Persistent Anemia in Otherwise Asymptomatic Severe Aortic Stenosis: A Possible Indication for Valve Replacement?

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Abstract

Background: The indication for aortic valve replacement in patients with significant aortic stenosis is symptomatology. Aortic stenosis may be associated with bleeding from colonic angiodysplasia, resulting in anemia. Persistent anemia in such patients, despite lack of an identifiable source of bleeding, is not considered an indication for valve replacement.

Objectives: To report our experience with two elderly female patients who suffered from severe asymptomatic aortic stenosis, low levels of large von Willebrand factor multimer (10% and 5% respectively) and persistent anemia requiring multiple blood transfusions.

Methods: Both patients underwent an intensive work-up, but a source of bleeding could not be identified. Aortic valve replacement was performed in both patients.

Results: Aortic valve replacement abolished the need for further blood transfusions during a follow-up period of 20 months with normalization of the vWF multimer level (20% and 30% respectively).

Conclusion: We suggest that aortic valve replacement be considered in selected patients with severe, otherwise asymptomatic aortic stenosis, who suffer from persistent anemia requiring multiple blood transfusions, lack an identifiable source of bleeding and have low levels of large vWF multimers.

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Calcific aortic stenosis is the most common cause of aortic valve replacement in patients with aortic stenosis. Aortic valve replacement is indicated for symptomatic patients with aortic stenosis who present with angina, syncope or heart failure or those with at least moderate aortic stenosis who need to undergo other cardiac surgery, regardless of symptoms. There is strong evidence in favor of AVR in asymptomatic patients with severe aortic stenosis who demonstrate left ventricular dysfunction or hypotensive response to exercise, but less established evidence for AVR in asymptomatic patients with severe aortic stenosis who manifest complex ventricular arrhythmias, excessive hypertrophy or a small valve area (< 0.6 cm^2) [1].

Aortic stenosis has been associated with bleeding episodes from colonic angiodysplasia [2]. Although some reports showed that AVR, rather then colectomy, corrects the bleeding from angiodysplasia [3,4], anemia and gastrointestinal bleeding are not considered an indication for AVR in such patients [1]. Anemia in these patients is accompanied by reduction in the size of the von Willebrand multimers. A recent report demonstrated that AVR may correct the underlying hematologic abnormality [5]. AVR led to an improvement in the levels of large multimers of vWF (with concomitant correction of platelet function). However, follow-up data on the need for blood transfusions following AVR are lacking.

We report two cases of patients with severe aortic stenosis who required multiple blood transfusions because of severe persistent iron deficiency anemia but were otherwise asymptomatic. AVR corrected the anemia and the underlying abnormality of the vWF multimers.

Methods

vWF multimer analysis was performed with the collagen binding assay as described previously [6], using 0.1 ml samples of normal and patient's plasma diluted 1:20 and 1:40. Transthoracic echocardiography was performed with an HP SONOS 5500 machine (Hewlett-Packard, Palo Alto, CA, USA) using a 2.5–4.5 MHz transducer. Aortic valve area was calculated according to the continuity equation [7].

Results

Two patients were admitted because of progressive weakness and anemia [Table 1]. The first patient, a 76 year old woman, was diagnosed with iron deficiency anemia. A comprehensive work-up (including upper and lower gastrointestinal series and obstetric/gynecologic examination) identified bleeding from colonic angiodysplasias as the cause of the anemia. Lactate dehydrogenase, haptoglobin and urine hemosiderin tests were within normal limits. The second patient, an 86 year old woman, was diagnosed with anemia due to progressive blood loss without an identifiable source of bleeding and with normal iron levels. Bone marrow showed a hypercellular red cell line. Reticulocyte count was elevated and there were no signs of hemolysis. Both women had severe aortic stenosis but were completely asymptomatic (no chest pains, syncope or symptoms compatible with heart failure). Both patients were diagnosed as suffering from aortic stenosis based on a heart murmur and a diminished second heart sound that were found on physical examination. Both patients were admitted repeatedly for multiple blood transfusions (overall 32 units) during a period of 24 months. They were found to have low levels of large vWF factor multimers.

Despite the absence of cardiac symptoms, due to the need for multiple admissions for recurrent blood transfusions the patients

vWF = von Willebrand factor
AVR = aortic valve replacement

Table 1. Laboratory and echocardiographic data, pre- and post-aortic valve replacement

	Patient 1		Patient 2	
	Pre-surgery	Post-surgery	Pre-surgery	Post-surgery
Follow-up (months)	13	12	11	8
Hemoglobin (g/dl)	9.5	12.3	9	12.2
MCV (fl)	78	87	81	91
No. of packed blood units	10	0	25	1*
Large vWF multimers (%)	10	20	5	30
Peak pressure gradient (mmHg)	143	36	93	22
Mean pressure gradient (mmHg)	85	21	69	12
Aortic valve area (cm^2)	0.4	1.8	Not calculated	Not calculated
Left ventricular ejection fraction (%)	75	60	65	60

* One unit of packed blood was given due to sepsis that occurred after acute calculus cholecystitis

were referred for AVR. The procedure abolished the need for further blood transfusions during a follow-up of 22 months. Concomitantly, the level of large vWF multimers increased significantly (Table 1). During the follow-up period, patient no. 2 was admitted because of acute calculus cholecystitis complicated by sepsis and mechanical ventilation, requiring prolonged hospitalization for one month. During this period the patient was given 1 unit of blood. Two months later she underwent cholecystectomy, with an uneventful course.

