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VIEWPOINT

Real-Time Monitoring of von Willebrand Factor in the Catheterization Laboratory

The Seatbelt of Mini-Invasive Transcatheter Aortic Valve Replacement?

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ABSTRACT

Significant paravalvular regurgitation (PVR) remains a relatively frequent (4% to 9%) and deleterious complication of transcatheter aortic valve replacement (TAVR), even with the latest generation of bioprosthesis. Although mini-invasive TAVR without general anesthesia or transesophageal echocardiography (TEE) is progressively becoming the predominant approach, identification and grading of PVR in the catheterization laboratory remain an important and challenging clinical issue. The authors discuss how a recently reported blood biomarker reflecting the von Willebrand factor activity, that is, the closure time with adenosine diphosphate, can be successfully applied during the TAVR procedure to detect and monitor PVR in real time, with an excellent negative predictive value. This point-of-care testing performed directly in the catheterization laboratory may improve the diagnosis of PVR and rationalize the decision of whether or not to perform corrective measures. They further discuss how such a test could be a substitute for the multimodal approach combining TEE, hemodynamics, and cine-angiography, and help to secure the transition to the mini-invasive approach and facilitate the expanding indications of less invasive procedures to lower-risk patients without jeopardizing procedural and clinical outcomes. (J Am Coll Cardiol Intv 2018;11:1775–8) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Transcatheter aortic valve replacement (TAVR) is the gold standard treatment for inoperable patients and is recommended for high-risk patients with severe aortic stenosis (1). The indications are growing and expanding toward intermediate-risk patients. With the conduction disorders, one major remaining issue preventing the generalization of TAVR to lower-risk patients is the rate of significant post-procedural paravalvular aortic regurgitation (PVR) that is associated with an increased (2.5-fold) mortality in high-risk patients (2,3).

DIFFICULTIES OF ACCURATE PVR ASSESSMENT IN THE CATHETERIZATION LABORATORY

Cine-angiography, hemodynamics, transesophageal echocardiography (TEE), and transthoracic echocardiography (TTE) are currently used to assess the presence and severity of PVR during TAVR (**Figure 1**).

Cine-angiography is highly subjective, dependent on the observer's experience and numerous technical factors inducing variability in grading (4). This

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ABBREVIATIONS AND ACRONYMS

CT-ADP = closure time with adenosine diphosphate

GA = general anesthesia

HMW-multimers defect = high-molecular-weight multimers of VWF

POC = point-of-care

PVR = paravalvular regurgitation

TAVR = transcatheter aortic valve replacement

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

VWF = von Willebrand factor

technique is not currently recommended by the Valve Academic Research Consortium (VARC-2) (5).

The invasive measurement of the hemodynamic aortic regurgitation index using the left ventricle and aortic pressures has been proposed to assess PVR. However, there is a significant overlap between aortic regurgitation grades with this index, which is influenced by diastolic dysfunction (generally abnormal) and heart rate. Variety of corrections have been suggested to overcome these limits (6).

TEE, mainly performed under general anesthesia (GA), has been widely used at the beginning of the TAVR era and is considered as the gold standard to assess the severity of PVR during procedures and guide the physician in performing corrective procedures (7). However, an accurate grading is demanding and requires a strong expertise because many echocardiography criteria are not applicable in the context of PVR because of typically multiple, irregular, and/or eccentric jets (8).

TTE, that does not require GA, is an alternative to TEE and is mainly used in TAVR performed with a mini-invasive approach in which the procedure is performed under conscious sedation. However, TTE is limited, with some echocardiographic windows not accessible due to patient positioning and interventional procedural factors. A single-center comparative study with cardiac magnetic resonance reported in a selected population that up to 14% of patients with moderate or severe PVR as determined by cardiac magnetic resonance were potentially misclassified ≤mild by TTE (9).

Overall, the echocardiographic PVR grading remains challenging especially for intermediate "mild-to-moderate" categories, and there is therefore a higher likelihood to misclassify PVR.

CONCERNS ABOUT PVR ASSESSMENT IN TAVR WITH A MINI-INVASIVE APPROACH

The largest randomized controlled trials evaluating the new generation of bioprosthetic valves have strongly supported the strategy of TEE guidance under GA in 85% of patients. These trials achieved excellent clinical outcomes, including low PVR rates as in the PARTNER (Placement of Aortic Transcatheter Valves) II SAPIEN 3 and the CoreValve Evolut R U.S. study (respectively, 3.5% and 5.3%) (10,11).

