Chapter 14
Patients with Native Cardiovascular Disease and Implantable Cardiac Devices

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Introduction

The association between cardiovascular disease and gastrointestinal bleeding has been well described. Gastrointestinal bleeding can occur with most cardiovascular conditions, including aortic stenosis, aortic regurgitation, mitral valve stenosis, mitral valve regurgitation, and hypertrophic cardiomyopathy. The most well reported association is between gastrointestinal bleeding and aortic stenosis, a condition called Heyde's syndrome. Like other forms of gastrointestinal bleeding, management of bleeding with cardiovascular disease centers around initial resuscitation, source identification, and subsequent hemostasis. More specific to bleeding associated with cardiovascular disease, management must also take into consideration the presence of pre-existing coagulopathies. In addition to the fact that most cardiac patients are on aspirin or other anti-platelet or anti-coagulant agents, most cardiac patients also suffer from an acquired bleeding disorder mediated by the loss of von Willebrand factor (VWF) multimers, a condition called acquired von Willebrand syndrome (AVWS). Overall, gastrointestinal bleeding associated with cardiovascular disease tends to be recurrent and resistant to endoscopic treatment alone, necessitating more aggressive pharmacologic and surgical interventions for sustained control.

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Aortic Stenosis

The association between calcific aortic stenosis and gastrointestinal bleeding was first described by Dr. Edward Heyde in 1958 [1]. His observations prompted further reports of similar patients with both aortic stenosis and idiopathic gastrointestinal bleeding [2–4]. The culprit lesion in these patients remained unidentified until advancements in imaging and histopathology came to recognize it as the small, tufted, red lesion known now as the angioectasia [5, 6]. The constellation of findings comprising aortic stenosis and gastrointestinal bleeding from angioectasias has since come to be called Heyde's syndrome after its eponymous first describer.

The diagnosis of Heyde's syndrome has been controversial since its first description in 1958. Initial reports based the diagnosis of aortic stenosis on less objective criteria such as auscultation and other exam findings, and critics have raised concerns about methodological deficiencies in these studies [7, 8]. The overall reported prevalence rates of aortic stenosis in patients with angioectasias range from 0% to 41% [9]. However, more recent studies using echocardiographic confirmation of aortic stenosis have suggested prevalence rates in the range of 0–1.6% [10, 11]. In patients with pre-existing aortic stenosis, the rates of gastrointestinal bleeding range from 2% to 20% [12]. Despite these criticisms, the diagnosis of Heyde's syndrome has remained durable, in part because of the elucidation of an explanatory mechanism and demonstrated treatment strategies.

Pathogenesis

Multiple mechanisms have been proposed to explain the gastrointestinal bleeding seen in patients with aortic stenosis and angioectasias. Initial proposals included the presence of a common connective tissue disorder, mucosal ischemia from low cardiac output, mucosal damage from cholesterol emboli, and mucosal damage and vasodilatation from decreased tissue perfusion [13]. The true mechanism appears to be multifactorial, resulting from a combination of increased angioectasia formation and an acquired predisposition to bleeding from the loss of hemostatic von Willebrand factor multimers.

The formation of angioectasias is believed to result from poor perfusion and chronic obstruction of submucosal veins. In patients with cardiac, vascular, or pulmonary disease, decreased perfusion to local gastrointestinal tissue leads to hypooxygenation. In response, gastrointestinal smooth muscle contracts in an attempt to compensate, causing an obstruction where the innervating vessels interface. This obstruction then leads to increased intravascular pressure and subsequent dilatation of the veins, venules, and capillaries. The vessels and capillaries become tortuous and form an arteriovenous communication, or angioectasia. There terms angiodysplasia and arteriovenous malformation (AVM) are often used synonymously with

angioectasia. Further ischemia or mechanical trauma to these lesions can then lead to gastrointestinal bleeding [5, 6].

