British Journal of Anaesthesia **108** (5): 754–62 (2012)
Advance Access publication 5 February 2012 · doi:10.1093/bja/aer512

BJA

Impact of loss of high-molecular-weight von Willebrand factor multimers on blood loss after aortic valve replacement

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Editor's key points

- Severe aortic stenosis is associated with loss of high-molecular-weight von Willebrand factor (vWF) multimers, but its impact on perioperative bleeding is unclear.
- In a prospective observational study of 60 subjects undergoing aortic valve replacement for severe aortic stenosis, vWF activity and multimer structure were measured.
- There was no association between reduced high-molecular-weight vWF multimers and postoperative blood loss.
- This could be due to rapid recovery of vWF after valve replacement.

Background. Severe aortic stenosis is associated with loss of the largest von Willebrand factor (vWF) multimers, which could affect primary haemostasis. We hypothesized that the altered multimer structure with the loss of the largest multimers increases postoperative bleeding in patients undergoing aortic valve replacement.

Methods. We prospectively included 60 subjects with severe aortic stenosis. Before and after aortic valve replacement, vWF antigen, activity, and multimer structure were determined and platelet function was measured by impedance aggregometry. Blood loss from mediastinal drainage and the use of blood and haemostatic products were evaluated perioperatively.

Results. Before operation, the altered multimer structure was present in 48 subjects (80%). Baseline characteristics and laboratory data were similar in all subjects. The median blood loss after 6 h was 250 (105–400) and 145 (85–240) ml in the groups with the altered and normal multimer structures, respectively (P=0.182). After 24 h, the cumulative loss was 495 (270–650) and 375 (310–600) ml in the groups with the altered and normal multimer structures, respectively (P=0.713). Multivariable analysis revealed no significant influence of multimer structure and platelet function on bleeding volumes after 6 and 24 h. After 24 h, there was no obvious difference in vWF antigen, activity, and multimer structure in subjects with and without the altered multimer structure before operation or in subjects with and without perioperative plasma transfusion.

Conclusions. The altered vWF multimer structure before operation was not associated with increased bleeding after aortic valve replacement. Our findings might be explained by perioperative release of vWF and rapid recovery of the largest vWF multimers.

Keywords: blood, transfusion; coagulation; surgery, cardiovascular

Accepted for publication: 16 December 2011

An association between aortic valve stenosis and gastrointestinal bleeding (Heyde's syndrome) was first reported in 1958.[1] The haemorrhagic diathesis in patients with severe aortic stenosis was explained by an acquired von Willebrand disease (vWD) type 2A, which is characterized by the loss of the largest (high-molecular-weight) multimers of von Willebrand factor (vWF) and decreased vWF-dependent platelet adhesion and aggregation.[2 3] The shear stress-dependent cleavage of the largest vWF multimers by ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) is claimed to be responsible for the laboratory findings similar to vWD 2A in patients with severe aortic stenosis.[4] vWF plays a pivotal role in primary haemostasis as a ligand that bridges platelet GP Ib/IX and collagen under high shear conditions, thereby inducing platelet adhesion to the denuded vessel wall followed by platelet activation and aggregation.[5] vWF is present in plasma as high-, middle-, and low-molecular-weight multimer forms. The largest multimers are thought to be most important for primary haemostasis and platelet activation.[3 5–7]

Several observational studies including more than 150 patients showed that loss of the largest vWF multimers

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was present in 33–92% of the patients depending on the severity of aortic stenosis, detection method, and diagnosis criteria used.[8–11] In addition, several studies using different platelet function analysers showed impaired platelet function associated with reduced levels of large vWF multimers in patients with severe aortic stenosis.[5 8 12 13] Aortic valve replacement in affected patients induced long-lasting correction of bleeding diathesis and the recovery of vWF multimer structure and platelet function within hours after surgery.[5 8 12 14] Potentially, loss of the largest vWF multimers compromises the capacity of primary haemostasis in patients undergoing aortic valve replacement.

The aim of this study was to investigate the effect of altered vWF multimer structure on bleeding from mediastinal drainage and transfusion requirements after aortic valve replacement. We hypothesized that patients with the altered vWF multimer structure have increased postoperative bleeding due to impaired primary haemostasis.

