Heyde syndrome: a common diagnosis in older patients with severe aortic stenosis

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Abstract

Heyde syndrome is a triad of aortic stenosis, an acquired coagulopathy and anaemia due to bleeding from intestinal angiodysplasia. The evidence that aortic stenosis is the root cause of this coagulopathy is compelling. Resolution of anaemia usually follows aortic valve replacement. This article discusses studies linking aortic stenosis with other conditions in the triad as well as diagnosis and management of this complex pathology.

Keywords: aortic stenosis, iron deficiency anaemia, angiodysplasia, gastrointestinal bleeding, elderly

Introduction

In 1958, EC Heyde published 10 cases of calcific aortic stenosis and severe gastrointestinal bleeding. The combination of calcific aortic stenosis and iron deficiency anaemia due to gastrointestinal bleeding was described as Heyde syndrome [1]. That same year Goldman reviewed 37,423 case notes and found a 3-fold higher than predicted incidence of gastrointestinal bleeding in cases of aortic stenosis [2]. In 1965, Cattell suggested that patients with aortic stenosis could bleed from a lesion in the ascending colon which had not been demonstrated by pathologists, and recommended blind right haemicolectomy in such patients as a cure for recurrent anaemia [3].

The association between aortic stenosis and intestinal angiodysplasia has been controversial as retrospective studies and cohort studies have reached opposing conclusions [3, 4]. The evidence that aortic stenosis is the root cause of the coagulopathy is much stronger than the evidence for a casual association with angiodysplasia.

Heyde syndrome now refers to a triad of aortic stenosis, acquired coagulopathy (von Willebrand syndrome type 2A, abbreviated here vWS-2A) and anaemia due to bleeding from intestinal angiodysplasia or from an idiopathic site. This article examines these conditions, the diagnosis and treatment of Heyde syndrome.

Aortic stenosis

Dystrophic calcification of heart valves was first described by Mönckeberg in 1904 [5]. Aortic stenosis is now the most common acquired valvular lesion in the elderly. The prevalence of critical aortic stenosis is 1–2% at age 75, rising to 6% at 85 years. The precipitating cause is unknown, but chronic inflammation of the valves causing thickening and fusion of the aortic valve cusps and calcification seems plausible [6]. Risk factors for aortic stenosis are similar to those for arterial atherosclerosis [6]. Critical aortic stenosis may present with syncope, angina and dyspnoea.

Intestinal angiodysplasia

Angiodysplasia may occur anywhere in the gastrointestinal tract, but is most common in the ascending colon, particularly the caecum. In a prospective study of colonoscopies of 1,938 patients, typical angiodysplasia was found in 3% of cases, but 80% were asymptomatic. The sites of highest prevalence of the lesions were the caecum (37%) and sigmoid colon (18%) [7]. A total of 1–6% of in-patient gastrointestinal bleeds are caused by angiodysplasia, while 30–40% of gastrointestinal bleeds of an obscure source are found to be linked to angiodysplasia and it is possibly the most common...
Association between aortic stenosis and angiodysplasia

There are methodological difficulties in proving statistical or causal links, partly because aortic stenosis and intestinal angiodysplasia are common conditions in the elderly. Aortic stenosis may only be detected in later symptomatic stages, while intestinal angiodysplasia will not always result in anaemia, and routine investigations may not reveal that they are the cause of a patient's anaemia. Thus, the prevalence of Heyde syndrome is not clear, and it is likely that many mild cases remain undiagnosed.

Some early studies on Heyde syndrome showed a correlation of a typical murmur of aortic stenosis with idiopathic gastrointestinal bleeding, while later studies have used echocardiographic and endoscopic diagnoses. Sigmoidoscopy is the most common investigation used to visualise the colon, but colonoscopic diagnoses are usually used in retrospective studies. Many studies have not distinguished bleeding from non-bleeding angiodysplasia; prosthetic valves may encroach on valvular orifices causing mild stenosis (patient-prosthesis mismatch) [8, 9].

According to one study, severe aortic stenosis is found in up to 15–25% of patients with repeated bleeding [10]. Mehta et al. investigated 29 patients with gastrointestinal angiodysplasia detected on endoscopy with echocardiography, but found no cases of aortic stenosis [11]. Similarly, Oneglia et al. investigated 59 patients and found that only one had aortic stenosis [12]. In a prospective, case-matched study of 40 patients who were found to have angiodysplasia, Bhutani and colleagues found no increased prevalence of aortic stenosis [3].

