Severe gastro-intestinal angiodysplasia in context of Heyde’s syndrome durably cured after aortic valve replacement

Angiodysplasies gastro-intestinales sévères dans le cadre d’un syndrome de Heyde, en rémission prolongée après remplacement de valve aortique

The association of aortic stenosis (AS) and gastro-intestinal bleeding (GIB) had been first suggested by Heyde in 1958 [1]. Since then, there have been numerous case reports [2–9]. Usually, indications for aortic valve replacement (AVR) in patients with significant AS are in relation with cardiac symptoms. GIB in the context of Heyde’s syndrome (HS) is not considered as an indication for AVR by cardiologist [10]. Several reports about HS indicated that AVR, rather than colectomy, was able to correct the bleeding from angiodysplasia [4,11–13], but the follow-up period was variable. We report here a patient with severe GIB definitely cured after AVR. This observation is presented in the context of a brief review concerning physiopathology and diagnosis of Heyde’s syndrome.

Case report

A 79 years old Caucasian man was admitted in 1997 for acute anaemia (5.4 g/dL) and melena. Since 1996 he presented a progressive weakness with iron deficiency. His medical history included calcify AS and hypercholesterolemia. AS was asymptomatic without chest pain, syncope, or congestive heart failure symptoms. Physical examination found diminished second heart sound. Endoscopy found multiple gastro-intestinal actively bleeding angiodysplasias in the duodenum, ileum, caecum and right colon. Smear blood tests do not show any excess of schisocytes (0.2%), reticulocyte count was 10%. Platelet count, activated partial-thromboplastin time and factor VIII coagulant level were normal. Lactate dehydrogenase, haptoglobin and bilirubine measurements were in normal range. Iron level was 4 (10–30 μg/L), ferritin was 18 (20–250 μg/L). Routine tests of von Willebrand antigen and ristocetin cofactor activity were in normal range. Analysis of Highest-Molecular-Weight Von Willebrand Factor Multimers was not performed (not available at diagnosis time in our laboratory).

The endoscopic photoacoulation by laser therapy of more than 15 angiodysplasias was performed. Later, he was admitted repeatedly for melena and acute anaemia requiring multiple blood transfusions (overall 31 blood-units during a period of 24 months, figure 1). Active bleeding angiodysplasias was

| Table 1 |
| Evolution of hemoglobin rate, blood transfusion needs and echocardiographic parameters, before and after the aortic valve replacement (AVR) |

<table>
<thead>
<tr>
<th></th>
<th>Pre-surgery (M-18)</th>
<th>Post-surgery (M + 18)</th>
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<tbody>
<tr>
<td><strong>Hemoglobin</strong></td>
<td></td>
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<tr>
<td>Hemoglobin rate (mean, g/dL)</td>
<td>8.6</td>
<td>11.2</td>
</tr>
<tr>
<td>Median (g/dL)</td>
<td>9.0</td>
<td>11.6</td>
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<tr>
<td>Standard deviation</td>
<td>1.7</td>
<td>0.8</td>
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<tr>
<td><strong>Number of blood transfusion</strong></td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td><strong>Echocardiographic features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic valve area (cm²)</td>
<td>0.64</td>
<td>2.70</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>65</td>
<td>60</td>
</tr>
<tr>
<td>Mean pressure gradient (mmHg)</td>
<td>75</td>
<td>17</td>
</tr>
<tr>
<td>Peak pressure gradient (mmHg)</td>
<td>140</td>
<td>29</td>
</tr>
</tbody>
</table>

1 Mean of all hemoglobin values 18 months before and 18 months after AVR.
2 During 18 months pre-surgery and 18 months post-surgery.
3 Gradient LV-Ao = gradient left ventricular − aorta.
unsuccessfully treated four times by photocoagulation. Octreotide 100 µg subcutaneous twice a day during 3 months also failed to prevent recurrence of the bleeding.

In light of the failure of the medical treatment to control severe anaemia, a right ileo-colectomy with ileo-transverse side-to-side anastomosis was performed in February 1998. Unfortunately, rapid recurrence of severe anaemia was observed requiring again multiple blood transfusions. Hemodynamic overload became poorly tolerated during transfusion with congestive heart failure, requiring rapid therapeutic choice to cure angiodysplasias. Echocardiographic features were ejection fraction left ventricular 65%, aortic valve area 0.64 cm², mean and peak pressure gradient left ventricular–aorta respectively at 75 and 140 mmHg (table 1). Despite the absence of clear indications of cardiac surgery relative to aortic stenosis, but considering the severe gastro-intestinal bleeding in context of Heyde’s syndrome, the patient was referred for AVR. AVR with Edwards Carpentier No. 21 mm bioprosthesis was performed in March 2000. After cardiac surgery, a remarkable stable rate of haemoglobin around 12 g/dl was noticed during a postoperative follow-up of 9 years. Improvement of echocardiographic features is related in table 1.

