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Extracorporeal Membrane Oxygenation Induces Short-Term Loss of High-Molecular-Weight von Willebrand Factor Multimers

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BACKGROUND: High-molecular-weight (HMW) von Willebrand factor (vWF) multimers are crucial for primary hemostasis. Increased shear stress from ventricular assist devices can provoke premature degradation of HMW vWF multimers. Whether similar loss of vWF multimers occurs during extracorporeal membrane oxygenation (ECMO) is not clear.

METHODS: We conducted a prospective observational study in a clinical cohort of patients who required ECMO for intractable cardiac and/or respiratory failure. The primary end point was the quantity and quality of HMW vWF multimer bands before, during, and after ECMO support. To investigate further changes in primary hemostasis, we also measured vWF antigen activity (vWF:Ag), vWF ristocetin cofactor activity (vWF:RCo), and factor VIII in 38 patients who required ECMO support before initiation of ECMO (baseline), after 24 and 48 hours on ECMO, and 24 hours after termination of ECMO therapy.

RESULTS: Compared with baseline, vWF:Ag and vWF:RCo decreased after 24 hours of ECMO (mean ± SD, vWF:Ag, 307% ± 152% to 261% ± 138%, $P = 0.002$; vWF:RCo 282% ± 145% to 157% ± 103%, $P < 0.0001$) and remained lower during ongoing support (vWF:Ag 265% ± 128%, $P = 0.025$; vWF:RCo 163% ± 94%, $P < 0.0001$). After termination of ECMO, vWF:Ag was greater than baseline (359% ± 131%, $P = 0.004$) and vWF:RCo was similar to baseline levels (338% ± 142%, $P = 0.046$). Compared with baseline, the calculated vWF:RCo/ vWF:Ag ratio decreased after 24 hours on support (0.96 ± 0.23 to 0.61 ± 0.17, $P \leq 0.0001$) and remained lower during 48 hours on ECMO (0.63 ± 0.18, $P \leq 0.0001$). After termination of ECMO support (0.94 ± 0.19, $P = 0.437$), values rapidly returned to baseline. The number of HMW vWF multimers (n) decreased from baseline after 24 hours on ECMO (21 ± 1.4 to 14 ± 1.8, $P \leq 0.0001$) and after 48 hours on ECMO (15 ± 2.1, $P \leq 0.0001$). Twenty-four hours after termination of ECMO support, HMW vWF multimeric pattern had returned to baseline values (21 ± 1.8, $P = 0.551$).

CONCLUSIONS: Loss of HMW vWF multimer bands occurred in patients undergoing ECMO support and resolved after the termination of ECMO. Although not detectable with coagulation screening tests, a vWF:RCo/vWF:Ag ratio <0.7 during ECMO was highly indicative for loss of HMW vWF multimers. Our findings may at least in part explain increased bleeding tendency during ECMO therapy. Administration of vWF concentrates may support restoration of primary hemostasis in patients with relevant bleeding during ECMO support. (Anesth Analg 2015;120:730–6)

Von Willebrand factor (vWF) is a large plasma protein composed of high-molecular-weight (HMW) multimers that mediate platelet adhesion to connective tissue after vascular injury and thus play a crucial role in primary hemostasis.[1,2] HMW vWF multimers are the hemostatically most active forms of vWF; their loss can result in severe bleeding and blood loss after trauma and surgery.[2–4] Diagnosis of qualitative defects of vWF, including loss of multimers, is challenging because these proteins are not normally assessed with usual coagulation screening tests or thrombelastography. Definitive detection of HMW vWF can be made only by analysis of von Willebrand multimers separated by agarose gel electrophoresis, which is a time-consuming method.[5]

Increased shear stress during mechanical circulatory support from ventricular assist devices (VAD)[6,7] or due to heart defects with high-flow velocities can provoke premature activation of the HMW vWF multimers, resulting in preterm degradation.[8–11] Only limited data are available on changes in HMW multimers during extracorporeal membrane oxygenation (ECMO) support.[12,13] Loss of vWF and its multimers is suspected to play a role in the clinically observed bleeding tendency in patients undergoing ECMO

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support.[12] Our primary hypothesis was that ECMO support leads to a transient loss of HMW multimers. The secondary hypothesis was that vWF antigen (vWF:Ag) to vWF ristocetin cofactor (vWF:RCo) ratio and factor VIII (F:VIII) will be reduced in patients requiring ECMO support.

