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A Novel Angiographic Quantification of Aortic Regurgitation After TAVR Provides an Accurate Estimation of Regurgitation Fraction Derived From Cardiac Magnetic Resonance Imaging

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ABSTRACT

OBJECTIVES This study sought to compare a new quantitative angiographic technique to cardiac magnetic resonance-derived regurgitation fraction (CMR-RF) for the quantification of prosthetic valve regurgitation (PVR) after transcatheter aortic valve replacement (TAVR).

BACKGROUND PVR after TAVR is challenging to quantify, especially during the procedure.

METHODS Post-replacement aortograms in 135 TAVR recipients were analyzed offline by videodensitometry to measure the ratio of the time-resolved contrast density in the left ventricular outflow tract to that in the aortic root (videodensitometric aortic regurgitation [VD-AR]). CMR was performed within an interval of ≤30 days (11 ± 6 days) after the procedure.

RESULTS The average CMR-RF was 6.7 ± 7.0% whereas the average VD-AR was 7.0 ± 7.0%. The correlation between VD-AR and CMR-RF was substantial ($r = 0.78$, $p < 0.001$). On receiver-operating characteristic curves, a VD-AR ≥10% corresponded to >mild PVR as defined by CMR-RF (area under the curve: 0.94; $p < 0.001$; sensitivity 100%, specificity 83%), whereas a VD-AR ≥25% corresponded to moderate-to-severe PVR (area under the curve: 0.99; $p = 0.004$; sensitivity 100%, specificity 98%). Intraobserver reproducibility was excellent for both techniques (for CMR-RF, intraclass correlation coefficient: 0.91, $p < 0.001$; for VD-AR intraclass correlation coefficient: 0.93, $p < 0.001$). The difference on rerating was -0.04 ± 7.9% for CMR-RF and -0.40 ± 6.8% for VD-AR.

CONCLUSIONS The angiographic VD-AR provides a surrogate assessment of PVR severity after TAVR that correlates well with the CMR-RF. (J Am Coll Cardiol Intv 2018;11:287–97) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AUC = area under the curve

CI = confidence interval

CMR = cardiac magnetic resonance

LV = left ventricle/ventricular

PVR = prosthetic valve regurgitation

RF = regurgitation fraction

TAVR = transcatheter aortic valve replacement

VD-AR = videodensitometric aortic regurgitation

Since the introduction of transcatheter aortic valve replacement (TAVR) as a minimally invasive alternative to surgery (1), significant improvements have been introduced to this technology. Currently, TAVR outperforms surgery in many aspects (2), but prosthetic valve regurgitation (PVR) still occurs at a higher rate than after surgery and portends worse prognosis (3). The quantification of PVR is challenging (4). Although long-term surveillance is typically based on echocardiography, recent data support a more reliable prognostic value of cardiac magnetic resonance-derived regurgitation fraction (CMR-RF) (5,6). This superior prognostication is added to some other well-known advantages of CMR over echocardiography, including more reproducible and quantitative assessment (4). CMR can, therefore, be considered as an ideal tool to quantify PVR but is limited by a number of logistic constraints. The high cost, limited availability, technical demand, and incompatibility with some implanted cardiac rhythm devices all make CMR a less practical tool for routine PVR assessment compared with echocardiography (4).

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Recently, the minimalist TAVR approach is increasingly adopted by large TAVR centers. In this approach, general anesthesia is replaced by sedation and transesophageal echocardiography is seldom an option. In this setting, angiographic assessment, which currently serves as the first screening tool in most laboratories, is becoming even more crucial in determining the severity of PVR during the procedure. Angiographic assessment using the classic visual (Sellers') method (7) bears many limitations, including subjectivity and lack of precise quantification (4). Quantitative videodensitometric aortic regurgitation (VD-AR) assessment was recently reported to overcome the limitations of the Sellers' method (4,8,9). In this study, we sought to compare 2 quantitative modalities for PVR assessment; a well-established modality that cannot be used in the cath lab (CMR-RF) and a novel one which has the potential to be applied in the cath lab for PVR quantification and decision-making guidance (VD-AR). The primary objective was to estimate the correlation between these 2 modalities, whereas the secondary objective was to compare their reproducibility.

METHODS

STUDY POPULATION. All patients who were treated with TAVR and had a CMR study performed after the procedure at the Heart Center, Segeberger Kliniken GmbH (Bad Segeberg, Germany), were screened for inclusion in this study. The flow chart of the study is displayed in Online Figure 1. The main reason for exclusion was VD-AR nonanalyzability (principally due to overlap of the regions of interest by the contrast-filled descending aorta [83%] or breathing motions [9%]). A total of 135 consecutive patients treated with TAVR who had quantitative angiographic and CMR assessments of PVR performed within an interval of ≤30 days constituted the study population. Data collection was approved by the institutional review board, and all patients signed a written informed consent.

QUANTITATIVE AORTIC ROOT ANGIOGRAPHY USING VIDEODENSITOMETRY. Aortic root angiography was performed after valve replacement using a nonionic contrast (25 to 30 ml) injected through a pigtail catheter positioned above the prosthetic valve (in case of a balloon- or mechanically-expandable device) or within the distal third of the prosthetic valve (in case of a self-expanding device). A dedicated software (CAAS A-Valve 2.0.2, Pie Medical Imaging, Maastricht, the Netherlands) was used for offline analysis of the angiograms. The details of this technique have been described elsewhere (9,10). Briefly, the aortic root and the subaortic (basal) one-third of the left ventricle (LV) are manually traced, and the aortic valve annular plane is indicated to define the distal end of the LV region of interest. Contrast time-density curves are generated for both the region of interest (in the LV) and the reference region (the aortic root) from at least 3 cardiac cycles after contrast

