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iREVIEWS

STATE-OF-THE-ART PAPERS

Systematic CT Methodology for the Evaluation of Subclinical Leaflet Thrombosis

Hasan Jilaihawi, MD,[a] Federico M. Asch, MD,[b] Eric Manasse, MD,[c] Carlos E. Ruiz, MD,[d] Vladimir Jelnin, MD,[d] Mohammad Kashif, MD,[e] Hiroyuki Kawamori, MD,[e] Yoshio Maeno, MD,[e] Yoshio Kazuno, MD,[e] Nobuyuki Takahashi, MD,[e] Richard Olson, BSME, MBA,[c] Joe Alkhatib, BSME,[c] Daniel Berman, MD,[e] John Friedman, MD,[e] Norman Gellada, RT, CRT,[e] Tarun Chakravarty, MD,[e] Raj R. Makkar, MD[e]

ABSTRACT

Subclinical leaflet thrombosis was recently described in a randomized trial of transcatheter aortic valve replacement. It was subsequently demonstrated in a series of registries that this was a commonly observed imaging finding seen in all transcatheter and surgical bioprostheses. The phenomenon has aroused considerable interest due to the as-yet-undefined risk for later clinical events and the possibility of pharmacological intervention with anticoagulation. Subclinical leaflet thrombosis is easily detected noninvasively by technically suitable computed tomography (CT) with a high degree of concordance to transesophageal echocardiography findings. The CT hallmarks were noted to be hypoattenuated leaflet thickening (HALT) associated with reduced leaflet motion (RELM). The combination of HALT and RELM signified hypoattenuation affecting motion, the standardized imaging endpoint used. This paper describes the systematic CT evaluation methodology that was devised during the Portico trial investigation and U.S. Food and Drug Administration submission; it also highlights the need for an ongoing discussion among experts to enable, with the help of the Valve Academic Research Consortium, standardization of reporting of this imaging finding to cater to the present and future needs of clinical trials. (J Am Coll Cardiol Img 2017;10:461-70) © 2017 by the American College of Cardiology Foundation.

We recently described the phenomenon of subclinical leaflet thrombosis in a randomized trial of transcatheter aortic valve replacement (TAVR) and 2 subsequent physician-initiated registries (1). Although the clinical repercussions of this observation remain unclear, the presence of this imaging finding following all forms of aortic bioprosthesis is now irrefutable and has been noted by several groups (1-3).

Thus far, transesophageal echocardiography (TEE) has been the gold standard for evaluating valve leaflet structure and function but the reduced invasiveness

From the [a]Heart Valve Center, New York University Langone Medical Center, New York, New York; [b]MedStar Cardiovascular Research Network at Washington Hospital Center, Washington DC; [c]St. Jude Medical, Minnepolis, Minnesota; [d]Hackensack University Medical Center, Hackensack, New Jersey; and the [e]Cedars-Sinai Heart Institute, Los Angeles, California. Dr. Jilaihawi is a consultant for Edwards Lifesciences and Venus Medtech. Mr. Olson and Mr. Alkhatib are employees of Abbott Vascular. Dr. Makkar has received a research grant and consulting fees from Edwards LifeSciences; and a research grant from Medtronic and St. Jude Medical. Dr. Asch directs an academic Echo Core lab for the Portico IDE trial, through an institutional contract with St. Jude Medical. Dr. Manasse is VP Medical Affairs for Abbott Laboratories. Dr. Ruiz has received research grants from Philips. Dr. Jelnin has received research grants from Philips and St. Jude Medical; and has received an educational grant from Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

CT = computed tomography

HALT = hypoattenuated leaflet thickening

HAM = hypoattenuation affecting motion

HU = Hounsfield unit

MPR = multiplanar reconstruction

RELM = reduced leaflet motion

SOV = sinus of Valsalva

TEE = transesophageal echocardiography

TAVR = transcatheter aortic valve replacement

VR = volume rendered

and potential to diminish the operator dependence of interpretation by using computed tomography (CT) afford considerable merit. However, the methodology for the evaluation of leaflet thrombosis by CT had not been described prior to the Portico investigation, and so a detailed description of the technique is warranted. In this paper, we describe the systematic Corelab-devised methodology (**Central Illustration**, **Figure 1**) used for its evaluation using CT, a methodology that was validated with complete concordance to TEE and is used systematically in the Portico trial (1).

CT APPEARANCE OF HYPOATTENUATED LEAFLET THICKENING

Hypoattenuation associated with bioprosthetic leaflets, also described as hypoattenuated leaflet thickening (HALT), is the hallmark of subclinical leaflet thrombosis. The hypoattenuating lesions involve the periphery and base of the leaflet and extend to varying degrees to the edges of the leaflet in the center of the bioprosthetic frame. Three-dimensional volume-rendered (VR) views may demonstrate abnormal leaflets visible as wedge-shaped or semilunar opacities in both systole and diastole (**Figure 2**).

In some scans, we observed the stent frame of TAVR prostheses generated considerable motion artifact such that a single-phase acquisition, as used in previous studies, may obscure a clear delineation of leaflet structure, particularly in denser stent frames. Indeed, the use of multiple phases with retrospective gating clarifies artifacts that may be observed in a single phase and also affords the incremental discrimination of leaflet motion (Online Figure 1). Moreover, the use of systolic VR images provides a perception of depth that can more clearly demonstrate the morphology of a nonplanar 3D structure such as a bioprosthetic leaflet which can be directly correlated to corresponding leaflet thickening on 2D multiplanar reconstruction (MPR) images.

