Acquired von Willebrand Syndrome in Aortic Stenosis

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BACKGROUND
Aortic-valve stenosis can be complicated by bleeding that is associated with acquired type 2A von Willebrand syndrome. However, the prevalence and cause of the hemostatic abnormality in aortic stenosis are unknown.

METHODS
We enrolled 50 consecutive patients with aortic stenosis, who completed a standardized screening questionnaire to detect a history of bleeding. Forty-two patients with severe aortic stenosis underwent valve replacement. Platelet function under conditions of high shear stress, von Willebrand factor collagen-binding activity and antigen levels, and the multimeric structure of von Willebrand factor were assessed at base line and one day, seven days, and six months postoperatively.

RESULTS
Skin or mucosal bleeding occurred in 21 percent of the patients with severe aortic stenosis. Platelet-function abnormalities under conditions of high shear stress, decreased von Willebrand factor collagen-binding activity and the loss of the largest multimers, or a combination of these was present in 67 to 92 percent of patients with severe aortic stenosis and correlated significantly with the severity of valve stenosis. Primary hemostatic abnormalities were completely corrected on the first day after surgery but tended to recur at six months, especially when there was a mismatch between patient and prosthesis (with an effective orifice area of less than 0.8 cm² per square meter of body-surface area).

CONCLUSIONS
Type 2A von Willebrand syndrome is common in patients with severe aortic stenosis. Von Willebrand factor abnormalities are directly related to the severity of aortic stenosis and are improved by valve replacement in the absence of mismatch between patient and prosthesis.

abstract

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Conclusions
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Aortic-valve stenosis can be complicated by bleeding, particularly that due to gastrointestinal angiodysplasia (Heyde’s syndrome). This hemorrhagic syndrome is associated with acquired type 2A von Willebrand syndrome, which is characterized by the loss of the largest multimers of von Willebrand factor. Proteolysis of von Willebrand factor as it passes through the stenotic valve is one of the proposed causes of the bleeding. High shear forces can induce structural changes in the shape of the von Willebrand factor molecule, leading to exposure of the bond between amino acids 842 and 843, which is sensitive to the action of a specific von Willebrand protease. This results in proteolysis of the highest-molecular-weight multimers of von Willebrand factor, which are the most effective in platelet-mediated hemostasis under conditions of high shear stress. This concept is further supported by the recent demonstration that the biologic abnormalities can be corrected by valve replacement.

Given these facts, we hypothesized that acquired von Willebrand syndrome could be a common feature in patients with aortic stenosis. The present study was designed to evaluate the prevalence and the determinants of hemostatic abnormalities in patients with aortic stenosis and their clinical consequences.

METHODS

PATIENTS

Between March and July 2001, 50 consecutive patients (20 women and 30 men) referred for evaluation of aortic stenosis were enrolled in the study. Patients were excluded if they were under 18 years of age or not competent to give consent, had active endocarditis, had multivalvular disease, had associated coronary disease, or were receiving antiplatelet treatment that could not be stopped 10 days before surgery. Written informed consent was obtained from each patient, and the local ethics committee approved the study.

Forty-two patients (18 women and 24 men, mean [±SD] age, 70±10 years) had severe aortic stenosis (a mean gradient of >50 mm Hg or an indexed effective orifice area of <0.5 cm² per square meter of body-surface area) and subsequently underwent aortic-valve replacement. Eight patients (mean age, 60±11 years) had only moderate aortic stenosis and did not undergo surgery.

SCREENING FOR BLEEDING DIATHESIS

Each patient’s bleeding symptoms were evaluated by the use of a standardized screening questionnaire, adapted from those of Rapaport and colleagues. Only bleeding during the six months preceding evaluation was taken into account. The same evaluation was repeated six months postoperatively in the group undergoing surgery.

ECHOCARDIOGRAPHIC EVALUATION

Using a Vingmed Five or an Acuson Sequoia echocardiographic system, one investigator assessed the hemodynamic performance of the aortic valve by transthoracic echocardiography at base line and at six months postoperatively in the surgical group. The mean and peak transvalvular pressure gradients were calculated with the modified Bernoulli equation, and the effective orifice area (EOA) was calculated by the continuity equation. The wall shear stress was calculated as 4µ×Vm+r, where µ is the blood viscosity, estimated at 0.035 poise; Vm is the mean transvalvular blood velocity; and r is the radius of the stenosis, with r=(EOA+πr)1/2. At six months postoperatively, a mismatch between the patient and prosthesis was defined as an indexed EOA of less than 0.8 cm² per square meter of body-surface area. The echocardiographic data are presented in Table 1.