Patients with aortic stenosis are also at increased risk of bleeding from an acquired bleeding disorder. Upwards of 80% of patients with severe aortic stenosis have been demonstrated to have loss of the high molecular weight variant of von Willebrand factor, a protein implicated in both hemostasis and angiogenesis [14]. High molecular weight multimers of VWF are created in the organelles of endothelial cells and platelets, before being secreted into plasma in order to contribute to hemostasis. HMW multimers are of particular importance in areas of turbulent blood flow, such as AVMs, which require the high molecular weight multimers for appropriate hemostasis [15, 16]. Once secreted into the plasma, multimers of von Willebrand factor undergo proteolysis at the hands of the enzyme ADAMTS13. In patients with aortic stenosis, the high shear stress imparted upon von Willebrand factor as it traverses the stenotic valve leads to conformational changes in the protein and exposure of additional binding sites. These previously protected binding sites are targeted and cleaved by ADAMTS13, resulting in accelerated degradation of the von Willebrand factor multimers. The end result is an increase in the destruction of high molecular weight multimers of von Willebrand factor and an acquired coagulopathy called acquired von Willebrand syndrome 2A (AVWS-2A).

Together, the combination of increased angioectasia formation and an acquired bleeding disorder from loss of hemostatic high molecular weight VWF multimers is thought to explain the increased risk of gastrointestinal bleeding seen in patients with Heyde's syndrome [15–18].

Diagnosis

Gastrointestinal bleeding in Heyde's syndromes can manifest as overt bleeding with melena or hematochezia or obscure bleeding with anemia or guaiac positive stools. The characteristic bleeding lesion in Heyde's syndrome is the angioectasia. Most patients will present with multiple angioectasias, with a few patients having more than 10 on initial evaluation. The most common location of bleeding lesions is in the jejunum, comprising up to 36% of all cases. The next most common locations are the duodenum and ileum, respectively [19].

The characteristic lab abnormality in Heyde's syndrome is the loss of HMW VWF. However, standard lab testing for the presence of von Willebrand disease is often normal, as the defect is specific to the HMW multimers. If available, a point-of-care platelet function analyzer can detect the presence of the bleeding disorder, although this is not specific for AVWS-2A [12, 14].

Standard guidelines should be followed in the approach to the patient with gastrointestinal bleeding [20]. Following resuscitation, endoscopy is the standard of care for its diagnostic and therapeutic capabilities. The initial endoscopic evaluation comprises upper endoscopy and colonoscopy. If the initial exam does not identify a

source of bleeding, second look endoscopy can be considered depending on the clinical presentation. Given the high rate of small bowel lesions, second look examination with push enteroscopy might have the added benefit of improved diagnostic yield. In cases of obscure bleeding, VCE is a first-line procedure for evaluation of the small bowel, followed by deep enteroscopy and, in rare cases, intra-operative enteroscopy, if needed [20].

The identification of angioectasias on endoscopy can be difficult. Lesions can often be missed or misidentified as endoscope trauma, tube trauma, artifact, or gastritis. Furthermore, the vascular nature of angioectasias means that alterations in blood flow, such as from intra-procedural narcotics or anesthesia, can influence their size and visibility. The use of naloxone has been suggested as a tool to enhance the appearance of angioectasias and improve detection during endoscopic evaluation [21].

Treatment and Prevention

Treatment of gastrointestinal bleeding associated with cardiac valvular disease can be challenging. The difficulties arise, in part, from the multifocal and recurrent nature of bleeding in these patients. Most patients with angioectasias will have multiple lesions across multiple sites. Over 60% of patients will have multiple upper gastrointestinal lesions, and in up to 50% of patients with an upper gastrointestinal tract lesion, there will be a concurrent colonic lesion as well [22].

In the acute setting, undifferentiated bleeding should be approached according to established societal guidelines, with attention paid first to patient resuscitation and stabilization [20, 23]. Medication lists should be reviewed for blood thinning agents and stopped if it is safe to do so. Coagulopathies should be reversed if present. In general, AVWS-2A does not respond to desmopressin or transfusion of clotting factors. However, it is reasonable to administer at least a test dose of desmopressin to identify the rare patient who will respond [24]. Proton pump inhibitors, while of questionable effectiveness, are still commonly administered.