CT ASSESSMENT OF REDUCED LEAFLET MOTION AND HYPOATTENUATION AFFECTING MOTION

Minor degrees of hypoattenuating material may be seen using contrast CT on recently implanted surgical and transcatheter valve bioprosthetic leaflets and frames, but the distinction between a physiological post-operative phenomenon with adherence of fibrin and a potentially pathological phenomenon demands a standardized threshold. We set this empirically as the significant (more than mild) reduction of leaflet motion (RELM), which may be determined by both 4D VR CT and/or TEE (en face projections or longitudinal views of the leaflets). In turn, we defined mild (nonsignificant) reduction in leaflet motion as <50% reduced leaflet excursion (**Figure 3**) and significant (≥50%) reduction in leaflet excursion (**Figure 2**).

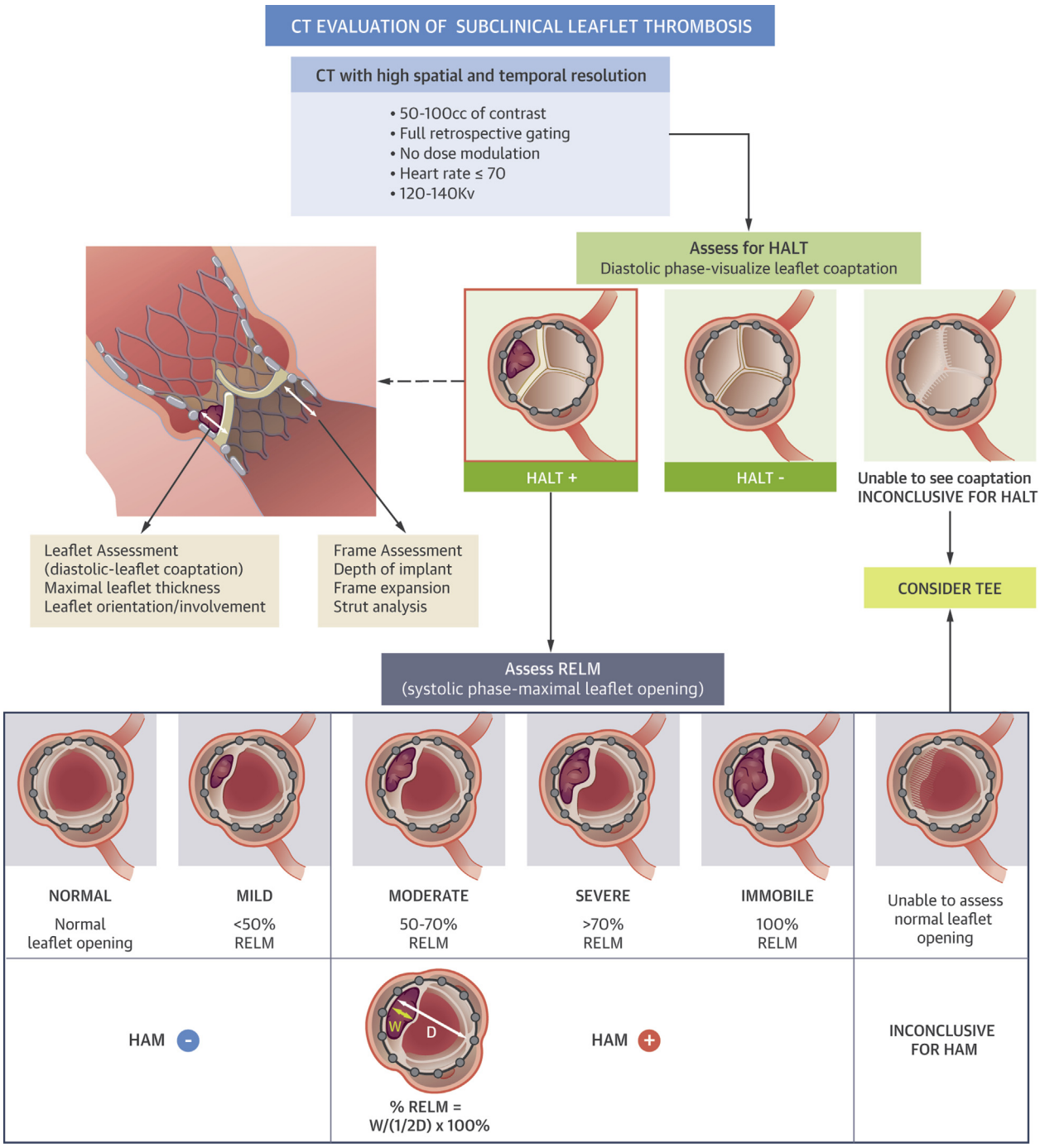
Maximal leaflet excursion is assessed using multiphase CT with at least 10 phases and a frame selected with maximal leaflet excursion. The distance between the frame margin and the maximally open leaflet tip of the most affected leaflet, taken as leaflet width (*W*) for the numerator and the distance between frame margin and the center of the frame, or half its diameter, was taken as the denominator ($^1/_2D$). The percentage of reduction in leaflet motion is thereby defined as: [%RELM = W/($^1/_2$D) • 100%] (**Figure 2**).

The 2 phenomena of hypoattenuating material on contrast CT (1) and significant (≥50%) reduction in leaflet motion on 4D assessment formed the bases of the definition for subclinical leaflet thrombosis used (specifically described as hypoattenuation affecting motion [HAM]). Although stratification of severity of reduced leaflet motion was further assigned as moderate (50% to 69%), severe (70% to 99%), and immobile, it is acknowledged that the present temporal resolution of CT (at ≥70 ms for the most technically capable scanners) may diminish the accuracy of these strata. The technique of 4D VR CT provided a 100% correlation to TEE in blinded analysis during the above-mentioned Portico trial in the 10 patients in the early part of the trial that underwent both investigations (1).