Methods

Subjects

After approval by the local ethics committee (Ethikkommission beider Basel, Basel, Switzerland) and obtaining written informed consent, we prospectively enrolled 67 consecutive subjects from September 2008 until March 2010 at the University Hospital Basel, Switzerland. Subjects were included if they underwent surgical aortic valve replacement for severe aortic valve stenosis, defined as calculated effective orifice area (EOA) $\leq$1.0 cm^2 or a mean pressure gradient over the aortic valve of $\geq$50 mm Hg. Patients were not included if they were under 18 yr of age or were not competent to give consent, if the surgical procedure was not restricted to aortic valve replacement, if surgery included the use of deep hypothermic cardiac arrest, or if they had kidney failure (calculated creatinine clearance $<$30 ml min^{-1}) or elevated liver enzymes (more than twice the upper normal level). According to the institutional practice, patients were allowed to take aspirin (100 mg day^{-1}) and clopidogrel (75 mg day^{-1}) until the day before surgery, whereas coumarins were stopped at least 3 days before surgery. Seven subjects were excluded from the analysis as indicated in Figure 1, leaving 60 subjects in the study.

Routine laboratory tests including blood count and measurement of international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen concentration were performed on the morning of the day before surgery, directly after arrival on the intensive care unit (ICU), and on the morning of the first and the second day after surgery. Echocardiographic evaluation was performed during routine preoperative evaluation. The mean and peak transvalvular pressure gradients were calculated using the modified Bernoulli equation, and the EOA was calculated with the continuity equation.

Screening for haemorrhagic disorders

Bleeding symptoms were evaluated by use of a standardized screening questionnaire adapted from those described by

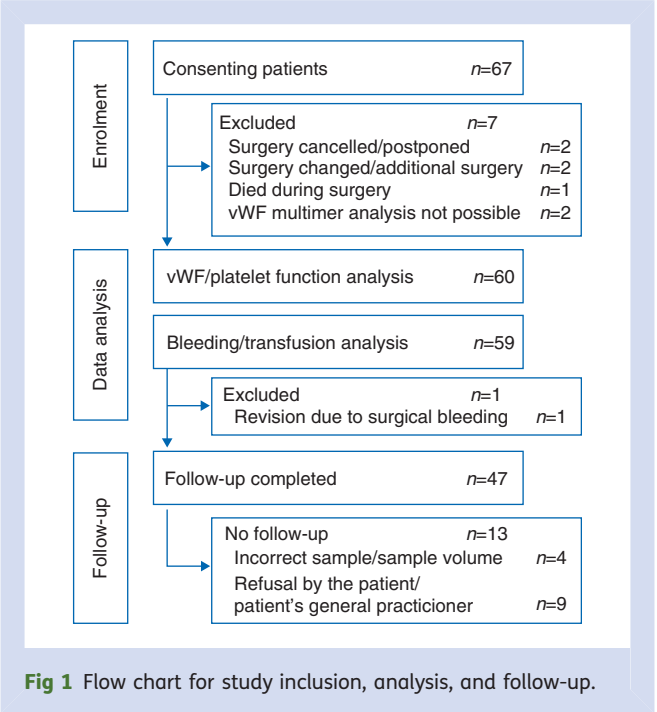

Fig 1 Flow chart for study inclusion, analysis, and follow-up.

Koscielny and colleagues[15] and Tosetto and colleagues.[16] Two authors (D.B. and S.D.-K.) blinded to other subject data independently evaluated bleeding risk. Subjects were rated as at 'increased bleeding risk' when there was (i) a haemorrhagic disorder within the last 24 months preceding surgery or (ii) intake of clopidogrel until the day before surgery.[17 18] Disagreement was resolved by consensus; agreement between the two raters was 0.91 as evaluated by κ statistics.

Blood collection and laboratory assays

Blood for study purposes was collected directly before surgery and 24 h after the end of surgery into sodium citrate tubes for vWF electrophoretic multimer analysis and into hirudin tubes for platelet function analysis (Sarstedt AG, Sevelen, Switzerland). Sodium citrate tubes were sent to the central laboratory and immediately centrifuged to obtain platelet-poor plasma, which was aliquoted and frozen at -70°C for vWF analysis (MEDILYS Coagulation Laboratory, Hamburg, Germany).

vWF antigen (vWF:Ag; in IU dl^{-1}) was measured immunologically according to standard protocols on a Behring Coagulation System analyser. vWF activity (in IU dl^{-1}) was determined photometrically by ELISA and described as collagen-binding capacity (vWF:CB).[19] For multimer analysis, vWF multimers were separated on low-resolution agarose gels (1.2% agarose), blotted on a polyvinylidene difluoride membrane, and detected using appropriate primary and secondary antibodies and chemiluminescence as described previously.[9 20] Pre- and postoperative samples were analysed in parallel on the same gel. Loss of the largest multimers (defined as band 11 or higher, corresponding to a molecular weight of $\sim$6000 kDa)[20] and percentage of large multimers were determined by the external coagulation laboratory

(MEDILYS), which was not involved in the study and was blinded for all other study data.

