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# Right Ventricular−Pulmonary Arterial Coupling in Secondary Tricuspid Regurgitation

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**Chronic pressure-overload induces right ventricular (RV) adaptation to maintain RV−pulmonary arterial (PA) coupling. RV remodeling is frequently associated with secondary tricuspid regurgitation (TR) which may accelerate uncoupling. Our aim is to determine whether the non-invasive analysis of RV−PA coupling could improve risk stratification in patients with secondary TR. A total of 1,149 patients (median age 72[IQR, 63 to 79] years, 51% men) with moderate or severe secondary TR were included. RV−PA coupling was estimated using the ratio between two standard echocardiographic measurements: tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (PASP). The risk of all-cause mortality across different values of TAPSE/PASP was analyzed with a spline analysis. The cut-off value of TAPSE/PASP to identify RV−PA uncoupling was based on the spline curve analysis. At the time of significant secondary TR diagnosis the median TAPSE/PASP was 0.35 (IQR, 0.25 to 0.49) mm/mm Hg. A total of 470 patients (41%) demonstrated RV−PA uncoupling (<0.31 mm/mm Hg). Patients with RV−PA uncoupling presented more frequently with heart failure symptoms had larger RV and left ventricular dimensions, and more severe TR compared to those with RV−PA coupling. During a median follow-up of 51 (IQR, 17 to 86) months, 586 patients (51%) died. The cumulative 5-year survival rate was lower in patients with RV−PA uncoupling compared to their counterparts (37% vs 64%, p < 0.001). After correcting for potential confounders, RV−PA uncoupling was the only echocardiographic parameter independently associated with all-cause mortality (HR 1.462; 95% CI 1.192 to 1.793; p < 0.001). In conclusion, RV−PA uncoupling in patients with secondary TR is independently associated with poor prognosis and may improve risk stratification.**  **(Am J Cardiol 2021;148:138−145)**

Significant (moderate or severe) tricuspid regurgitation (TR) is associated with increased morbidity and mortality.[1−3] Secondary TR is the predominant mechanism of TR and is frequently due to left-sided valvular heart disease and left ventricular diastolic or systolic dysfunction.[4−6] These conditions commonly result in elevated pulmonary pressures and increased right ventricular (RV) afterload, with the RV adapting to the increased load through hypertrophy and/or dilation.[7] RV dilation is accompanied by progressive tricuspid annular dilation and papillary muscle displacement, key factors in the development of secondary TR. Quantification of RV−pulmonary arterial (PA) coupling may provide important insights into the mechanism of adaptation of RV contractility to afterload in patients with secondary TR. The ratio between RV end-systolic elastance (Ees) and pulmonary arterial elastance (Ea) estimated from invasive pressure−volume loops is the reference standard.[7] Recently, the ratio between tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (PASP) measured on echocardiography has shown a good correlation with invasively estimated RV−PA coupling.[8] A reduced TAPSE/PASP ratio suggests that RV contractility is uncoupled from its load and portends a poor prognosis in patients with pulmonary hypertension.[9] The aim of the present study is to determine whether the noninvasive analysis of RV−PA coupling with the use of the TAPSE/PASP ratio could improve risk stratification in patients with significant secondary TR.

## Methods

A query of the echocardiographic database of the Leiden University Medical Center (Leiden, The Netherlands) was performed to identify patients diagnosed with moderate or severe secondary TR between June 1995 and September 2016. Patients with primary TR (due to valve prolapse, endocarditis, rheumatic or carcinoid heart disease), congenital heart disease, and those who underwent tricuspid valve

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interventions after the diagnosis of significant TR were excluded. In addition, patients with incomplete data to assess RV−PA coupling (i.e., TAPSE and/or PASP) were specifically excluded. Clinical and demographic data at the time of the diagnosis of significant secondary TR were collected from the departmental Cardiology Information System (EPD-VisionVR; Leiden University Medical Centre, Leiden, The Netherlands). This retrospective analysis of clinically acquired data was approved by the institutional review board of the Leiden University Medical Centre that waived the need for patient written informed consent.