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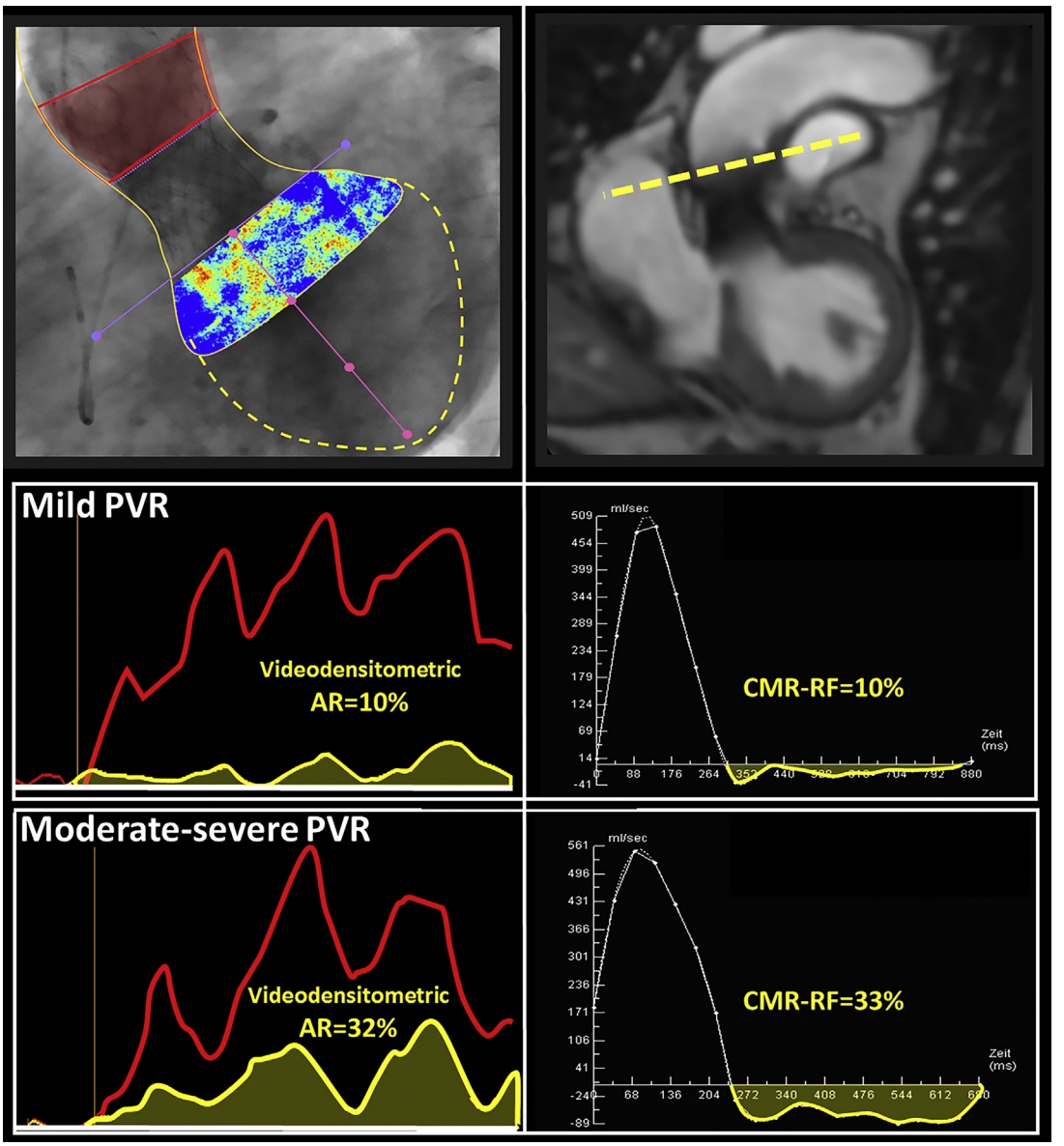
FIGURE 1 Quantitative Assessment of Prosthetic Valve Regurgitation by Videodensitometric Aortography and CMR



(Top, left) A post-transcatheter aortic valve replacement aortogram with videodensitometric analysis. A color-weighted contrast time-density map is superimposed on the subaortic segment of the ventricle, whereas the reference region (aortic root) is highlighted with **red color**. **(Top, right)** Steady-state free precession cardiac magnetic resonance (CMR) image (**yellow dotted line** = imaging plane for velocity mapping). **(Middle and Bottom)** Two examples of post-transcatheter aortic valve replacement patients with mild and moderate-to-severe prosthetic valve regurgitation. On videodensitometric angiographic analysis **(left)**, the area under the contrast time-density curve of the left ventricular outflow tract **(yellow)** is divided by that of the aortic root **(red)** to yield videodensitometric aortic regurgitation (AR). On CMR **(right)**, the backward flow (below the baseline) is divided by the forward flow (above the baseline) to yield the regurgitation fraction (RF) (CMR-RF).

injection. From these time-density curves, the area under the curve (AUC) is automatically calculated to represent the time-density integral. VD-AR corresponds to the relative AUC, which is automatically calculated by dividing the AUC of the LV region of interest by the AUC of the aortic root (Figure 1). VD-AR was analyzed by an independent core laboratory (Cardialysis Clinical Trials Management and Core

Laboratories, Rotterdam, the Netherlands) and observers were blinded to all baseline, procedural, and CMR data. Rerating by the same observer was performed in 75 cases to test the intrinsic variability of the method.

CMR IMAGING PROTOCOL AND DATA ANALYSIS. All patients were investigated by electrocardiogram-gated CMR in the supine position with a 5-element cardiac phased-array coil using a 1.5-T whole-body scanner (Magnetom Espree, Siemens AG, Erlangen, Germany). The flow signal at the level of the stent of the prosthetic valve could be safely interrogated by CMR as previously described (11,12).

For flow measurements, a breath-hold velocity-encoded phase contrast magnetic resonance sequence was used ("through plane," segmented fast low-angle shot 2-dimensional sequence, repetition time = 46.0 ms, echo time = 2.7 ms, velocity encoding = 150 to 300 cm/s^{-1}, scan in expiration, scan duration around 10 s). The slice was positioned perpendicular to the long axis of the ascending aorta closely beneath the upper margin of the stent of self-expanding prostheses or at a corresponding distance from the aortic annulus for all other shorter TAVR prostheses. This position was chosen as it had been proven to be less susceptible to artifacts caused by the valve and stent compared with a lower position, and a perpendicular cut through the ascending aorta could be achieved more accurately. In fact, no visible artifacts of the valve or the stent were seen on the analyzed images. Contrast administration was not necessary for both cine imaging and flow measurements. Consequently, no patients were excluded because of impaired renal function.