In the pre- and postoperative blood samples, platelet function analysis was performed using multiple electrode aggregometry (Multiplate™, Dynabite, Munich, Germany) according to the manufacturer's instructions by two experienced members of the study team (M.G. and U.Z.) blinded to all other study data. This system has been previously described in detail.[21] Briefly, 300 μl of hirudin-anticoagulated whole blood was diluted with 300 μl of saline. After incubation at 37°C, a platelet agonist was added to the test cell. Subsequently, the impedance change, which is proportional to the amount of activated platelets adhering to the sensors, was continuously monitored for 6 min and transformed to arbitrary 'units' (U). Platelets were activated by thrombin receptor-activating peptide (TRAP)-6 (32 μM) in the TRAP test, by collagen (3.2 μg ml^{-1}) in the COL test, and by ristocetin (0.77 mg ml^{-1}) in the RISTO test.

Perioperative period and follow-up

Anticoagulation during cardiopulmonary bypass (CPB) was performed by an initial 350 IU kg^{-1} bolus of heparin and additional doses to maintain activated clotting time >480 s. Antifibrinolytic therapy with a 30 mg kg^{-1} bolus of tranexamic acid was administered to every subject at the beginning of surgery. Heparin was neutralized with 1.5 mg protamine per 100 IU of the initial bolus according to institutional practice. An additional bolus of protamine was administered when activated clotting time was >110% of the preoperative value.

Erythrocyte concentrates and haemostatic products including fresh-frozen plasma (FFP), platelet concentrates, and fibrinogen concentrate (Haemocomplettan®, CSL Behring, Switzerland) were administered at the discretion of direct care providers (anaesthesiologist or intensivist) who were not involved in the study. The study had no influence on the surgical procedure or on haemostatic and transfusion management.

During the immediate postoperative course, blood loss from mediastinal drainage after arrival on the ICU, 3, 6, 12, 24, and 36 h after surgery, was assessed and prospectively recorded by the caregivers on the ICU, blinded to all other study data. In addition, transfusion of erythrocyte concentrates and haemostatic products during surgery and hospital stay was evaluated and also any additional surgery or adverse event during the hospital stay.

The subject's general practitioners were asked to collect blood for vWF analysis during a routine follow-up visit. The blood samples collected in the 3.8% sodium citrate tubes were shipped at room temperature on the same day to our hospital's central laboratory. At the central laboratory, samples were immediately processed and handled as described above. No platelet aggregometry or echocardiography was performed during follow-up.

Statistical analysis

The sample size calculation was based on preliminary data, estimating that the altered vWF multimer structure was present in ~60% of the patients undergoing aortic valve replacement, which is in agreement with recently published studies.[8–11] Assuming a normal distribution, a mean difference of 500 ml within the first 24 h was estimated as a relevant increase in postoperative mediastinal blood loss, which could be detected by a sample size of 60 patients assuming a standard deviation of 500 ml in both groups using an unpaired *t*-test (α=0.05 and β=0.8).

Results are presented as median (inter-quartile range) or numbers (percentage) and compared by the χ^2 test or Mann–Whitney *U*-test. Due to the right-skewed distribution of postoperative blood loss, we modelled the blood loss after 6 and 24 h in a log-linear regression model with five prespecified covariates without any model selection. Loss of the largest vWF multimers, gender, and increased bleeding risk were inserted as dichotomous variables, whereas age (per 10 yr increase) and COL test values (per 10 U increase) were entered into the model as continuous variables. Sensitivity analyses were performed excluding subjects with transapical valve replacement or patients with FFP transfusion to investigate the changes of the covariate estimates and confidence intervals (CIs). All analyses and graphs were performed using Intercooled Stata version 11.0 for Macintosh (StataCorp, College Station, TX, USA).

Results

Baseline biological and surgical data

Of the 60 subjects included in the study, 48 (80%) showed altered vWF multimer structure evident by the loss of the largest vWF multimers before operation. Baseline data were similar in both groups (Table 1). INR values were <1.5 in each patient, and aPTT values were within the normal range in all but one subject with the altered multimer structure.

Three subjects (aged 76–84 yr) with redo-cardiac surgery (EuroSCORE[22] range 11–17) were treated with transapical valve replacement not requiring CPB. In the remaining 57 subjects (EuroSCORE range 2–11), aortic valve replacement was performed with the use of CPB.