Pate and colleagues studied 3.8 million discharge summaries retrospectively, and found a significant association ($P < 0.0001$) between aortic stenosis and gastrointestinal bleeding presumed to be due to angiodysplasia. Age was statistically significant as a confounding factor, as patients who had been diagnosed with both conditions were older than patients with only one or neither ($P < 0.0001$) [6, 13]. In another retrospective case-note study of 3,623 patients with either aortic or mitral stenosis, gastrointestinal bleeding was found to be significantly more common in the aortic stenosis group ($P < 0.001$) [4].

In a study of patients diagnosed with angiodysplasia of the gastrointestinal tract over a 10-year period, echocardiography significantly correlated with aortic stenosis but not with mitral stenosis. Significant aortic stenosis was 2.6 times more common than in controls, and severe aortic stenosis was 4.1 times more common than in the general population. The study included patients diagnosed by angiography as well as endoscopy in contrast to the study of Bhutani et al. [9].

Aetiological theories

In 1971, Boss and Rosenbaum described distension of vessels in the intestinal mucosa in post-mortem cases of aortic stenosis and attributed the blood loss to this [14]. Low-grade chronic hypoxia may stimulate reflex sympathetic vasodilation and smooth muscle relaxation, progressing to true ectasia of vessel walls [9, 15].

Another theory is that colonic mucosal hypoxia might be caused by cholesterol emboli from the aortic valve or by the altered pulse waveform in aortic stenosis. Angiodysplasia have been described in hypertrophic cardiomyopathy, in which alteration of the pulse waveform is also found [6]. Several studies comparing cases of aortic and mitral valve stenosis have shown a higher prevalence of gastrointestinal bleeding in the former [4, 16]. Other valvular lesions might cause chronic hypoxia in the intestinal mucosa, but do not induce altered pulse waveforms [4]. Some found no association of aortic stenosis with angiodysplasia but found a high frequency of colonic polyps and tumours whereas others have suggested that Heyde syndrome is the end result of senile degeneration of both aortic valvular and gastrointestinal mucosal tissue [16, 17].

Coagulopathy

Aortic stenosis has been shown to cause acquired vWS-2A. First described in 1968, approximately 270 cases of acquired vWS had been published by 2000. In 12% of cases, it was caused by a cardiovascular disorder [18]. Von Willebrand factor (vWF) synthesised by endothelial cells is stored in ultra-large multimers and mediates platelet adhesion at sites of vascular damage [19, 20]. It circulates as large multimers, one of which exceeds the size of platelets [21, 22]. The high velocity of blood flow within telangiectasia requires the largest multimers of vWF to maintain haemostasis [6].

Acquired vWS-2A in aortic stenosis arises from degradation of vWF multimers by the shear stress across the diseased valve. An aortic pressure gradient of 50 mmHg may cause coagulopathy [23]. vWF multimers unfold from a coiled structure to an elongated filament [24, 25] and are then cleaved [24–27]. Degradation of the heaviest multimers of vWF, which are most effective in platelet-mediated haemostasis, is the basis for coagulopathy in Heyde syndrome [25].

In a study of 50 consecutive patients with aortic stenosis, 84% of whom were treated with aortic valve replacement (AVR), 21% of patients with severe aortic stenosis suffered from cutaneous or mucosal bleeding, and 67–92% had haematological abnormalities which correlated with the severity. Haematological investigations were performed 1 day, 7 days and 6 months postoperatively. The abnormalities corrected on the first day, but tended to recur at 6 months, especially when there was a mismatch between patient and prosthesis [25].

Yoshida and colleagues showed electrophoretic deficits of large multimers of vWF in patients with aortic stenosis
which resolved postoperatively, but no differences in pre- and postoperative vWF were found in patients with severe mitral regurgitation [10].

In a study of patients with aortic stenosis, a higher incidence of prolonged bleeding time was found which corrected following surgery [16]. Others have reported loss of large multimer vWF preoperatively but bleeding time normalised 2 days after surgery and vWF multimers normalised after 7 days [26]. Yet others demonstrated a causal relationship between aortic stenosis and vWS-2A [27, 28].

By 1987, 30 cases of upper and lower gastrointestinal angiodysplasia had been cured by AVR. Angiodysplasia might remain visible at endoscopy even after AVR, but only 1 of the 30 cases ever developed recurrent gastrointestinal bleeding [2].