CT ACQUISITION PROTOCOLS

All acquisition protocols enabling the formal assessment of leaflet hypoattenuation and motion (Portico-IDE and registries) have used contrast CT with retrospective gating (1). Although this is the subject of further study, several principles are clear (**Table 1**). 1) Scans require contrast, probably at least 50 ml, ideally 100 ml. From a renal perspective, our practice has been to set the upper limit of contrast volume, administered in milliliters, to twice the patient's numerical creatinine clearance in milliliters per minute. For instance, a creatinine clearance of 30 ml/min would set our maximal contrast dose to 60 ml for a particular patient; this is based on data from percutaneous coronary intervention studies for contrast dose thresholds for the avoidance of contrast-induced

CENTRAL ILLUSTRATION **CT Evaluation of Subclinical Leaflet Thrombosis**



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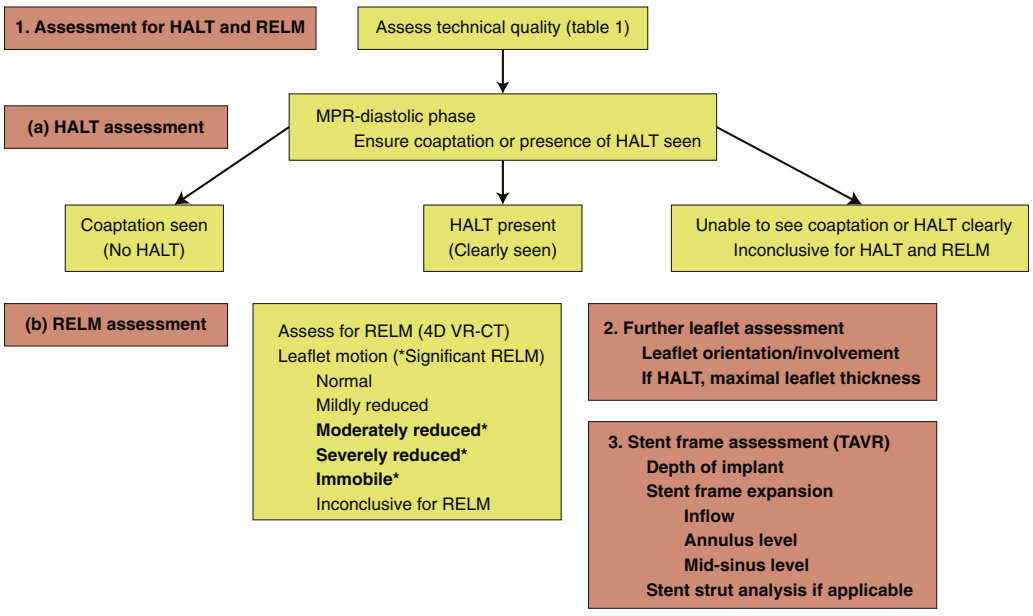
(Top) HALT is assessed in a diastolic phase with visualization of leaflet coaptation required for a conclusive scan. There is an additional assessment of the valve leaflets in the presence of HALT in the diastolic phase. Basal leaflet thickness is measured, and leaflet orientation of thickened leaflets is described (Figure 4). Stent frame characteristics, which may influence the development of HALT, are also assessed (**middle** [Figure 5]). In the presence of HALT, RELM is quantified in a systolic phase with a VR en face projection **(bottom)** at maximal leaflet opening (Figures 1 and 2). Moderate, severe, or leaflet immobility on RELM analysis in the presence of HALT is described as HAM. With inconclusive HALT (or HAM), TEE may be considered.

FIGURE 1 Systematic Methodology for Evaluation of Leaflet Thrombosis



1(a) Assessment for HALT: clear demonstration of leaflet coaptation in diastole without HALT excludes its presence; its presence may be noted in systole or diastole. **1(b)** There is then assessment for RELM, using 4D VR-CT; the systolic phase with maximal leaflet opening is identified and the 3D VR en face view used to assess the extent of RELM, expressed as a percentage for each leaflet and further stratified as mild (<50%), moderate (50% to 69%), severe (70% to 99%) and immobile. HALT with RELM >50% signifies an empirically set threshold for significantly reduced leaflet motion and hence HAM. **(2)** Additional leaflet assessment: there is further assessment of native commissural/bioprosthetic leaflet orientation as well as for maximal affected leaflet thickness (as well as maximal affected leaflet area and volume). **(3)** For TAVR bioprostheses, there are additional TAVR frame analyses: these include assessment of device depth, stent frame expansion at multiple levels, and stent-strut separation at the inflow level, if applicable. These parameters are further illustrated in Figures 2 to 4. If CT is either low quality or contraindicated, TEE may be used for the evaluation of leaflet thrombosis, given the excellent agreement between modalities including visualization of thrombus (presence and location in relation to native leaflets) and leaflet mobility. CT = computed tomography; HALT = hypoattenuated leaflet thickening; HAM = hypoattenuation affecting motion; RELM = reduced leaflet motion; TAVR = transcatheter aortic valve replacement; TEE = transesophageal echocardiography; VR-CT = volume-rendered computed tomography.

