ORIGINAL ARTICLE

Acquired von Willebrand Syndrome in Aortic Stenosis

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ABSTRACT

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.

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Aortic-valve stenosis can be complicated by bleeding, particularly that due to gastrointestinal angiodysplasia (Heyde's syndrome).[1-3] 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.[4-7] 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.[8-10] 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.[11] This concept is further supported by the recent demonstration that the biologic abnormalities can be corrected by valve replacement.[12-14]

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 cm^2 per square meter of body-surface area) and subsequently underwent aortic-valve replacement. Eight patients (mean age, 66±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[15] and Blery and colleagues.[16] 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 $4\mu \times V_m \div r$, where μ is the blood viscosity, estimated at 0.035 poise; V_m is the mean transvalvular blood velocity; and r is the radius of the stenosis, with $r=(EOA \div \pi)^{1/2}$. At six months postoperatively, a mismatch between the patient and prosthesis was defined as an indexed EOA of less than 0.8 cm^2 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.[17,18] 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,[19] with the use of

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.[6] 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.

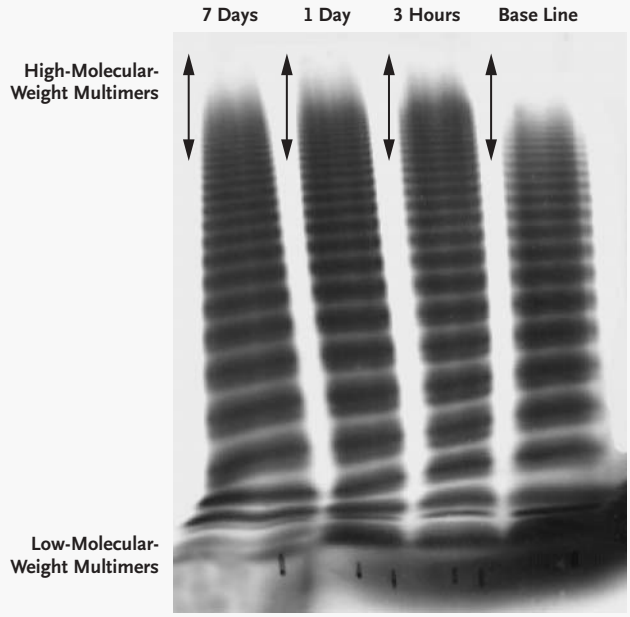

Figure 2. Analysis of Highest-Molecular-Weight Von Willebrand Factor Multimers in One Patient, before and 3 Hours, 24 Hours, and Seven Days after Valvular Replacement.

Arrows indicate the area where the highest-molecular-weight multimers migrate.

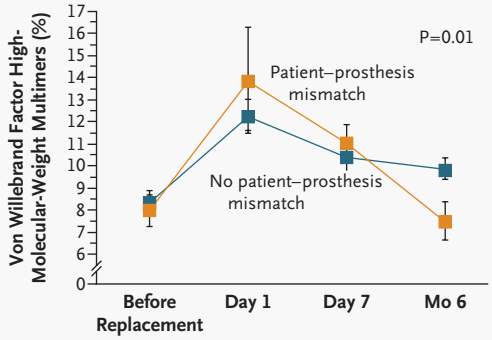

Figure 3. Mean (±SE) Evolution of Highest-Molecular-Weight Von Willebrand Factor Multimers after Valvular Replacement in Patients with and Patients without a Mismatch between Patient and Prosthesis.

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

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