JACC: CARDIOVASCULAR INTERVENTIONS
© 2018 PUBLISHED BY ELSEVIER ON BEHALF OF THE
AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 11, NO. 17, 2018

VIEWPOINT

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

The Seatbelt of Mini-Invasive Transcatheter Aortic Valve Replacement?

Flavien Vincent, MD,[a,b,c,*] Antoine Rauch, MD, PhD,[b,c,d,*] Hugues Spillemaeker, MD,[a] André Vincentelli, MD. PhD,[b,c,e] Camille Paris, MD,[b,c,d] Mickael Rosa, PhD,[b,c] Annabelle Dupont, PharmD, PhD,[b,c,d] Cedric Delhaye, MD,[a] Basile Verdier, MD,[a] Emmanuel Robin, MD, PhD,[b,c,f] Peter J. Lenting, PhD,[g] Sophie Susen, MD,PhD,[b,c,d,*] Eric Van Belle, MD, PhD[a,b,c,*]

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

From the [a]CHU Lille, Institut Coeur-Poumon, Cardiology, Lille, France; [b]University Lille, Inserm U1011 - EGID, Lille, France; [c]Institut Pasteur de Lille, Lille, France; [d]CHU Lille, Hematology Transfusion, Lille, France; [e]CHU Lille, Cardiac surgery, Lille, France; [f]CHU Lille, Anesthesia and Intensive Care, Lille, France; and the [g]Inserm, UMR_S 1176, University Paris-Sud, Université Paris-Saclay, Le Kremlin-Bicêtre, France. This work was supported by Lille-II University and by the National Research Agency (Programme d'Investissement d'Avenir) with the Hospital-University Research in Health program (Recherche Hospitalo-Universitaire, WILL-ASSIST HEART ANR-17-RHUS-0011). Dr. Vincent has received a research grant from the Fédération Française de Cardiologie. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. *Drs. Vincent, Rauch, Susen, and Van Belle contributed equally to this work.

Manuscript received April 17, 2018; revised manuscript received May 15, 2018, accepted May 22, 2018.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2018.05.047

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