Ambivalent effect of aortic stenosis on von Willebrand factor and thrombin generation. Is transvalvular gradient the guilty party?

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Aortic valve sclerosis-stenosis is the most common valvular pathology in industrialised countries, evolving from aortic valve sclerosis into aortic stenosis (AS). Aortic valve sclerosis is present in 25% and AS in 2% of people aged >65 years.

Heyde syndrome is an acquired and intricate pathology encountered in AS and in the obstructive form of hypertrophic cardiomyopathy (HOCM).1–5 In its initial description Heyde syndrome is a syndrome of AS associated with gastrointestinal (GI) bleeding of idiopathic origin, which was subsequently linked to angiodysplasia. Angiodysplasia is predominantly observed in the elderly and is characterised by small vascular dilatations of GI submucosal veins and capillaries, ultimately leading to arteriovenous communications. This vascular malformation is more often multiple than single and is regarded as a GI degenerative ageing process involving mainly the caecum and the right colon. Angiodysplasia is a fortuitous finding in endoscopy in 2–5% of non-bleeding patients aged >65 years but is also widely recognised as a major cause of digestive bleeding in elderly people. In patients with GI bleeding angiodysplasia is found in 2.6–6.2% of patients by colonoscopic examination.4

Bleeding can occur in patients with severe AS or HOCM when there is a pathological association with a bleeding-prone lesion, the most common being GI angiodysplasia. The pathological association of these two diseases is not rare and 2–3% of patients aged >65 years with severe AS would also have GI angiodysplasia, and 2% of patients aged >65 years with GI angiodysplasia would have AS. Other bleeding-prone lesions can also favour minor or major bleeding such as epistaxis, menorrhagia or haematuria in AS and HOCM.2,3

However, a higher incidence of association between AS and GI bleeding (unexplained or due to angiodysplasia) than expected by chance alone was suggested in 1961 by Williams in 1441 patients admitted with GI bleeding4 and confirmed later by Pate et al in 2004 in a large epidemiological analysis of 3.8 million hospital discharges.6 An odds ratio of 6.4 (95% CI 3.8 to 10.7, p<0.0001) and 4.5 (95% CI 3.0 to 6.8, p<0.0001) was calculated for this association in the two studies, respectively.

To explain this excess frequency of bleeding a third factor of Heyde syndrome has been identified. As suggested by Warkentin et al in 1992 this third player is the acquired type 2A von Willebrand syndrome characterised by a qualitative and acquired defect of von Willebrand factor (vWF) with the loss of high molecular weight multimers (HMWM) of vWF owing to high shear stress lesions.1 High shear forces can induce conformational changes of vWF, probably leading to exposure of sites of cleavage sensitive to a vWF-specific metalloproteinase, ADAMTS 13, and a subsequent decrease in HMWM level.

Shear stress is proportional to blood flow velocity and inversely proportional to vessel diameter. Under normal physiological conditions the highest shear stress or wall shear rate of the cardiovascular system occurs in the microcirculation and, more precisely, in arterioles. Whereas shear rate does not exceed 4000/s in normal arterioles, it can reach 10 000/s in angiodysplasia and in aortic valve or outflow tract stenosis.1 Aortic stenosis is a high shear stress lesion with systemic impact (all blood flow goes through the aortic valve), and GI angiodysplasia is also a high-shear-stress lesion, which can further locally impair vWF.1 As described previously2 and confirmed in the elegant study by Natorska et al published in Heart the percentage of HMWM is decreased in patients with severe AS. The loss of HMWM and therefore the decrease of active vWF3 affects platelet adhesion and aggregation.9 Together these defects (acquired vWF impairment and angiodysplasia) explain the bleeding tendency observed in severe AS. It is noteworthy that in patients with congenital von Willebrand disease, severe GI bleeding is rare until middle age but those who bleed usually bleed from angiodysplasia, with an increased risk of GI haemorrhage with ageing in parallel with GI degenerative vascular changes.

In addition, it has been lately shown that endothelial vWF regulates angiogenesis and that vWF impairment in von Willebrand disease (congenital or acquired) may promote angiogenesis.10 This new role for vWF in vascular biology might also explain a stronger than expected association between vascular abnormalities such as angiodysplasia, bleeding and severe AS.

By contrast, coagulation activation has also been reported in severe AS, both in circulating blood11 and within the valve,12,13 irrespective of vascular atherosclerotic burden. Thrombin generation correlates positively with gradient and shear stress in AS but also in HOCM.11 In their paper, Natorska et al also demonstrate for the first time in the same patients that markers related to thrombin generation are enhanced in severe AS and correlate negatively with HMWM of vWF. Even though this result was expected in view of the relation of both HMWM and thrombin with the magnitude of transvalvular gradient, the study of Natorska et al highlights the ambivalent effect of high shear stress in AS on haemostasis. This results in an alteration of vWF, on the one hand, and activation of coagulation, on the other (figure I), which can explain, at least in part, two aspects of AS—Heyde syndrome5 and excess thromboembolic risk.14

Although originally thought to be a passive degenerative disease, it is now widely accepted that AS is an inflammatory, active atherosclerotic-like process characterised by infiltration of macrophages and T lymphocytes, extracellular lipid depositions and active calcification.13 Tissue factor (TF), the major initiator of

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Figure 1  Haemostatic balance in aortic stenosis: relation of transvalvular gradient-shear forces to primary haemostasis impairment (von Willebrand Factor) and coagulation activation.

Hence, the study of Natorska et al highlights a new paradigm, the tight interplay between haemostasis and aortic valve degeneration in AS. Progressive narrowing of the aortic valve orifice enhances shear forces, eliciting primary haemostasis impairment through HMWM of vWF proteolysis while the TF-related coagulation pathway is activated in plasma (and within leaflets). These ambivalent and even paradoxical effects on haemostasis, for which transvalvular gradient could be regarded a guilty, might account for opposite manifestations of AS—a small but significant excess bleeding risk and a small excess thromboembolic risk. Finally, whether or not increased thrombin generation partly counterbalances vWF impairment and bleeding tendency in severe AS or HOCM is a tempting hypothesis, which nevertheless remains to be demonstrated.

Competing interests None.

Contributors TIT: conception, design and writing the manuscript; JB: figure review, writing and review of the manuscript; SS: conception, writing and review of the manuscript, figure drawing.

Provenance and peer review Commissioned; internally peer reviewed.

Published Online First 2 September 2011

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Heart 2011 97: 1997-1998 originally published online September 2, 2011
doi: 10.1136/heartjnl-2011-300715

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