Heyde's Syndrome: A Review

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Bleeding from gastrointestinal angiodysplasia in patients with aortic stenosis (AS), termed Heyde's syndrome, has been recognized for many years. Intestinal angiodysplasia (IA) and AS are chronic degenerative diseases that are often asymptomatic, with a higher prevalence in the population than is clinically apparent. The incidence of both conditions increases with age, and both are associated with traditional cardiovascular risk factors. Many studies suggest that there is an increased prevalence of IA in AS and vice versa, but there is wide variation between studies. Evidence is mounting that severe AS may cause Type 2 acquired von Willebrand's disease, also termed von Willebrand's syndrome. This involves loss of the large multimers, which are required to maintain hemostasis in high flow conditions, such as occur in angiodysplastic arteriovenous malformations. Heyde's syndrome appears to consist of bleeding from previously latent intestinal angiodysplasia as a result of this acquired hematological defect, which is associated with aortic stenosis. Treatment options include localization of angiodysplastic bleeding points with cauterization, but this is associated with a high recurrence rate. Aortic valve replacement has been shown to improve the hematological abnormalities, and this is paralleled by clinical improvements. Valve replacement appears to offer the best hope of long-term resolution of the bleeding, and should be considered in most cases, particularly in those in whom the AS is symptomatic. In those patients deemed unfit for surgery in whom no bleeding point can be identified, recurrent blood transfusions may offer some symptomatic relief.

The Journal of Heart Valve Disease 2004;13:701-712

The association of aortic stenosis (AS) and gastrointestinal bleeding (GI) was first suggested by Heyde in 1958 (1). He recollected several patients with "...massive GI bleeding..." in whom no bleeding point was subsequently identified. Since then, there have been numerous case reports in the medical literature worldwide (2-39). Subsequent authors have suggested that the bleeding is due to intestinal angiodysplasia (IA), and have termed the association of gastrointestinal bleeding due to angiodysplasia in the presence of aortic stenosis Heyde's syndrome (40). However, the exact nature of the association remains unclear and its existence as a true, rather than coincidental, association is disputed (41-47). The aim of the present review is to summarize the published literature concerning this condition.

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Aortic stenosis

Degenerative AS is the most common acquired valvular heart disease in the elderly (48). It consists of a gradual progressive narrowing of the aortic valve orifice as a result of a chronic inflammatory process causing thickening and fusion of the valve leaflets, with a variable amount of calcification (48-53). The precipitating cause is unknown. The condition is more common and occurs at an earlier age in patients with congenitally abnormal valve structures (54), such as bicuspid valves, and this appears to have a genetic basis (55,56). However, most cases occur in people with tricuspid valves. Whatever the precipitating cause, once the process has commenced, it progresses asymptomatically at a variable rate over many years. Initially, left ventricular hypertrophy occurs, maintaining cardiac output by increasing the force of ejection through the stenotic valve, the high-velocity, turbulent jet giving rise to the characteristic murmur (57). The increased shear stress causes further endothelial damage and inflammation, leading to a vicious circle. Eventually, severe stenosis leads to decompensation

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with the development of chest pain, heart failure and syncopal episodes. The development of symptoms heralds a poor prognosis and merits surgery (58). In asymptomatic disease the role of valve replacement surgery is controversial. The prevalence of critical AS increases with age, rising from 1-2% at 75 years of age up to almost 6% in those aged over 85 years (59). The risk factors associated with aortic valve disease are similar to those with atherosclerosis - another inflammatory condition (60) - and include male gender, current tobacco smoking and hypertension, as well as high serum levels of lipoprotein(a) and cholesterol (61-63). Coronary artery disease, requiring concomitant bypass grafting, is present in about 50% of patients at the time of valve surgery (64,65).

