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Full Length Article

Transcatheter aortic valve implantation leads to a restoration of von Willebrand factor (VWF) abnormalities in patients with severe aortic stenosis – Incidence and relevance of clinical and subclinical VWF dysfunction in patients undergoing transfemoral TAVI

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ABSTRACT

Background: In this study, we sought to analyze the incidence and relevance of von Willebrand factor (VWF) abnormalities in patients undergoing transcatheter aortic valve implantation (TAVI), especially on perioperative bleeding. Furthermore, we hypothesized that, similar to aortic valve surgery, TAVI results in a restoration of VWF abnormalities.

Methods and results: We performed a prospective analysis of periinterventional VWF parameters in 74 patients (80 ± 7 years, female in 37.5%) undergoing transfemoral TAVI for severe symptomatic aortic valve stenosis. At baseline, VWF:Ag was 210 ± 90 IU/dl with a mean VWF activity of 166 ± 106 IU/dl; activity-to-antigen ratio was 0.85 ± 0.45. Heyde's syndrome (severe aortic stenosis plus GI bleeding from angiodyplasia) was observed in 2/74 (2.7%). Whereas preprocedural loss of high-molecular-weight (HMW) VWF multimers was found in thirty-six patients (48.6%), none of the patients fulfilled criteria for possible acquired VW syndrome. After TAVI, an increase of both VWF:Ag and activity compared to baseline was observed ($p < 0.01$). In patients with HMW multimer loss, post-interventional recovery of multimers occurred in all cases. In the two patients with Heyde's syndrome, a trend towards reduced VWF:Ag was seen, with loss of HMW multimers in one patient. Of interest, all patients suffering from periprocedural major bleeding (5/74; 6.8%) exhibited activity-to-antigen ratios <0.7, indicating subclinical VWF dysfunction.

Conclusion: Whereas clinically relevant VWF dysfunction is rare, loss of HMW VWF multimers is common in TAVI patients. Similar to surgery, TAVI leads to a restoration of this loss. Furthermore, VWF parameters may be useful parameter to evaluate risk of periprocedural bleeding.

1. Background

Acquired von Willebrand syndrome type 2A (aVWS Type 2A) is caused by the loss of large von Willebrand factor (VWF) multimers, which may be due to increased VWF clearance (e.g. caused by antibodies), increased binding of VWF to cell surfaces (e.g. in malignancies) or by proteolytic loss of high-molecular weight (HMW) VWF multimers induced by high-shear forces [1]. In aortic stenosis, aVWS Type 2A is the consequence of a loss of HWM VWF multimers due to increased proteolytic VWF cleavage by ADAMTS13, which is promoted by shear-stress dependent conformational changes of these multimers [2]. As a result of the loss of functional VWF multimers and subsequent impairment of hemostasis, patients with aortic stenosis are prone to gastrointestinal bleeding from submucosal angiodysplasias, so-called Heyde's syndrome [3]. In addition to the loss of HMW VWF multimers, recent analyses indicate an impact of impaired angiogenesis in the context of gastrointestinal bleeding and angiodysplasia [4].

It has been shown, that surgical therapy of aortic stenosis leads to an improvement/recovery of VWF multimers resulting in restoration of

Abbreviations: ACT, activated clotting time; AVWS, acquired von Willebrand syndrome; LES, Logistic EuroScore; (HMW-) VWF, (High molecular weight)- von Willebrand factor; PVL, paravalvular leakage; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons – predicted risk of mortality score; TAVI, transcatheter aortic valve implantation; VARC [2], valve academic research consortium; VWD, von Willebrand disease.

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VWF function and a subsequent reduction of bleeding complications in several studies [5,6]. For inoperable patients and patients with an increased operative risk suffering from severe symptomatic aortic valve stenosis, transcatheter aortic valve implantation (TAVI) has evolved as an established therapy in the last decade [7,8]. Similar to surgical aortic valve replacement (SAVR), transcatheter treatment for aortic stenosis appears to reduce gastro-intestinal bleeding in patients with clinical Heyde's syndrome by restoring physiological aortic valve hemodynamics [9]. As historical data suggest a correlation of bleeding during cardiac surgery with impaired VWF function [10], this topic is of special interest in TAVI, where bleeding complications are common and are associated with unfavorable outcome [11]. Although the natural course of plasmatic markers of VWF function and VWF multimers after TAVI has recently been evaluated [12,13], overall data on this topic are limited.

We therefore sought to analyze the incidence and relevance of VWF abnormalities in patients undergoing TAVI, especially on perioperative bleeding. Furthermore, we hypothesize that, similar to surgical aortic valve implantation, TAVI results in an improvement of VWF function and a restoration of VWF abnormalities.

2. Methods

2.1. Study population and procedural details

We performed a prospective observational study analyzing designated von Willebrand factor parameters in 74 unselected patients undergoing transfemoral TAVI at our institution between January and December 2013. All patients underwent routine clinical preoperative assessment, including left-heart catheterization, transthoracic and transesophageal echocardiography and CT-angiography. After preoperative evaluation, the patients were discussed within the local heart team and subjected to transfemoral TAVI. All patients agreed to participate in the local TAVI registry and gave written informed consent. This registry had been approved by the Ethical Committee of the University Hospital Bonn. TAVI was performed using all available CE-marked prostheses and included post-operative monitoring in an intensive-care unit (ICU) ward for 24–48 h. Patients with post-operative need for intensive cardio-circulatory support (i.e. extracorporeal membrane oxygenation/ECMO) were excluded from the analysis. All baseline characteristics as well as procedural and post-procedural data were collected in a prospective manner and subjected to the local registry.

