

Acquired von Willebrand Syndrome and Desmopressin Resistance During Venovenous Extracorporeal Membrane Oxygenation in Patients With COVID-19: A Prospective Observational Study

OBJECTIVES: Although COVID-19 is associated with high von Willebrand factor (vWF) parameters promoting thrombosis, venovenous extracorporeal membrane oxygenation (vvECMO) is associated with the development of acquired von Willebrand syndrome (AVWS) promoting bleeding. This study was designed to assess both the incidence and severity of AVWS in COVID-19 patients undergoing vvECMO, and the benefit of comprehensive vWF analyses.

DESIGN: Prospective observational study.

SETTING: ICU at a tertiary-care center.

PATIENTS: Twenty-seven consecutive COVID-19 patients with acute respiratory distress syndrome (ARDS) requiring vvECMO.

MEASUREMENTS AND MAIN RESULTS: Comprehensive vWF analyses (including sodium dodecyl-sulfate polyacrylamide gel electrophoresis) were performed before, during, and after vvECMO. In a subgroup of 12 patients with AVWS, effectiveness of treatment with desmopressin was assessed. The patients' mean age was 53 years (range, 23–73), 70% were male, and all had various comorbidities. Following markedly elevated vwf antigen (vWF: Ag; mean, 546% [SD, 282]), vWF collagen binding capacity (mean, 469% [SD, 271]), vWF activity (vWF:A; mean, 383% [SD, 132]), and factor VIII activity (mean, 302% [SD, 106]), and only borderline decreases in high-molecular-weight (HMW) vWF multimers before vvECMO, all of these variables decreased and HMW vWF multimers became undetectable within hours following initiation of vvECMO. All variables fully recovered within 3–38 hours after discontinuation of vvECMO. During vvECMO, decreases in the vWF:A/vWF:Ag ratio correlated with absent HMW vWF multimers. Desmopressin did not affect vWF parameters.

CONCLUSIONS: In patients with COVID-19-associated ARDS, AVWS developed soon after initiation of vvECMO. The vWF:A/vWF:Ag ratio was a suitable screening test for AVWS. As desmopressin was ineffective, bleeding during vvECMO-associated AVWS should preferably be treated with concentrates containing vWF.

KEY WORDS: bleeding; COVID-19; desmopressin; extracorporeal membrane oxygenation; hemostasis; von Willebrand syndrome

In patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced acute respiratory distress syndrome (ARDS) undergoing venovenous extracorporeal membrane oxygenation (vvECMO), safe and effective management of coagulation is a crucial part of the overall medical care. It poses considerable diagnostic and therapeutic

Johannes Kalbhenn, MD¹
 Hannah Glonnegger, MD²
 Martin Büchsel, MD³
 Hans-Joachim Priebe, MD¹
 Barbara Zieger, MD²

Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/CCM.0000000000005467

challenges because of the often differing and rapidly changing hemostaseological conditions. Early COVID-19 is mostly associated with a prothrombotic state promoted among others by endothelial inflammation and dysfunction with consecutive release of prothrombotic factors and exposure of collagen and tissue factor (1–3). This results in thrombotic events in up to one-third of patients with COVID-19 (4). At the same time, disruption of the vascular endothelial layer, reduced platelet count and function, and accompanying anticoagulation promote bleeding complications like spontaneous intracranial hemorrhage (5, 6). The use of vvECMO is regularly associated with bleeding diathesis caused by shear stress-induced platelet dysfunction, consumption of coagulation factors, and anticoagulation (7–9). It is increasingly being recognized that acquired von Willebrand syndrome (AVWS) frequently develops during vvECMO and likely contributes to the associated hemorrhagic complications (10).

The von Willebrand factor (vWF) is a multimeric glycoprotein that facilitates primary hemostasis by promoting platelet adhesion and aggregation at sites of vascular injury. It is synthesized and polymerized to high-molecular-weight (HMW) vWF multimers in endothelial cells and stored in the intracellular Weibel-Palade bodies (11). It is released into the blood by exocytosis as folded glycoprotein presenting binding sites for collagen. When getting into contact with collagen at sites of endothelial injury, HMW vWF multimers unfold, with each multimeric subunit of vWF exposing its binding sites to platelet glycoprotein receptors (12). The larger the vWF multimers, the more effective the binding to collagen and platelets will be. This is the main mechanism of primary hemostasis (13).

AVWS is characterized by deficiency or complete loss of HMW vWF multimers, increasing the risk of spontaneous bleeding from mucous membranes and, for example, catheter insertion sites (9, 11, 14). Routine coagulation analyses (e.g., international normalized ratio or activated partial thromboplastin time) are unsuited in detecting AVWS. The diagnosis of AVWS requires documentation of reduced vWF binding to either collagen (vWF collagen binding capacity [vWF:CB]) or to platelet glycoprotein Ib receptors (vWF activity [vWF:A]) in relation to overall vWF (vWF antigen [vWF:Ag]). In case of decreased vWF:CB/vWF:Ag or vWF:A/vWF:Ag ratio, differentiation between AVWS

and some types of inherited von Willebrand disease requires subsequent documentation of deficiency or loss of HMW vWF multimers by sodium dodecyl-sulfate-agarose (SDS) gel electrophoresis (15).

We have previously documented changes in vWF characteristics in six patients with SARS-CoV-2-induced ARDS before, during, and after vvECMO (16). Before vvECMO, various vWF parameters were markedly elevated, and HMW vWF multimers were present. However, following initiation of vvECMO, vWF:CB/vWF:Ag and vWF:A/vWF:Ag ratios decreased, and HMW vWF multimers became undetectable, consistent with AVWS.

The aims of the present study were to confirm our previous findings in a larger cohort of consecutive patients, to define incidence and severity of AVWS in this setting, and to determine the value of different vWF assay methods in the diagnosis of AVWS. We hypothesized that COVID-19-associated increased vWF parameters before vvECMO would not protect patients from developing AVWS during vvECMO. As desmopressin (1-desamino-8-D-arginin-vasopressin [DDAVP]) is the treatment of choice for AVWS (17), we additionally investigated its efficacy in a subgroup of patients with documented AVWS.

