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Clinical Research

Beyond 2-Dimensional Echocardiography: A Novel Multiparametric Assessment of Right Ventricular Dysfunction in Transcatheter Tricuspid Valve Repair

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ABSTRACT

Background: Right ventricular (RV) heart failure as assessed by RV to pulmonary artery coupling (RVPAc) is a prognostic marker in transcatheter tricuspid valve repair (T-TEER). However, quantification of RVPAc components by 2-dimensional (2D) echocardiography in patients with severe tricuspid regurgitation (TR) has significant limitations, and the traditional RVPAc parameter neglects the degree of volume overload/dilatation of the RV, which is another key clinical indicator for right ventricular dysfunction (RVD). Therefore, we aimed to assess RVD by a novel RVPAc parameter, including the 3 important drivers of RVD, for an improved prediction of 1-year mortality after T-TEER.

Methods: We analyzed 262 patients undergoing T-TEER with complete 3D RV echocardiography and 1-year follow-up.

Results: Increased 3D-RV end diastolic volume (3D-RVEDV: hazard ratio [HR], 1.85; 1.10-3.12; $P = 0.020$) and impaired RV free-wall longitudinal strain (RVFWLS: HR, 1.73, 1.02-2.92; $P = 0.042$) predicted 1-year mortality. A novel RVPAc parameter (RVFWLS/[3D-RVEDV*sPAP$_{invasive}$]) including all 3 important drivers for RVD was developed, associating RVPA-uncoupling with a tripled risk for 1-year mortality (HR, 3.19, 1.7-6.0; $P < 0.001$). The novel RVPAc parameter significantly outperformed the traditional noninvasive RVPAc parameter in 1-year mortality prediction (C-index: 0.68 vs 0.57 for novel vs traditional noninvasive RVPAc; $P = 0.027$).

RÉSUMÉ

Contexte : L'insuffisance ventriculaire droite telle qu'évaluée à l'aide du couplage ventriculo-artériel (ventricule droit et artère pulmonaire) ou CVA est un marqueur pronostique de la réparation transcathéter de la valve tricuspide (T-TEER pour *tricuspid transcatheter edge-to-edge repair*). Toutefois, la quantification des composantes du paramètre CVA par échocardiographie bidimensionnelle chez les patients atteints d'une régurgitation tricuspidienne sévère présente d'importantes limites, et le paramètre CVA classique néglige le degré de surcharge volémique/dilatation du ventricule droit, un autre indicateur clinique clé de dysfonction ventriculaire droite. Nous nous sommes donc employés à évaluer la dysfonction ventriculaire droite au moyen d'un paramètre CVA novateur, qui repose sur les trois principaux facteurs intervenant dans la dysfonction ventriculaire droite pour mieux prédire la mortalité un an après une T-TEER.

Méthodologie : Nous avons analysé 262 patients ayant subi une T-TEER avec échocardiographie tridimensionnelle complète du ventricule droit, suivis pendant au moins un an après l'intervention.

Résultats : Le volume accru en fin de diastole à l'échocardiographie ventriculaire droite tridimensionnelle (3D-RVEDV : rapport des risques instantanés [RRI] : 1,85; 1,10 à 3,12; $p = 0,020$) et la déformation longitudinale de la paroi libre du ventricule droit (RV-FWLS : RRI : 1,73; 1,02 à 2,92; $p = 0,042$) ont permis de prédire la mortalité à un an. Nous avons élaboré un paramètre CVA novateur (RV-FWLS/

Transcatheter tricuspid edge-to-edge repair (T-TEER) has emerged as an increasingly used therapeutic option for patients with inoperable heart failure suffering from severe tricuspid regurgitation (TR).[1] Right ventricular (RV) function has shown to play a key prognostic role in patients with left-sided but also right-sided valvular diseases and symptoms of heart failure.[2-5,6-9] For the assessment of RV function, the concept of RV to pulmonary coupling (RVPAc) has emerged as a promising parameter, adjusting RV contractility to its afterload.[10,11]

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Conclusions: The novel RVPAc parameter, integrating RV function, volume stress, and pressure stress is a powerful metric for RV failure and a superior predictor for survival post-T-TEER.
Clinical Trial Registration: Data is based on the EveryValve Registry (ethical code number: 19-840). No further clinical Trial registration.

**[3D-RVEDV*sPAPinvasive]) reposant sur les trois principaux facteurs intervenant dans la dysfonction ventriculaire droite associant le découplage ventriculo-artériel à un risque triplé de mortalité à un an (RRI : 3,19; 1,7 à 6,0; $p < 0,001$). Ce paramètre novateur a surpassé de loin le paramètre CVA non invasif classique pour prédire la mortalité à un an (indice c : 0,68 [paramètre novateur] *vs* 0,57 [paramètre non invasif classique]; $p = 0,027$).
Conclusions : Le paramètre CVA novateur, qui intègre la fonction ventriculaire droite, le stress volémique et la contrainte de pression, est un outil puissant pour mesurer l'insuffisance ventriculaire droite et un meilleur outil de prédiction de la survie après une T-TEER.**

Accordingly, the traditional noninvasive RVPAc ratio of tricuspid annular plane systolic excursion (TAPSE) to the estimated systolic pulmonary artery pressure ($sPAP_{echo}$) describes RV contractility in relation to the pressure stress and has been shown to be a predictor of outcomes in medically managed and transcatheter device-treated patients.[8,12,13]

Even though well established in certain clinical conditions, the traditional noninvasive RVPAc ratio has significant limitations, especially in patients undergoing T-TEER for severe TR. First, TAPSE alone has demonstrated insufficient prognostic effect in T-TEER patients.[14] Second, $sPAP_{echo}$ fails to describe pulmonary artery pressure precisely, especially in patients with severe TR compared with invasive sPAP assessments.[11,15] Third, the estimation of RV afterload using only sPAP fails to accurately reflect the most relevant measure of afterload: wall stress. Pressure measurements alone neglect the component of RV dilatation (or volume) that contributes to wall stress. Thus both "pressure stress" and "volume stress" may be important determinants of afterload in chronic right heart failure.