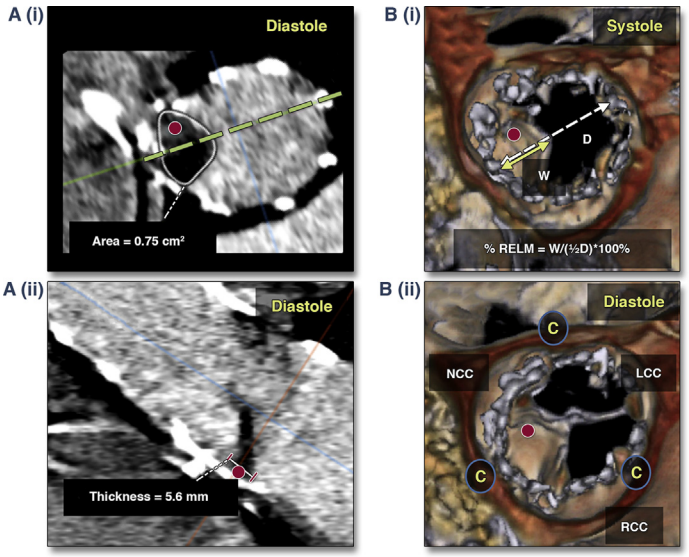
nephropathy, such as that of Gurm et al. (4). This practice requires further validation in multicentric series. 2) In addition, full retrospective gating is required for leaflet motion assessment. 3) Scan slice thickness should be sub-millimeter, and a scanner with the highest resolution available should be used. 4) Dose modulation should preferably not be used. 5) Heart rate should be limited with beta blockade if possible, ideally below 70 beats/min, which is often feasible after TAVR or surgical aortic valve replacement, even if there are reservations pre-procedure. This is especially important in the setting of atrial fibrillation, which may generate considerable artifact. 6) One-hundred twenty kilovolts is the standard scanner acquisition voltage used, but there may be some benefit in increasing this to 140 kV, particularly in the presence of a large body habitus, a denser bioprosthetic frame (such as the Lotus prosthesis [Boston Scientific, Natick, Massachusetts] or an earlier generation Corevalve [Medtronic, Minneapolis, Minnesota] or Edwards Sapien or Sapien XT [Edwards Lifesciences, Irvine, California] prosthesis) or additional intracardiac devices such as pacemaker leads or coexisting mechanical or bioprosthetic valves (including TAVR valve-in-valve), although this may be at the expense of contrast delineation of hypoattenuation; 140 kV increases the dose of radiation, and the field of scan may thus be limited to the prosthesis alone. The optimal timing of CT scanning following valve implantation, in the detection of HALT, remains unclear but is the subject of investigation with some ongoing studies, most notably the SAVORY registry from Copenhagen, specifically assessing the presence of HALT and HAM at multiple time points.

TECHNICAL CONSIDERATIONS FOR CT SCAN INTERPRETATION

Technical quality is critical to the standardization of assessment and reporting of subclinical leaflet thrombosis and leaflet motion. For this reason, an empirical quality score was used so that reporting could be standardized, particularly taking into consideration the fact that different prostheses have different frames that could generate varying degrees of artifact (Table 2). For instance, of the TAVR devices, the Lotus and the earlier generation Medtronic, Corevalve, and Edwards frames are the most dense and may generate the most artifacts, whereas the Portico device has the thinnest struts and could have the least artifacts with CT, and similarly, most surgical bioprostheses have little metal in their frames and probably produce little artifact; this is our observation over several studies including Portico, RESOLVE (Assessment of TRanscathetEr and Surgical Aortic BiOprosthetic Valve Thrombosis and Its TrEatment With Anticoagulation), and SAVORY (Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed With 4D CT) registries and requires further confirmation in systematic comparisons; examples of stent frame artifact and other potential sources of artifact including pacemaker and pre-existing prosthetic valves are shown (Online Figure 2).

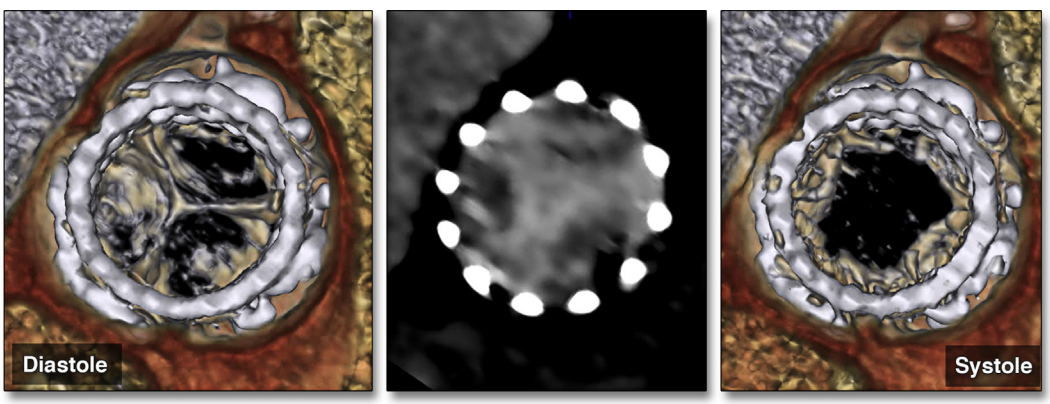
For a scan to exclude subclinical leaflet thrombosis (i.e., be documented as normal), the absence of hypoattenuation should be accompanied by leaflet coaptation visible in diastole, indicating an adequate degree of leaflet visualization to exclude

FIGURE 2 Appearance and Evaluation of Leaflet Thrombosis



Shown as characteristic wedge-shaped or semilunar opacities in the form of HALT. **(A) (i)** 2D axial MPR; **(A) (ii)** corresponding 2D longitudinal MPR (derived from **green dashed line** in **(i)**); **(B)** 3D en-face VR projection in both systole (maximal leaflet opening) **(B) (i)** and diastole **(B) (ii)** (clear coaptation should be seen, generally 80% used). Efforts to quantify HALT include measurement of maximal area for each leaflet affected **(A) (i)** and maximal thickness **(B) (ii)**; volumetric methods may also be used. A further quantitative parameter of percentage of reduced leaflet motion (% RELM) may also be used as: [a = W/(½D) • 100%], where, on a 3D en face VR projection during maximal leaflet opening, *W* is the base-to-tip width, and *D* is the diameter within the stent frame **(B) (i)**. A %RELM >50% denotes HAM. The orientation of the affected bioprosthetic leaflet(s) **([B] [ii] red dot)** is designated in relation to the native commissures **(C)** and sinuses; there is prosthesis-native leaflet misalignment in this case, and the affected leaflet is denoted NR by the proposed nomenclature (see Figure 4 for more details). LCC = left-coronary cusp; NCC = noncoronary cusp; RCC = right-coronary cusp; other abbreviations as in Figure 1.

