

Original Article

Unexpectedly High Prevalence of Acquired von Willebrand Syndrome in Patients with Severe Aortic Stenosis as Evaluated with a Novel Large Multimer Index

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Aim: Severe gastrointestinal bleeding sometimes occurs in patients with aortic stenosis (AS), known as Heyde's syndrome. This syndrome is thought to be caused by acquired von Willebrand syndrome and is characterized by reduced large von Willebrand factor (vWF) multimers. However, the relationship between the severity of AS and loss of large vWF multimers is unclear.

Methods: We examined 31 consecutive patients with severe AS. Quantitative evaluation for loss of large vWF multimers was performed using the conventional large vWF ratio and novel large vWF multimer index. This novel index was defined as the ratio of large multimers of patients to those of controls.

Results: Loss of large vWF multimers, defined as the large vWF multimer index < 80%, was detected in 21 patients (67.7%). The large vWF multimer ratio and the large vWF multimer index were inversely correlated with the peak aortic gradient ($R = -0.58$, $p = 0.0007$, and $R = -0.64$, $p < 0.0001$, respectively). Anemia defined as hemoglobin < 9.0 g/dl was observed in 12 patients (38.7%), who were regarded as Heyde's syndrome. Aortic valve replacement was performed in 7 of these patients, resulting in the improvement of anemia in all patients from a hemoglobin concentration of 7.5 ± 1.0 g/dl preoperatively to 12.4 ± 1.3 g/dl postoperatively ($p < 0.0001$).

Conclusions: Acquired von Willebrand syndrome may be a differential diagnosis in patients with AS with anemia. The prevalence of AS-associated acquired von Willebrand syndrome is higher than anticipated.

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Key words: Aortic stenosis, Gastrointestinal bleeding, Heyde's syndrome, Acquired von Willebrand syndrome, Large vWF multimer index

Introduction

The prevalence of valvular aortic stenosis (AS)

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has been increasing in aging societies in developed countries. The prognosis of patients AS is poor once they suffer from angina pectoris, syncope, or heart failure¹. These patients are sometimes affected by another severe complication of massive gastrointestinal bleeding. Although AS was first reported to be associated with gastrointestinal bleeding by Dr. Heyde in 1958², Heyde's syndrome is not widely known. Recently, the mechanism of Heyde's syndrome has

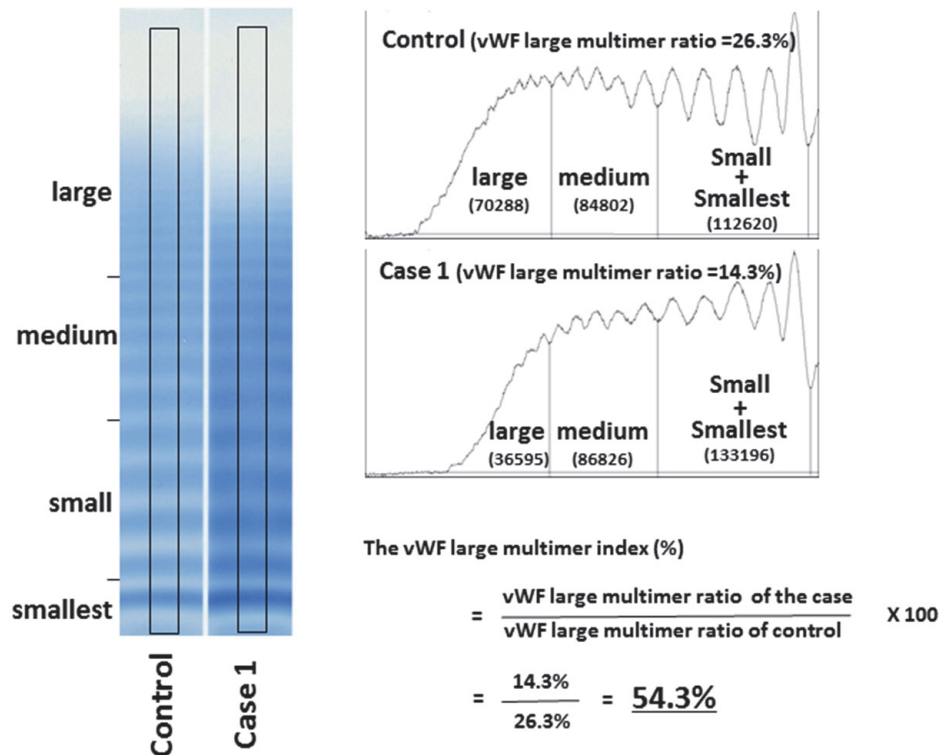


Fig. 1. Quantification method of large vWF multimers. Ratios of areas corresponding to large multimers were calculated based on scanning results (right panels) as described in the Methods section. The large vWF multimer index was calculated according to the equation described in the figure.

been identified to be bleeding from gastrointestinal angiodysplasia, enhanced by AS-associated acquired von Willebrand syndrome³.

