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Heyde Syndrome as a Presentation of Acquired Von Willebrand Syndrome: What the Gastroenterologist Should Know

EM. Daza[1], AC. Córdoba[2]

Corresponding author: AC. Córdoba

[1]Residente de Gastroenterología y endoscopia digestiva, Fundación Universitaria Sanitas , Bogotá, Colombia.
[2]Especialista en medicina interna Universidad El Bosque, Bogotá, Colombia.

Abstract: Heyde syndrome was first described in 1958 by Dr. Eward C. Heyde who sent a letter to the editor of The New England Journal Of Medicine describing a series of 10 cases of patients whom all had in common the presence of aortic stenosis and frequent gastrointestinal bleeding (1). Nevertheless it wasn't until 28 years later that the cause of the gastrointestinal bleeding in these patients was documented, which was related to the presence of angiodysplasias (2). Subsequent observations in different clinical studies reported the healing of the bleeding in these patients after aortic valve replacement, suggesting a cause-effect relationship between these two clinical entities and laid the first foundations in the pathophysiology of the disease, by finding alterations in the concentrations of von Willebrand factor multimers, thus explaining the predisposition to bleeding in these patients, due to defects in primary hemostasis. This is how Heyde syndrome is currently considered, as an acquired type 2 von Willebrand syndrome (AVWS Type 2), and different proposals in the treatment have been made in which comprehension of the main pathophysiological mechanism of the disease, aortic valve replacement remains the best treatment option(3). In this document we will review the pathophysiological bases of the disease, its presentation and treatment options.

Key Words: Heyde syndrome, Aortic stenosis, von Willebrand factor, Angiodysplasia, Gastrointestinal Bleeding

Introduction

In 1958, Dr. Edwar C. Heyde, a general practitioner in Vancouver, Washington, sent a letter to the editor of The New England Journal Of Medicine describing an association between calcified aortic valve stenosis and gastrointestinal bleeding in 10 patients who shared characteristics such as being older than 60-70 years, having stenotic aortic disease due to calcification and the presence of systolic murmurs with thrill and irradiation to the neck and back, without having, at that time, an explanation about the relationship between these two pathologies and assuming that the bleeding was generated by the presence of sclerotic vessels which could condition a higher

risk of gastrointestinal bleeding in these patients compared to those without heart disease, this clinical condition was denominated Heyde Syndrome(1). It wasn't until 28 years later, that the presence of submucous angiodysplasias was documented as the cause of gastrointestinal bleeding (GIB) in these patients, however for the next 10 years the association between aortic stenosis (AS) and angiodysplasia was controversial due to not having a strong statistical association and not finding a clear pathophysiology (2).

Subsequent studies would help to clarify the pathophysiology of the disease by describing the resolution of the bleeding after surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR). Particularly a study conducted in 1987 where follow-up was performed for more than 8 years to a cohort of 87 patients with AS and GIB or anemia, were bleeding resolved in 93% (n=14) of the patients who underwent SAVR (3). At the same time, two studies conducted in patients with congenital heart disease and valve disease reported defects in high molecular weight multimers of von Willebrand factor (HMWM of VWF), mimicking acquired type 2 von Willebrand syndrome (c) but with less compromise of the intermediate size multimers of the von Willebrand factor, which is why it is considered as an acquired type 2a von Willebrand syndrome (AVWS Type 2a). It was also found that in these patients the values of HMWM of vWF returned to normal once SAVR was performed and that patients with non- bleeding angiodysplasias had normal values of HMWM of vWF (3,4).

Epidemiology

The prevalence of gastrointestinal angiodysplasias is difficult to determine since most of them are asymptomatic and found incidentally in up to 5% of patients who undergo endoscopic studies for different reasons. They are frequently found in adults over 60 years, reason why a degenerative component has been associated with them, explaining why their incidence increases with age (5). Angiodysplasias can be found in any segment of the gastrointestinal tract and before the development of video capsule endoscopy (VCE) the most frequent site was thought to be the cecum and the ascending colon, however it is now known that they are more frequent in the small intestine (57% to 80%) with a proximal predilection, followed by the colon (44%) and stomach (33%); they are usually found in multiple segments in up to 60% of cases and 77% of patients will present a bleeding episode requiring transfusion, the remaining 33% will need iron administration due to chronic anemia at least once during their lifetime. Mortality due to angiodysplasias associated with major bleeding is estimated in up to 2% of cases (5).