CMR data were analyzed by 2 independent and experienced observers. No formal blinding was performed, but observers had no access to the results of echocardiography or angiography data at the time of CMR evaluation. Rerating by the same observer was performed in 75 randomly elected cases to test the intrinsic variability of the method.

For the assessment of the aortic RF, the cross-sectional area of the ascending aorta was defined and manually corrected for motion artifacts that occurred during the breath hold scan. Using a standard software (Argus WIP 2.3, Siemens AG, Erlangen, Germany), the forward and reverse volumes within this region of interest were determined, and the RF was calculated as follows: (regurgitant volume/total forward volume) × 100 (**Figure 1**). CMR-RF of ≤15% was graded as trace-mild and >30% was graded as moderate-to-severe PVR according to criteria used in previous TAVR studies (11–13).

STATISTICS. When nonparametric statistical methods were used, we summarized data as median (interquartile range) instead of mean ± SD. Categorical variables were summarized as frequencies and percentages. The distribution of CMR-RF and VD-AR across the angiographic visual Sellers' grades was compared using Mann–Whitney *U* test. The relationship between continuous parameters of AR severity was tested using Pearson correlation whereas the relation between quantitative and qualitative parameters was tested using Spearman correlation. For the correlation between VD-AR and CMR-RF, the sample size was estimated to be at least 19 data pairs (for α level of 0.05, a β level of 0.20 [power = 80%], and a hypothesized correlation coefficient r = 0.60 [denoting at least moderate correlation]). Fisher r-to-z transformation was used to assess the significance of the difference between 2 correlation coefficients. Receiver-operating characteristic curves were generated for the VD-AR values that correspond to mild and moderate-to-severe PVR as defined by CMR-RF. The area under the receiver-operating characteristic curve was calculated and the cutpoints were defined on the basis of the highest sum of sensitivity and specificity. The reproducibility of CMR-RF and VD-AR was assessed by calculating the intraclass correlation coefficient presented with its 95% confidence interval (CI). The difference on rerating was displayed using the Bland-Altman method and the 95% limits of agreement were estimated as ± 1.96 × SD of the difference. Statistical analysis was performed with SPSS version 23 (IBM Corporation, Armonk, New York). All probability values were 2 tailed, and a value of $p < 0.05$ was considered statistically significant.

RESULTS

The study included 135 patients who underwent TAVR principally through a transfemoral approach (97.0%) and were treated either with a balloon-expandable (60.5%), self-expanding (32.0%), or mechanically expanding (7.5%) bioprosthesis. The baseline characteristics of the study population are summarized in **Table 1**.

ASSESSMENT OF PVR. PVR severity was assessed by procedural angiography and by CMR performed within 30 days (11 ± 6 days) after the procedure. During CMR, 83 patients (62%) were in sinus rhythm with an average heart rate of 67 ± 12 beats/min.

TABLE 1 Baseline Characteristics of the Study Population (n = 135)

Age, yrs	81 ± 6
Male	57 (42)
BMI, kg/m^2	27 ± 5
Logistic EuroSCORE	23.2 ± 16.7
STS score	6.2 ± 6.7
Hypertension	125 (93)
Diabetes mellitus	36 (27)
Dyslipidemia	68 (50)
NYHA functional class III–IV	88 (65)
Atrial fibrillation	52 (39)
Chronic obstructive pulmonary disease	20 (15)
Coronary artery disease	93 (69)
Previous PCI	48 (36)
Previous CABG	28 (21)
Previous SAVR	8 (6)
Cerebrovascular disease	20 (15)
Peripheral arterial disease	20 (15)
Chronic kidney disease	30 (22)
LV ejection fraction, %	54 ± 13
Transaortic valve mean PG, mm Hg	44 ± 18
Aortic valve area, cm^2	0.64 ± 0.28
Aortic annulus diameter (on TEE), mm	23.1 ± 2.2
sPAP, mm Hg	46.5 ± 15.9
Mitral regurgitation, moderate-severe	34 (25)
Aortic regurgitation, moderate-severe	23 (17)

Values are mean ± SD or n (%).

BMI = body mass index; CABG = coronary artery bypass grafting; LV = left ventricle; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PG = pressure gradient; SAVR = surgical aortic valve replacement; sPAP = systolic pulmonary artery pressure; STS = Society of Thoracic Surgeons; TEE = transesophageal echocardiography.

The remainder had atrial fibrillation with an average heart rate of 69 ± 12 beats/min. The average CMR-RF was (6.7 ± 7.0%; median 4.7% [interquartile range: 1.6% to 9.2%]) whereas the average VD-AR was (7.0 ± 7.0%; 5.0% [interquartile range: 2.0% to 9.0%]). Online Figure 2 displays the cumulative curves of PVR severity as assessed by both techniques. On pre-discharge transthoracic echocardiography, PVR was graded as none or trace in 77 patients (57%), as mild in 54 patients (40%), and as moderate in 4 patients (3%).

QUANTITATIVE VERSUS QUALITATIVE ASSESSMENT OF PVR BY CMR AND ANGIOGRAPHY. The visual (Sellers') grades of PVR severity on post-implantation angiography were none (Sellers' 0) in 39 patients (28.9%), mild (Sellers' I) in 74 patients (54.8%), moderate (Sellers' II) in 15 patients (11.1%), and moderate-to-severe (Sellers' III) in 8 patients (5.9%). The distributions of CMR-RF and VD-AR across the Sellers' grades are shown in **Figures 2A and 2B**. Spearman's coefficient of correlation between Sellers' grades and CMR-RF was 0.25 and between Sellers' grades and VD-AR was 0.55 ($p < 0.001$).