Clinical characteristics included cardiovascular risk factors, comorbidities, New York Heart Association (NYHA) functional class, medical therapy, and the presence of cardiac devices. Transthoracic echocardiographic data were acquired with patients at rest in the left lateral decubitus position using available ultrasound systems (Vivid 7, E9, and E95 systems; GE-Vingmed) equipped with 3.5 MHz or M5S transducers. Data were stored digitally in a cine-loop format for offline analysis with the EchoPac software (EchoPac version 203 and 204, GE-Vingmed). The digitized echocardiographic data were retrospectively reanalyzed taking into account current guidelines and therefore, the present study does not simply concern tabulation of descriptive data included in the clinical reports. RV dimensions were measured on an RV-focused apical view and included end-diastolic basal and mid diameter, end-diastolic base-to-apex length, end-diastolic, and end-systolic areas.[10] RV systolic function was estimated based on TAPSE measured on M-mode recordings of the lateral tricuspid annulus. RV fractional area change was also calculated with the following formula: (end-diastolic area - end-systolic area)/end-diastolic area × 100. TR grade was assessed by a multiparametric approach, including qualitative, semi-quantitative, and quantitative parameters.[11] PASP was estimated from the TR jet peak velocity applying the simplified Bernoulli equation and adding mean right atrial pressure.[10] Mean right atrial pressure was derived based on the inferior vena cava diameter and collapsibility during inspiration.[10]. Left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson method.[12] RV−PA coupling was estimated non-invasively using the ratio between two standard echocardiographic measurements: TAPSE and PASP. TAPSE/PASP ratio is a surrogate for Ees/Ea, based on the assumption that TAPSE provides an estimate of RV contractility and PASP an estimate of RV afterload.[8,13-14] Moreover, it was recently demonstrated that TAPSE/PASP is the only echocardiographic index that is independently associated with the gold standard invasive measurement of RV−PA coupling (i.e., Ees/Ea).[8]

The primary endpoint of this study was all-cause mortality. All patients were followed-up for the occurrence of the primary endpoint. Survival data were collected from the departmental Cardiology Information System and the Social Security Death Index.

The statistical analyses were performed using the SPSS version 25.0 (SPSS Inc, IBM Corp) and in R environment 3.6.4 (R Foundation for Statistical Computing). Categorical variables are expressed as numbers and percentages. For continuous variables, adherence to a normal distribution was verified through visual assessment, comparing a histogram of the sample data to a normal probability curve. Normally distributed continuous variables are presented as mean ± standard deviation while variables that are non-normally distributed are presented as median and interquartile range. To assess the hazard ratio (HR) change for all-cause mortality across a range of TAPSE/PASP values at baseline a spline curve analysis was performed. The cut-off value of TAPSE/PASP to define RV−PA uncoupling was chosen based on mortality excess and previously published data.[8] Differences between RV−PA coupling versus uncoupling were analyzed using the unpaired Student t-test for normally distributed continuous variables, the Mann−Whitney U test for non-normally distributed continuous variables and the Pearson's chi-square test for categorical variables. The 1- and 5-year cumulative survival rates were estimated with Kaplan−Meier curves and differences between groups were analyzed using the Mantel−Cox log-rank test. A multivariable Cox proportional hazard regression analysis was conducted to assess the clinical and echocardiographic features that were independently associated with all-cause mortality. Possible confounders with a p value $< 0.05$ at the univariable analysis were included in the multivariable Cox regression analysis. HRs and 95% confidence intervals (CIs) were calculated. Two-sided p values $< 0.05$ were considered statistically significant.

## Results

A total of 1,149 patients with a median age of 72 (interquartile range, 63 to 79) years fulfilled the study inclusion criteria (Supplementary Figure 1). Of these, 909 (79%) had moderate TR and 240 (21%) had severe TR. To investigate the relationship between TAPSE/PASP ratio and all-cause mortality, a spline curve analysis was performed (Figure 1). After an initial slow rise of HR, there was an increase in the HR of all-cause mortality for reduced values of TAPSE/PASP ratio (<0.31 mm/mm Hg). Based on this analysis and previously published data,[8] a TAPSE/PASP value $< 0.31$ mm/mm Hg was used to define RV−PA uncoupling and to dichotomize the population. RV−PA uncoupling at the time of significant secondary TR diagnosis was present in 470 patients (41%). When compared to patients with RV−PA coupling, those with RV−PA uncoupling were more frequently men, had a higher prevalence of cardiovascular risk factors and coronary artery disease, worse renal function, were more symptomatic (heart failure symptoms and peripheral edema), and used diuretics more frequently (Table 1). Patients with RV−PA uncoupling had significantly larger left ventricular and RV dimensions, lower LVEF, larger left atrial (LA) volumes, and more frequently had significant mitral regurgitation than those without RV−PA uncoupling (Table 2). Interestingly, those with RV−PA uncoupling had larger tricuspid regurgitant volume and vena contracta width when compared to those with RV−PA coupling.