GIB associated with angiodysplasias is the main characteristic of Heyde Syndrome although it must be taken into account that this only explains 10 to 20% of all bleeding episodes in patients with AS. The prevalence of GIB in patients with AS is unknown but has been proposed to range from 2% to 25% and these patients are considered to have a 3 to 100 fold increased risk of bleeding compared to patients without AS. Patients with valvular heart disease (VHD) do not generally develop massive hemorrhagic diathesis since the intermediate-sized von Willebrand factor multimers are not very affected and are capable of achieving hemostasis in the sites of greatest physiological stress to the blood flow by shear forces (3).

Risk Factors:

Many comorbidities have been associated with the formation of angiodysplasias in the digestive tract, including hypoxemia in relation to chronic lung disease, chronic kidney disease, venous thromboembolism, liver cirrhosis and heart disease, however the common denominator in these pathologies is advanced age, for which a causal relationship is difficult to establish between them (5). Heyde syndrome was initially associated exclusively with aortic stenosis and not with other valvulopathies, however the pathophysiology of the disease has also been described in mitral valve dysfunction with regurgitation and in other cardiac conditions such as hypertrophic cardiomyopathy with outflow tract obstruction, left ventricular assist devices and extracorporeal circulation and HMWM of vWF have been proposed as a way to quantify the severity of these diseases (3). Table 1 describes the main risk factors for the development of angiodysplasias (5).

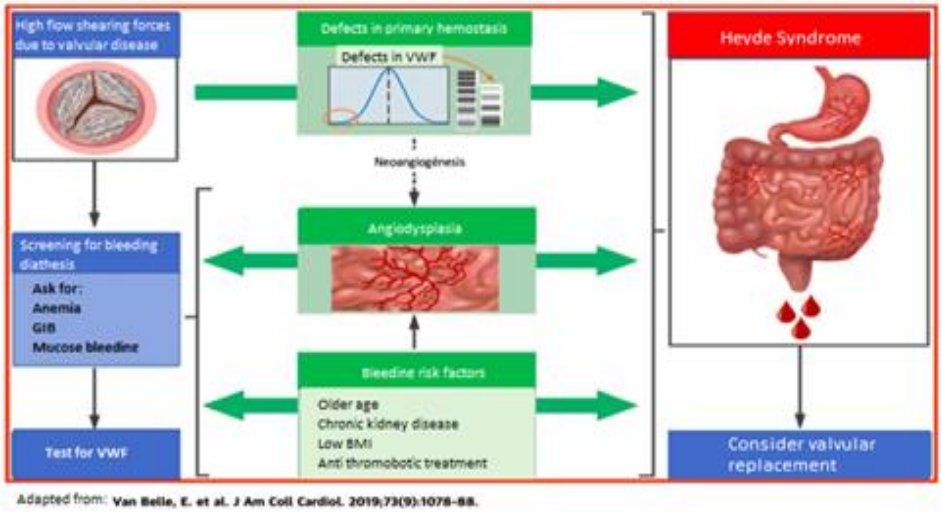
Table 1. Risk factors for gastrointestinal angiodysplasias (5).

Risk factors for gastrointestinal angiodysplasias
● Age over 60 years ● Chronic obstructive pulmonary disease ● Left ventricular assist device ● Von Willebrand disease ● Venous thromboembolism ● Ischemic heart disease ● Liver cirrhosis Medicines: ● Antiplatelet ● Anticoagulants ● Antithrombotic

Von Willebrand factor:

Von Willebrand factor (vWF) is a multimeric glycoprotein with a size ranging from 600,000 to 20 million Daltons (Da) and a weight greater than 20,000 Kilodaltons, which participates in platelet adhesion to injured vascular surfaces and also fulfills the transport function of FVIII, protecting it from proteolysis and prolonging its half-life in circulation. The vWF gene is located on the short arm of chromosome 12 and is synthesized by megakaryocytes and endothelial cells. In platelets it's stored in the Weibel Palade bodies and is released during endothelial injury through their migration to the platelet surface, once released it interacts with Vitronectin alpha VB3 and GPIb receptors on the endothelial surface in order to facilitate platelet aggregation and thrombus formation during hemostasis, however vWF is also constitutively secreted into the circulation.