Intestinal angiodysplasia

Angiodysplasia accounts for 1-6% of hospitalized gastrointestinal bleeds which, although usually insidious in nature, are occasionally massive or fatal (66-71). Small bowel angiodysplasia accounts for 30-40% of cases of gastrointestinal bleeding of obscure origin, and represents the single most common cause for hemorrhage in this subset of patients (69,72). The detection of angiodysplasia is increasing, due to improved diagnostic techniques and increased awareness, and it may be the most common cause of lower intestinal bleeding in the elderly (70,73,74). Angiodysplasia consists of dilated blood vessels in the mucosa and submucosa, the pathogenesis of which is not well understood. It can occur throughout the gastrointestinal tract; however, it is diagnosed most often in the right colon and particularly in the cecum, where the thinness of the wall and increased wall tension may predispose to its development (75-77). Diagnosis may require multiple investigations including endoscopy, mesenteric angiography, exploratory laparotomy, or a combined procedure (78). Some of these procedures have associated morbidity and mortality risks, which may be increased in patients with severe AS (79). One classification system of intestinal arteriovenous malformations identifies three types of lesion (80): non-palpable, non-visible lesions occurring in the right colon in elderly patients (typical IA); larger small intestinal lesions in younger patients; and angiomas associated with hemorrhagic telangiectasia - another condition which has been associated with AS (81).

The exact prevalence of gastrointestinal angiodysplasia in the overall population is not well known, since asymptomatic individuals usually do not undergo endoscopic evaluation. One prospective colonoscopic study in 1,938 patients found IA in 59 cases (3%), 47 of whom were asymptomatic. The sites of the lesions were the cecum (37%), ascending colon (17%), transverse colon (7%), descending colon (7%), sigmoid colon (18%) and rectum (14%) (77). However, endoscopy under-detects the presence of lesions, and a more accurate pathological diagnosis can be made by using a vessel injection and tissue-clearing technique (82). In a post-mortem study of 52 unselected individuals aged between 34 and 90 years, IA was found in 50% of cases (83). The incidence of IA increased with age, being particularly common over the age of 70 years, and the lesions were often multiple. Angiodysplasia has been purported to occur with higher frequency in patients with AS, hypertrophic cardiomyopathy (HCM), renal failure, cirrhosis, Turner's syndrome, systemic sclerosis, pulmonary disease, and also in smokers and those with other atherogenic risk factors, although the level of evidence for each of these associations varies (68-70,84-91). Although congenital angiodysplasia has been described, no genetic associations have been identified, and the condition appears to be pathologically distinct from acquired IA (80). IA has also been associated with an acquired form of Type 2 von Willebrand's disease, von Willebrand's syndrome (vWS-2A), which in some cases may be explained by an immune phenomenon (92-94).

Epidemiological evidence of association

The relative rarity of this clinical association makes it difficult to study (95). Case-control studies of patients with AS have produced inconsistent findings with regard to associated IA (24,76,79,96-98). Similar inconsistencies have been found in studies of IA looking for associated AS (67,98-102). One review, in which data from eight retrospective studies were pooled, found that the prevalence of AS in patients with IA ranged from 7% to 60%, with a mean of 23% (67,68,103-106). However, a subsequent review examined the methodology of these investigations more critically, and concluded that the published data did not support any association (98). More recent studies have included a large retrospective review of case records which found that 21 of 1,811 patients with AS - compared with only one of 1,812 patients with mitral stenosis - had concomitant cryptogenic gastrointestinal hemorrhage, and that this was statistically significant, albeit at an incidence of 1.2% (76). Another study found a prevalence of AS of 32% in 73 elderly patients with gastrointestinal arteriovenous malformations, versus 14% in a comparison group (99).

One of the present authors, in a retrospective analysis of 3.8 million hospital discharge summaries, found a significant association between bleeding due to IA or presumed due to IA (ICD-9 codes 569.84, 569.85, 578.1, 578.9) and AS (odds ratio of 4.5; 95% confidence inter-

val 3.0-6.8). However, a discharge diagnosis of bleeding was found in only 0.9% of those patients with AS, while a discharge diagnosis of AS was present in only 1.5% of those with IA, which may explain why some smaller studies have failed to demonstrate such an association (107). It is also important to remember that not all gastrointestinal bleeding in AS is from angiodysplasia, and peptic ulcer disease and other causes of bleeding must be excluded. However, AS does not appear to be more prevalent in patients with other identifiable sources of bleeding (79).