INTERMODALITY AGREEMENT IN THE QUANTITATIVE ASSESSMENT OF PVR. The correlation between VD-AR and CMR-RF was substantial (Pearson $r = 0.78$; $p < 0.001$) (**Figure 3**). The correlation remained significant in the following patient subgroups: patients with atrial fibrillation ($n = 52$; $r = 0.77$), patients who received a self-expanding device ($n = 42$; $r = 0.86$), patients in whom balloon post-dilatation was performed ($n = 24$; $r = 0.82$), and patients in whom aortographic acquisition projection was LAO ($n = 96$; $r = 0.73$; $p < 0.001$ for all).

On receiver-operating characteristic curves, a VD-AR ≥10% corresponded to >mild PVR as defined by CMR-RF (AUC: 0.94; 95% CI: 0.90 to 0.98; $p < 0.001$; sensitivity: 100%; specificity: 83%), whereas a VD-AR ≥25% corresponded to moderate-to-severe PVR (AUC: 0.99; 95% CI: 0.98 to 1.00; $p = 0.004$; sensitivity: 100%; specificity: 98%).

REPRODUCIBILITY OF THE 2 QUANTITATIVE TECHNIQUES OF PVR ASSESSMENT. To investigate the inherent variability of the method, CMR-RF was rerated by the same analyst in the same session in 75 randomly selected cases. The intraclass correlation coefficient was 0.91 (95% CI: 0.86 to 0.95; $p < 0.001$). As shown in Online Figure 3A, the average bias on rerating was −0.04% whereas the 95% limits of agreement were ±7.9%.

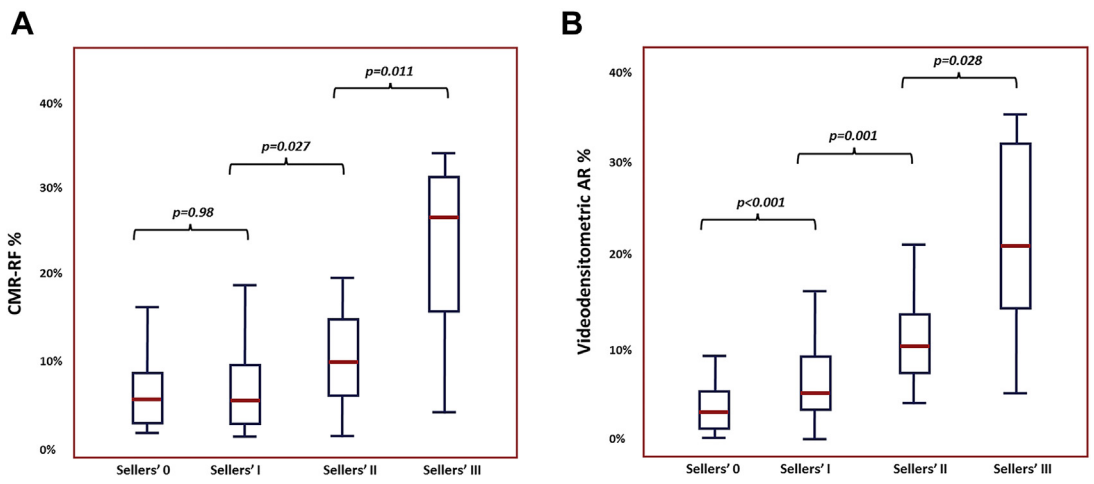
In Online Figure 4, patient-dots were labeled to indicate the cardiac rhythm (atrial fibrillation vs. sinus rhythm) during CMR acquisition. The average bias was similar regardless of the cardiac rhythm, but the limits of agreement were wider apart in patients with atrial fibrillation (±10.6%) than in patients in sinus rhythm (±6.7%).

VD-AR was also rerated by the same analyst in the same 75 cases. The intraclass correlation coefficient was 0.93 (95% CI: 0.88 to 0.95; $p < 0.001$). As shown in Online Figure 3B, the average bias on rerating was −0.40% and the 95% limits of agreement were ±6.8%.

DISCUSSION

In the present study, VD-AR was shown to provide a surrogate assessment of the regurgitant fraction (as defined by CMR) with a comparable reproducibility. Therefore, VD-AR has a 2-fold advantage: 1) it is angiography based, and hence is available in all procedures; and 2) it provides a reproducible quantitative assessment of PVR severity.

FIGURE 2 Distribution of CMR-RF and Videodensitometric AR Across the Angiographic Sellers' Grades of Prosthetic Valve Regurgitation Severity



(A) There has been an overlap between cardiac magnetic resonance–derived regurgitation fraction (CMR-RF) and Sellers' grades of aortic regurgitation (AR), especially between Sellers' 0 and Sellers' I ($p > 0.05$). **(B)** The overlap between videodensitometric AR and Sellers' grades was less remarkable.

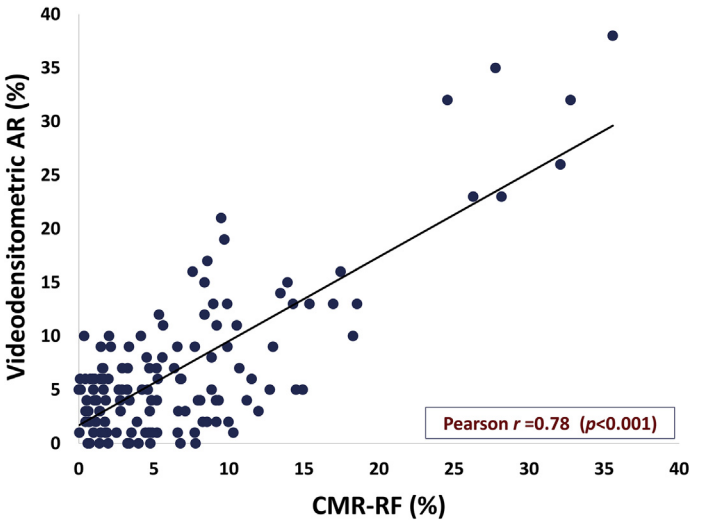
VD-AR has been shown to be feasible (10) and reproducible (9,10) and to correlate with echocardiographic assessment (8) and with clinical outcomes (8,9). Additionally, in an in vitro validation (n = 29 observations) in a PVR model of a balloon-expandable device implanted in a mock circulation system (14-16), VD-AR was shown to closely correlate ($r^2 = 0.964$; $y = 0.816x - 3.049$) with the regurgitation fraction measured by a transonic flow probe. In the present study, in vivo accuracy and precision of this technique were further confirmed.

