HIGH GRADIENT WITH MILD AORTIC STENOSIS?

A Vicious Circle: Heyde Syndrome in Mild Aortic Stenosis

Johannes P. Schwaiger, MD, Othmar Ludwiczek, MD, Ivo Graziadei, MD, and Wilhelm Grander, MD, Tirol, Austria

INTRODUCTION

Patients with severe aortic stenosis have an increased risk of gastrointestinal (GI) bleeding that can be due to angiodysplasias in the GI tract; this association has been termed Heyde syndrome. High gradients across a severely stenotic aortic valve cause disruption of the von Willebrand factor and deficiency of large von Willebrand multimers. In one study, nine out of 42 (21%) patients with severe aortic stenosis had a history of bleeding, most often from skin or mucosal sites. In the same study, two out of eight patients with moderate aortic stenosis also had a history of hemorrhagic syndrome that required treatment. True mild aortic stenosis has, to at least our knowledge, not been described in the literature as a cause for Heyde syndrome. We here present a case of a 42-year-old man with a body weight of 160 kg who was diagnosed with Heyde syndrome in mild aortic stenosis. Loss of large von Willebrand multimers were proven by multimeric analysis. Gradients across a mildly stenotic aortic valve were significantly increased secondary to high-output cardiac state, which was itself caused by the combination of anemia and high body weight. Once the anemia was corrected and the patient lost 20% of his body weight (30 kg) with diuresis, the high-output state and flow across the aortic valve improved, gradients decreased, and the patient had no further episode of GI bleeding. We conclude that the patient was in a vicious circle where anemia eventually triggered further GI blood loss caused by Heyde syndrome in high-output cardiac state.

CASE PRESENTATION

A 42-year-old man was admitted to the hospital because of significant weight gain to 160 kg, worsening leg swelling, dyspnea, and anemia. These symptoms had been present for at least 3 years to a lesser extent but got significantly worse. One week before admission he presented to a different hospital with acute dyspnea where a computed tomography (CT) chest examination was performed, pulmonary embolism was excluded, and the patient was subsequently discharged. A dilated right heart and main pulmonary artery (39 mm) were also reported. Furthermore, right heart and main pulmonary artery pressures were 42/17 mm Hg with a mean of 32 mm Hg. Mean right atrial pressure was 13 mm Hg, and pulmonary artery saturations were 54%, and pulmonary wedge pressure was 17 mm Hg. Pulmonary vascular resistance was 64 dyn. Pulmonary artery saturations were 54%, and

His past medical history included recurrent GI bleeding of unknown cause, iron deficiency anemia, a history of thrombosis of the left jugular and subclavian vein, obstructive sleep apnea, hypertension, restless legs syndrome, and obesity. Three years earlier colonoscopy was performed during an episode of severe rectal bleeding requiring hospital admission and transfusion of two units of red cells. At that time no source of bleeding was found. However, there was diffuse blood clot formation in the entire colon. Repeat CT virtual colonoscopy 6 weeks later was reportedly normal.

Upon current admission his weight was 160 kg and height was 185 cm, resulting in a body mass index of 46 and a body surface area of 2.7 m². He was afebrile, heart rate was 82, blood pressure was 140/80 mm Hg, and oxygen saturation was 94% breathing ambient air. There was a mild systolic murmur, and his chest was clear. There was gross pitting edema on both legs up to the thighs. He was admitted to a medical ward for further investigation.

Blood results showed a microcytic anemia (hemoglobin, 8.9 g/dL; mean cellular hemoglobin, 18 pg); platelet count was 160,000. Lactate dehydrogenase was 292 U/L (135-225); ferritin was 14 ng/mL, and gamma-GT was 69 U/L. Liver and kidney function parameters were otherwise normal. NT-proBNP levels were elevated to 886 pg/mL. Thyroid-stimulating hormone was normal. Repeated fecal occult blood tests were highly positive. Electrocardiogram showed a normal sinus rhythm without repolarization abnormalities.

Echocardiogram showed significant but proportional dilatation of all cardiac chambers (Figure 1, Video 1). Systolic function of both the left and right ventricle was normal (Videos 1 and 2). There was no evidence of abnormal atrial or left ventricular filling (Figures 2 and 3) or mitral regurgitation (Video 3).

There was significant aortic sclerosis of a probable bicuspid valve (Figure 4; Videos 4 and 5); maximal velocity at the aortic valve was significantly elevated to 3.7 m/sec, and the mean gradient was 37 mm Hg (Figure 5). There was no aortic insufficiency (Video 6). Calculated aortic valve area was 2.2 cm² by continuity equation methods. There was trivial tricuspid regurgitation, and systolic pulmonary artery pressure could not be reliably estimated. There was no other significant valvular abnormality. Transesophageal echocardiogram confirmed a calcified bicuspid aortic valve with good opening (Video 7) and an aortic valve area of 2.4 cm² (Figure 6). Agitated saline contrast study was performed to exclude an atrial septal defect and hepatopulmonary syndrome.

