Acquired von Willebrand syndrome in respiratory extracorporeal life support: a systematic review of the literature

MV Malfertheiner, LP Pimenta, V von Bahr, JE Millar, NG Obonyo, JY Suen, V Pellegrino and JF Fraser

ABSTRACT

Background and objective: Venovenous extracorporeal membrane oxygenation (VV ECMO) and extracorporeal CO₂ removal (ECCO2R) are increasingly used in the management of severe respiratory failure. With bleeding complications being one of the major risks of these techniques, our aim in this systematic review was to assess the available literature on acquired von Willebrand syndrome (AvWS) and extracorporeal support. AvWS has previously been associated with bleeding and shear stress.

Design and data sources: A systematic review, using Medline via PubMed, was performed to identify eligible studies up to January 2017.

Results and conclusion: The prevalence of AvWF among patients on VV ECMO or ECCO2R is high, but only a limited number of studies are reported in the literature. AvWS testing should be performed, including vWF multimer analysis, vWF activity and vWF antigen concentration. The extent to which vWF contributes to bleeding during ECMO, or how much changes in ECMO management can influence high molecular weight vWF multimer levels, cannot be answered from the currently available evidence and there remains a need for future studies.


Biology of von Willebrand factor

Von Willebrand factor (vWF) is a multimeric glycoprotein synthesised and stored in large or ultra-large (> 10 000 kDa) forms in endothelial cells and megakaryocytes. In the circulation, large multimers are hyperadhesive and can cause spontaneous agglutination, which has been attributed to its many binding sites for platelets and collagen and extraordinarily long structure. However, excessive breakdown of large multimers can result in higher concentrations of low molecular weight multimers and is associated with severe bleeding complications, as seen in patients with type 2A von Willebrand disease. The size of vWF multimers is therefore tightly regulated and ultralarge forms are cleaved by the enzyme ADAMTS13 into smaller, less reactive molecules. Under normal conditions, these molecules take on a conformation that shields binding sites for platelet glycoprotein 1b (GP1b) receptor, inducing further platelet activation and aggregation. This ultimately results in the formation of a platelet plug. vWF also plays a role in secondary haemostasis by acting as a carrier protein for coagulation factor VIII in plasma, reducing its degradation and clearance.

Von Willebrand syndrome is the most common hereditary blood-clotting disorder in humans. Apart from hereditary forms, there is also an acquired form with similar symptoms. Acquired von Willebrand syndrome (AvWS) is a rare haemorrhagic diathesis, and is characterised by a lack of previous bleeding symptoms, negative familial history and occurs most commonly in the course of other conditions.
Association of acquired von Willebrand syndrome and shear stress

AvWS has been described in various conditions, including aortic stenosis, in patients with mitral valve regurgitation, and in patients treated with left ventricular assist devices (LVAD). Although antigen levels of vWF are typically higher in these patients, subnormal activity is also seen, usually due to an abnormal vWF multimer pattern with an increased ratio of low molecular weight multimers. ECMO and LVAD implantation share several common features; artificial surfaces and continuous flow patterns, both of which have been shown to significantly increase shear rate and stress.

The large and flexible structure of the vWF multimer makes it prone to conformational change and susceptible to shear stress. In these conditions, the three-dimensional structure of the vWF multimer is altered, in that it unfolds and exposes important domains of the protein. Two opposing effects are described because of this interaction. One effect is that an increased fluidic shear stress can cause excessive multimer cleavage by ADAMTS-13, resulting in a bleeding diathesis. In the opposing effect, large shear forces may induce and promote vWF binding to platelet GP-1ba (Figure 1).

There are several other proposed haemostatic mechanisms that are altered during high shear stress. For example, an increased self-association of vWF has been described, exposing a higher number of platelet-binding sites, and resulting in enhanced platelet adhesion.

Severely compromised platelet function has been observed in outpatient LVAD patients, and an uncoiling of the vWF multimer may reduce the capability to bind collagen and platelets, resulting in thrombosis, fibrinolysis and impaired platelet function in patients receiving ECMO or with LVADs. Haemolysis is often seen during ECMO treatment, and studies suggest that free haemoglobin may augment platelet adhesion on an extracellular matrix in a GP1b and vWF-dependent manner. Haemoglobin may also sterically hinder ADAMTS-13-vWF-interaction. Oxidative stress has also been shown to make vWF hyper-reactive and resistant to ADAMTS-13.

Methods

Data were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist was used for study design and manuscript preparation.