MATERIALS AND METHODS

The study was conducted in the ICU of the Department of Anesthesiology and Critical Care at the Medical Center of the University of Freiburg, Germany. It was approved by the local Ethics Committee (EK 336/20) and registered in the German Clinical Trials Register (DRKS No. 00006961). Informed consent was waived because treatment entirely followed departmental standard of care, and the study design was purely descriptive. The study adheres to the initiative for Strengthening the Reporting of Observational Studies in Epidemiology and is compliant with the International Society of Heart and Lung Transplantation ethics statement (18). We prospectively analyzed the data of 27 consecutive patients with COVID-19-associated severe ARDS undergoing vvECMO in our ICU between March 2020 and March 2021. SARS-CoV-2 infection had been diagnosed by positive real-time reverse transcriptase-polymerase chain reaction test results of specimens from the upper or lower respiratory tract.

Management of vvECMO

vvECMO was initiated either in the ICU or by the ECMO outreach team followed by immediate transport of the patient to our ICU. Elixhauser criteria were applied to describe comorbidities (19). Treatment followed a standardized protocol. The indication for vvECMO was persistent hypoxemia despite lung protective ventilation and prone positioning. The patients were connected to the vvECMO circuit either via a transjugular double-lumen Avalon Elite catheter or via two single-lumen HLS catheters (Maquet Holding GmbH KG, Rastatt, Germany). The vvECMO circuit consisted of two parallel EOS Phisio- (polymethylpentene) oxygenators and a Revolution5 centrifugal pump (Sorin Group, Mirandola, Italy). Oxygenators, tubes, and centrifugal pump were coated with phosphorylcholine. The system was actively warmed by heated water. During the first couple of days, pump flow was routinely set at 3–7 L/min and then gradually reduced to a minimum of 1.8 L/min. Stable vital signs for several hours without vvECMO support were required before the circuit was explanted.

Coagulation and Blood Management

During vvECMO, patients received low-molecular-weight heparin (LMWH) targeting an antifactor-Xa concentration of 0.15–0.35 international units (IU)/mL at 4 hours after injection. One hour after removal of the vvECMO cannulae, the patients started to receive LMWH bid aiming for an antifactor-Xa activity of 0.5–0.8 IU/mL (9). In the absence of contraindications (e.g., intracranial bleeding), therapeutic anticoagulation was continued until patients were fully mobilized after ICU discharge and for at least 4 weeks after decannulation of ECMO. Thresholds for transfusion of packed RBCs and platelet concentrates were a hemoglobin concentration of less than or equal to 10 g/dL and a platelet count of less than or equal to 100 000/ μ L, respectively.

AVWS was presumed to have developed when the vWF:A/vWF:Ag ratio was less than 0.73. In such case, desmopressin (DDAVP) was intravenously administered at 0.3- μ g/kg body weight (maximum dose, 28 μ g).

Screening for Acquired von Willebrand Syndrome

Plasma concentrations of vWF:A (normal range, 50–170%), vWF:Ag (normal range, 60–150%), and factor VIII activity (normal range, 81–215%) were

measured at the hospital's central laboratory using the commercially available test INNOVANCE vWF:Ac and vWF:Ag, and the one-stage clotting assay Pathromtin SL (all by Siemens Healthineers, Erlangen, Germany). Subsequently, the vWF:A/vWF:Ag ratio (normal range, 0.73–1.16) was calculated. Blood samples were obtained at the following predefined time points: t1, within 24 hours before cannulation of vvECMO; t2, within 48 hours after its start; t3, during vvECMO; t4, within 48 hours before decannulation at completion of vvECMO; t5, within 24 hours; and t6, at least 3 days after explantation of vvECMO.

Comprehensive Analysis of von Willebrand Factor

HMW vWF multimers and vWF:CB were measured immediately before the start of vvECMO, 30 minutes, and 3 and 6 hours after its start, every 3 days during vvECMO, shortly before, and finally 30 minutes, and 3, 6, and 48–72 hours after its explantation. HMW vWF multimers were determined by SDS gel electrophoresis with subsequent transfer of the resolved multimers to a polyvinylidene fluoride membrane. On the basis of visual inspection of the gel electrophoretic samples by two highly experienced examiners (H.G., B.Z.), the content of HMW vWF multimers was classified as “normal,” “borderline,” (reduced but not entirely absent) and “missing.” Following presumed diagnosis of AVWS based on a decreased vWF:CB/vWF:Ag ratio of less than 0.7, AVWS was confirmed by loss of HMW vWF multimers.

For determination of vWF:CB (normal range, 60–150%), an in-house enzyme-linked immunosorbent assay was used. This assay is far more sensitive than commercially available tests because it contains collagen type I. Collagen type I (Nycomed Pharma, Unterschleissheim, Germany) was immobilized on a microtiter plate. vWF:CB was quantified on the basis of changes in optical density. Subsequently, the vWF:CB/vWF:Ag ratio was calculated (normal value, ≥ 0.7).

Statistical Analysis

Data were imported and explored in Microsoft Excel sheets (Microsoft, Redmond, WA). Calculations, figure designs, and statistical analyses were performed using Graphpad Prism 8.0 (Graphpad Software, San Diego, CA) and Statistical Package for the Social Sciences

(Statistical Package for Social Sciences for Windows, Version 27; SPSS, Chicago, IL). Metric data were analyzed by one-way analysis of variance test, followed by post hoc Tukey test, and ordinal data by Friedman test. Data acquired before and after desmopressin treatment were analyzed by paired *t* test. A *p* value of less than or equal to 0.05 was considered to indicate statistical significance.