Accordingly, the rationale of this study was to develop a novel RVPAc parameter that surpasses the current limitations of the traditional noninvasive RVPAc parameter and that demonstrates improved 1-year survival prediction in patients with severe TR undergoing T-TEER.

Methods

Study cohort and procedural technique

This is a single-centre observational study and included consecutive patients with 3-dimensional (3D) transthoracic echocardiography of the RV and who underwent T-TEER for significant symptomatic TR from April 2016 until February 2022. An individual treatment decision was made for each patient in the interdisciplinary heart team after discussing the course of disease, comorbidities, surgical risk, and life expectancy. All patients were considered to be on optimal diuretic and, if indicated, heart failure medication before treatment. T-TEER was performed as previously described,[1,16] either using the PASCAL device (Edwards Lifesciences, Irvine, CA) or the MitraClip/TriClip system (Abbott, Santa Clara, CA). Heart failure symptoms were classified using New York Heart Association (NYHA) functional class. Patients were followed for 1 year according to standard of care. The study was approved by the local ethics committee and adheres to the principles outlined in the declaration of Helsinki.

Data collection and follow-up

Collected data included demographic data (age, sex, and body mass index), medical history, echocardiographic, and clinical parameters. All echocardiograms were performed and analyzed by experienced physicians at each study site according to current echocardiographic guidelines.[17-19] Baseline TR severity and anatomy of the tricuspid valve were assessed according to current recommendations.[20,21] RV parameters were assessed through an RV-focused apical 4-chamber view. The 3D echocardiography was analyzed with dedicated 3D software (4D RV-Function, TomTec Imaging Systems, Munich, Germany). RV free-wall longitudinal strain (RVFWLS) imaging was performed by 2D speckle tracking on RV-focused view. Parameters for RV dimensions were indexed to the individual patients body surface area (BSA) and sex-specific cutoffs were used according to American Society of Echocardiography and the European Association of Cardiovascular Imaging.[22] Follow-up was completed on the last medical interview date, the last examination date, or the date when an endpoint event was observed, whichever came first. At follow-up examinations, we assessed NYHA functional class and survival status in our outpatient clinic.

Procedural methods

All procedures were performed in a cardiac catheterization laboratory equipped with fluoroscopic and echocardiographic capabilities. The patient was placed under general anesthesia with hemodynamic monitoring, and venous access was obtained via conventional percutaneous techniques. Under TEE and fluoroscopic guidance, the guide sheath was advanced to the right atrium. The implant catheter was then advanced and the clip arms were used to capture 2 tricuspid valve leaflets. If needed, the implant was repositioned or removed. Once correct positioning was confirmed and sufficient TR reduction was achieved, the implant was fully deployed and released from the catheter, and the delivery system was retrieved.

Statistical analysis

Normality of data distribution was assessed using the Shapiro-Wilk test. For descriptive statistics, continuous data were presented as means with standard deviation (SD) and medians with interquartile ranges (IQRs), respectively. Categorical data were presented as proportions. Comparisons among groups were performed using the χ^2 test for categorical variables, and Student's *t*-test or Mann-Whitney-U test for unpaired continuous variables, and Wilcoxon rank-sum test

for paired variables, according to data distribution. To assess the correlation between 2D and 3D RV dimension measurements, Pearson correlation analysis was performed. To establish a cutoff for 3D RV dilation in this TR patient cohort, receiver operating characteristic (ROC) analysis was performed according to the best discriminatory value for 1-year mortality. In addition, ROC analysis with Youden (J) index method was performed to define the optimal cutoff value for dichotomizing the novel modified RVPAc parameter according to its discriminatory value for 1-year mortality. Cumulative survival after 1 year was estimated and graphically displayed using Kaplan-Meier curves. The risk of mortality was assessed using Cox multivariate regression analysis with backward elimination and expressed as hazard ratios (HRs), 95% confidence intervals (95% CIs), and *P* value. The discriminative ability of the traditional noninvasive and novel RVPAc parameters were quantified using the C-statistic and provide a measure of the models' accuracy in distinguishing among patient outcomes.

The statistical tests applied yielded a 2-sided *P* values with a level of significance (alpha) of < 0.05 to determine statistical significance. The statistical software used for data analysis and visualization was R version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline study characteristics and overall outcomes

The study included 262 patients (46.6% women) at a median age of 83 (IQR: 79-87) years with overall increased surgical risk (TriScore points 6.1 ± 2.1, TriScore mortality estimate of 22 ± 3%). Etiology of TR was secondary in 88.5% of patients, and 95.5% of patients suffered from severe exertional dyspnea according to a NYHA Class ≥ III. Detailed patient characteristics are shown in Table 1. TR was torrential in 32 patients (12.2%), massive in 88 patients (33.6%), severe in 131 patients (50%), and moderate in 11 patients (4.2%).

Echocardiographic details regarding quantitative TR parameters are listed in Table 2. Left ventricular function was preserved in the majority of patients (left ventricular ejection fraction [LVEF]: 54.4 ± 12.0%), whereas RV function was borderline (TAPSE: 17.9 ± 4.7 mm; RVFWLS: −23.5 ± 6.1; 3D RV EF 44.0 ± 9.0%). The mean number of implanted devices was 1.99 ± 0.65. TR was effectively reduced after T-TEER (Supplemental Fig. S1).

Median follow-up was 716 (IQR: 307-1170] days. Overall 1-year survival of all eligible T-TEER−treated patients was 77.7%.