Review questions

We included all articles about AvWS and VV ECMO or ECCO2R in our review, including case series. A further selection was applied to answer specific questions, according to the population, intervention, comparator, outcome (PICO) approach, as follows:

1. Population: all patients on VV ECMO/ECCO2R with reported AvWF
2. Intervention: all devices and techniques for VV ECMO/ECCO2R
3. Control: patients not treated with extracorporeal support
4. Outcomes:
   a) What is the prevalence of AvWS in VV ECMO and ECCO2R?
   b) Which is the appropriate test for AvWS in ECMO patients?
   c) What is the rate of complication with AvWS?
   d) Is there a correlation between pump speed and blood flow?

Inclusion and exclusion criteria

All studies published as full-text articles in indexed journals and which reported AvWS in VV ECMO and ECCO2R patients were considered for inclusion. No restriction of publication status was imposed. The search was limited to publications in English. Reviews and studies published in abstract form were excluded.

Search strategy and study selection

We searched the Medline database (via PubMed) up to 30 January 2017, using the following terms: “acquired von Willebrand syndrome AND ECMO OR extracorporeal membrane oxygenation...”
OR extracorporeal life support OR extracorporeal CO2 removal OR ECCO2R” OR “von Willebrand AND ECMO OR extracorporeal membrane oxygenation extracorporeal life support OR extracorporeal CO2 removal OR ECCO2R”.

The websites of relevant journals were searched to identify studies in press, and references from identified studies and relevant review articles were also searched for additional eligible citations.

Data extraction and analysis
For each study included in the final analysis, the following data were extracted: age and sex, type of disease, associated device, device settings, method of testing for AvWS, duration of device implementation to diagnosis of AvWS, ICU and hospital length of stay, ICU and hospital mortality, and complications.

Study population data were summarised using mean or median values, as reported in the original articles. Because of the limited number of patients per study and the methodological limitations, we did not specifically assess heterogeneity and did not perform a meta-analysis. The overall percentage of categorical outcomes (eg, need for endotracheal intubation, and mortality) was reported using a χ² test. Statistical analyses were performed using SPSS, version 24.0 (SPSS).

Grading
The quality of evidence was independently and blindly assessed by two authors (L P and M M) based on the presence of limitations (risk of bias), indirectness, inconsistency and imprecision according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. Disagreements between assessors were resolved by consensus.

Results
Study selection
The initial PubMed search yielded 23 records; no additional records were identified through forward search. After screening of abstracts, 14 articles were discarded because they had no correlation with the study topic. Nine studies were considered for full-text analysis; one was excluded as no measurement of vWF was reported, one was excluded because it reported on VA ECMO patients only, and one further case was excluded because it reported a conversion of VV to VA ECMO before AvWS testing (Figure 2).

Six studies with a total of 189 patients were included in our review. Some of the studies included VA and VV ECMO patients as well as control patients without mechanical support. After exclusion of VA ECMO patients, a total of 76 adult VV ECMO patients with 37 associated controls, six paediatric VV ECMO patients and eight ECCO2R cases were assessed. All analysed studies are summarised in Tables 1 and 2. The overall quality of evidence varied from low to very low.

Prevalence of AvWS in VV ECMO and ECCO2R
From the studies reporting on AvWS in adult VV ECMO patients, all four are single-centre, observational studies; one

![Figure 2. CONSORT style diagram of study selection](image)

![Table 1. Definition of the study aims and quality of evidence](table)

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Definition of study aim</th>
<th>Evidence quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalbhenn, 2017</td>
<td>Assess the influence of ECCO2R to blood cells and the coagulation system in order to appraise whether low flow systems are really “less invasive” with regard to blood injury. The study hypothesised that coagulation disorders known from ECMO would also be identified during ECCO2R.</td>
<td>Low</td>
</tr>
<tr>
<td>Lukito, 2016</td>
<td>Investigate whether loss of platelet receptors occurs in vivo, and the relationship with AvWS.</td>
<td>Very low</td>
</tr>
<tr>
<td>Kalbhenn, 2015</td>
<td>Evaluate a coagulation protocol for the regular analysis of acquired coagulation disorders and the systematic substitution of coagulation factors to reach pre-defined target values.</td>
<td>Very low</td>
</tr>
<tr>
<td>Tauber, 2015</td>
<td>Investigate whether loss of vWF and its multimers play a role in the clinically observed bleeding tendency in patients undergoing ECMO support.</td>
<td>Low</td>
</tr>
<tr>
<td>Kalbhenn, 2015</td>
<td>Investigate the development of AvWS in patients treated with VV ECMO support.</td>
<td>Low</td>
</tr>
<tr>
<td>Pasala, 2014</td>
<td>Investigate whether changes in HMW VWF multimers occur over time after the initiation of ECMO in children.</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of selected studies on acquired von Willebrand Syndrome