During a median follow-up of 51 (interquartile range, 17 to 86) months, 586 patients (51%) died. Kaplan−Meier analysis demonstrated significantly reduced survival in patients with RV−PA uncoupling at 1-year (59% vs 82%, log-rank chi-square = 62.379, $p < 0.001$) and 5-year follow-up (37% vs 64%, log-rank chi-square = 86.247, $p < 0.001$;

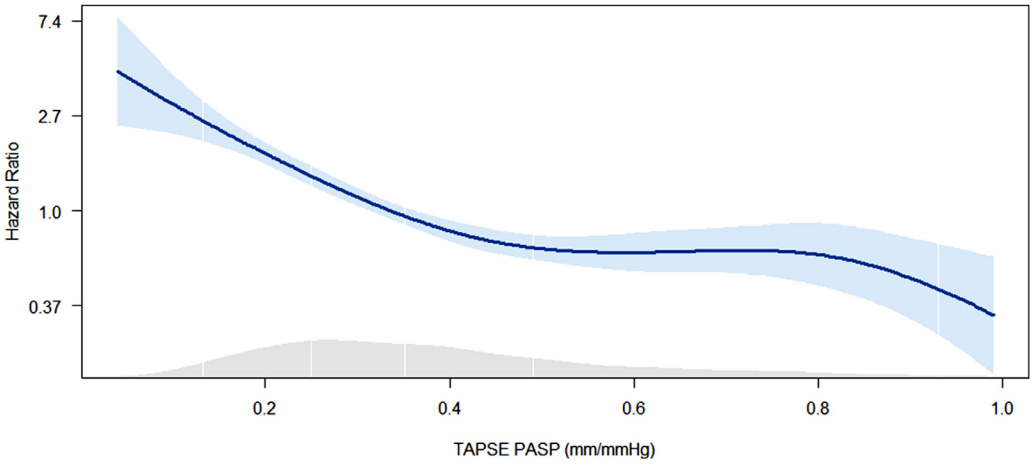


Figure 1. Spline curve for all-cause mortality according to TAPSE/PASP ratio. The curve represents the hazard ratio change for all-cause mortality with overlaid 95% confidence intervals (light-blue) across a range of TAPSE/PASP ratio at the time of significant secondary TR diagnosis. The grey density plot shows the distribution of the study population according to values of TAPSE/PASP.
TAPSE/PASP = Tricuspid annular plane systolic excursion / pulmonary artery systolic pressure ratio; TR = Tricuspid regurgitation

Figure 2). To further investigate the association between the TAPSE/PASP ratio and all-cause mortality, univariable and multivariable Cox proportional hazards models were constructed (Table 3). TAPSE/PASP was introduced as a categorical variable, utilizing the threshold derived from the spline curve analysis (0.31 mm/mm Hg). Univariable Cox regression analysis demonstrated a significant association between the following parameters and the risk of all-cause mortality: age, male gender, diabetes mellitus, known coronary artery disease, chronic obstructive pulmonary disease, renal function, heart failure symptoms, diuretic use, left ventricular systolic function, LA volume, significant left-sided valvular heart disease, RV dimensions and systolic function, PASP, individual parameters of TR severity, and RV−PA uncoupling (i.e., TAPSE/PASP < 0.31). On multivariable Cox regression analysis, RV−PA uncoupling (i.e., TAPSE/PASP < 0.31) was the only echocardiographic parameter that retained an independent association with all-cause mortality (HR 1.46; 95% CI 1.19 to 1.79; p < 0.001). As shown in Figure 3, the incremental prognostic value of the TAPSE/PASP ratio and RV−PA uncoupling (i.e., TAPSE/PASP < 0.31 mm/mm Hg) was evaluated by adding these parameters to a baseline model. The addition of TAPSE/PASP ratio as a continuous variable improved the predictivity of the model compared to the addition of standard echocardiographic parameters of RV systolic function (i.e., TAPSE or fractional area change). Moreover, the addition of RV−PA uncoupling (i.e., TAPSE/PASP < 0.31 mm/mm Hg) to the same basal model yielded a higher increase in predictivity compared to the addition of RV systolic dysfunction either evaluated with TAPSE (< 17 mm) or fractional area change (<35%) using the cut-off values recommended by current guidelines[15] (Figure 3).

