Disappearance of Angiodysplasia Following Transcatheter Aortic Valve Implantation in a Patient with Heyde’s Syndrome: A Case Report and Review of the Literature

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Introduction

Aortic stenosis (AS) is sometimes associated with gastrointestinal bleeding. This combined state is referred as Heyde’s syndrome1, 2). The origin of the bleeding is most often gastrointestinal angiodysplasia that is characterized by focal or diffused venous/capillary lesions presenting as bright red ectatic vessels or pulsatile red protrusions, with surrounding venous dilatation or patchy erythema with or without oozing3, 4) and is known to easily bleed. Heyde’s syndrome has been reported to occur in approximately 20% of

Key words: Heyde’s syndrome, Aortic stenosis, Gastrointestinal angiodysplasia

An 83-year-old woman with severe aortic stenosis was admitted to our hospital due to heart failure with refractory anemia requiring blood transfusions. She had repetitive bleeding episodes from endoscopically proven angiodysplasia in the stomach. Moreover, she repeatedly underwent endoscopic argon plasma coagulation for hemostasis. Importantly, she had a deficiency of the high-molecular-weight (HMW) multimers of von Willebrand factor (VWF), and she was diagnosed with Heyde’s syndrome.

After she underwent transcatheter aortic valve implantation (TAVI), aortic valve area and mean left ventricular aorta pressure gradient improved. Notably, endoscopy showed cessation of bleeding at 10 days after TAVI and the disappearance of angiodysplasia at 4 months after TAVI. Even at 2 years after TAVI, follow-up endoscopy showed remaining free of angiodysplasia in the stomach. She experienced no episodes of anemia since TAVI procedure. Additionally, analysis of HMW multimers demonstrated immediate and lasting recovery after TAVI.

Recovery of HMW multimers of VWF with cessation of gastrointestinal bleeding following aortic valve replacement has been previously reported in a patient diagnosed with Heyde’s syndrome. To the best our knowledge, this is the first case to demonstrate that angiodysplasia disappears after TAVI for a long term with endoscopic images in a patient with Heyde’s syndrome. Here, we summarized case reports of patients with Heyde’s syndrome that required aortic valve intervention. Cessation of gastrointestinal bleeding and anemia after aortic valve intervention for severe aortic stenosis may be attributed not only to recovery of HMW multimers of VWF but also to the disappearance of angiodysplasia.

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patients with severe AS\(^5\). Von Willebrand factor (VWF) is generated and secreted from endothelial cells and megakaryocytes as a giant multimer and shear stress dependently cleaved by its specific protease, ADAMTS13\(^2, 6\). Among the VWF multimers, the high-molecular-weight (HMW) multimer is critical for its hemostatic function\(^7\). AS generates unphysiologically high flow at the narrowed valve, thereby generating excessively high shear stress, which causes loss of HMW multimers of VWF. It designates as a hemostatic disorder the acquired von Willebrand syndrome (AVWS)\(^4\). AVWS also occurs in other conditions requiring left ventricular assist device implantation\(^9\).

The AS-associated AVWS is not rare because the loss of HMW multimers of VWF was already noted in approximately 67% of patients with severe aortic stenosis\(^6\). Anemia and bleeding can be controlled by the release of the narrowed aortic valve by operation\(^6\). Nevertheless, it remains unknown whether gastrointestinal angiodysplasia persists or disappears after the valve treatment. This issue is important for evaluating the bleeding risk of patients with AS. Here, we report the case of Heyde’s syndrome that shows disappearance of angiodysplasia and recovery of HMW multimers of VWF following transcatheter aortic valve implantation (TAVI).

**Case Presentation**

In April 2016, an 83-year-old woman with severe AS was admitted to our hospital due to heart failure with repetitive bleeding episodes requiring blood transfusions. She had been diagnosed with AS in 2014, and the severity of AS had progressed up to the mean aortic valve pressure gradient, 81 mmHg; peak aortic flow, 5.61 m/s; and aortic valve area, 0.5 cm\(^2\). She was found to have bleeding from angiodysplasia in the stomach (Fig. 1A, 1B). Although she repeatedly underwent endoscopic argon plasma coagulation (APC) for hemostasis, she had repetitive bleeding from angiodysplasia even after APC. In addition, her plasma analysis demonstrated a deficiency of the HMW multimers of VWF, defined as the 11th and the upper bands in the VWF multimer analysis (Fig. 1C). Thus, she was diagnosed with Heyde’s syndrome.