**Discussion**

Angiodysplasia is characterized as a vascular lesion of 2 to 10 mm in diameter, with clusters of submucosal arterioles and prominent central draining vein [2,14]. This may occur throughout the gastro-intestinal tract, however standard endoscopic procedure found it most often in the right colon and particularly in the caecum, where the wall’s thickness increased wall tension and may predispose its constitution [15]. Since development of videocapsule, angiodysplasias are commonly found in small bowel, especially in the elderly [16]. The exact prevalence in the overall population remains unknown. One prospective colonoscopic study found intestinal angiodysplasias in 59/1938 (3%) patients [17].

Angiodysplasia has been purposed to occur with higher frequency in patients with severe AS, but has also been documented in numerous vascular diseases (hypertrophic cardiomyopathy, peripheral arterial occlusive diseases and atherogenic risk factor, renal failure with haemodialysis, systemic sclerosis and vascular pulmonary disease) [5,18,19]. Batur et al. found an AS prevalence of in 23/73 (32%) elderly patients with gastro-intestinal arteriovenous malformations, which was significantly higher than in the echocardiogram comparison group (P < 0.001). Interestingly, the prevalence of mitral stenosis was not statistically different between these groups [7].

Bleeding tendency in Heyde syndrome is relative to an acquired von Willbrand’s disease type II, now termed von Willebrand’s syndrome 2A (vWS-2A) [5]. In AS, large von Willebrand factor (vWF) multimers are reduced by shear stress during the turbu-
lent passage of blood through the narrowed valve. Exposures to shear stress induce a specific conformational unfolding of large multimers in VWF, thereby enhancing susceptibility to cleavage by ADAMTS13 [20,21]. These large multimers mediate platelet adhesion, and a lack of these factors would be expected to prolong bleeding from the vessels. Of note, the anaemia profile in HS is iron deficiency and not haemolytic, despite the shear stress due to AS [5,12,22,23].

Our case report underlined that biologic Heyde syndrome diagnosis is difficult. Indeed, routine screening tests for von Willebrand’s disease could be normal, including vWF ristocetin cofactor activity [20,24,25]. In the Vincentelli report [21], 30% of patients with severe AS had a ratio of collagen-binding activity to antigen in normal range. Specific gel electrophoresis is necessary to confirm the loss of large multimers, but this assay is expensive and time-consuming. Measurement of primary hemostasis using PFA-100 test closure time device could be a rapid alternative test [5,26].

The first case report suggesting that AVR might cure bleeding angiodysplasia was reported in 1979 [9]. Furthermore, King described 14 patients with Heyde’s syndrome who had successfully undergone AVR (11 mechanical and 3 bioprosthesis) [27]. Recently, Thompson report the cessation of GIB in 47/57 patients who underwent AVR, with a very better outcome in case of bioprostheses [13].

Medical and endoscopic treatments of angiodysplasias seem to be disappointing [28]. Based on apparent efficacy of hormones in patients suffering from Osler-Rendu Disease, oestrogen and progesterone may reduce bleeding from angiodysplasias [29]. Nevertheless, randomized placebo-controlled study in 72 patients with non-hereditary angiodyplasias failed to show an effect of hormonal treatment on the incidence of rebleeding and transfusion requirements [30]. Octreotide which reduces venous pressure in the portal venous system could decrease the GIB due to angiodysplasia in some cases of Heyde’s syndrome [31,32]. Usually, bleeding angiodysplasias can be treated by laser photocoagulation during endoscopy with good but temporary success [28]. Surgical resection of the affected bowel could be realised after medical treatment failure; however rebleeding occurs in about one-third of the patients [3]. Recent experimental clinical data suggest that antiangiogenic substances like thalidomide or lenalidomide seem to inhibit gastro-intestinal bleeding [33–35].

Currently, AVR is required for symptomatic patients with AS (angina, syncope, heart failure) or those who need to undergo other cardiac surgical interventions. Furthermore, there is considerable evidence in favour of AVR in asymptomatic patients with severe AS who demonstrate left ventricular dysfunction or hypotensive response to exercise or complex ventricular arrhythmias or excessive hypertrophy or a small valve area (<0.6 cm²) [10]. We suggest that severe Heyde syndrome (severe gastro-intestinal bleeding in the presence of significant AS) could be also considered as a potential indication for AVR with bioprosthesis.

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References


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