Table 1.
Clinical and demographic characteristics

| Variable | Overall (n = 1,149) | RV−PA coupling (TAPSE/PASP ≥ 0.31) (n = 679) | RV−PA uncoupling (TAPSE/PASP < 0.31) (n = 470) | p value |
|---|---|---|---|---|
| Age (years) | 72 (63-79) | 72 (62 to 78) | 72 (63 to 79) | 0.271 |
| Men | 582 (51%) | 317 (47%) | 265 (56%) | 0.001 |
| Body mass index (kg/m$^2$) | 26 ± 4 | 26 ± 4 | 25 ± 4 | 0.489 |
| Hypertension | 854 (81%) | 497 (80%) | 357 (83%) | 0.312 |
| Hypercholesterolemia | 501 (48%) | 266 (43%) | 235 (55%) | <0.001 |
| Diabetes mellitus | 208 (20%) | 82 (13%) | 126 (29%) | <0.001 |
| Coronary artery disease | 457 (40%) | 221 (33%) | 236 (51%) | <0.001 |
| Chronic obstructive pulmonary disease | 154 (15%) | 84 (14%) | 70 (16%) | 0.258 |
| Glomerular filtration rate (ml/min/1.73 m$^2$) | 65 ± 29 | 68 ± 28 | 59 ± 28 | <0.001 |
| Current or former smoker | 319 (31%) | 192 (31%) | 127 (30%) | 0.584 |
| Atrial fibrillation | 539 (50%) | 314 (49%) | 225 (51%) | 0.692 |
| New York Heart Association functional class III-IV | 464 (44%) | 220 (36%) | 244 (56%) | <0.001 |
| Peripheral edema | 249 (23%) | 109 (17%) | 140 (31%) | <0.001 |
| Diuretic use | 645 (58%) | 329 (50%) | 316 (69%) | <0.001 |

PA = pulmonary arterial; PASP = pulmonary arterial systolic pressure; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion.
Values are presented as mean ± SD, median (IQR) or n (%). Percentages are calculated based on data availability.

Table 2.
Echocardiographic characteristics

| Variable | Overall (n = 1,149) | RV−PA coupling (TAPSE/PASP ≥ 0.31 )(n=679) | RV−PA uncoupling (TAPSE/PASP < 0.31) (n=470) | p value |
|---|---|---|---|---|
| Left-sided heart | | | | |
| Left ventricular end-diastolic diameter (mm) | 48 ± 11 | 47 ± 11 | 50 ± 12 | <0.001 |
| Left ventricular end-systolic diameter (mm) | 39 ± 13 | 37 ± 13 | 41 ± 14 | <0.001 |
| Left ventricular end-diastolic volume (ml) | 113 (80-167) | 105 (80-154) | 125 (82-190) | <0.001 |
| Left ventricular ejection fraction (%) | 44 ± 16 | 46 ± 15 | 41 ± 16 | <0.001 |
| Left atrial maximum volume (ml) | 92 (59-127) | 80 (56-119) | 104 (70-137) | <0.001 |
| Significant aortic stenosis | 263 (24%) | 145 (22%) | 118 (26%) | 0.106 |
| Significant mitral regurgitation | 304 (27%) | 155 (23%) | 149 (32%) | 0.001 |
| Right-sided heart | | | | |
| RV basal diameter (mm) | 45 ± 8 | 45 ± 9 | 46 ± 8 | 0.409 |
| RV mid diameter (mm) | 35 ± 9 | 34 ± 9 | 36 ± 9 | 0.001 |
| RV longitudinal diameter (mm) | 72 ± 12 | 71 ± 13 | 74 ± 12 | <0.001 |
| RV end-diastolic area ($cm^2$) | 25 ± 12 | 25 ± 14 | 26 ± 9 | 0.025 |
| Right atrial area ($cm^2$) | 28 ± 11 | 27 ± 11 | 28 ± 10 | 0.078 |
| Fractional area change (%) | 34 ± 13 | 36 ± 14 | 31 ± 12 | <0.001 |
| Tricuspid annular plane systolic excursion (mm) | 15 ± 5 | 18 ± 5 | 12 ± 3 | <0.001 |
| PASP (mm Hg) | 44 ± 16 | 37 ± 11 | 55 ± 15 | <0.001 |
| Tricuspid valve | | | | |
| Tricuspid annulus diameter (mm) | 42 ± 8 | 42 ± 8 | 42 ± 8 | 0.106 |
| Vena contracta (mm) | 11 ± 4 | 10 ± 4 | 11 ± 4 | 0.023 |
| Effective regurgitant orifice area ($mm^2$) | 68 (43-105) | 68 (41-110) | 68 (46-101) | 0.905 |
| Regurgitant volume (ml/beat) | 65 (39-104) | 59 (35-102) | 73 (46-106) | <0.001 |
| Pacemaker/Implantable cardioverter defibrillator lead | 413 (37%) | 245 (37%) | 168 (36%) | 0.887 |

