Cardiovascular Intervention and Therapeutics (2019) 34:358–363
https://doi.org/10.1007/s12928-019-00568-y

ORIGINAL ARTICLE

Acquired von Willebrand syndrome in patients treated with veno-arterial extracorporeal membrane oxygenation

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Received: 8 November 2018 / Accepted: 31 December 2018 / Published online: 17 January 2019

Abstract

Veno-arterial extracorporeal membrane oxygenation (VA ECMO) is a powerful device for treatment of patients with life-threatening heart failure. Although bleeding is often associated with VA ECMO and sometimes results in a fatal outcome, its precise causes remain unknown. On the other hand, excessive high shear stress in the cardiovascular system causes acquired von Willebrand syndrome (aVWS), characterized by loss of von Willebrand factor (vWF) large multimers. vWF large multimers of five consecutive patients treated with VA ECMO were quantitatively evaluated using the vWF large multimer indices, defined as the ratio of the large multimer ratio of a patient to that of a healthy subject analyzed simultaneously. All 5 patients exhibited oozing type of bleeding at the skin insertion sites under treatment with PCPS at flow rates of 2.5–3.0 l/min/m^2, including two severe cases of bleeding; one patient had massive gastrointestinal bleeding and another had hemothorax. Their vWF large multimer indices were 20.8, 28.8, 27.6, 51.0, and 31.0% (means 31.8 ± 11.4%). Surprisingly, these values are much lower than those observed in severe aortic stenosis reported previously by us (Tamura et al. in J Atheroscler Thromb 22:1115–1123, 2015), where vWF multimer indices in 31 severe aortic stenosis patients with peak pressure gradient through the aortic valves of 85.1 ± 29.4 mmHg were 75.0 ± 21.7% ($p < 0.0001$), indicating that much higher grade of aVWS occurred in patients with VA ECMO than severe aortic stenosis patients. All the 5 patients treated with VA ECMO developed aVWS that was much more severe than in patients with severe aortic stenosis.

Keywords VA ECMO · Bleeding · Acquired von Willebrand syndrome · Aortic stenosis · Large VWF multimer index

Introduction

The veno-arterial extracorporeal membrane oxygenation (VA ECMO) consists of a centrifugal pump and membrane oxygenator that provides adequate oxygenation of blood and hemodynamic stabilization. In daily clinical practice, VA ECMO is a very powerful device to maintain a stable hemodynamic state during treatment of patients with life-threatening cardiac failure caused by various conditions such as acute myocardial infarction [2], fulminant myocarditis, and acute pulmonary embolism [3]. However, we often experience massive bleeding at the site of sheath insertion of the skin, oral cavity, and gastrointestinal tract. Such bleeding has been considered due to anticoagulant therapy with heparin concomitantly used during VA ECMO treatment for the prevention of thrombotic complications even if the anticoagulation is within a therapeutic range, and also due to decrease in platelet counts that is often accompanied with the VA ECMO treatment.

von Willebrand factor (vWF) plays a critical role in hemostasis [4]. It is produced from megakaryocytes and endothelial cells as a huge multimer that is shear-stress dependently cleaved in blood stream by its specific cleaving enzyme ADAMTS13 into multimers composed of 2–80 subunits. Importantly, among vWF multimers, high molecular weight (large) vWF multimers play critical roles in hemostasia [5]. Therefore, the loss of large vWF multimers causes the bleeding tendency classified as von Willebrand

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disease type IIA [6]. Recently, it is considered that extraordinarily high shear stress causes acquired von Willebrand syndrome (aVWS) by excessive cleavage of vWF multimers, the pathophysiology of which is equivalent to that of in Willebrand disease type IIA. aVWS is diagnosed with the vWF multimer analysis, although the results of it had been hardly evaluated quantitatively. We have recently analyzed the vWF multimer large multimers in 31 severe aortic stenosis patients with a proposed quantitative value, the vWF large multimer index, and reported that most patients have exhibited aVWS and that the loss of vWF large multimers was strongly associated with the peak pressure gradient at the aortic valve [1].