Bleeding history

Before operation, one subject with loss of the largest vWF multimers and clopidogrel treatment reported frequent nose bleeds. Two other subjects reported increased bleeding during previous surgery, one of them with the altered vWF multimer structure.

Perioperative bleeding and transfusion of blood products

One subject underwent surgical re-exploration within 2 h after valve replacement due to massive bleeding from an arterial vessel in the mediastinum and was excluded from further analysis regarding postoperative bleeding and transfusion. Blood loss from mediastinal drainage after 6 h was 250 ml (105–400) in the group with altered vWF multimers and 145 ml (85–240) in the group with normal multimers

Table 1 Subject characteristics. Data are numbers (%) or median (inter-quartile range). AV, aortic valve; aPTT, activated partial thromboplastin time; INR, international normalized ratio; vWF, von Willebrand factor. *Exact values of mean gradient and orifice area were only present in 56 and 46 subjects, respectively. †Measurements for aPTT and fibrinogen were only available in 59 and 58 subjects, respectively

	All subjects ($n=60$)	Altered vWF multimer structure ($n=48$)	Normal vWF multimer structure ($n=12$)
Male gender	33 (55%)	25 (52%)	8 (67%)
Age (yr)	74 (67–80)	75 (66–81)	73 (68–80)
EuroSCORE[22]	6 (5–8)	7 (5–8)	6 (5–7)
Blood group O	23 (38%)	17 (35%)	6 (50%)
Mean gradient AV (mm Hg)*	49 (40–56)	50 (40–58)	43 (41–51)
Orifice area AV (cm^2)*	0.71 (0.60–0.80)	0.70 (0.60–0.80)	0.75 (0.67–0.90)
Aspirin intake	29 (48%)	26 (54%)	3 (25%)
Clopidogrel intake	2 (3%)	2 (4%)	0 (0%)
Haemoglobin (g $litre^{-1}$)	133 (123–144)	134 (124–146)	132 (117–141)
Creatinine (μmol $litre^{-1}$)	80 (71–103)	79 (71–101)	90 (75–108)
Platelet count ($\times 10^9$ $litre^{-1}$)	248 (194–267)	248 (190–265)	242 (204–344)
INR	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)
aPTT (s)†	29 (27–31)	29 (27–32)	28 (27–29)
Fibrinogen (g $litre^{-1}$)†	3.2 (2.7–3.6)	3.2 (2.7–3.6)	3.1 (2.8–3.8)

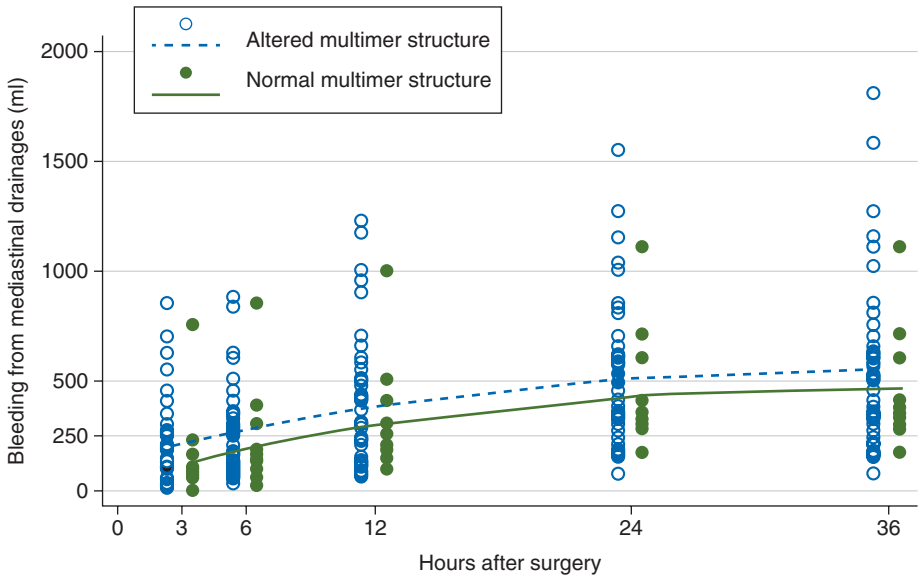

Fig 2 Scatter plot of postoperative bleeding volumes. Subjects with preoperative loss of the largest vWF multimers are marked with blue hollow circles, and subjects with normal vWF multimers are marked with green filled circles. Dashed and straight lines are lowess smothers (i.e. a non-linear regression line) in each group.