The incidence of PVR after TAVR has dramatically improved thanks to improved valve design and size range and, most importantly, to proper sizing (4). However, the incidence of mild PVR remains high—albeit with controversial prognostic relevance (17-20)—and the extension of TAVR indications to patients with bicuspid or predominantly-regurgitant aortic valves is expected to increase the potential for PVR (4). PVR remains, therefore, an important limitation of TAVR as compared with surgery and its timely detection, accurate quantification, and effective elimination remain of crucial importance. For this target to be achieved, a reliable intraprocedural tool to detect and quantify PVR is required. Transesophageal echocardiography, which has long been the standard intraprocedural tool for PVR assessment, is now progressively less utilized in the era of "minimalist TAVR" (21). Although transthoracic echocardiography was reported to be an efficient alternative for procedural guidance (22), its intraprocedural use is complicated by important technical constraints (23). The invasively measured AR index was shown to define the severity of PVR and an AR index of <25 correlated with clinical outcome after TAVR (24). However, the specificity of AR index is modest and an AR index of <25 often coexists with no or trivial AR, particularly in the presence of relative bradycardia (25).

Aortic root angiography is the first screening tool for PVR in most laboratories and is a quick and friendly tool to the interventionists. However, the visual (Sellers') assessment is subjective, qualitative, and nonvalidated in the post-TAVR setting (4). It has been previously reported that native aortic valve regurgitation volume and fraction measured by magnetic flowmetry (26) and by cardiac catheterization (using Fick's method and left ventriculography) (27-29) markedly overlap between the Sellers' grades. In the setting of TAVR, comparison of the Sellers' grades with PVR volume and fraction revealed that there is only a moderate correlation with a significant overlap between the Sellers' grades and PVR volume or fraction (30). In the present study, this overlap was further confirmed (**Figures 2A and 2B**).

IMPLEMENTATION OF THE VD-AR TECHNOLOGY INTO ROUTINE CLINICAL PRACTICE. There are currently 3 main issues that need to be dealt with, to allow for the routine use of VD-AR (**Figure 4**). First, the limited analyzability rate, ranging from 43% (in the present study) to 65% and 68% (in previous studies) (8,9), is a major shortcoming of this new angiographic technique when applied retrospectively to aortograms that have not been acquired following a standardized acquisition protocol. The limited yield is principally (>90%) due to technical operator-dependent factors, mostly involving an overlap of the contrast-filled descending aorta on the LV outflow tract or aortic root (**Figure 4A**) (31). The definition of a patient-specific overlap-free fluoroscopic projection is now possible, thanks to computed tomographic planning, and is reliable in 98% of cases (32). As shown in **Figures 4B and 4C**, an overlap-free projection can be predicted using computed tomography well in advance of the procedure. An alternative simplified rule is to choose an angulation of ≥35° to 40° toward the same side as the descending aorta relative to a vertical line that hemisects a diagonal line extending from LV apex to the ascending aorta (**Figures 4D and 4E**).

FIGURE 3 Linear Correlation Between CMR-RF and Videodensitometric AR



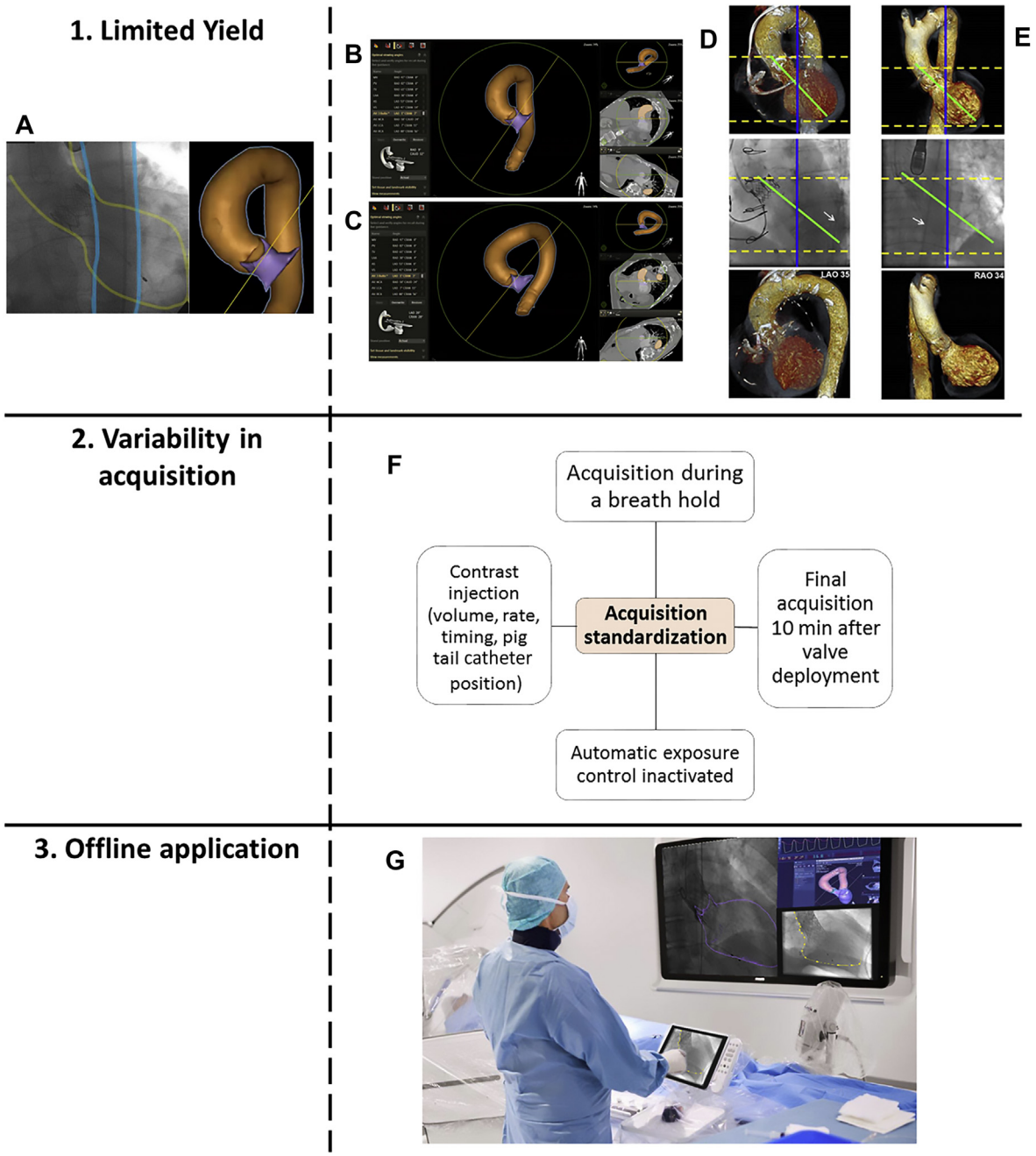
The scatter plot shows that the linear relationship is weaker at the lower CMR-RF values (<5%). Abbreviations as in **Figure 2**.