Because she was frail with a comorbidity of liver dysfunction due to primary biliary cirrhosis, she underwent TAVI with a 23-mm Edwards Sapien 3 valve (Edwards Lifesciences, Irvine, California) (Fig. 1D). After the procedure, aortic valve area and mean aortic valve pressure gradient improved from 0.5 cm\(^2\) to 1.5 cm\(^2\) and from 81 mmHg to 10 mmHg, respectively. As an antithrombotic therapy, she was treated with only heparin during perioperative period for TAVI and with clopidogrel 75 mg/day from at 1 week after TAVI. At 10 days after TAVI, an endoscopy presented remaining angiodysplasia but not the cessation of bleeding in the stomach. Since TAVI procedure, she had no more episodes of anemia due to angiodysplasia in the stomach. Notably, there was clear disappearance of angiodysplasia at 4 months after TAVI (Fig. 1E). Moreover, HMW multimers of VWF revealed immediate and lasting recovery after TAVI (Fig. 1C). While she continued single antiplatelet therapy with clopidogrel after TAVI, neither bleeding nor thromboembolic episode occurred. Even at 2 years after TAVI, follow-up endoscopy showed remaining free of angiodysplasia in the stomach (Fig. 1F).

**Discussion**

To the best of our knowledge, this is the first case to describe that angiodysplasia disappears after TAVI for a long term with endoscopic images and to present the recovery of the loss of HMW multimer in a patient with Heyde’s syndrome.

Gastric erosions are defined as endoscopically detectable mucosal breaks that do not penetrate the muscularis mucosae\(^8\). In contrast, angiodysplasia is characterized by focal or diffused venous/capillary lesions presenting as bright red ectatic vessels or pulsatile red protrusions, with surrounding venous dilatation or patchy erythema with or without oozing\(^5, 4\). In the present case, the patient suffered oozing not from erosion but from the focal venous/capillary lesions (Fig. 1A and 1B). Based on these endoscopic images, the experts in the field of gastroenterology (TF, WH, and TK) diagnosed the patient with angiodysplasia, and she underwent endoscopic APC.

We searched for Heyde’s syndrome and aortic valve replacement or implantation in PubMed, which then revealed 74 articles. We excluded 40 articles (1) not written in English \((n=11)\), (2) without treatment intervention for aortic valves \((n=6)\), (3) only abstract \((n=3)\), and (4) original articles including the number of patients over 2 \((n=20)\). We summarized the remaining 34 articles of case reports following aortic valve intervention in patients with Heyde’s syndrome, with special references to angiodysplasia and HMW multimers of VWF\(^10-43\) (Table 1). To the best of our knowledge, there were seven reports that demonstrated persistence or disappearance of angiodysplasia after aortic valve intervention\(^10, 11, 16, 30, 31, 35, 41\). Importantly, although gastrointestinal bleeding ceased after aortic valve intervention in many case reports, follow-up endoscopic images to confirm the presence or absence of angiodysplasia and alterations of HMW multimers are limited.
Fig. 1.

(A) Endoscopy before transcatheter aortic valve implantation (TAVI) showed angiodysplasia (yellow circle) and bleeding (black circle) in the stomach. Green arrowhead indicates the pyloric ring.

(B) Endoscopy showed angiodysplasia after washing. The area in the black circle corresponds to that in Fig. 1A. Green arrowhead indicates the pyloric ring.

(C) von Willebrand factor (VWF) multimer analysis. Plasma of the patient was collected multiple times, and sodium dodecyl sulfate agarose gel electrophoresis was used to detect the VWF multimers. Compared with normal plasma, plasma of the patient lacked high-molecular-weight (HMW) of VWF before TAVI. However, the loss of HMW of VWF quickly recovered at 1 day after TAVI and lasted until 4 months.