Reasons for association

Several hypotheses have been postulated to explain this association between IA and AS. The two conditions have certain common risk factors; for example, both occur more frequently in the elderly, as might be expected with acquired conditions. Several studies also found an increased incidence of IA among those patients with traditional cardiovascular risk factors (105,106,108), which are also associated with AS (109). Aortic stenosis may predispose to IA, the vascular lesions being acquired as a consequence of hypo-oxygenation of the colonic mucosa (105,110), possibly related to cholesterol emboli from the aortic valve or atheromatous aortic plaques (111), or to the altered pulse wave form in AS (40,76,112). Angiodysplasia has also been described in HCM, another condition with an altered pulse wave form (113). Another hypothesis suggests that existing IA may bleed as a result of ischemic necrosis in AS patients who have a low cardiac output, but this appears unlikely as bleeding from IA has not been noted in other forms of heart disease associated with a low cardiac output (79,97). However, the high prevalence of IA at autopsy in asymptomatic patients, combined with the low clinical incidence of bleeding in patients with AS, suggests that other factors may be important.

Aortic stenosis and acquired von Willebrand's syndrome

An alternative hypothesis is that IA is not more common in patients with AS, but that bleeding from IA is more apparent (40,114). There is evidence that some patients with AS have an increased bleeding tendency due to acquired von Willebrand's disease (Type II), now termed von Willebrand's syndrome (vWS-2A) (114-117). Although there are many causes of acquired vWS-2A (often it is due to an immune phenomenon) (118), in AS the mechanism is thought to involve mechanical disruption of large von Willebrand factor (vWF) multimers, from shear stress during turbulent passage through the narrowed valve (91,117,119-121). Exposure to shear stress causes conformational unfolding of vWF, enhancing its susceptibility to cleavage by a plasma zinc metalloprotease (a disintegrin and metalloprotease with a thrombospondin type 1 motif [ADAMTS13]) (122). A similar phenomenon has also been described in other high shear stress conditions such as hypertrophic obstructive cardiomyopathy (38,41,89,123-130), supravalvular AS (131), ventricular septal defect (132), and patent ductus arteriosus (133). The large multimers are important for hemostasis, as they mediate platelet adhesion to the vessel wall in situations of high-velocity blood flow. Angiodysplastic vessels themselves are associated with a high-velocity blood flow, and therefore a lack of large multimers would be expected to prolong any bleeding from these vessels (91). Thus, patients with vWS-2A due to AS may be more likely to bleed from existing IA.

A recent report demonstrated that 46 of 50 patients (92%) with AS had either platelet-function abnormalities or decreased vWF collagen-binding activity with loss of the largest multimers (115). The abnormalities correlated significantly with the severity of aortic valve stenosis, and improved after valve replacement. Interestingly, these authors noted that if there was a mismatch between the patient and prosthesis size, the hemostatic abnormalities tended to recur. It is worth

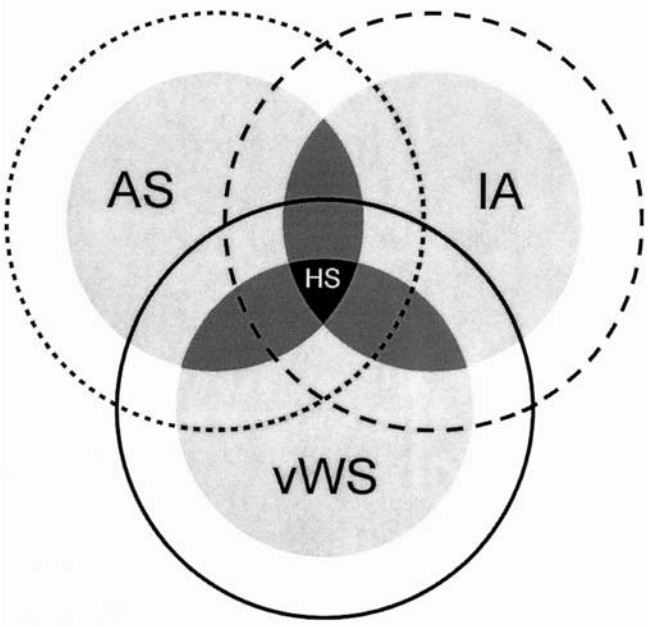

Figure 1: Diagram representing Heyde's syndrome (HS) as an overlap of aortic stenosis (AS), intestinal angiodysplasia (IA) and acquired von Willebrand's syndrome (vWS). Each condition may be either symptomatic (shaded) or asymptomatic (unshaded). (The sizes of the circles and shaded portions are not representative of the relative incidences of symptomatic or asymptomatic disease.)