Second, one further step to optimize the accuracy and reproducibility of the results of this new technique, is angiographic acquisition standardization. This includes standardization of the volume, rate, and timing of contrast injection as well as the position of the catheter tip. Based on an in vitro validation model, injection of 20 ml of contrast at a rate of 20 ml/s with the catheter tip positioned ≤20 mm above the aortic (prosthetic) valve leaflets seems to provide excellent accuracy and reproducibility (16). A short diastolic injection synchronized to an electrocardiographic trigger can also help reduce the contrast volume to 8 ml per injection (16). Due to the observation seen in some TAVR cases, that PVR shows a marked improvement within few minutes after valve implantation (likely due to the interaction of the external sealing skirt with the landing zone, which probably needs few minutes to be established), it is recommended to delay the final aortographic acquisition to 10 min after final valve deployment. It is also important not to overlook the influence of "Automatic Exposure Control" characteristic built into most of angiographic acquisition systems. This mode implies a dynamic adjustment of the x-ray exposure, and hence change of pixel darkness, to maintain a constant image quality at the expense of oscillating brightness. Such a property can influence the automatic VD assessment of contrast density, and should thus be inactivated when VD assessment is intended.

Third, enabling a real-time online use of VD-AR within the cath lab helps guide the decision making as whether a corrective measure is required and judging its effectiveness. Currently, offline analysis entails a manual contour tracing. Although this tracing typically requires <1 min, it can be made even faster and more reproducible through the overlay of the pre-loaded computed tomographic contours of the heart and aortic root on the fluoroscopic images. This can potentially enable instant analysis of VD-AR within few seconds, instead of the current method, which requires, on average, 3 min per analysis. A feasibility study of the online implementation of the technology is currently underway with the results being anticipated in 2018 (31). **Figure 4** summarizes the current technical limitations of the technology and the respective ongoing or proposed solutions to help its clinical implementation.

Overall, one intrinsic limitation of aortography in assessing PVR, is the inability to discriminate transvalvular from paravalvular regurgitation. Although significant post-TAVR PVR is often paravalvular, confirmation of the mechanism of regurgitation is still important before performing a corrective maneuver

FIGURE 4 Technical Limitations of Videodensitometric AR and the Respective Practical Solutions



The 3 major technical limitations of videodensitometric AR technology are listed in the **left-hand side column** and their respective ongoing or proposed solutions listed in the respective cells of the **right-hand side column**. The limited yield (analyzability) is principally due to **(A)** an overlap of the contrast filled descending aorta on the regions of interest. **(B, C)** An overlap free-projection can be predicted using baseline computed tomography. **(D, E)** Another option to get an overlap-free projection has been proposed by Teng et al. (32): the posterior-anterior projection on fluoroscopy **(middle)** and on computed tomography **(top)** as well as an overlap-free fluoroscopic projection **(bottom)** of 2 patients **(D, E)** are shown. A **diagonal green line** extending from the left ventricular apex to ascending aorta is hemisected by a **blue vertical line**. The catheter path in the descending aorta is indicated by the white arrows. **(D)** The descending aorta is predominantly to the **left side of the blue line**, and an LAO 35° projection was overlap-free. **(E)** The descending aorta is predominantly on the **right side of the blue line**, and an RAO 34° projection was overlap-free. **(F)** The main elements of a standardized aortographic acquisition protocol to improve accuracy and reproducibility of videodensitometric AR. Figure **G** shows how the integration of the videodensitometric AR technology into an on-line workflow in the cath lab can be helped by the HeartNavigator technology (Philips Healthcare, Eindhoven, the Netherlands) to impose the cardiac contours over the fluoroscopic images precluding the need for manual tracing. Adapted with permission from Sahyoun (31) and Teng et al. (32).

(e.g., post-dilatation). Therefore, in selective cases where VD-AR reveals a significant regurgitation, an ad hoc echocardiographic confirmation of a paravalvular mechanism of regurgitation before a corrective measure is undertaken is reasonable.

It should also be noted that the increasing reliance on aortography in procedural guidance will require the use of a larger volume of contrast medium with the potential to increase the risk of acute kidney injury. This caveat calls even more for complimentary roles of VD-AR and echocardiography. The higher sensitivity of videodensitometry in detecting contrast density, as compared with visual assessment, enabled the introduction of a novel contrast-sparing synchronized (diastolic-only) aortographic injection technique. The latter has been tested in an in vitro setting, and enabled the reduction of the contrast volume from 20 ml to 8 ml per injection without compromising diagnostic accuracy (16).