**Diagnosis**

In an elderly patient with established aortic stenosis, development of iron deficiency anaemia should raise the possibility of Heyde syndrome. Initial investigations should explore other possibilities such as underlying gastrointestinal malignancy, coeliac disease or nutritional deficiency. The presence of angiodysplasia on sigmoidoscopy or colonoscopy or a failure of the investigations to find any clear site of gastrointestinal bleeding, should raise the possibility of Heyde syndrome. For patients in whom initial investigations show no abnormality, angiodysplasia may be diagnosed by capsule endoscopy.

Patients presenting with gastrointestinal bleeding should be examined carefully for aortic stenosis and there should be a low threshold for arranging echocardiogram in patients with normal colonoscopies or proven arteriovenous malformations. It is important to consider the possible presence of Heyde syndrome if metallic AVR is being considered, as there is a need for lifelong anticoagulation subsequently.

In vWS-2A, routine screening tests for vWS are usually normal. The gold standard is gel electrophoresis of vWF [6]. vWS-2A is characterised by absence of large vWF multimers seen on SDS-agarose electrophoresis [21]. The sensitivity of various tests for vWS-2A has been ranked as follows: gel electrophoresis (most sensitive), PFA-100 closure time, skin bleeding time, vWF ristocetin cofactor activity and vWF antigen level (least sensitive) [2].

**Treatment**

Patients with Heyde syndrome who are treated by intestinal resection generally continue to bleed from other sites, while AVR usually cures the clotting disorder and anaemia. A retrospective study of 91 patients with aortic stenosis and chronic unexplained gastrointestinal bleeding revealed that bleeding ceased in 93% of patients treated by valve replacement, compared with 5% of those managed surgically, with or without bowel resection. The figure of 5% represents one patient though, who had recurrent bleeding due to warfarin toxicity [6, 29].

Treatments of vWS-2A itself include factor VIII/vWF concentrates and desmopressin [6], but acquired vWS does not respond well to these [22]. Patients with acquired vWS-2A may be more prone to bleeding under cardiopulmonary bypass, and there is a case for investigating and treating it prophylactically, even if it is not symptomatic. It has been proposed that guidelines for the management of aortic stenosis should have bleeding from intestinal angiodysplasia with demonstrable acquired vWS added as an indication for valve replacement, and that monitoring of the severity of acquired vWS-2A should be considered as one of the factors determining the timing of surgery [6, 20]. The PFA-100 system may provide a commercially available screening tool for vWS-2A [2].

Episodes of severe bleeding may necessitate blood transfusions and emergency bowel resection. The resolution of gastrointestinal bleeding following AVR has strengthened the recommendation for AVR in Heyde syndrome [6, 13, 15, 30, 31]. Some authors have supported AVR in the presence of iron deficiency anaemia, even if the aortic valve stenosis is clinically insignificant.

Many elderly patients may be unfit for AVR or may refuse surgery. Conservative management includes oral iron supplements but regular blood transfusions may be necessary. Combined oestrogen and progesterone have been used to reduce bleeding from angiodysplasia, although the mechanism of action is not understood [2]. In serious cases this could halve transfusion requirements [32]. In patients with severe recurrent bleeding, endoscopy with laser therapy may be an option. In these circumstances treatment with octreotide may be considered [33]. Many elderly patients have co-morbidities requiring anticoagulants or antiplatelet agents, but they should be avoided, particularly in severe cases.

**Conclusion**

Iron deficiency anaemia and aortic stenosis are common in the elderly, but their association with angiodysplasia and bleeding is not generally recognised. Heyde syndrome is a complex disorder, resulting from interactions between aortic stenosis, intestinal angiodysplasia and acquired vWS-2A. AVR rather than bowel resection leads to long-term resolution of anaemia and should be considered in severe cases. Early diagnosis and appropriate treatment of Heyde syndrome is essential but requires teamwork and liaison between different specialities.

**Key points**

- There is an association between severe aortic stenosis and bleeding from intestinal angiodysplasia.
- Aortic stenosis leads to acquired vWS-2A.
- Valve replacement offer long-term resolution of bleeding.
• All patients with aortic stenosis should be screened for iron deficiency anaemia.
• Antiplatelet and anticoagulants should be used with caution in these patients to reduce the risk of bleeding.

Conflicts of interest
None.

Supplementary data
Supplementary data are available at Age and Ageing online.

References
(The long list of references supporting this review has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available at Age and Ageing online as appendix 1)


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