Impact of RV volume stress on outcomes after T-TEER

The mean 3D end-diastolic volume index ($RVEDV_i$) and end-systolic volume index ($RVESV_i$) were 113.0 ± 37.7 mL/m^2 and 63.3 ± 22.0 mL/m^2, respectively. To establish a prognostic cutoff for 3D $RVEDV_i$ in this TR patient cohort, ROC analysis was performed to define the best discriminatory value for 1-year mortality. Accordingly, a 3D volume of ≥ 107 mL/m^2 was used to define significant RV dilation in this study; 121 (46.2%) of the patients showed an RV dilatation (Table 1). RV dilation measured by 3D $RVEDV_i$ was associated with impaired survival after T-TEER in univariate analysis (HR, 2.13; 95% CI, 1.24-3.64; $P = 0.006$,

Table 1. Baseline characteristics of the study cohort

	Overall	No /low volume stress	Volume stress		No/low pressure stress	Pressure stress	
n	262	141	121	*P* value	188	48	*P* value
Age (years)	83.0 [79.3, 87.0]	83.0 [80.0, 86.0]	83.0 [78.0, 87.0]	0.338	83.0 [79.8, 86.3]	83.0 [79.0, 87.3]	0.850
Sex (male)	140 (53.4)	58 (41.1)	82 (67.8)	<0.001	105 (55.9)	18 (37.5)	0.035
BMI	24.4 [22.5, 27.5]	24.4 [22.7, 27.5]	24.5 [22.4, 27.4]	0.848	24.4 [22.4, 27.0]	24.5 [23.0, 27.9]	0.343
TriScore points	6.08 (2.14)	5.68 (2.27)	6.59 (1.85)	0.001	5.96 (2.08)	6.37 (2.37)	0.246
STS score	4.57 [2.72, 8.66]	4.74 [2.83, 7.52]	4.36 [2.67, 9.15]	0.932	4.36 [2.69, 8.10]	6.03 [3.02, 10.07]	0.242
TR etiology				0.630			0.540
Primary	9 (3.4)	6 (4.3)	3 (2.5)		7 (3.7)	2 (4.2)	
Secondary	232 (88.5)	125 (88.7)	107 (88.4)		164 (87.2)	44 (91.7)	
Mixed	21 (8.0)	10 (7.1)	11 (9.1)		17 (9.0)	2 (4.2)	
NYHA				0.428			0.078
NYHA II	12 (4.6)	5 (3.5)	7 (5.8)		9 (4.8)	0 (0.0)	
NYHA III	204 (77.9)	108 (76.6)	96 (79.3)		149 (79.3)	35 (72.9)	
NYHA IV	46 (17.6)	28 (19.9)	18 (14.9)		30 (16.0)	13 (27.1)	
Coronary artery disease	113 (43.1)	58 (41.1)	55 (45.5)	0.563	81 (43.1)	19 (39.6)	0.784
History of CABG	30 (11.5)	16 (11.3)	14 (11.6)	1.000	17 (9.0)	8 (16.7)	0.204
RV pacemaker lead	79 (30.2)	31 (22.0)	48 (39.7)	0.003	20 (10.7)	6 (12.4)	0.840
Previous PCI	58 (22.2)	31 (22.1)	27 (22.3)	1.000	45 (23.9)	8 (17.0)	0.413
History of atrial fibrillation/flutter	233 (88.9)	125 (88.7)	108 (89.3)	1.000	166 (88.3)	44 (91.7)	0.684
NTproBNP	2594 [1394, 5182]	2606 [1446, 4535]	2503 [1372, 6420]	0.481	2457 [1315, 5080]	2682 [1620, 4993]	0.423
Loop diuretics	252 (96.2)	136 (96.5)	116 (95.9)	1.000	179 (95.2)	47 (97.9)	0.668
Thiazides	66 (25.2)	34 (24.1)	32 (26.4)	0.771	43 (22.9)	15 (31.2)	0.310
MRA	112 (42.7)	53 (37.6)	59 (48.8)	0.090	83 (44.1)	21 (43.8)	1.000
Beta blockers	221 (84.4)	124 (87.9)	97 (80.2)	0.119	157 (83.5)	39 (81.2)	0.875

Qualitative data are presented as n (%); Quantitative data are presented as means (SD) or medians [IQR].

BMI, body mass index; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrilator; MRA, mineralocorticoid antagonists; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RV, right ventricle; STS, Society of Thoracic Surgeons; TR, tricuspid regurgitation.