Finally, it is important to establish a VD-AR cutpoint that defines device success and the need for—and the efficacy of—a corrective measure. Although a VD-AR of ≥25% corresponded to moderate-severe AR as defined by CMR in the present study, current evidence (8,9,33) suggests that even lower VD-AR values (>17%) correspond to a "clinically-relevant" PVR.

CMR-RF AS A REFERENCE STANDARD. Echocardiographic criteria of PVR severity, although advocated by the Valve Academic Research Consortium, are not adequately validated (34). Additionally, the reproducibility of these criteria is limited (35), and can be improved through an approach that combines qualitative and semi-quantitative but not quantitative parameters (36). Although not without limitations (4), CMR-RF is a reliable measure of PVR severity, and outperforms echocardiography in predicting clinical outcomes in patients with native (6) and prosthetic (5) AR. Moreover, like angiography, accuracy of CMR is less influenced by the number and eccentricity of the paravalvular leaks than echocardiography. Therefore, we used CMR-RF as a reference standard in the present study. It should be noted, however, that the diagnostic accuracy of CMR-RF is lower in mild AR (4). CMR-RF was not significantly different in patients with mild AR (as defined by echocardiography) than in healthy subjects in some studies (37,38). The closing volume (3.3 ± 1.2 ml per beat) (39) and the coronary flow (1.5 ml to 3.0 ml per beat in average) (40) are possible explanations of this phenomenon. It is also worth-mentioning that there is no consensus on the CMR-RF cutpoints of AR severity (4), and that the cutpoints used in this study are not well established. In the setting of TAVR, the underlying LV is hypertrophied with a small cavity and stroke volume. Therefore, a relatively small absolute regurgitation volume might correspond to a large regurgitation fraction (18). Accordingly, regurgitation fraction is likely more reliable in the setting of TAVR than regurgitation volume to reflect the actual severity of PVR. Additionally, the concept of the relative AUC on videodensitometry is more in line with the fraction—than the absolute volume—of regurgitation.

STUDY LIMITATIONS. An interval of 30 days (average = 11 days) between angiography and CMR was allowed and changes of blood pressure and heart rate might have influenced the assessment of AR severity between the 2 time points. Therefore, the correlation between both methods might have been stronger if both techniques were performed in the same day. However, this ideal scenario is impractical for a TAVR patient.

The regions of interest were drawn manually and this might have introduced some variability to the measurements. However, this effect seems to be minor as evidenced by the excellent reproducibility on repeat assessment. Efforts to make this process automated using co-registration with baseline computed tomographic images are underway.

CONCLUSIONS

The present study aimed at comparing a novel tool to a well-established tool of PVR quantification. The novel tool (VD-AR) provides a surrogate assessment of PVR after TAVR that correlated well with the CMR-RF. Moreover, the reproducibility of VD-AR is very much the same as that of CMR-RF.

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PERSPECTIVES

WHAT IS KNOWN? Aortic regurgitation quantification is required during TAVR procedures to guide timely corrective measures and improve outcomes.

WHAT IS NEW? Angiographic quantification of AR using VD provides an accurate estimation of the CMR-derived regurgitation fraction.

WHAT IS NEXT? Online application and standardized angiographic acquisition of this novel technique will enable implementation into routine clinical practice.

REFERENCES

1. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106:3006–8.

2. Abdelghani M, Serruys PW. Transcatheter aortic valve implantation in lower-risk patients with aortic stenosis: is it justified to be the preferred treatment? Circ Cardiovasc Interv 2016;9:e002944.

3. Athappan G, Patvardhan E, Tuzcu EM, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. J Am Coll Cardiol 2013;61:1585–95.

4. Abdelghani M, Soliman OI, Schultz C, Vahanian A, Serruys PW. Adjudicating paravalvular leaks of transcatheter aortic valves: a critical appraisal. Eur Heart J 2016;37:2627–44.

5. Ribeiro HB, Orwat S, Hayek SS, et al. Cardiovascular magnetic resonance to evaluate aortic regurgitation after transcatheter aortic valve replacement. J Am Coll Cardiol 2016;68:577–85.

6. Harris AW, Krieger EV, Kim M, et al. Cardiac magnetic resonance imaging versus transthoracic echocardiography for prediction of outcomes in chronic aortic or mitral regurgitation. Am J Cardiol 2017;119:1074–81.

7. Sellers RD, Levy MJ, Amplatz K, Lillehei CW. Left retrograde cardioangiography in acquired cardiac disease: technic, indications and interpretations in 700 cases. Am J Cardiol 1964;14:437–47.

8. Abdelghani M, Tateishi H, Miyazaki Y, et al. Angiographic assessment of aortic regurgitation by video-densitometry in the setting of TAVI: echocardiographic and clinical correlates. Catheter Cardiovasc Interv 2017;90:650–9.

9. Tateishi H, Campos CM, Abdelghani M, et al. Video densitometric assessment of aortic regurgitation after transcatheter aortic valve implantation: results from the Brazilian TAVI registry. EuroIntervention 2016;11:1409–18.

10. Schultz CJ, Slots TL, Yong G, et al. An objective and reproducible method for quantification of aortic regurgitation after TAVI. EuroIntervention 2014;10:355–63.

11. Sherif MA, Abdel-Wahab M, Beurich HW, et al. Haemodynamic evaluation of aortic regurgitation after transcatheter aortic valve implantation using cardiovascular magnetic resonance. EuroIntervention 2011;7:57–63.

12. Merten C, Beurich HW, Zachow D, et al. Aortic regurgitation and left ventricular remodeling after transcatheter aortic valve implantation: a serial cardiac magnetic resonance imaging study. Circ Cardiovasc Interv 2013;6:476–83.

13. Abdel-Wahab M, Mehilli J, Frerker C, et al. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. JAMA 2014;311:1503–14.

