When Edward Heyde, a general practitioner, described the syndrome of gastrointestinal bleeding in the presence of aortic stenosis that bears his name (1), there is no way he could have known that his observations would open doors for a procedure that was completely inconceivable at the time of his writing. After several decades of search for a mechanism the group from Lille demonstrated that turbulent blood flow at a narrowed aortic valve leads to degradation of circulating levels of the adhesive macromolecule von Willebrand Factor (vWF), resulting in a bleeding diathesis that is correctable only by surgical replacement of the valve, which in turn leads to rapid restoration of circulating vWF levels (2). The same group recently reported that transcatheter aortic valve replacement (TAVR) had a similar effect. These mechanistic observations also have important diagnostic implications. The Lille investigators have now tied them to one of the major problems that continues to confound the field—paravalvular leak following TAVR—by demonstrating that the previously observed coagulation defect continues in patients who have persistent aortic regurgitation after TAVR (3). Potentially, these findings have profound diagnostic utility.

In order to understand these possibilities, it is important to take a moment to understand the role of vWF, hemodynamic shear, and arterial thrombosis. The term shear refers to the conversion of laminar flow to turbulent flow, and its accompanying energy loss. Shear occurs physiologically at sites of arterial puncture, and pathophysiologically at sites or severe atherosclerotic narrowing, as well as across narrowed aortic valves. The biologic response to shear involves a complex and balanced interaction between platelets and vWF. It is produced by endothelial cells and megakaryocytes, is stored in Weibel Palade bodies and in the α granules of megakaryocytes, and is rapidly secreted as high molecular weight multimer strings in response to endothelial cell activation. Because of its structure, vWF is uniquely sensitive to changes in shear. The vWF multimers circulate in a coiled form, which prevents them from being biologically active by cloaking their active sites. This configuration also protects them from enzymatic degradation. High shear rates (beyond 10-15 piconewtons) lead to uncoiling of these multimers, with two important results. First, exposure to high shear activates vWF’s A1 domain allowing it to interact with the platelet glycoprotein (GP) Ib/IX/V and to initiate platelet adhesion to injured surfaces. An accompanying conformational change in the molecule opens vWF’s A2 domain which permits the molecule’s degradation by an enzyme with the unlikely name a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13 (ADAMTS-13) (4). A third effect of high shear is that it activates platelets, allowing them to cross-link through the binding of vWF with activated integrin αIIbβ3 leading to a process known as shear-induced platelet aggregation (5). These three effects are critical in the response to TAVR.

Although replacement of a critically narrowed aortic valve removes a source of shear, it can provide a source of even greater shear when paravalvular leaks (PVL) are present. Conceptually, PVL occur when the TAVR prosthesis fails to make complete contact with the annulus of the native aortic valve, leaving small gaps between the native and prosthetic valves. Blood flow through these narrow apertures leads to high shear. Enzymatic degradation of vWF by ADAMTS-13 rises sigmoidally as shear increases (6). The result is that when PVL occurs, degradation of high molecular weight vWF multimers is accelerated and the ratio between these multimers and their degradation products is decreased. The work of Van Belle...
and colleagues takes advantage of this physiology. They observed that among 183 patients undergoing TAVR with an Edwards Sapien XT valve, those in whom PVL [defined by transeosophageal echo using the VARC-2 criteria (7)] persisted after the procedure also had persistently low multimer levels. Those with no aortic regurgitation and those in whom paravalvular leads were corrected by post implant dilation, had multimer levels that reverted to normal values. The parameter that they chose to measure, HMW-multimer ratio, was able to discriminate between patients with and without PVL on transeosophageal echo with an impressive a C-statistic of 0.94, and had a negative predictive value of 98.4%. Equally important, inclusion of the HMW-multimer ratio to the logistic EURO score improved the ability of the score to predict mortality 1 year after the procedure.

While vWF multimers are not routinely measured in clinical practice, and have a significant laboratory turnaround time, the investigators also took an extremely important step by including a more readily available test whose results are in part vWF-dependent. They measured ADP-mediated closure time (CT-ADP) using the PFA-100 platelet monitoring device. In this test, whole blood is exposed to adenosine diphosphate (ADP) in the device and the time required to produce a clot that closes a small aperture is measured. This process indirectly measures vWF activity since ADP-induced platelet aggregation is highly dependent on vWF activity (8). The discriminating ability of CT-ADP for the presence of aortic regurgitation and of HMW-multimer ratio were virtually identical, as were the abilities to predict mortality at one year.

These findings are potentially of great importance to the field for a simple reason. Following TAVR, paravalvular aortic regurgitation of more than trace severity occurs in approximately 40% of patients, and in several series, has been associated with increased mortality at one year. Large severe PVL generally does not require much diagnostic sophistication to identify, but such leaks have become extremely rare.

Data concerning patients who have received the Edwards Sapien valve indicate that the association with mortality is present even if the degree of regurgitation is mild (9), while data from the CoreValve trials indicates that among patients treated with a self-expanding valve only more severe degrees of regurgitation are associated with mortality increases (10). Whether these differences are due to differences in the valves or to differences in the assessment of aortic regurgitation is not clear. Regardless, it is clearly preferable not to have residual aortic regurgitation at the conclusion of a TAVR procedure. However, the steps taken to reduce or eliminate AR are not risk-free. Balloon post dilation carries a risk of annular or ventricular septal rupture, and possibly of stroke (11); implanting a second valve risks coronary ostial occlusion, while placing a plug can be fairly labor-intensive. Unfortunately, determining the severity of acute aortic regurgitation is difficult, and it is generally accepted that most of the current techniques are merely approximations, in part because of the irregularity of the regurgitant jets. Transesophageal echo is probably superior to transthoracic echo, but is more invasive. Measuring CT-ADP is considerably more reproducible, and can be done very simply and quickly. If the findings of Van Belle are replicated, then identifying aortic regurgitation may well become relatively easy. Of course, the current study still leaves several important knowledge gaps. The study was confined to patients treated with a Sapien XT valve. This valve has largely been supplanted by the Sapien S3 valve, whose annular skirt appears to have reduced the frequency of aortic regurgitation significantly (12), as has the design of other new valves (13). Additionally, neither HMW-multimer ratios nor CT-ADP have been assessed in patients treated with self-expanding valves.

In addition to refining the ability to diagnose PVL, these findings also open other important doors in the management of patients undergoing TAVR. Shear leads to platelet activation; if it promotes platelet cross-linking (homotypic aggregation), it may lead to consumption of circulating platelets. Some degree of thrombocytopenia occurs in the majority of patients within the first few days after TAVR. More than a third develop nadir platelet counts <100×10⁹/L; when severe, thrombocytopenia is associated with an increase in mortality at 30 days and at 1 year (14). Platelet activation as a result of shear is a potential explanation for this phenomenon. An additional implication of this work concerns periprocedural stroke. The incidence of strokes after TAVR is biphasic; the first phase occurs within the first week of the procedure. While many of these events are the result of central emboli from the native valve and aorta that occur during the procedure, the high frequency stage persists for several days beyond which procedure-related emboli might be expected (15). Platelet activation at high shear areas in and around the implant site might conceivably predispose patients to embolic stroke. It is thus possible that reduction in the vWF HMW multimers might serve as an indicator that platelet activation is occurring.
The findings of Von Belle open a new vista on how we regard TAVR. Just as the introduction of percutaneous coronary intervention was first focused on technique and only later expanded to include a focus of conjunctive pharmacology, it is likely that the same will occur with TAVR. A meaningful diagnostic technique appears to have been provided, but the mechanisms observed promise that the future will become quite interesting.

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Footnote

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