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Review Article

Increased bleeding risk in patients with aortic valvular stenosis: From new mechanisms to new therapies

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ABSTRACT

Aortic stenosis (AS), the most prevalent acquired valvular disease in the adults that requires invasive treatment, coexists with coagulopathy, resulting in bleeding in approximately 20% of patients. In the current review, we summarize the available knowledge on the mechanisms underlying the bleeding tendency observed in AS, and discuss potential compensatory mechanisms preventing most patients with severe AS from experiencing bleeding. We offer an update on Heyde's syndrome and other types of bleeding, and study extensively their pathobiology, providing insights into the new emerging concepts on coagulation regulation in AS. The focus is given to the impact of valvular interventions on coagulation abnormalities in AS. Both surgical valve replacement and transcatheter aortic valve implantation are discussed. Finally, we discuss current treatment recommendations in AS related bleeding.

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Contents

1. Introduction

Aortic stenosis (AS) is the most common acquired valvular disease in adults that requires invasive treatment. In the United States alone almost 100,000 patients undergo surgical aortic valve replacement (SAVR) yearly, and the population requiring transcatheter valvular interventions is growing steadily. The prevalence of AS increases with age, and is 1.3% in subjects aged from 65 to 75 years, 2.4% in subjects from 75 to 85 years, and 4% in subjects > 85 years [1]. AS has repeatedly been reported to be associated with coagulation impairment related with bleeding tendency (bleeding occurs approximately in 20% of AS patients [2]). Most commonly, mucous nasopharyngeal and cutaneous bleeds can be observed (Fig. 1). The incidence of 1–3% has been reported for gastrointestinal (GI) bleeding, the potentially most dangerous clinical scenario in severe AS [3]. In this review we discuss the clinical manifestations of AS-related bleeding tendency and propose the molecular mechanisms that could underlie these pathologies. We also discuss the current concepts on potential compensatory mechanisms present in AS patients, in order to elucidate why most of them never experience bleeding episodes.

2. Heyde's syndrome

In 1958, Edward C. Heyde described for the first time a series of 10 cases in which calcific AS coexisted with GI bleeding [4]. Most common

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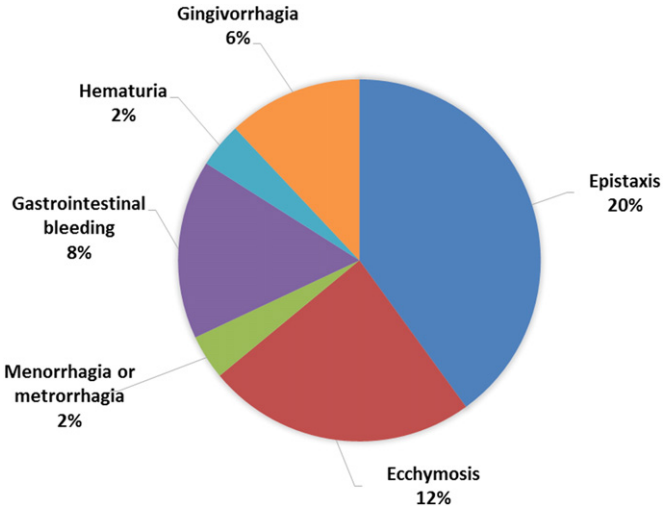

Fig. 1. Bleeding disorders in individuals with aortic stenosis who reported a spontaneous bleeding by Vincentelli et al. [2].

sites of GI bleeds were identified as angiodysplasia and the coexistence of AS and GI bleeding was termed the Heyde's syndrome (HS) [5]. The term angiodysplasia describes the most common, sporadic, acquired vascular abnormality found in the GI tract. Angiodysplastic vessels (thin, tortuous, with no internal elastic layer) may occur anywhere in the GI tract, but the most common locations are the right colon, caecum, and jejunum [6]. Although the prevalence of GI angiodysplasia in the general population is not well known, its incidence clearly rises with age. AS is an age-related lesion too, with increased prevalence in the elderly similarly to GI angiodysplasia [7]. Furthermore, compared to the normal aortic valve, jet-like flow and perturbed flow patterns are observed in patients with AS, resulting in increased shear stress [8]. Angiodysplasia, associated with progressive venular dilatation and concomitant incompetence of precapillary sphincters, results in arteriovenous malformation. The high rate of blood flow through these malformations can arguably result in shear rates higher than would usually be found in normal vessels [7].

The link between AS and GI bleeding in HS was questioned by several relatively small studies which found no relationship between angiodysplasia-related GI bleeding and AS. Nevertheless, compelling evidence supporting the HS existence derives from the complete resolution of GI bleeding commonly reported after SAVR. Recently, Thompson et al. reported 57 patients with HS treated with SAVR, of whom 79% were completely free from GI bleeding during median follow-up of 4.4 years, and in the remaining subjects the risk of this complication was reduced by half [6].

