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Comparison of the Usefulness of Strain Imaging by Echocardiography Versus Computed Tomography to Detect Right Ventricular Systolic Dysfunction in Patients With Significant Secondary Tricuspid Regurgitation



Kensuke Hirasawa, PhD, Philippe J. van Rosendael, MD, Marlieke F. Dietz, MD, Nina Ajmone Marsan, PhD, Victoria Delgado, PhD, and Jeroen J Bax, PhD*

Assessment of right ventricular (RV) systolic function in patients with significant secondary tricuspid regurgitation (STR) remains challenging. In patients with severe aortic stenosis treated with transcatheter aortic valve implantation (TAVI), STR and RV enlargement have been associated with poor outcomes. In these patients, speckle tracking echocardiography (STE) may detect RV systolic dysfunction better than 3-dimensional (3D) RV ejection fraction (EF). The purpose of this study was to investigate the prevalence of RV dysfunction when assessed with STE in patients with significant STR ($\geq 3+$) compared with patients without significant STR ($< 3+$) matched for 3D RV dimensions and RVEF on dynamic computed tomography (CT). Patients with dynamic CT data before TAVI were evaluated retrospectively. To assess the performance of RV-free wall strain (RVFWS) for identifying patients with impaired RV systolic function, patients were subsequently matched 1:1 based on age, gender, indexed RV end-diastolic volume (RVEDVi), indexed RV end-systolic volume (RVESVi), RVEF, and left ventricular ejection fraction (LVEF). In a total 267 patients (80 ± 8 years, 48% male), significant STR ($\geq 3+$) was observed in 67 patients. Patients with STR $\geq 3+$ had larger RVEDVi, larger RVESVi, lower LVEF, and more impaired RVFWS compared with patients with STR $< 3+$ ($n = 200$). After propensity score matching, patients with STR $\geq 3+$ ($n = 53$) had significantly more impaired RVFWS compared with patients with STR $< 3+$ ($n = 53$): $-18.2 \pm 5.0\%$ versus $-21.1 \pm 3.7\%$, $p = 0.001$. In conclusion, patients with significant STR have more pronounced RV systolic dysfunction as assessed with STE than the patients without significant STR despite having similar 3D RV dimensions and RVEF on dynamic CT. © 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license. (<http://creativecommons.org/licenses/by/4.0/>) (Am J Cardiol 2020;134:116–122)

The interest in secondary tricuspid regurgitation (STR) has grown since it is an independent predictor of poor prognosis in various cardiovascular diseases.^{1,2} Significant STR is not rare in the patients with aortic stenosis (AS) who are referred for transcatheter aortic valve implantation (TAVI) and has been associated with impaired prognosis.³ In addition, right ventricular (RV) systolic function is a determinant of prognosis in this population.^{4–6} However, due to the shape, assessment of RV volumes is challenging with 2-dimensional (2D) imaging techniques. Therefore, 3-dimensional (3D) analyses are recommended for quantification of RV volumes and ejection fraction (EF).^{7–9} Nonetheless, in the presence of significant TR, RVEF may not accurately reflect the active myocardial shortening as it represents the volume change between diastole and systole and does not take into account the STR and the reduced RV forward

flow. Conversely, RV-free wall strain (RVFWS) may better reflect RV systolic function.¹⁰ This study aimed to investigate the RV systolic function by speckle tracking echocardiography (STE) in patients with severe AS treated with TAVI.

Methods

A total of 418 patients who underwent dynamic CT before TAVI at the Leiden University Medical Center were included. In all patients, echocardiography was performed within 30 days of CT and before TAVI. Patients with an intracardiac device ($n = 64$), organic TR ($n = 1$), history of tricuspid valve surgery ($n = 1$), and insufficient quality of the echocardiography or CT images ($n = 85$) were excluded. The remaining 267 patients were classified into 2 groups based on the STR severity ($\geq 3+$ vs STR $< 3+$).

To assess the performance of RVFWS for identifying patients with impaired RV systolic function, patients were subsequently matched 1:1 according to the following variables: age, gender, indexed RV end-diastolic volume (RVEDVi), indexed RV end-systolic volume (RVESVi),

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*Corresponding author: Tel: +31715262020; fax: +31715266809.