2.2. Antithrombotic regimen

All patients were loaded with a dual antiplatelet regimen consisting of 500 mg aspirin and 300 mg clopidogrel on the day before the procedure. Our standard post-interventional antithrombotic regimen consisted of dual antiplatelet therapy with clopidogrel (75 mg QD) and aspirin (100 mg QD). During TAVI, intravenous heparin was administered in a dose of 50–70 IU/kg and titrated to maintain an activated clotting time (ACT) of >250 s during the procedure. Postoperatively, heparin was administered according to the individual thrombotic risk. In patients without need for active anticoagulation and without contraindications, low-dose heparin (100 IU/h) was given from the first postprocedural day and discontinued by the discretion of the treating physician.

2.3. Analysis of von Willebrand factor (VWF) parameters

Blood samples were drawn from patients assessing VWF:Ag and VWF activity, activity-to-antigen ratios and HMW VWF multimer analysis on the day before the procedure (pre-TAVI) as well as on the first (d1) and seventh (d7) day after TAVI. Plasma VWF:Ag was measured by immunoturbidimetry whereas VWF activity was determined using a VWF ristocetin cofactor assay (VWF:RCo) [14]. Additionally, we calculated the ratio between VWF activity and VWF antigen, with a ratio < 0.7 indicating VWF dysfunction [15]. Laboratory reference ranges were as follows: blood type 0: 50–130% for VWF:Ag and 46–125% for VWF activity; non-0 blood type: 65–165% for VWF:Ag and 64–150% for VWF activity.

VWF multimer analysis was performed using electrophoresis with 0.1% sodium dodecyl sulfate (SDS) agarose at 1.2 and 1.6% agarose gel concentrations, followed by an electroblot transfer of the VWF multimers to nitrocellulose membranes and was subsequently visualized by western blot immunostaining using polyclonal anti-VWF antibodies, horseradish peroxidase (HRP)-labeled antibodies and Luminol™ luminography [5]. Hereby, loss of high-molecular-weight (HMW) VWF multimers was defined as a loss of >10th band. Interpretation of HMW VWF multimers was performed by experienced specialists in the field (JD and HJH).

Semiquantitative analysis of highest molecular weight multimers was performed by densitometry. Optical density values representing the concentration of VWF multimers of molecular weights were presented as a gray scale and quantified using Image J-Software Version 1.48 (National Institutes of Health, Bethesda, Maryland) [16]. Pooled normal platelet-poor plasma was used as reference material in all electrophoretic runs, in relation to which the percentage loss of HMW VWF multimers at baseline was calculated.

2.4. Study endpoints

Evaluation for the clinical diagnosis of von Willebrand disease/syndrome and Heyde's syndrome was performed by assessment of medical records and patient interviews. Clinically suspected Heyde's syndrome was defined as the presence of severe aortic stenosis alongside a history of gastrointestinal angiodysplasia and gastrointestinal bleeding therefrom documented by endoscopy.

Possible acquired VWS (AVWS) was defined as proposed by Federici et al. in the presence of the following: history of bleeding symptoms plus a) reduced VWF activity (<50 or 65 IU/dl depending on blood type) and b) reduced VWF activity-to-antigen ratio of (<0.7) [17]. Confirmed Heyde's syndrome was defined as the presence of severe aortic stenosis, bleeding from intestinal angiodysplasia and the loss of HMW-VWF multimers [18]).

Baseline characteristics, as well as post-TAVI complications were defined according to the updated VARC-2 criteria [19]. Hereby, minor and major vascular complications were assessed including a further differentiation of access-site and access-related vascular injury was made according to the angiographic classification. Hereby, access-site complications were divided into four types ASARVI types: type I - blush or minimal extravasation; type II - moderate extravasation (<5 mm); type III - major extravasation (>5 mm) including vessel perforation/rupture; and type IV - vessel dissection or occlusion [20]. Acute kidney injury (AKI) in this study was defined as stage III acute kidney injury based on VARC-2 criteria, i.e. an increase in serum creatinine > 3× compared with baseline or serum creatinine levels of 4.0 mg/dl with an acute increase of at least 0.5 mg/dl. Paravalvular (PVL) was defined as more than moderate (>°II) paravalvular aortic valve regurgitation as assessed by echocardiography. Additionally, all-cause mortality after 30 days and 1 year were calculated and compared in patients with and without loss of HMW VWF multimers.

2.5. Statistical analysis

Data are presented as mean ± standard deviation if normally distributed. Continuous variables were tested for normal distribution with the use of the Kolmogorov–Smirnov test. Categorical variables are given as frequencies and percentages. For continuous variables, a Student's *t*-test was performed for comparison between the two groups.

For categorical variables, the χ^2 or Fisher's exact test were used for further analysis. Discriminatory power of VWF parameters for the