Increased Prevalence of Aortic Stenosis in Patients With Arteriovenous Malformations of the Gastrointestinal Tract in Heyde Syndrome

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Background: Heyde syndrome is described as the association of arteriovenous malformations (AVMs) of the gastrointestinal (GI) tract and aortic stenosis (AS); its existence, however, has been questioned. We examined whether there is an association between AVMs and AS when objective measures are used to diagnose these findings.

Methods: We identified all patients who were diagnosed with AVMs between 1990 and 2000 by means of gastrointestinal endoscopy or mesenteric angiography. We compared the prevalence of AS and mitral stenosis (MS) in the 73 patients with AVMs who also had echocardiograms. For a comparison with the general population, the prevalence of AS and MS in all patients who had echocardiograms between 1990 and 2000 was calculated (MS was chosen for comparison as a lesion with similar likelihood of prompting an echocardiographic evaluation).

Results: The prevalence of AS was 31.7% in patients with AVMs, which was significantly higher than the 14.0% found in the general population comparison group (P < .001). The prevalence of MS was 1.6% in the AVM group, which was not statistically different from the 6.0% MS prevalence in the general echocardiogram population (P = .14). Significant AS was 2.6 times more common, and severe AS was 4.1 times more common, in patients with AVMs than in the general population. Age and sex were not associated with Heyde syndrome, but the association was more prevalent in blacks.

Conclusions: Our study confirmed an association between AVMs and AS, although the etiology of the Heyde syndrome remains unclear. Clinicians need to be aware of this syndrome because it may affect their management of patients with gastrointestinal bleeding or AS.

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In 1958, E. C. Heyde reported an association between arteriovenous malformations (AVMs) of the gastrointestinal (GI) tract and aortic stenosis (AS). Subsequent studies in support of Heyde’s discovery used indirect clinical criteria, such as idiopathic GI bleeding or heart murmur consistent with AS, to determine the presence of AVMs or AS. Other authors, however, have questioned whether the Heyde syndrome is a real entity. No previous study has shown an association between AS proven by echocardiography and AVMs visualized by GI endoscopy or angiography. The purpose of our study was to determine if there is an association between AS and AVMs of the GI tract using objective diagnostic criteria.

Our database included patients who underwent esophagogastroduodenoscopy, push-enteroscopy, colonoscopy, or a mesenteric angiogram between the years 1990 and 2000, and we selected the 177 patients diagnosed with GI AVMs (or any of the synonyms: telangiectasia, angiodysplasia, or vascular malformation). Of these 177 patients, 143 (80.7%) were diagnosed by endoscopy and 34 (19.2%) by angiogram, and 73 (41.2%) also had an echocardiogram at our institution during the same period. The results of the echocardiogram were recorded, with specific attention to the presence and characterization of aortic and mitral stenoses. Mitral stenosis (MS) was selected as a comparative valve lesion, with the assumption that it is equally likely as AS to prompt echocardiographic evaluation.

The severity of stenosis was classified using standard Doppler-derived mean gradient criteria. For AS, mild corresponded to a reading of less than 25 mm Hg; moderate, of 25 to 40 mm Hg; and severe, of 40 mm Hg or higher. For MS, mild corresponded to a reading of less than 8 mm Hg; moderate, of 8 to 12 mm Hg; and severe, of 12 mm Hg or higher. Significant stenoses were defined as valve lesions with moderate or severe stenosis. The age, sex, and race of the patients were recorded. Because of the encroachment of a prosthesis on the valve orifice area, normally functioning artificial valve replacements often have mean gradients that...
patients with MS

B

Figure 1. Overview of methods. AVMs indicates arteriovenous malformations; AS, aortic stenosis; and MS, mitral stenosis.

Table 1. Severities of Valvular Stenosis in Patients With AVM and in General Population*

<table>
<thead>
<tr>
<th>Patients With AS</th>
<th>Patients With MS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>AVM Group</td>
<td>Gen Pop Group</td>
</tr>
<tr>
<td>(n = 63)</td>
<td>(n = 92 012)</td>
</tr>
<tr>
<td>Severe stenosis</td>
<td>9 (14.3)</td>
</tr>
<tr>
<td>Moderate stenosis</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Mild stenosis</td>
<td>10 (15.9)</td>
</tr>
<tr>
<td>All Patients</td>
<td>20 (31.7)</td>
</tr>
</tbody>
</table>

Abbreviations: AS, aortic stenosis; AVM, arteriovenous malformation; Gen Pop, general population with echocardiograms; MS, mitral stenosis.

*Data are number (percentage) of patients.

fit the categories of mild stenosis. Therefore, patients with aortic or mitral prosthetic valves were excluded to prevent this group from contributing to stenosis prevalence (Figure 1). In the AVM group, 10 patients with valve replacements were excluded for this reason (7 aortic valves for AS, 1 aortic valve for insufficiently, and 2 mitral valves for stenosis).

