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Letter to the Editors-in-Chief

Acquired von Willebrand syndrome in patients on long-term left ventricular assist device support: Results of a Belgian center

Dear editor,

Acquired von Willebrand syndrome (aVWS) in patients treated with a left ventricular assist device (LVAD) is characterized by a loss of high molecular weight (HMW) von Willebrand factor (VWF) multimers which often coincides with an impaired VWF function reflected by a decreased VWF collagen-binding capacity and decreased binding of VWF to the platelet glycoprotein (GP) Ib receptor [1]. The high shear stress generated by the device leads to unfolding of the HMW VWF multimers and cleavage of VWF by ADAMTS13 (A Disintegrin And Metalloprotease with a ThromboSpondin type 1 motif, member 13) [2]. These VWF abnormalities can contribute to bleeding complications often observed in LVAD patients [1,3]. Many short-term (< 4 months) follow-up studies of LVAD patients further document the persistence of aVWS in these patients [4,5]. However, information concerning the changes in VWF parameters on long-term support (> 4 months to years after LVAD implant) and after heart transplantation is scarce [2]. In addition, only a few studies describe ADAMTS13 parameters after LVAD implantation and found either normal or decreased ADAMTS13 activities [6–8]. Hence, the aim of this study was a long-term follow up of VWF (VWF multimer size, antigen and activity) and ADAMTS13 (ADAMTS13 antigen and activity) parameters in LVAD patients and in those patients undergoing heart transplantation.

Following local ethical committee approval, plasma samples of 16 LVAD patients (11 men, 5 women with an age ranging from 31 to 68 years) were collected. Long-term follow up ranged from 1 month up to 2 years after device implantation and in total 59 plasma samples from these 16 LVAD patients were available for this study (Table 1). Four patients underwent subsequent heart transplantation (HT) after 15 to 25 months of LVAD support. The pump speed was comparable between the devices. All patients were on standard anticoagulation therapy with vitamin K antagonists (international normalized ration (INR) 2.5). None of the patients had a previous history of bleeding. In addition, plasma samples of 20 healthy donors (HD, 6 men, 14 women, age 23–60 years) were collected and used as a reference. VWF antigen (VWF:Ag) and the capacity of VWF to bind the platelet GPIb receptor (VWF GPIbR binding activity or VWF:GPIbR) were determined via immunoturbidimetric assays (HemosIL, Instrumentation Laboratory, Bedford, MA) on a ACLTOP (fully automated haemostasis testing system). VWF collagen binding activity (VWF:CB) was determined as described [9]. Next, the normalized VWF collagen binding and VWF GPIbR binding activities were determined by calculating the VWF collagen binding activity/VWF antigen (VWF:CB/VWF:Ag) and VWF GPIbR binding activity/VWF antigen (VWF:GPIbR/VWF:Ag) ratios. When these ratios are < 0.7, VWF activity is defined as decreased [9]. ADAMTS13 antigen levels were determined via ELISA [10]. ADAMTS13 activity in plasma was determined with a fluorescence resonance energy transfer (FRETS) assay using a fluorogenic FRETS-VWF73 synthetic peptide (Peptide institute, Osaka, Japan). VWF multimer analysis on patients plasma samples was performed as described before [9]. The percentage of high molecular weight (HMW) VWF multimers was determined via densitometric analysis using ImageJ software (version 1.47, NIH, Bethesda, MD).

HMW VWF multimers were normal in the 3 LVAD patients of whom plasma samples were available before LVAD implantation (Table 1) (compared to HMW VWF multimers of healthy donors, 25–43%) (Fig. 1A). In contrast, HMW VWF multimers were lower in all 16 patients after LVAD implantation and remained decreased > 2 years after implantation of the device as reflected by the observed decrease in HMW VWF multimers in 45 of the 49 studied plasma samples (Fig. 1A and B). Interestingly, in 3 patients, the VWF multimeric distribution pattern during one single time point of LVAD support remained normal. This is in line with previous reports showing a drop in HMW VWF multimers after LVAD implantation in all or the majority of LVAD patients [1,3,6]. This loss of HMW VWF multimers was also reflected by a decreased normalized VWF collagen binding activity and normalized VWF GPIbR binding activity (< 0.7) in 38 and 35 of the 49 plasma samples respectively (Fig. 1C and D) after LVAD implantation which corroborates previous observations [2]. Hence, aVWS could be detected in all patients. VWF antigen levels were above normal range (77–140% in healthy donors) pre-LVAD and remained high in 31 of the 49 samples tested after LVAD implantation (Fig. 1E). These increased VWF antigen levels could be explained by an acute phase reaction as a consequence of an inflammatory response occurring in the heart failure and LVAD

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Table 1
Overview of the available blood samples and bleeding events after long-term follow-up of LVAD patients.