FIGURE 3 HALT-Positive and HAM-Negative



HALT may be noted in the absence of significant RELM and hence the absence of HAM. In this case, HALT was present in all 3 leaflets, but motion was nearly normal in each, with RELM <50% for each, thus denoted HALT^{+}/HAM^{-}. Abbreviations as in Figure 1.

TABLE 1 Acquisition Protocols for the CT Evaluation of Subclinical Leaflet Thrombosis

Guidelines for the Optimization of Scan Technical Quality
1. At least 50 ml of contrast, ideally 100 ml
2. Full retrospective gating
3. Submillimeter scan slice thickness
4. No dose modulation
5. Heart rate below 70 beats/min, with beta blockade where feasible
6. 120-kV scanner voltage, increased to 140 kV in the presence of 1) Denser stent frames (e.g., Lotus); 2) coexisting permanent pacemaker; 3) coexisting mechanical bioprosthetic valves; 4) large body habitus

hypoattenuation. This is evaluated in a cross-sectional 2D MPR view (Figure 2). The presence of hypoattenuation associated with a bioprosthetic leaflet should prompt an assessment of leaflet motion with 4D VR CT to determine the severity. Although a borderline quality scan (Table 2) can determine the presence or absence of leaflet-associated hypoattenuation, it cannot determine the severity of reduced leaflet motion, which requires at least a "good" quality scan (Table 2).

TABLE 2 CT Technical Quality in the Assessment of Subclinical Leaflet Thrombosis*

Quality Score	Description	Evaluation for HALT 2D Assessment (Cross-Sectional 2D MPR)	Evaluation for RELM 4D Assessment (En face 4D-VR)
1	Extremely poor	HALT not clearly seen with considerable artifact (HALT inconclusive)	RELM/HAM inconclusive
2	Poor	HALT not clearly seen with no significant artifact BUT leaflet coaptation cannot be seen on a 2D MPR diastolic phase or considerable scan artifact precludes definitive assessment (HALT inconclusive)	RELM/HAM inconclusive
3^-	Borderline	HALT clearly seen on cross-sectional 2D MPR in any phase OR no HALT and leaflet coaptation can be seen on a 2D MPR diastolic phase.	Leaflet motion seen, but not clear through systolic phases (RELM/HAM inconclusive)†
3^+	Good	As above	Leaflet motion seen, clear through all or most systolic phases but not clear through all phases
4	Very good	As above	Leaflet motion seen clearly through all phases
5	Excellent	As above	Leaflet motion seen very clearly through all phases

*A comprehensive assessment for subclinical leaflet thrombosis requires a structural and functional assessment of the leaflets. The presence of leaflet-associated hypoattenuation, also known as hypoattenuated leaflet thickening (HALT), assessed with 2D MPR, is correlated with reduced leaflet motion (RELM), which is assessed with 4D-VR CT. Borderline or better quality scans can evaluate for HALT, but scans must be good or better to determine severity of reduced leaflet motion. †Single or limited phase systolic phase CT demonstrating hypoattenuation on 2D MPR and reduced leaflet excursion on 4D VR is also considered borderline in technical quality for the assessment of leaflet motion. Single and limited diastolic phases without systolic phases cannot assess for leaflet motion.

MPR = multiplanar reconstruction; VR = volume rendered.

Hence, in reporting a subclinical leaflet thrombosis (Central Illustration, Figure 1) HALT may be: 1) present and so require further assessment of RELM; or 2) absent and so by definition HAM-negative (HAM^-) without the need for RELM assessment (scan quality borderline to excellent), or 3) indeterminate (scan quality poor or very poor); and if HALT is present, severity of RELM may be graded as: 1) significantly reduced (≥50%) and thus HAM-positive (HAM^+); 2) not significantly reduced (<50%) and hence HAM^- (scan quality good to excellent); or 3) indeterminate (scan quality poor, very poor, or borderline). This framework, although empirical, offers a clear definition for reporting that enables further study and collaboration. If CT is either low quality or contraindicated, TEE may be used for the evaluation of leaflet thrombosis, given the excellent agreement between modalities including visualization of thrombus (presence and location in relation to native leaflets) and leaflet mobility.

CT ANALYSIS SOFTWARE AND PROTOCOLS

Several software programs are available that can assess hypoattenuation and leaflet motion. All workstations may assess HALT in a diastolic-phase 2D MPR; for the assessment of RELM and hence HAM using the methodology described, the ability to reconstruct multiphase 3D VR images throughout the cardiac cycle is required to create 4D VR.

The valve leaflets are assessed systematically using both 2D MPR (axial cross-sectional assessment) and 3D VR. The window level is adjusted individually for each patient to maximize leaflet visualization and to minimize artifact. The 3D VR images are generated throughout the cardiac cycle and provide an animated movie of the valve (4D VR CT), with an emphasis on assessment of systolic leaflet opening. Although leaflets with normal thickness and motion are difficult to visualize clearly on 4D VR CT, thickened leaflets with reduced motion are clearly seen in 3D or 4D images. The systematic methodology used for CT analysis is further summarized in Figure 1.

LEAFLET THICKNESS/THROMBUS BURDEN

This is determined in diastole (leaflets seen to coapt) on the affected leaflet, and the crosshairs in a cross-sectional MPR projection are aligned through the middle of the leaflet, generating a corresponding longitudinal projection (Figure 2). The maximal leaflet

thickness can then be determined and potentially compared to subsequent scans. The leaflet is usually thickest at the insertion point, with the frame or the base, and there may be variable involvement at the inward aspect of the leaflet, which is likely the reason for variability of severity of reduced leaflet motion. Alternative quantification of thrombus burden has also been assessed using maximal HALT area on axial cross-section (Figure 2). Volume of hypoattenuation can also be performed by setting a specific Hounsfield unit (HU) range for detection, although there are perhaps software limitations to this; we have also used Mimics software (Materialise NV, Leuven, Belgium) for this purpose, setting the lower HU range to −200 and the upper HU range to 200.