In its basal state, vWF is in a folded form which is considered its inactive form. The multimeters or larger molecules have a greater thrombogenic potential once they are deployed, and these are regulated through enzymes with metalloprotease functions such as ADAMS13, which split the multimeter into smaller molecules with less capacity to generate platelet aggregation. The main stimulus that generates the deployment and subsequent fractionation of vWF is the stress or shear forces of the blood flow on the vascular surface greater than 60 Dynes/cm2. Alterations in ADAMS13 function, quantity or quality of vWF are considered pathological and cause disease, hence von Willebrand disease is related to defects in the quantity, quality or function of VWF, which can be congenital or acquired (6).



Adapted from: Van Belle, E. et al. J Am Coll Cardiol. 2019;73(9):1078-88.

Figure 1. . Mechanisms involved in the pathophysiology of Heyde syndrome.

Heyde syndrome pathophysiology:

In patients with aortic stenosis, blood flow is under high stress due to turbulence or shear forces during its passage over the stenotic valve and the degree of stress is directly proportional to the severity of the valve stenosis. This stress stimulates the endothelium which exposes vWF, which is deployed by shear forces, making it more susceptible to rupture from HMWM of vWF to molecules of intermediate and small sizes by the metalloprotease ADAMS13, which is more active in areas of higher shearing forces. The smaller residual molecules generated by proteolysis have little platelet aggregation activity. The continuous breakdown of the HMWM of vWF by ADAMS13 generates its consumption, which cannot be compensated by its synthesis in the megakaryocytes and the vascular endothelium (7).

The constant consumption of this HMWM of vWF explains the difficulty in achieving true hemostasis during endothelial injury, however the clarity on the formation of angiodysplasias in relation to AS is less clear (7). The current proposal is that this HMWM have an antiangiogenic effect that is lost when the levels of this molecule decrease in relation to permanent proteolysis. Different proteins are related to this antiangiogenic effect such as main binding molecules on the surface of the vascular endothelium, Vitronectin VB3 alpha which is also decreased in patients with vWF deficiency (8). In addition, Angiopoetin 2 (Ang-2), which is normally stored in Weibel Palade bodies, bodies that depend on vWF for their formation and cannot be synthesized in the absence of it, is constitutively released into circulation favoring its interaction with other proangiogenic factors such as Interleukin 8, Galectin 3 and connective tissue growth factor (8). This is how we obtain a relationship between an entity that generates defects in the coagulation mechanisms and also facilitates neovascularization and therefore bleeding (9). Figure 1 summarizes the mechanisms involved in the pathophysiology of Heyde syndrome (3).

There are other mechanisms that could explain the GIB in patients with heart disease, who undergo placement of intra cardiac devices, such as left ventricular assist devices (LVADs) and extracorporeal circulation (EC), circumstances where the shear forces of the blood flow on these endovascular devices and the modifications they generate in the pulse patterns cause an activation of the HMWM of vWF and a greater fractionation by ADAMS13, promoting the development of vascular malformations and thus facilitating bleeding (10). Bleeding in these circumstances was initially considered to be related to the use of anticoagulants to maintain the device and prevent thrombosis, however rates of gastrointestinal bleeding greater than those found in patients receiving anticoagulation for other reasons have been documented, and suggesting underlying bleeding mechanisms. This is possibly related to the fact that constant blood flow generates less opening of the aortic valve compared to pulsatile flow, sharing the pathophysiology of Heyde's disease (11).

This was confirmed in a study conducted in patients with continuous-flow LVAD, which showed defects in platelet aggregation and how these defects were corrected once the patients underwent heart transplantation. Although GIB in patients with AS or heart disease and device carriers could be explained by the pathophysiology of Heyde's disease, other more frequent causes of bleeding in these patients should be studied(12,13).

Finally, not only aortic valve disease and the placement of devices on the vasculature are related to Type 2a AvWD, in studies carried out in patients with hypertrophic cardiomyopathy who presented with GIB, this resolved once they underwent myomectomy in order to resolve the obstruction in the outflow tract (14). Additionally, this condition could be related to auto-antibodies against vWF as a substrate for autoimmunity, decreased synthesis of thyroid hormones and the use of some drugs such as ciprofloxacin, valproic acid and griseofulvin. Table 2 describes the main causes of AVWS Type 2 (15).