RESULTS

The mean time interval between the patients' hospital admission and their endotracheal intubation was 5 days (range, 0–13 d) and that between endotracheal intubation and initiation of vvECMO was 4 days (range, 0–15 d). The patient's mean age was 53 years (range, 23–73 yr), 70% were male, and all had various comorbidities. Mean vvECMO duration was 12 days (range, 2–24 d), mean length of ICU stay 23 days (range, 2–55 d), and inhospital mortality 51.8% (**Table 1**).

von Willebrand Factor Multimeric Structure Analysis

In all patients, HMW vWF multimers began to decrease shortly after initiation of vvECMO and became undetectable within approximately 3 hours, indicating development of AVWS. By 3 and 6 hours after decannulation of the vvECMO circuit, HMW vWF multimers became again detectable in 13 (41%) and 14 (53%) patients, respectively (**Fig. 1**). Representative findings on SDS gel electrophoresis acquired in patient 25 are depicted in **Supplemental Figure 1** (<http://links.lww.com/CCM/G990>).

von Willebrand Factor Concentrations and Factor VIII Activity

Although VWF:Ag did not significantly change throughout the observation period, VWF:CB and VWF:CB/VWF:Ag ratio significantly decreased shortly after the start of vvECMO and began to normalize 3 hours after discontinuation of vvECMO (**Fig. 2**). At six predefined observation points, the findings were confirmed by commercially available assays as part of our routine laboratory diagnostic (**Fig. 3**). The median time intervals between the various observation points were as follows: between t1 and cannulation 4.8 hours (SD, 7.5 hr), between cannulation and t2 and t3 10.3

TABLE 1.
Patient, Venovenous Extracorporeal Membrane Oxygenation, and Outcome Characteristics (*n* = 27)

Sex	<i>n</i> (%)
Male	19 (70.4)
Female	8 (29.6)
Age, mean (SD), yr	53 (11.9)
Comorbidities, <i>n</i> (%)	
Hypertension	17 (63)
Diabetes	12 (44.4)
Cardiac arrhythmia	1 (3.7)
Renal failure	2 (7.4)
Congestive heart failure	4 (14.8)
Chronic pulmonary disease	5 (18.5)
Obesity (BMI ≥ 30)	14 (51.9)
BMI, mean (SD), kg/m ²	31.38 (6.3)
Nicotine abuse, <i>n</i> (%)	13 (48.2)
vvECMO cannulation, <i>n</i> (%)	
Avalon 31 F	14 (51.9)
Avalon 27 F	6 (22.2)
Femoral–jugular	5 (18.5)
Bifemoral	2 (7.4)
vvECMO duration, mean (SD), d	12 (5.3)
Length of ICU stay, mean (SD), d	23 (14.7)
Died during extracorporeal membrane oxygenation, <i>n</i> (%)	8 (29.6)
Inhospital mortality, <i>n</i> (%)	14 (51.8)

BMI = body mass index, vvECMO = venovenous extracorporeal membrane oxygenation.

hours (SD, 15.1 hr) and 127.8 hours (SD, 38.1 hr), respectively, between t4 and decannulation 14.6 hours (SD, 15.3 hr), and between decannulation and t5 and t6 17.7 hours (SD, 3.2 hr) and 90.1 hours (SD, 32 hr), respectively. At these time points, factor VIII activity significantly decreased within 48 hours after initiation of vvECMO and recovered within 48 hours after its discontinuation.

There were considerable agreements between categories of concentrations of HMW vWF multimers and vWF:CB/vWF:Ag ratios. When the concentrations of HMW vWF multimers were classified as “normal,” “borderline,” or “missing,” the respective vWF:CB/vWF:Ag ratios were greater than 0.7 in 92% of blood samples, between 0.5 and 0.7 in 85% of samples, and