Endoscopic intervention is both safe and effective in Heyde's syndrome. The most commonly used endoscopic intervention is APC [19]. Thermal cauterization has also been demonstrated to be safe and effective, and in studies has been demonstrated to reduce the number of blood transfusions needed in treated patients [25]. Close to half of patients will require eventual additional endoscopic procedures for full control, with an average number of procedures of 1.94 per patient [25]. Surgical resection, while the historic treatment of choice, is no longer considered first-line and has not been demonstrated to be superior to endoscopic therapy alone [26].

Following initial hemostasis, prevention must then be considered. The rate of rebleeding in Heyde's syndrome is high, with rebleeding occurring in up to 33–50% of patients, often from other lesions in the gastrointestinal tract [27]. Iron supplementation is popular, and in patients who suffer from iron-deficiency anemia despite

oral supplementation, intravenous infusions should be administered [19, 27]. Other pharmacologic treatments to prevent recurrent bleeding in Heyde's syndrome include octreotide, thalidomide, and hormones. Octreotide does not cure the culprit lesion, but has been shown to reduce bleeding and the need for blood transfusions [28]. Octreotide also benefits from being well tolerated. Hormone treatment, on the other hand, has not been shown to be effective. In 1 RCT of 72 patients randomized to ethinylestradiol and norethisterone or placebo, there was no difference in the number of bleeding episodes or number of transfusions [29]. Furthermore, adverse events were significantly higher in the treatment group, with the most common adverse event being metrorrhagia, affecting 29% of patients. Other worrisome complications of hormone therapy include pulmonary embolism and stroke. Thalidomide has gained interest because of its anti-neoangiogenesis properties through the inhibition of VEGF. It has been demonstrated to reduce bleeding episodes, hospital admissions, hospital readmissions, hospital admission duration, and number of blood transfusions in patients with refractory bleeding. However, its use has been limited by its high rate of adverse events, which approach 72% and include fatigue, dizziness, and abdominal discomfort [30]. More rare but serious side effects include thrombosis, peripheral neuropathy, and childbirth defects. Despite its reported efficacy in international studies, thalidomide has not been widely adopted in part because of these side effects.

The most durable treatment for gastrointestinal bleeding in Heyde's syndrome is aortic valve replacement (AVR). AVR offers the best chance for long-term resolution of bleeding and should be offered to patients who are surgical candidates [31]. The overall success rate of AVR in stopping further bleeding is 93% [32]. AVR has been demonstrated to not just resolve further bleeding, but also increase VWF multimers and in doing so correct the underlying coagulopathy [33, 34]. Vincentelli and colleagues, for example, reported that in 92% of patients with Heyde's syndrome and AVWS-2A who underwent AVR, *all* had their VWF abnormalities corrected on the first post-operative morning [15]. The reduction in bleeding episodes post-AVR appears durable up to at least 12 months out post-operatively [35].

Both surgical and transcatheter aortic valve replacement have demonstrated benefit in resolving bleeding and returning HMW VWF to normal levels. However, when possible, use of a bioprosthetic valve has still been advocated for in order to minimize the need for oral anticoagulation post-operatively [35–37].

Aortic and Mitral Regurgitation

There is more limited data on the association between regurgitant valvular disease and gastrointestinal bleeding. There are case series reporting the loss of VWF multimers and AVWS in patients with aortic regurgitation from various causes [12]. The overall prevalence of gastrointestinal bleeding in severe aortic regurgitation without co-existing aortic stenosis is 9% [38]. The degree of bleeding disorder, as determined by abnormal VWF, appears to be less than that seen in aortic stenosis.

The association between mitral regurgitation and gastrointestinal bleeding has been better described. Several case series have described the constellation of mitral regurgitation, bleeding, loss of HMW VWF multimers, and AVWS which corrected after surgical repair of the mitral valve [12]. The presence of AVWS in patients with MR increases with more severe valve disease, reaching up to 85% in patients with severe MR. In patients with mild and moderate MR, the presence of AVWS is 8% and 64%, respectively. The rate of gastrointestinal bleeding in patients with MR is 17%, of which 89% of cases have severe MR [12, 39].