Since the frequency of AS is not the same among individuals with MS and in the general population, we determined the frequency of these 2 lesions in our total echocardiogram population to compare stenosis frequency in the general population and the AVM group. We evaluated the records of all patients who underwent echocardiograms at this institution for any indication between 1990 and 2000. The same database and search methods were used for the general and the AVM population review. Over 10 years, 102 525 patients had an echocardiogram for any indication. Of these, 10 513 patients were excluded because of the presence of an aortic or mitral prosthesis. The valvular stenoses in the remaining patients were categorized with the same mean gradient criteria as those used for the AVM group, and the demographic characteristics were studied.

The prevalences of AS and MS in the AVM group vs the general echocardiogram population were compared using the Pearson χ² test in a 2 × 2 contingency table. The significance level was set at α = .01. The variation in stenosis severity in each group was compared in a similar manner. Baseline demographic characteristics between groups were compared using the t test with unequal variance and a significance level set at α = .01.

RESULTS

Of the 63 patients with AVMs who had echocardiographic evaluations, 20 (31.7%) had AS of any severity, with an average mean aortic gradient of 32.2 mm Hg. In contrast, only 1 patient in this group of 63 patients had MS (1.6%), with a mean gradient of 6 mm Hg (mild stenosis) (Figure 2A). Interestingly, this patient had concomitant AS. When those with mild stenosis were excluded, the prevalence of significant (moderate or severe) stenosis in patients with AVMs was 15.9% (10/63) for AS, compared with 0% (0/63) for MS (Figure 2B).

Of the general comparison group of 92 012 patients without a valve prosthesis who were examined using echocardiograms, 12 870 had AS of any severity (14.0%), and 5 557 had MS of any severity (6.0%). Excluding patients with mild stenosis, the prevalence of significant (moderate or severe) stenosis in the general comparison population was 6.0% (5 548/92 012) for AS, and 1.9% (1 769/92 012) for significant MS (Figure 2).

These data reflect a significant 2.3-fold increase in prevalence of AS of any severity in the AVM population compared with the general population (31.7% vs 14.0%; P < .001). Similarly, there was a 2.6-fold increase in significant AS in the AVM population (15.9% vs 6.0%; P = .001), and a 4.1-fold increase in severe AS (14.3% vs 3.5%; P < .001) (Table 1). In contrast, the prevalence of MS was not statistically different between the AVM and general populations, among patients with any MS (1.6% vs 6.0%; P = .14), or those with significant MS (0% vs 1.9%; P = .27) (Figure 2).

There were no significant differences in the demographic distribution of the AVM and general population.
Heyde syndrome should be approached cautiously, be-vestigated. In particular, mechanical AVR in a patient with is found, the possibility of Heyde syndrome should be in-screened for occult GI blood loss. If ill-defined bleedingpared with a 93% effectiveness with AVR.

GI bleeding in only 5% of the patients with AVMs, com-prered that GI surgery was successful in preventing recurrentGI surgery.14-16 Although these studies didnot support the association of GI-tract AVMs have usedechocardiographic methods to define AS and visualizedcal criteria to demonstrate the presence of AVMs or AS,existence of Heyde syndrome used only indirect clinici-anisms for this strong association include cholesterol em-bolization from the stenotic valve,20 hypoxia-induced symp-thetic nerve–mediated vasodilation,11 and senescent pro cesses that might affect both organs.10 Recent reports have hypothesized that a connective tissue abnormality might causeboth AVMs and AS; however, the absence of AVMs in con-genital AS makes this theory less likely.18 Another fre-quently cited explanation is that mucosal ischemia fromthe stenotic valve causes necrosis and bleeding from AVM lesions. However, because cardiac output is compromisedonly during the latest stages of AS, most of our patients do not fit this description. Anderson et al19 studied the theorythat the stenotic valve causes an acquired coagulopathy and showed abnormalities of the von Willebrand factor func-tion in 3 patients with Heyde syndrome, with resolution in 3 patients with Heyde syndrome, with resolution of these abnormalities after AVR. Other potential explana-tions for this strong association include cholesterol embolization from the stenotic valve,20 hypoxia-induced symp-thetic nerve–mediated vasodilation,11 and senescent pro cesses that might affect both organs.10 Recent reports have characterized AS as an atherosclerotic-like pro cess.21,22 Future studies should look for a potential link between AVMs and atherosclerosis that may provide another connection between these 2 entities.

The association between AS and AVMs shown in this study will affect decisions for patients presenting with aortic valve or intestinal manifestations. Patients who present with GI bleeding, particularly those in whom no cause is found during the initial endoscopic investigations, should have a thorough examination to detect a possiblea systolic murmur. Physicians should have a low threshold for performing an echocardiogram to exclude AS. In extensive GI bleeding due to AVMs, bowel resection is sometimes needed. In Heyde syndrome, even if the GI bleeding has been controlled with a bowel resection, the patient is left unprotected from a potentially le-thal valve disease when AS is not detected. Numerous authors have reported cessation of GI bleeding after aortic valve replacement (AVR),21-11 and King et al12 showed that GI surgery was successful in preventing recurrentGI bleeding in only 5% of the patients with AVMs, com-pared with a 93% effectiveness with AVR.