However, these outcomes are not replicated in clinical practice. The recent FRANCE-TAVI registry (Registry of Aortic Valve Bioprostheses Established by Catheter) (12) reported a rate of PVR of 9%, much higher than the results reported in the preceding text.

The poorer outcomes observed in real life have several explanations, including higher risk patients, no core-laboratory valve sizing with multidetector computed tomography, or no selection of participating centers.

However, one of the main differences with clinical trials is the absence of TEE guidance in 73% of the interventions, emphasizing the strong current trend for using a mini-invasive approach.

Several former studies raised concerns about the safety of routine use of these "TEE-less" procedures. The FRANCE-2 registry (3,13) reported a significantly higher incidence of PVR in the conscious sedation group (without TEE) as compared with the GA group (with TEE). In a large Brazilian registry, the use of TEE was associated with a 2-fold reduction in mortality (14).

Overall, these studies suggest that simplified TAVR procedures without TEE are feasible but associated with a higher PVR rate related to less comprehensive imaging that further increases misclassification of PVR and underutilization of corrective procedures such as balloon post-dilatation.

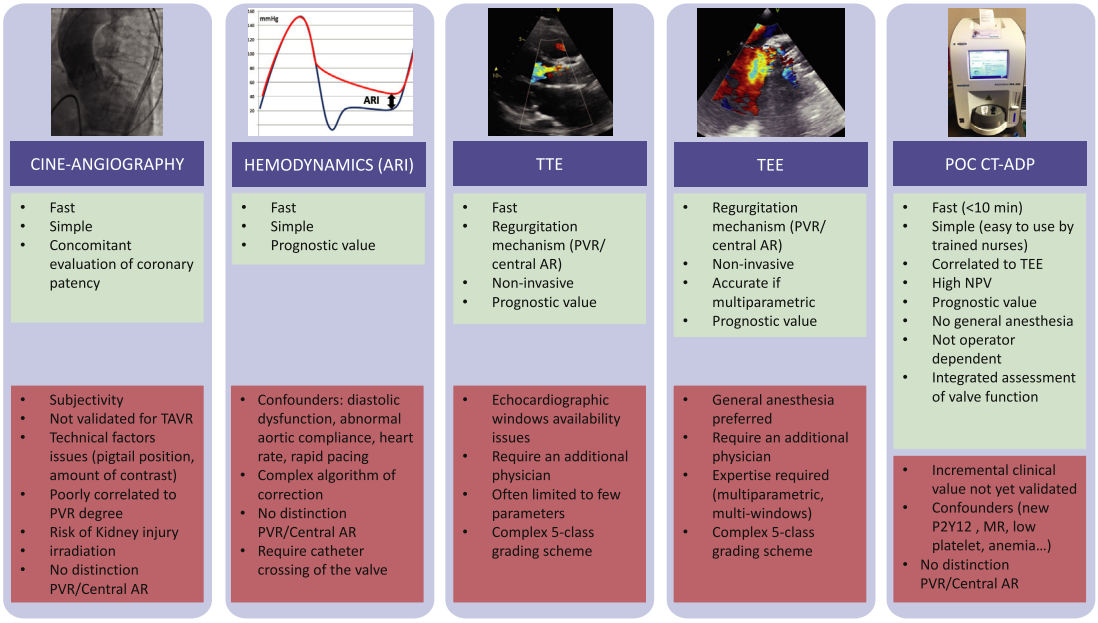
VON WILLEBRAND FACTOR: A NEW OPTION TO IMPROVE THE MINI-INVASIVE APPROACH IN TAVR?

Our recent study reported that a blood biomarker reflecting the von Willebrand factor (VWF) activity, that is, the closure time with adenosine diphosphate (CT-ADP), can be successfully applied during the TAVR procedure to detect and monitor PVR (15).

