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Reappraising the spectrum of bleeding gastrointestinal angioectasia in a degenerative calcific aortic valve stenosis: Heyde's syndrome

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Abstract

Background: The occurrence of bleeding gastrointestinal angioectasia in elderly patients with degenerative calcific aortic stenosis is one of the most challenging clinical scenarios. A number of studies have shown that this clinical phenomenon is known as Heyde's syndrome.

Main body of the abstract: The pathogenesis of Heyde's syndrome is mainly due to the loss of high-molecular-weight von Willebrand factor (HMW vWF) multimers, as a consequent fragmentation of HMW vWF multimers as they pass through the stenosed aortic valve leading to acquired von Willebrand syndrome type IIA. Aortic valve replacement has proven to be a more effective management approach in the cessation of recurrent episodes of gastrointestinal bleeding.

Short conclusion: Physicians should have a high index of suspicion when dealing with elderly patients with established aortic stenosis presenting with iron deficiency anemia or unclear gastrointestinal bleeding. Parallel consultations between different specialties are essential for appropriate management.

Keywords: Aortic valve stenosis, Heyde's syndrome, Angioectasia, Angiodysplasia, Gastrointestinal hemorrhage

Background

Heyde's syndrome

Heyde's syndrome (HS) is a rare clinicopathological syndrome first described by Edward Heyde, as an association of gastrointestinal bleeding and a degenerative calcific aortic valve stenosis. Dr. Heyde gave a report of 10 patients in 1958 with classic signs of calcific aortic valve stenosis, with harsh systolic murmur radiating widely into the neck or back, had massive gastrointestinal bleeding for which he could not establish the cause [1].

In subsequent decades, HS has been further studied to fully reinforce the exact pathological mechanism [2–4], eventually leading to the discovery of hemostatic disorder, acquired von Willebrand syndrome type IIA (vWS-IIA), as a potential predisposing factor to patients with otherwise clinically silent gastrointestinal angioectasia to bleed [5, 6].

Despite a debate surrounding the actual definition of HS, many authors agree that it refers to a clinical syndrome comprising a triad of degenerative calcific aortic valve stenosis, acquired von Willebrand syndrome, and recurrent bleeding gastrointestinal angioectasia [7, 8].

This article aims at giving an updated review of studies that explored the clinical association between these conditions, its prevalence, and accurate diagnosis and proper management of the syndrome.

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Aortic stenosis

Aortic stenosis is the most common valvular heart disease, frequently caused by calcification of the aortic valve leaflets [9, 10]. Several studies in developing countries have reported the prevalence of aortic stenosis progressively increases with age ranging from as low as 0.02% in patients aged 18–44 years to as high as 9.8% in patients in the eighth decade of life [11–13]. Consequently, aortic stenosis is one of the most common causes of morbidity and mortality in older patients [14].

The pathobiology of calcific aortic stenosis is not only explained by aging but also involves a dynamic inflammatory process of endothelial damage due to lipid accumulation, oxidative stress, angiogenesis, and genetic factors leading to fibrosis, valve leaflets thickening, and, ultimately, calcification [15, 16]. Calcific aortic valve stenosis causes increased leaflet stiffness and a narrowed aortic valve opening that results in a pressure gradient across the valve [17, 18].

It is important to note that progressive aortic valve narrowing with coexistent left ventricular pressure overload and subsequently left ventricular hypertrophy may transition to heart failure and development of symptoms [19].

Angioectasia

Angioectasia is the most common vascular lesion in the gastrointestinal tract. They can be found throughout the gastrointestinal tract, with the most common site being the cecum and ascending colon [20]. They are characterized by dilated, ectatic, tortuous thin-walled vessels of the gastrointestinal tract mucosa or submucosa—including the arterioles, capillaries, and venules without inflammation or fibrosis [21, 22].

