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Clinical implication of gastrointestinal bleeding in degenerative aortic stenosis: An update

Wojciech Gola, Małgorzata Lelonek

Department of Cardiology, Sterling Memorial University Hospital, Medical University of Lodz, Poland

Abstract

Gastrointestinal (GI) bleeding due to colonic angiodysplasias can be associated with calcifying aortic stenosis (AS). GI angiodysplasias and AS are defined as chronic degenerative disorders, and the prevalence of both diseases increases with age. Moreover, degenerative AS is associated with increased destruction of high molecular weight multimers of von Willebrand factor which can promote bleeding from intestinal angiodysplasias. The coincidence of gastrointestinal bleeding angiodysplasias and AS has been known for many years as Heyde's syndrome. Aortic valve replacement is the first line therapy for advanced stage AS-patients, but can also be an effective treatment for co-existent bleeding angiodysplasias and acquired von Willebrand disease.

In this study, we tried to collect as well as systemized data about the etiopathogenesis of AS coagulation abnormalities and diagnostic, clinical and therapeutic implications of AS-patient with GI angiodysplasias. (Cardiol J 2010; 17, 4: 330–334)

Key words: aortic stenosis, angiodysplasia, von Willebrand disease, Heyde's syndrome

Introduction

Aortic stenosis (AS) can be complicated by coagulation abnormalities. The commonest and best documented clinical manifestation is hemorrhagic tendency, such as gastrointestinal (GI) [1, 2] and nasal bleeding [3, 4]. Bleeding from the GI system usually occurs in elderly patients with co-existent GI angiodysplasias. An association between AS and GI bleeding was first suggested in 1958 by Edward J. Heyde, an internist working in Vancouver. He noted (in a letter to the *New England Journal of Medicine*) ten cases of coincidence between calcifying AS and GI bleeding of obscure origin [5]. GI bleeding angiodysplasia with co-existent autopsy-proven AS was first corroborated in 1971 by Boss and Rosenblum [6]. The hypothesis of association between degenerative AS and GI bleeding due to colonic angiodysplasia was confirmed by further studies and has been termed Heyde's syndrome (HS). Warkentin et al. [7] suggested that GI bleeding angiodysplasia in AS-patients is caused by acquired type 2A von Willebrand disease (vWD-2A), characterized by decreased level of high molecular weight (HMW) von Willebrand factor (vWF) multimers. Recent research confirmed this etiology of the HS phenomenon (Fig. 1) [7–9].

Prevalence

AS is the commonest valvular heart defect and affects 3–5% of the population aged 65 and over [10, 11]. But, the prevalence of AS in patients with bleeding from colonic angiodysplasia is still undefined and controversial. The incidence of GI bleeding in the general population is about 0.9% [12]. According to different sources, between 7–29% [13, 14] of patients with diagnosed GI bleeding angiodysplasias suffer from AS or aortic sclerosis, and 3% of advanced AS-patients have GI bleeding [12].

Address for correspondence: Wojciech Gola, Department of Cardiology, Sterling Memorial University Hospital, Medical University of Lodz, Sterlinga 1/3, 91–425 Łódź, Poland, e-mail: golawojtek@gmail.com

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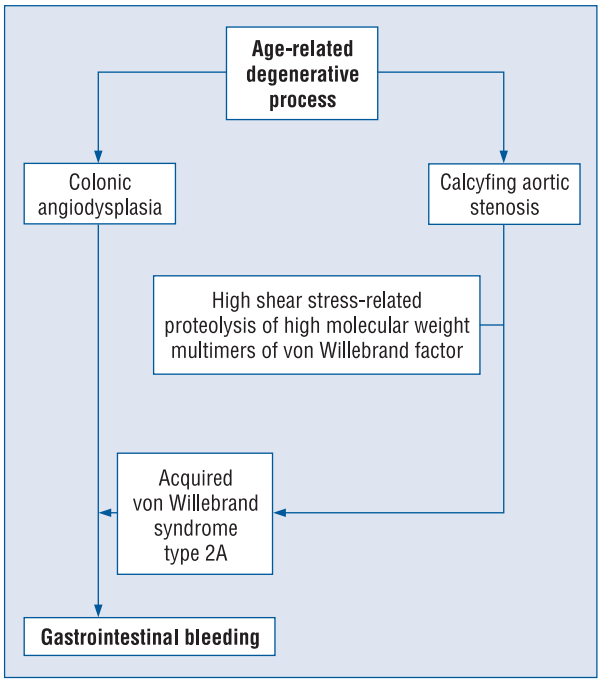

Figure 1. Pathogenesis of Heyde's syndrome.

Table 1. Commonest disorders causing von Willebrand syndrome type 2A [9, 22–25].