A ventilation/perfusion scan of the lungs was normal. CT imaging of the abdomen showed mild steatosis of the liver, mild hypertrophy of left liver segments, a spleen that was the upper limit of normal in size (14.7 cm), and trace ascites but was otherwise normal. Right heart catheterization was performed and showed significantly elevated cardiac output (thermodilution method) of 12.6 L/min (cardiac index 4.7 L/min). Mean right atrial pressure was 13 mm Hg, and pulmonary artery pressures were 42/17 mm Hg with a mean of 32 mm Hg. Pulmonary wedge pressure was 17 mm Hg. Pulmonary vascular resistance was 64 dyn. Pulmonary artery saturations were 54%, and

From the Department of Internal Medicine, Academic Teaching Hospital of the Medical University Innsbruck, Hall in Tirol, Austria.

Keywords: Heyde Syndrome, Aortic stenosis, von Willebrand factor, High-output cardiac failure

Conflicts of interest: The authors report no actual or potential conflicts of interest relative to this document.

Copyright 2019 by the American Society of Echocardiography. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

2468-6441

https://doi.org/10.1016/j.case.2019.04.005
Systemic saturation was 97%. Anemia and the positive fecal occult blood test were further investigated. Gastroscopy revealed mild gastritis and no evidence of varices or acute bleeding. Capsule endoscopy was performed and showed no signs of acute bleeding; however, several enlarged, angiodysplastic tortuous mucosal vessels were seen throughout the small intestines (Figure 7). Multimeric analysis of von Willebrand multimers was performed to investigate for an acquired von Willebrand syndrome (Heyde syndrome) and confirmed loss of large von Willebrand multimers (Figure 8).

The diagnosis was made of high-output cardiac failure, most likely driven by anemia and obesity. GI blood loss was finally attributed to bleeding from GI angiodysplasias associated with an acquired deficiency of large von Willebrand multimers, that is, Heyde syndrome.\textsuperscript{1,2} Heyde syndrome was found to be secondary to mild aortic stenosis; however, gradients across the bicuspid aortic valve were nearly equivalent to those reported in severe aortic stenosis and were therefore a consequence of the high output state. The patient received intravenous furosemide as a continuous infusion and intravenous iron and subsequently lost 30 kg in weight within a week followed by discharge after 10 days. One month later during an outpatient clinic visit, a full blood count showed a hemoglobin of 12.6 and NT-proBNP of 210 pg/mL, and the patient reported resolution of all symptoms. Repeat echocardiography showed normalization of all cardiac chambers (left ventricular end-diastolic volume, 157 mL; indexed 59, mL/m²; right

**VIDEO HIGHLIGHTS**

**Video 1:** Transthoracic four-chamber view demonstrating proportional dilatation of all cardiac chambers and preserved left and right ventricular function. **Video 2:** Transthoracic parasternal long-axis view demonstrating good left ventricular function. **Video 3:** Transthoracic four-chamber view color flow mode excluding significant mitral regurgitation. **Video 4:** Transthoracic parasternal long-axis zoomed view demonstrating significant aortic sclerosis with good opening of aortic valve. **Video 5:** Transthoracic five-chamber view demonstrating significant aortic sclerosis with good opening of aortic valve. **Video 6:** Transthoracic five-chamber view color flow mode excluding aortic regurgitation. **Video 7:** Transesophageal, midesophageal short-axis view of aortic valve demonstrating a calcified bicuspid aortic valve with good opening.

*View the video content online at www.cvcasejournal.com.*

---

**Figure 1** Echocardiogram demonstrating significant but proportional dilatation of all cardiac chambers. **(A)** The left ventricular end-diastolic volume was 230 mL (indexed 85 mL). **(B)** The tricuspid annulus was 4.78 cm, and the basal right ventricular diameter was 5.89 cm. **(C)** The left atrial area was 38 cm² (indexed 14 cm²). **(D)** The right atrial area was 33.2 cm² (indexed 12 cm²).
ventricular basal diameter, 40 mm), maximal velocity of 3.1 m/sec, and a mean gradient of 26 mm Hg across the aortic valve. After having lost 30 kg, his weight was 128 kg, resulting in a body mass index of 37 and a body surface area of 2.5 m². The patient had no further GI bleeding during follow-up.