Table 2. Main causes of Acquired Von Willebrand syndrome

Cardiovascular disease ● Aortic stenosis ● Hypertrophic cardiomyopathy with outflow tract obstruction ● Ventricular septal defect ● Patent ductus arteriosus ● Left Ventricular Assist Device
Autoimmune diseases ● Systemic lupus erythematosus ● Scleroderma ● Mixed connective tissue disease
Lymphoproliferative diseases ● Monoclonal gammapathy of uncertain significance ● Lymphoma ● Multiple myeloma
Myeloproliferative diseases ● Essential thrombocythemia ● Polycythemia vera ● Chronic myeloid leukemia
Non hematologic neoplasms ● Wilms tumor ● Adenocarcinoma
Medicines ● Ciprofloxacin ● Griseofulvin ● Valproic acid ● Recombinant factor VIII
Chronic Kidney disease
Hepatic cirrhosis

Diagnosis:

Taking into account the relationship between AS and GIB due to angiodysplasias in Heyde syndrome, the two entities should be documented to configure the syndrome. With the development of echocardiography, the diagnosis of AS is now more frequent. By definition severe aortic stenosis is considered as a mean aortic pressure greater than 40 mmHg, with a peak flow velocity greater than 4 m/sec or a valve area less than 1.0 cm2. When AS is accompanied by heart failure, syncope, or angina, surgical or transcatheter aortic valve replacement is generally required, although Heyde syndrome is currently considered another indication for surgical or percutaneous valve intervention. The diagnosis of AVWS Type 2 is essential to define the hemostatic disorder as the culprit of bleeding, and a decrease in HMWM of vWF levels has been described beginning at 40 mmHg of mean valve gradient with an inverse relationship, proportional to the severity of the AS. vWF multimers can be quantified and separated by agarose gel electrophoresis and are detected by anti-vWF antibodies to classify them according to their molecular weight in low, medium and high, but these studies are not performed routinely and are generally used for clinical trials only (13). Figure 2 shows an

electrophoresis of vWF and quantification of HMWM of vWF from a patient with Heyde syndrome compared to a healthy subject (13).

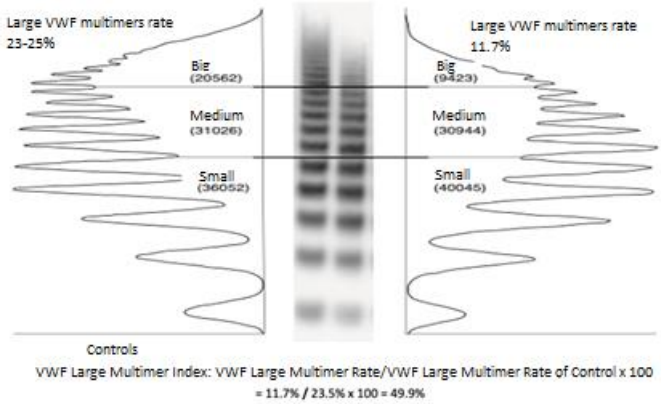


Figure 2. Quantification method for calculating the large multimer index of vWF in Heyde syndrome.

The index is defined as the patient's vWF large multimer rate divided by the control patient's vWF large multimer rate quantified on agarose gel electrophoresis. The plasma of the patient in figure 2 is from a patient with severe aortic stenosis with a mean aortic pressure of 68 mmHg and a peak blood flow of 5.24 m/sec. (13).

On the other hand, objectification of GIB and the presence of angiodysplasias should initially be done with endoscopic studies of the upper and lower digestive tract using conventional endoscopic techniques, and if the site of bleeding is not documented, the midgut should be evaluated by ECV or enteroscopy with the help of complementary radiological studies such as CT arteriography, scintigraphy with Technetium 99 (Tc-m99) or conventional arteriography in order to define the treatment in patients with evident or occult bleeding (16). Figure 3 and Table 3 show the endoscopic characteristics and the classification of angiodysplasias, estimating the risk of bleeding for each one (5).