PA = pulmonary arterial; PASP = pulmonary artery systolic pressure; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion.
Values are presented as mean ± SD, median (IQR) or n (%). Percentages are calculated based on data availability.

## Discussion

In patients with moderate or severe secondary TR, the assessment of RV−PA coupling by TAPSE/PASP ratio is superior for risk stratification compared to the evaluation of conventional indices of RV systolic function such as fractional area change or TAPSE. Interestingly, in this large cohort of patients with moderate and severe secondary TR, 41% presented with RV−PA uncoupling at the time of significant TR diagnosis, potentially indicating advanced disease and late diagnosis.

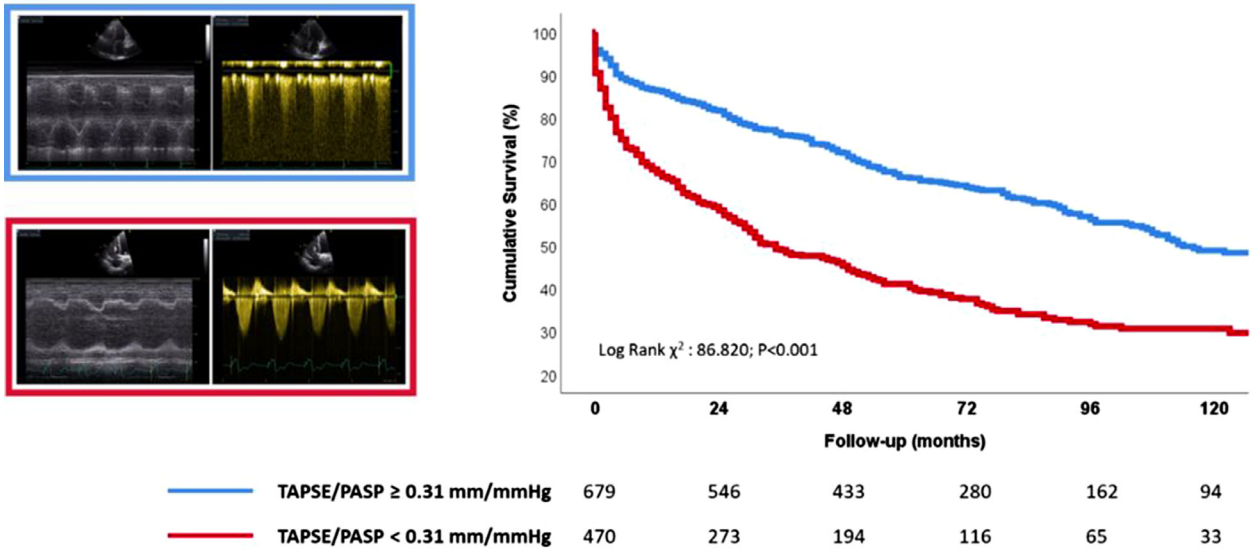


Figure 2. Kaplan−Meier curves for all-cause mortality. The Kaplan−Meier curves demonstrate the higher survival rates of patients with RV−PA coupling (TAPSE/PASP ratio: ≥0.31 mm/mm Hg, blue line and box) compared to those with RV−PA uncoupling (TAPSE/PASP ratio <0.31 mm/mm Hg, red line and box) during the follow-up after significant secondary TR diagnosis.
RV-PA = Right ventricular − pulmonary arterial; TAPSE/PASP = Tricuspid annular plane systolic excursion / pulmonary artery systolic pressure ratio; TR = Tricuspid regurgitation.