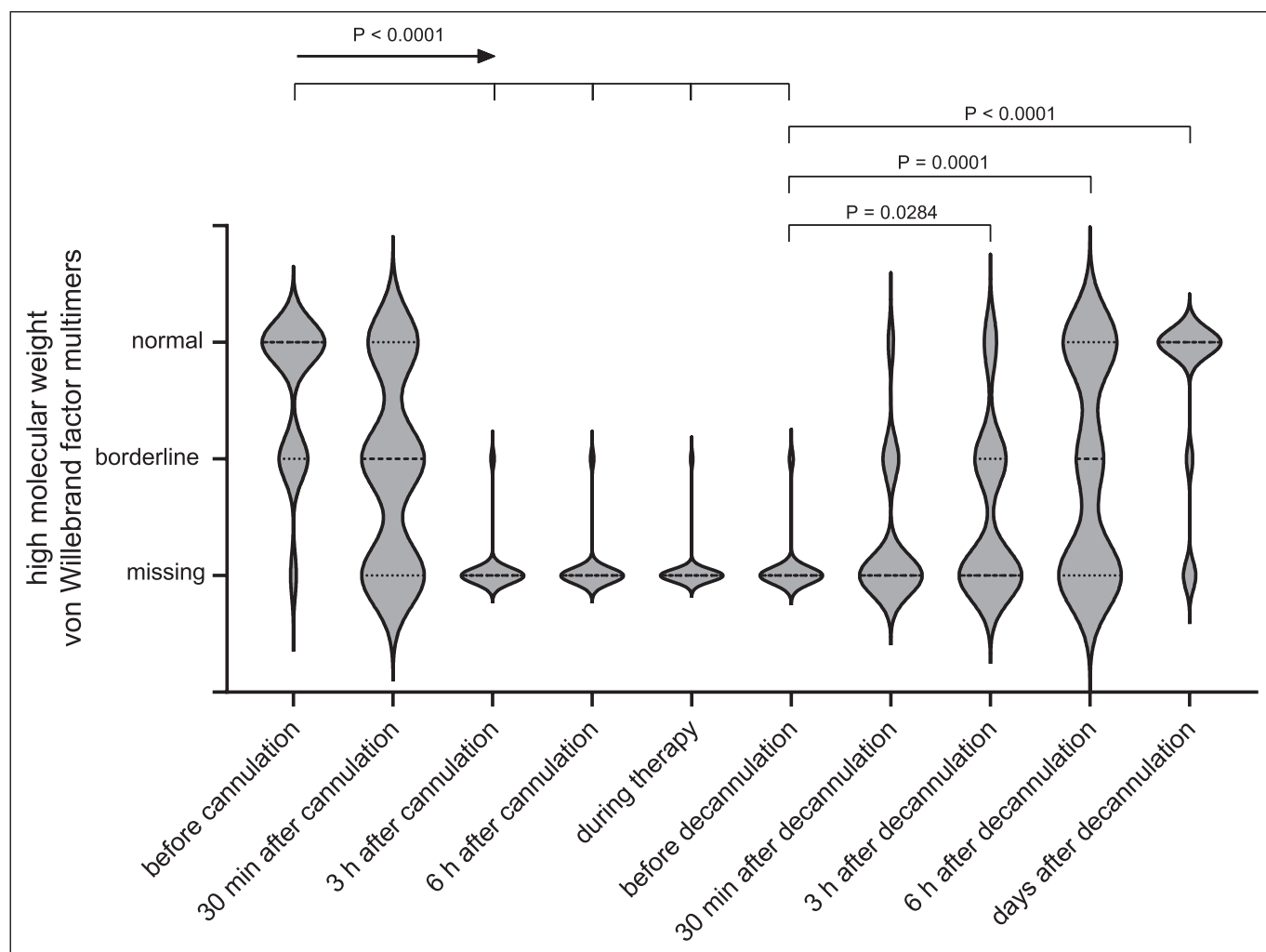


Figure 1. Violin plots of high-molecular-weight von Willebrand factor multimers. t1: before cannulation of venovenous extracorporeal membrane oxygenation (vvECMO), t2: 30 min, t3: 3 hr, t4: 6 hr after cannulation of vvECMO; t5 during vvECMO therapy, t6: shortly before, t7, t8, t9, and t10: 30 min, and 3, 6, and 24 hr after decannulation of vvECMO. --- = median, = 25–75 quartiles.

less than 0.5 in 96% of samples. When the vWF:CB/vWF:Ag ratio was less than 0.7, the vWF:A/vWF:Ag ratio was less than 0.73 in all but one blood sample.

Desmopressin Effects

As all 27 patients demonstrated vWF:A/vWF:Ag ratios less than 0.73 during ECMO, all of them received a desmopressin infusion. In those 12 of these 27 patients in whom we assessed the effect of desmopressin, the responses in VWF:Ag, VWF:A, and VWF:A/VWF:Ag ratio were not statistically significant (all *p* values greater than or equal to 0.05; **Fig. 4**).

DISCUSSION

The main findings of this study in 27 consecutive patients with SARS-CoV-2-induced ARDS undergoing vvECMO are the following. First and foremost, severe

AVWS developed in all patients during vvECMO, reflected by complete loss of HMW vWF multimers. This occurred despite normal or only slightly decreased HMW vWF multimers before vvECMO. This confirms our hypothesis that COVID-19-associated increased vWF:Ag, vWF:A, and vWF:CB would not protect patients from developing AVWS during vvECMO. Second, loss of HMW vWF multimers detected by SDS gel electrophoresis was associated with decreased vWF:CB/vWF:Ag and vWF:A/vWF:Ag ratios. Such decreases can thus serve as surrogate for AVWS. Third, desmopressin did not increase vWF parameters in the 12 of the 27 patients with AVWS in whom we assessed such effect. To the best of our knowledge, this is the first systematic investigation of the incidence and severity of AVWS in such patient population using comprehensive vWF assessment, including vWF multimeric structure analysis at numerous time points.