		Available plasma samples										
Patient	Device	Before implantation	1-3 M PI	4-6 M PI	7-9 M PI	10-12 M PI	>12 M PI	HT	<6 D after HT	>6 D after HT	Deceased	Bleedings	Blood transfusion products (PRC)
1	(Heartware HVAD)			x	x	x		x (19M)	x	x	x		
2	(Heartware HVAD)		x		x	x		x (15M)	x	x			
3	(Heartware HVAD)	x	x	x	x	x	x						
4	(Excor)						x	x (25 M)	x	x		Ovarian cyst (7M PI)	
5	(Heartware HVAD)		x	x							x	Nasopharyngeal (1M PI)	
6	(Heartware HVAD)		x	x	x	x		x (23M)	x				
7	Heartware (HVAD)	x	x	x		x	x					GI (2J3M PI)	x (2 units)
8	(Heartware HVAD)		x								x	Epistaxis (2,5 M)	
9	(Heartware HVAD)		x									GI (3M PI)	x (2 units)
10	(Heartware HVAD)		x	x	x	x	x						
11	(Heartware HVAD)		x	x		x							
12	(Heartware HVAD)		x	x		x	x					Ischemic colitis (9M PI)	
13	(Heartware HVAD)		x	x	x		x					GI AD (4M PI)	x (3 units)
14	Heartmate II		x	x	x	x							
15	Heartware (HVAD)		x										
16		x	x	x	x	x							

D, days; M, months; PI, post implantation; HT, heart transplantation; AD, angiodysplasia; PRC, packed red cells.
The colours refer to the individual data points in figure 1 where the colour of every datapoint corresponds to the individual data of the patient with the same colour in table 1

patients [8]. Despite the fact that HMW VWF multimers were decreased during the entire study period, significant bleedings, necessitating transfusion occurred in only 19% of the patients (Table 1). This suggest that other factors besides aVWS might contribute to the bleeding complications in LVAD patients [5,8,9].

ADAMTS13 activity/ADAMTS13 antigen ratio was decreased in 2 of the 3 samples that were collected pre-implant and in 40 of the 49 samples collected after LVAD implantation (Fig. 1F) when compared to ADAMTS13 activity/ADAMTS13 antigen ratios in healthy donors (0.86–1.58). Similar to previous work [7], this was due to a decrease in ADAMTS13 activity as ADAMTS13 antigen levels were within the range of ADAMTS13 antigen levels in healthy donors (66–115%). One possible explanation could be that the shear stress generated by the device might lead to activation of coagulation and inhibition of ADAMTS13 activity by thrombin [11]. Four out of 16 patients underwent heart transplantation (HT) (Table 1). For 2 of these patients (patients 2 and 4 and plasma samples < 6 days after HT, Table 1), the percentage of HMW VWF multimers normalized to levels present in healthy donors (Fig. 1A and B). HMW VWF multimers remained normal during the postoperative period (plasma samples > 6 days after HT). Accordingly, this also resulted in an increased normalized VWF collagen binding activity and increased normalized VWF GPIbR binding activity (> 0.7) (Fig. 1C and D). These findings corroborates previous observations demonstrating aVWS reversal after heart transplantation [3]. In the other 2 patients (patients 1 and 6 and plasma samples < 6 and > 6 days after HT, Table 1), no increase in HMW VWF multimers, and hence in normalized VWF collagen binding activity and normalized VWF GPIbR activity, were observed (Fig. 1A–D). In these patients, we hypothesize that the initiation of extracorporeal life support (ECLS) because of graft failure immediately after transplantation may have accounted for this observation [12].

In conclusion, this long-term follow-up study shows that aVWS is not only present early after LVAD implantation but persists over time. However, this aVWS was only related to bleeding complications in a minority of patients, suggesting that other mechanisms may contribute to the increased bleeding diathesis observed in LVAD patients.

Declaration of competing interest

None declared.