Recently, it has been indicated that aVWS plays an important role as a cause of the bleeding complication of mechanical circulatory support, such as with the left ventricular assist device [7–11] and vein–vein extracorporeal membrane oxygenation [12]. In this study, we evaluated 5 consecutive patients treated with VA ECMO and compared the severity of aVWS with that in patients with severe aortic stenosis evaluated with the vWF large multimer index [1].

Methods

Patients evaluated

Five consecutive patients in an unstable hemodynamic state due to cardiovascular diseases treated with VA ECMO in our institution from November 2013 to February 2016 were evaluated. All of the inserted VA ECMO circuits consisted of an X-coated centrifugal pump, polypropylene hollow fiber membrane oxygenator, and thin-walled cannula (CAPIOX EBS, Terumo Corp., Tokyo, Japan). VA ECMO was instituted in the veno-arterial mode by cannulating the common femoral artery using a 15–16.5 Fr sheath (CX-EB16ALX, Terumo Corp.) and vein using a 21 Fr sheath (CX-EB21VLX, Terumo Corp.). VA ECMO blood flow in all patients ranged from 2.5 to 3.0 l/min and a rotation rate of the biopump was 2500–3000 rpm using a Capiox SP Pump Controller Sp-100 plus (Terumo Corp.). This study was approved by the Institutional Ethical Committee of the Tenri Hospital and written informed consent for study participation was obtained from the family of each participating patient.

Evaluation of large vWF multimers

The multimeric structure of vWF was analyzed within 19–82 h after VA ECMO insertion according to the method of Ruggeri and Zimmerman [13], by SRL Co., Tokyo, Japan. Quantitative evaluation of large vWF multimers was performed using the "large vWF multimer index" as described previously [1]. Briefly, the bands of vWFs of plasma of a patient and a healthy control, analyzed simultaneously in a western blot, were analyzed with densitometry using Image J. Then, for each datum, the large multimer area was divided by the corresponding total vWF area, the value of which was designated as the vWF large multimer ratio. Finally, the vWF large multimer index was measured as the ratio of the patient's vWF large multimer ratio to the healthy subject's. Accordingly, the amount of a patient's vWF large multimers is expressed as the percentage of that of a healthy control.

Statistical analyses

All statistical analyses were performed using JMP version 7 (SAS Institute Inc., Cary, NC, USA). All continuous variables are expressed as the mean value ± standard deviation. Intergroup comparison of continuous variables was performed using the Student's t test or, if not normally distributed, Wilcoxon's two-sample test. A p value < 0.05 was considered statistically significant.

Results

Case presentation

As shown in Table 1 and Fig. 1, all of the 5 patients treated with VA ECMO exhibited deficiency of vWF large multimers. Two patients had massive bleeding events, while oozing type of bleeding at the sites of sheath insertion into the skin was observed in all 5 patients during the VA ECMO therapy.

Case 1

A 71-year-old male was admitted because of cardiogenic shock caused by inferior acute myocardial infarction. Supported with VA ECMO and intra-aortic balloon pumping (IABP), the occluded right and left circumflex coronary arteries were successfully recanalized by emergent percutaneous coronary intervention. During mild hypothermia therapy under VA ECMO and IABP treatment, massive gastrointestinal bleeding occurred on the 2nd day, when the large vWF multimer index was 20.8% at 24 h after VA ECMO insertion. Upper gastrointestinal endoscopic examination revealed that the massive bleeding was caused by an acute gastric mucosal lesion. The VA ECMO was removed on the 5th day because the massive bleeding became uncontrollable by the endoscopic hemostatic procedure with radiofrequency ablation. The patient died of multiple organ failure on the 6th day.

Table 1 Clinical characteristics of 5 VA ECMO-treated patients

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	Male	Female	Male	Female	Female
Age (years)	71	78	32	65	67
Blood type	A	O	O	O	B
Diagnosis	Acute myocardial infarction	Acute pulmonary embolism	Fulminant myocarditis	Acute myocardial infarction	Acute pulmonary embolism
Use of unfractionated heparin	(+)	(+)	(+)	(+)	(+)
Warfarin	(−)	(−)	(−)	(−)	(−)
Thrombolysis	(−)	(+)	(−)	(−)	(−)
Bleeding at sheath insertion	(+)	(+)	(+)	(+)	(+)
Massive bleeding	Gastrointestinal bleeding	Hematothorax	(−)	(−)	(−)
Large vWF multimer index (%)	20.8	51.0	27.6	28.8	31.0
Activity of ADAMTS13	48.0	57.0	91.0	110.0	83.0
Hemoglobin (g/dl)	7.9	8.7	11.0	10.8	11.3
Platelet counts ($\times 10^4$/μl)	5.8	9.1	5.2	16.0	5.1
APTT (second)	134.1	113.0	54.8	90.4	37.0
VA ECMO flow rate (l/min)	2.9	1.2	3.0	2.6	1.4
Sheath size of femoral vein	21	21	21	21	21
Sheath size of femoral artery	16.5	15	16.5	16.5	15
Clinical outcome	Deceased	Deceased	Alive	Alive	Alive

