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Clinical Research

Effects of Transcutaneous Aortic Valve Implantation on Aortic Valve Disease-Related Hemostatic Disorders Involving von Willebrand Factor

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ABSTRACT

Background: Aortic valve stenosis (AVS) can be complicated by bleeding associated with acquired type 2A von Willebrand syndrome. The association of AVS and gastrointestinal bleeding from angiodysplasia is defined as Heyde syndrome. We sought to evaluate the effect of transcutaneous aortic valve implantation (TAVI) on hemostasis disorders and to assess its effectiveness to treat Heyde syndrome.

Methods: We prospectively enrolled 49 consecutive patients with severe AVS addressed for TAVI at our institution. Biological hemostasis parameters involving von Willebrand factor (vWF) were assessed at baseline and 1 week after the procedure.

Results: At baseline, a significant link between vWF abnormalities and the severity of AVS was evidenced: mean aortic transvalvular gradient was negatively correlated with the levels of vWF antigen (vWF:Ag)

RÉSUMÉ

Introduction : La sténose valvulaire aortique (SVA) peut se compliquer de saignements associés au syndrome de von Willebrand acquis de type 2A. L'association entre la SVA et l'hémorragie gastro-intestinale par angiodysplasie est définie comme étant le syndrome de Heyde. Nous avions comme objectif d'évaluer l'effet de l'implantation valvulaire aortique par voie percutanée (IVAP) sur les troubles de l'hémostase et d'évaluer son efficacité à traiter le syndrome de Heyde.

Méthodes : Nous avons inscrit de manière prospective 49 patients consécutifs souffrant d'une SVA qui ont été dirigés à notre établissement pour subir une IVAP. Nous avons évalué les paramètres biologiques de l'hémostase impliquant le facteur von Willebrand (FvW) au début et 1 semaine après l'intervention.

Aortic valve stenosis (AVS) is the most frequent acquired valvular pathology in industrialised countries and is present in 4% of people older than 85 years of age.[1] Patients with severe AVS often suffer from complex comorbidities, including a higher risk for thrombotic events (stroke, myocardial infarction) and for bleeding (including gastrointestinal hemorrhage in the the situation of Heyde syndrome). Heyde syndrome is defined by the association of AVS and gastrointestinal bleeding (GIB) from angiodysplasia. It has been shown that AVS is responsible for an acquired type 2A von Willebrand syndrome, causing bleeding in patients with severe AVS. Von Willebrand factor (vWF) is a multimeric protein (twice the diameter of a platelet) that is secreted by endothelial cells and by platelets. It mediates the adhesion of platelets to sites of vascular damage through glycoprotein Ib-vWF interactions. Previous data have underlined that in the case of aortic stenosis with concomitant high shear stress in the blood the proteolysis of vWF by the metalloprotease a disintegrin and metalloproteinase with a thrombospondin 13 is also enhanced. It leads to the cleavage of large multimers (hemostatically most competent) of vWF into smaller (inactive) derivates.[2] The lack of these large multimers can cause bleeding, especially from pre-existing lesions of gastrointestinal angiodysplasia.[3] The pathophysiology of Heyde syndrome might also have a much wider effect than was commonly thought: it is likely that the vWF abnormalities could be extrapolated to a wide range of bleeding disorders, and could not be limited to the

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($r = -0.29$; $P < 0.05$), vWF ristocetin cofactor activity ($r = -0.402$; $P = 0.006$), and vWF collagen-binding activity (vWF:CB; $r = -0.441$; $P = 0.005$). One week after the procedure, a significant increase of vWF:Ag, vWF ristocetin cofactor activity, and vWF:CB was evidenced in the whole cohort (respectively, 3.32 vs 2.29 IU/mL, $P < 0.001$; 2.98 vs 1.86 IU/mL, $P < 0.001$; and 3.16 vs 2.16 IU/mL, $P < 0.001$). Patients with pre-TAVI vWF abnormalities consistent with a type 2A vWF syndrome (ratio vWF:CB/vWF:Ag < 0.7) preferentially improved their vWF function with respect to patients with a normal ratio (relative increase of vWF:CB of 63.8% vs 3.5%).

Conclusions: Hemostasis parameters involving vWF are improved after TAVI, especially in patients with pre-existing abnormalities consistent with acquired type 2A von Willebrand syndrome.