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study design</th>
<th>Sample size</th>
<th>VV ECMO indication</th>
<th>ECMO device* (oxygenator and pump)</th>
<th>Cannula size (Fr)</th>
<th>Cannula site</th>
<th>Blown flow</th>
<th>Device RPM</th>
<th>Tests for AvWS</th>
<th>Timepoints</th>
<th>Bleeding complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lukito, 2016</td>
<td>Single-centre observational</td>
<td>n = 6 VV ECMO, total n = 60</td>
<td>Respiratory failure</td>
<td>Medtronic centrifugal pump and Quadrox oxygenator</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>vWF:Ag; vWF:RCo; vWF:CB; vWF multimers</td>
<td>Single, not uniform time point</td>
<td>–</td>
</tr>
<tr>
<td>Kalbhenn, 2015</td>
<td>Retrospective observational</td>
<td>n = 60</td>
<td>Lung transplant bridging, pneumonia, IE OPD, ARDS following sepsis, aspiration, trauma and severe air leak syndrome</td>
<td>Revolution centrifugal pump and EOS or Hilite oxygenator</td>
<td>2-lumen</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>vWF-Ag; vWF:RCo; vWF:CB; vWF multimers</td>
<td>–</td>
<td>Intracranial haemorrhage</td>
</tr>
<tr>
<td>Tauber, 2015</td>
<td>Prospective observational</td>
<td>n = 13 VV ECMO, total n = 40</td>
<td>End-stage pulmonary fibrosis, pneumonia, ARDS post trauma, Goodpasture syndrome, pneumonia due to aspiration, respiratory failure after lung transplantation</td>
<td>Centrimag centrifugal pump with Quadrox D oxygenator</td>
<td>–</td>
<td>VV femoral-jugular</td>
<td>50–80 mL/kg/ min</td>
<td>3300–3600 RPM</td>
<td>vWF:Ag; vWF:RCo; vWF multimers</td>
<td>Before and after ECMO initiation, at 24 and 48 h and 24 h after ECMO termination</td>
<td>–</td>
</tr>
<tr>
<td>Kalbhenn, 2015</td>
<td>Retrospective observational</td>
<td>n = 36</td>
<td>Pneumonia, aspiration, ARDS, interstitial lung fibrosis, bridge to transplant, COPD, H1N1, peritonsillar abscess and mediastinitis</td>
<td>Revolution centrifugal pump and EOS or Hilite oxygenator</td>
<td>2-lumen</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>vWF-Ag; vWF:RCo; vWF multimers</td>
<td>Before and after ECMO initiation, during ECMO therapy, and after ECMO explantation</td>
<td>Diffuse bleeding, spontaneous haemorrhage at mucosal, bronchial and puncture sites, macrohaematuria, GI bleeding, haematochezia</td>
</tr>
<tr>
<td>Pasala, 2014</td>
<td>Prospective, single-centre, observational cohort pilot</td>
<td>n = 6</td>
<td>ARDS, Cardiac failure and persistent pulmonary hypertension</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>vWF-Ag; vWF:RCo; vWF:CB; vWF multimers</td>
<td>Before and after ECMO initiation, at 6, 12 and 24 h, daily 7 days.</td>
<td>Intracranial haemorrhage</td>
</tr>
<tr>
<td>Kalbhenn, 2017</td>
<td>Observational prospective</td>
<td>n = 8</td>
<td>Avoidance of intubation or facilitating extubation in patients with persistent hypercarbia</td>
<td>Hemolung respiratory assist system</td>
<td>Dual-lumen 15.5-Fr catheter or jugular or femoral</td>
<td>300–600 Max 1400</td>
<td>vWF:Ag; vWF:RCo; vWF:CB; vWF multimers</td>
<td>Before implantation, during and after explantation</td>
<td>Abnormal bloody bronchial secretion; haematoma after venous puncture; macrohaematuria</td>
<td></td>
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</tr>
</tbody>
</table>