Table 2. Baseline echocardiographic characteristics

	Overall	No /low volume stress	Volume stress		No/low pressure stress	Pressure stress	
n	262	141	121	*P* value	188	48	*P* value
LV ejection fraction, %	54.42 (11.99)	55.36 (11.40)	53.29 (12.62)	0.170	54.55 (11.82)	54.74 (12.08)	0.924
LVEDV, index (Simpson, mL/m^2)	61.58 (29.11)	53.80 (21.00)	70.69 (34.30)	<0.001	61.89 (29.87)	56.61 (21.64)	0.277
LVESV, index (Simpson, mL/m^2)	29.82 (20.67)	25.20 (14.72)	35.28 (25.00)	<0.001	29.72 (20.67)	26.30 (14.36)	0.308
LA volume, index (mL/m^2)	68.11 (31.37)	62.47 (23.19)	74.40 (37.63)	0.005	69.52 (32.59)	59.81 (26.45)	0.086
Mitral regurgitation grade				0.307			0.582
0	19 (7.4)	12 (8.8)	7 (5.8)		14 (7.6)	3 (6.4)	
1+	119 (46.3)	64 (46.7)	55 (45.8)		91 (49.5)	22 (46.8)	
2+	54 (21.0)	26 (19.0)	28 (23.3)		38 (20.7)	8 (17.0)	
3+	52 (20.2)	25 (18.2)	27 (22.5)		35 (19.0)	10 (21.3)	
4+	13 (5.1)	10 (7.3)	3 (2.5)		6 (3.3)	4 (8.5)	
RVEDA, index (cm^2/m^2)	15.62 (4.34)	13.82 (3.09)	17.55 (4.58)	<0.001	15.89 (4.57)	14.23 (3.14)	0.020
RVESA, index (cm^2/m^2)	9.88 (3.25)	8.53 (2.23)	11.32 (3.49)	<0.001	10.08 (3.44)	8.96 (2.08)	0.034
3D RVEDV, index (mL/m^2)	113.04 (37.72)	86.13 (13.34)	143.14 (30.84)	<0.001	118.52 (38.70)	89.41 (11.64)	<0.001
3D RVESV, index (mL/m^2)	63.28 (21.96)	48.92 (10.74)	79.19 (18.20)	<0.001	65.68 (21.13)	50.28 (10.20)	<0.001
RA area (cm^2)	38.79 (12.43)	34.80 (11.58)	43.25 (11.86)	<0.001	39.81 (12.95)	33.23 (10.00)	0.002
Invasive sPAP, mm Hg	49.78 (17.06)	40.91 (13.33)	44.27 (14.47)	0.056	46.16 (15.91)	63.92 (13.84)	<0.001
Echo sPAP, mm Hg	42.62 (14.11)	40.94 (13.37)	44.67 (14.77)	0.041	42.01 (13.42)	46.58 (16.47)	0.053
TAPSE, mm	17.86 (4.74)	18.09 (4.65)	17.49 (4.83)	0.310	18.15 (4.75)	16.65 (4.17)	0.046
RVFAC (%)	36.85 (10.24)	38.26 (10.36)	35.25 (9.91)	0.020	36.66 (10.03)	36.77 (10.94)	0.945
RVFWLS (%)	-23.53 (6.10)	-23.03 (6.23)	-23.68 (6.10)	0.396	−23.53 (5.98)	−22.52 (6.83)	0.314
RVPA coupling (TAPSE/sPAP, mm/mm Hg)	0.46 (0.19)	0.48 (0.18)	0.44 (0.20)	0.126	0.48 (0.20)	0.40 (0.17)	0.012
RV ejection faction, 3D (%)	0.44 (0.09)	0.43 (0.09)	0.44 (0.08)	0.372	0.44 (0.08)	0.44 (0.09)	0.840
Tricuspid regurgitation grade				0.002			0.001
2+	11 (4.2)	10 (7.1)	1 (0.8)		4 (2.1)	6 (12.5)	
3+	131 (50.0)	78 (55.3)	53 (43.8)		90 (47.9)	24 (50.0)	
4+	88 (33.6)	43 (30.5)	45 (37.2)		64 (34.0)	18 (37.5)	
5+	32 (12.2)	10 (7.1)	22 (18.2)		30 (16.0)	0 (0.0)	
TR VC (biplane, mm)	10.23 (4.57)	8.85 (3.27)	11.82 (5.31)	<0.001	10.76 (4.89)	8.01 (2.69)	<0.001
TR EROA, cm^2	0.59 (0.68)	0.48 (0.27)	0.72 (0.94)	0.004	0.63 (0.77)	0.47 (0.31)	0.173
TR volume, mL	42.88 (22.93)	37.49 (20.53)	49.34 (24.05)	<0.001	44.06 (23.04)	40.08 (24.20)	0.293

Qualitative data are presented as n (%). Quantitative data are presented as mean (SD).

EDA, end diastolic area; EDV, end diastolic volume; EROA, effective regurgitant orifice area; ESA, end-systolic area; ESV, end systolic volume; LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; PA, pulmonary artery; RV, right ventricle; SD, standard deviation; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; VC, vena contracta.

Supplemental Fig. S2). Multivariate regression analyses demonstrated, that 3D RVEDV$_i$, NYHA class IV, and RV free wall strain were associated with increased 1-year mortality after T-TEER (3D RVEDV$_i$: HR, 1.08; 95% CI, 1.02-1.15; $P = 0.012$; NYHA IV: HR, 3.3; 95% CI, 1.9-5.7; $P < 0.001$, RVFWLS: HR, 1.1; 95% CI, 1.01-1.11; $P = 0.013$; Supplemental Table S1).

A minority of TR patients showed increased RV pressure (sPAP$_{invasive} \geq 50$ mm Hg 20.3%). Baseline and echocardiographic characteristics of patients with RV pressure stress are shown in Supplemental Tables S2 and S3.

The RV dependence on both pressure and volume stress is demonstrated in Fig. 1A. Patients with both conditions—pressure and volume stress (n = 67 [28.4%])—showed the lowest survival rates (1-year survival: 63% vs 92% for pressure and volume stress vs no/low stress, respectively, $P < 0.001$, Fig. 1B).

Novel RVPA coupling parameter in T-TEER patients

Continuous RV function parameters (across all measured 2D and 3D parameters) did not differ between groups (Table 2). However, there was a higher rate of impaired RV free wall longitudinal strain among patients without RV dilatation (23.4 vs 34.7% for with vs without RV dilatation), whereas measurements for TAPSE where within normal ranges (17.9 ± 4.7 mm).

Respecting the predictive value of 3D RV dilation and function according to RVFWLS, we integrated these parameters into the concept of RVPAc. A novel RVPAc-parameter was established (**Graphical Abstract**):

Novel RVPAc

$$\frac{\text{RVFWLS}}{(\text{3D RVEDV} \times \text{invasive sPAP})}$$

A lower novel RVPAc ratio describes progressive RV failure. An RVPAc ratio below 0.454 (RVPA uncoupling) was associated with a 1-year survival rate of 67.3% in T-TEER−treated patients. The adjusted risk for 1-year mortality was 3-fold higher in these patients (1-year survival of 88% in patients with RVPA coupling). Furthermore, the novel RVPAc parameter and NYHA-IV were independent predictors for 1-year mortality after T-TEER (novel RVPAc: HR, 0.08; 95% CI, 0.02-0.34; $P < 0.001$; NYHA-IV: HR, 2.86; 95% CI, 1.6-5.0; $P < 0.001$, Table 3). In addition, the novel RVPAc parameter outperformed the traditional noninvasive RVPAc parameter in 1-year mortality prediction (C-index 0.688 vs 0.572, $P = 0.018$, Fig. 2, A-C).[8] The novel RVPAc showed superior 1-year mortality prediction also