METHODS

This study was approved by the Ethics Committee of Innsbruck Medical University (UN4013;289/4.3; e-mail: Ethikkommission@i-med.ac.at). Forty patients requiring ECMO support because of refractory cardiac (venoarterial ECMO, n = 27) and/or pulmonary failure (venovenous ECMO, n = 13) were prospectively enrolled in this observational study. Because ECMO implantation is an emergency intervention and the patients usually are sedated or not conscious and their trachea intubated before the decision for intervention, written informed consent was obtained after recovery in survivors or from relatives in nonsurvivors. Exclusion criterion was age <18 years.

Clinical ECMO Management

Anesthesia was induced with fentanyl, midazolam, and rocuronium and maintained with remifentanil and sevoflurane. The inspired oxygen fraction was adapted to target an oxygen saturation >90%, measured by pulse oximetry. Pressure-controlled ventilation was performed to maintain normocapnia. IV fluids administered included modified 4% gelatin solution (7 mL/kg; Gelofusin®, Braun, Melsungen, Germany) and Ringer's lactate solution. Routine monitoring included invasive arterial blood pressure measurement, electrocardiogram, pulse oximetry, capnography, pulmonary artery catheter, and transesophageal echocardiography. The patients received 100 IU/kg unfractionated heparin (Gilvasan®, Gilvasan Pharma, Vienna, Austria) before cannulation. During ECMO support, heparin was administered continuously to maintain activated clotting time (Hemochron Jr. Signature+, Biomedica GmbH, Vienna, Austria) between 150 and 180 seconds. The vascular cannulation site was chosen on the basis of institutional clinician preference: 27 patients received venoarterial ECMO; of these, 19 patients were cannulated solely via the femoral vessels, 5 patients were cannulated via the femoral vein and the axillary artery, and 3 patients received central cannulae to the right atrium and the aorta.

The 13 patients who required venovenous ECMO were cannulated via the femoral (inflow) and the jugular vein (outflow). Three different types of centrifugal pump were used for ECMO: a Centrimag® magnetically levitated centrifugal pump (n = 12; Levitronix, Zürich, Switzerland), a Rotaflow centrifugal pump (n = 20; Maquet Cardiopulmonary AG, Hirrlingen, Germany), and a Biomedicus centrifugal pump (n = 8; Medtronic, Tolochenaz, Switzerland) after insertion of the appropriate cannulae (Medtronic). Patients with the Biomedicus centrifugal pump (n = 8) received the Quadrox D® oxygenator and the corresponding tubes (Maquet Cardiopulmonary AG). In the other patients (n = 32), ECMO was performed with the PLS System® (Quadrox PSL® oxygenator and tubes, Maquet Cardiopulmonary AG). All used oxygenators and tubes were coated with an albumin-heparin composition specified by the manufacturer (Maquet Cardiopulmonary AG). Target circuit flows were 50 to 80 mL/kg/min.

Study Protocol

Blood sampling and recording of ECMO variables were performed at 4 time points: before initiation of ECMO support (baseline, before administration of heparin, and before insertion of cannulae), after 24 hours on ECMO support, after 48 hours on ECMO support, and 24 hours after termination of ECMO support. Blood samples were obtained through a 3F radial catheter (Becton Dickinson, Swingdon, United Kingdom) inserted for clinical indication. To diminish preanalytic laboratory errors, >3 mL of blood was discarded. For analysis, samples were filled in 3-mL tubes containing 0.3 mL (0.106 mol/L) of buffered (pH 5.5) sodium citrate (Sarstedt, Nuermbrecht, Germany).

Laboratory Analysis

vWF:Ag, vWF:RCo, and F:VIII were determined by photooptical measurement on a Siemens BCS XP analyzer using vWF:Ag, BC von Willebrand, and F:VIII-deficient plasma assays (Siemens, Marburg, Germany). The vWF:RCo cofactor activity/vWF:Ag ratio (normal range >0.7)[7] was calculated by dividing vWF:RCo by the vWF:Ag results. vWF antigen levels (vWF:Ag assay®, Siemens, normal range 58%–174%) were measured by turbidimetric detection of antibody-mediated binding of polystyrene particle on vWF protein. Validation of the assay showed a 3% lower limit of quantification. Intra-assay precision ranged from 1.4% to 4.2%; interassay precision ranged from 0.9% to 2.6%.

vWF:RCo activity (BC von Willebrand assay®, Siemens; normal range 58%–172%) was determined by turbidimetric detection of ristocetin-induced agglutination of stabilized platelets by vWF in the patient sample. The vWF:RCo activity assay showed a 10% lower limit of quantification. Intra-assay coefficients of variation ranged from 8.0% to 9.6%; interassay precision ranged from 8.0% to 10.3%. F:VIII activity was determined using the 1-stage Coagulation Factor VIII® assay (Siemens).