VWF is a large, multimeric glycoprotein promoting platelet aggregation. A loss of high-molecular-weight multimers of VWF (HMW-multimers defect) is observed in patients with aortic stenosis because the increased shear stress from the turbulent flow unfolds the VWF and promote its cleavage by the protease ADAMTS-13 (16). Such defect is corrected within minutes after valve replacement (17,18) but does not resolve when PVR occurs after TAVR (maintained high shear stress from AR regurgitant flow). The point-of-care (POC) testing Platelet Function Analyzer 100 (PFA-100, Siemens Healthcare Diagnostics, Tarrytown, New York) is highly sensitive to HMW-multimers defect which causes a prolongation of the CT-ADP.

Blood is drawn from the venous or the arterial peripheral line in anticoagulated citrate tubes and placed into test cartridges. After 180 s of incubation at 37°C, the blood is aspirated through a microscopic aperture and a capillary into a collagen- and ADP-coated

FIGURE 1 **Strengths and Limitations of Modalities of PVR Assessment in the Catheterization Laboratory**



AR = aortic regurgitation; ARI = aortic regurgitation index; CT-ADP = closure time of membrane coated with adenosine diphosphate; MR = mitral regurgitation; NPV = negative predictive value of moderate or greater paravalvular regurgitation; POC = point-of-care; PVR = paravalvular regurgitation; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

membrane under high-shear flow produced and controlled by a constant vacuum. The analyzer monitors the time required for occlusion of the aperture by the platelet plug, thus defining the closure time. Including sample handling, results are available within 5 min of blood drawn. POC CT-ADP testing is designed as a compact instrument, automatically calibrated, rapid and simple to use, and requiring minimal maintenance and sample manipulation. These features are making its use easy for nurses working in the catheterization laboratory after a short training.

In our single-center study of transfemoral TAVR (n = 183), CT-ADP >180 s discriminated patients with or without PVR (assessed by TEE under GA) with negative predictive values of 98.6%. These results were replicated in a second multicenter cohort of 201 patients, with a negative predictive value of 96.9%. The normalization of CT-ADP occurred within 10 min after PVR correction by additional valve dilatation. This dynamic relationship allows a fast evaluation for PVR during the procedure that could challenge the multiparametric approach combining TEE, hemodynamics, and cine-angiography. Moreover, final CT-ADP >180 s is a strong and independent predictor of mortality at 1 year (3.4-fold increased risk).

Whether this new method can be applied to all patients merits further assessment. Other causes of HMW-multimers defect such as a significant mitral regurgitation could make the interpretation of CT-ADP difficult. The assay can also be impaired in case of a very low hematocrit, or low platelet count but is not sensitive to aspirin or direct oral anticoagulant administration (19). We have also provided reassuring data on the use of clopidogrel (17). It remains unclear, however, whether more potent $P2Y_{12}$ inhibitors, which are currently rarely used in the context of planned TAVR, might affect CT-ADP (20). The increased speed of VWF clearance associated with the O blood group quantitatively affects mainly the VWF levels. However, even if CT-ADP functional assay can be prolonged in this subset of patients, it does not impact its ability to exclude a VWF defect (21). Clinicians must keep this information in mind when interpreting the results of CT-ADP in the context of TAVR.

Overall, these findings suggest that flow-related biomarkers provide an integrated assessment of valve function that is distinct from, and perhaps more

accurate than, the assessment obtained with imaging (**Figure 1**). This attractive POC testing method should be further investigated in larger-scale studies.

CONCLUSIONS

The last generation of prosthetic valves has achieved a tremendous reduction of PVR in clinical trials. However, real-life results in mini-invasive procedure cannot be considered completely satisfying, particularly true in an era in which TAVR is being progressively offered to younger and to lower-risk patients.

We developed a new indication for POC testing that appears to be a valuable noninvasive, highly reproducible, and easy to perform alternative to TEE for PVR evaluation. This test may improve the diagnosis of PVR and rationalize the decision of whether or not to perform corrective procedures. This method will be helpful to secure the transition to a mini-invasive approach and will facilitate the expanded indications of less invasive procedures to lower-risk patients without jeopardizing clinical and procedural outcomes. But only a large-scale multicenter randomized clinical trial will be able to address the incremental value of this test to the PVR assessment obtained by standard methods (TEE, cineangiography) and bring evidence strong enough to support the routine implementation of POC CT-ADP in mini-invasive TAVR.

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