In hemostasis and thrombosis, von Willebrand factor (vWF) plays multiple roles. When endothelial cells are lost, vWF is recruited to subendothelial collagen fibers and is exposed to the blood stream. Further, vWF changes its conformation, causing platelets to roll on the vessel wall by the interaction of collagen-associated vWF with the GPIb complex on the surface of platelets. When vWF is produced in endothelial cells and megakaryocytes, it forms a huge multimer⁴. The vWF multimer is shear stress-dependently cleaved by the plasma protease a disintegrin and metalloproteinase with a thrombospondin-type motif, member 13 (ADAMTS13) into smaller pieces⁴. Consequently, vWF multimers are present in the serum of healthy persons as 2–80 mers⁴. The potency for inducing platelet thrombus formation is dependent on the vWF multimer size. Patients lacking ADAMTS13 are known to contain ultra-large vWF multimers and exhibit hereditary thrombotic thrombocytopenic purpura because of excessive platelet thrombus formation

in the microcirculation, known as the Upshaw–Shulman syndrome⁵. In contrast, loss of large vWF multimers causes bleeding tendencies, classified as von Willebrand syndrome type IIA⁶.

In patients with AS, vWFs are exposed to extremely high shear stress at the site of the stenotic aortic valve, which causes exposure of cleavage sites of vWF by ADAMTS13. Accordingly, loss of large vWF multimers occurs, which is von Willebrand syndrome type IIA *per se*².

However, the prevalence of acquired von Willebrand syndrome and Heyde's syndrome in the clinical setting has not yet been adequately evaluated. Furthermore, the relationship between the severity of AS and the loss of large vWF multimers has not been adequately determined⁷. Therefore, we systematically evaluated 31 consecutive cases of severe AS by focusing on vWF multimer formation.

Methods

Study Population

The study population consisted of 31 consecu-

tive hospitalized patients with severe AS. Severe AS was defined as an aortic valve area ≤ 1.0 cm², peak aortic velocity >4.0 m/s, or a mean pressure gradient >40 mm Hg as determined by Doppler echocardiography. The peak aortic pressure gradient was calculated with the modified Bernoulli equation. We defined anemia as a patient with hemoglobin concentrations <9.0 g/dl. Clinical courses of patients with anemia were evaluated from patients' clinical charts or by contacting the patients. Data of upper and lower endoscopy examinations were carefully evaluated by experts to identify angiodysplasia. Indication for an endoscopic study was based on the discretion of the attending physicians. Definite Heyde's syndrome was defined as severe AS with anemia and endoscopically confirmed angiodysplasia. Possible Heyde's syndrome was defined as severe AS with anemia without apparent cause of anemia, such as cancer and gastric ulcer, although angiodysplasia was not confirmed by the endoscopic examination.

The study was performed according to the Declaration of Helsinki. The study protocol was approved by the institutional ethics committee. Written informed consent was obtained from each patient.

Evaluation of Large vWF Multimers

The multimeric structure of vWF was analyzed according to the method of Ruggeri and Zimmerman⁸⁾, by SRL Co., Tokyo, Japan. Quantitative evaluation for loss of large vWF multimers was performed with the following two parameters: the "large vWF multimer ratio" and the "large vWF multimer index." Large vWF multimers were quantified from images of vWF multimer analysis vWF by gel electrophoresis (Fig. 1). Using ImageJ, the central one-third of the lane was scanned. vWF multimers were divided into four parts (large, medium, small, and smallest multimers). First, we calculated the large vWF multimer ratio as the ratio of the large vWF multimer area to the total vWFs. We calculated the large vWF multimer index, proposed in this study, which was defined as the ratio of the large multimer area of a patient to that of a control whose plasma was analyzed in the next lane of the same vWF multimer analysis (a Western blot; Fig. 1).

Statistical Analyses

All statistical analyses were performed using JMP version 7 (SAS Institute Inc., Cary, NC, USA). All continuous variables are expressed as the mean value \pm standard deviation (SD). Intergroup comparison of continuous variables was performed using the Student's *t*-test or, if not normally distributed, Wilcoxon's