We used the protocol by Ott et al.[14] for optimum immunolocalization and detection of vWF multimer bands. In brief, vWF multimer bands were separated using high-resolving (2%) and low-resolving (1%) sabouraud dextrose agarose gels. Immunolocalization was performed by polyclonal rabbit anti-vWF (DAKO, Glostrup, Denmark) and detected by Cy5-labeled ECL Plex goat anti-rabbit IgG (GE Healthcare Life Sciences, Vienna, Austria). Densitometric analysis of vWF multimers was performed with a fluorescent laser scanner using 633-nm exciting and a limit of detection of 200 nmol for Cy™5, Typoon 9410 (GE Healthcare Life Sciences).

The normal vWF triplet structure contains small-molecular-weight (bands 1–5), intermediate-molecular-weight (bands 6–13), and HMW multimeric (>13 bands) components. Loss of HMW vWF multimers was diagnosed when bands 14 to 21 were missing, based on fluorescence labeling and densitometry accompanied by vWF:RCo/vWF:Ag ratio <0.7 (Figs. 1 and 2). von Willebrand factor-cleaving protease (ADAMTS 13) activity was measured using the FRET-adamts 13 assay (Sekisui, Stamford, CT). The lower limit of quantification was 11.2 ng/mL; intra-assay and interassay coefficients of variation were determined to be 4.1% and 4.4%, respectively. For determination of C-reactive protein (CRP), the CRPL3 test (Roche, Mannheim, Germany) was used.

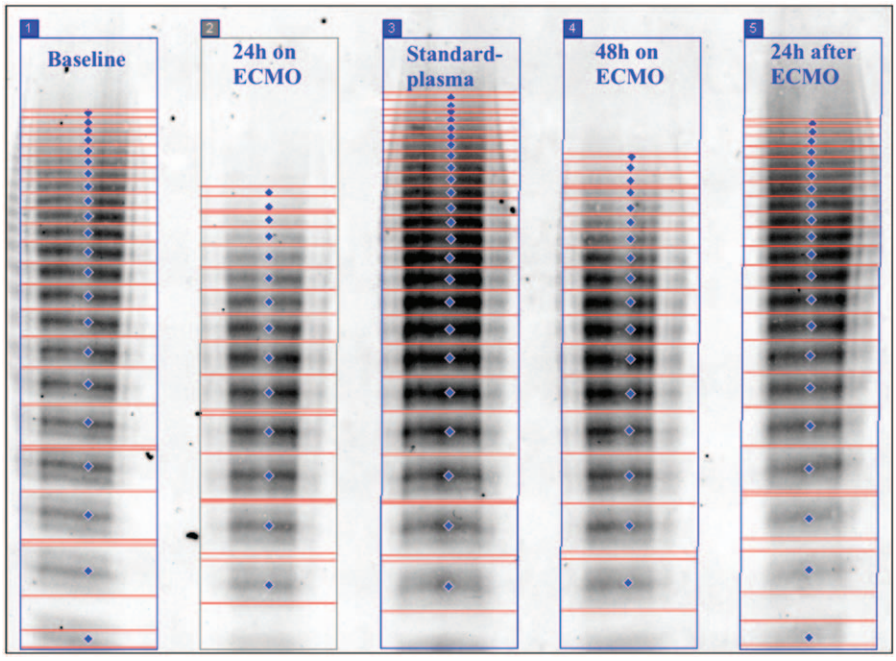

Figure 1. Low-resolution electrophoresis gel (1%) results demonstrating a typical example of von Willebrand factor multimers before, during, and after extracorporeal membrane oxygenation (ECMO) support compared with standard plasma sample.