VV = venovenous. ECMO = extracorporeal membrane oxygenation. RPM = revolutions per minute. AvWS = acquired von Willebrand syndrome. Ag = antigen concentration. vWF = von Willebrand factor. RCo = ristocetin cofactor. CB = collagen binding. OPD = obstructive pulmonary disease. ARDS = acute respiratory distress syndrome. A = activity. COPD = chronic obstructive pulmonary disease. GI = gastrointestinal. * Rotaflo centrifugal pump, Quadrox PLS and Quadrox oxygenator (Maquet Cardiopulmonary); Revolution centrifugal pump, EOS oxygenator (Sorin); Hilite oxygenator (Medos); Centrimag magnetically levitated centrifugal pump (Medtronic); Hemolung respiratory assist system (Alung).
is prospective and three are retrospective studies. Regarding the prevalence of AvWS in VV ECMO patients, only two of these studies provided data on prevalence. The studies from Lukito and Tauber included patients on VV and VA ECMO and did not give specific information on the prevalence of AvWS for VV ECMO patients. Kalbehnn and colleagues reported 79% (n = 19) of patients to have exhibited AvWS within the first 7 days of ECMO. In a second study from the same group, AvWS was present in 18/18 ECMO patients but in none of the control patients.

One study on ECCO2R determined vWF activity (vWF:A) and vWF antigen concentration (vWF:Ag) in five patients, of whom all five developed pathological values for the vWF:A/vWF:Ag ratio of < 0.73. In three of them, collagen-binding capacity to vWF-antigen (vWF:CB) and multimer analysis were performed and showed a significant drop after ECCO2R implementation. There is only one study on VV ECMO and AvWS in pediatric patients. This study, by Pasala and colleagues, included six pediatric patients on ECMO, all of whom showed decreasing vWF multimers. However, this study did not discriminate between VA and VV ECMO.

Testing for AvWS in VV ECMO patients

Several tests were used for diagnosis of AvWS in the evaluated studies. These included vWF:Ag, vWF:CB, the activity of vWF as ristocetin cofactor (vWF:RCo), vWF:A, and high molecular weight (HMW) vWF multimers. From these single parameters, ratios have been used to increase diagnostic accuracy, including vWF:RCo/vWF:Ag, vWF:CB/vWF:Ag and vWF:A/vWF:Ag. The tests performed in each study are listed in Table 2. Apart from the parameters used for diagnosis, the time point of testing is also relevant for AvWS. Time lines were established in four studies, as AvWS tests were performed before ECMO implementation, after ECMO/ECCO2R implementation, during therapy and after termination of the mechanical support therapy. In all four studies, changes relevant to AvWS diagnosis occurred within the first 24 hours of mechanical support. Details of time points are given in Table 2.

Bleeding complications

Of the analysed studies reporting on adult VV ECMO patients, only two reported on bleeding complications. One study focused on intracranial bleeding only and compared different coagulation protocols with a focus on acquired coagulation disorders. Therefore, only one study gave detailed information on bleeding in association with AvWS in adult VV ECMO patients (Kalbehnn and colleagues). The reported diffuse bleeding appeared as spontaneous haemorrhage at mucosal, bronchial or puncture sites in 17/18 patients. These were macrohaematuria (n = 2), haemorrhagic gastritis (n = 1), haematochezia (n = 2) and one patient who was rejected for emergency lung transplantation due to bleeding diathesis. There is no literature available reporting on AvWS associated bleeding in comparison with controls.

The study on ECCO2R and AvWS reported bleeding complications in four of seven patients; including abnormal bloody bronchial secretions (n = 3), unexpected large haematoma after venous puncture (n = 2) and tamponade of the urinary bladder due to spontaneous macrohaematuria (n = 1).

Pasala and colleagues did not report on any clinical signs of bleeding in their study of six paediatric patients.

Correlation between pump speed and blood flow

The study on ECCO2R is the only study with information on cannula size, administered blood flow and rotations per minute (rpm) of the device. Only one adult VV ECMO study reported on blood flow and rpm of the ECMO device. No specific information was available on device setting or cannula size in the remaining studies.

Discussion

Diffuse bleeding disorders remain a relevant complication in the emerging field of respiratory extracorporeal life support. AvWS appears to be one piece of the puzzle in this unsolved problem. The aim of this manuscript was to assess the existing evidence on the association of respiratory extracorporeal life support with AvWS with regards to diagnostic criteria, prevalence, related complications and risk factors. We identified seven studies reporting on AvWS in patients receiving either VV ECMO or ECCO2R as a respiratory support therapy. With two manuscripts reporting on prevalence of AvWS in adult VV ECMO patients the overall prevalence reported in the literature is high with 88% (37/42 patients). However, the diagnosis is based on laboratory findings of reduced ratios of vWF:RCo/vWF:Ag (< 0.6) and/or vWF:A/vWF:Ag (< 0.73) and the loss of HMW vWF, and these findings are not necessarily associated with clinical bleeding disorders.