Angioectasia is often associated with advanced age, and their clinical presentation varies from being an asymptomatic incidental finding to a life-threatening severe gastrointestinal bleeding [23]. Its prevalence is estimated to be 0.8–6.2% [24] and accounting for up to 40% of colonic bleeding lesions [20].

The pathogenesis of angioectasia is not fully elucidated; however, numerous hypotheses have been proposed including one which suggests angioectatic lesions develop with aging due to chronic low-grade intermittent obstruction of the submucosa venules as a result of increased contractility at the level of the muscularis propria, consequently leading to congestion of the capillaries and failure of the pre-capillary sphincters, mucosa ischemia, and eventually formation of small arteriovenous collaterals (neovascularization) [20]. Furthermore, angiogenesis factors such as vascular endothelial growth factors (VEGF) and deficiency in von Willebrand factor (vWF) have also been implicated to play an active role in the pathogenesis [25, 26].

Main text

Correlation between aortic stenosis and angioectasia

Several authors have encountered a challenge in proving the statistical causal link between aortic stenosis and gastrointestinal angioectasia. This is mainly attributed to individual study methodological shortcomings [27]. Given the circumstance that both conditions are predominantly due to chronic degenerative processes, consequently, they may as well coexist in older patients.

Some studies have reported no significant association between aortic stenosis and angioectasia. A study that evaluated echocardiographic findings of 29 patients with angioectasia found out none had evidence of aortic stenosis [28]. Furthermore, Bhutani et al. conducted a prospective case-control study of 40 patients with gastrointestinal angioectasia detected by endoscopy and reported no increased prevalence of aortic stenosis [29].

However, the most recent clinical observations had shown the association between calcific aortic stenosis and gastrointestinal bleeding secondary to angioectasia. Table 1 summarizes the results of some of the most detailed studies.

Pathophysiology

There are several conceivable explanation for the pathogenesis of HS. However, the deficiency of high-molecular-weight (HMW) multimer of vWF is the most plausible link between degenerative calcific aortic valve stenosis and bleeding gastrointestinal angioectasia [5, 33]. HMW vWF multimers play a major role in the hemostatic function of the compromised blood vessels, i.e., gastrointestinal angioectatic vessels through mediating the platelet-subendothelial adhesion and inducing the platelet-platelet aggregation [34].

In HS, however, these HMW vWF multimers passing through a stenosed aortic valve are subjected to high mechanical shear stress leading to fragmentation as a result of elevated vWF protease activity-disintegrin and metalloprotease mediated by thrombospondin-type motif, member 13 (ADAMTS13). This leads to acquired von Willebrand's disease (vWD) [35–37]. Therefore, reduced levels of circulating HMW vWF multimers impair platelet-mediated hemostasis in the gastrointestinal angioectatic vessels hence predispose patients to bleeding [38].

Diagnosis

The diagnosis of Heyde's syndrome is common in elderly individuals with structural heart disease who present with a recent history of unexplained episodes of lower gastrointestinal bleeding [39, 40]. Moreover, it can present with unexplained recurrent iron deficiency anemia in patients with established aortic stenosis [41]. Therefore, it is imperative to have a high degree of

Table 1 Studies evaluating the association between angioectasia and aortic stenosis

Source	Study design	Number of participants or events	Summary of findings
Batur et al. [30] 2003, USA	Retrospective study	92,075	2.3-fold increase in the prevalence of AS of any severity in patients with GI AVMs compared with the general population [31.7%, 14.0%; *P*<0.001] 4.1-fold increase in severe AS in the AVMs group compared with the general population [14.3% vs 3.5%; *P*<0.001]
Pate et al. [31] 2004, Canada	Retrospective study	3,800,000	Significant association *P*<0.0001 between aortic stenosis and bleeding gastrointestinal angioectasia with an odds ratio of 4.5 (95% CI 3.0–6.8)
Jehangir et al. [32] 2018, USA	Retrospective study	32,079	7.02% prevalence of aortic valve disease in patients with bleeding intestinal angioectasia Adjusted odds ratio still reveals significant association (odds ratio = 2.37, 95% CI 2.10–2.66, *P*<0.001).