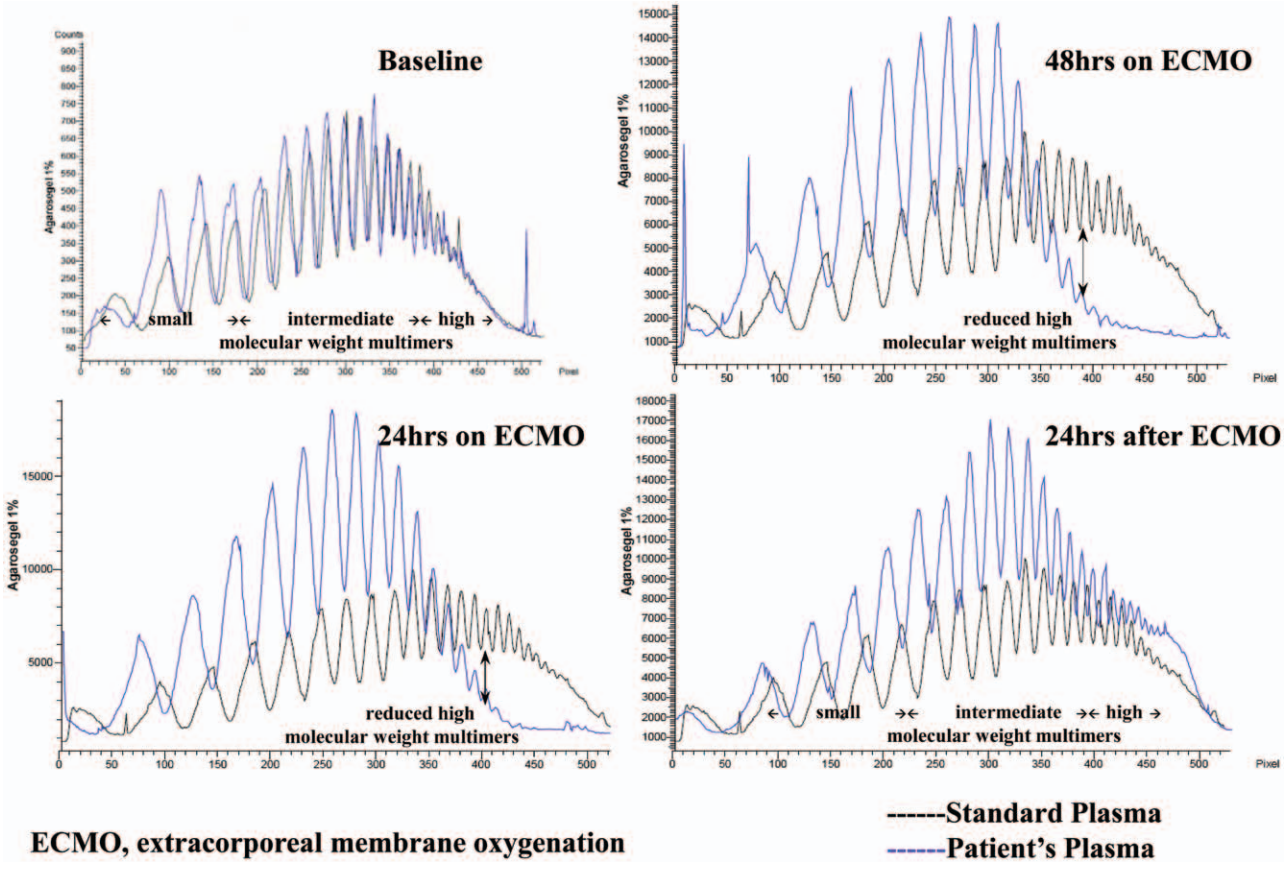

Figure 2. Densitogram results depicting the time course of von Willebrand factor multimers in low-resolution electrophoresis gel (1%) before, during, and after extracorporeal membrane oxygenation (ECMO) support (indicated by arrows) plasma; x-axis: counts = intensity of the signal (16-bit tif images), y-axis: pixel = real position of the signal.

Statistical Analysis

A sample size of 40 patients was chosen to be able to detect the differences among the 4 time points (baseline, after 24 hours on ECMO support, after 48 hours on ECMO support, and 24 hours after termination of ECMO support) for the primary outcome variable vWF:Ag with a power of 80%

when the effect size is 0.07 in a univariate 1-way repeated-measures analysis of variance. Because no data from previous or pilot studies were at hand, we chose the effect size to the best of our knowledge based on our clinical experience and expertise.