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noting that this report and others describing the resolution of hematological parameters and bleeding after aortic valve replacement (AVR) may be criticized since they were mostly case series, small-sized, often lacked control data, and were of uncertain clinical relevance (134). Furthermore, reports have been made demonstrating a transient increase in vWF levels, including multimers, as a response to the stress of cardiac surgery, and this may confound the results (135-139).

Despite these concerns, evidence is mounting to support the view that the bleeding from IA in AS is exacerbated by vWS-2A, and that this accounts for the association described as Heyde's syndrome (140) (Fig. 1). The hypothesis is further strengthened by the fact that surgical AVR has resulted in either an improvement or complete resolution of the hematological abnormalities (40,141-146). This resolution is paralleled by clinical improvement (6,10,13,112,141-143,147-155), a phenomenon observed even with the introduction of oral anticoagulation (31,156). Furthermore, the observation that bleeding ceases following AVR despite the persistence of endoscopically proven IA supports this hypothesis (103). That shear stress is a factor is also supported by data from congenital heart disease where correction of stenosis has resulted in improvements in vWS-2A (157) including one case of vWS-2A which developed following iatrogenic pulmonary stenosis and was resolved after corrective surgery (158).

The diagnosis of vWS-2A is not straightforward, and routine screening tests for von Willebrand's disease are usually normal (159). The topic has been reviewed recently, and the following tests may be of benefit (140). Gel electrophoresis is the 'gold standard' to confirm loss of the larger multimers, but it is expensive and resource-intensive. Measurement of primary hemostasis using the PFA-100 device, skin bleeding time, vWF ristocetin co-factor activity and vWF antigen are alternatives, in decreasing order of usefulness. Other available tests of platelet function may also be of use (121)

Treatment options

Treat the angiodysplasia

The treatment of bleeding from IA is challenging. The lesions are often multiple, and it may be necessary to examine the entire gastrointestinal tract to detect all potential bleeding sites. If a distinct bleeding point can be localized endoscopically, cauterization can be attempted (160). IA can also be diagnosed using angiography, which may permit embolization therapy in patients who are actively bleeding. Surgical resection of the offending portion of intestine is another therapeutic option. However, all of these treatment modalities are often followed by recurrence of symptoms from previously latent disease in other segments (143). Treatment of IA in the presence of AS encounters similar problems, including that of recurrence (106,143,161,162). Bleeding from other sites in the upper and lower gastrointestinal tract has also been recognized, including the nose and jejunum and stomach and cecum (115,163-167). Furthermore, bowel surgery in patients with AS is associated with an increased risk during anesthesia (168). Without definitive treatment, chronic iron therapy and sometimes frequent blood transfusions may be required (169), taking into account the fact that AS itself may also cause anemia due to hemolysis (170,171). Other therapies, such as estrogen or progesterone preparations, have not been proven in clinical trials, although the results of some small studies have suggested possible benefits for these treatments (87,172-176).

Treat the von Willebrand's syndrome

Several treatments are available for von Willebrand's disease, including factor VIII/vWF concentrates and desmopressin. However, experience in the use of these approaches in vWS-2A with IA is very limited (177), and the best means of treating vWS-2A is to remove the cause. It is worth noting that treatment of IA with hormone preparations may reduce vWF levels, thus negating any potential benefit (178,179).

Treat the aortic stenosis

An alternative strategy in those patients with severe AS and symptomatic IA is to consider AVR first, before performing abdominal surgery. In symptomatic patients, unoperated AS is associated with a two-year mortality as high as 50%, whereas the mortality for IA, while not negligible, is much lower (57,71). Even in these elderly patients, the level of surgical mortality is acceptable in selected cases, and surgery is now recommended for virtually all patients (180,181). The situation with asymptomatic AS is less clear-cut however (182-185), and current AHA/ACC guidelines do not recommend surgery, despite acknowledging that clinicians differ in their views (181). Exercise testing and echocardiography may help to identify higher-risk patients, but this approach has not been validated.