Degenerative aortic stenosis	
Hypertrophic cardiomyopathy with left ventricular outflow tract obstruction	Cardiovascular diseases
Ventricular septal defect	
Patent ductus arteriosus	
Immunologic disorders (systemic lupus erythematosus, scleroderma, mixed connective tissue disease, diabetes mellitus)	
Acute leukemia and non-hematologic neoplasms	
Drugs (hydroxyethyl starch, ciprofloxacin, griseofulvin, valproic acid, recombinant factor VIII)	
Monoclonal gammopathies	
Uremia	
Renal insufficiency	
Cirrhosis of the liver	
Pulmonary hypertension	

On the other hand, one study showed no relation between AS and GI bleeding [15].

Association between degenerative aortic stenosis and von Willebrand disease

Von Willebrand factor

Von Willebrand factor (vWF) is a multimeric glycoprotein (20,000 kD) that circulates in blood plasma and binds to coagulation factor VIII in a non-covalent complex. vWF is produced constitutively in endothelium (in the Weibel-Palade bodies), megakaryocytes (α-granules of platelets), and subendothelial connective tissue. vWF plays a role in primary hemostasis and helps in the proper adhesion of platelets to the exposed subendothelium due to damage occurring to the blood vessels [16]. In forming thrombus, and during normal wear, large multimers of vWF are cut by plasma vWF-cleaved metalloprotease called ADAMTS 13 (a disintegrin and metalloprotease with thrombospondin type 1 motifs) [17].

Acquired type 2A von Willebrand disease as a consequence of high shear stress

In AS-patients, HMW von Willebrand factor multimers, normally circulating in plasma, are subject to high fluid shear stress presented in narrowed aortic valve [18]. During passing stenotic aortic valve, under conditions of high shear stress, large multimers of vWF are subject to increased exposure of ADAMTS 13 [19, 20]. High shear stress changes the structure of vWF and makes it more prone to proteolysis. The effect of increased vWF proteolysis is depletion of HMW multimers that are the most hemostatically important in primary hemostasis. There is significant dependence between numbers of HMW multimers and aortic valve gradient (AVG) [21]. Decreased number of HMW von Willebrand multimers is a laboratory manifestation of acquired vWD-2A.

Acquired depletion of HMW multimers, also called von Willebrand syndrome type 2A (vWS-2A), can be a result of many other disorders. The commonest reasons for vWS-2A are shown in Table 1.

Laboratory manifestations of vWS-2A

Loss of HMW vWF multimers is a basic laboratory manifestation of acquired vWD-2A in patients suffering from AS. Electrophoretic analysis of vWF multimers is the method of choice [26]. Prolonged bleeding time, decreased ristocein co-factor activity (vWF:RCo), and decreased vWF antigen (vWF:Ag) are also common laboratory symptoms of vWD-2A and can be useful in the diagnostic process [27]. Moreover, a lower level of vWF:RCo than vWF:Ag is characteristic for most patients with vWD-2A [27]. However, partial thromboplastin time is usually normal and factor VIII level is often not lowered [26]. HMW multimers are markedly lowered even in subtle form of vWD-2A with normal results of skin bleeding time, vWF:RCo and vWF:Ag [27].

Aortic stenosis and angiodysplasia

Angiodysplasia is a mucosal and submucosal vascular malformation that occurs typically in a colon. Histologically, it is similar to teleangiectasia and is formed by enlarged and fragile vessels. The typical location for angiodysplastic changes is the right side of the colon (cecum and ascending colon) but it can also occur in the stomach and the small intestine [28]. Other locations of bleeding angiodysplasias like nasal mucosa have also been described [4]. Colonic angiodysplasia can be found in 1–6% of patients admitted to the hospital with GI bleeding symptoms [29, 30]. Depletion of HMW multimers of vWF in AS (vWS-2A) increases risk of bleeding from co-existent angiodysplasia [7, 22].

Degenerative process as a causative factor of angiodysplasia and aortic stenosis

The degenerative age-related process plays a major role in forming GI angiodysplasia [31]. The same process is a main etiology of calcifying AS (degenerative AS, age-related AS) [32] and connects these two disorders. Angiodysplasia and degenerative AS typically appear in advanced age.

Hypoxemic theory

Narrowed aortic valve decreases perfusion in the GI tract, causes hypoxemia and is the main reason for persistent vasodilatation in GI mucosa. Permanent dilatation of GI vessels promotes intestinal angiodysplasias [33].

Genetic predisposition

Other factors like genetic predisposition may also result in colonic angiodysplasias and calcifying AS [31]. Congenital connective tissue disorders can intensify the degenerative process in colonic connective tissue and accelerate the age-related degeneration process in the aortic valve (congenital bicuspid aortic valve) [34].

Investigation for angiodysplasia

The investigation of intestinal angiodysplasia is still imperfect because malformed vessels may sometimes be very tiny and impossible to detect, hence some patients may be under-diagnosed. However, selective angiography of mesenteric arteries is recommended as a 'gold standard' (Fig. 2) [29]. One limitation of this procedure is that it has to be performed during an episode of bleeding, otherwise it is not reliable. Angiodysplastic lesions can also be identified via colonoscopy (Fig. 3) but some patients with GI bleeding who are diagnosed with angiodysplasia show a normal result to this procedure [28, 29, 35]. Other investigations that can help diagnose angiodysplasia include capsule enteroscopy and double-balloon enteroscopy, both of these facilitate visualization of the small intestine [36], labeled red blood cell scintigraphy and endoscopic Doppler sonography.