Hypertrophic Cardiomyopathy

Gastrointestinal bleeding has been well described in patients with HCM. Despite a structurally normal valve, subvalvular obstruction creates an environment of turbulent blood flow in the outflow tract that resembles that seen with aortic stenosis and Heyde's syndrome. Abnormal VWF multimers and Heyde's syndrome-like bleeding have both been reported [12]. The degree of abnormality is related to the severity of outflow obstruction, and can be corrected with septal reduction therapy, as with septal myectomy or ablation [12, 14, 27].

Summary

Gastrointestinal bleeding has been well associated with cardiovascular disease. While the most well-known association is with aortic stenosis, it also occurs with other valvular diseases including aortic regurgitation, mitral regurgitation, and HCM. The pathogenesis in each case is centered on an acquired bleeding disorder resulting from the loss of HMW multimers of VWF as blood courses past the abnormal valve. Clinical presentation varies, and an ultimate diagnosis can be difficult, but evaluation should proceed according to standard guidelines with the exception of consideration of early small bowel investigation. Once identified, gastrointestinal bleeding is often remedied with correction of the underlying valvular problem. In patients who are not surgical candidates, various pharmacologic options have been studied with iron-supplementation and octreotide being among the best tolerated.

Implantable Cardiac Devices

The evolution of cardiac assist devices has introduced new problems for the practicing gastroenterologist, including complications related to a range of prosthetic devices, spanning from simple prosthetic and mechanical cardiac replacement valves to entire implantable pumps such as the Impella or intra-aortic balloon pump.

These devices have all been associated with significant rates of gastrointestinal bleeding. In recent times, the introduction of the left ventricular assist device, or LVAD, has seen even higher post-operative rates of gastrointestinal bleeding. Given the expansion of cardiac assist devices in clinical care, it is important for the gastroenterologist to be comfortable and capable in the management of bleeding in patients with these devices.

Left Ventricular Assist Devices (LVADs)

LVADs are surgically implanted mechanical pumps that provide circulatory support to patients with end stage heart failure. Initial iterations of the LVAD used a pulsatile flow mechanism that mimicked natural cardiac physiology. More recent iterations have evolved to use a non-pulsatile flow or continuous flow mechanism. Compared to their predecessors, the continuous flow devices are smaller, easier to implement, and more durable, leading to their widespread adoption [40]. LVADs have demonstrated improved quality of life and increased survival in patients with end stage heart failure, leading to a proliferation in their use over the past decade [41]. LVADs can be used now as both a bridge to transplantation or as a destination treatment in patients who are not transplant candidates but desire life-prolonging treatment.

One of the most common complications following LVAD implantation is gastrointestinal bleeding. The incidence of gastrointestinal bleeding in the newer continuous flow LVADs is ten times that of their older pulsatile flow counterparts [40]. Additional risk factors for gastrointestinal bleeding include patient age, an elevated creatinine, an elevated INR, a low platelet count, right ventricular dysfunction, and a post-LVAD ejection fraction >30% [40, 42–44]. The incidence of gastrointestinal bleeding is estimated between 20% and 61% [43–46]. Most bleeding occurs late after implantation at an average onset of 159 days after implantation [47]. Recurrent bleeding is common with estimates ranging from 9% to 43% and as high as 71% [40, 43, 44].

Pathogenesis

The mechanism behind bleeding in patients with LVADs is multifactorial, involving anticoagulant use, alterations in hemodynamics, and loss of von Willebrand factor multimers [40]. Most patients following LVAD implantation will be placed on anticoagulation. However, the rates of bleeding seen following LVAD implantation exceed those expected with anticoagulation alone by more than fourfold [48].

Implantation with continuous flow LVADs also disrupts normal cardiovascular hemodynamics through loss of the physiologic pulsatile flow [40]. Instead, LVADs result in an environment similar to that seen in aortic stenosis, with a narrow pulse

pressure, reduced aortic valve opening, and high shear stress. Similar to aortic stenosis, there is loss of high molecular weight multimers of VWF associated with LVADs from increased shear forces and subsequent multimer degradation. This same loss of VWF multimers is not seen in patients following heart transplantation. The loss of VWF multimers contributes to an acquired bleeding disorder and an increased predisposition to bleeding [49, 50]. LVAD implantation has also been associated with impaired platelet aggregation [51].