All patient characteristics and laboratory measurements were analyzed descriptively (absolute and relative frequency and mean and SD) and stratified for the type of ECMO (venoarterial and venovenous) and the study testing period. Student *t* test or Fisher exact test (for dichotomous data) was performed to test for equality of baseline characteristics. To test the differences in means among the 4 time points, univariate 1-way repeated-measures analysis of variance was performed for each parameter (vWF:Ag, vWF:RCo, vWF:RCo/vWF:Ag, vWF bands, F:VIII, ADAMTS 13, and CRP). To account for possible sphericity violation among time points, *P* values were corrected according to the Greenhouse-Geisser method.[15] If the *P* value of the innersubject effect time point was statistically significant (<0.05), pairwise comparisons (time points: baseline versus 24 hours on ECMO; baseline versus 48 hours on ECMO support; baseline versus 24 hours after ECMO support; and 24 vs 48 hours on ECMO support) were made with paired *t* tests as post hoc tests. A significance level of $\alpha = 0.05$ (2 sided) was used, except for the post hoc tests, in which case we used a significance level of $\alpha = 0.0125$, accounting for the type 1 error rate inflation in multiple testing (in our case 4 tests) according to the Bonferroni correction approach. Statistical analyses were performed using the statistical software package SPSS, version 20.0 (SPSS Inc., Chicago, IL).

Table 1. Demographic Data of Patients, Indications for ECMO, and Flow Characteristics (Average Rotating Speed and ECMO Flow)

Patient characteristics	Venoarterial ECMO (*n* = 26)	Venovenous ECMO (*n* = 12)	*P*
Sex			0.73
Female	13	7	
Male	13	5	
Age (y)	53 ± 15	43 ± 13	*0.02*
Weight (kg)	73 ± 14	75 ± 15	0.62
Height (cm)	173 ± 9	167 ± 8	0.38
Indications for venoarterial ECMO			*n* = 26
Ischemic cardiomyopathy			*n* = 5
Dilatative cardiomyopathy			*n* = 4
Myocarditis			*n* = 3
Postcardiotomy heart failure			*n* = 13
Right heart failure			*n* = 1
Indications for venovenous ECMO			*n* = 12
End-stage pulmonary fibrosis			*n* = 1
Pneumonia due to infection			*n* = 6
ARDS after multiple trauma			*n* = 1
Goodpasture syndrome			*n* = 1
Pneumonia due to aspiration			*n* = 2
Respiratory failure after lung transplantation			*n* = 1
Flow characteristics	**24 h on ECMO**	**48 h on ECMO**	***P***
Flow (L/min)	4.4 ± 0.9	3.9 ± 1.0	*0.02*
Rates per minute (rpm)	3614 ± 514	3307 ± 628	*0.03*

Data are shown as mean ± SD.
ECMO = extracorporeal membrane oxygenation; ARDS = acute respiratory distress syndrome.

RESULTS

Forty patients presenting with severe cardiopulmonary disease requiring ECMO support between July 2010 and June 2012 were enrolled. Two patients died within 24 hours of initiation of ECMO support and were excluded from the analysis. Thus, data from 38 patients were available for analysis. Demographics of the patients requiring venoarterial or venovenous ECMO support did not differ, with the exception of patient age, which was greater in the venoarterial ECMO support group (Table 1). Six patients subsequently died during ongoing support (1 patient died while receiving venovenous ECMO support after 24 hours, 4 patients receiving venoarterial ECMO support, and 1 patient receiving venovenous ECMO support died 48 hours after commencement of ECMO support). Thirty patients were successfully weaned from ECMO support; 2 patients were converted from ECMO support to left VAD support. A complete dataset (comprising data from all 4 study time points) was available for 32 patients.

Twenty-six patients received venoarterial ECMO due to cardiogenic shock (mean ± SD, time on ECMO, 170 ± 168 hours), and 12 patients were treated with venovenous ECMO for pulmonary failure (mean ± SD, time on ECMO, 249 ± 224 hours, $P = 0.284$). Indications for support are presented in Table 1. Average rotating speed and ECMO flow during support did not differ among groups. Compared with 24 hours on ECMO, pump rotating speed was slower after 48 hours on ECMO ($P = 0.03$); similar ECMO flow was slower at 48 hours on ECMO ($P = 0.02$) (Table 1).

Laboratory Results

The results of the laboratory measurements and analysis of vWF multimer bands are shown in Table 2 as well as in Figures 3 and 4. There were no differences between venoarterial and venovenous ECMO, cannula type, or pump type for any of the measured variables. Therefore, the data were combined for the analyses.