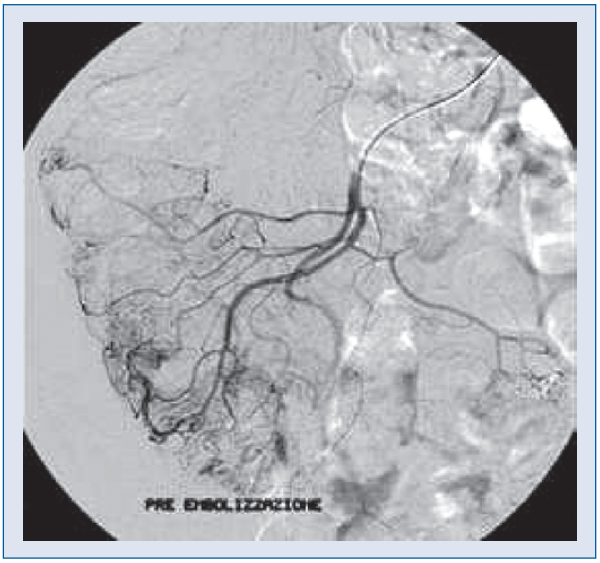

Figure 2. Selective angiography of superior mesenteric artery. Multiple areas of small angiodysplasias localized at cecum and ascending colon (http://www.eurorad.org/eurorad/case.php?id=7814).

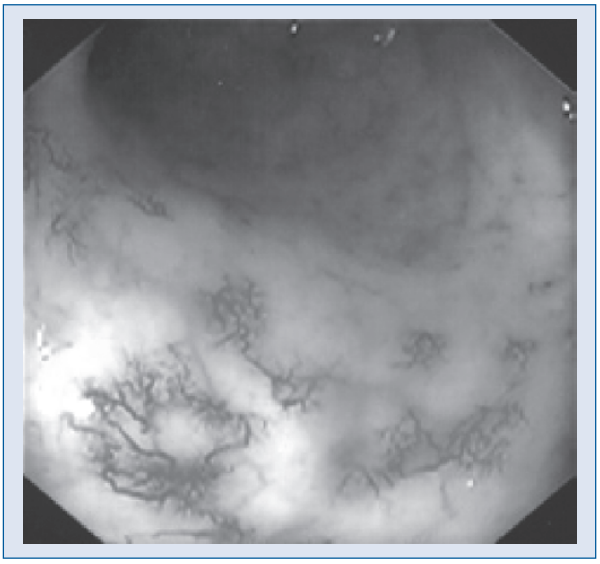

Figure 3. Colonoscopic view of gastrointestinal angiodysplasias (http://www.gihealth.com/html/education/photo//colonAngiodysplasia.html).

Management of Heyde's syndrome

Aortic valve replacement as a treatment of choice

There are many methods of HS therapy. However, aortic valve replacement (AVR) should be recommended as a 'gold standard' [37, 38]. It is proven that AVR corrects the blood supply in the gut. Moreover, decreased number of HMV vWF multimers undergoes normalization after valve replacement [39]. It is reported that 95% of AS-patients with GI bleeding due to angiodysplasia have no bleeding symptoms after AVR [40]. Replacement with biologic prosthesis is recommended as the first line treatment for AS-patients with co-existent gastrointestinal bleeding [41]. Patients with a replaced mechanical valve should take anticoagulants, which would increase angiodysplasias bleeding [42].

Other treatment options for angiodysplasia

Another (though less effective) management method for GI angiodysplasia is endoscopy including laser photocoagulation, sclerotherapy and electrocoagulation [43]. Selective embolization during mesenteric angiography can be useful in patients with severe bleeding lesions and can be an alternative to surgical treatment [44, 45]. Laparotomy and gastrointestinal surgery in the form of segmental bowel resection or blind right colectomy is recommended in some cases [46]. There have been positive reports of systemic treatment in GI bleeding angiodysplasia. Hormonal therapy including small doses of ethinyl estradiol [47], progesterone, somastatin [48] and long-acting octreotid [49] can help control bleeding. Thalidomide, oral iron, antifibrinolytics, and vWF/factor VII (FVIII) concentrate [45, 50] have also been reported as treatment methods for GI angiodysplasias.

Conclusions

Calcifying aortic stenosis can be complicated by GI bleeding which is linked to colonic angiodysplasia. Co-existent type-2A von Willebrand syndrome in AS-patients promotes hemorrhagic tendency from angiodysplasias. Both of these disorders, calcifying AS and angiodysplasias, appear in elderly patients and are promoted by age-related degenerative process. Episodes of GI bleeding may become dangerous and problematic, especially in elderly patients, and may complicate the diagnostic and therapeutic process. It is very important to know that HS in the form of both its components can be efficiently cured by one valve replacement therapy.

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