Table 3
Univariable and multivariable Cox proportional hazard models for all-cause mortality

| | Univariate analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | HR (95% CI) | p value | HR (95% CI) | p value |
| Patient demographics and comorbidities | | | | |
| Age | 1.023 (1.015-1.030) | <0.001 | 1.030 (1.020-1.040) | <0.001 |
| Men | 1.199 (1.019-1.410) | 0.029 | 1.135 (0.908-1.419) | 0.267 |
| Atrial fibrillation | 0.992 (0.841-1.170) | 0.922 | | |
| Current or former smoker | 1.178 (0.985-1.409) | 0.073 | | |
| Hypertension | 0.956 (0.771-1.185) | 0.681 | | |
| Diabetes mellitus | 1.765 (1.454-2.143) | <0.001 | 1.294 (1.024-1.634) | 0.031 |
| Coronary artery disease | 1.690 (1.436-1.989) | <0.001 | 1.229 (0.995-1.517) | 0.055 |
| Chronic obstructive pulmonary disease | 1.641 (1.322-2.037) | <0.001 | 1.157 (0.902-1.484) | 0.251 |
| Estimated glomerular filtration rate | 0.983 (0.980-0.987) | <0.001 | 0.992 (0.987-0.996) | <0.001 |
| New York Heart Association III-IV | 2.466 (2.077-2.927) | <0.001 | 1.774 (1.445-2.177) | <0.001 |
| Diuretics | 2.188 (1.826-2.563) | <0.001 | 1.328 (1.045-1.688) | 0.020 |
| Peripheral edema | 1.768 (1.462-2.137) | <0.001 | 1.060 (0.839-1.338) | 0.626 |
| **Echocardiographic parameters** | | | | |
| Left ventricular ejection fraction | 0.984 (0.979-0.989) | <0.001 | 0.997 (0.990-1.004) | 0.359 |
| Left atrial maximum volume | 1.002 (1.001-1.004) | 0.001 | 1.000 (0.998-1.002) | 0.748 |
| Significant mitral regurgitation | 1.473 (1.236-1.756) | <0.001 | 1.163 (0.941-1.437) | 0.162 |
| Significant aortic stenosis | 1.454 (1.210-1.747) | <0.001 | 1.200 (0.967-1.489) | 0.098 |
| Tricuspid annulus diameter | 1.014 (1.004-1.025) | 0.006 | | |
| Right ventricular basal diameter | 1.020 (1.011- 1.030) | <0.001 | 1.008 (0.994-1.022) | 0.259 |
| Right ventricular base-to-apex length | 1.015 (1.008-1.022) | <0.001 | 1.008 (0.998-1.018) | 0.106 |
| Right ventricular end-diastolic area | 1.009 (1.006-1.013) | <0.001 | | |
| Fractional area change | 0.198 (0.108-0.366) | <0.001 | | |
| TAPSE | 0.940 (0.923-0.957) | <0.001 | | |
| Right atrial area | 1.006 (1.000-1.013) | 0.063 | | |
| PASP | 1.022 (1.017-1.027) | <0.001 | | |
| Pace-maker/implantable cardioverter defibrillator lead | 1.312 (1.112-1.548) | 0.001 | 1.149 (0.938-1.409) | 0.180 |
| Vena contracta width | 1.027 (1.006-1.048) | 0.010 | 1.010 (0.985-1.035) | 0.445 |
| Regurgitant volume | 1.002 (1.001-1.004) | 0.001 | | |
| RV-PA uncoupling (TAPSE/PASP<0.31) | 2.117 (1.799-2.492) | <0.001 | 1.462 (1.192-1.793) | <0.001 |

CI = confidence intervals; HR = hazard ratio; PA = pulmonary arterial; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion.