There were significant changes in the concentration of vWF:Ag, vWF:RCo, and the vWF:RCo/vWF:Ag ratio over time ($P < 0.0001$ for each). Compared with baseline measurements, vWF:Ag (mean ± SD, 307% ± 152%) and vWF:RCo (282% ± 145%) decreased after 24 hours of ECMO support (vWF:Ag, 261% ± 138%, $P = 0.002$; vWF:RCo 157% ± 103%, $P < 0.0001$) and remained lower during ongoing support (vWF:Ag 265% ± 128%, $P = 0.025$; vWF:RCo 163% ± 94%, $P < 0.0001$). After patients were weaned from ECMO support, vWF:Ag (359 ± 131) increased above baseline ($P = 0.004$), and vWF:RCo (338% ± 142%) was comparable with baseline levels ($P = 0.046$ [not considered significant due to multiple testing], Table 2). Compared with baseline, the calculated vWF:RCo/vWF:Ag ratio (0.96 ± 0.23) decreased after 24 hours on ECMO support (0.61 ± 0.17, $P \leq 0.0001$) and remained lower until 48 hours on ECMO support (0.63 ± 0.18, $P \leq 0.0001$). After ECMO support was terminated (0.94 ± 0.19, $P = 0.437$), values rapidly returned to baseline (Table 2, Fig. 3). F:VIII levels decreased during support and returned to baseline values after patients were weaned from ECMO support. There were no significant differences in F:VIII levels among the study testing periods (Table 2).

The number and triplet structure of vWF multimers (*n*) were normal in all 38 patients before ECMO support. The number of HMW vWF multimers decreased after 24 and

Table 2. Laboratory Test Results

Variables (normal range)	Baseline	24 h on ECMO	48 h on ECMO	24 h after ECMO	Overall *P*
vWF:Ag (58%–174%)	307 ± 152	261 ± 138	265 ± 128	359 ± 131	*<0.001*
vWF:RCo (58%–172%)	282 ± 145	157 ± 103	163 ± 94	338 ± 142	*<0.001*
vWF:RCo/vWF:Ag (>0.7)	0.96 ± 0.23	0.61 ± 0.17	0.63 ± 0.18	0.94 ± 0.19	*<0.001*
vWF bands (maximum *n* = 21)	21 ± 1.4	14 ± 1.8	15 ± 2.1	21 ± 1.8	*<0.001*
F:VIII (70%–150%)	161 ± 77	124 ± 56	131 ± 63	180 ± 66	*0.005*
ADAMTS 13 (531%–801%)	404 ± 140	400 ± 136	407 ± 135	474 ± 149	0.055
CRP (<0.5 mg/dL)	20 ± 12	12.5 ± 9	16.1 ± 11	15.9 ± 6.0	0.102

Variables	*P* (baseline versus 24 h on ECMO)	*P* (baseline versus 48 h on ECMO)	*P* (baseline versus 24 h after ECMO)	*P* (24 h versus 48 h on ECMO)
vWF:Ag	*0.002*	*0.025*	*0.004*	0.088
vWF:RCo	*<0.001*	*<0.001*	*0.046*	0.235
vWF:RCo/vWF:Ag	*<0.001*	*<0.001*	0.437	0.706
vWF bands	*<0.001*	*<0.001*	0.551	*0.007*
F:VIII	*0.016*	0.086	0.079	0.424
ADAMTS 13	0.308	0.889	*0.036*	0.667
CRP	0.762	0.175	0.109	0.053

Data are given as mean ± SD. Overall *P* values are from univariate 1-way repeated-measures analysis of variance corrected according to the Greenhouse-Geisser method,[15] post hoc tests (baseline versus 24 h on ECMO, baseline versus 48 h on ECMO, baseline versus 24 h after ECMO, and 24 vs 48 h on ECMO from paired *t* tests. Post hoc tests are considered statistically significant if $P < 0.0125$.

ECMO = extracorporeal membrane oxygenation; vWF = von Willebrand factor; vWF:Ag = vWF antigen; vWF:RCo = von Willebrand factor ristocetin cofactor activity; F:VIII = factor VIII; ADAMTS 13 = von Willebrand factor-cleaving protease; CRP = C-reactive protein.