($P=0.182$). After 24 h, the cumulative loss was 495 (270–650) and 375 (310–600) ml in the group with altered and normal multimer structures, respectively ($P=0.713$; Fig. 2). Multivariable analysis showed a weak tendency to increased postoperative bleeding in the group with the altered multimer structure (1.55-fold increase; 95% CI: 0.84–2.82; $P=0.153$), which disappeared completely after 24 h (Table 2). The sensitivity analyses excluding subjects with FFP transfusions or with transapical valve replacement did not reveal relevantly changed point estimates or CI (data not shown). The incidence of major bleeding defined as >1000 ml within 24 h was similar in both groups (11% and 8% in subjects with altered and normal multimers, respectively).

During surgery and the first 24 h, red blood cell concentrates were administered in 23 (49%) and 9 (75%) of the subjects with altered and normal vWF multimers, respectively. In subjects with altered vWF multimers, three subjects (6%) received platelet concentrates and seven patients (15%) received FFP. In subjects with the normal vWF structure, no platelet

Table 2 Univariate and multivariable log-linear regression analysis for mediastinal blood loss 6 and 24 h after surgery (n=59). Exponentiated coefficients are given to simplify the interpretation. For example, a factor of 2 would indicate a blood loss twice as high in subjects with the specific characteristic as those without the specific characteristic. One subject was excluded from analysis due to surgical bleeding requiring revision

	Univariate analysis		Multivariable analysis	
	e^{β} (95% CI)	*P*-value	e^{β} (95% CI)	*P*-value
6 h				
Altered vWF multimers	1.52 (0.87–2.65)	0.141	1.55 (0.84–2.82)	0.153
AUC_{COL} (per 10 U)	0.92 (0.84–1.02)	0.116	0.98 (0.86–1.10)	0.685
Increased bleeding risk	1.42 (0.63–3.22)	0.396	1.40 (0.61–3.19)	0.417
Age (per 10 yr)	1.17 (0.89–1.55)	0.253	1.18 (0.85–1.64)	0.312
Female gender	0.87 (0.55–1.37)	0.533	0.81 (0.50–1.31)	0.389
24 h				
Altered vWF multimers	1.05 (0.69–1.59)	0.834	1.05 (0.66–1.66)	0.837
AUC_{COL} (per 10 U)	0.97 (0.90–1.04)	0.341	0.98 (0.90–1.08)	0.705
Increased bleeding risk	1.44 (0.79–2.62)	0.234	1.41 (0.75–2.64)	0.275
Age (per 10 yr)	1.06 (0.86–1.30)	0.601	1.05 (0.82–1.35)	0.680
Female gender	0.88 (0.63–1.23)	0.447	0.88 (0.61–1.26)	0.457

concentrates or FFP were used. The fibrinogen concentrate was administered in 14 subjects (30%) with altered vWF multimers and in two subjects (17%) with normal multimers. There was no difference in the percentage of subjects requiring blood or haemostatic products or in haemoglobin levels, platelet counts, fibrinogen levels, and classical coagulation parameters in the measurements before, directly after surgery, and on the first postoperative day. No subjects received desmopressin during the hospital stay.

Perioperative vWF levels and multimer structure

There was no relevant difference in preoperative measurements of vWF:Ag and vWF:CB (Fig. 3). Preoperative vWF:Ag and vWF:CB were normal (i.e. $\geq$50 IU dl^{-1}) in all but one subject who also showed loss of the largest vWF multimers. In the postoperative measurement, vWF:Ag and vWF:CB were normal in all subjects and were about twice as high compared with the preoperative values (Fig. 3). The vWF:CB/vWF:Ag ratio[9 23] was similar in subjects with loss of the largest multimers before and after operation (Fig. 3). There was no obvious difference in perioperative vWF parameters in subjects with and without FFP transfusion (Table 3).

In the vWF multimer analysis on the first postoperative day, the largest vWF multimers were present in all subjects. The percentage of large vWF multimers was 21 (18–24)% before and 34 (30–39)% after surgery in the group with the altered multimer structure and 26 (25–28)% before and 39 (32–42)% after surgery in the group with the normal multimer structure, respectively. This resulted in a per cent increase of 61 (39–86)% and 45 (17–60)% in subjects with and without loss of the largest multimers, respectively.

Perioperative platelet activity

The median perioperative platelet activity, as evaluated by TRAP, COL, and RISTO tests, was slightly lower in subjects with loss of the largest vWF multimers (Table 4). Before operation, 22 subjects (37%) showed AUC_{TRAP} values $<$71 U, which is the lower normal range for these patients.[21] In 20 of these subjects (91%), the largest vWF multimers were missing. On the first postoperative day, TRAP test values decreased, while COL and RISTO test values were comparable with preoperative measurements (Table 4). In the multivariable analysis, low AUC_{COL} values were not associated with increased postoperative bleeding (Table 2).