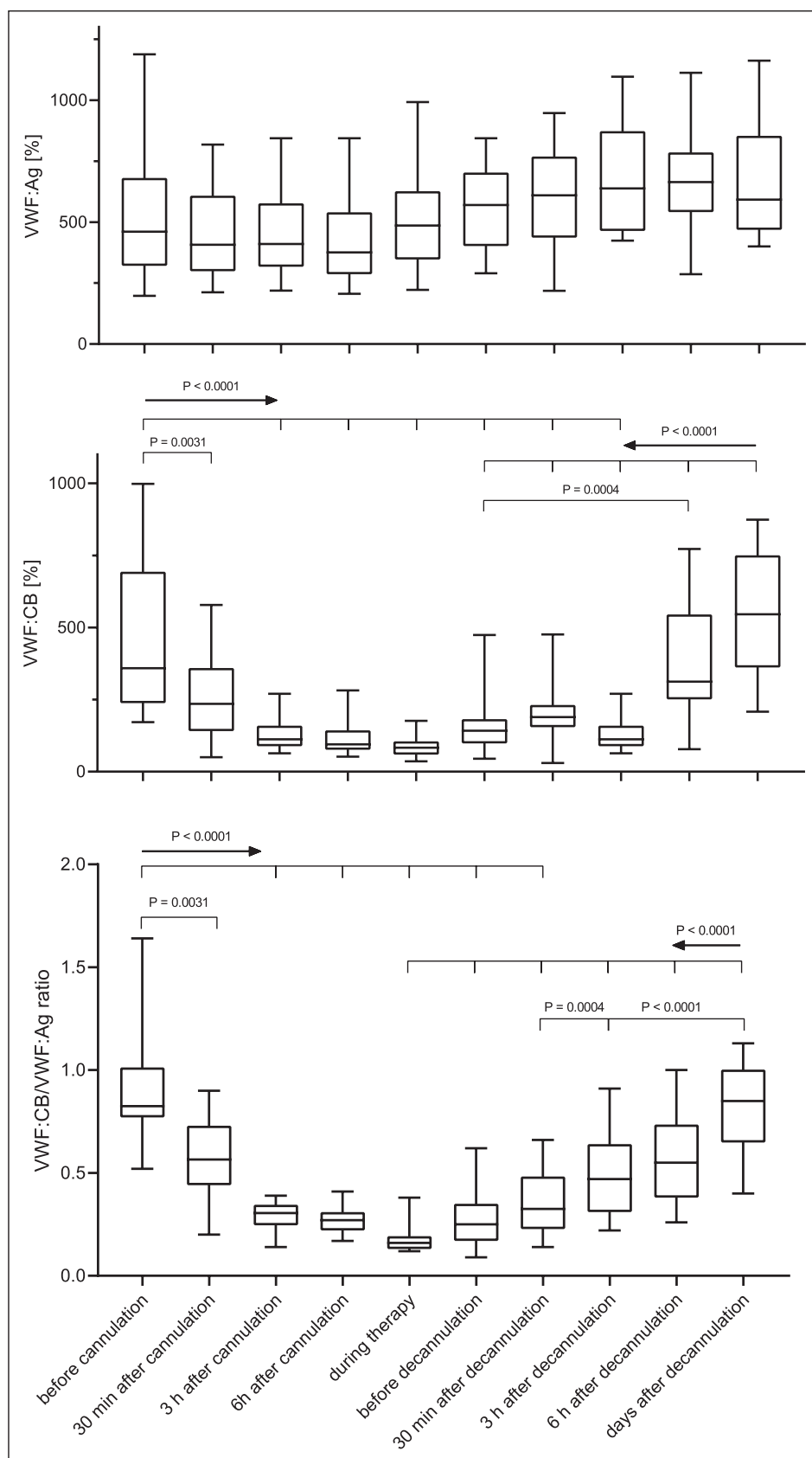


Figure 2. von Willebrand factor analysis using collagen binding capacity. *Upper and lower whiskers, box, and the inside horizontal line* represent range of values, interquartile range, and median, respectively. VWF:Ag = von Willebrand factor antigen, VWF:CB = von Willebrand factor collagen binding capacity.

Coagulation Status

Immediately before vvECMO, vWF:Ag, vWF:CB, vWF:A, and factor VIII activity exceeded normal concentrations manyfold. These findings are in agreement with previous reports (20, 21). In the acute phase of COVID-19, endothelial cell infection and endotheliitis develop (22). The associated endothelial cell activation causes secretion of vWF from Weibel-Palade bodies that, in turn, lead to increased circulating vWF and depletion of Weibel-Palade bodies (2, 3). Increased concentrations of vWF parameters result in a procoagulatory state explaining the frequent thrombotic complications observed in COVID-19 patients (6, 21, 23).

Following initiation of vvECMO, although vWF:Ag remained statistically unchanged, vWF:A and vWF:CB concentrations and factor VIII activity decreased resulting in decreased vWF:CB/vWF:Ag and vWF:A/vWF:Ag ratios. The clinically most relevant finding was the rapid decline and subsequent loss of HMW vWF multimers in all patients, reflecting development of AVWS. High and changing shear stress forces to which blood is exposed during vvECMO rapidly induce conformational changes of the vWF multimers with subsequent excessive cleavage of those multimers by A Disintegrin And Metalloprotease with Thrombospondin-1-like Domains (ADAMTS-13) (24). As development of AVWS