(D) Angiogram showed TAVI with the balloon expandable Edwards Sapien 3 heart valve system.

(E) Endoscopy showed cessation of bleeding and disappearance of angiodysplasia in the stomach at 4 months after TAVI. Green arrowhead indicates the pyloric ring.

(F) Endoscopy showed that angiodysplasia was not noted in the stomach at 2 years after TAVI. Green arrowhead indicates the pyloric ring.
multimers remained to be examined or presented. To our knowledge, this is the first case to demonstrate that angiodysplasia disappears for a long term after TAVI with endoscopic images and recovery of the loss of HMW multimer in a patient with Heyde’s syndrome.

Recovery of HMW multimers of VWF and cessation of gastrointestinal bleeding following aortic valve replacement and left ventricular assist device implantation have been previously reported in patients with Heyde’s syndrome. Indeed, the HMW multimers of VWF rapidly recovered at 1 day after surgical aortic valve replacement (SAVR). Notably, the disappearance of angiodysplasia was noted at 20 months after SAVR. In line with the previous cases, in the present case, the levels of HMW multimers of

Table 1. Summary of case reports of a Heyde’s syndrome in patients undergoing aortic valve intervention

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Age</th>
<th>Procedures</th>
<th>Bleeding episodes</th>
<th>Angiodysplasia</th>
<th>Loss of VWF HMW</th>
<th>Bleeding episodes</th>
<th>Angiodysplasia</th>
<th>Loss of VWF HMW</th>
<th>Follow-up timing for bleeding</th>
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<td>10</td>
<td>67</td>
<td>SAVR</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
<td>(-)</td>
<td>6 months</td>
</tr>
<tr>
<td>11</td>
<td>87</td>
<td>SAVR</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>20 months</td>
</tr>
<tr>
<td>12</td>
<td>67</td>
<td>SAVR</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>13</td>
<td>68</td>
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<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>9 months</td>
</tr>
<tr>
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<td>(+)</td>
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<td>N/A</td>
<td>N/A</td>
<td>8 months</td>
</tr>
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<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>9 months</td>
</tr>
<tr>
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<td>(+)</td>
<td>N/A</td>
<td>N/A</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>1 month</td>
</tr>
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<td>SAVR</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>2 months</td>
</tr>
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<td>79</td>
<td>SAVR</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>9 years</td>
</tr>
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<td>74</td>
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<td>(+)</td>
<td>(+)</td>
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<td>(-)</td>
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<td>N/A</td>
<td>7 months</td>
</tr>
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<td>SAVR</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
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<td>46</td>
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<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>12 months</td>
</tr>
<tr>
<td>22</td>
<td>78</td>
<td>SAVR</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>7 days</td>
</tr>
<tr>
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<td>70</td>
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<td>(+)</td>
<td>(+)</td>
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<td>(+)</td>
<td>N/A</td>
<td>N/A</td>
<td>10 months</td>
</tr>
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<td>76</td>
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<td>(+)</td>
<td>N/A</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>4 months</td>
</tr>
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<td>71</td>
<td>SAVR</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>5 months</td>
</tr>
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<td>SAVR</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>20 months</td>
</tr>
<tr>
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<td>82</td>
<td>SAVR</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>1 month</td>
</tr>
<tr>
<td>28</td>
<td>67</td>
<td>SAVR</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>12 months</td>
</tr>
<tr>
<td>29</td>
<td>77</td>
<td>SAVR</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>1 month</td>
</tr>
<tr>
<td>30</td>
<td>77</td>
<td>SAVR</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>3 months</td>
</tr>
<tr>
<td>31</td>
<td>80</td>
<td>SAVR</td>
<td>(+)</td>
<td>N/A</td>
<td>N/A</td>
<td>(-)</td>
<td>(+)</td>
<td>N/A</td>
<td>3 months</td>
</tr>
<tr>
<td>32</td>
<td>75</td>
<td>SAVR</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>33</td>
<td>76</td>
<td>SAVR</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>42 months</td>
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<td>SAVR</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>35</td>
<td>83</td>
<td>SAVR</td>
<td>(+)</td>
<td>N/A</td>
<td>N/A</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>36</td>
<td>85</td>
<td>TAVI</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>6 months</td>
</tr>
<tr>
<td>37</td>
<td>81</td>
<td>TAVI</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>6 months</td>
</tr>
<tr>
<td>38</td>
<td>89</td>
<td>TAVI</td>
<td>(+)</td>
<td>(+)</td>
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<td>N/A</td>
<td>N/A</td>
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<tr>
<td>39</td>
<td>86</td>
<td>TAVI</td>
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<td>N/A</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>3 months</td>
</tr>
<tr>
<td>40</td>
<td>77</td>
<td>TAVI</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>N/A</td>
<td>(-)</td>
<td>10 months</td>
</tr>
<tr>
<td>41</td>
<td>75</td>
<td>TAVI</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>(-)</td>
<td>N/A</td>
<td>2 months</td>
</tr>
<tr>
<td>42</td>
<td>56</td>
<td>TAVI</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(+)</td>
<td>2 weeks</td>
</tr>
<tr>
<td>43</td>
<td>83</td>
<td>BAV</td>
<td>(+)</td>
<td>(+)</td>
<td>N/A</td>
<td>(-)</td>
<td>N/A</td>
<td>N/A</td>
<td>3 months</td>
</tr>
</tbody>
</table>