All patients who present with AS should at least be screened for occult GI blood loss. If ill-defined bleeding is found, the possibility of Heyde syndrome should be in-vestigated. In particular, mechanical AVR in a patient with Heyde syndrome should be approached cautiously, be-cause anticoagulation could exacerbate the GI bleeding ifit persists after surgery.13 The threshold for performing an AVR on patients with Heyde syndrome should be affected by the anticipated effects on both the GI bleeding and the valvular hemodynamics. Some patients with Heyde syndrome may develop anemia owing to a slow GI bleeding, which causes them to become symptomatic earlier in the course of AS. If GI lesions can be treated endoscopi-cally, this may reduce perioperative bleeding and stabili-ze hemodynamics at the time of aortic valve surgery.

To date, the very existence of Heyde syndrome has been controversial. In addition to the original report by Heyde, Williams2 found that 25% of patients with unex-plained GI bleeding had AS and Cody et al3 found that patients with AS were 100 times more likely to have idio-pathic GI bleeding. Many early studies in support ofthe existence of Heyde syndrome used only indirect clin-cal criteria to demonstrate the presence of AVMs or AS, such as the presence of idiopathic GI bleeding or mur-mur consistent with AS.4,5

Some authors have questioned whether Heyde syn-drome is a real entity, however,6,7 and recent studies that do not support the association of GI-tract AVMs have used echocardiographic methods to define AS and visualizedAVMs by GI endoscopy.14-16 Although these studies did not show an association between these 2 entities, they were limited by their small sample sizes or lack of control groups.

### POTENTIAL EXPLANATIONS FOR HEYDE SYNDROME

The mechanism of the Heyde syndrome remains unexplained, and none of the potential explanations were investigated in the present study. An earlier speculation sug-gested that syphilitic arteritis might cause bleeding from smaller mesenteric vessels,13 but it has been abandoned be-cause of the disorder’s present rarity. Weaver et al17 hy-pothesized that a connective tissue abnormality might cause both AVMs and AS; however, the absence of AVMs in con-genital AS makes this theory less likely.18 Another fre-quentely cited explanation is that mucosal ischemia from the stenotic valve causes necrosis and bleeding from AVM lesions. However, because cardiac output is compromised only during the latest stages of AS, most of our patients do not fit this description. Anderson et al19 studied the theory that the stenotic valve causes an acquired coagulopathy and showed abnormalities of the von Willebrand factor func-tion in 3 patients with Heyde syndrome, with resolution of these abnormalities after AVR. Other potential explana-tions for this strong association include cholesterol embolization from the stenotic valve,20 hypoxia-induced symp-thetic nerve–mediated vasodilation,11 and senescent pro cesses that might affect both organs.10 Recent reports have characterized AS as an atherosclerotic-like pro cess.21,22 Future studies should look for a potential link between AVMs and atherosclerosis that may provide another connection between these 2 entities.

### LIMITATIONS

In our study, despite the significantly increased prevalence of AS in patients with AVMs, the true prevalence of the Heyde syndrome may be underestimated given the strict inclusion and exclusion criteria used for patient selec-tion. For example, patients were not included into our calculations of prevalence if one of their diagnostic procedures was performed at another hospital. Excluded pa-tients also included those with idiopathic GI bleeding but negative results for multiple diagnostic procedures—a common occurrence in Heyde syndrome because AVM lesions are often difficult to visualize. Since our data-base did not include patients who underwent sigmoi-
doscopy, we could not include anyone diagnosed with AVMs by the most common procedure used to visualize the colon. This certainly caused us to underestimate the prevalence of the Heyde syndrome.

Similarly, 8 patients with AVMs were excluded because of an AVR, but 7 of them had received it because of severe AS. If these patients were included in calculations of Heyde syndrome prevalence, this would increase the prevalence of AS of any severity from 31.7% (20 of 63 patients) to 37.0% (27 of 73 patients), and the prevalence of significant AS from 15.9% (10 of 63 patients) to 23.3% (17 of 73 patients). In contrast, there would have been only small increases in the prevalences of MS of any severity, from 1.6% (1 of 63 patients) to 4.1% (3 of 73), and of significant MS from 0% (0 of 63 patients) to 2.7% (2 of 73 patients).

Finally, any limitations present in a retrospective evaluation apply also to our study. As it was undertaken in a tertiary care center, the study and comparison populations may have been more selected than they would have in a general community population. Conversely, general population prevalences are likely to be underestimated at a large referral center; therefore, in a community setting the difference of AS prevalence between a general population group and patients with AVMs may be even more marked. Furthermore, our use of MS as a comparison group also introduces some bias, though the use of a general population MS control group likely compensates for this difference.

CONCLUSIONS

Our study shows that AS is significantly more prevalent in patients who have concomitant AVMs, and that the stenoses are more severe, and this may affect the management of both AVMs and AS. Current studies probably underestimate the true prevalence of the Heyde syndrome; and since there are potential changes in management of patients with a recognized Heyde syndrome, more research in this area is needed.

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REFERENCES