One study examined outcomes in 91 patients with chronic intestinal bleeding and AS, 10 of whom had had previous bowel resection with recurrence of bleeding (143). Of 37 patients who underwent abdominal surgery, 35 (95%) continued to bleed postoperatively. Sixteen patients (two of whom had had a previous abdominal procedure) underwent AVR. At follow up, which ranged from 8 to 12 years, only one patient who had undergone AVR had recurrent bleeding secondary to excessive anticoagulation. Thus, the chance of cessa-

tion of bleeding after AVR seems to be greater than after bowel surgery. However, cessation of bleeding may not always occur (186,187), and strong consideration should be given to the use of a bioprosthesis which obviates the need for oral anticoagulation (152,188,189). In those patients in whom resolution does not occur, subsequent anesthesia to facilitate bowel procedures would be less risky. However, the role of AVR should be based on the life expectancy of the patient as well as any operative risk.

Questions still to be answered

Larger prospective studies of patients undergoing AVR are required to confirm the resolution of hematological abnormalities, that this is paralleled by clinical improvement, and that the cessation of bleeding is durable. If this is the case, then it might warrant a revision of guidelines for the management of AS to include bleeding from IA with demonstrable acquired von Willebrand's disease as being a symptom warranting valve replacement. The monitoring of vWS-2A may act as a surrogate of AS severity, and may facilitate decisions regarding the timing of surgery in otherwise asymptomatic individuals. In patients not eligible for AVR, trials of alternative treatments directed at increasing vWF activity or reducing bleeding from angiodysplasia are required.

In certain patients, balloon valvuloplasty may be an option for the treatment of AS (190). Generally, the outcome for this approach is poor, and it should be reserved as a palliative procedure for patients not deemed to be operative candidates (191). Potentially, this might ameliorate the vWS-2A and therefore bleeding from IA, but as yet there is no evidence to support this suggestion.

On a more speculative note, in patients undergoing AVR for reasons other than AS, it would be interesting to determine whether vWS-2A might develop for the first time after surgery, as a result of shear stress across the prosthetic valve, and whether this relates to valve mis-sizing. There is indirect evidence to support this hypothesis, in that levels of serum p-selectin - a marker of platelet activation which is associated with vWF levels - have been reported to be increased following the insertion of a mechanical aortic valve (146,192). Potentially vWS-2A could contribute to anemia in patients with valve replacement in whom hemolysis across the valve does not appear to be a factor. This could also apply to patients with high-velocity jets associated with paravalvular leaks.

Conclusions

The association of AS and bleeding due to IA appears to be real, but weak. There is some evidence that the mucosal lesions may be more common in AS, but whether this is due to the presence of AS - or simply that AS and IA have common risk factor(s) - is unclear. Given the high prevalence of asymptomatic IA at autopsy, the most likely explanation for the association is the occurrence of vWS-2A in AS, which results in an increased clinical presentation of otherwise latent IA. Subclinical abnormalities, such as vWS-2A, appear to be much more common in AS than clinically relevant bleeding.

Management strategies directed towards the treatment of IA alone are associated with a high risk of recurrence, likely due to the presence of multiple lesions and the persistence of vWS-2A. On the other hand, surgical replacement of the valve often results in a clinical improvement in bleeding, even with the introduction of oral anticoagulation, in parallel with a reduction in hematological abnormalities. In patients with severe AS and chronic gastrointestinal bleeding, AVR should therefore be considered as a first-line therapy, and the use of a bioprosthetic valve may be preferable in order to avoid the need for long-term anticoagulation. However, the decision to perform AVR should be based on the life expectancy of the patient and the operative risk. In patients in whom AVR is considered too high a risk, endoscopic localization of bleeding points with cauterization or multiple blood transfusions may offer some symptomatic relief, though the outlook without valve replacement surgery is poor.

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Erratum

In the article J Heart Valve Dis. 2001;10:628-635, Clinical results of the ATS prosthetic valve in 240 implants and review of the literature by Ozeren M, DoGan OV, Dolgun A, Kocyldirim E, Karapinar K, Yucel E. the surname of the fourth author was misspelt. It is, correctly, Kocyildirim.