TAVR-SPECIFIC ANALYSES

Alignment between leaflets and sinus of Valsalva is predictable when a bioprosthesis is surgically implanted, as rotational alignment, stent frame morphology depth, and symmetry of implantation are consistent and is dictated by a standardized surgical technique. However, these factors may be highly variable with TAVR devices and may be relevant to the genesis of subclinical leaflet thrombosis and should also be documented for precise surveillance of changes in a particular leaflet over time; therefore, alignment and these other stent frame-related factors should be assessed systematically, assessing native commissural/bioprosthetic leaflet orientation (Figures 2 and 4), stent frame expansion, and any possible stent frame fracture, depth, and symmetry of implantation (Figure 5).

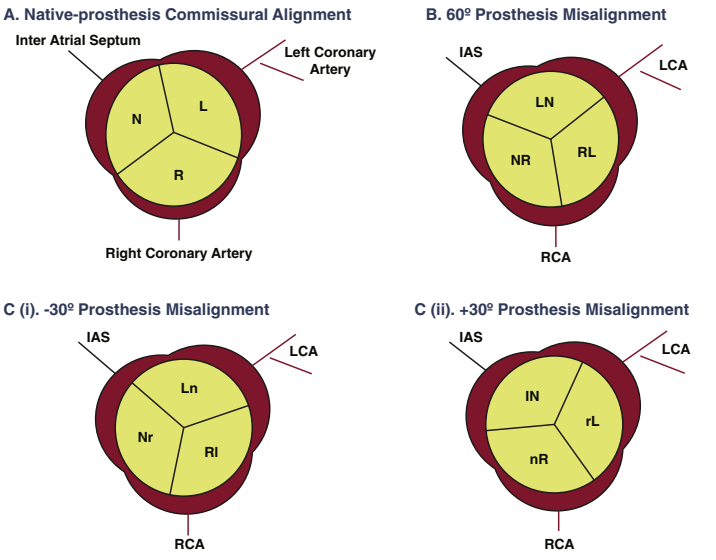
COMMISSURAL/LEAFLET ORIENTATION

Native commissural/bioprosthetic leaflet orientation is important for the precise localization of hypoattenuation and associated reduced leaflet motion (Figures 2 and 4). Whenever leaflets with HALT or, more specifically, abnormal motion are seen, their location is identified on the 2D MPR image based on the orientation with the native aortic valve leaflets. Leaflets within the transcatheter aortic valve are designated right (R), left (L), or noncoronary (N) whenever the bioprosthetic and native commissures are well aligned (Figure 4). If, due to bioprosthetic commissural rotational misalignment with the native commissures, the native commissures bisect the prosthetic commissures, the abnormal leaflets are designated RL, LN, and NR. If there are lesser degrees of commissural rotational misalignment, lower-case letters are used to designate the smaller portion of the affected cusp and an upper-case letter to designate the larger portion of cusp, as divided by native commissures and labeled according to the corresponding native leaflets. This provides 6 additional variations: rL, Rl, lN, Ln, nR, and Nr. This nomenclature was developed to precisely localize any leaflet abnormalities in a way to facilitate direct comparisons between CT and TEE, and to facilitate comparisons with serial imaging.

STENT FRAME, DEPTH, AND SYMMETRY OF IMPLANTATION

A center-line curved multiplanar reconstruction (CMPR) is performed through the center of the prosthesis, with special attention made to ensure that a cross-sectional plane cuts the inflow (most proximal portion) of the stent frame with a precisely coaxial

FIGURE 4 Native Commissural/Bioprosthetic Leaflet Orientation



Whenever a leaflet with abnormal motion was seen, the location of the leaflet was labeled on the 2D axial image based on the relative orientation to the native aortic valve leaflets. Leaflets within the TAVR were designated R (right), L (left), and N (noncoronary) whenever the bioprosthetic and native commissures were well aligned **(A)**. If there was bioprosthetic commissural rotational misalignment with the native commissures, such that the native commissures bisected the prosthetic commissures (60° rotation), then the abnormal leaflets were designated RL, LN, and NR **(B)**. If there were lesser degrees of commissural rotational misalignment (±30° rotation), lower-case letters were used to designate the smaller portion of the affected cusp and an upper-case letter to designate the larger portion of the cusp, as divided by native commissures and labeled according to the corresponding native leaflets **(C) (i and ii)**. This provided 6 additional variations: Rl, Ln, Nr, rL, lN, and nR. This nomenclature was originally developed to localize any leaflet abnormalities to facilitate direct comparisons between CT scans and TEEs. Abbreviations as in Figure 1.