E-mail address: j.j.bax@lumc.nl (J.J. Bax).

RVEF, and LV ejection fraction (LVEF) (Figure 1). The Institutional Ethics Committee approved this retrospective evaluation and waived the need for patient written informed consent.

Comprehensive transthoracic echocardiography data, including 2D images and color, pulsed, and continuous-wave Doppler data were acquired using commercially available ultrasound systems equipped with 3.5 MHz transducers (E9 or E95, GE-Vingmed, Horten, Norway). Data were stored in cine-loop format digitally for offline analysis (EchoPAC Version 203.0.1, GE Medical Systems, Horten, Norway). Standard data acquisition was performed according to the current recommendations.^{11,12} With the patients in the left lateral decubitus position, parasternal, apical, and subcostal views were acquired. Left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were measured using Simpson's biplane method from the apical 4- and 2-chamber views and indexed to the body surface area. LVEF was calculated using the following formula: $[(LVEDV - LVESV) / LVEDV] \times 100$.¹¹

The severity of STR was assessed using an integrated approach as recommended in current guidelines and included an analysis of the vena contracta width:² none or trivial STR (0–1+) if the vena contracta width was <2.0 mm, mild STR (2+) if the vena contracta width ranged from 2.0 to 4.9 mm, moderate STR (3+) if the vena contracta width ranged from 5.0 to 7.0 mm and severe STR (4+) if the vena contracta width was >7.0 mm. The vena contracta width of the STR jet was measured in the apical

4-chamber view. The RV systolic pressure gradient was quantified with the maximum STR jet velocity according to the modified Bernoulli equation and subsequently the estimated right atrial pressure was added to determine systolic pulmonary artery pressure (SPAP). Right atrial pressure was estimated by measuring the diameter and respiratory change of the inferior vena cava, as recommended.^{12,13}

For the accurate assessment of RV myocardial deformation, the RV-focused apical 4-chamber view (>60 frames/s) was obtained. Using 2D STE (EchoPAC Version 203.0.1, GE Medical Systems, Horten, Norway), RVFWS measurements were performed according to current recommendations.^{14,15} RVFWS was calculated as an average of the 3 RV-free wall segments strain (basal, mid, and apical) (Figure 2).

CT data were acquired with a 64-detector (Aquilion64, Toshiba Medical Systems, Otawara, Japan) or 320-detector row CT scanner (AquilionOne, Toshiba Medical Systems, Tochigi-ken, Japan) according to a dedicated cardiac CT protocol, as previously described.^{16,17} With prospective electrocardiogram-triggered dose modulation, an entire cardiac cycle image was acquired at each 10% of RR interval.

For the assessment of RV volumes, the end-systolic and end-diastolic phases were defined by visual inspection of the cardiac cycle and were frequently the 30% to 45% and 80% to 100% phase of the cardiac cycle, respectively. Using the 3mensio software, release 10.0 (Pie Medical Imaging, Bilthoven, the Netherlands), the whole RV was traced every 4-mm slices in the transverse plane, and semi-automatically both the RV end-diastolic (RVEDV) and RV