It has been extensively demonstrated that RV systolic performance is closely related to afterload and should be evaluated together with the assessment of RV−PA coupling.[8,9,13,14,16] The noninvasive assessment of RV−PA coupling with the TAPSE/PASP ratio has been shown to correlate well with invasive hemodynamics and more importantly, predict outcomes in several cardiovascular diseases, such as pulmonary arterial hypertension, heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, and severe aortic stenosis.[8,9,13,14,16] Although these cardiovascular pathologies may coexist with significant TR, the prognostic importance of RV−PA coupling has not been extensively examined in a cohort of patients with significant secondary TR. The relationship between TAPSE and PASP evaluates the adaptation of RV systolic function to afterload and the ability of the RV to generate pulmonary pressures. Optimal RV−PA coupling occurs when RV contractility (Ees) and afterload (Ea) are equal or the ratio between the 2 is above 1, as this minimizes energy expenditure and maximizes efficiency.[7,13] The RV adapts initially to pressure overload through RV hypertrophy to increase RV contractility at the expense of an increase in RV filling pressures and diastolic dysfunction. However, with progressive RV−PA uncoupling (Ees/Ea ratio < 0.8 that approximately corresponds to TAPSE/PASP ratio < 0.31 mm/mm Hg,[8]) the RV progressively dilates and RV systolic dysfunction occurs.[8,13,14] In secondary TR, pressure overload is likely the primary determinant of RV−PA uncoupling. However, in contrast to heart failure, aortic stenosis and pulmonary arterial hypertension, volume overload due to significant TR can contribute to RV dilatation and dysfunction. Volume overload may result in increased wall tension[17] leading to myocardial fibrosis and altered RV chamber geometry, directly contributing to impaired RV contractility and therefore, RV−PA uncoupling.[7,18] From this perspective, RV−PA uncoupling represents a final common pathway of chronic RV pressure and volume overload in secondary TR.

In this large cohort of patients with moderate or severe secondary TR, 41% of the study population presented with a TAPSE/PASP ratio < 0.31 mm/mm Hg at the time of significant TR diagnosis, reflecting RV−PA uncoupling. Patients with RV−PA uncoupling showed a higher prevalence of heart failure symptoms and comorbidities, with more severe TR and advanced RV remodeling. This is in accordance with previous studies where a lower TAPSE/PASP ratio was related to advanced right heart remodeling, secondary TR, and impaired functional capacity.[8,9,13,14] Importantly, after adjusting for known comorbidities, cardiovascular risk factors and several echocardiographic