FIGURE 5 TAVR Stent Frame Analysis

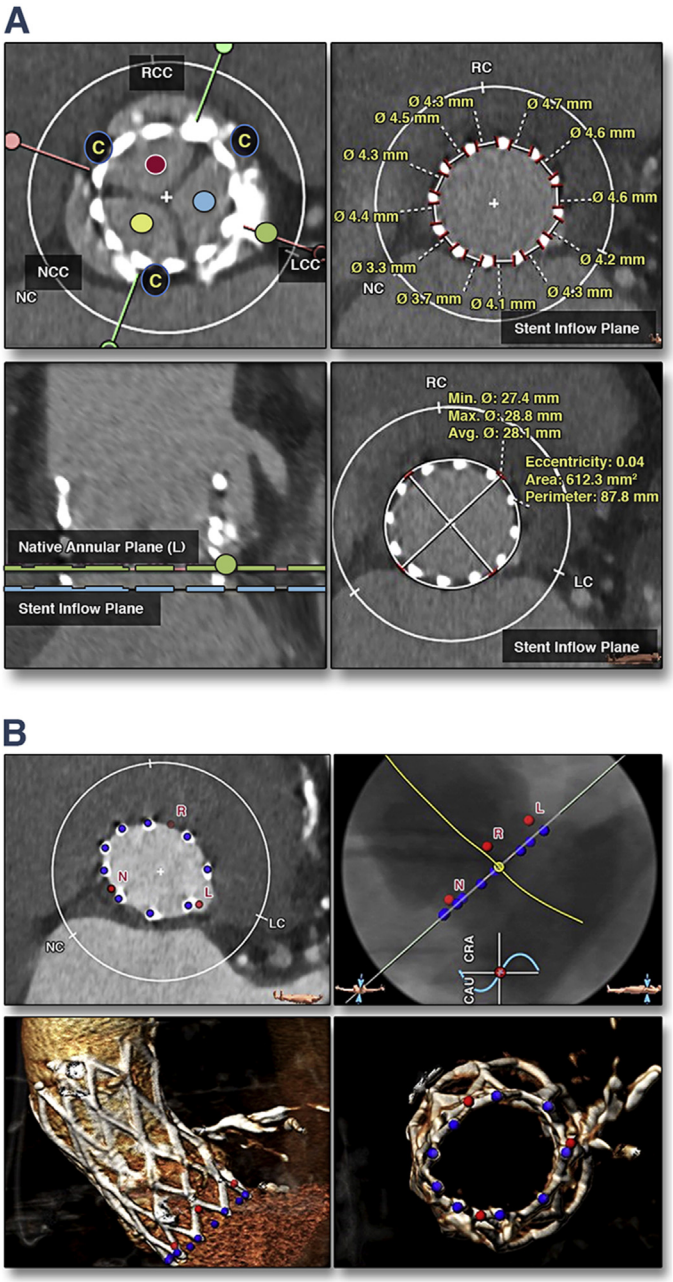


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FIGURE 5 Continued

Detailed analysis of the stent frame and its interaction with the native aortic root, using CT, has contributed to addressing engineering hypotheses for potential leaflet stress that could in turn contribute to leaflet thrombosis. The rotational orientation of bioprosthetic leaflets **([A] top left, red, blue, yellow dots)** is denoted according to native commissures **(C)** and cusps (as described in Figures 2 and 4). A CMPR is used for the stent inflow as the basal plane **([A] bottom left, blue dashed line)**. The vertical distance from the stent frame inflow plane can then be measured to the base of each native leaflet (L, **green dot**, giving LCC native annular plane). This permits an accurate assessment of stent frame depth and stent canting (with the DDEI: difference between largest and smallest depth) that may contribute to nonlaminar flow within the prosthesis, a potential substrate for leaflet thrombosis. **([B] top right** and **bottom left)** The depth of the frame inflow **(blue dots)** in relation to the base of each native leaflet (Left, L, right, R and noncoronary, N, **red dots**) may vary substantially. The exterior aspect of the frame is measured on axial MPR at the inflow **([A] bottom right)**, native annular level, native mid-sinus level. Strut separation is assessed at the inflow level **([A] top right**, **[B] top left** and **bottom right)**; stent frames vary in terms of number of struts at the inflow: in Portico there are 9 **(B)**, in Sapien 3 there are 12 **(A)**, in Evolut-R there are 15, and Lotus has a mesh without struts. The eccentricity of strut separation with some struts close to one another is sometimes referred to by engineers as bunching and is thought to contribute to leaflet stress. The frame is assessed for fracture by using 3D VR **([B] bottom)** and axial projections. CMPR = curved multi-planer center-line reconstruction; DDEI = deployed depth eccentricity index; LCC = left-coronary cusp; MPR = multiplanar reconstruction; NCC = noncoronary cusp; RCC = right coronary cusp.

cut, so that a reliable assessment of stent frame strut separation can be made at this level (Figure 5). This center line reconstruction enables cross-sectional stent frame measurements (minor, major, mean, area, perimeter, and eccentricity) at multiple levels, including at the level of the inflow, as well as at the level of the native aortic annulus and at the mid sinus of Valsalva.

Using the CMPR reconstruction, the external border of the stent frame is measured at the level of the inflow, documenting minor, major, perimeter, and area dimensions (Figure 5). This is repeated at the mid sinus of Valsalva level and may also be performed at the native annular level. At the inflow, the stent strut spaces are measured individually. The first stent strut numbered is defined as the strut closest to the commissure between the noncoronary and right coronary sinuses superiorly. The subsequent struts and their corresponding spaces are then numbered clockwise in ascending order. They are numbered 1 to 9 (Portico, 23 and 26 mm; Sapien or Sapien XT), 1 to 12 (29-mm Sapien XT and 20-, 23-, 26-, and 29-mm S3), and 1 to 15 (Corevalve). Lotus and Direct flow (Direct Flow Medical, Santa Rosa, California) do not have struts and so are excluded from this strut assessment. Strut separation data are used to document maximal strut distance, minimal strut distance, mean strut distance and a strut

eccentricity index (maximal minus minimal strut separation).

Importantly, depth of implantation is also defined as the center line-derived longitudinal distance between the inflow of the stent and the base of the native right, left, and noncoronary leaflets, respectively, the average giving the mean depth of implantation (Figure 5). The maximal and minimal values of these three dimensions are also recorded, and the differences are calculated as the depth eccentricity index, a measurement of degree of angulation of prosthesis alignment in relation to native aortic valve anatomy, a lower number indicating a more coaxial deployment and a higher number a more canted, less coaxial, deployment. This achieved a highly reproducible methodology that precisely accounted for co-axiality of deployment as well as a precise assessment of TAVR depth of implantation.

Potentially relevant factors thus derived from CT scan imaging data include depth of implantation (both as a continuous variable and stratified according to height [<4 mm] and nominal [4 to 8 mm] or low [>8 mm] depth of implantation in relation to the native aortic annulus), stent strut separation (maximal, minimal, mean, and eccentricity), stent dimensions at the inflow (minor, major, mean, perimeter, area, and eccentricity), and mid sinus of Valsalva level. These targeted analyses addressed several engineering hypotheses about potential mechanisms for developing a leaflet mobility issue.