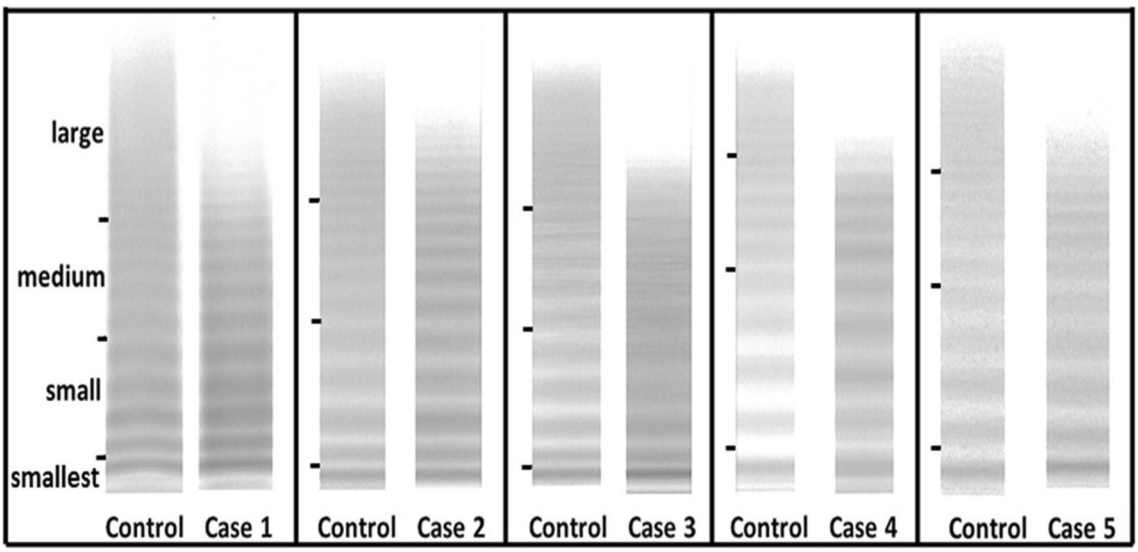

Fig. 1 vWF multimer analysis in 5 VA ECMO-treated patients

Case 2

A 78-year-old female was admitted because of pulmonary embolism in a state of shock. After cardiac resuscitation, VA ECMO and intra-aortic balloon pumping (IABP) were inserted and thrombolytic therapy using 800,000 U monteplase (Cleactor®; Eisai Co., Ltd., Tokyo, Japan), a genetic recombinant tissue-type plasminogen activator, was performed. On the 2nd day the large vWF multimer index was 51.0% at 23 h after VA ECMO insertion and massive hemothorax developed. Then, VA ECMO was removed since the patient's clinical state had gradually improved on the 2nd day. IABP was removed on the 5th day, and the ventilator was removed on the 9th day. Although she was stable without apparent bleeding for a while, massive pulmonary embolism recurred on the 23rd

day in spite of oral anticoagulant therapy with warfarin. The patient died on the 22nd day.

Case 3

A 32-year-old male was admitted because of fulminant myocarditis and underwent IABP and VA ECMO insertion on the 2nd day because of hemodynamic collapse. Although an apparent bleeding event did not occur, the large vWF index at 47 h after VA ECMO insertion was 27.6%. The patient's general condition had worsened without improvement in left ventricular function. He was transferred to another hospital to undergo therapy with a left ventricular assist device on the 5th day.