Table 1. Clinical characteristics of the 31 enrolled patients

| | |
|---|------------------|
| Patient number | 31 |
| Male | 12 (38.7) |
| Age (year) | 78.7 \pm 8.4 |
| Hemoglobin (g/dl) | 9.5 \pm 2.4 |
| Hemoglobin <9.0 g/dl | 38.7% (12) |
| Platelet ($\times 10^4/\mu$ l) | 15.9 \pm 5.5 |
| vWF antigen (%) | 179.9 \pm 50.0 |
| Activity of vWF (%) | 134.7 \pm 49.2 |
| Activity of ADAMTS13 (%) | 73.5 \pm 27.9 |
| Echocardiography findings | |
| Left ventricular ejection fraction (%) | 58.8 \pm 12.9 |
| Left ventricular diastolic dimension (mm) | 46.5 \pm 7.4 |
| Peak aortic velocity (m/s) | 4.6 \pm 0.8 |
| Peak aortic gradient (mm Hg) | 85.1 \pm 29.4 |
| Aortic valve area (cm ²) | 0.63 \pm 0.17 |
| Upper gastrointestinal endoscopy | 35.5% (11) |
| Lower gastrointestinal endoscopy | 25.8% (8) |
| Aortic valve replacement | 54.8% (17) |

Values are mean \pm SD or n (%).

vWF = von Willebrand factor.

ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin-type motif, member 13.

two-sample test. Categorical variables are presented as frequency counts and percentages, and intergroup comparisons of categorical variables were analyzed using the chi-square test. A *p* value <0.05 was considered statistically significant.

Results

Study Population

Clinical characteristics and echocardiographic and hematological parameters of 31 patients with severe AS are shown in Table 1. As expected, the patients were relatively old at a mean age of 78.7 \pm 8.4 years. The mean peak aortic gradient was 85.1 \pm 29.4 mm Hg and the mean aortic valve area was 0.63 \pm 0.17 cm².

Severity of AS and Loss of Large vWF Multimers

As shown in Fig. 2a, the large vWF multimer ratio was inversely correlated with the peak aortic gradient ($R = -0.58$, $p = 0.0007$). However, the large vWF multimer ratios of control subjects, which were analyzed in the next lane of each patient ($n = 31$), were varied (27 \pm 5.4%; maximum, 41.0%; minimum, 8.6%), and a rather large portion overlapped with those of patients'. To overcome the issue of overlap, we evaluated the large vWF multimer index. It was inversely correlated with the peak pressure gradient ($R = -0.64$, $p < 0.0001$; Fig. 2b), and was positively

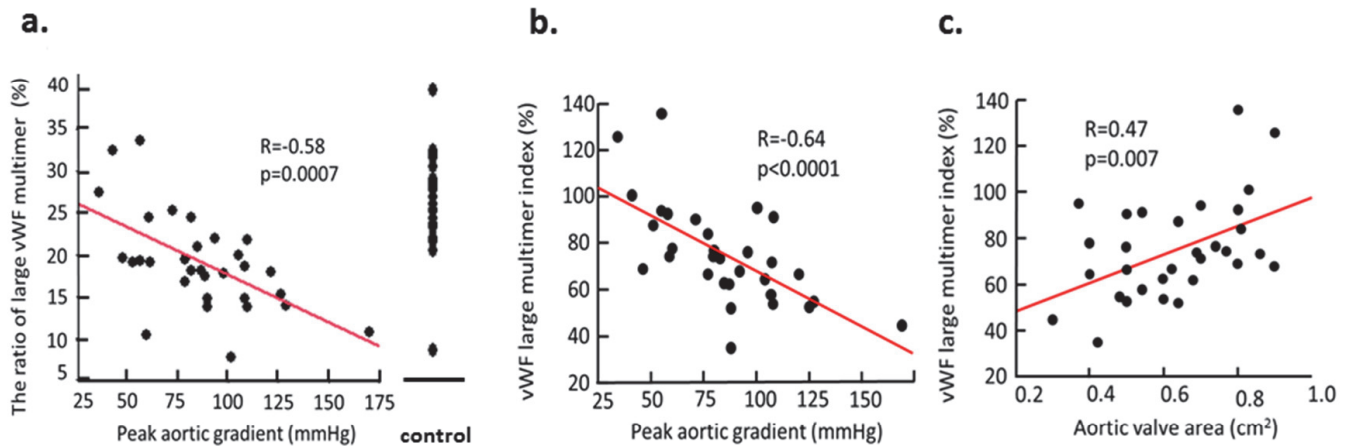


Fig. 2. Scatter plot of the large vWF multimer ratios (a) and index (b and c). The relationship between the large vWF multimer ratio and the peak pressure gradient through the aortic valve in each patient is shown (a). The relationship between the large vWF multimer index and the peak pressure gradient through the aortic valve (b) and the aortic valve area (c) in each patient is shown. Correlation curves are shown in a straight line. The distribution of the large vWF multimer ratio in each control subject is shown (a).