Follow-up

A laboratory follow-up was performed in 47 subjects (78%) after a median period of 56 days (43–88). Thirteen subjects or their general practitioners abstained from sending blood samples or sent blood samples that could not be analysed. The largest vWF multimers were missing in four (8%) of the analysed blood samples, but vWF:Ag and vWF:CB were $>$50 IU dl^{-1} and the vWF:CB/vWF:Ag ratio was $\geq$0.7 in all subjects.

Discussion

We found that the preoperative loss of high-molecular-weight vWF multimers in subjects undergoing aortic valve replacement due to severe stenosis did not affect early (6 h) and late (24 h) postoperative mediastinal blood loss. This finding might be explained by perioperative release of vWF and rapid recovery of the largest multimers. Our study is, therefore, in agreement with two recently published studies including a total of 86 patients with severe aortic stenosis which found no association of the altered vWF multimer structure before operation and increased bleeding within 24 h after aortic valve replacement.[10 11] However, neither of these studies evaluated the influence on early blood loss and the effect of FFP transfusion containing vWF.

vWF is an acute-phase protein, which is released together with FVIII from the endothelium during major surgery.[9]

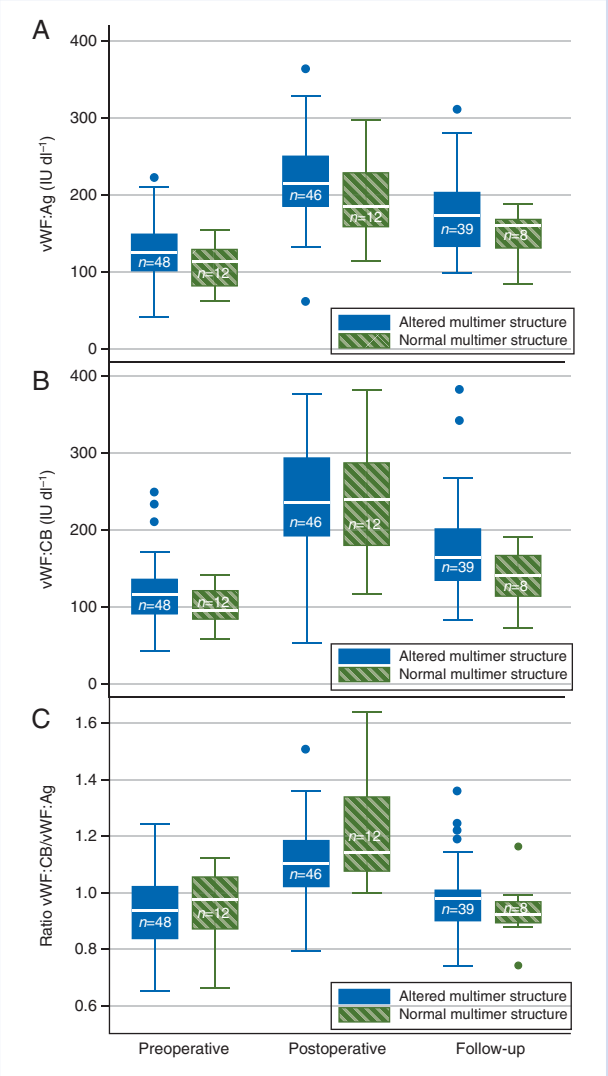

Fig 3 (A–C) Box-whisker plots of vWF antigen (vWF:Ag) activity (in IU dl^{-1}), vWF collagen-binding (vWF:CB) activity (in IU dl^{-1}), and their ratio before surgery, on the first morning after surgery, and at follow-up. Subjects with preoperative loss of the largest vWF multimers are marked in blue, and subjects with the normal multimer structure are marked in green.

Table 3 Influence of plasma transfusion on vWF measurements in subjects with the altered vWF multimer structure. Data are number (proportion) or median (inter-quartile range). Altered vWF multimer structure normalized within 24 h in all subjects

Parameter	Time point	No FFP transfusion ($n=41$)	With FFP transfusion ($n=7$)
vW:Ag	Preop	124 (100–145)	136 (112–166)
	Postop	214 (182–249)	215 (194–254)
vW:CB	Preop	115 (93–137)	125 (90–135)
	Postop	239 (188–301)	215 (195–262)
vW:CB/vW:Ag ratio	Preop	0.94 (0.86–1.03)	0.85 (0.70–0.99)
	Postop	1.11 (1.03–1.18)	1.03 (0.92–1.18)
Large multimers (%)	Preop	21 (18–25)	22 (21–22)
	Postop	35 (30–40)	29 (21–33)

