patient 14), potentially stress related.

During MCS, 18 children on ECLS/ECMO were tested a median 3 days (range 1–14 days), and 12 patients on VAD support were analysed a median 14 days (range 3–369 days) after device im-
plantation. All children fulfilled the AVWS criteria, presenting loss of HMW VWF multimers and reduced VWF:CB/VWF:Ag ratios <0.7 (Figs 2 and 3).

During MCS, in the ECLS/ECMO group, 72% of the patients revealed reduced levels of VWF:CB, leading to reduced VWF:CB/ VWF:Ag ratios. The remaining 28% of the patients had normal VWF:CB values. Sixty-seven percent of the children had elevated VWF:Ag values >1.5 U/ml.

During VAD support, 33% of the patients exhibited reduced levels of VWF:CB, leading to reduced VWF:CB/VWF:Ag ratios. Fifty percent of the patients had normal VWF:CB levels. VWF:CB levels in 2 children were above normal; however, VWF:Ag was upregulated at the same time, which lowered the VWF:CB/VWF:Ag ratio to <0.7 due to the loss of HMW VWF multimers. Overall, 67% presented elevated VWF:Ag levels >1.5 U/ml.

Interestingly, children on ECLS/ECMO tended to present lower VWF:CB levels (median 0.45 vs 0.8 U/ml) and VWF:CB/VWF:Ag ratios (median 0.26 vs 0.44) during MCS than the VAD patients.

Finally, after removing MCS (ECLS/ECMO $n=11$; VAD $n=7$), AVWS was no longer detectable, as reflected in normalized VWF:CB/VWF:Ag ratios in all patients already on day 1 after device explantation (median 0.26 during ECLS/ECMO vs median 0.92 after ECLS/ECMO, $P=0.003$; median 0.44 during VAD vs median 0.97 after VAD, $P=0.018$). VWF:CB normalized in both groups (median 0.45 U/ml during ECLS/ECMO vs median 2.16 U/ ml after ECLS/ECMO, $P=0.003$; median 0.81 U/ml during VAD vs median 1.78 IU/ml after VAD, $P=0.018$). Interestingly, some patients even revealed upregulated VWF:CB >2.5 U/ml. Loss of HMW VWF multimers was no longer detectable.

### Bleeding complications

Bleeding events were distributed similarly in both groups (Table 2). In 61% children on ECLS/ECMO, we documented 19 bleeding events, corresponding to a rate of 0.11 bleeding events per day on MCS. The median time to first bleeding event was 3 days from device implantation (range: 1–14 days). On VAD, 9 (75%) patients had 22 bleeding events - a rate of 0.01 bleeding events per day on MCS. The median time to event was 12 days from device implantation (range: 1–125 days). Figure 4 shows the freedom from bleeding complications in both groups.

Considering our entire study cohort, approximately 53% required surgical revision in addition to conservative therapy, and approximately two-thirds were conspicuous due to recurring bleeding complications. No patient succumbed to haemorrhage during support. We found no association with patients’ ages, bleeding location or overall outcome and risk of bleeding in either group. Bleeding events occurred regardless of varying support systems.

---

**Table 1**

<table>
<thead>
<tr>
<th>MCS</th>
<th>LVAD $n=12$</th>
<th>ECLS / ECMO $n=13$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(as oxygenator included)</td>
<td>(oxygenator included)</td>
</tr>
<tr>
<td>BH EXCOR</td>
<td>$n=8$</td>
<td>$n=4$</td>
</tr>
<tr>
<td>adult sized VAD</td>
<td>$n=4$</td>
<td></td>
</tr>
<tr>
<td>HVAD, HM II, HM 3: Thoracic</td>
<td>$n=6$</td>
<td>$n=7$</td>
</tr>
<tr>
<td>ECLS</td>
<td>$n=11$</td>
<td>$n=2$</td>
</tr>
<tr>
<td>central (RA + Ao ascendens)</td>
<td></td>
<td>peripherical</td>
</tr>
<tr>
<td>ECLS</td>
<td>$n=11$</td>
<td></td>
</tr>
<tr>
<td>peripherical (v-regular)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Mechanical circulatory support (MCS)—ECLS, ECMO, VAD. Ao asc: Aortic ascendens; BH: Berlin Heart; ECLS: extracorporeal life support; ECMO: extracorporeal membrane oxygenation; HM II: Heart Mate II; HM 3: Heart Mate 3; HVAD: Heart Ware; LVAD: left ventricular assist device; MCS: mechanical circulatory support; RA: right atrial; va: veno-arterial; vv: veno-venous; y: years.
Table 1: Patient basic characteristics including MCS-related data and outcome