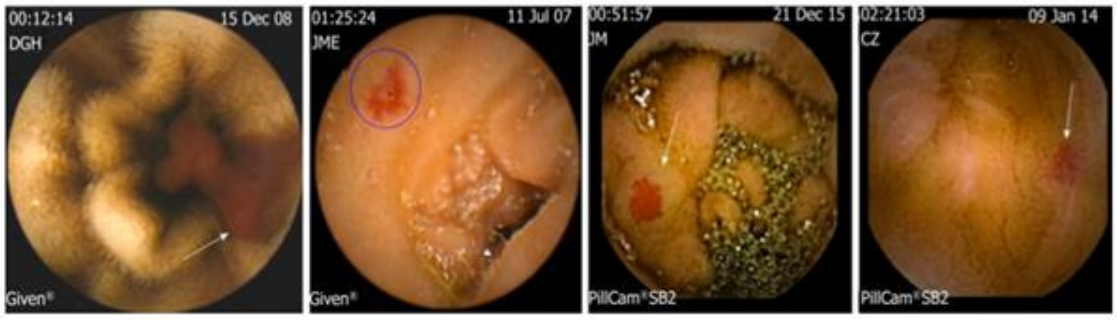


Figure 3. Endoscopic characteristics of angiodysplasias due to ECV

A: Patchy lesions with active non-pulsatile bleeding (Arrow)(Lesion type 1); B: Lesion without bleeding with central excavated ulcer (Circle)(Lesion Type 2); C: Bright red spots in patches (Arrow)(Lesion type 3); D: Pale red spots (arrow)(Lesion type 4). (García-Compeán D et al)(5).

Type	Endoscopic features	Causality with Bleeding	Clinical manifestations	Recurrence of bleeding
Type 1	Punctate or patchy lesions with active non-	Certainty	Obvious bleeding, high frequency of hemodynamic	Very high without hemostatic treatment

	pulsatile bleeding		instability	
Type 2	Lesion without active bleeding; stigmata of hemorrhage (ulcer, adhering clot, traces of digested blood)	High	Often overt bleeding; low frequency of hemodynamic instability compared to type 1 injuries	Highly probable
Type 3	Bright red spots in patches; typical images	Moderate - Low	Overt or occult bleeding; low or no frequency of hemodynamic instability; iron deficiency anemia (IDA)	Moderate rate, frequent ADH dependent on supplementation or blood transfusion
Type 4	Pale red spots	Low - null	Generally occult bleeding, chronic ADH, extra digestive causes of bleeding should be ruled out	When other causes of bleeding have been ruled out, re bleeding is low.

ADH: Anemia por déficit de hierro.

Treatment:

Aortic valve replacement

Taking into account the pathophysiological mechanisms of Heyde syndrome in which the trigger of the hemostatic defect that facilitates gastrointestinal angiogenesis and the presence of angiodysplasias is AS, the definitive treatment should be focused on the valve repair, either surgically or percutaneously. Observations from clinical trials documented the resolution of bleeding in patients undergoing SAVR, with rates of up to 93% in control of bleeding, although in this initial description, the mechanism by which the bleeding resolved was not yet clear (17). However, with the understanding of the pathophysiology and the development of current technology, it is thought that the vast majority of patients with Heyde syndrome who underwent correction of the AS improved bleeding episodes by resolving the defects in primary hemostasis. So unless the patient has a contraindication for valve intervention, this should be considered as the first treatment option (18). This clinical improvement is not equally clear when mitral valve interventions are performed, although there is some recovery in HMWM levels, there are no clinical changes in terms of bleeding manifestations according to some case reports (19). Clinical improvement is not only attributed to the resolution of the AVWS Type 2 but also to the disappearance of the gastrointestinal angiodysplasias (20). Figure 4 shows a pathophysiological proposal of the implications of aortic valve replacement on Heyde syndrome (3).

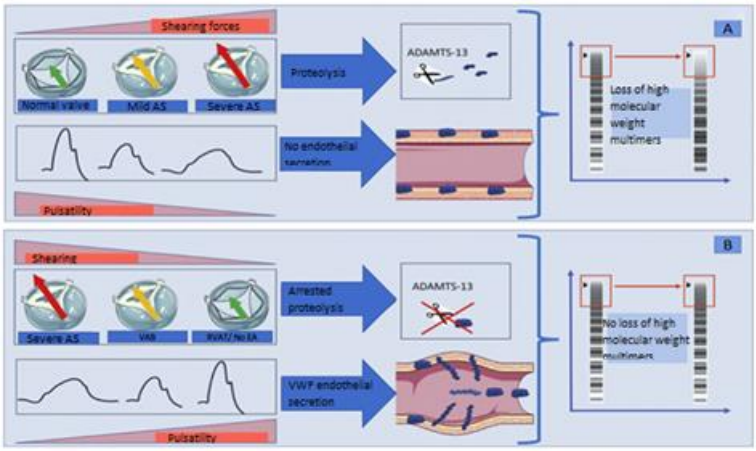


Figure 4. Proposed pathophysiological model for the dynamic changes in the VWF multimer profile during the course of aortic stenosis and its repair.