The present knowledge indicates that the common morphologic denominator of HS-underlying conditions is concurrent aortic valve and GI mucosa senile degeneration. Interestingly, however, although SAVR resolves GI bleeding, it does not cause regression of angiodysplasia, which remains visible during endoscopy after surgery [9]. This led to a conclusion that the molecular mechanism leading to bleeding must be AS related.

3. von Willebrand factor and AS

In 1992 Warkentin et al. discovered acquired type 2A von Willebrand syndrome accompanying AS, characterized by an acquired qualitative defect of VWF associated with the loss of VWF high molecular weight multimers (HMWM) [7]. The loss of HMWM was proposed as a missing link and the major mechanism in the pathogenesis of GI bleeding in AS.

VWF is a multimeric glycoprotein essential for normal hemostasis that is found in blood plasma, platelet α-granules and subendothelial connective tissue. The half-life of VWF in circulation is 12–20 h and its plasma level ranges between 50 and 200 IU/dL in the general population [10]. Several other factors, besides blood type, also influence the VWF levels, including single-nucleotide polymorphisms in the VWF gene, age, thyroid status and stress. VWF is produced as a polypeptide and assembled from identical monomers into multimers that may range in size from 500 kDa to >20,000 kDa. This HMWM are hyperactive in recruiting circulating platelets to the site of endothelial activation or injury. Once VWF is immobilized in subendothelial connective tissue, platelets recognize and adhere to it by interaction with platelet glycoprotein GpIb-IX-V complex, followed by platelets aggregation initiated by activated GpIIb-IIIa complex.

Under normal conditions the VWF HMWM released into solution rapidly assume a "closed" conformation that is highly resistant to proteolysis by a specific metalloprotease ADAMTS13 (ADAMTS13; A, Disintegrin And Metalloproteinase with ThromboSpondin) in the absence of shear stress. This protein is probably constitutively secreted from cells as an active protease, and its amount is about 100-fold lower than that of VWF (100 ng/mL) produced *in vitro* under the same conditions [11]. Since there has been no inhibitor to ADAMTS13, it seems that ADAMTS13 function must be regulated at the substrate level.

Under high shear stress the conformational structure of the VWF can be altered and regain its sensitivity to ADAMTS13, by exposure of the bond between Tyr842 and Met843, [12]. On one hand, ADAMTS13 released from endothelial cells may cleave newly formed HMWM on the cell surface, providing an additional mechanism to maintain a VWF-free surface [11]. On the other, under high fluid shear stress ADAMTS13 drives increased VWF proteolysis, leads to reduction of the plasma VWF activity to antigen ratio, and increases the risk of bleeding [13]. Such high shear conditions can be found in AS, where blood components pass the stenotic aortic orifice at greater than normal velocity. In patients with severe AS, ADAMTS13 activity was reported to decrease significantly after SAVR (generally, normal ranges for both ADAMTS13 antigen and activity are 50–150 IU/dL, however they depend on the method used and there is no international standardization), but not after balloon valvuloplasty [14]. This suggests that ADAMTS13 contributes to coagulation abnormalities in AS on one hand, and that ADAMTS13 decrease after the surgery is one of the mechanisms contributing to hematologic benefit of SAVR in severe AS. We previously reported that ADAMTS13 antigen, along with VWF ristocetin cofactor activity, predicted occurrence of elevated postoperative drainage in cardiosurgical patients [15]. However, in patients undergoing SAVR for severe AS there is no evidence on the influence of VWF multimers structure and platelet function on postoperative chest tube output volumes [16]. This might potentially be attributed to rapid recovery of VWF in the perioperative period after valve replacement.

Also, clinically relevant bleeds reported by AS patients appear to be less common in clinical practice than would be expected. This may suggest the existence of mechanisms promoting efficient hemostasis despite the decreased levels of HMWM. These mechanisms might compensate, at least to some extent, VWF deficiency, and their identification may explain why majority of AS patients do not experience bleeding episodes (on one hand not all AS patients present decreased HMWM – this abnormality is observed in about 80% of the severe AS patients [2,16], on the other hand not all AS patients with decreased HMWM bleed).

In addition to its effects on VWF, it is also known that shear stress induces tissue factor procoagulant activity [17], resulting in enhanced thrombin generation [18]. Another aspect of high shear stress conditions in AS is microparticles generation, likewise contributing to increased thrombin generation [19]. Moreover, the enhanced thrombin generation reported both in circulating blood [18] and within valve [20], as well as simultaneous increased platelet activation [18] might in part counterbalance the primary hemostasis impairment and in turn lead to faster formation of fibrin clots, additionally more resistant to lysis, as proved by prolonged clot lysis time [21]. Higher

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