Discussion

We describe two patients with severe calcified aortic stenosis who were otherwise symptomatic. In addition, they required multiple blood transfusions for resistant iron deficiency anemia that was resolved by aortic valve replacement. Colonic angiodysplasia, accompanied by low level of large vW multimers, are presumably the underlying mechanism for the anemia. AVR resulted in normalization of the high vW multimers level, leading to elimination of the anemia with no further need for blood transfusion.

Aortic stenosis has been associated with bleeding episodes from colonic angiodysplasia [2]. von Willebrand factor is the missing link that connects aortic stenosis and bleeding to colonic angiodysplasias [8]. Since the congenital von Willebrand disease type IIA is associated with bleeding from colonic angiodysplasias, similar to patients with aortic stenosis [9], Warkentin et al. [8] hypothesized that the syndrome of bleeding episodes in patients with severe aortic stenosis (Heyde syndrome) is an acquired form of vW disease type IIA.

vWF plays a key role in the plug formation under high shear conditions, such as in the arterioles. VWF interacts with glycoprotein 1β on the platelet surface [10], thereby slowing the platelet's motion so it can adhere firmly to the vWF and to the subendothelium using other receptors (mostly IIb3) [9]. High weight multimers of vWF are more efficacious than small multimers for platelet-vWF interaction during high shear conditions [11]. It has been shown that vWF multimers are spontaneously truncated and reduced in size in the plasma, and this phenomenon is more pronounced if vWF is exposed to high shear conditions for longer periods [12]. Aortic stenosis is known to cause high shear in the vasculature [13]. It is therefore understandable that the high shear condition in patients with aortic stenosis is responsible for a reduction in the size of the vWF multimers. This fact explains the low percentage of large vWF multimers found in patients with severe calcified aortic stenosis [14,15] and the improvement in the percentage of large multimers after valve replacement. It is logical to speculate that the low levels of large vWF multimers are responsible for the bleeding episodes in patients with severe aortic stenosis, since without vWF the first adherence and slowing of platelet motion is diminished [9].

In fact, it has been shown that patients with bleeding angiodysplasias had a low percentage of large vWF multimers, as compared to non-bleeding angiodysplasia and to bleeding from colonic diverticula [16]. Interestingly, most patients with bleeding angiodysplasia suffered from aortic stenosis, while none of the patients included in the other groups had aortic stenosis.

We present two female patients with severe aortic stenosis accompanied by resistant anemia due to gastrointestinal bleeding that required multiple blood transfusions, despite iron supplementation. AVR abolished the need for blood transfusions and cured the resistant anemia in these patients. The clinical improvement was correlated with normalization of the large vWF multimer level. A similar observation was recently made by Warkentin et al. [16], who reported two elderly women who underwent AVR and the procedure both improved the percentage of large vWF multimers and cured the bleeding episodes due to colonic angiodysplasias. Vincentelli et al. [5] showed that AVR corrects the Von Willebrand factor abnormalities, and that the correction remained significant for 6 months among patients who had a matched prosthesis [5]. The authors also report that the onset of re-stenosis that was observed in one patient was accompanied by the recurrence of bleeding; however, not all mismatched prostheses were accompanied by bleeding episodes, despite the reduction in large vWF multimers. It is possible that there is a threshold for this association, and the reduction in percentage of large vWF multimers beyond this threshold might cause a tendency towards bleeding.

An interesting question is the association of female gender and bleeding from colonic angiodysplasias among patients with aortic stenosis. Besides our report, Warkentin and colleagues [16] reported two female patients with bleeding episodes due to angiodysplasias that did not recur after AVR. Female sex was also predominant in the report of Veyradier et al. [15], who found a 2:1 ratio of female sex among patients with bleeding colonic angiodysplasias, and among two other case reports by Cappel and Lebwohl [17] and Alam and Lewis [18] (both were females). However, earlier large-scale reports by Williams [19] and King et al. [20] did not show a predominance of female gender among the patients with aortic stenosis and unexplained bleeding from the gastrointestinal tract. It is likely that the female predominance in our report is coincidental.

Guidelines for AVR in severe calcified aortic stenosis were

recently reviewed [21]. In view of the evidence that connects aortic stenosis, acquired vW disease type IIA and gastrointestinal bleeding, we suggest that low levels of large vWF multimers, recurrent gastrointestinal bleeding and/or persistent iron deficiency anemia requiring multiple blood transfusions, in the presence of significant aortic stenosis, should be considered, in some cases, an indication for AVR, even if the patient is otherwise asymptomatic.

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