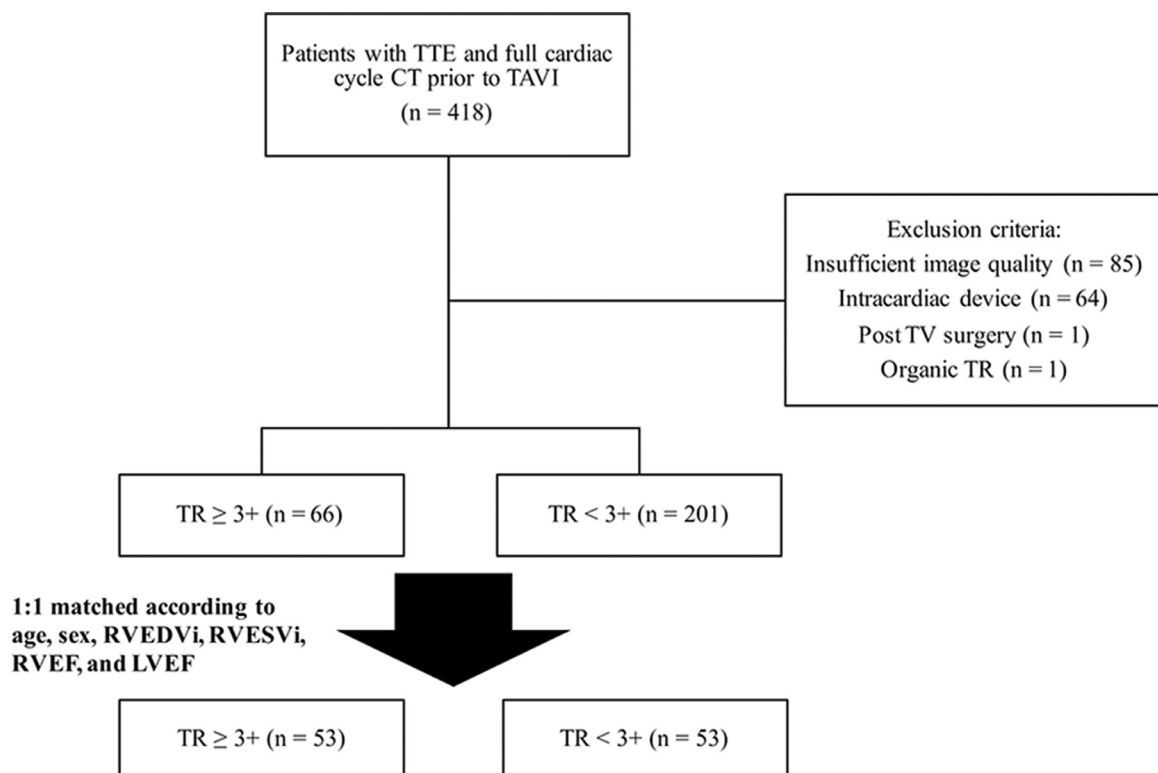


Figure 1. Patient population. CT = computed tomography; LVEF = left ventricular ejection fraction; RVEDVi = indexed right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESVi = indexed right ventricular end-systolic volume; TAVI = transcatheter aortic valve implantation; TR = tricuspid regurgitation; TV = tricuspid valve.

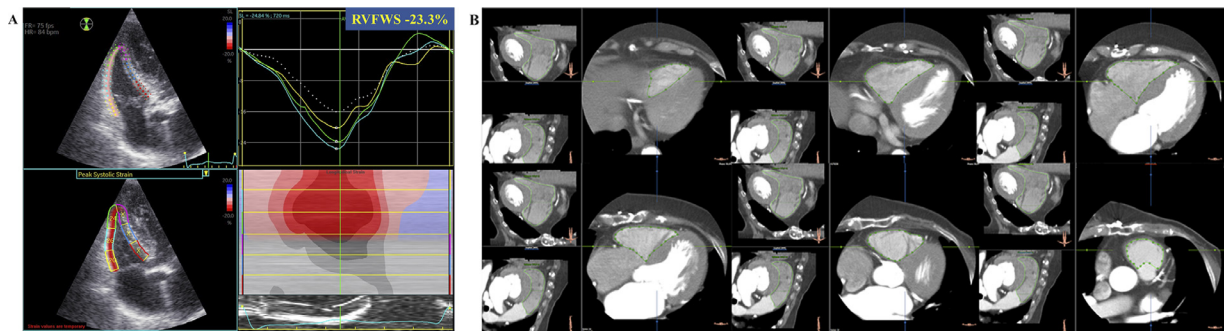


Figure 2. Assessment of RV systolic function with speckle tracking echocardiography and dynamic computed tomography. (A) Measurement of right ventricular free wall longitudinal strain (RVFWs) using speckle tracking echocardiography. According to the recommendation, 6 right ventricular segments were traced and RVFWs was calculated as an average of the longitudinal strain of the 3 free wall segments. (B) Assessment of right ventricular volumes according to computed tomography (CT). The endocardial border of the right ventricle was traced every 4-mm slice on CT and the end-diastolic volume, end-systolic volume, and ejection fraction were measured.

end-systolic (RVESV) were measured and indexed for body surface area (Figure 2). RVEF was calculated using the following formula: $RVEF = [(RVEDV - RVESV) / RVEDV] \times 100\%$.