Table 3. Cox regression model for 1-year all-cause mortality

	Univariable			Multivariable		
Characteristic	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years)	0.99	0.96, 1.03	0.7			
Sex (male)	1.21	0.71, 2.04	0.5			
BMI	0.97	0.92, 1.03	0.3			
STS score	1.00	1.00, 1.00	0.8			
NYHA IV	3.05	1.77, 5.26	<0.001	2.79	1.47, 5.31	0.002
TR etiology						
primary	Ref.	Ref.	Ref.			
secondary	0.81	0.20, 3.34	0.8			
mixed	0.85	0.16, 4.38	0.8			
Coronary artery disease	0.98	0.58, 1.65	>0.9			
Presence of RV leads	1.51	0.88, 2.59	0.13			
History of atrial fibrillation/flutter	1.04	0.45, 2.42	>0.9			
COPD	1.18	0.60, 2.33	0.6			
LVEF, %	0.99	0.97, 1.01	0.3			
LVEDV index (Simpson, mL)	1.01	1.00, 1.02	0.049			
LVESV index (Simpson, mL)	1.01	1.00, 1.02	0.011			
LA volume index (biplane, mL)	1.00	0.99, 1.01	0.6			
RVEDV, index (mL/m^2)	1.01	1.00, 1.01	0.037			
RVESV, index (mL/m^2)	1.01	1.00, 1.02	0.034			
RA area (cm^2)	1.01	0.99, 1.03	0.4			
sPAP, mm Hg	1.01	0.98, 1.03	0.08			
TAPSE, mm	0.95	0.90, 1.01	0.10			
RV fractional area change (%)	0.98	0.95, 1.00	0.080			
RVFWLS (%)	1.05	1.01, 1.09	0.025			
RV to PA coupling	0.61	0.14, 2.56	0.5			
3D RV ejection fraction (%)	1.74	0.09, 31.8	0.7			
TR VC (biplane, mm)	1.05	0.99, 1.11	0.088			
TR EROA, cm^2	1.06	0.79, 1.42	0.7			
TR volume, mL	1.00	0.99, 1.01	0.7			
Novel RVPAc	0.10	0.02, 0.44	0.002	0.10	0.02, 0.44	0.002

BMI, body mass index; CI, confidence interval; COPD, chronic pulmonary artery disease; CRT, cardiac resynchronization therapy; EDA, enddiastolic area; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; ESA, end-systolic area; FWLS, free-wall longitudinal strain; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; novel RVPAc, RVFWLS/(3D RVEDV*invasive sPAP); NYHA, New York Heart Association; PA, pulmonary artery; RV, right ventricle; sPAP, systolic pulmonary artery pressure; STS, Society of Thoracic Surgeons; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VC, vena contracta.

compared with RV SV/RV ESV, another well-established RVPAc metric (C-index 0.688 vs 0.49, $P < 0.001$, Supplemental Fig. S3). According to postprocedural TR, patients with and without RVPA-uncoupling both demonstrated significant TR reduction, whereas patients with RVPA-uncoupling showed higher rates of postprocedural TR $\geq$ 2+ (Supplemental Fig. S1). Symptomatic improvement at follow-up was comparable between patients with and without RVPA-uncoupling (Fig. 3).

Discussion

In patients with heart failure and severe TR, the RV has to manage and cope with 2 stress components: the "pressure stress" and the "volume stress" (Fig. 1A). The pressure stress is characterized by the pressure, which the RV needs to generate for pumping blood through the pulmonary circulation, also known as RV afterload. Volume stress is characterized by the increased total stroke volume, defined by the forward stroke volume and regurgitant volume, resulting in a compensatory RV dilatation. Both stress components, which are often considerably increased in patients with TR, result in right ventricular dysfunction (RVD) and symptomatic right heart failure over time. The concept of RVPAc has emerged as a promising prognostic parameter to better describe RVD in patients undergoing transcatheter tricuspid interventions.[8] This traditional noninvasive RVPAc ratio describes RV contractility in relation to the pressure stress of the RV.[10,11] Because of the availability of the respective echocardiographic data, the traditional noninvasive RVPAc ratio is usually calculated from the TAPSE to echocardiographically estimated pulmonary artery pressure ($sPAP_{echo}$). A quotient of < 0.406 has been considered as RVPA uncoupling, and such values were associated with increased mortality after tricuspid interventions.[8] Other multiparametric RVPAc approaches using such as RV stroke volume/RV end systolic volume (ESV) or RVFWLS/sPAP have also demonstrated to highly predict outcome in patients with TR. Of note, the established novel RVPAc parameter outperformed both, traditional TAPSE/sPAP and RV SV/RV ESV.

Even though established in different patient cohorts, the traditional noninvasive RVPAc ratio is subject to important limitations, especially in patients with severe TR. Although TAPSE is generally used to describe RV contractility, the longitudinal contraction is only assessed at a single point of the tricuspid annulus. Finally, pericardial adhesions might impair the longitudinal contraction component of the RV, especially in patients with previous cardiac surgery who constitute a