AS aortic stenosis, *GI* gastrointestinal, *AVMs* arteriovenous malformations

suspicion in these patients, especially if they have concomitant aortic stenosis and gastrointestinal bleeding.

A typical sign in keeping with aortic stenosis is the presence of systolic murmur at the second right intercostal space with radiation toward the right carotid artery which should be confirmed with an echocardiogram. Gastrointestinal angioectasia may be diagnosed by endoscopic imaging or radiographic imaging depending on the clinical scenario and severity of bleeding [20].

There are various tests that have been developed for screening and diagnosing von Willebrand disease. Unfortunately, there is no single assay that can diagnose vWD with complete confidence. vWF antigen activity (vWF:Ag) assays quantify the plasma vWF protein levels, VWF ristocetin cofactor activity (VWF:RCo) most commonly used to assess the binding capacity of vWF to platelet glycoprotein Ibα (GPIbα), and VWF collagen binding (VWF:CB) which assesses binding of vWF to the platelet collagen receptor. A decreased VWF:RCo/VWF:Ag is indicative of either absence or lack of high-molecular-weight multimer levels. Therefore, a confirmatory test of VWF multimer distribution should be performed using gel electrophoresis [42, 43].

However, although HS is developing as a common clinical entity, the initial diagnostic workup should target to explore more common causes of gastrointestinal bleeding, including gastric or duodenal ulcer, gastrointestinal malignancy, and inflammatory bowel disease.

Treatment

Due to the complexity nature of Heyde's syndrome, the optimal management strategy should be tailored on a patient-by-patient basis and often times requiring a multidisciplinary approach. There is inadequate evidence from prospective randomized controlled trials evaluating the management of HS. Therefore, most of the available data on treatment are based on case reports.

Aortic valve replacement

Expert consensus recommends aortic valve replacement (AVR) as the first-line treatment in the management of Heyde's syndrome [4, 44]. It reduces the mechanical shear stress on the HMW vWF multimers inhibiting their cleavage by ADAMTS13 and consequently improves coagulation abnormalities implicated in Heyde's syndrome. There are several observational studies that have demonstrated potential therapeutic benefits of AVR [45–53]. All studies were published between 2010 and 2020; cessation of gastrointestinal bleeding following AVR was the most measured outcome. The authors reported no further episodes of gastrointestinal bleeding with normalization of HMW vWF multimer as summarized in Table 2. Although these findings were not replicated in a few case reports [54, 55], most of the evidence available in the literature has proven AVR to be more effective.

Pharmacological therapies

There are various medical therapies that have been used to lessen episodes of bleeding from gastrointestinal angioectasia, including hormonal therapy, octreotide, and thalidomide. Octreotide, a somatostatin analog, is considered to inhibit angiogenesis by downregulation of VEGF and has demonstrated a significant therapeutic benefit [56]. In an open-label, randomized controlled trial including 55 patients assessing the treatment response of thalidomide in reducing bleeding episodes, Ge et al. [57] confirmed a significantly higher response rate in the treatment group 71% compared with iron-controlled group 4%. Junquera et al. noted a slight beneficial effect of combined estrogen and progesterone therapy in the management of bleeding angioectasia [58]. It is important to note that patients' clinical improvements observed in medical therapy are usually temporary as this approach does not address the primary pathophysiological mechanism of Heyde's syndrome.