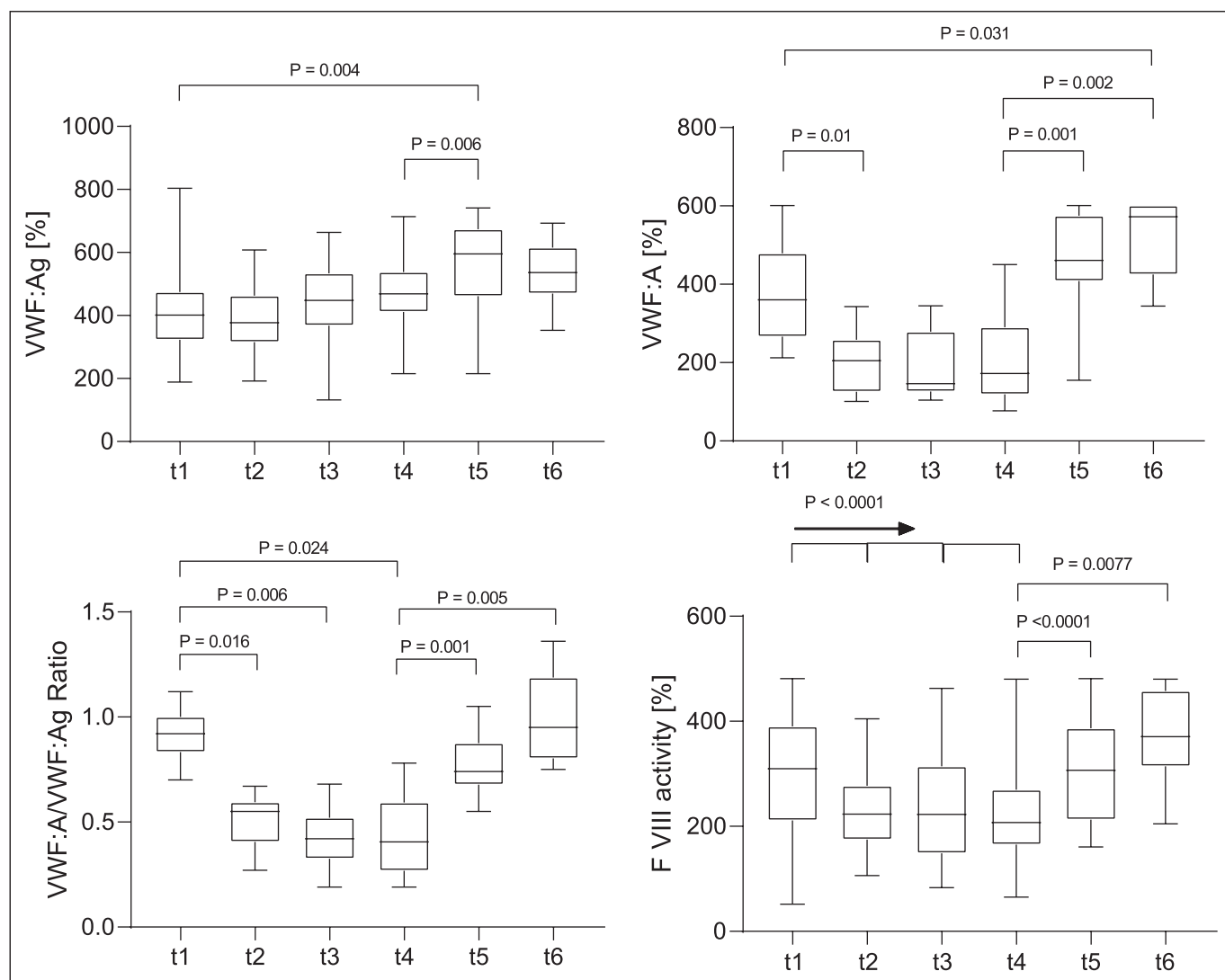


Figure 3. von Willebrand factor parameters and factor VIII activity before, during, and after extracorporeal membrane oxygenation using commercially available assays. T1, within 24 h before cannulation of venovenous extracorporeal membrane oxygenation (vvECMO); T2, within 48 hr after cannulation of vvECMO; T3, during vvECMO; T4, within 48 hr before decannulation of vvECMO; T5, within 24 hr after decannulation of vvECMO; and T6, at least 3 d after decannulation of vvECMO circuit. VWF:A = von Willebrand factor activity, VWF:Ag = von Willebrand factor antigen.

combined with virus- and immune response-induced endothelial injury and platelet dysfunction may increase the risk of bleeding, only minimal anticoagulation with LMWH was used during vvECMO, aiming for antifactor-Xa activity of at most 0.15–0.35 IU/mL, which is lower than usually reported (3, 21, 23, 25).

Within hours after decannulation of vvECMO, HMW vWF multimers fully recovered. Furthermore, vWF:A, vWF:CB, and factor VIII activity not only recovered, but there was a tendency for overcorrection beyond the already pathologically elevated values before vvECMO. These findings imply that the risk of thromboembolic events is particularly high after vvECMO decannulation, which needs to be taken

into account when planning appropriate anticoagulation.(9) At the same time, incomplete recovery of platelet function from damage by the extracorporeal system (16), virus-induced platelet exhaustion (21, 26), and apoptosis (27) could increase the risk of bleeding. These opposing effects complicate the hemostaseological management (26, 27). We started therapeutic anticoagulation with enoxaparin 1 hour after explantation of the vvECMO cannulae and continued it until patients' full recovery from critical illness. Despite this management, occlusive intestinal ischemia requiring surgical intervention was diagnosed in two patients only 2 days after vvECMO discontinuation.

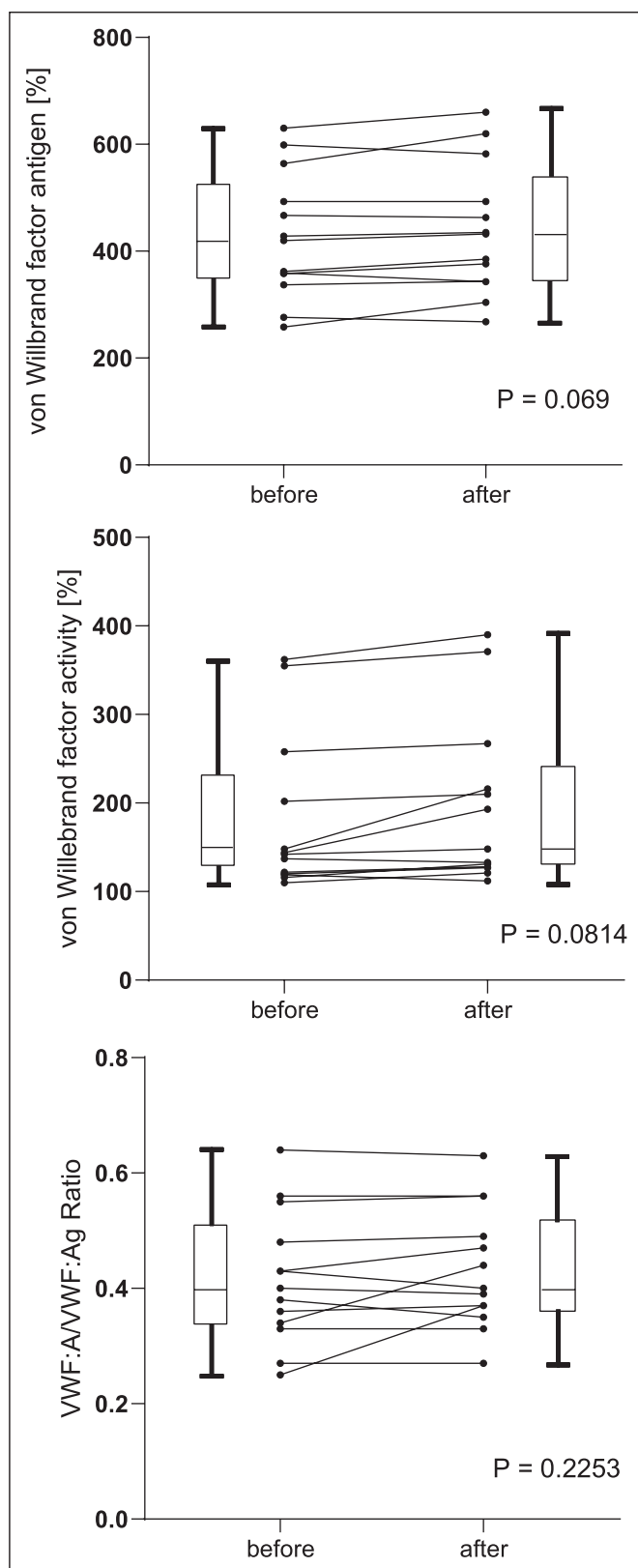


Figure 4. von Willebrand factor parameters before and after treatment with desmopressin ($n = 12$). VWF:Ag = von Willebrand factor antigen; VWF:A = von Willebrand factor activity.