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (days)</th>
<th>Sex</th>
<th>BW (kg)</th>
<th>Diagnose</th>
<th>Indication</th>
<th>Device</th>
<th>MCS support (days)</th>
<th>Bleeding event</th>
<th>Outcome</th>
<th>Discharge home</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECLS/EMCO</td>
<td>1</td>
<td>17</td>
<td>F</td>
<td>3.0</td>
<td>TAC Typ 4, IAA</td>
<td>Failure to wean from CPB</td>
<td>DP2</td>
<td>20</td>
<td>Yes</td>
<td>Death on MCS</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>62</td>
<td>M</td>
<td>3.4</td>
<td>DORV, LV hypoplasia</td>
<td>Cardiopulmonary arrest</td>
<td>DP2</td>
<td>23</td>
<td>Yes</td>
<td>Death on MCS</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>22</td>
<td>M</td>
<td>6.5</td>
<td>HLHS</td>
<td>Cardiopulmonary arrest</td>
<td>DP2</td>
<td>9</td>
<td>Yes</td>
<td>Death on MCS</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>7</td>
<td>F</td>
<td>3.1</td>
<td>HLHS</td>
<td>Cardiopulmonary arrest</td>
<td>DP2</td>
<td>9</td>
<td>Yes</td>
<td>Successful weaning</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2070</td>
<td>M</td>
<td>22.0</td>
<td>Myocarditis</td>
<td>Failure to wean from CPB</td>
<td>DP2</td>
<td>4</td>
<td>Yes</td>
<td>Bridging to VAD</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1674</td>
<td>M</td>
<td>14.5</td>
<td>ARDS</td>
<td>Pulmonary failure</td>
<td>DP3</td>
<td>7</td>
<td>No</td>
<td>Successful weaning</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>14</td>
<td>M</td>
<td>3.0</td>
<td>HLHS</td>
<td>Cardiopulmonary arrest</td>
<td>DP3</td>
<td>4</td>
<td>Yes</td>
<td>Successful weaning</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>13</td>
<td>F</td>
<td>3.2</td>
<td>Myocarditis</td>
<td>Cardiopulmonary arrest</td>
<td>DP3</td>
<td>9</td>
<td>Yes</td>
<td>Successful weaning</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>142</td>
<td>M</td>
<td>5.6</td>
<td>ARDS</td>
<td>Pulmonary failure</td>
<td>DP3</td>
<td>6</td>
<td>Yes</td>
<td>Successful weaning</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>8</td>
<td>M</td>
<td>3.6</td>
<td>dTGA, coronary anomaly</td>
<td>Failure to wean from CPB</td>
<td>DP3</td>
<td>16</td>
<td>Yes</td>
<td>Successful weaning</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>3</td>
<td>F</td>
<td>3.2</td>
<td>Tricuspid atresia 1A</td>
<td>Failure to wean from CPB</td>
<td>DP3</td>
<td>14</td>
<td>No</td>
<td>Death on MCS</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>8</td>
<td>M</td>
<td>3.2</td>
<td>HLHS</td>
<td>Failure to wean from CPB</td>
<td>DP3</td>
<td>3</td>
<td>No</td>
<td>Successful weaning</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>10</td>
<td>F</td>
<td>3.0</td>
<td>Ebstein anomaly</td>
<td>Failure to wean from CPB</td>
<td>DP3</td>
<td>4</td>
<td>No</td>
<td>Successful weaning</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>1200</td>
<td>M</td>
<td>14.0</td>
<td>ARDS</td>
<td>Pulmonary failure</td>
<td>DP3</td>
<td>19</td>
<td>Yes</td>
<td>Death on MCS</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>46</td>
<td>F</td>
<td>3.3</td>
<td>DORV, ITGA</td>
<td>Failure to wean from CPB</td>
<td>DP3</td>
<td>3</td>
<td>No</td>
<td>Successful weaning</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>177</td>
<td>F</td>
<td>4.0</td>
<td>ARDS</td>
<td>Pulmonary failure</td>
<td>DP3</td>
<td>13</td>
<td>No</td>
<td>Successful weaning</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>135</td>
<td>F</td>
<td>4.7</td>
<td>ARDS</td>
<td>Pulmonary failure</td>
<td>DP3</td>
<td>19</td>
<td>No</td>
<td>Successful weaning</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>7158</td>
<td>M</td>
<td>51.0</td>
<td>HTX, primary graft failure</td>
<td>Failure to wean from CPB</td>
<td>Revolution</td>
<td>6</td>
<td>Yes</td>
<td>Successful weaning</td>
</tr>
<tr>
<td>Median</td>
<td>34</td>
<td></td>
<td></td>
<td>3.5</td>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>3–19 years</td>
<td></td>
<td>3–51</td>
<td>3–23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discharge home rate 50%