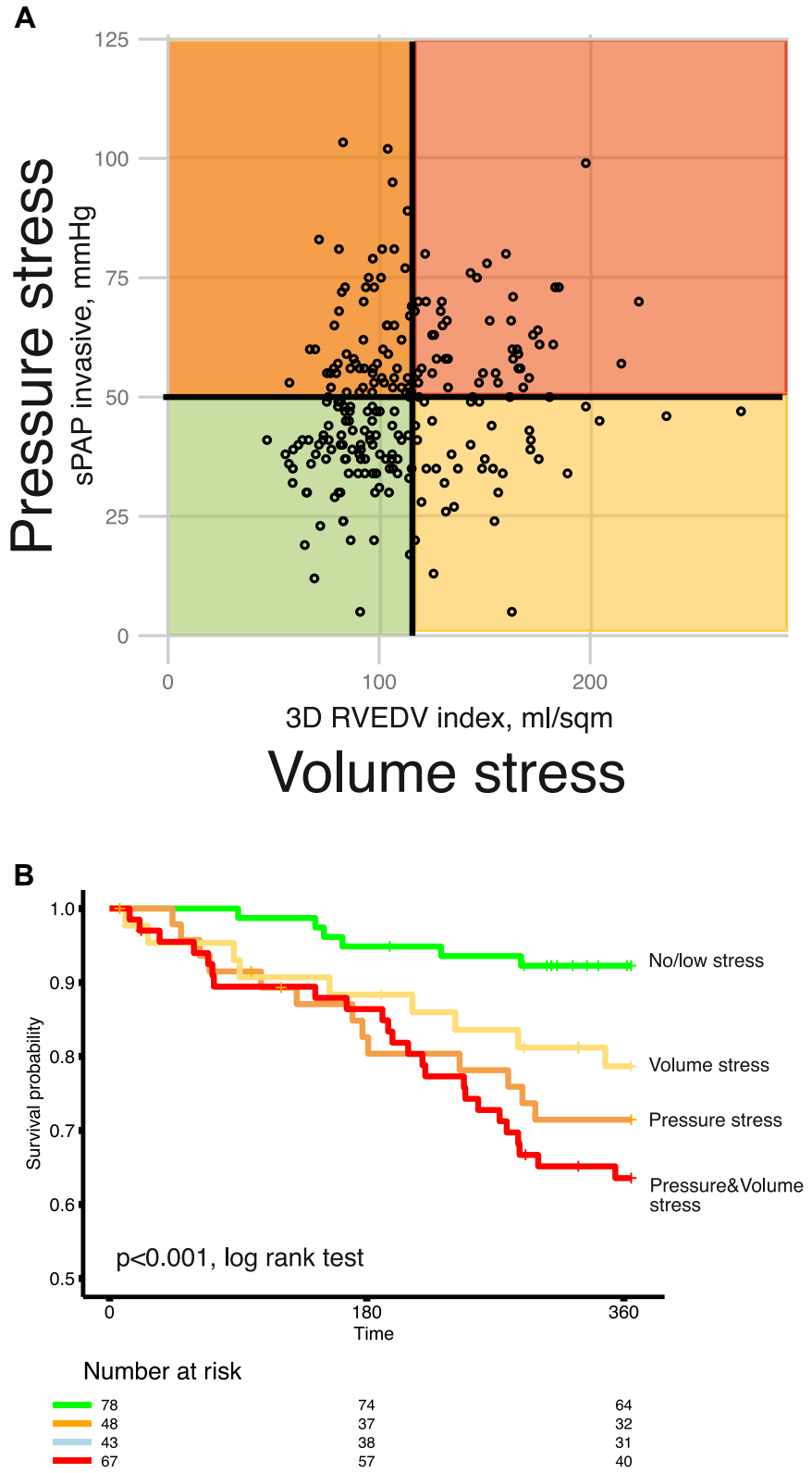
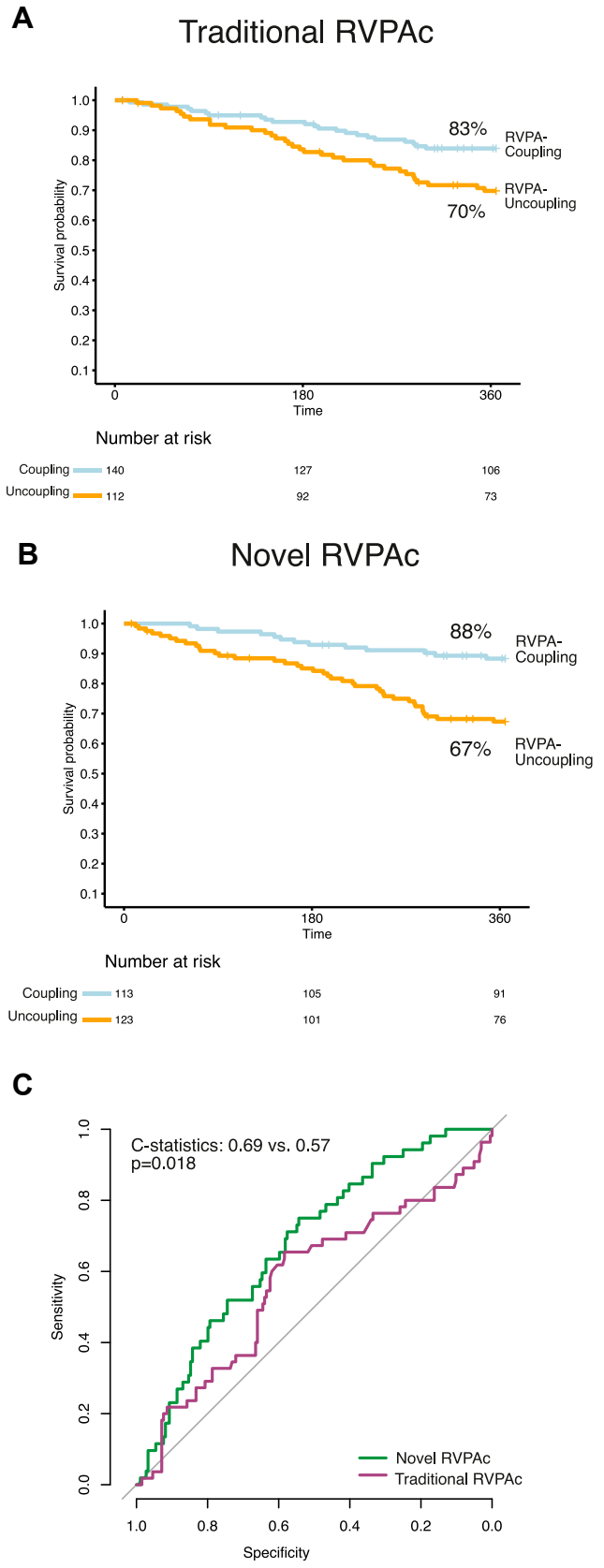