von Willebrand Factor and Factor VIII Interaction

Like vWF, factor VIII is synthesized and stored in endothelial cells and constitutes a key factor in the cascade of secondary hemostasis. Factor VIII activity mirrored vWF concentrations throughout the study period. This is explained by the vWF-factor VIII interaction. vWF serves as carrier of most of factor VIII in plasma and protects it from proteolytic degradation (28). High factor VIII activity is mostly caused by increased vWF concentrations consistent with decreased clearance of the vWF-factor VIII complex. Thus, vWF is not only essential for primary but also for secondary hemostasis.

Assessment of Tests

Our investigation provides novel information regarding testing for AVWS. Normal or only slightly decreased concentrations of HMW vWF multimers before vvECMO, and deficient and ultimately absent HMW vWF multimers after institution of vvECMO correlated well with normal and decreased vWF:CB/vWF:Ag and vWF:A/vWF:Ag ratios, respectively. Provided normal ratios have been documented before vvECMO, decreasing ratios during vvECMO can serve as surrogate for AVWS. Nevertheless, the definitive diagnosis of AVWS requires not only the documentation of decreased vWF function (e.g., as reflected by decreased vWF:CB or cVW:A) in relation to vWF:Ag resulting in decreased vWF:CB/vWF:Ag and vWF:A/vWF:Ag ratios, but also requires the loss of HMW vWF multimers (29).

When patients start bleeding during vvECMO, AVWS should be considered. As vWF multimeric structure analysis using SDS gel electrophoresis is a labor-intensive, time-consuming, and costly technique, it is not routinely available at all healthcare centers. In such case, vWF:Ag, vWF:A, and vWF:A/vWF:Ag ratio should be determined before initiation of vvECMO. If the ratio had been normal before and decreases during vvECMO, AVWS is very likely, and appropriate hemostaseologic treatment should be initiated. In any case, the suspected diagnosis of AVWS should be quickly confirmed in a specialized laboratory.

In five of the 27 patients, HMW vWF multimer concentrations were slightly reduced even before vvECMO

(Fig. 1). This may reflect increased binding of HMW vWF multimers to COVID-19-activated endothelium and platelets, increased vWF adhesive function caused by the markedly elevated vWF concentrations, a multifactorial downregulation in ADAMTS-13 function, and/or mechanical damage of vWF multimers within vessels partly occluded by thrombosis (30).

Desmopressin Effects

The lacking effect of desmopressin on vWF parameters in patients with AVWS was unexpected and is of clinical relevance. Desmopressin usually acts by inducing exocytosis of vWF and other factors stored in the Weibel-Palade bodies within endothelial cells followed by release into the blood (11). However, in the acute phase of COVID-19, Weibel-Palade bodies become depleted of vWF. Lack of effect of desmopressin is consistent with exhausted endothelial storage sites. Desmopressin may thus not be the drug of first choice in the treatment of AVWS developing in COVID-19 patients during vvECMO. In case of hemorrhage in this situation, transfusion of vWF-containing concentrates or fresh frozen plasma and treatment with tranexamic acid may be preferable (17).

Limitations

This is a single-center study with a limited number of 27 patients. However, the single-center design allowed us to fully standardize and control all aspects of medical care, most importantly those of vvECMO and coagulation management. The routine sophisticated testing for vWF parameters, especially the SDS gel electrophoreses required highly experienced personnel and advanced equipment to assure expeditious and reliable processing of blood samples. Organization of a multicenter study in the early phase of the corona pandemic would have considerably delayed acquisition of respective data that we considered to have an impact on clinical care of this patient population. The analysis of HMW vWF multimers is based on visual inspection of gel electrophoretic samples. In contrast to optical densitometry, this provides a merely semiquantitative assessment of HMW vWF multimers. However, the assessment was carried out by two highly experienced examiners, and the loss of HMW vWF multimers is easily recognizable on visual inspection.

CONCLUSIONS

Despite elevated vWF parameters and normal concentrations of HMW vWF multimers in COVID-19-patients with ARDS, severe AVWS may develop only hours after initiation of vvECMO. Initially normal vWF:A/vWF:Ag or vWF:CB/vWF:Ag ratios decreasing in the course of vvECMO are indicative of AVWS. Nevertheless, confirmation of AVWS requires additional documentation of loss of HMW vWF multimers by SDS gel electrophoresis. The rapid changes between prothrombotic and prohemorrhagic conditions require effective hemostaseological monitoring and adjustment of coagulation therapy. Desmopressin may not be the drug of choice in the treatment of AVWS developing during vvECMO in COVID-19 patients.

ACKNOWLEDGMENT

We thank Christoph Benk and his technicians for their valuable support in our extracorporeal membrane oxygenation center.

- 1 Department of Anesthesiology and Critical Care, Institute of Clinical Chemistry and Laboratory Medicine, Medical Center—University of Freiburg, Faculty of Medicine, Freiburg, Germany.
- 2 Department of Pediatrics and Adolescent Medicine, Division of Pediatric Hematology and Oncology, Institute of Clinical Chemistry and Laboratory Medicine, Medical Center—University of Freiburg, Faculty of Medicine, Freiburg, Germany.
- 3 Institute of Clinical Chemistry and Laboratory Medicine, Medical Center—University of Freiburg, Faculty of Medicine, Freiburg, Germany.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/ccmjjournal>).