| VAD      | 1          | 874 | F       | 6.4                           | DCM                               | Heart failure, NYHA IV             | BHE     | 191                | No            | HTX | Yes            |
|          | 2          | 104 | F       | 4.4                           | DCM                               | Heart failure, NYHA IV             | BHE     | 462                | Yes           | HTX | No             |
|          | 3          | 1525| M       | 15.0                          | DCM                               | Heart failure, NYHA IV             | BHE     | 286                | No            | HTX | Yes            |
|          | 4          | 1052| F       | 13.0                          | DCM                               | Heart failure, NYHA IV             | BHE     | 17                 | Yes           | HTX | Yes            |
|          | 5          | 269 | M       | 8.5                           | Congenital aortic stenosis         | Heart failure, NYHA IV             | BHE     | 210                | Yes           | Death under MCS | No |
|          | 6          | 3114| F       | 17.0                          | Combined aortic valve lesion       | Heart failure, NYHA IV             | BHE     | 89                 | Yes           | Death under MCS | No |
|          | 7          | 2074| F       | 22.0                          | Myocarditis                       | Heart failure, NYHA IV             | BHE     | 21                 | Yes           | Successful weaning | No |
|          | 8          | 161 | M       | 5.2                           | HLHS                              | Heart failure, NYHA IV             | BHE     | 31                 | Yes           | Death under MCS | No |
|          | 9          | 2200| M       | 18.0                          | HOCM                              | Heart failure, NYHA IV             | HW      | 130                | Yes           | HTX | Yes            |
|          | 10         | 5830| F       | 59.0                          | Myocarditis                       | Heart failure, NYHA IV             | Thoratec | 15                 | No            | Successful weaning | Yes |
|          | 11         | 6673| M       | 51.0                          | DORV                              | Heart failure, NYHA IV             | HMII    | 485                | Yes           | Successful weaning | Yes |
|          | 12         | 4934| M       | 39.4                          | DCM                               | Heart failure, NYHA IV             | HM3     |                    | Yes           | On support | Yes            |
| Median   | 5 years    |     | 16.0        | 130                           |                                  |                                    |         |                    |               |              |                |
| Range    | 0.4–18 years |     | 4.4–59.0     | 15–485                        |                                  |                                    |         |                    |               |              |                |

Discharge home rate 67%

---

aPatient 5 in the ECLS/ECMO group equals patient 7 in the VAD group: the first support on ECLS afterwards bridging to VAD.
bPatient 11 in the VAD group equals patient 18 in the ECLS/ECMO group: the first support on ECMO afterwards ECLS support due to primary graft failure after HTX.

ARD: acute respiratory distress syndrome; AVWS: acquired von Willebrand syndrome; BHE: Berlin Heart EXCOR; BS: body surface; BW: body weight; CBP: cardiopulmonary bypass; DCM: dilatative cardiomyopathy; DORV: double outlet right ventricle; DP2: Deltastream®; DP2: Deltastream®; DP3: Deltastream®; DORV: dextrotransposition of great arteries; ECMO: extracorporeal membrane oxygenation; F: female; HLHS: hypoplastic left heart syndrome; HM3: HeartMate 3®; HMII: HeartMate II®; HOCM: hypertrophic obstructive cardiomyopathy; HTX: heart transplantation; HW: HeartWare®; IAA: interrupted aortic arch; ITGA: left transposition of great arteries; LV hypoplasia: left ventricular hypoplasia; M: male; MCS: mechanical circulatory support; NYHA: New York Heart Association; TAC: truncus arteriosus communis; VAD: ventricular assist device.
Haemolysis parameters

All children in both groups had elevated serum LDH levels $\geq 500$ U/l (exceeding by two-and-a-half the normal range’s upper limit) beyond 72 h postimplant (Fig. 5). The LDH levels of both the groups dropped during MCS. All but 1 VAD patient showed normalized LDH values beyond 60 days of support. Haemoglobin levels were stable during MCS with no significant difference between several time points in both groups.