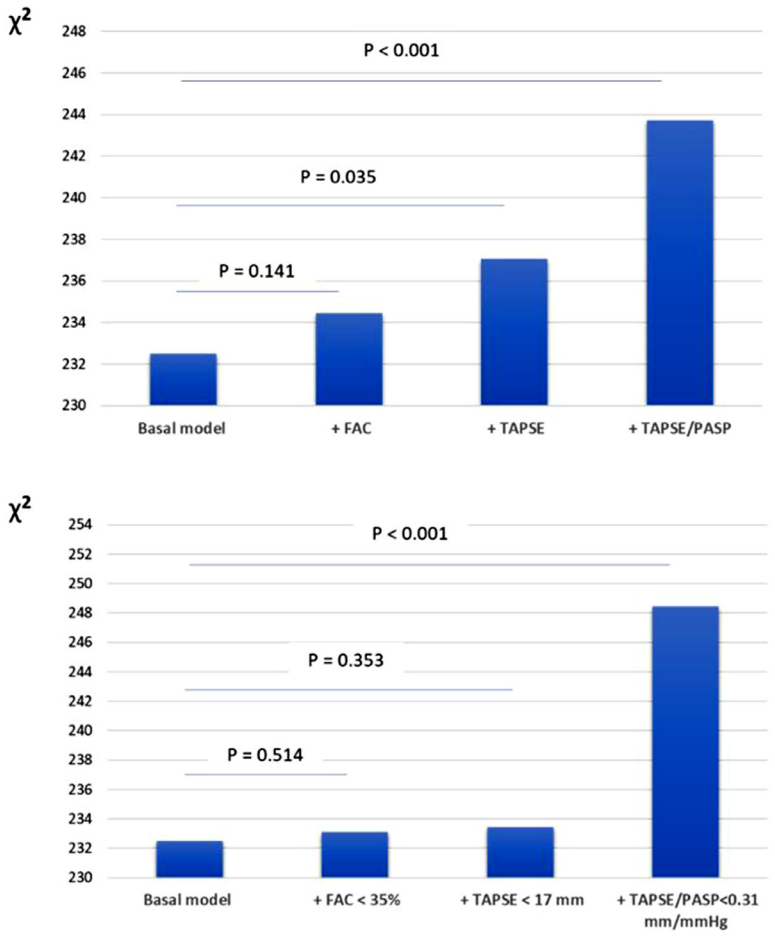


Figure 3. Incremental prognostic value of RV−PA uncoupling. The bar-graph in the upper panel shows a statistically significant increase in Chi-square with the addition of TAPSE/PASP as a continuous variable to a basal model (including age, gender, diabetes, known coronary artery disease, chronic obstructive pulmonary disease, estimated glomerular filtration rate, NYHA classes III and IV, diuretic use, peripheral edema, LVEF, LA volume, significant mitral regurgitation, significant aortic stenosis, RV basal diameter, RV base-to-apex length, presence of PM/ICD lead, tricuspid regurgitation VC width) compared to the addition of standard echocardiographic indices of RV systolic function (i.e., FAC or TAPSE). The bar-graph in the lower panel demonstrates a greater increase in chi-square with the addition of RV−PA uncoupling (i.e., TAPSE/PASP < 0.31 mm/mm Hg) to the basal model compared to the addition of RV systolic dysfunction either defined with FAC (<35%) or TAPSE (<17 mm).
FAC = Fractional area change; ICD = Implantable cardioverter defibrillator; LA = Left atrial; LVEF = Left Ventricular Ejection Fraction; NYHA = New York Heart Association; PM = Pace-maker; RV = Right ventricular; RV-PA = Right ventricular − pulmonary arterial; TAPSE/PASP = Tricuspid annular plane systolic excursion / pulmonary artery systolic pressure ratio; TR = Tricuspid regurgitation; VC = Vena contracta.

parameters, the noninvasive evaluation of RV−PA coupling (i.e., TAPSE/PASP ratio) was independently associated with prognosis and was incremental to the evaluation of conventional RV systolic function indices that do not take RV afterload into account. Interventions aimed at reducing RV pressure and volume overload could have a beneficial effect on RV systolic function and therefore improve RV−PA coupling and patient prognosis. In patients with heart failure due to reduced left ventricular systolic function and significant functional mitral regurgitation, sacubitril/valsartan showed to have a beneficial effect on left ventricular systolic and diastolic function and to reduce mitral regurgitation severity,[19] potentially leading to a progressive decrease in pulmonary pressures and improved RV−PA coupling. Supplemental oxygen in patients with chronic obstructive pulmonary disease may reduce hypoxemia and pulmonary pressures, optimizing RV−PA coupling.[20] Finally, tricuspid valve interventions can reduce RV volume overload.[21,22] and therefore could have a beneficial effect on RV−PA coupling, potentially improving the prognosis of these patients. Although we showed that RV−PA uncoupling in patients with significant TR is independently associated with a worse prognosis if TR is left untreated, prospective studies potentially including also invasive hemodynamic data are warranted to provide further insights on the role of the non-invasive assessment of RV−PA coupling to improve patient selection for tricuspid valve interventions.[23]

The limitations of the present study are inherent to its single-center retrospective design. Although echocardiography may underestimate pulmonary pressures in the presence of significant TR, the correction of RV systolic function for PASP significantly improved the predictivity of the Cox models compared to the independent use of conventional echocardiographic indices of RV systolic function. Despite the higher accuracy of invasive pressure

−volume loops to estimate RV−PA coupling, standard echocardiography provides a reliable measure of the adaptation of RV to the increased afterload,[8] is widely available and allows for repetitive non-invasive assessment without any additional risk for patients. Finally, in the present study, RV−PA coupling was assessed only at rest, further studies would be needed to investigate the role of exercise echocardiography to unmask RV−PA uncoupling and risk-stratify patients with secondary TR.

In conclusion, the echocardiographic estimation of RV−PA coupling with the TAPSE/PASP ratio improves risk stratification of patients with significant secondary TR compared to the use of conventional echocardiographic indices of RV systolic function.

## Authors' contributions

Federico Fortuni: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing—original draft. Steele C. Butcher: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Resources; Validation; Writing—original draft. Marlieke Dietz: Conceptualization; Data curation; Methodology; Resources; Validation; Writing—review & editing. Pieter van der Bijl: Conceptualization; Data curation; Methodology; Resources; Validation; Writing—review & editing. Edgard A. Prihadi: Data curation; Resources; Validation; Writing—review & editing. Gaetano De Ferrari: Writing—review & editing. Nina Ajmone Marsan: Conceptualization; Funding acquisition; Methodology; Project administration; Supervision; Validation; Writing—review & editing. Jeroen J. Bax: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Writing—review & editing. Victoria Delgado: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Writing—review & editing.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.02.037.


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