BLOOD COLLECTION AND LABORATORY ASSAYS

In patients with severe aortic stenosis, blood samples were collected the day before surgery and one day, seven days, and six months after surgery. In patients with moderate aortic stenosis, blood samples were collected on the day of echocardiography.

Platelet-related hemostasis was tested with a platelet-function analyzer (PFA-100, Dade International) by determining closure time of adenine diphosphate cartridges (normal value, less than 114 seconds). The platelet-function analyzer is a high-shear system for in vitro testing of platelet function that simulates primary hemostasis after injury to a small vessel. It is a highly sensitive way to screen patients for von Willebrand factor defect. Plasma von Willebrand factor antigen was measured by immunoturbidimetry, and factor VIII coagulant activity by a one-stage clotting assay with factor VIII–deficient plasma. Functional analysis of von Willebrand factor was performed by measuring its collagen-binding activity with an enzyme-linked immunosorbent assay, as previously described, with the use of...
equine type I collagen (Horm, Nycomed). The ratio between collagen binding and von Willebrand factor antigen was calculated (the normal value is greater than 0.7).

The multimeric structure of plasma von Willebrand factor was analyzed by electrophoresis with 0.1 percent sodium dodecyl sulfate and 1.5 percent agarose gel.20 The percentage of multimers of the highest molecular weight (more than 15 mers) was determined after densitometric scanning, as previously described.20-22 A pool of normal platelet-poor plasma was used as a reference in each gel electrophoresis. The lower limit of the normal range for the percentage of highest-molecular-weight multimers, which is defined as 2 SD below the mean value for normal plasma samples, was 10.5 percent.

Flow-cytometric analysis of platelet surface antigens was performed on an XL flow cytometer (Beckman Coulter) with the use of anti-CD61 (glycoprotein IIIa) antigen (Immunotech), antihuman von Willebrand factor antibody (WAK-Chemie Medical), and antihuman P selectin antibody (WAK-Chemie Medical).

**STATISTICAL ANALYSIS**
Statistical analysis was performed with Statview (SAS Institute), with the Mann–Whitney U test used to determine significant differences (P<0.05) between groups and the Wilcoxon signed-rank test used to compare the different time points in each group. Discrete variables were compared by Fisher’s exact test. Correlations between variables were assessed by Spearman’s rank-correlation test.

**RESULTS**

**PREVALENCE OF BLEEDING**
Among the 42 patients with severe aortic stenosis, 11 had episodes of bleeding in the six months before surgery. In two, the bleeding episode occurred during oral anticoagulant treatment and was not taken into account in further analysis. Thus, 9 of 42 patients (21.4 percent) had at least one episode of bleeding, most frequently skin or mucosal bleeding (Table 2). Among these, one patient had a history of major bleeding (epistaxis) that needed transfusion. Among the eight patients with moderate aortic stenosis, two had a history of hemorrhagic syndrome, both while receiving antiplatelet agents. There was no difference between patients with O and non-O blood types with respect to the occurrence of bleeding episodes.

<table>
<thead>
<tr>
<th>Table 1. Mean ±SD Echocardiographic Data.</th>
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<tr>
<td>Variable</td>
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<tr>
<td>Mean gradient (mm Hg)</td>
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<td>Effective orifice area (cm²)</td>
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<tr>
<td>Indexed effective orifice area (cm²/m² of body-surface area)</td>
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<td>Wall shear stress (dyn/cm²)</td>
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<th>Table 2. Hemorrhagic Disorders That Occurred in the Patients.</th>
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<td>Disorder</td>
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<td>Spontaneous bleeding</td>
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<td>Epistaxis</td>
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<td>Ecchymosis</td>
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<td>Menorrhagia or metrorrhagia</td>
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<td>Gastrointestinal hemorrhage</td>
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<td>Hematuria</td>
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<td>Gingivorrhagia</td>
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<td>Induced bleeding</td>
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<td>Dental extraction</td>
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**BASE-LINE BIOLOGIC DATA**
The closure time determined by the platelet-function analyzer (which measures platelet function under conditions of high shear stress) was prolonged in 92 percent of the patients with severe aortic stenosis and in 50 percent of those with moderate aortic stenosis. The ratio of collagen-binding activity to antigen and the percentage of highest-molecular-weight multimers were decreased in 67 and 79 percent of the patients with severe aortic stenosis and in 25 and 75 percent of the patients with moderate aortic stenosis, respectively. All patients with prolonged closure time according to the platelet-function analyzer had decreased percentages of highest-molecular-weight multimers. Patients with severe and moderate aortic stenosis had significantly different values for closure time according to the platelet-function analyzer and the ratio of collagen-binding activity to antigen (medians, 173 and 107 seconds [P=0.007] and 0.64 and 0.80 seconds.
The new england journal of medicine