Transfusion requirement

Figure 6 compares the substitution of blood products in both groups. Children on ECLS/ECMO support significantly required more transfusions of red blood cells ($P = 0.032$) within the first week of MCS than patients with VAD. After the first week, we still noted a trend towards increased demand for red blood cells in the ECLS/ECMO group. Children on ECLS/ECMO support also needed more platelets ($P = 0.013$) than those on VAD assistance.

Thromboembolic events

On day 6, only 1 patient on ECLS presented with large thrombus formation, detected behind the oxygenator. Central thromboembolic events did not occur in children receiving ECLS/ECMO. Thromboembolism occurred in 33% of the patients on VAD at a median time of 185 days after device implantation (range: 17–239). We confirmed 7 cases of clot formation in the pump typically close to the sinus of the valve in three children with BHE.

Figure 2: Box-whisker plots illustrating changes in VWF-associated parameters: (A) ratio of CB capacity to VWF-Ag $(\text{VWF:CB/VWF:Ag})$, (B) CB capacity of VWF $(\text{VWF:CB})$ and (C) VWF:Ag in patients before, during and after ECLS/ECMO support (grey boxes) and in patients before, during and after VAD support (white boxes). Statistical testing with Wilcoxon signed-rank test. Ag: antigen; CB: collagen binding; ECLS: extracorporeal life support; ECMO: extracorporeal membrane oxygenation; MCS: mechanical circulatory support; VAD: ventricular assist device; VWF: von Willebrand factor.
One child with one event; two other patients suffered three events each. All affected pump chambers were readily exchanged. Two patients suffered ischaemic stroke (one of whom had an ischemic stroke and pump thrombosis).

**DISCUSSION**

In this study, we examined the prevalence of AVWS in what is thus far the largest published paediatric cohort undergoing temporary or long-term MCS. Our data demonstrate that all patients develop AVWS and that AVWS is always reversible after device removal. These results are consistent with data from studies on adult patients [10, 12–14] and confirm the assumption of the high prevalence of AVWS during MCS in paediatric patients as well [15–17].

AVWS could already be diagnosed during the very early postoperative period by relying on the 3 typical indicators, namely the loss of HMW VWF multimers, reduced VWF:CB, and a continuous drop in the VWF:CB/VWF:Ag ratio. Our in-house VWF:CB analysis is highly sensitive to the loss of HMW VWF multimers because we employed collagen type I for this analysis. Therefore, VWF:CB analyses can help to identify AVWS. VWF:Ag is an acute-phase protein that is often unspecifically enhanced in patients on MCS, as in our findings. Its diagnostic value as a single parameter is thus low; therefore, a VWF functional parameter such as VWF:CB should also be analysed.

We demonstrated a tendency towards lower VWF:CB levels and VWF:CB/VWF:Ag ratios in patients with ECLS/ECMO compared to patients on VAD support, hinting at a more severe form of AVWS in patients on ECLS/ECMO, a finding that concurs with those of Kalbhenn et al. [18]. Gossai et al. have reported on potential predisposing factors such as older age in children and larger VADs in paediatric patients with BHE, which can trigger bleeding [16]. However, we could not confirm these results. Our result may be attributable to the heterogeneity of our study cohort.

After terminating the MCS, we observed excessive VWF:CB upregulation, meaning that the increase in VWF parameters after MCS may even contribute to enhanced thrombogenicity, which must be considered in follow-ups after MCS termination. Our study cohort suffered no thromboembolic event after MCS. Ultimately, after removing MCS, AVWS was no longer detectable in any child—a fact consistent with data from adult cohorts. In contrast to patients with inherited von Willebrand disease, VWF parameters normalize in patients with AVWS within hours after weaning or heart transplantation [10, 13].

Several studies in adults have provided evidence on the differences in the severity of AVWS and haemolysis among patients implanted with different types of long-term VADs [4, 19, 20]. Haemolysis is also a typical adverse phenomenon during MCS [18, 21]. All children in this study had elevated LDH levels on MCS. We noted a tendency towards lower LDH levels in patients on VAD support compared to those on ECLS/ECMO, but this

---

**Table 2: Bleeding complications during MCS**

<table>
<thead>
<tr>
<th></th>
<th>ECLS/ECMO support (patients n = 18)</th>
<th>VAD support (patients n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with bleeding events, n (%)</td>
<td>11 (61)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Surgical revision, n (%)</td>
<td>9 (50)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Total number of bleeding events</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Rate of bleeding events per day on MCS</td>
<td>0.11</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Location of bleeding**