The literature on paediatric VV ECMO patients and adult ECCO2R patients is sparse, with six and eight patients reported, respectively. However all patients that have been reported on showed laboratory findings indicative of AvWS.

The diagnosis of AvWS is complicated by the need for different laboratory tests to help differentiate between AvWS and some subtypes of congenital von Willebrand disease. The vWF:Ag, vWF:RCo and vWF:CB parameters should be routinely used in the evaluation of patients with suspected AvWS. The vWF:RCo/vWF:Ag and vWF:RCo/vWF:CB ratios should also be determined, as these parameters are typically...
decreased during the course of AvWS. An important test, helpful in distinguishing between vWD and AvWS, is vWF multimer analysis. Usually, AvWS is associated with complete loss of HMW vWF or a decreased level of it. All the analysed studies screened for, at least, the vWF:RCo/vWF:Ag or vWF:RCo/vWF:CB ratios and HMW vWF levels, which is in line with the suggested diagnostic algorithm of the American Society of Hematology. With four of the analysed studies reporting vWF measurements before, during and after mechanical support therapy, there is evidence that there is an immediate decrease in HMW vWF multimers once ECMO is initiated, and this decrease persists up to 48 hours after ECMO support has been stopped.

With > 85% of patients on respiratory mechanical support having a laboratory constellation of AvWS, the burning question is its clinical relevance. The study from Kalbhenn and colleagues reported on bleeding complications in detail. There is no evidence, however, that loss of HMW vWF is associated with higher bleeding rates in ECMO patients. These findings are also in line with data on LVAD patients, for whom loss of HMW vWF occurs in almost all patients, but neither the loss of the large multimers nor reduced vWF:RCo activity is associated with bleeding, thrombosis, or the need for transfusion in patients on LVAD support.

To compare bleeding complications on extracorporeal life support from the available literature is a complicated task, because several definitions of bleeding are in use. As reported by Kalbhenn and colleagues, over 90% of patients showed signs of bleeding, a number much higher than that for comparable bleeding complications as reported in the Extracorporeal Life Support Organization registry 2016, which describes bleeding at the cannulation site in 13.2% of patients and surgical haemorrhage in 10.5%. However, these numbers have to be interpreted with caution because no general definition for bleeding is used and a reporting bias cannot be excluded.

All forms of mechanical support have been related to thrombotic and bleeding complications and this is no different for respiratory extracorporeal life support. As soon as blood comes in contact with the artificial surface of the circuitry and the oxygenator membrane, and is exposed to elevated shear stress by the forces applied by the pump, homeostasis is altered.

A large body of clinical and laboratory evidence suggests that the loss of large vWF multimers may be caused by shear and oxidative stress. However, it is not clear to what extent each aspect contributes. The available literature provides no information on differences in the prevalence of AvWS in VV ECMO patients based on factors which influence shear stress, such as blood flow, rpm of the device or cannula size.

If diffuse bleeding occurs in patients on respiratory extracorporeal life support, the best available action has been shown to be termination of mechanical support, or if the patient is still dependent, to exchange the oxygenator. Other therapeutic approaches to treat AvWS include infusions of vWF-containing factor VIII (FVIII) concentrates, desmopressin, tranexamic acid and recombinant factor VIIa (rFVIIa). AvWS may play a crucial role in the occurrence of bleeding complications in ECMO and ECCO2R patients. However, as thrombocytopenia, factor XIII deficiency and fibrinogen deficiency are also related to mechanical support and bleeding disorders, AvWS may only be one piece of a bigger puzzle. To better understand the relative influence of decreasing HMW vWF and its importance in altering clinical outcomes, more data are required.

Conclusions
The key messages from our systematic literature review are that AvWF is present in most patients on VV ECMO/ECCO2R support, but only a small population of patients are tested for its presence. This situation may need to change. At the very least, AvWS testing should be performed in patients showing signs of bleeding, including vWF multimer analysis. Currently, there is no information available to suggest whether modifications in ECMO management, such as reduced blood flows, would have a positive effect on HMW vWF multimer levels. Finally, this article must be seen in the context of a dedicated issue that explores multiple aspects of extracorporeal life support in the critically ill.

Competing interests
None declared.

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