Continuous variables as mean \pm standard deviation or as median with interquartile range depending on the presence or absence of a normal distribution. For the comparison of the variables between patients with $STR \geq 3+$ or $STR < 3+$ the Student's *t* test or the Mann-Whitney U test were used as appropriate. Categorical variables were expressed as frequency (percentage) and compared with the chi-square or Fisher's exact test as appropriate. P values < 0.05 were considered statistically significant. Comparisons between patients with $STR \geq 3+$ and patients with $STR < 3+$ were performed using a propensity score calculated for the variables age, gender, RVEDVi, RVESVi, RVEF, and LVEF. Matching was then performed using the 1:1 nearest neighbor method with a small tolerance (0.2 standard deviations of the logit of the propensity score). All statistical analyses

were performed using SPSS version 25 (SPSS, Inc., Chicago, IL).

Results

Among 267 patients (mean age 80 ± 8 years old, 128 (48%) male), $STR \geq 3+$ was observed in 67 (25%) patients (Table 1). The demographic and clinical characteristics of the patients are shown in Table 1. Age, gender, body surface area, the prevalence of hypertension, diabetes, and history of previous myocardial infarction were comparable in both groups. Patients with $STR \geq 3+$ had a higher prevalence of atrial fibrillation and were more frequently using diuretics than their counterparts. Patients with $STR \geq 3+$ had more frequently New York Heart Association functional class III-IV heart failure symptoms, although this did not reach statistical significance.

Table 2 shows the echocardiographic and CT characteristics. Patients with $STR \geq 3+$ had a larger indexed LVESV

Table 1
Demographic and clinical characteristics of the overall population

Variable	All (n = 267)	$STR \geq 3+$ (n = 67)	$STR < 3+$ (n = 200)	p value*
Age (years)	80.1 ± 7.9	80.1 ± 7.9	80.2 ± 8.0	0.964
Men	128 (48%)	35 (52%)	93 (47%)	0.416
BSA (m^2)	1.82 ± 0.20	1.83 ± 0.20	1.81 ± 0.20	0.600
Atrial fibrillation	36 (14%)	24 (36%)	12 (6%)	< 0.001
Hypertension	206 (77%)	46 (69%)	160 (80%)	0.065
Diabetes mellitus	69 (26%)	13 (19%)	56 (28%)	0.198
Previous myocardial infarction	55 (21%)	18 (27%)	37 (19%)	0.163
Medication				
β -blockers	163 (61%)	36 (54%)	127 (64%)	0.193
ACEi/ARBs	128 (48%)	32 (48%)	96 (48%)	1.000
Diuretics	162 (61%)	54 (81%)	108 (54%)	< 0.001
NYHA class				
I	21 (8%)	1 (1%)	20 (10%)	0.076
II	99 (37%)	23 (34%)	76 (38%)	
III	122 (46%)	34 (51%)	88 (44%)	
IV	25 (9%)	9 (13%)	16 (8%)	

ACEi/ARBs = angiotensin converting enzyme inhibitor/angiotensin receptor blockers; BSA = body surface area; NYHA = New York Heart Association; TR = tricuspid regurgitation.

Values are mean \pm SD or n (%).

* p value between $STR \geq 3+$ versus $STR < 3+$.

Table 2.
Echocardiographic and CT parameters in the overall population

Variable	All (n = 267)	STR $\geq 3+$ (n = 67)	STR $< 3+$ (n = 200)	p value*
Echocardiographic measurements				
Indexed LVEDV (mL/m ²)	51.4 \pm 21.0	54.5 \pm 24.4	50.3 \pm 19.6	0.157
Indexed LVESV (mL/m ²)	24.3 \pm 17.7	28.7 \pm 21.0	22.9 \pm 16.3	0.020
LVEF (%)	56.9 \pm 14.4	51.6 \pm 16.0	58.6 \pm 13.4	<0.001
TR vena contracta width (mm)	3.0 [1.0 – 6.0]	8.0 [7.0 – 9.0]	2.0 [0.0 – 3.0]	<0.001
RVFWS (%)	-24.2 \pm 6.6	-17.1 \pm 5.0	-26.6 \pm 5.2	<0.001
SPAP (mm Hg)	34.8 \pm 13.9	44.5 \pm 14.0	31.2 \pm 12.0	<0.001
CT measurements				
Indexed RVEDV (mL/m ²)	81.8 \pm 21.2	95.3 \pm 27.3	77.3 \pm 16.4	<0.001
Indexed RVESV (mL/m ²)	43.1 \pm 16.7	55.3 \pm 22.5	39.0 \pm 11.7	<0.001
RVEF (%)	47.9 \pm 11.2	42.7 \pm 12.5	49.6 \pm 10.3	<0.001

CT = computed tomography; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVFWS = right ventricular free wall strain; SPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

Values are mean \pm SD, median (interquartile range), or n (%).