Table 2. Comparison of clinical data between the high and low large vWF multimer index groups by univariate analysis

| | High index group (<i>n</i> = 16) | Low index group (<i>n</i> = 15) | <i>P</i> Value |
|--------------------------------------|--------------------------------------|-------------------------------------|----------------|
| Age (year) | 78.8 ± 9.0 | 78.7 ± 8.1 | 1.00 |
| Male (%) | 50 | 26.7 | 0.18 |
| Hemoglobin (g/dl) | 9.3 ± 2.6 | 9.6 ± 2.2 | 0.72 |
| vWF antigen (% of control) | 173.2 ± 39.4 | 189.8 ± 65.8 | 0.55 |
| Activity of vWF (% of control) | 150.1 ± 52.2 | 111.5 ± 36.6 | 0.14 |
| Activity of ADAMTS13 (% of control) | 66.0 ± 32.2 | 81.0 ± 21.5 | 0.19 |
| Peak aortic gradient (mm Hg) | 69.2 ± 21.2 | 102.0 ± 27.8 | 0.0009 |
| Aortic valve area (cm ²) | 0.68 ± 0.17 | 0.58 ± 0.16 | 0.10 |

A high large vWF multimer index was >73.2%

correlated with the aortic valve area ($R=0.47$, $p=0.0007$; **Fig. 2c**). The loss of large vWF multimers, defined as the large vWF multimer index <80%, was detected in 21 examined patients with severe AS (67.7%). The severity of the loss was strongly correlated with the peak aortic gradient. A stronger correlation was obtained in the analysis with the large vWF multimer index compared with the large vWF multimer ratio.

Factors Affecting Loss of Large vWF Multimers

To evaluate factors affected by the large vWF multimer index, we divided patients into the high index group ($n=16$) and the low index group ($n=15$) using the mean large vWF multimer index value of 73.2%. As shown in **Table 2**, only the peak aortic gradient (102.0 ± 27.8 mm Hg in the high index group vs 65.0

± 19.8 mm Hg in the low index group, $p=0.0009$) was significantly associated with the index levels, whereas aortic valve area, ADAMTS13 activity, vWF antigen level, and vWF activity level showed no associations.

Clinical Course of Patients with Anemia

We observed that hemoglobin concentrations in all 31 patients with severe AS were low (mean, 9.5 ± 2.4 g/dl). Anemia was present in 12 patients (38.7%, **Table 1**). Among 12 patients with anemia, angiodysplasia was detected in four patients who had “definite Heyde’s syndrome,” and the remaining 8 patients had no apparent findings suggestive of cancer or ulcers, and were diagnosed with “possible Heyde’s syndrome” (**Table 3**). Three patients who received aortic valve replacement among these 8 patients showed improved anemia. These 12 patients with anemia were consid-

Table 3. Clinical characteristics and course of the 12 patients with anemia

| | Case. 1 | Case. 2 | Case. 3 | Case. 4 | Case. 5 | Case. 6 | Case. 7 | Case. 8 | Case. 9 | Case. 10 | Case. 11 | Case. 12 |
|---|---------|--------------------------|---------|---------|---------|-----------------|---------|---------|---------|----------|----------|----------|
| Sex | Male | Female | Female | Female | Female | Male | Male | Female | Male | Female | Female | Female |
| Age (years) | 80 | 78 | 80 | 86 | 80 | 77 | 72 | 90 | 80 | 82 | 89 | 90 |
| Hemoglobin (g/dl) | 6.6 | 6.9 | 8.6 | 8.3 | 6.4 | 8.4 | 7.0 | 6.2 | 8.7 | 7.9 | 6.2 | 6.3 |
| Peak aortic gradient (mm Hg) | 108 | 127 | 169 | 51 | 80 | 108 | 77 | 59 | 83 | 77 | 71 | 100 |
| Ejection Fraction (%) | 65 | 60 | 43 | 52 | 60 | 62 | 59 | 76 | 45 | 56 | 70 | 60 |
| Aortic valve area (cm ²) | 0.60 | 0.48 | 0.30 | 0.64 | 0.74 | 0.54 | 0.81 | 0.77 | 0.86 | 0.50 | 0.50 | 0.37 |
| Multimer Index (%) | 53.6 | 54.5 | 44.7 | 87.0 | 76.4 | 57.7 | 83.8 | 74.2 | 73.2 | 66.3 | 90.1 | 95.1 |
| History of massive gastro intestinal bleeding | No | Yes | No | No | No | Yes | No | No | No | No | No | No |
| Location of Angiodysplasia | Colon | Small intestine Colon | unknown | unknown | unknown | Small intestine | Colon | None | unknown | unknown | unknown | unknown |
| Definite Heyde's syndrome | Yes | Yes | No | No | No | Yes | Yes | No | No | No | No | No |
| Possible Heyde's syndrome | No | No | Yes | No | Yes | No | No | No | Yes | No | No | No |
| Aortic valve replacement | Yes | Yes | Yes | No | Yes | Yes | Yes | No | Yes | No | No | No |

ered as having Heyde's syndrome (definite=4, possible=8), and the prevalence of this syndrome was 38.7% among 31 enrolled patients with severe AS.