A: AD progression generating increased shear forces to blood flow with defects in VWF multimers generated by increased proteolysis secondary to decreased blood flow pulsatility. B: Recovery of VWF multimer concentrations after AD treatment and recovery of pulsatile flow (3).

AS: aortic stenosis; BAV: balloon aortic valvuloplasty; TAVR; Transcatheter aortic valve replacement, VWF: von Willebrand factor; ADAMS-13: Disintegrin and metalloprotease with a thrombospondin type 1 with repeat 13.

Endoscopic treatment

Although valve replacement is the definitive treatment for Heyde's disease, endoscopic management of acute bleeding or angiodysplasias with a high risk of bleeding is essential for the control of life-threatening hemorrhages or the management of chronic anemia. Different treatments have been proposed, however coagulation with argon plasma has become the main tool for the management of angiodysplasias. This method uses an electrical current applied through argon gas and directed by an endoscopic probe without direct contact with the vascular lesion with a high rate of effectiveness and low penetrance on the mucosa, which makes it a safe method and with less risk of perforation compared to direct contact techniques such as monopolar and bipolar electrocoagulation, as with laser photocoagulation. This technique is limited only to vascular lesions with endoscopic access (5, 21).

Selective Arterial Embolization

It is an invasive diagnostic method and treatment for angiodysplasias that can't be accessed endoscopically, most frequently used for cases of active bleeding with a minimum of 0.5 to 1.0 ml/min; biodegradable sponges and microcoils are generally embolized. It has a high rate of effectiveness in controlling bleeding, with a higher rate of complications compared to endoscopic treatment, reaching up to 5 to 9% of cases, and 2% for serious complications. The disadvantage is the need of iodinated contrast media, increasing the risk of nephropathy and that a highly specialized radiology team is required (22).

Pharmacological therapy

Patients with angiodysplasias generally have high rates of re-bleeding, despite receiving endoscopic or embolization treatment, for which some drugs have been shown to reduce re-bleeding and the need for transfusions in patients with chronic anemia. Amongst the most studied and with the best evidence are; somatostatin analogs such as Octreotide and Lanreotide, which reduce bleeding by several recognized mechanisms like their antiangiogenic effect, decreased splanchnic flow, increased vascular resistance and improved platelet aggregation, for which they are considered a prophylactic option with different administration schemes proposed, for patients with Heyde syndrome with refractoriness to endoscopic or radiological treatment and even in those who have already undergone valve replacement (23).

Thalidomide

It is a drug with a sedative and antiemetic effect, initially recognized for its high teratogenic effect. Its potential in the treatment of angiodysplasias has recently been described, given its direct effect in reducing the concentrations of vascular endothelial growth factor (VEGF), for which it is has been awarded an antiangiogenic potential. These effects have been verified in clinical studies that demonstrate its usefulness in the management of angiodysplasias, reducing bleeding rates and the need for transfusions in these patients when they receive a daily dose of at least 100 mg, however, its side effects are a limitation to recommend its widespread use, as well as the contradictory results of its effectiveness in more recent studies (24).

Hormone treatment

Previous studies suggested a possible beneficial effect of combined estrogen and progestogen hormone therapy in patients with gastrointestinal bleeding due to angiodysplasias, however current publications do not find differences in bleeding rates in patients undergoing hormone therapy that justify its use and due to the On the contrary, side effects are high, as demonstrated by a study carried out in 72 non-cirrhotic patients with SGI due to angiodysplasia, for which its routine use is currently discouraged (25).

Surgical Management

Surgical treatment of angiodysplasias is currently reserved as a salvage measure for patients who are refractory to endoscopic, embolization, or pharmacological management. Patients who receive surgical interventions for digestive bleeding are the minority due to the high effectiveness of other less invasive treatments. Despite using more conservative techniques, morbidity and mortality remain high and depend on the patient's comorbidity. For now, surgical interventions are reserved for when all other treatments have failed (26).

Potential Biomarkers

Angiopoetin 1 (Ang-1) and Angiopoetin 2 (Ang-2) are members of the vascular growth factor family and play a major role in embryonic and postnatal angiogenesis. Both are ligands for the Tie2 receptor which is expressed almost exclusively on endothelial cells. Ang-1 stabilizes endothelial cells, facilitating their maturation, preventing endothelial leaks, and suppressing the activation of proinflammatory genes; Ang-2 in the presence of VEGF increases the proliferation and migration of endothelial cells, it also involves the activation of TNF alpha that regulates the activity of metalloproteinases that degrade the extracellular matrix that surrounds the blood vessels, generating instability of the walls, passive dilation and risk of rupture. In the future Ang-2 could be used as a biomarker of angiogenesis and a potential therapeutic target. Its use as a biomarker of vascular disease is not currently recommended (27).