* p value between STR $\geq 3+$ versus STR $< 3+$.

and a lower LVEF compared with patients with STR $< 3+$. In addition, patients with STR $\geq 3+$ had a more impaired RVFWS and a higher SPAP compared with their counterparts. On the CT data, patients with STR $\geq 3+$ showed significant larger RV volumes. In patients with STR $\geq 3+$, RVEF was significantly lower compared with patients with STR $< 3+$ (Table 2).

According to the propensity score, 106 patients were matched 1:1 in groups of STR $\geq 3+$ and STR $< 3+$. Similarly to the nonmatched population analysis, the prevalence of atrial fibrillation was higher and the use of diuretics was also more frequent in patients with STR $\geq 3+$ compared with patients with STR $< 3+$ (Table 3).

Table 4 shows the echocardiographic and CT characteristics in the propensity-matched cohort divided according to the STR severity. RVFWS was significantly more

impaired and the SPAP was significantly higher in the patients with STR $\geq 3+$ compared with patients with STR $< 3+$ (Figure 3).

Discussion

This study demonstrates that RV function in patients with significant STR is more frequently impaired when measured with RVFWS than by assessment of 3D RVEF. In the nonmatched cohort, significant STR was associated with RV and LV remodeling, but after matching for LVEF, RV volumes and RVEF, the RVFWS remained significantly more impaired in patients with significant STR compared with patients without significant STR.

The pathophysiology of STR and RV failure is intertwined: the presence of STR may lead to further RV

Table 3.
Comparison between STR $\geq 3+$ group and STR $< 3+$ group after propensity score matching

Variable	All (n = 106)	STR $\geq 3+$ (n = 53)	STR $< 3+$ (n = 53)	p value*
Age (years)	80.9 \pm 6.3	80.2 \pm 6.0	81.6 \pm 6.6	0.244
Men	46 (43%)	27 (51%)	19 (36%)	0.117
BSA (m ²)	1.79 \pm 0.19	1.82 \pm 0.19	1.77 \pm 0.19	0.133
Atrial fibrillation	26 (25%)	22 (42%)	4 (8%)	<0.001
Hypertension	75 (71%)	34 (64%)	41 (77%)	0.135
Diabetes mellitus	22 (21%)	10 (19%)	12 (23%)	0.632
Previous myocardial infarction	26 (25%)	15 (28%)	11 (21%)	0.367
Medication				
β -blockers	62 (59%)	30 (57%)	32 (60%)	0.693
ACEi/ARBs,	53 (50%)	28 (53%)	25 (47%)	0.560
Diuretics	72 (68%)	41 (77%)	31 (59%)	0.037
NYHA class				
I	8 (8%)	1 (2%)	7 (13%)	0.115
II	40 (38%)	19 (36%)	21 (40%)	
III	48 (45%)	28 (53%)	20 (38%)	
IV	10 (9%)	5 (9%)	5 (9%)	

ACEi/ARBs = angiotensin converting enzyme inhibitor/angiotensin receptor blockers; BSA = body surface area; NYHA = New York Heart Association; TR = tricuspid regurgitation.

Values are mean \pm SD or n (%).

* p value between STR $\geq 3+$ versus STR $< 3+$.