Table 4 Platelet aggregometry measurements. Data are median (inter-quartile range) of area under the curve (AUC) values. Postoperative data were available in 59 patients (47 patients with altered vWF multimers) for the TRAP and COL tests and in 58 patients (47 with altered vWF multimers and 11 with normal vWF multimers) for the RISTO test

	All subjects ($n=60$)	Altered vWF multimer structure ($n=48$)	Normal vWF multimer structure ($n=12$)
AUC_{TRAP} (U)			
Preop	86 (62–97)	80 (60–94)	94 (86–99)
Postop	45 (35–62)	42 (34–59)	53 (40–67)
AUC_{COL} (U)			
Preop	41 (23–60)	36 (23–51)	62 (30–72)
Postop	34 (22–51)	32 (22–49)	45 (23–70)
AUC_{RISTO} (U)			
Preop	49 (30–84)	45 (30–75)	69 (30–122)
Postop	43 (28–68)	41 (26–68)	56 (37–77)

Previous studies in patients undergoing cardiac surgery demonstrated that vWF antigen level and vWF ristocetin cofactor (vWF:RCo) activity before and directly after surgery were comparable but increased within 24 h after surgery to about 200–300 IU dl^{-1},[9 24 25] which is in agreement with our data. In contrast, metalloprotease ADAMTS13, which is responsible for degradation of vWF,[4] was relatively low after operation probably due to haemodilution.[24] Elevated vWF activity persisted for several days.[8 11 24] However, the minimal or optimal amount of vWF for adequate haemostasis after cardiac surgery is not known. The largest vWF multimers recovered within the first hours after cardiac surgery[8] or even within the time of surgery in 12 of the 14 patients undergoing aortic valve surgery.[9] In agreement, the largest multimers were present in all of our subjects in the postoperative measurements. In addition, we found that a perioperative increase in large vWF multimers was more evident in the group with the altered multimer structure. A potential influence of altered vWF multimers before operation on early but not late postoperative bleeding seems reasonable and important, as most haemostatic products are transfused early after surgery. We found that the altered multimer structure had a small, not statistically significant, effect on increased blood loss after 6 h (1.55-fold increase; 95% CI: 0.84–2.82; $P=0.153$), which was not evident after 24 h. FFP transfusion had no obvious effect on postoperative vWF levels and multimers. However, plasma was likely to be transfused in subjects with increased bleeding, creating a potential increase in vWF. Accordingly, the influence of the substitution of vWF by plasma transfusion might remain undetected in our study.

The prevalence of altered vWF multimer structure similar to vWD type 2A in patients with severe aortic stenosis is still under debate. Depending on the method and diagnosis criteria, the prevalence of altered multimer structure similar to vWD type 2A has been reported to be between 0% and 90% in patients with severe aortic stenosis.[8 9 11 26 27] Aside from the loss of the largest vWF multimers, additional changes such as increases in low and intermediate vWF multimers due to degradation by ADAMTS13 are required for the diagnosis of vWD type 2A.[11] The altered multimer structure in patients with severe aortic stenosis should, therefore, not be referred to as vWD type 2A.

We found that vWF:Ag, vWF:CB, and vWF:CB/vWF:Ag ratios before and after surgery were similar in subjects with the altered and normal multimer structures, which is in agreement with a former study.[10] Preoperative vWF:Ag or vWF:CB levels were below the normal range (i.e. $<$50 IU dl^{-1}) and aPTT was prolonged in one subject only. In former studies, loss of high-molecular-weight vWF multimers has been frequently associated with haemorrhagic disorders such as gastrointestinal bleeding, epistaxis or increased bleeding after dental procedures.[2 7 8] In agreement with previous studies showing haemorrhagic disorders in 0–26% of the patients with severe aortic stenosis,[8 9 11] 5% of our subjects reported a haemorrhagic diathesis. Previous reports in patients with vWD type 2A also reported that clinical manifestations were often subtle, and severe bleeding was rare.[23 28] In the multivariable analyses, we did not find increased bleeding in subjects with haemorrhagic disorders, but the small number of subjects does not allow definite conclusions. Our findings are, therefore, in agreement with a recent study,[11] whereas the former study by Vincentelli and colleagues[8] reported increased bleeding in patients with haemorrhagic diathesis.

