

An Epidemiological Study of Heyde's Syndrome: An Association between Aortic Stenosis and Gastrointestinal Bleeding

Gordon E. Pate, Aisling Mulligan¹

Saint Paul's Hospital, Vancouver, Canada, ¹HIPE Unit (Hospital In-Patient Enquiry), The Economic and Social Research Institute, Dublin, Ireland

Background and aim of the study: An association between aortic stenosis (AS) and gastrointestinal (GI) bleeding attributed to intestinal angiodysplasia has been termed Heyde's syndrome. Case-control studies of patients with AS or intestinal angiodysplasia assessing the degree of association have produced discrepant findings.

Methods: Data were examined for all patients discharged from public hospitals in the Republic of Ireland between 1997 and 2001 (3.8 million events) with a primary or secondary discharge diagnosis of AS (ICD-9-CM code 424.1), GI bleeding presumed due to intestinal angiodysplasia (ICD-9-CM codes 569.84, 569.85, 578.1, 578.9), or both. Proportions were compared using chi-squared testing.

Results: There was a significant ($p < 0.0001$) association between AS and GI bleeding, with an odds ratio

of 4.5 (95% confidence interval 3.0-6.8). Age was a significant confounding factor; patients with both conditions were significantly older than patients with one or none of the conditions ($p < 0.0001$). The incidence of GI bleeding in patients with AS was 0.9%, and the incidence of AS in patients with GI bleeding was 1.5%.

Conclusion: The results of this large retrospective analysis support the existence of an association between AS and GI bleeding presumed due to intestinal angiodysplasia. However, the percentage of patients with both conditions was low, and this may explain why some smaller studies have failed to demonstrate such an association.

The Journal of Heart Valve Disease 2004;13:713-716

An association between aortic stenosis (AS) and intestinal bleeding was first mooted by Heyde in 1958 (1). Since then, many case reports have been outlined with bleeding varying from massive life-threatening hemorrhage (as originally described) to chronic blood loss requiring repeated transfusions. This bleeding has been attributed to intestinal angiodysplasia, and the association has been termed Heyde's syndrome (2). Aortic stenosis is a chronic progressive degenerative condition; in its severe form the condition has typical clinical characteristics, and the diagnosis is readily confirmed using echocardiography. Intestinal angiodysplasia, on the other hand, is more difficult to diagnose and exact localization of a bleeding point is often not possible with endoscopy, though mesenteric angiography may be helpful (2). A diagnosis is often presumptive after finding melena in the absence of any

other source of bleeding. There is mounting evidence that bleeding from angiodysplastic lesions in these patients may be due to acquired von Willebrand's syndrome (3,4) which may resolve after aortic valve replacement (4-6).

Case-control studies of patients with AS or intestinal angiodysplasia have produced discrepant findings, with a relative risk of association varying from 1 to 15 (7-17); consequently, some doubt has been expressed as to whether this represents a true association (18-20). The aim of the present epidemiological study was to investigate the incidence of AS and gastrointestinal (GI) bleeding presumed due to intestinal angiodysplasia in the Irish population.

Materials and methods

Summary data for all patients, children and adults, discharged from acute public hospitals in the Republic of Ireland are collated by the Hospital In-Patient Enquiry unit at the Economic and Social Research Institute. The coding scheme used is ICD-9-CM (October 1998). The coverage, based on estimates com-

Address for correspondence:

Gordon E. Pate, Interventional Cardiology Research, 5CD Providence Building, Saint Paul's Hospital, 1081 Burrard Street, Vancouver, B.C., Canada V6Z 1Y6
e-mail: gordon@studiominerva.com/gpate@providencehealth.bc.ca

plied by the Department of Health & Children, stands at 95-96% for the period investigated. A search was conducted for patients with a primary or secondary discharge diagnosis of AS (ICD-9-CM code 424.1), GI bleeding presumed due to intestinal angiodysplasia, or both. For the purposes of this study, GI bleeding included diagnostic codes for intestinal angiodysplasia with and without bleeding (ICD-9-CM codes 569.84, 569.85) and unspecified hemorrhage of the gastrointestinal tract or melena not due to duodenal, gastric, gastrojejunal or peptic ulcer (ICD-9-CM codes 578.1, 578.9). Data were averaged for the years 1997 to 2001, and proportions were compared using chi-squared testing.