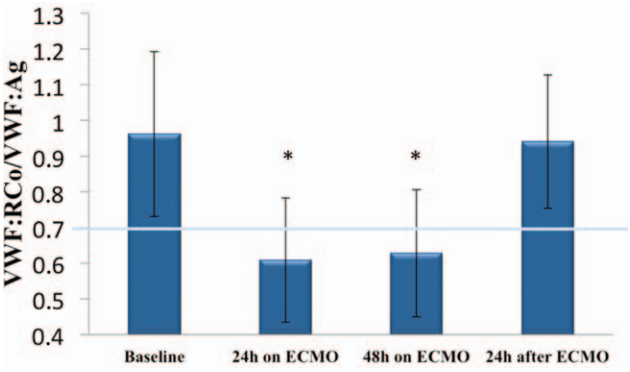

Figure 3. Von Willebrand factor antigen/von Willebrand factor ristocetin cofactor activity ratio (vWF:RCo/vWF:Ag) before, during, and after extracorporeal membrane oxygenation (ECMO) support. The line within the figure designates the normal range (>0.7). The height of the bars indicates the mean, and the error bars indicate the SD. *$P < 0.0125$ baseline versus 24 and 48 h on ECMO support, respectively (Bonferroni corrected).

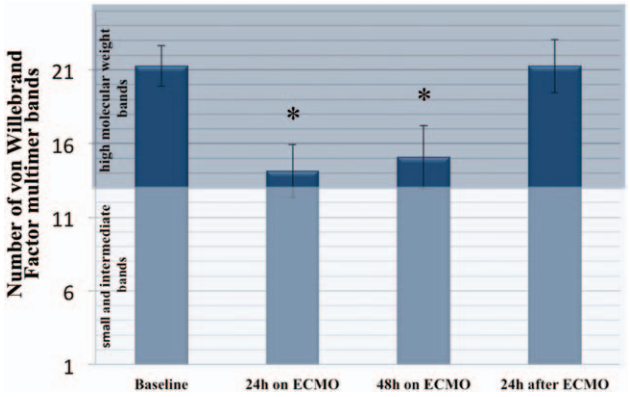

Figure 4. Number of von Willebrand Factor multimer bands before, during, and after extracorporeal membrane oxygenation (ECMO). The dark shading indicates the range of the high-molecular-weight multimer bands. The height of the bars indicates the mean, and the error bars indicate the SD. *$P < 0.0125$ baseline versus 24 and 48 h on ECMO, respectively (Bonferroni corrected).

48 hours of ECMO support ($P < 0.0001$), as shown in Table 2 and Figure 4. The reduction in HMW vWF multimers persisted in all patients except 1 during ongoing support. Twenty-nine of the 32 patients showed normal distribution of vWF multimers 24 hours after weaning from ECMO (Table 1, Fig. 4). In the 2 patients switched from ECMO to left VAD support, loss of vWF HMW multimer bands persisted. In 1 patient, vWF multimers could not be analyzed after termination of ECMO support due to blurring of multimers. ADAMTS 13 and CRP did not change over time (Table 2). CRP was increased at baseline and remained above normal values during and after support, without reaching statistical significance over time.

DISCUSSION

In this study of patients with intractable cardiac and/or respiratory failure requiring emergency ECMO support, we found a decrease in HMW vWF multimer bands 24 and 48 hours after initiation of ECMO support. This loss affected only the HMW proportion of vWF multimers because intermediate- and low-molecular-weight levels did not change. HMW vWF multimers normalized promptly after patients were weaned from ECMO support. Decreased vWF:RCo/vWF:Ag ratio during support reflected a proportional loss of HMW vWF multimers. The underlying condition of the patient as well as severity of disease, age, type of ECMO support, and type of vascular access as well as vWF baseline values had no influence on onset or extent of loss of HMW vWF multimers.

Vascular access cannulae and centrifugal pumps generating continuous blood flow for mechanical assist devices such as ECMO support or VADs alter blood shear stress profiles.[16,17] De Bartolo et al.[18] demonstrated in a 3-dimensional computational fluid dynamics study of the Wang-Zwische double-lumen cannula that turbulent flow at the lateral holes of the drainage cannula produced a wall shear stress that was approximately 4 times greater than that in the centric

lumen of the infusion cannula and thus potentially inducing disturbances in primary hemostasis.[18] In our study, we used Bio-Medicus cannulae (Medtronic) with multiple side ports, which allow greater drainage flow, but create local vortices and turbulences shown in computational fluid dynamics studies.[19,20] Mizunuma and Nakajima[17] demonstrated distribution of shear stress on the head of a centrifugal blood pump (Nikkiso HPM-15; Nikkiso Co. Ltd, Tokyo, Japan). The increase in shear stress was approximately proportional to the rotating speed (e.g., at 3000 rpm, the measured shear stress in this model was >4 times as high as at 1500 rpm). In agreement with the findings by Sidebotham et al.,[21] our patients required an average rotating speed of 3300 to 3600 rpm to achieve the recommended circuit flow of 50 to 80 mL/kg/min. In accordance with the findings by Mizunuma and Nakajima,[17] in these circumstances, high shear stress must be assumed in all our patients; all our patients presented with significant loss of HMW vWF multimers.