- Thoracic and mediastinal: 16, 15
- Anaemia of undetermined source/haemolysis: 0, 1
- Gastrointestinal bleeding: 0, 2
- Pulmonary haemorrhage: 3, 2
- Cerebral haemorrhage: 0, 2

<table>
<thead>
<tr>
<th>Number of bleeding events per patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECLS/ECMO</td>
<td>6</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAD</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Figure 4:** The Kaplan–Meier curves showing freedom from bleeding complication on ECLS/ECMO (A) and on VAD (B). *Censored patients. ECLS: extracorporeal life support; ECMO: extracorporeal membrane oxygenation; MCS: mechanical circulatory support; VAD: ventricular assist device.
difference was not statistically significant. Interestingly, LDH levels normalized after 2 months on VAD support.

AVWS is characterized by significant variations in the severity of bleeding propensity among patients on MCS (including clinically mute patients) [9, 10, 16, 17, 22]. The pronounced extent of AVWS in children on ECLS/ECMO is reflected in a 10-fold higher rate of bleeding complications per day on MCS in this group compared to the VAD group. Thus, patients on ECLS/ECMO required more red blood cell and platelet transfusions. Bleeding predominated during the early postoperative period and was primarily located in the surgical wound area, as previously described [5, 12]. Although more than two-thirds of our patients experienced recurrent bleeding events, none died of bleeding. Only the VAD group experienced gastrointestinal bleeding and cerebral haemorrhage. Gastrointestinal bleeding is typical in patients with VWF abnormalities and has been frequently described in adult patients on long-term MCS [23, 24]. Although all children developed AVWS, not all children experienced a bleeding event. Patients with decreased VWF parameters sometimes develop bleeding symptoms only in triggering situations (i.e. surgery or trauma), a phenomenon also described in patients with inherited von Willebrand disease.

Infections may constitute another triggering situation. Incidentally, patient 2 with BHE developed cerebral haemorrhage (Table 1) 305 days after device implantation. This 13-month-old girl had presented stable coagulation and platelet parameters for weeks under therapy with acetylsalicylic acid and clopidogrel. She had viral infection when she began to bleed and developed a very severe platelet function defect, a factor that potentially exacerbated the bleeding tendency. Therefore, children with MCS and infections should be closer monitored.

Further causes contributing to impaired haemostasis are inherited platelet disorders, hepatic insufficiency, temporary thrombocytopenia and inflammation [5, 9, 20]. AVWS can aggravate bleeding tendencies. Therefore, VWF parameters should be investigated in children with MCS and non-surgical bleeding. Since the bleeding event may be triggered by several causes, a score incorporating several parameters, eg, pronounced haemolysis, infections or lower VWF:CB/VWF:Ag ratios, may help to identify patients with an increased risk for bleeding complications.

The therapy for bleeding remains difficult. AVWS treatment must address the underlying disorder, which is only achievable by MCS termination. Open revision is mandatory in patients with surgical bleeding. The response rate to desmopressin is only 10% [11, 25]. As VWF is an acute-phase protein, patients’ VWF storage may already be depleted, thus compromising desmopressin’s efficacy. Antifibrinolytic agents such as tranexamic acid may be used as an add-on therapy, especially in mucocutaneous bleeding [11]. In case of life-threatening bleeding, substitution of VWF-containing FVIII concentrates or recombinant von Willebrand concentrates may be considered [25, 26].

**Limitations**

This is a small series with the corresponding limitations regarding statistical analysis. A preoperative analysis of von Willebrand factor (VWF) was often unfeasible because of the urgent nature of ECLS/VAD implantation after weaning failure or resuscitation. Serial analyses of blood samples were sometimes restricted because of the children’s young age and low body weight. Since this was not possible in all children, we could not determine when exactly the AVWS had developed and thus could not define the level of severity over time. VWF parameters may vary
CONCLUSION

In conclusion, the prevalence of AVWS in paediatric patients on MCS is 100% regardless of the type of devices tested in this study. AVWS is associated with a broad variety of bleeding propensity.

ACKNOWLEDGEMENTS

The authors thank Carole Curten for language editing, Claudia Schmoor for statistical advices and Stefan Heinz for graphic design. They appreciate the technical support by Simone Rosenfelder regarding the laboratory analyses.

Funding

This work was supported by the German Research Foundation [Deutsche Forschungsgemeinschaft, DFG: STI 631/1-1 and DFG ZI486/7-1].

Conflict of interest: none declared.

REFERENCES