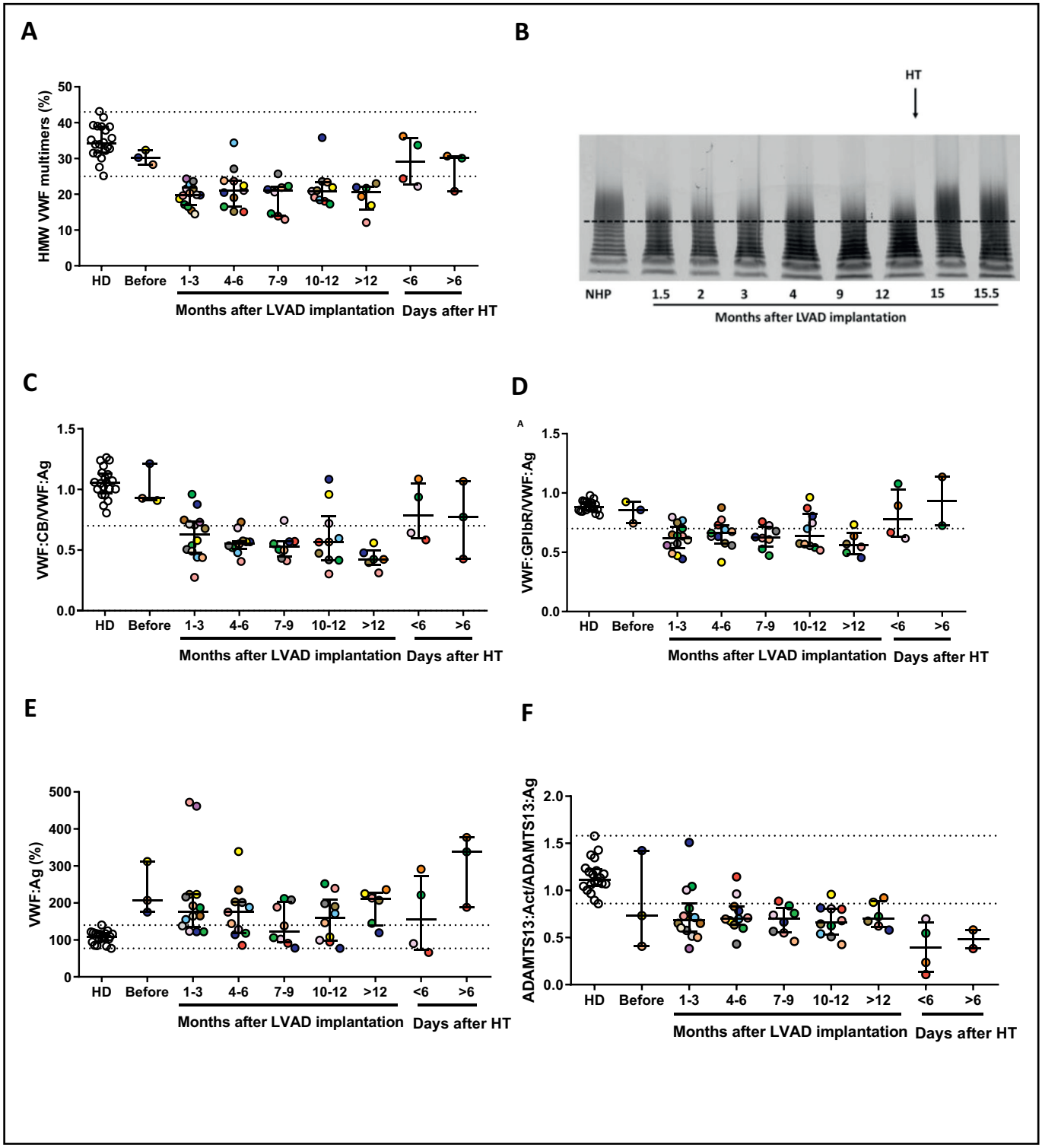

Fig. 1. HMW VWF multimers, VWF antigen, VWF collagen binding activity, VWF GPIbR binding activity, ADAMTS13 activity and antigen levels in LVAD patients. HMW VWF multimers, VWF antigen (VWF:Ag), VWF collagen binding activity (VWF:CB), VWF GPIbR binding activity (VWF:GPIbR), ADAMTS13 activity (ADAMTS13:Act) and ADAMTS13 antigen (ADAMTS13:Ag) levels were determined in plasma of the healthy donors (HD, n = 20) and in 49 plasma's of 16 patients implanted with an LVAD (Table 1). (A) HMW VWF multimers were reduced in all patients on LVAD support and recovered after pump explantation in 2 out of 4 LVAD patients. HD were used as control samples. Dotted lines indicate the range of HMW VWF multimers in the healthy donors (HD, 25–43%). (B) Representative VWF multimeric pattern of an LVAD patient during LVAD support and after heart transplantation (HMW VWF multimers are situated above the dashed line). (C) Normalized VWF collagen binding activity (VWF:CB/VWF:Ag) and (D) Normalized VWF GPIbR binding activity (VWF:GPIbR/VWF:Ag) was decreased in LVAD patients compared to HD and returned to normal after heart transplantation. Dotted lines in C and D indicate cut-off values, set at 0.7 for ratios [9]. (E) VWF antigen levels were elevated in patients before and during LVAD implantation. Dotted lines indicate the VWF antigen levels in the healthy donors (HD, 77–140%). (F) ADAMTS13 activity/ADAMTS13 antigen ratio was decreased in LVAD patients compared to HD. Dotted lines indicate the ADAMTS13:Act/ADAMTS13:Ag ratio in the healthy donors (HD, 0.86–1.58). (A, C, D, E and F) Graphs show individual data points with a different color for each patient (Table 1), as well as median and interquartile ranges (25th and 75th percentile) per time point.

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Shannen J. Deconinck[a], Claudia Tersteeg[a], Els Bailleul[b], Leen Delrue[b], Nele Vandeputte[a], Inge Pareyn[a], Hans Deckmyn[a], Simon F. De Meyer[a], Karen Vanhoorelbeke[a], Marc Vanderheyden[b,*]

[a] *Laboratory for Thrombosis Research, IRF Life Sciences, KU Leuven Campus Kulak Kortrijk, Kortrijk, Belgium*

[b] *Cardiovascular Center Aalst, OLV Hospital, Aalst, Belgium*

E-mail address: marc.vanderheyden@olvz-aalst.be (M. Vanderheyden).

* Corresponding author at: Cardiovascular Center Aalst, OLV Hospital, Moorselbaan 164, B-9300 Aalst, Belgium.