Diagnosis

The most common presentation of gastrointestinal bleeding in patients with LVADs is overt upper gastrointestinal bleeding. Half of patients will present with melena and another 7% of patients will present with hematemesis. Lower gastrointestinal bleeding with hematochezia is relatively rare and occurs in 13% of cases. Most patients present from the outpatient setting as hemodynamic instability is uncommon [47].

The diagnostic approach to gastrointestinal bleeding in patients with LVADs is similar to the approach in the general population. Following resuscitation, endoscopic evaluation is the standard of care [40]. Endoscopy will identify the bleeding lesion in 60–90% of cases [52, 53]. EGD is the best first test with a diagnostic yield approaching 50%. If no bleeding lesion is found, colonoscopy should then be pursued, followed with deep enteroscopy. One alternative to this conventional approach to endoscopy favors early enteroscopy. Early small bowel evaluation with device-assisted enteroscopy has been associated with decreased number of transfusions, decreased number of days to treatment, and decreased number of diagnostic tests [54]. Initial evaluation with push enteroscopy might be an effective compromise and has been advocated for by some practitioners [40]. Colonoscopies, on the other hand, are likely overused [52]. Multiple procedures are often required before a definitive diagnosis is reached, and the average patient will undergo 3.3 procedures during the course of his investigation [52].

If small bowel evaluation is pursued, video capsule endoscopy is an important adjunct to device-assisted enteroscopy. VCE allows the endoscopist to localize the site of bleeding, plan his approach, and provide targeted treatment. VCE has been demonstrated to be both safe and effective in patients with LVADs. In patients with obscure gastrointestinal bleeding, the diagnostic yield of VCE ranges up to 80–100%. The most common finding is intraluminal blood and the most common location is the jejunum [55, 56]. While there have been concerns related to LVAD interference with capsule image acquisition, this can be minimized by positioning the device leads as far away as possible from the capsule recorder. In over 100 studies of VCE in patients with implantable electromedical devices, including pacemakers, ICDs, and LVADs, VCE did not result in disturbance of the cardiac devices function [57].

Treatment and Prevention

Standard guidelines for the management of gastrointestinal bleeding should be followed in the initial approach to bleeding in patients with LVADs. The initial approach includes establishing appropriate peripheral access, adequate resuscitation with intravenous fluids and packed red blood cell transfusion, acid suppression in cases of suspected upper gastrointestinal bleeding, and ongoing hemodynamic monitoring. Reversal agents, such as phytonadione, FFP, and concentrated VWF can be used but must be done so with caution and in consideration of the risk of pump thrombosis. It can be prudent to consult with a Cardiologist before reversal if safety is in question.

Once the patient has been well resuscitated, endoscopy is the initial treatment of choice. The most common bleeding lesion in LVAD-associated bleeding is the peptic ulcer, being identified in over 30% of cases. Behind peptic ulcers, vascular malformations (27%), colitis (7%), and polyps (5%) are the next most commonly identified lesions [47]. Endoscopic intervention of high-risk lesions results in successful hemostasis in 90% or more of cases [52, 53]. Multiple modalities have demonstrated success in LVAD-associated bleeding including argon plasma coagulation, contact coagulation, and mechanical clips, with no one technique demonstrating superiority over the others. Both moderate and deep sedation have been demonstrated to be safe in the setting of endoscopy [40].

Rebleeding is frequent and can occur in up to half of cases but often remains amenable to endoscopic intervention [53]. The median time to rebleeding is 7 days and half of patients will bleed from a separate site than the initial target of hemostasis. In cases of refractory bleeding, lowering the speed of the LVAD to increase pulsatility might help to reduce bleeding. However, concerns related to the risk of thrombosis has limited its widespread adoption outside of certain centers [58]. Endovascular embolization remains another treatment option for bleeding resistant to endoscopic intervention [59].