Table 4
Echocardiographic and CT parameters after propensity score matching

Variable	All (n = 106)	STR $\geq 3+$ (n = 53)	STR $< 3+$ (n = 53)	P value*
Echocardiographic measurements				
Indexed LVEDV (mL/m ²)	49.7 \pm 21.3	49.4 \pm 21.6	50.0 \pm 21.2	0.886
Indexed LVESV (mL/m ²)	22.9 \pm 16.3	23.3 \pm 16.2	22.6 \pm 16.4	0.835
LVEF (%)	57.2 \pm 14.5	55.2 \pm 14.4	59.3 \pm 14.5	0.150
TR vena contracta width (mm)	6.0 [3.0 – 7.3]	7.0 [7.0-9.0]	3.0 [0.0 – 4.0]	<0.001
RVFWS (%)	-21.7 \pm 5.6	-18.1 \pm 4.6	-25.2 \pm 4.2	<0.001
SPAP (mm Hg)	38.5 \pm 14.0	41.9 \pm 13.8	34.9 \pm 13.4	0.011
CT measurements				
Indexed RVEDV (mL/m ²)	86.0 \pm 19.8	87.5 \pm 21.1	84.4 \pm 18.5	0.418
Indexed RVESV (mL/m ²)	46.6 \pm 14.5	47.2 \pm 14.6	46.1 \pm 14.5	0.698
RVEF (%)	45.8 \pm 11.5	46.0 \pm 11.3	45.5 \pm 11.7	0.828

CT = computed tomography; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVFWS = right ventricular free wall strain; SPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

Values are mean \pm SD, median (interquartile range), or n (%).

* p value between STR $\geq 3+$ versus STR $< 3+$.

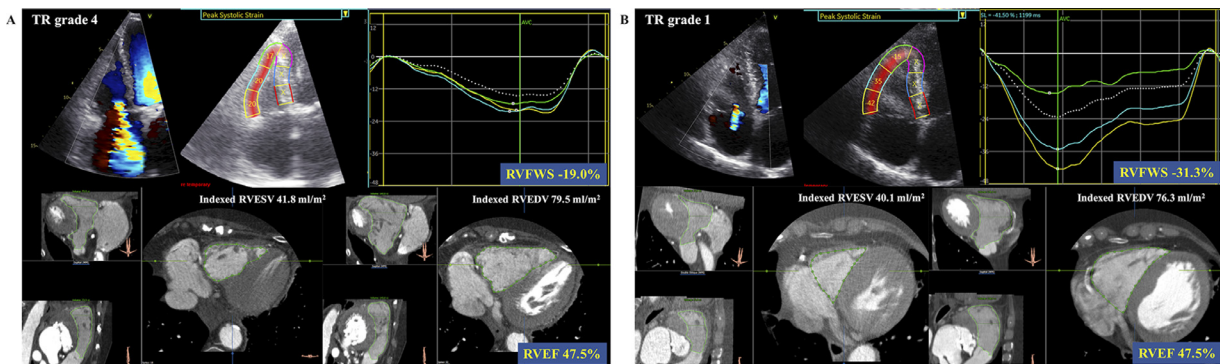


Figure 3. Representative examples of right ventricular systolic function assessment in a patient with severe tricuspid regurgitation (A) and a patient with trivial tricuspid regurgitation (B). Although these patients had comparable right ventricular volumes and ejection fraction on multidetector row computed tomography, the patient with severe tricuspid regurgitation had more impaired right ventricular-free wall longitudinal strain than the patient with trivial tricuspid regurgitation. RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVFWS = right ventricular free wall longitudinal strain; TR = tricuspid regurgitation.

dilation and failure, which in turn may cause more severe STR. Assessment of RV dimensions and systolic function with conventional echocardiography is limited since the RV has a characteristic 3D shape that cannot be fully evaluated with 2D echocardiography. Therefore, 3D imaging techniques such as echocardiography, cardiac magnetic resonance, CT, or nuclear imaging are needed. Furthermore, the presence of TR facilitates the unloading of the RV into the right atrium through the regurgitant jet which may lead to a falsely preserved RVEF.