Résultats : Au début, un lien significatif entre les anomalies du FvW et la gravité de la SVA a été mis en évidence : le gradient transvalvulaire moyen corrélait négativement avec les concentrations d'antigène du FvW (FvW : Ag; r = −0,29; $P < 0,05$), l'activité du cofacteur de la ristocétine du FvW ($r = -0,402$; $P = 0,006$) et l'activité de liaison au collagène du FvW (FvW : LC; $r = -0,441$; $P = 0,005$). Une semaine après l'intervention, une augmentation significative du FvW : Ag, de l'activité du cofacteur de la ristocétine du FvW et du FvW : LC a été mise en évidence dans la cohorte entière (respectivement, 3,32 vs 2,29 UI/ml, $P < 0,001$; 2,98 *vs* 1,86 UI/ml, $P < 0,001$; et 3,16 *vs* 2,16 UI/ml, $P < 0,001$). Les patients ayant des anomalies du FvW avant l'IVAP qui correspondent au syndrome de vW de type 2A (ratio FvW : LC/FvW : Ag $< 0,7$) ont particulièrement amélioré leur fonctionnement du FvW par rapport aux patients ayant un ratio normal (augmentation relative du FvW : LC de 63,8 % *vs* 3,5 %).

Conclusions : Les paramètres de l'hémostase impliquant le FvW s'améliorent après l'IVAP, particulièrement chez les patients ayant des anomalies préexistantes qui correspondent au syndrome de von Willebrand acquis de type 2.

initial described association of AVS and GIB due to angiodysplasia.

The treatment of this pathology can be achieved using surgical aortic valve replacement.[3-5] However, it is still unclear if these benefits could be applicable to patients who undergo transcatheter aortic valve implantation.

In the present study we hypothesized that transcather aortic valve implantation could improve hemostasis disorders in patients with AVS. Therefore, we sought to investigate the effect of transcutaneous aortic valve implantation (TAVI) on hemostasis parameters involving vWF and on Heyde syndrome. We also sought to assess the relationship between these hemostasis abnormalities and periprocedural bleeding.

Methods

Patients

From November 2012 to December 2013, 49 patients (27 men and 22 women) with severe aortic stenosis referred for TAVI at our institution (Nouvel Hôpital Civil, Strasbourg, France) were prospectively enrolled in the study.

All patients had severe aortic stenosis with preserved or poor left ventricular function, and high perioperative risk of mortality assessed using the logistic EuroSCORE. All patients were referred to a multidisciplinary heart team and were contraindicated for conventionnal aortic valve replacement.

All participants were instructed about the aims of the study and gave their informed written consent before the procedure and agreed to anonymous processing of their data (France 2 Registry). The study was approved by the local ethics committee.

Both commercially available valves were used, the balloon-expandable Edwards SAPIEN/SAPIEN XT prosthesis (Edwards Lifesciences LLC, Irvine, CA) and the self-expandable CoreValve (Medtronic CV, Irvine, CA).

After TAVI, double antiplatelet therapy was prescribed for 6 months, except for patients with atrial fibrillation, who received single antiplatelet therapy in addition to anticoagulant therapy.

Blood collections and laboratory assays

Blood samples were collected just before TAVI for all patients, and at 1 week (mean of 7.8 ± 1.3 days) after TAVI (for 40 patients).

Several biological tests were performed, among which were hemoglobin level, leukocyte count, platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen.

Primary hemostasis was analyzed using several tests:

- Determination of closure times with a platelet function analyzer (PFA-100 [Siemens Healthcare, Marburg, Germany]), sensitive for the detection of defects of primary hemostasis including shear stress-induced vWF abnormalities.[6] Closure times of epinephrine-collagen (EPI) (normal value < 160 seconds) and adenosine diphosphate (ADP)-collagen cartridges (normal value < 125 seconds) were determined.
- vWF antigen (vWF:Ag; normal value > 0.5 IU/mL) was measured using immunoturbidimetry.
- Functional analysis of vWF was performed by measuring its collagen-binding activity (vWF:CB; normal value > 0.5 IU/mL) with an enzyme-linked immunosorbent assay and its cofactor ristocetin activity (vWF:RCo; normal value > 0.5 IU/mL) using turbidimetry. The ratio between vWF:CB and vWF:Ag were calculated (vWF:CB/vWF:Ag, normal value > 0.7), and the ratio between vWF:RCo and vWF:Ag (vWF:RCo/vWF:Ag, normal value > 0.7).

vWF:CB is a quantitative measure of vWF binding to collagen, and this assay is based on preferential binding of larger vWF multimers to collagen. It is more sensitive than vWF:RCo to the loss of highest multimers.

Collection of data and outcome measures

All patient information and procedure-related variables were entered into a dedicated database.

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