VWF rapidly recovered at 1 day after TAVI. However, incomplete recovery of HMW multimers of VWF in the present study may be explained by the presence of aortic regurgitation after TAVI \(^{45}\). Notably, we were able to demonstrate that follow-up endoscopy showed cessation of bleeding at 10 days after TAVI and disappearance of angiodysplasia in the stomach at 4 months after TAVI.

Improvement of anemia and sustained lack of blood transfusion following TAVI in this patient may be attributed to the disappearance of angiodysplasia in the stomach. Indeed, several supposed mechanisms of angiodysplasia in AS have been proposed \(^{46, 47}\). First, enhanced angiogenesis is caused by increased vascular endothelial growth factor (VEGF)-dependent proliferation due to mucosal and submucosal hypoxia by reduced cardiac output \(^{48}\). Second, angiogenesis is also caused by the loss of HMW multimers of VWF by high shear stress in AS \(^{49}\). Recent studies indicate that loss of VWF enhances angiogenesis via an Ang-2/Tie-2/VEGFR-2 pathway \(^{50}\). Third, the loss of HMW multimers of VWF causes hemorrhage as a result of AVWS \(^{51}\) because VWF, particularly HMW multimers of VWF, is essential in mediating the adhesion and aggregation of platelets to the sub-endothelium of damaged blood vessels \(^{52}\). In the present study, it is possible that angiodysplasia gradually disappeared at 4 months after TAVI through the increased cardiac output and remarkable recovery of the HMW multimers of VWF.

In patients with liver cirrhosis, bleeding in the gut occurs not only from esophageal varices but also from chronic peptic ulcer or erosive gastritis \(^{52}\). A previous study reported that the incidence of peptic ulcer in patients with liver cirrhosis was 11.3% \(^{53}\). In patients with liver cirrhosis, the levels of VWF are highly elevated due to endothelial damage, increased synthesis of VWF, and increased levels of vasoconstrictors \(^{54-56}\); however, those of HMW multimers are reduced \(^{57}\). In the present case, regardless of the comorbidity of liver dysfunction due to primary biliary cirrhosis, the loss of HMW multimers was recovered after TAVI.

Angiodysplasia is recognized as an important source of bleeding \(^{58}\). In the present case, before TAVI procedure, treatment with endoscopic APC for gastric angiodysplasia was temporarily successful. Unfortunately, the patient again began to have bleeding and anemia. However, after TAVI, angiodysplasia disappeared with a long-term follow-up of endoscopic images and free of bleeding. Based on our and previous study reports that showed rapid recovery of structural VWF and improvement of bleeding following aortic valve intervention, physicians could rather aggressively perform TAVI or SAVR even in patients diagnosed with Heyde’s syndrome.

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