Case 4

A 65-year-old female was admitted because of acute myocardial infarction with total occlusion of the main trunk of the left coronary artery. She was immediately treated with VA ECMO and IABP insertion, and the area of occlusion was successfully recanalized by emergent percutaneous coronary intervention (PCI). Her large vWF multimer index was 28.8% at 19 h after VA ECMO insertion, and bleeding events did not occur. Her cardiac function and general condition gradually improved and the VA ECMO was removed on the 4th day. She was discharged from our hospital on foot on the 40th day.

Case 5

A 67-year-old female was admitted because of pulmonary embolism in a state of shock. Immediately after cardiac resuscitation, VA ECMO and IABP were inserted. Pulmonary arteriography revealed a massive thrombus in the main pulmonary artery. On the day of admission, she received an emergent surgical pulmonary embolectomy. On the 2nd day the large vWF multimer index was 31.0% at 82 h after VA ECMO insertion and 77 h after the operation. Her clinical state gradually improved after surgery and the VA ECMO was removed on the 4th day. During the periods of treatment with VA ECMO, massive bleeding did not occur. She was discharged on the 59th day without sequelae.

Comparison of the vWF large multimer indexes of VA ECMO-treated patients with those of aortic stenosis patients

We analyzed and calculated the vWF large multimer indices in the VA ECMO-treated patients in this study in the same way used in our previous study [1]. In that study, we examined 31 patients (Table 2) with severe aortic stenosis with peak pressure gradient through the aortic valve of 85.1 ± 29.4 mmHg and showed that most of them exhibit aVWF with their vWF large multimer indices of 75.0 ± 21.7% (range 34.5–135.5%). On the other hand, the vWF large multimer indices in 5 VA ECMO-treated patients analyzed in this study were 31.8 ± 11.4% (range 20.8–51.0%). If we dare to compare these values, the vWF large multimer indices in VA ECMO-treated patients were much lower than those in severe aortic stenosis patients (31.8 ± 11.4% vs 75.0 ± 21.7%, $p < 0.0001$, Fig. 2). Thus,

Table 2 Clinical characteristics of 31 severe aortic stenosis patients

Male	12 (38.7%)
Age (years)	78.7 ± 8.4
Gastrointestinal bleeding	2 (6.5%)
Large vWF multimer index (%)	75.0 ± 21.7
Activity of ADAMTS13	73.5 ± 27.9
Hemoglobin (g/dl)	9.5 ± 2.4
Hemoglobin < 9.0 g/dl	12 (38.7%)
Platelet counts ($\times 10^4$/μl)	15.9 ± 5.5
APTT	32.4 ± 6.7
Peak aortic velocity (m/s)	4.6 ± 0.8
Peak aortic gradient (mmHg)	85.1 ± 29.4
Aortic valve area (cm^2)	0.63 ± 0.17
Aortic valve replacement	17 (54.8%)

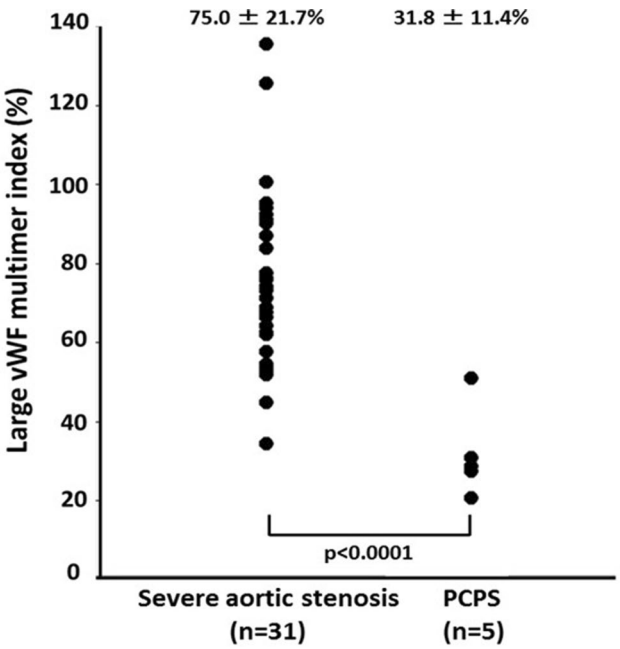

Fig. 2 Comparison of vWF large multimer indices between severe aortic stenosis and VA ECMO-treated patients. Data on patients with severe aortic stenosis were adopted from our previously published paper [1]

much severer aVWS occurred in the VA ECMO-treated patients than in the severe aortic stenosis patients.