Final considerations

Gastrointestinal bleeding due to angiodysplasia is a common cause in patients with valvular aortic stenosis (Heyde syndrome) and should be suspected in patients with occult or evident bleeding. Despite the understanding of the pathophysiology of this entity and the proposal of different therapeutic targets, the current treatment options in addition to valve replacement or repair remain limited and additional studies are required to more firmly support their usefulness. At the moment, the molecular understanding of this disease and the technological capability of the quantification of von Willebrand factor multimers are of clinical importance in the postoperative follow-up of patients undergoing aortic valve replacement and of the treatments available for other entities related to the acquired von Willebrand syndrome.

Abbreviations:

Ang-1: Angiopoetin 1

Ang-2: Angiopoetin 2

LVAD: Left Ventricular Assist Device

AS: Aortic Stenosis

vWF: von Willebrand factor

HMWM of vWF: High molecular weight multimers of von Willebrand factor

MOEC: membrane extracorporeal oxygenation

SAVR: Surgical Aortic Valve Replacement

TAVR: Transcatheter aortic valve replacement

GIB: Gastrointestinal bleeding

AVWS Type 2a: Acquired von Willebrand Syndrome Type 2

CT: Computerized axial tomography

Tc-m99: Technetium 99

TNF: tumor necrosis factor

BAV: balloon aortic valvuloplasty

VCE: Video Capsule Endoscopy

References

1. Heyde, E. C. (1958). Gastrointestinal bleeding in aortic stenosis. *N Engl J Med*, *259*, 196.
2. Loscalzo, J. (2012). From clinical observation to mechanism—Heyde's syndrome. *New England Journal of Medicine*, *367*(20), 1954-1956.
3. Van Belle, E., Vincent, F., Rauch, A., Casari, C., Jeanpierre, E., Loobuyck, V. Paris, C. (2019). Von Willebrand factor and management of heart valve disease: JACC review topic of the week. *Journal of the American College of Cardiology*, *73*(9), 1078-1088.
4. Warkentin, T. E., Morgan, D. G., & Moore, J. C. (1992). Aortic stenosis and bleeding gastrointestinal angiodysplasia: Is acquired von Willebrand's disease the link? *The Lancet*, *340*(8810), 35-37.
5. References García-Compeán, D., Del Cueto-Aguilera, Á N., Jiménez-Rodríguez, A. R., González-González, J. A., & Maldonado-Garza, H. J. (2019). Diagnostic and therapeutic challenges of gastrointestinal angiodysplasias: A critical review and view points. *World Journal of Gastroenterology*, *25*(21), 2549.
6. Mehta, R., Athar, M., Girgis, S., Hassan, A., & Becker, R. C. (2019). Acquired von Willebrand syndrome (AVWS) in cardiovascular disease: A state of the art review for clinicians. *Journal of Thrombosis and Thrombolysis*, *48*(1), 14-26.
7. Makris, M. (2006). Gastrointestinal bleeding in von Willebrand disease. *Thrombosis Research*, *118*, S13-S17.
8. Randi, A. M., Laffan, M. A., & Starke, R. D. (2013). Von Willebrand factor, angiodysplasia and angiogenesis. *Mediterranean Journal of Hematology and Infectious Diseases*, *5*(1)
9. Randi, A. M., Smith, K. E., & Castaman, G. (2018). Von Willebrand factor regulation of blood vessel formation. *Blood*, *132*(2), 132-140.
10. Chapin, J. (2018). Von Willebrand disease in the elderly: Clinical perspectives. *Clinical Interventions in Aging*, *13*, 1531.
11. Cushing, K., & Kushnir, V. (2016). Gastrointestinal bleeding following LVAD placement from top to bottom. *Digestive Diseases and Sciences*, *61*(6), 1440-1447.
12. Guha, A., Eshelbrenner, C. L., Richards, D. M., & Monsour Jr, H. P. (2015). Gastrointestinal bleeding after continuous-flow left ventricular device implantation: Review of pathophysiology and management. *Methodist DeBakey Cardiovascular Journal*, *11*(1), 24.
13. Horiuchi, H., Doman, T., Kokame, K., Saiki, Y., & Matsumoto, M. (2019). Acquired von Willebrand syndrome associated with cardiovascular diseases. *Journal of Atherosclerosis and Thrombosis*, RV17031.
14. Pruthi, R. K. (2011). Hypertrophic obstructive cardiomyopathy, acquired von Willebrand syndrome, and gastrointestinal bleeding. Paper presented at the *Mayo Clinic Proceedings*, *86*(3) 181-182.
15. Hudzik, B., Wilczek, K., & Gasior, M. (2016). Heyde syndrome: Gastrointestinal bleeding and aortic stenosis. *Cmaj*, *188*(2), 135-138.
16. Gerson, L. B., Fidler, J. L., Cave, D. R., & Leighton, J. A. (2015). ACG clinical guideline: Diagnosis and management of small bowel bleeding. *Official Journal of the American College of Gastroenterology| ACG*, *110*(9), 1265-1287.
17. King, R. M., Pluth, J. R., & Giuliani, E. R. (1987). The association of unexplained gastrointestinal bleeding with calcific aortic stenosis. *The Annals of Thoracic Surgery*, *44*(5), 514-516.
18. Sedaghat, A., Kulka, H., Sinning, J., Falkenberg, N., Driesen, J., Preisler, B. Oldenburg, J. (2017). Transcatheter aortic valve implantation leads to a restoration of von Willebrand factor (VWF) abnormalities in patients with severe aortic stenosis–incidence and relevance of clinical and subclinical VWF dysfunction in patients undergoing