Figure 1. (**A**) A scatter-plot showing the distribution and dependency of pressure and volume stress in T-TEER treated patients with 4 stress-levels. (**B**) The survival according to different stress levels. T-TEER, transcatheter tricuspid edge-to-edge repair.



significant proportion of patients undergoing tricuspid interventions. Accordingly, it is not too surprising that TAPSE alone failed to predict survival in a large cohort of patients undergoing T-TEER.[14] Of note, TAPSE combined with RV fractional area change (FAC) has demonstrated predictive value following T-TEER.[23] In contrast, echocardiographic methods including 3D-RVEF and 2D-RVFWLS have been associated with a superior outcome prediction in T-TEER patients, thus surpassing the limitations of TAPSE.[24,25] Consequently, RVFWLS was introduced as a better parameter to describe RV contractility in our novel RVPAc parameter. An intriguing finding in our study was the greater impairment of RVFWLS in patients without significant RV dilation. Although this observation may initially appear counterintuitive, it can be explained by differences in the pathophysiological remodelling processes in chronic right heart failure. RV dilation typically occurs as a compensatory mechanism in response to acute or chronic volume overload, which allows the RV to maintain adequate stroke volume despite progressive functional impairment. In this scenario, RVFWLS may remain relatively preserved until later stages of remodelling. In contrast, patients without RV dilation may represent a distinct phenotype of RV dysfunction in which intrinsic myocardial contractility is significantly impaired earlier in the disease process, even in the absence of overt structural remodelling. This could be related to myocardial fibrosis, ischemia caused by microvascular dysfunction or other intrinsic myocardial processes that reduce contractile function without necessarily leading to dilation. Also, nondilated RVs may face increased afterload from elevated pulmonary pressures, leading to disproportionate strain impairment without compensatory volume changes.

These findings underscore the heterogeneity in RV response to stress and emphasize the importance of multiparametric evaluation of RV function, including both structural and functional metrics.

Another important limitation of the traditional noninvasive RVPAc parameter is the use of echocardiographically estimated $sPAP_{echo}$ as determinant of the RV pressure stress or RV afterload. Numerous studies have shown that $sPAP_{echo}$ is significantly underestimated with increasing grades of TR severity compared with invasive hemodynamics assessment.[11,26,27] Accordingly, the predictive value of the traditional noninvasive RVPAc parameter is likely to be diminished and less precise in patients with advanced TR grades. This might be of particular relevance because the assessment of RVD might be of utmost value in patients with massive or torrential TR and severe symptoms of advanced

Figure 2. (**A**) One-year survival of T-TEER patients according to the traditional noninvasive RVPAc. (**B**) One-year survival according to the novel RVPAc (RVFWLS/[3D RVEDV*invasive sPAP]). **(C)** ROC analysis comparing the traditional with the novel RVPAc parameter indicating superiority of the novel RVPAc. ROC, receiver operating characteristic; RVEDV, right ventricle end-diastolic volume; RVPAc, right ventricle to pulmonary artery coupling; RVFWLS, right ventricle free-wall longitudinal strain; sPAP, systolic pulmonary artery pressure; T-TEER, transcatheter tricuspid edge-to-edge repair.

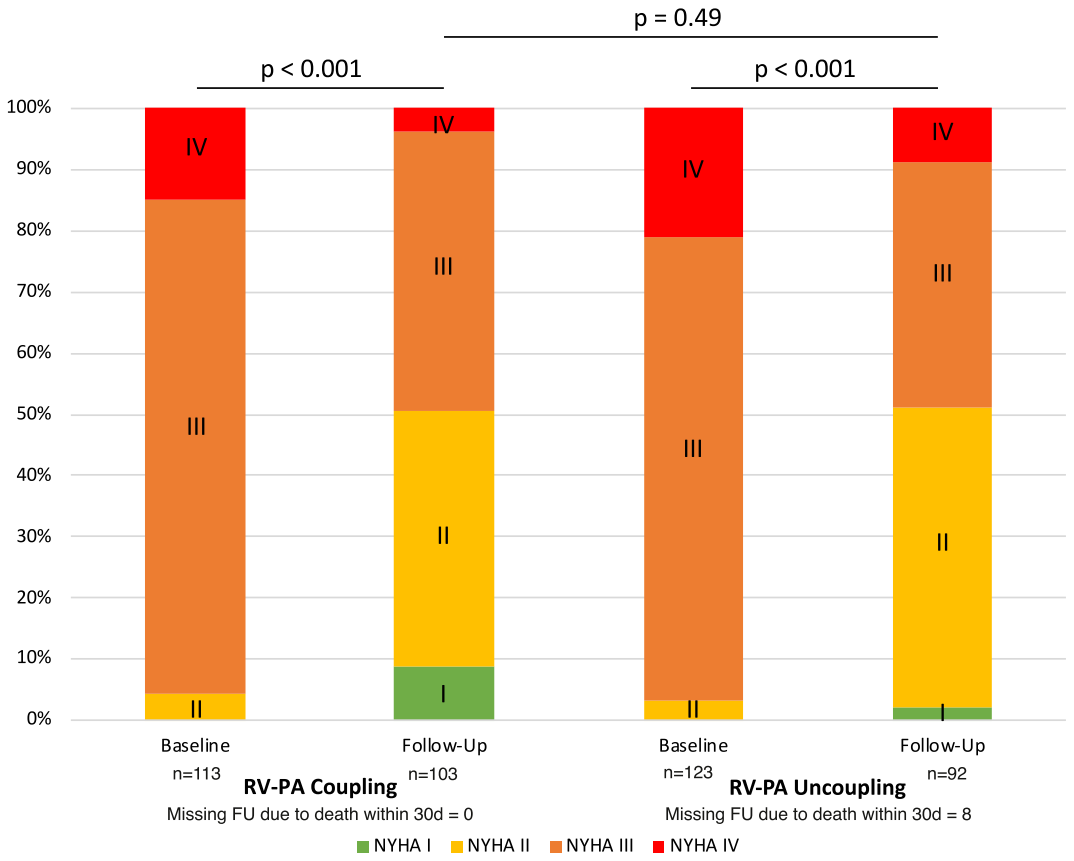


Figure 3. This bar chart shows the heart failure symptomatic measured by NYHA class at baseline and last available follow-up according to the cutoff for the novel RVPA coupling and uncoupling. NYHA, New York Heart Association; RVPA, right ventricle pulmonary artery.