Discussion

Bleeding is often associated with VA ECMO treatment and is sometimes critical for patients' outcome. Here, we showed that all 5 VA ECMO-treated patients exhibited bleedings. It has been considered that anticoagulant therapy and decrease in platelet counts are the main causes of VA ECMO-associated bleeding complication. Since their platelet counts were maintained over 50,000/mm^3 and continuous heparin administration was 10,000–15,000 units/day, decrease in platelet counts and too strong anticoagulant therapy might not be major causes of bleeding. On the other hand, we here showed that all the 5 patients exhibited high-grade aVWS that was much severer than that observed in patients with severe aortic stenosis. Thus, VA ECMO-associated aVWS could play a critical role in development of bleeding complication under VA ECMO treatment.

Severity of shear stress-caused aVWS has not been evaluated quantitatively because of lack of a comprehensive method. We have recently proposed a value quantitatively evaluating vWF large multimers by a novel comprehensive method [1], which is the large vWF multimer index. The index expresses the amount of a patient's large vWF multimers as a percent of that of a healthy control analyzed simultaneously [1]. Using these indexes, we showed that most patients with severe aortic stenosis examined exhibited loss of large vWF multimers and the degree of that loss is well correlated with the severity of aortic stenosis [1]. Here, we first compared the severity of VA ECMO-associated aVWS with aortic stenosis-associated aVWS using the vWF large multimer indexes. The results clearly indicated that the severity of VA ECMO-associated aVWS (20.8–51.0%) was far greater than that of aortic stenosis-associated aVWS (75.0 ± 21.7%) ($p < 0.0001$). While some aortic stenosis patients develop bleeding, most of the VA ECMO-treated patients had bleeding. Thus, much severer VA ECMO-associated aVWS than aortic stenosis-associated aVWS could contribute to the difference.

aVWS develops due to excessive high shear stress such as severe aortic stenosis. Inside a VA ECMO apparatus, a centrifugal pump generates blood flow by rotating at 2500–3000 rpm, where also very high shear stress is generated. Thus, the site of excessive cleavage of vWF could be inside the apparatus. Otherwise, the site could be the inflow or outflow cannulation tube since such tubes are narrow and long through which blood flows at a high rate. It is important to determine the vWF cleavage site because VA ECMO-associated bleeding may be avoided by using wider tubes if the cause is the inflow or outflow cannulation tube. If the cause is in the pump, to avoid bleeding, we need to reduce the pump flow or improve the pump system in future. It would also be possible that an ADAMTS-13 inhibitor, if it is developed, would improve VA ECMO-associated bleeding. Further investigation is essential for the improvement of VA ECMO therapy.

However, any possibility such as very severe pulmonary hypertension caused by pulmonary embolism or very unstable conditions may be involved regarding the development of aVWS.

Thus, very severe aVWS developed in all VA ECMO-treated patients and its severity was far greater than that observed in aortic stenosis patients. Since aVWS could play a major role in the complication of VA ECMO-associated bleeding, we should improve our understanding of it and provide proper therapy for VA ECMO-treated patients with bleeding.

Study limitations

There are several limitations to the present study. First, this study contained a small number of patients with an underpowered design, though large vWF multimer index was obviously low in all patients. A larger study is necessary to further validate these current findings. Second, with regard to comparison of vWF large multimer indices between severe aortic stenosis and VA ECMO-treated patients, data on patients with severe aortic stenosis were examined at different times which were adopted from our previously published paper [1]. Third, VWF multimer analysis was only performed once under anticoagulant therapy and VA ECMO insertion.

Conclusion

All the 5 patients treated with VA ECMO developed aVWS that was much more severe than in patients with severe aortic stenosis. aVWS might be considered as a cause of bleeding complication in patients with VA ECMO.

Acknowledgements This study was partly supported by a Health and Labour Sciences Research Grant for the 'Research on rare and intractable diseases' from the Ministry of Health, Labour and Welfare, Japan, to HH and YN, and grants from the SENSHIN Medical Research Foundation and the Suzuken Memorial Foundation to HH.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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