Results

There was a mean of 758,522 discharges annually during this period (Table I). On average, GI bleeding was the primary or secondary diagnosis in 0.2% of cases, and GI bleeding in 0.33%. The incidence of AS bleeding in the presence of AS was 0.9%, a significant increase ($p < 0.0001$), with an odds ratio for the association of 4.5 (95% confidence interval 3.0-6.8). The incidence of AS in patients with GI bleeding was 1.5%. There was no significant gender-related difference, but patients with both conditions were significantly older than those with one or none of the conditions ($p < 0.0001$). The relationship was consistent and significant for each of the component diagnoses of GI bleeding.

Discussion

Several other studies have explored the presence of an association between AS and bleeding due to intestinal angiodysplasia. In a study of 244 patients, Williams found AS in 26% of cases with an undetermined source of GI bleeding, as opposed to 5% of those who had an identified bleeding source (8). Of note, few patients had endoscopy and none had echocardiographic documentation of AS, which was diagnosed clinically. McNamara and Austen documented idiopathic GI bleeding in five out of 211 patients with AS,

but in none of 110 controls (9). Cody et al. identified idiopathic GI bleeding in seven of 225 patients with AS compared with none of 335 controls (10). Shoenfeld et al., in a retrospective study of 152 patients with AS requiring surgery, determined that four (2.6%) had a diagnosis of idiopathic GI bleeding compared with none of 152 patients with mitral stenosis (11). These authors also found that seven of 34 patients (29%) with GI bleeding had AS, as opposed to only two of 130 (1.5%) with a known source of GI bleeding and three patients among 154 (1.9%) without GI bleeding.

A larger retrospective record review study by Greenstein et al. found that 21 of 1,811 patients with AS, but only one of 1,812 patients with mitral stenosis, had concomitant cryptogenic GI bleeding, and this was statistically significant, albeit at an incidence of 1.2% (12). Mehta et al. pooled data from eight retrospective studies of intestinal angiodysplasia and calculated a prevalence for AS of 23%, concluding that there was evidence to support the association (7,21-25). On the other hand, Imperiale et al. looked more critically at the methodology of previous reports and concluded that the published data did not support any such association (13). More recently, Batur et al. (14) determined a prevalence for AS of 32% among 73 elderly patients with gastrointestinal arteriovenous malformations, which was significantly higher than the prevalence in the control group (14%).

The results of the present study - the largest conducted to date - confirmed that AS and GI bleeding are significantly associated, although age may be a confounding factor. The prevalence of both conditions was found to increase with age, as would be expected with degenerative conditions, and this was consistent with the observation that there is an increased incidence of intestinal angiodysplasia in those with the traditional cardiovascular risk factors (24) that are also associated with aortic stenosis (26). The fact that GI bleeding occurs in only a relatively small percentage of patients with AS, and vice versa, suggests that the association is weak, and may explain why some smaller studies have failed to demonstrate its presence.

Table I: Numbers of patients discharged annually with aortic stenosis (AS), gastrointestinal bleeding (GIB) presumed due to intestinal angiodysplasia, both diagnoses, or neither.

Diagnosis	Year					Average	Mean age (years)	Males (%)
	1997	1998	1999	2000	2001			
AS and GIB	20	16	20	30	31	23	79	44
GIB no AS	1,321	1,360	1,545	1,671	1,676	1,515	65	55
AS no GIB	2,299	2,294	2,555	2,568	2,753	2,494	71	52
No GIB or AS	676,605	693,817	754,976	794,688	852,364	754,490	44	46
Total	680,245	697,487	759,096	798,957	856,824	758,522	42	46

Study limitations

In the present study, diagnoses were determined by the discharging physician, and the nature of the tests performed to confirm the diagnoses was not examined. Allowance must also be made for the limitations of hospital discharge data, including coding errors and the fact that hospital admissions likely over-represent more serious forms of both conditions. The HIPE system was designed to examine hospital activity, not to track patients, and does not include unique patient identifiers. It was possible to exclude multiple admissions of a patient to the same hospital, and re-examination of the subsequent data did not weaken the association. However, multiple admissions to different hospitals could not be excluded, and this may have led to bias as patients with both conditions might have been re-admitted or transferred to another hospital for further management. A more detailed analysis to examine the confounding effect of age could not be performed. Finally, the possibility of diagnostic bias as the result of an increasing awareness of this association cannot be excluded.

In conclusion, the results of this large epidemiological study support the existence of an association between AS and bleeding due to intestinal angiodysplasia. However, the percentage of patients with both conditions was low, and may explain why some smaller studies have failed to demonstrate any association.

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