Several studies have previously described impaired platelet function in a large proportion of patients with severe aortic stenosis.[5 8 12 13] In these studies, different platelet function analysers were used including PFA-100, the cone and plat(elet) analyser, P-selectin expression on platelet surface, and shear-induced platelet aggregation. Impaired platelet activity in patients with severe aortic stenosis has been attributed not only to high shear stress damage[14] but also to selective deficiency of the largest vWF multimers.[5 12] In the present study, we used multiple electrode aggregometry for the first time in these patients. Preoperative testing revealed median AUC_{TRAP} values of 86 (62–97) U. These values are substantially lower than the mean (SD) AUC_{TRAP} values 101 (20) U reported in patients undergoing coronary artery bypass graft surgery.[21] The proportion of patients with AUC_{TRAP} below the normal range was significantly higher in patients with aortic stenosis than in patients undergoing bypass surgery (37% *vs* 5%). Our finding is, therefore, in agreement with previous studies reporting that 50–92% of the patients with severe aortic stenosis have impaired platelet function depending on the analysis method. However, lower test values from multiple electrode aggregometry were not associated with increased postoperative bleeding in our multivariable analysis. This is in agreement with recent data in paediatric cardiac patients.[29] A recent study showed that the RISTO test can identify patients with vWD type 1.[30] We found no difference between subjects with the altered and normal multimer structures using this test. We speculate that the RISTO test depends on vWF concentrations that are low in vWD type 1, but were normal in all but one of our subjects. Values of multiple electrode aggregometry strongly depend on platelet count,[21] leading to lower postoperative TRAP values. Remarkably, RISTO test values were not obviously lowered, potentially due to increased vWF concentration after surgery.

Most patients with loss of the largest vWF multimers show sustained corrections of clinical and biological haemostatic abnormalities after aortic valve replacement.[5 8] However, previous studies have found the recurrence of the altered multimer structure after a few months in up to 5% of the patients.[5 8] Similarly, four of our subjects (8%) showed a relative loss of the largest multimers after a median follow-up of 56 days. Residual flow disturbances could be responsible for recurrent loss of the largest multimers.[8]

Our study has some limitations: first, we cannot exclude that small differences in postoperative bleeding volumes and clinically more relevant outcomes, such as transfusions of blood products or incidence of major bleeding, might have become significant with a larger sample size. In fact, our sample size calculation did not match well with the actual findings, resulting in the need for us to adapt our statistical analysis. We do not think that this has influenced the interpretation of our data or the clinical relevance of our results. Secondly, vWF levels[31] and multiple electrode aggregometry[21] show fluctuations and variation, which might have influenced our study results. Thirdly, strict application of institutional guidelines for transfusion of blood and haemostatic products was not enforced by the investigators in this observational study. Finally, our results might not be directly transferred to patients with other cardiac conditions associated with loss of the largest vWF multimers[5 8 32 33] or to patients undergoing major non-cardiac surgery, that is, when the aortic stenosis persists.

In conclusion, the altered vWF multimer structure and reduced platelet function are common in patients with severe aortic stenosis but had no relevant effect on postoperative bleeding after aortic valve replacement probably due to rapid correction of multimer structure and vWF release during the perioperative period. In asymptomatic patients undergoing aortic valve replacement, vWF levels and multimers need not be checked before operation. Based on our findings, coagulopathy after aortic valve replacement might not be explained by the lack of the largest vWF multimers. Accordingly, treatment options aiming to restore vWF (e.g. desmopressin[13] and vWF concentrate)[9] might not be useful, and other causes of postoperative coagulopathy such as low levels of fibrinogen,[34 35] impaired thrombin generation, heparin rebound, and inhibitors of platelet aggregation[17 18] must be excluded.

Acknowledgements

The authors thank Esther Seeberger, RA, Department of Anaesthesia and Intensive Care Medicine, for help with data collection and Allison Dwileski, BS, Department of Anaesthesia and Intensive Care Medicine, University Hospital Basel, Basel, Switzerland, for editorial assistance.

Declaration of interest

D.B. and M.F. have received honoraria and travel support for consulting or lecturing from CSL Behring, Bern, Switzerland; Novo Nordisk, Kuesnacht, Switzerland; Sanofi/Bristol–Meyers Squibb, Meyrin, Switzerland; and Essex Chemie, Lucerne, Switzerland.

Funding

This study was supported by a grant from the Verein zur Förderung von Ausbildung und Forschung, Department of Anaesthesia and Intensive Care Medicine, University Hospital Basel, Switzerland, by an unrestricted research grant from CSL Behring, Berne, Switzerland, and by Axonlab AG, Baden, Switzerland, who provided disposals and reagents for Multiplate™ analysis. The study was planned and performed, data were collected and analysed, and the manuscript was independently written by the authors only.

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