The individual clinical courses of 12 patients with severe AS complicated with anemia are shown in **Table 3**. Among them, 7 patients were treated with aortic valve replacement and anemia improved in all of the patients, with an increase in hemoglobin concentration of 7.5 ± 1.0 g/dl preoperatively to 12.4 ± 1.3 g/dl postoperatively ($p < 0.0001$). The large vWF multimers recovered after the operation (**Fig. 3**). A patient (shown in **Table 3**) refused to undergo the operation and suffered from >30 times of massive bleeding despite the clipping treatment during 1.5 years until he was treated with aortic valve replacement (**Fig. 4**).

Discussion

Main Findings

We systematically examined vWF multimer formation in 31 patients with severe AS. This study showed that 1) most patients showed hematologically acquired von Willebrand syndrome type IIA, 2) the prevalence of definite/possible Heyde's syndrome was as high as 38.7%, 3) loss of large vWF multimers was correlated with the severity of AS, and 4) severe AS was often complicated with anemia, which was improved in most patients after successful aortic valve replacement.

Quantitative Evaluation of Large vWF Multimers

vWFs are produced as a giant multimer from endothelial cells and megakaryocytes. They are known to be degraded by its specific cleaving enzyme, ADAMTS13, in blood stream. The cleavage is shear stress dependent because the cleavage site of vWF is exposed due to its conformational change in a high shear stress condition. Therefore, an excess cleavage of vWF is proposed to occur in cardiovascular diseases such as aortic stenosis, where tremendously high shear stress is generated when blood passes through the stenotic valve⁴.

In this study, we evaluated the loss of large vWF multimers using the large vWF multimer index, which was defined as the ratio of the large multimer ratio of a patient to that of a control. We propose that this novel index is more useful for the diagnosis of hematologically acquired von Willebrand disease IIA than previously used vWF multimer ratios⁷. This is because the previous ratios were widely distributed and a large portion of them in patients with AS overlapped with those in healthy subjects because of an inevitable variation of immunostaining. Furthermore, the large vWF multimer index showed a strong inverse correlation with the severity of AS. Using this index, we showed that most of our patients with severe AS exhibited acquired von Willebrand syndrome IIA, at least hematologically. The severity of acquired von Willebrand syndrome IIA was dependent on the severity of AS and was more strongly correlated with the maximal

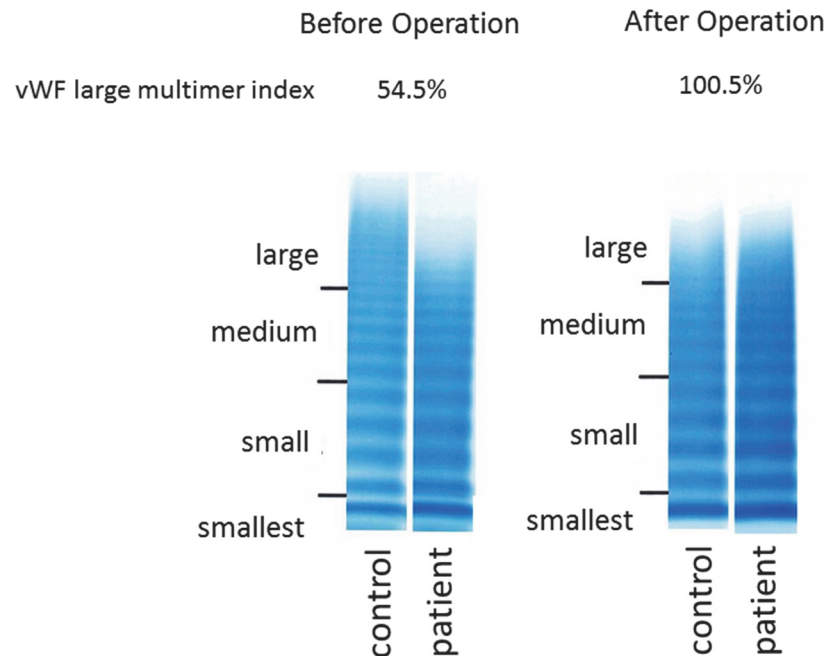


Fig. 3. vWF multimer analysis before and after aortic valve replacement in case 3 showing recovery of large vWF multimers after the operation.