The new england journal of medicine

349;4

www.nejm.org

july 24, 2003

[P=0.006], respectively). They did not differ in the percentage of highest-molecular-weight multimers, which was low in both groups (median, 8 percent in patients with severe aortic stenosis and 9 percent in those with moderate aortic stenosis). The results did not differ in patients with O and non-O blood types. The levels of factor VIII coagulant activity and von Willebrand antigen were normal in all patients (more than 0.5 IU per milliliter).

Platelet-function–analyzer values were positively correlated, and percentages of highest-molecular-weight multimers were negatively correlated, with the mean transvalvular gradient (r=0.58 [P<0.001] and r=−0.56 [P<0.001], respectively) and stenosis-induced shear stress (r=0.65 [P<0.001] and r=−0.59 [P<0.001], respectively) (Fig. 1). The ratio of collagen-binding activity to antigen was also weakly correlated with the mean transvalvular gradient and stenosis-induced shear stress (r=0.37 [P=0.021] and r=0.49 [P=0.007], respectively).

The platelet count was within the normal range in all but two patients (one with severe and one with moderate aortic stenosis). Flow-cytometric analysis found no difference between patients and controls in platelet membrane–associated glycoprotein IIIa, von Willebrand factor, or P selectin.

No significant differences in hemostatic values were observed between patients with and patients without a preoperative history of bleeding.

Surgical Treatment

Eleven patients 65 years of age or younger received a mechanical bileaflet prosthetic device (Mira, Edwards, or Regent, St. Jude Medical), and 31 patients over 65 years of age received a biologic device (29 pericardial valves [Perimount, Carpentier-Edwards], 1 stentless porcine aortic valve [Toronto, St. Jude Medical], and 1 cryopreserved aortic homograft [European Homograft Bank]). Mechanical devices were implanted in three patients with a preoperative history of bleeding.

Immediate Postoperative Course

The median blood loss 24 hours after valvular replacement was 415 ml (range, 120 to 1580). One patient underwent reoperation for bleeding on the day after surgery. One other patient died from ventricular fibrillation 10 days after surgery.

The platelet-function–analyzer values were corrected in all patients on days one and seven. The levels of factor VIII coagulant activity and of von Willebrand factor antigen increased significantly by six months after surgery, as compared with the preoperative values (P<0.001 and P=0.002, respectively). The percentage of highest-molecular-weight multimers was corrected (i.e., was at least 10.5 percent) in all patients on days 1 and 7. The multimeric pattern of von Willebrand factor determined in one patient three hours after surgery was also normalized (Fig. 2).

The postoperative blood loss was significantly higher in patients with preoperative bleeding than in those without preoperative bleeding (median, 565 ml [range, 195 to 1580] vs. 370 ml [120 to 700]; P=0.04). Six patients, all with a preoperative history of bleeding, had a blood loss greater than 700 ml. In these patients, the base-line percentage of highest-molecular-weight multimers was significantly lower than in those with no excessive blood loss (P=0.007).