Once initial endoscopic hemostasis has been achieved, attention is turned to the prevention of recurrent bleeding. Pharmacologic treatments are similar to those used for the prevention of angioectasia-related bleeding, and include octreotide, thalidomide, and danazol. Octreotide alone has not been demonstrated to reduce the rate of recurrent bleeding, the need for blood transfusions, or the need for further endoscopic procedures outside of small case reports [60, 61]. However, there was a favorable trend in the direction of these reductions. Thalidomide has been used in case reports in the treatment of refractory gastrointestinal bleeding. However, its use is limited by severe adverse events and regulations surrounding its prescription [62]. There has been one successful case report describing the use of danazol in the prevention of gastrointestinal bleeding [63]. Omega-3 acids have been demonstrated to increase days free from gastrointestinal bleeding in limited reports [64].

The decision of what to do with anticoagulation is difficult and without uniform guidance. Management of anticoagulation must include consideration of both the risks of gastrointestinal bleeding and the risks of pump thrombosis. Some centers have moved to lower international ratio targets in patients with LVADs and experimented with a target of 1.8–2.2 down from 2 to 3. Further studies with longer follow up are needed before the lower target range can be universally recommended [65].

The most durable treatment is cardiac transplant. Similar to sclerotic aortic valvular disease, the gastrointestinal bleeding seen in association with LVADs resolves with correction of the underlying flow problem. Cardiac transplant and removal of the device has been shown to prevent further episodes of bleeding [40].

Aortic Valve Prothesis

The lifetime of an aortic valve prosthesis is between 7 and 20 years. Prosthetic failure can occur as a result of thrombosis, calcification and obstruction, leaflet tear, and paravalvular leakage [12, 14]. Failure of the prosthetic valve leads to recurrent aortic stenosis or regurgitation and resumption of the previous pathophysiology. Overall, gastrointestinal complications comprise close to 40% of bleeding complications in patients who undergo transcatheter aortic valve replacement. The rate of late major bleeding seen after transcatheter aortic valve replacement is 5.9% and occurs at a median time of 132 days [67]. The presence of a moderate or severe paravalvular leak is an independent predictor of bleeding complications. Other risk factors include baseline anemia, atrial fibrillation or flutter, and greater left ventricular mass. Compared to normal valves, abnormal valves have higher rates of abnormal VWF multimers. The abnormal VWF multimers correct in patients with minimal to no paravalvular regurgitation compared to those with moderate to severe regurgitation, and intraprocedure measurement of abnormal VWF multimers using PFA have been used to predict later valve dysfunction.

Mitral Valve Prosthesis

Mitral valve protheses are associated with gastrointestinal bleeding in cases with abnormal valve function. For example, both gastrointestinal bleeding and abnormal VWF multimers have been described with mitral paravalvular leak [12, 14]. Compared to normal valves after replacement or repair, dysfunctional valves are associated with abnormal VWF and have an incidence of gastrointestinal bleeding of 26%. In most cases, the bleeding originates from an angioectasia [12, 14]. Both gastrointestinal bleeding and abnormal VWF multimers correct after surgical repair of the abnormal valve.

Other Cardiac Assist Devices

Other implantable cardiac devices associated with increased rates of gastrointestinal bleeding include the Impella and intra-aortic balloon pump. The rates of gastrointestinal bleeding in these devices can reach upwards of 31% and is driven by a similar shear-stress acquired bleeding disorder [66].

Summary

Gastrointestinal bleeding is a common complication associated with implantable cardiac devices. The LVAD, in particular, has been associated with bleeding in over half of cases, and gastrointestinal bleeding is also seen with protheses and other ICDs. Like with native cardiovascular disease, the pathogenesis is centered around an acquired bleeding disorder resulting from destruction of HMW multimers of VWF that degrade from shear stress as blood courses past the foreign device. Clinical presentation varies, and resuscitation and investigation is similar to other sources of gastrointestinal bleeding with the exception of consideration of early small bowel investigation. In patients with a correctable problem – such as a paravalvular leak – correction can result in hemostasis. In patients with an LVAD who are transplant candidates, heart transplantation is among the most durable treatment option. In other patients who are not operative candidates, recurrent bleeding is common, and prevention is multifactorial including device settings, anticoagulation adjustment, and various pharmacologic agents.

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