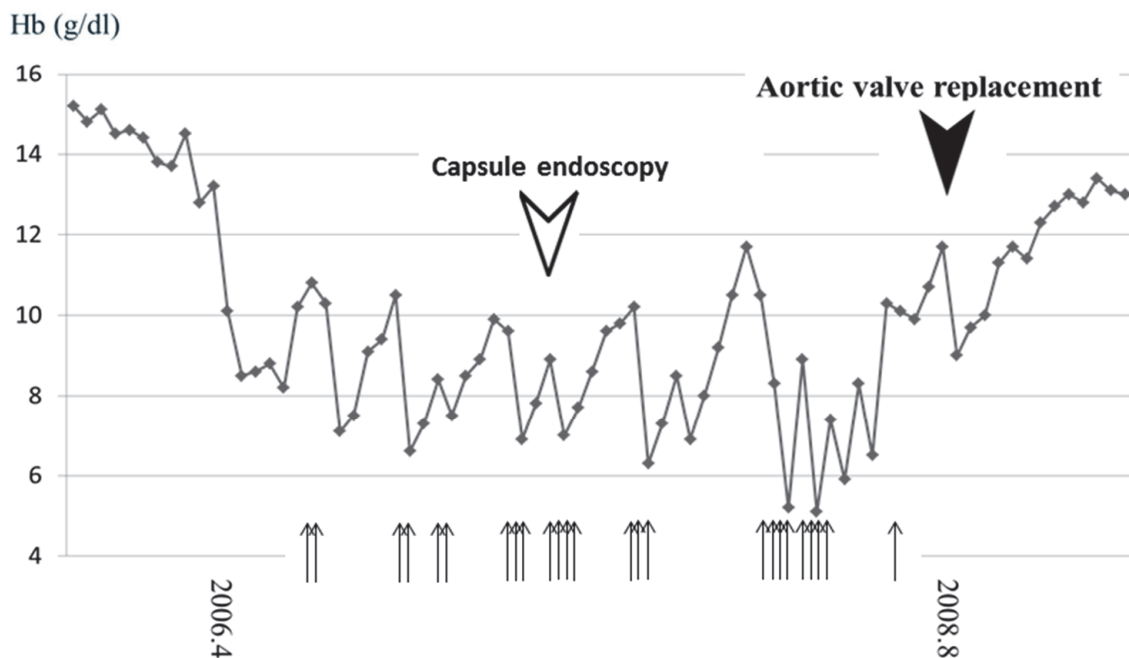


Fig. 4. Clinical course and transition of hemoglobin levels in case 6. White arrow head, capsule endoscopy; black arrow head, aortic valve replacement; black arrow, blood transfusion.

pressure gradient (**Fig. 2b**) than with the narrowed aortic valve areas (**Fig. 2c**). This may be related to the fact that patients with severe AS with a low ejection

fraction gradually decrease their maximal pressure gradient. These results indicate that loss of large vWF multimers is strongly affected by high shear stress, as

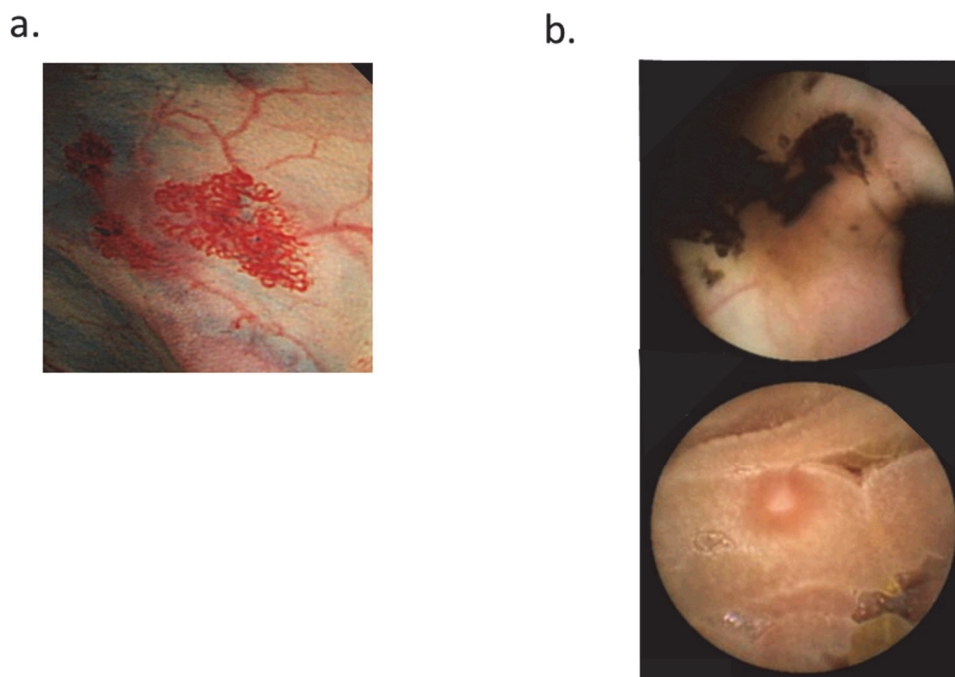


Fig. 5. Typical findings of angiodysplasia in the colon in case 1 (a) and in the small intestine in case 6 (b) as detected by capsule endoscopy.

expected theoretically. Therefore, patients with severe AS are likely to have anemia, even though no apparent major gastrointestinal bleeding develops.