Follow-up at Six Months in the Patients Who Underwent Surgery

Two patients were lost to follow-up at six months. One patient presented with early homograft valve stenosis that required reoperation at six months. In this patient, repeated epistaxis was observed at the onset of restenosis. The other 38 patients were asymptomatic at six months, without bleeding episodes, even those who had a preoperative history of bleeding and had a mechanical prosthesis requiring oral anticoagulant therapy. A mismatch between patient and prosthesis was observed in 10 cases.
At six months, the platelet counts were normal, and platelet flow-cytometric analysis found no change from base line. The platelet-function-analyzer values, although significantly lower than at base line (P < 0.001), were abnormal in 66 percent of the patients (median, 189 seconds; range, 73 to 300). The percentage of highest-molecular-weight multimers was below the normal range in 74 percent of the patients (median, 8.7 percent; range, 3.9 to 13). Figure 3 shows the time course of the percentage of multimers of highest molecular weight according to the presence or absence of a mismatch between patient and prosthesis. The percentage was significantly lower in patients with a mismatch (P = 0.01). The lowest percentage of highest-molecular-weight multimers was observed in the patient with severe homograft stenosis. There was no effect of the type of prosthesis (mechanical or biologic) on the changes in hemostatic values.

**Discussion**

This study evaluated the frequency and determinants of acquired von Willebrand syndrome and bleeding in consecutive patients with aortic stenosis. Careful investigation showed that bleeding (mostly from the skin or mucosa) was present in about 20 percent of the patients with severe aortic stenosis. Moreover, prolongation of the platelet-function–analyzer closure time (a measure of platelet function under conditions of high shear stress), abnormalities of von Willebrand factor, or both were common in severe aortic stenosis. We also demonstrated that von Willebrand factor abnormalities increased with the pressure gradient and the stenosis-induced shear stress, indicating that von Willebrand factor abnormalities are related to the severity of aortic stenosis. Together, these data suggest that the hemostatic defect is related mostly to direct proteolysis of the largest multimers of von Willebrand factor.

Veyradier and colleagues have shown that vascular malformations, such as angiodysplasia, are at high risk of bleeding in patients with aortic stenosis, since effective hemostasis in these high-shear-stress lesions requires the presence of high-molecular-weight multimers of von Willebrand factor. We found no differences in the biologic features that we measured between patients with and without a preoperative history of bleeding, suggesting that bleeding depends on the presence of bleeding-prone lesions.

All patients with major postoperative bleeding also had preoperative bleeding and had very low percentages of highest-molecular-weight multimers before surgery. All patients with severe aortic stenosis without valve replacement are probably also at
high risk for bleeding during noncardiac surgery. However, the therapeutic possibilities for the control of bleeding are limited.\textsuperscript{23} As previously suggested, the best correction is probably achieved by valve replacement.\textsuperscript{13} Early correction of the percentage of highest-molecular-weight multimers was observed after surgery, suggesting that the risk of hemorrhage in the first hours after surgery is probably limited.

Warkentin and colleagues recently reported long-lasting correction (lasting more than 10 years) of clinical and biologic hemostatic abnormalities in two patients who had undergone surgical treatment of severe aortic stenosis with acquired von Willebrand syndrome and bleeding.\textsuperscript{24} In our study, a significant improvement in biologic values was observed at six months. However, all patients did not have a complete, sustained correction. A recurrence of prolonged platelet-function–analyzer values and a decreased percentage of highest-molecular-weight multimers occurred in some patients, especially those with a mismatch between patient and prosthesis, which appears to be one of the determinants of relapse of von Willebrand syndrome. Other determinants, such as residual flow disturbances through the implanted prosthesis, could also interfere with the outcome.

No patient who had a mechanical prosthesis and was receiving oral anticoagulant therapy had a recurrence of bleeding. Whether mechanical prostheses can be safely implanted in patients who have a history of severe bleeding remains debatable. Additional studies are required to confirm that preoperative hemorrhagic syndrome does not have to be considered in deciding between a biologic and a mechanical valve substitute in patients with aortic stenosis, as long as a mismatch between patient and prosthesis is avoided.

At the present time, it is well accepted that patients with severe aortic stenosis who become symptomatic require aortic-valve replacement.\textsuperscript{25} However, only cardiac symptoms are considered in the evaluation of the indications for valve replacement.\textsuperscript{26} The present study demonstrates that acquired von Willebrand syndrome is a consequence of the mechanical obstruction of blood flow and that hemostatic abnormalities and bleeding are symptoms of severe stenosis. Further prospective studies are needed to determine whether hemostatic disturbances should be taken into account in the indications for valve replacement.

Supported by grants (EA 2693 and IFR 114) from the University of Lille II and from St. Jude Medical and Edwards Life Science.

We are indebted to Olivier Fouquet, Claudine Caron, Claudine Mazurier, and Bruno Jegou for their help in the performance of the study.

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