POTENTIAL MECHANISMS OF SUBCLINICAL LEAFLET THROMBOSIS AND THE VALUE OF MULTIMODAL IMAGING

The underlying mechanisms of leaflet thrombosis remain under study (Table 3). Virchow's triad of: 1) flow; 2) vessel wall; and 3) rheology as the drivers for thrombosis is highly relevant. Preliminary data from the Portico trial suggested that low (ventricular) device implantation and low-flow states could be relevant. Cardiac magnetic resonance can determine flow and low-flow states and are also assessed by echocardiography, using gradients, stroke volume, and stroke volume index. The inclusion of many low-flow/low-gradient cases in the early part of the Portico trial might have contributed to the high frequency of subclinical leaflet thrombosis that was observed for all prostheses that was higher than that seen in RESOLVE, SAVORY (1), and other European studies (4,5).

TABLE 3 Putative Underlying Mechanisms for Subclinical Leaflet Thrombosis: Virchow's Triad

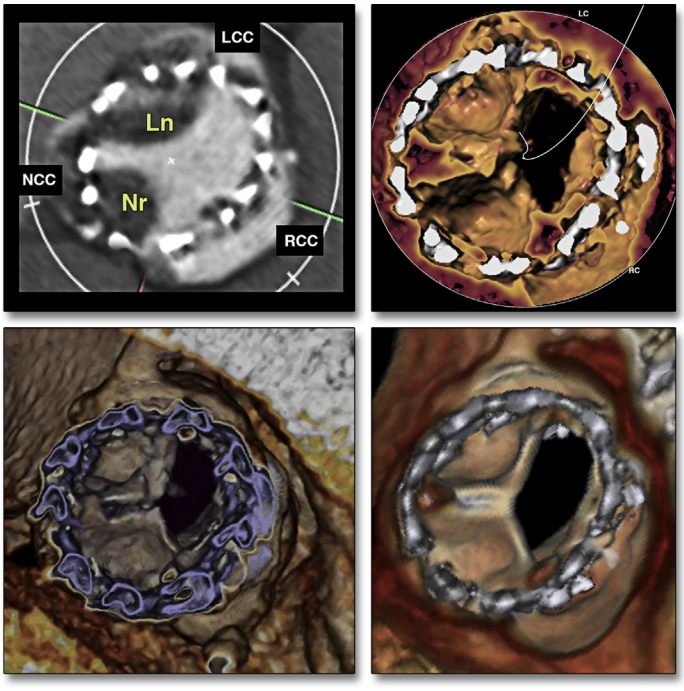
Stasis	Vessel Wall: Endothelial Injury	Rheology: Hypercoagulability
Low flow states (e.g., low EF, LFLG/PLFLG AS)	Leaflet injury (during chemical leaflet fixation, TAVR loading/crimping, balloon dilation or post-dilatation)	Pro-thrombotic states
Device depth: more ventricular placement contributing to nonlaminar flow	Immune activation with leaflet "rejection"	Frame distortion or "strut bunching" causing leaflet asymmetry, folding and pro-coagulable pockets

AS = aortic stenosis; EF = ejection fraction; LFLG = low-flow low-gradient; PLFLG = paradoxical low-flow low gradient; TAVR = transcatheter aortic valve replacement.

POTENTIAL FOR CLINICAL SEQUELAE OF SUBCLINICAL IMAGING FINDING

Although subclinical leaflet thrombosis does not have immediate clinical sequelae by definition (with often normal aortic valve gradients seen on transthoracic echocardiography), there is concern

FIGURE 6 Consistent Findings for HALT and HAM With Different CT Analysis Software



HALT **(top left)** is identified consistently in all 3 software programs used for the evaluation of subclinical leaflet thrombosis. Consistent findings with HALT corresponding to HAM in 2 immobile leaflets (Ln; Nr [abbreviations as in Figure 4]) was noted on 4D VR reconstructions for each software (3D **[top-right]**, Terarecon **[bottom left]**, and VITAL images **[bottom right]**). Abbreviations as in Figures 1 and 4.

for the possibility of later manifestations of serious complications such as embolic phenomena (stroke/myocardial infarction) or premature degeneration (1,6).

It is established that anticoagulation can reverse the hypoattenuation observed and can restore normal leaflet motion but several unanswered questions remain, not least the risk-benefit ratio of such pharmacotherapy in a population at high risk of bleeding. Ongoing and forthcoming clinical trials and registries including Portico, RESOLVE, SAVORY, and GALILEO-4D (Comparison of a Rivaroxaban-based Strategy With an Antiplatelet-based Strategy Following Successful TAVR for the Prevention of Leaflet Thickening and Reduced Leaflet Motion as Evaluated by Four-dimensional, Volume-rendered Computed Tomography [4DCT]) and imaging substudies of TAVR in low-surgery-risk patients from Medtronic and Edwards will help address such questions. A systematic CT imaging methodology, such as that presented here, reproducible regardless of the CT software used (**Figure 6**), is crucial in the standardization of reporting of data from these studies.

CONCLUSIONS

A systematic methodology for the assessment of leaflet thrombosis in aortic bioprostheses detected on CT was devised in the Portico trial; this phenomenon, when imaging was technically optimal, was commonly seen in a range of transcatheter and surgical bioprostheses but largely without apparent clinical sequelae. The methodology presented has contributed to an ongoing discussion among experts to enable, with the help of the Valve Academic Research Consortium, a much-needed standardization of reporting of this imaging finding to cater to the present and future needs of clinical trials.

ADDRESS FOR CORRESPONDENCE: Dr. Hasan Jilaihawi, Heart Valve Center, NYU Langone Medical Center, 530 1st Avenue, Suite 9V, New York, New York 10016. E-mail: hasanjilaihawi@gmail.com.

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APPENDIX For supplemental figures, please see the online version of this article.