Treatment and Prognosis of Patients with Heyde's Syndrome

Surgical aortic valve replacement and transcatheter aortic valve implantation can be performed in appropriately selected high-risk patients with good outcomes⁹. Radical therapy for acquired von Willebrand disease is the surgical aortic valve replacement¹⁰. Furthermore, transcatheter aortic valve implantation can be effective for treating Heyde's syndrome patients at a high risk of aortic valve implantation¹¹. A recovery of reduced large vWF multimers has been observed after an operation in cases 2¹² and 3 (**Fig. 3**) in our study, as shown previously⁷. Seven patients with anemia underwent this operation without severe issues and haemoglobin concentrations recovered in all 7 patients. Without an operation, patients would suffer from repetitive bleeding, which occurred in case 6 (**Table 3**). Therefore, a radical operation should be performed, despite a tendency for bleeding in treatment of AS with gastrointestinal bleeding caused by acquired von Willebrand syndrome type IIA, namely Heyde's syndrome.

Prevalence and Diagnosis of Heyde's Syndrome

The origin of gastrointestinal bleeding in patients with Heyde's syndrome is reported to be angiodysplasia, which can develop in the gastrointestinal tract¹³. **Fig. 5a** shows typical colonic angiodysplasia in case 1. Among 12 enrolled patients with anemia, angiodysplasia was detected only in 4 patients. The reason for this failure to observe angiodysplasia could be because of low rates of performance of endoscopic examination. Another reason could be because the origin of bleeding may not have been the stomach or colon, but the small intestine. In general, we do not often perform endoscopic examination of the small intestine. Two patients showed angiodysplasia in the small intestine (**Fig. 5b**), and one of two (case 2) patients showed angiodysplasia in the intestine and colon. Therefore, we consider that a complete endoscopic study, including not only upper and lower endoscopic studies but also capsule endoscopy for examining the small intestine is required to identify the origin of bleeding in Heyde's syndrome patients.

Impact of Acquired von Willebrand Syndrome IIA in Other Cardiovascular Diseases

Acquired von Willebrand syndrome IIA may be caused by high shear stress in blood flow. In addition to aortic stenosis, several cardiovascular diseases may

cause high shear stress. Acquired von Willebrand syndrome IIA has been reported in patients with hypertrophic obstructive cardiomyopathy¹⁴), congenital structural cardiac diseases¹⁵), pulmonary hypertension¹⁶), and mitral stenosis¹⁷). Furthermore, mechanical circulatory support has drastically advanced and contributes much to the treatment of severe heart failure and it is inevitable that high shear stress is generated inside the pumps used in the devices. Acquired von Willebrand syndrome IIA has been reported in patients treated by LVAD¹⁸) and ECMO¹⁹). The incidence of the hematological abnormality and the related bleedings, situations prone to cause bleeding, and proper treatment for the bleedings are unclear. It is urgently important to clarify these to advance cardiovascular medicine.

Study Limitations

There are several limitations to the present study. First, this study comprised a relatively small number of patients with an underpowered design. Therefore, this study did not allow us to interpret ADAMTS13 activity between the high and low large vWF multimer indices. However, patients in the low index group tended to show higher ADAMTS13 activity than those in the high index group. A larger study is necessary to further validate the current findings. Second, an endoscopic examination was not systematically performed in all patients. This relatively low performance rate of endoscopic examination may have caused underdiagnosis of angiodysplasia. Third, vWF multimer analysis was only performed once at admission. Fourth, it is difficult to exclude the possibility that anemia was caused by other factors such as iron and folic acid/vitamin B12 deficiency, chronic inflammatory disease, or chronic renal deficiency besides the acquired von Willebrand syndrome. However, we could not completely evaluate all the possibilities because of the data obtained was incomplete.

Conclusion

Acquired von Willebrand syndrome may be considered as a differential diagnosis in patients with AS with anemia. The prevalence of acquired von Willebrand syndrome in patients with AS is relatively high.

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None.

Disclosures

The authors have no relationships or conflicts to disclose.