The RV systolic function depends on the loading conditions, myocardial contractility, pericardial constraint and the interventricular dependence represented by the interventricular septum. Normal forward RV flow is the result of an intrinsic inward motion of the RV-free wall, longitudinal shortening of the fibers from the tricuspid annulus in the direction of the RV apex and traction on the free wall secondary to LV contraction.¹⁸ This interplay is complicated if severe tricuspid regurgitation is present, since tricuspid regurgitation leads to increased RV volume overload, and increased wall stress on the myocardial fibers that may

impair the intrinsic myocardial performance of the thin-walled RV. Recently, Prihadi et al showed in 896 patients that RV dysfunction as assessed by RVFWS (using a cutoff value $> -23\%$) was present in 84.9% of patients with significant STR.¹⁰ Moreover, Prihadi et al demonstrated that RVFWS was a more sensitive parameter for detection of RV dysfunction compared with conventional parameters including tricuspid annular plane systolic excursion and fractional area change which identified RV dysfunction in 71.7% and 49.4% of the 896 patients with STR.¹⁰ RVFWS using STE has been considered to be less dependent of volume load compared with conventional RV functional parameters. However, it is important to realize that RVFWS is not completely load independent.^{13,19} The relationship between the preload and tension development underscores the importance of taking the RVEDV (as a marker of preload) into consideration for comprehensive assessment of RV contractility. Therefore, to investigate the association between significant STR and the intrinsic RV myocardial performance adjusted for preload, the present study performed a propensity score-matched analysis including RV

volumes and RVEF. In the presence of similar RV volumes and RVEF, RVFWS was more impaired in patients with STR $\geq 3+$ compared with those without STR $\geq 3+$. Accordingly, for a comprehensive assessment of RV function in patients with significant STR, the information of 3D RV volumes may be combined with assessment of RVFWS, as this parameter may reflect in more detail the inotropic status of the RV.

Furthermore it is important to note that after performing the matched analysis, there remained differences in SPAP. Patients with STR $\geq 3+$ had significantly higher SPAP than their counterparts and this may have impact on the value of RVFWS.

The clinical implications of these findings are important, since RV systolic function has demonstrated to be an important prognostic marker in various cardiac conditions.¹⁸ When considering the current clinical scenario of TAVI patients, several studies showed the association between RV dysfunction and the outcomes after TAVI.^{20–22} Data from the Swiss TAVI registry showed in 1,116 patients that RV dysfunction was present in 29.1% of the patients, defined by a tricuspid annulus plane systolic excursion < 17 mm, a systolic velocity of the RV lateral wall < 9.5 cm/s on tissue Doppler imaging, or a fractional area change $< 35\%$.²¹ In addition, the presence of RV dysfunction was associated with a 2-fold increase in cardiovascular mortality after 1-year follow-up (20% vs 7%, adjusted hazard ratio = 2.94, 95% confidence interval: 2.02 to 4.27).²¹

Of interest, recovery of RV function can be observed after TAVI in 57% of patients. However, the presence of persistent RV dysfunction was associated with increased 1-year cardiovascular mortality (adjusted hazard ratio = 2.16, 95% confidence interval: 1.16 to 4.02).²¹

However, since these conventional parameters are more influenced by volume overload compared with RVFWS by STE,¹⁹ the assessment of RVFWS may potentially have incremental prognostic value in patients with significant STR.

The present study had several limitations. First, this is a single-center retrospective observational study having limitation inherent to the study design. Second, the current analysis included only patients who had undergone TAVI, since those patients had ECG-gated CT data acquired throughout the entire cardiac cycle allowing the measurement of RVEF without geometrical assumptions.

In conclusion, patients with significant STR have more RV systolic dysfunction assessed with STE than the patients without significant STR despite having similar 3D RV dimensions and RVEF measured on dynamic CT.

Author Contribution

Kensuke Hirasawa: Conception and design of the study; collection, analysis and interpretation of data; statistical analysis; drafting of the manuscript; final approval of the manuscript; Philippe J. van Rosendael: Conception and design of the study; collection, analysis and interpretation of data; statistical analysis; drafting of the manuscript; final approval of the manuscript; Marlieke F. Dietz: Conception and design of the study; collection, analysis and interpretation of data; statistical analysis; drafting of the manuscript;

final approval of the manuscript; Nina Ajmone Marsan: Conception and design of the study; collection, analysis and interpretation of data; statistical analysis; drafting of the manuscript; final approval of the manuscript; Victoria Delgado: Conception and design of the study; collection, analysis and interpretation of data; statistical analysis; drafting of the manuscript; final approval of the manuscript; Jeroen J Bax: Conception and design of the study; collection, analysis and interpretation of data; statistical analysis; drafting of the manuscript; final approval of the manuscript.

Disclosures

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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