Table 2 Studies assessing the effectiveness of AVR in patients with Heyde's syndrome

Study	Age (years)	Follow-up	Summary of findings
Mirna et al. [45] 2019, Austria	73	3 months	Normal quantity of vWF multimers, normal Hb concentration
Ramachandran et al. [46] 2018, USA	85	6 months	No need for blood transfusion with a normal Hb concentration
Alshuwaykh et al. [47] 2018, USA	56	6 months	No further episodes of GI bleeding
Iijima et al. [48] 2018, Japan	77	20 months	Cessation of recurrent GI bleeding
Shibamoto et al. [49] 2017, Japan	87	20 months	No episodes of GI bleeding and no need for blood transfusion
Balbo et al. [50] 2017, Brazil	81	6 months	No episodes of recurring GI bleeding
Benton et al. [51] 2014, USA	77	10 months	Normal levels of HMW vWF multimers and free from recurrent GI bleeding
Saad et al. [52] 2013, UK	76	4 months	Free from iron deficiency anemia
Pyxaras et al. [53] 2012, Italy	89	6 months	Normal hematological parameters with no episodes of GI bleeding

vWF von Willebrand factor, *Hb* hemoglobin, *HMW* high molecular weight, *GI* gastrointestinal

Endoscopic therapies

This is generally challenging, particularly in a setting of multiple gastrointestinal angioectatic lesions. Nevertheless, it can be used as a bridge therapy to AVR or in patients considered unfit for AVR [59]. Several endoscopic options for the management of bleeding gastrointestinal lesions been have evaluated for safety, efficacy, and long-term outcomes. In a prospective cohort study of 100 patients, the long-term outcome of the argon plasma coagulation (APC) method was evaluated [60]. In which, bleeding resolved in 85% of patients after a median follow-up of 20 months. Transfusion requirements ceased in 90% of patients, and a statistically significant increase in the mean hemoglobin levels was observed. The endoscopic clip technique has been shown to be useful in cases of isolated and relatively large bleeding colonic lesions [61]. Other beneficial approaches include photocoagulations (laser) and endoscopic multiband ligation, while electrocoagulation technique is not currently recommended due to its relatively higher rates of re-bleeding. Endoscopic procedure-related complications including perforation have also been reported in several studies [62, 63].

Bowel resection

Emergency bowel resection can be employed in selected cases of an acute, severe localized area of bleeding refractory to other treatment options. It is often considered curative [20], but accurate localization of bleeding lesion is crucial in order to avoid bleeding recurrence from a missed angioectatic lesion located elsewhere in the gastrointestinal tract [64]. It is important to note, however, this option may not be suitable in most cases as it carries a higher risk of excessive bleeding secondary to coagulopathy.

Superselective transcatheter arterial embolization

Superselective arterial embolization uses embolic agents such as gelfoam, microcoils, and n-butyl cyanoacrylate to occlude the bleeding vessel in a gastrointestinal angioectasia. This technique has been shown to be successful in the management of bleeding angioectasia [65]. A systematic review reported a number of procedure-related complications such as bowel infarction, arterial dissections, and hematomas [66].

Conclusions

Heyde's syndrome is developing as a common and significant clinical entity, particularly among elderly patients with significant aortic stenosis. Therefore, physicians are recommended to have a high index of suspicion when dealing with elderly patients with established aortic stenosis presenting with iron deficiency anemia or unclear gastrointestinal bleeding. Parallel consultations between different specialties are critical for appropriate diagnosis and treatment approach, although current evidence suggests aortic valve replacement should be considered in most cases. In hemodynamically unstable patients with a high risk of complications from a more invasive therapy, a conservative management with oral iron supplements and regular transfusions with packed red blood cells is beneficial.

Abbreviations

AVR: Aortic valve replacement; AVMs: Arteriovenous malformations; HS: Heyde's syndrome; HMW: High molecular weight; vWD: von Willebrand disease; vWF: von Willebrand factor; vWS-IIA: von Willebrand syndrome type IIA; VEGF: Vascular endothelial growth factor

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Authors' contributions

NM has made a substantial contribution to the conception of the idea, relevant literature search, and discussion of the article's contents and wrote the initial manuscript draft. ZH and CH made substantial contributions to the discussion of the article's content and improving the initial manuscript draft. All authors have read and approved the final manuscript for submission.

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