14. Schampaert S, Pennings KA, van de Molengraft MJ, Pijls NH, van de Vosse FN, Rutten MC. A mock circulation model for cardiovascular device evaluation. Physiol Meas 2014;35:687–702.

15. Bozkurt S, van de Vosse FN, Rutten MC. Enhancement of arterial pressure pulsatility by controlling continuous-flow left ventricular assist device flow rate in mock circulatory system. J Med Biol Eng 2016;36:308–15.

16. Miyazaki Y, Abdelghani M, de Boer ES, et al. A novel synchronized diastolic injection method to reduce contrast volume during aortography for aortic regurgitation assessment: in-vitro experiment of a transcatheter heart valve model. EuroIntervention 2017;13:1288–95.

17. Buzzatti N, Castiglioni A, Agricola E, et al. Five-year evolution of mild aortic regurgitation following transcatheter aortic valve implantation: early insights from a single-centre experience. Interact Cardiovasc Thorac Surg 2017;25:75–82.

18. Jerez-Valero M, Urena M, Webb JG, et al. Clinical impact of aortic regurgitation after transcatheter aortic valve replacement: insights into the degree and acuteness of presentation. J Am Coll Cardiol Intv 2014;7:1022–32.

19. Kampaktsis PN, Bang CN, Chiu Wong S, et al. Prognostic importance of diastolic dysfunction in relation to post procedural aortic insufficiency in patients undergoing transcatheter aortic valve replacement. Catheter Cardiovasc Interv 2017;89:445–51.

20. Kodali S, Pibarot P, Douglas PS, et al. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. Eur Heart J 2015;36:449–56.

21. Oguri A, Yamamoto M, Mouillet G, et al. Clinical outcomes and safety of transfemoral aortic valve implantation under general versus local anesthesia: subanalysis of the French Aortic National CoreValve and Edwards 2 registry. Circ Cardiovasc Interv 2014;7:602–10.

22. Sengupta PP, Wiley BM, Basnet S, et al. Transthoracic echocardiography guidance for TAVR under monitored anesthesia care. J Am Coll Cardiol Img 2015;8:379–80.

23. Bartel T, Edris A, Velik-Salchner C, Muller S. Intracardiac echocardiography for guidance of transcatheter aortic valve implantation under monitored sedation: a solution to a dilemma? Eur Heart J Cardiovasc Imaging 2016;17:1–8.

24. Sinning JM, Hammerstingl C, Vasa-Nicotera M, et al. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. J Am Coll Cardiol 2012;59:1134–41.

25. Jilaihawi H, Chakravarty T, Shiota T, et al. Heart-rate adjustment of transcatheter haemodynamics improves the prognostic evaluation of paravalvular regurgitation after transcatheter aortic valve implantation. EuroIntervention 2015;11:456–64.

26. Mennel RG, Joyner CR Jr., Thompson PD, Pyle RR, Macvaugh H 3rd The preoperative and operative assessment of aortic regurgitation. Cineaortography vs. electromagnetic flowmeter. Am J Cardiol 1972;29:360–6.

27. Hunt D, Baxley WA, Kennedy JW, Judge TP, Williams JE, Dodge HT. Quantitative evaluation of cineaortography in the assessment of aortic regurgitation. Am J Cardiol 1973;31:696–700.

28. Croft CH, Lipscomb K, Mathis K, et al. Limitations of qualitative angiographic grading in aortic or mitral regurgitation. Am J Cardiol 1984;53:1593–8.

29. Michel PL, Vahanian A, Besnainou F, Acar J. Value of qualitative angiographic grading in aortic regurgitation. Eur Heart J 1987;8 Suppl C:11–4.

30. Frick M, Meyer CG, Kirschfink A, et al. Evaluation of aortic regurgitation after transcatheter aortic valve implantation: aortic root angiography in comparison to cardiac magnetic resonance. EuroIntervention 2016;11:1419–27.

31. Sahyoun C. Video-densitometric assessment of aortic regurgitation: standardising acquisition and implementation into daily practice. Presented in: EuroPCR 2017; May 16, 2017; Paris, France.

32. Teng J, Nijenhuis V, Swaans M, Yong G, Schultz C. How to plan an Overlap Free Projection on CTA or fluoroscopy to facilitate quantitative analysis. EuroIntervention 2017 June 13 [E-pub ahead of print].

33. Tateishi H, Abdelghani M, Cavalcante R, et al. The interaction of de-novo and pre-existing aortic regurgitation after TAVI: Insights from a new quantitative aortographic technique. EuroIntervention 2017;13:60–8.

34. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). Eur J Cardiothorac Surg 2012;42:S45–60.

35. Hahn RT, Pibarot P, Weissman NJ, Rodriguez L, Jaber WA. Assessment of paravalvular aortic regurgitation after transcatheter aortic valve replacement: intra-core laboratory variability. J Am Soc Echocardiogr 2015;28:415–22.

36. Abdelghani M, Ren B, Spitzer E, et al. A granular approach to improve reproducibility of the echocardiographic assessment of paravalvular regurgitation after TAVI. Int J Cardiovasc Imaging 2016;32:1519–27.

37. Honda N, Machida K, Hashimoto M, et al. Aortic regurgitation: quantitation with MR imaging velocity mapping. Radiology 1993;186:189–94.

38. Gabriel RS, Renapurkar R, Bolen MA, et al. Comparison of severity of aortic regurgitation by cardiovascular magnetic resonance versus transthoracic echocardiography. Am J Cardiol 2011;108:1014–20.

39. Botnar R, Nagel E, Scheidegger MB, Pedersen EM, Hess O, Boesiger P. Assessment of prosthetic aortic valve performance by magnetic resonance velocity imaging. MAGMA 2000;10:18–26.

40. van Rossum AC, Visser FC, Hofman MB, Galjee MA, Westerhof N, Valk J. Global left ventricular perfusion: noninvasive measurement with cine MR imaging and phase velocity mapping of coronary venous outflow. Radiology 1992;182:685–91.

KEY WORDS angiography, aortic valve, magnetic resonance, regurgitation, stenosis, transcatheter

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