Dr. Büchsel received travel/congress support by CSL Behring, Bayer, SOBI, and Takeda, but these companies or their products are not involved in any part of the present study. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Study was performed at the Department of Anesthesiology and Critical Care, Medical Center—University of Freiburg, Germany.

For information regarding this article, E-mail: johannes.kalbhenn@uniklinik-freiburg.de

REFERENCES

1. Loo J, Spittle DA, Newnham M: COVID-19, immunothrombosis and venous thromboembolism: Biological mechanisms. *Thorax* 2021; 76:412–420

2. Bonaventura A, Vecchié A, Dagna L, et al: Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. *Nat Rev Immunol* 2021; 21:319–329
3. Perico L, Benigni A, Casiraghi F, et al: Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. *Nat Rev Nephrol* 2021; 17:46–64
4. Middeldorp S, Coppens M, van Haaps TF, et al: Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 2020; 18:1995–2002
5. Jiménez D, García-Sánchez A, Rali P, et al: Incidence of VTE and bleeding among hospitalized patients with coronavirus disease 2019: A systematic review and meta-analysis. *Chest* 2021; 159:1182–1196
6. Bermea RS, Raz Y, Sertic F, et al: Increased intracranial hemorrhage amid elevated inflammatory markers in those with COVID-19 supported with extracorporeal membrane oxygenation. *Shock* 2021; 56:206–214
7. Doyle AJ, Hunt BJ: Current understanding of how extracorporeal membrane oxygenators activate haemostasis and other blood components. *Front Med (Lausanne)* 2018; 5:352
8. Aubron C, DePuydt J, Belon F, et al: Predictive factors of bleeding events in adults undergoing extracorporeal membrane oxygenation. *Ann Intensive Care* 2016; 6:97
9. Kalbhenn J, Schlagenhauf A, Rosenfelder S, et al: Acquired von Willebrand syndrome and impaired platelet function during venovenous extracorporeal membrane oxygenation: Rapid onset and fast recovery. *J Heart Lung Transplant* 2018; 37:985–991
10. Panholzer B, Bajorat T, Haneya A, et al: Acquired von Willebrand syndrome in ECMO patients: A 3-year cohort study. *Blood Cells Mol Dis* 2021; 87:102526
11. Leebeek FW, Eikenboom JC: Von Willebrand's disease. *N Engl J Med* 2016; 375:2067–2080
12. Stocksclaeder M, Schneppenheim R, Budde U: Update on von Willebrand factor multimers: Focus on high-molecular-weight multimers and their role in hemostasis. *Blood Coagul Fibrinolysis* 2014; 25:206–216
13. Lenting PJ, Christophe OD, Denis CV: von Willebrand factor biosynthesis, secretion, and clearance: Connecting the far ends. *Blood* 2015; 125:2019–2028
14. Franchini M, Mannucci PM: Acquired von Willebrand syndrome: Focused for hematologists. *Haematologica* 2020; 105:2032–2037
15. Federici AB, Budde U, Castaman G, et al: Current diagnostic and therapeutic approaches to patients with acquired von Willebrand syndrome: A 2013 update. *Semin Thromb Hemost* 2013; 39:191–201
16. Kalbhenn J, Glonnegger H, Wilke M, et al: Hypercoagulopathy, acquired coagulation disorders and anticoagulation before, during and after extracorporeal membrane oxygenation in COVID-19: A case series. *Perfusion* 2021; 36:592–602
17. Budde U, Scheppenheim S, Dittmer R: Treatment of the acquired von Willebrand syndrome. *Expert Rev Hematol* 2015; 8:799–818
18. Vandembroucke JP, von Elm E, Altman DG, et al; STROBE Initiative: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. *Int J Surg* 2014; 12:1500–1524
19. Elixhauser A, Steiner C, Harris DR, et al: Comorbidity measures for use with administrative data. *Med Care* 1998; 36:8–27
20. Kalbhenn J, Schmidt R, Nakamura L, et al: Early diagnosis of acquired von Willebrand Syndrome (AVWS) is elementary for clinical practice in patients treated with ECMO therapy. *J Atheroscler Thromb* 2015; 22:265–271
21. Heinz C, Miesbach W, Herrmann E, et al: Greater fibrinolysis resistance but no greater platelet aggregation in critically ill COVID-19 patients. *Anesthesiology* 2021; 134:457–467
22. Varga Z, Flammer AJ, Steiger P, et al: Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; 395:1417–1418
23. Jiritano F, Serraino GF, Ten Cate H, et al: Platelets and extracorporeal membrane oxygenation in adult patients: A systematic review and meta-analysis. *Intensive Care Med* 2020; 46:1154–1169
24. Levy GG, Motto DG, Ginsburg D: ADAMTS13 turns 3. *Blood* 2005; 106:11–17
25. Vandembriele C, Vanassche T, Price S: Why we need safer anticoagulant strategies for patients on short-term percutaneous mechanical circulatory support. *Intensive Care Med* 2020; 46:771–774
26. Manne BK, Denorme F, Middleton EA, et al: Platelet gene expression and function in patients with COVID-19. *Blood* 2020; 136:1317–1329
27. Althaus K, Marini I, Zlamal J, et al: Antibody-induced procoagulant platelets in severe COVID-19 infection. *Blood* 2021; 137:1061–1071
28. Pipe SW, Montgomery RR, Pratt KP, et al: Life in the shadow of a dominant partner: The FVIII-VWF association and its clinical implications for hemophilia A. *Blood* 2016; 128:2007–2016
29. Budde U, Pieconka A, Will K, et al: Laboratory testing for von Willebrand disease: Contribution of multimer analysis to diagnosis and classification. *Semin Thromb Hemost* 2006; 32:514–521
30. Ward SE, Fogarty H, Karampini E, et al; Irish COVID-19 Vasculopathy Study (iCVS) investigators: ADAMTS13 regulation of VWF multimer distribution in severe COVID-19. *J Thromb Haemost* 2021; 19:1914–1921