One year later the patient underwent aortic valve replacement due to endocarditis. After successful valve replacement, multimeric analysis of von Willebrand multimers was repeated and demonstrated a normal von Willebrand profile (Figure 8).

**DISCUSSION**

This is the first report of Heyde syndrome in mild aortic stenosis; however, transvalvular gradients were significantly increased due to high-output cardiac state, a consequence of anemia and high body weight. Once the anemia was corrected with intravenous iron and the patient lost 30 kg of fluid with diuresis, the mean transvalvular gradient decreased to values compatible with mild to moderate aortic stenosis, his symptoms abated, and there was no further adverse events. This
case confirms that the severity of the abnormality is not related to the aortic valve orifice but to the mean transvalvular gradient. Our patient demonstrated a bicuspid aortic valve, a common congenital malformation with a suspected genetic basis. It is not known whether Heyde syndrome is associated with bicuspid aortic valves. Most cases of Heyde syndrome were demonstrated in patients with tricuspid aortic stenosis given the high frequency of this condition.

In Heyde syndrome, the risk of bleeding is a direct consequence of loss of large von Willebrand multimers during turbulent passage through the narrowed valve, which can also occur in other types of valvular regurgitation or in moderate aortic stenosis. An earlier study reported the loss of large multimers in patients with bleeding from colonic angiodysplasias in “mild” aortic stenosis; however, in that study transvalvular gradients were not presented and an effective orifice area of 1-1.5 cm² was classified as mild. According to contemporary guidelines, an effective orifice area of 1-1.5 cm² is classified as moderate aortic stenosis.

Our patient also had a history of thrombosis of the left jugular and subclavian vein, which is compatible with the notion that von Willebrand factor also interacts with platelets and that severe aortic

Figure 4  M-Mode aortic valve demonstrating good opening of aortic valve.

Figure 5  Continuous-wave Doppler signal across aortic valve demonstrating a maximum velocity of 3.7 m/sec and a mean gradient of 36.9 mm Hg.
stenosis is also associated with enhanced thrombin and platelet formation, that is, activation of blood coagulation. The effect of high shear stress in patients with aortic stenosis is ambivalent and comprises two aspects, the presence of bleeding prone lesions and the increased risk of thromboembolism, both of which were evident in our patient.
CONCLUSION

This is the first case report of Heyde syndrome in mild aortic stenosis, even though transvalvular gradients were significantly elevated secondary to high-output cardiac state. Our patient was in a vicious circle where anemia eventually triggered further GI blood loss as a consequence of Heyde syndrome with high-output cardiac failure. Once the vicious circle was halted by correction of anemia and significant weight reduction due to diuresis, his symptoms abated and there was no further GI blood loss during follow-up.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2019.04.005.

REFERENCES

1. Vincentelli A, Susen S, Le TT, Six I, Fabre O, Juthier F, et al. Acquired von Willebrand syndrome in aortic stenosis. N Engl J Med 2003;349:343-9.
2. Undas A, Natorska J. Bleeding in patients with severe aortic stenosis in the era of transcatheter aortic valve replacement. JACC Cardiovasc Interv 2015;8:701-3.
3. Blackshear JL, Wysokinska EM, Safford RE, Thomas CS, Stark ME, Shapiro BP, et al. Indexes of von Willebrand factor as biomarkers of aortic stenosis severity (from the Biomarkers of Aortic Stenosis Severity IBASSI study). Am J Cardiol 2013;111:374-81.
4. Natorska J, Mazur P, Undas A. Increased bleeding risk in patients with aortic valvular stenosis: from new mechanisms to new therapies. Thromb Res 2016;139:85-9.
5. Blackshear JL, Wysokinska EM, Safford RE, Thomas CS, Shapiro BP, Ung S, et al. Shear stress-associated acquired von Willebrand syndrome in patients with mitral regurgitation. J Thromb Haemost 2014;12:1966-74.
6. Van BE, Rauch A, Vincent F, Robin E, Kibler M, Labreuche J, et al. Von Willebrand factor multimers during transcatheter aortic-valve replacement. N Engl J Med 2016;375:335-44.
7. Natorska J, Bykowska K, Hlawaty M, Marek G, Sadowski J, Undas A. Increased thrombin generation and platelet activation are associated with deficiency in high molecular weight multimers of von Willebrand factor in patients with moderate-to-severe aortic stenosis. Heart 2011;97:2023-8.
8. Veyradier A, Bailian A, Wolf M, Giraud V, Montembault S, Obert B, et al. abnormal von Willebrand factor in bleeding angiodysplasias of the digestive tract. Gastroenterology 2001;120:346-53.
9. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr 2009;22:1-23.