right heart failure. Accordingly, the echocardiographically estimated $sPAP_{echo}$ is substituted by the invasively assessed PA pressure to reflect the RV pressure stress accurately.

As pointed out previously, volume stress constitutes an additional component in RV burden in patients with TR. The prognostic relevance of RV dilatation in patients scheduled for T-TEER has been underestimated so far. The current study demonstrated that RV dilatation is often prevalent in T-TEER patients and that it is associated with reduced survival outcomes. This is of clinical importance because the RV pressure and volume stress do not necessarily go in parallel in different TR phenotypes. Patients with atrial secondary TR usually present with lower PA pressures but less dilated RV, whereas patients with nonatrial secondary TR often have higher PA pressures and more dilated RVs. Furthermore, the relationship between pressure stress and volume stress might change over time in the process of ventricular remodelling in advanced right heart failure. This is highlighted by the findings in our study, that the presence of both conditions, pressure and volume stress, were associated with a significantly lower 1-year survival compared with T-TEER patients with low/no stress or either lone pressure or lone volume stress. Accordingly, we added RV dilatation as important additional RVD parameter to our novel RVPAc parameter, so that both stress components to the RV are integrated in this new parameter. This modified multiparametric approach is certainly far more complex than TAPSE, FAC, $sPAP_{echo}$ or the traditional noninvasive RVPAc, especially in everyday clinical practice. However, increasing experience and recent data demonstrated, that these "easy to assess"; parameters alone are inferior to multiparametric approaches predict outcome in our patients with right heart failure and TR.[28] In contrast with patients with a left-sided pathology, RV dysfunction in patients with TR seems to be far more complex in terms of pathophysiology and therefore requires a more complex and multiparametric echocardiographic and hemodynamic assessment. Novel concepts to predict invasive pulmonary pressures with artificial intelligence-enabled assessment of RV to pulmonary artery coupling will certainly enrich and facilitate RV function assessment in the future.[26] The combination of all 3 important drivers and indicators of RVD—loss of RV contractility, RV dilatation, and increased afterload—may allow for an improved prediction of survival outcomes after tricuspid interventions. In the current cohort, RVPA uncoupling was associated with 3-fold higher risk of mortality when using the novel RVPAc parameter. Although the individual components of the novel RVPAc parameter—RV function, volume stress, and pressure stress—are well-established metrics, their integration into a single multiparametric index represents a novel approach. This innovative combination enhances the predictive value for outcomes in T-TEER patients, addressing key limitations of traditional methods. This novel parameter might be one of the next steps toward overcoming the difficulties in precise RV function assessment. Although the novel

RVPAc parameter integrates multiple dimensions of RV function, volume, and pressure stress for a more comprehensive assessment of RV dysfunction, its clinical adoption may be limited by the requirement for advanced imaging and invasive measurements. To facilitate integration into routine practice, we suggest stepwise implementation. First, use of the novel parameter could be reserved for high-risk patients undergoing T-TEER in whom precise risk stratification is critical. Second, advances in automated echocardiographic analysis and the integration of artificial intelligence (AI)-driven algorithms may further streamline this process, allowing for faster and broader adoption. These observational results need to be validated in different patient populations undergoing interventional valve procedures to evaluate the generalizability of this metric. These findings are of certain relevance because they may help to improve risk stratification in patients with heart failure before T-TEER.

Limitations

The study is subject to the usual imitations of a retrospective study. Patients with incomplete 3D echocardiographic data had to be excluded before the analysis. A general limitation of 3D echocardiography is its dependence on adequate imaging windows, which can be challenging in patients with poor acoustic access because of obesity, lung disease, or previous surgeries. These limitations may lead to suboptimal image quality and reduced accuracy in RV volume and function assessment, potentially excluding such patients from comprehensive analyses. Even though echocardiographic data were analyzed by experienced physicians at each study centre, no core laboratory supervision was available. The small sample size and single-centre design of this study limit the generalizability of our findings, highlighting the need for validation in larger multicentre cohorts of different valvular diseases. Long-term follow-up beyond 1-year is absent. Finally, we acknowledge a higher rate of missing NYHA class follow-up in the RV-PA Uncoupling group mainly explained by the significantly higher death rates within 30 and 90 days. In these patients, it has to be considered that NYHA functional class may be significantly compromised.

Conclusions

Three-dimensional echocardiography is a key diagnostic tool for the assessment of RV volume stress. RV dimension, function, and afterload play important roles in the prediction of RV dysfunction and survival after T-TEER. Respecting all 3 factors (RV dilatation, loss of contractility, and increased afterload) in the estimation of RV function may be 1 step toward more precise detection and characterization of RVD. In addition, these results further highlight the importance of adequate timing of intervention in the context of severe TR and RV dysfunction because the likelihood for survival after T-TEER is higher when RV volume and pressure stress is not advanced in the progress of tricuspid disease.

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Data Availability

All data are incorporated into the article and its online supplementary material.

Ethics Statement

The research reported adhered to the ethical guidelines and was approved by the local ethics committee.

Patient Consent

The authors confirm that a patient consent form(s) has been obtained for this article.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2025.01.026.