References

- 1) Alec V, Ottavio A, Felicita A, Manuel JA, Gonzalo BE, Helmut B, Michael A, Thierry PC, Michele DB, Arturo E, Volkmar F, Bernard I, Patrizio L, Luc P, Susanna P, Hans-Joachim S, Gerhard S, Janina S, Karl S, Johanna T, Ulrich OVO, Stephan W, Jose LZ, Marian Z: Guidelines on the management of valvular heart disease: The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*, 2012; 33: 2451-2496
- 2) Heyde EC: Gastrointestinal bleeding in aortic stenosis. *N Engl J Med*, 1958; 259: 196
- 3) Loscalzo J: From clinical observation to mechanism--Heyde's syndrome. *N Engl J Med*, 2012; 367: 1954-1956
- 4) Sandra Haberichter RM: Structure and function of von Willebrand factor. V. Marder, W. Aird, J. Bennett, S. Schulman, G. White II editor. *Hemostasis and Thrombosis*, 6th edn. 2013; 197-207
- 5) Furlan M, Robles R, Solenthaler M, Wassmer M, Sandoz P, Lammle B: Deficient activity of von Willebrand factor-cleaving protease in chronic relapsing thrombotic thrombocytopenic purpura. *Blood*, 1997; 89: 3097-3103
- 6) Sadler JE, Budde U, Eikenboom JC, Favaloro EJ, Hill FG, Holmberg L, Ingerslev J, Lee CA, Lillicrap D, Mannucci PM, Mazurier C, Meyer D, Nichols WL, Nishino M, Peake IR, Rodeghiero F, Schneppenheim R, Ruggeri ZM, Srivastava A, Montgomery RR, Federici AB, Working Party on von Willebrand Disease, C: Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. *J Thromb Haemost*, 2006; 4: 2103-2114
- 7) Vincentelli A, Susen S, Le Tourneau T, Six I, Fabre O, Juthier F, Bauters A, Decoene C, Goudemand J, Prat A, Jude B: Acquired von Willebrand syndrome in aortic stenosis. *N Engl J Med*, 2003; 349: 343-349
- 8) Ruggeri ZM, Zimmerman TS: The complex multimeric composition of factor VIII/von Willebrand factor. *Blood*, 1981; 57: 1140-1143
- 9) Petronio AS, Giannini C, Misuraca L: Current state of symptomatic aortic valve stenosis in the elderly patient. *Circ J*, 2011; 75: 2324-2325
- 10) Pate GE, Chandavimol M, Naiman SC, Webb JG: Heyde's syndrome: a review. *J Heart Valve Dis*, 2004; 13: 701-712
- 11) Godino C, Lauretta L, Pavon AG, Mangieri A, Viani G: Heyde's syndrome incidence and outcome in patients undergoing transcatheter aortic valve implantation. *JACC*, 2013; 61: 687-689
- 12) Morishima A, Marui A, Shimamoto T, Saji Y, Nishina T, Komeda M: A case of interleukin-6-producing cardiac myxoma resembling multicentric Castleman's disease. *J Thorac Cardiovasc Surg*, 2009; 138: 499-501

- 13) Veyradier A, Balian A, Wolf M, Giraud V, Montembault S, Obert B, Dagher I, Chaput JC, Meyer D, Naveau S: Abnormal von Willebrand factor in bleeding angiodysplasias of the digestive tract. *Gastroenterology*, 2001; 120: 346-353
- 14) Pruthi RK: Hypertrophic obstructive cardiomyopathy, acquired von Willebrand syndrome, and gastrointestinal bleeding. *Mayo Clin Proc*, 2011; 86: 181-182
- 15) Onimoe G, Grooms L, Perdue K, Ruymann F: Acquired von Willebrand Syndrome in congenital heart disease: does it promote an increased bleeding risk? *Br Jitish j Haematol*, 2011; 155: 622-624
- 16) Sokkary NA, Dietrich JE, Venkateswaran L: Idiopathic pulmonary hypertension causing acquired von Willebrand disease and menorrhagia. *J Pediatr Adolesc Gynecol*, 2011; 24: e107-109
- 17) Blackshear JL, Wysokinska EM, Safford RE, Thomas CS, Shapiro BP, Ung S, Stark ME, Parikh P, Johns GS, Chen D: Shear stress-associated acquired von Willebrand syndrome in patients with mitral regurgitation. *J Thromb Haemost*, 2014; 12: 1966-1974
- 18) Slaughter MS: Hematologic effects of continuous flow left ventricular assist devices. *J Cardiovasc Transl Res*, 2010; 3: 618-624
- 19) Kalbhenn J, Schmidt R, Nakamura L, Schelling J, Rosenfelder S, Zieger B: Early Diagnosis of Acquired von Willebrand Syndrome (AVWS) is Elementary for Clinical Practice in Patients Treated with ECMO Therapy. *J Atheroscler Thromb*, 2015; 22: 265-271