In our study, we found increased vWF:Ag levels and vWF:RCo activity before initiating ECMO support. vWF:Ag is increased in acute and chronic inflammatory states[22] and may reflect the acute phase response due to endothelial dysfunction in circulatory shock conditions. CRP levels, another marker of inflammation, were simultaneously increased.[23] Similarly, F:VIII levels remained unchanged during ECMO support.

There was a marked decrease in HMW vWF multimer bands during ECMO support, as demonstrated by gel electrophoresis, despite having considerably increased vWF:Ag levels. Although vWF plasma levels decreased during ECMO support, plasma levels of vWF:Ag did not decrease below the critical threshold typically associated with spontaneous bleeding and blood loss.[24] We did observe that during ECMO support, the vWF:RCo/vWF:Ag ratio decreased below the critical value of 0.7 associated with bleeding.[24] Our results are similar to the findings by Heilmann et al.,[12] who demonstrated missing HMW vWF multimer bands in all but 1 patient during extracorporeal life support, accompanied by a reduced vWF:RCo/vWF:Ag ratio.

Degradation of vWF is also accomplished by the vWF-cleaving protease, ADAMTS 13. vWF is resistant to ADAMTS 13 under static conditions; under shear stress conditions, vWF is rapidly cleaved, most likely due to exposure of the vWF cleavage site.[25] In our study, ADAMTS 13 levels did not change over time. We assume that ECMO support induced high shear stress, resulting in unfolding of vWF, exposing vWF cleavage site, and consecutive loss of HMW vWF multimers.

The HMW vWF multimers are most essential for primary hemostasis, whereas the lower-molecular-weight multimers are less functionally active.[5] In this study, we performed multimeric analysis of HMW vWF multimers. Technical requirements and delayed availability of results have hampered introduction of this method in clinical practice. In contrast, determination of vWF:Ag and vWF:RCo is readily available in most laboratories. A vWF:RCo/vWF:Ag ratio reduced to <0.7 is highly indicative for significant reduction or loss of HMW vWF multimer bands.[24] In our opinion, an early available ratio can be useful in clinical decision making. Normal or even increased plasma levels of vWF:Ag do not exclude loss of HMW vWF multimer bands because HMW vWF multimer bands may decrease disproportionately as compared with vWF:Ag levels.

Bleeding risk and blood loss during and shortly after ECMO support may be greater when loss of HMW vWF multimers occurs. Bleeding complications during ECMO support typically are treated with transfusion of platelet concentrates and fresh-frozen plasma and by decreasing the intensity of the anticoagulation regimen.[21,26] In addition, our findings support the early use of high doses of vWF:antigen-containing concentrates such as Humate-P/Haemate-P (CSL Behring, Marburg, Germany) or Wilfactin (LFB, Les Ulis, France) concentrates if bleeding persists and the vWF:RCo/vWF:Ag ratio is low.[7] Commonly available vWF:Ag concentrates also contain different amounts of F:VIII. Because increased F:VIII levels increase the thromboembolic risk,[27] F:VIII levels should be determined before considering administration of vWF/F:VIII concentrate. Close monitoring of clinical response is needed when tailoring doses and dose intervals of vWF-containing F:VIII concentrates.

CONCLUSIONS

Loss of HMW vWF multimer bands occurred in all patients undergoing ECMO support and resolved after termination of ECMO. Although not detectable with coagulation screening tests, a vWF:RCo/vWF:Ag ratio <0.7 during ECMO support was highly indicative for loss of HMW vWF multimers. Our findings may at least in part explain the increased bleeding tendency during ECMO support. Administration of vWF concentrates may support restoration of primary hemostasis in patients with relevant bleeding during ECMO support. Doses and dose intervals have to be tailored individually.

DISCLOSURES

Name: Helmuth Tauber, MD.
Contribution: This author helped in conduct of the study, data collection, and manuscript preparation.
Attestation: Helmuth Tauber approved the final manuscript. He attests to the integrity of the original data and the analysis reported in the manuscript.
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Contribution: This author helped in study design, conduct of the study, data collection, data analysis, and manuscript preparation.
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