transfemoral TAVI. *Thrombosis Research*, *151*, 23-28.
19. Meindl, C., Paulus, M., Koller, T., Rogalski, D., Hamerle, M., Schach, C. Debl, K. (2021). Acquired von Willebrand syndrome and factor VIII in patients with moderate to severe mitral regurgitation undergoing transcatheter mitral valve repair. *Clinical Cardiology*, *44*(2), 261-266.
20. Tsuchiya, S., Matsumoto, Y., Doman, T., Fujiya, T., Sugisawa, J., Suda, A. Kikuchi, Y. (2020). Disappearance of angiodysplasia following transcatheter aortic valve implantation in a patient with heyde's syndrome: A case report and review of the literature. *Journal of Atherosclerosis and Thrombosis*, *27*(3), 271-277.
21. Olmos, J. A., Marcolongo, M., Pogorelsky, V., Varela, E., & Dávolos, J. R. (2004). Argon plasma coagulation for prevention of recurrent bleeding from GI angiodysplasias. *Gastrointestinal Endoscopy*, *60*(6), 881-886.
22. Othman, M. H., Radwan, M. E., Korany, M., Maghraby, H., & Abdel-Rahem, E. M. (2010). Gastrointestinal bleeding caused by angiodysplasia; one stop angiographic diagnosis and endovascular treatment by super selective embolization with polyvinyl alcohol particles. *The Egyptian Journal of Radiology and Nuclear Medicine*, *41*(4), 491-496.
23. Jackson, C. S., & Gerson, L. B. (2014). Management of gastrointestinal angiodysplastic lesions (GIADs): A systematic review and meta-analysis. *American Journal of Gastroenterology*, *109*(4), 474-483.
24. Kamalaporn, P., Saravanan, R., Cirocco, M., May, G., Kortan, P., Kandel, G., & Marcon, N. (2009). Thalidomide for the treatment of chronic gastrointestinal bleeding from angiodysplasias: A case series. *European Journal of Gastroenterology & Hepatology*, *21*(12), 1347-1350.
25. Junquera, F., Feu, F., Papo, M., Videla, S., Armengol, J. R., Bordas, J. M. Malagelada, J. (2001). A multicenter, randomized, clinical trial of hormonal therapy in the prevention of rebleeding from gastrointestinal angiodysplasia. *Gastroenterology*, *121*(5), 1073-1079.
26. Pfeifer, J. (2011). Surgical management of lower gastrointestinal bleeding. *European Journal of Trauma and Emergency Surgery*, *37*(4), 365-372.
27. Chetcuti Zammit, S., Koulaouzidis, A., Sanders, D. S., McAlindon, M. E., Rondonotti, E., Yung, D. E., & Sidhu, R. (2018). Overview of small bowel angioectasias: Clinical presentation and treatment options. *Expert Review of Gastroenterology & Hepatology*, *12*(2), 125-139.

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