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ORIGINAL PAPER

Right atrial and right ventricular strain: prognostic value depends on the severity of tricuspid regurgitation

Elizabeth Curtis[1], Léo Lemarchand[1], K. Charlotte Lee [2], Elena Galli [1], Guillaume L'Official[1], Vincent Auffret [1], Guillaume Leurent[1], Emmanuel Oger [3], and Erwan Donal [1]*

[1]Cardiology, University of Rennes, CHU Rennes, Inserm, LTSI – UMR 1099, 2 Rue Henri le Guilloux, F-35000 Rennes, France; [2]Perelman School of Medicine, University of Pennsylvania, 3400 Civic Center Boulevard, Philadelphia 19104, PA, USA; and [3]Clinical Section of Fundamental and Clinical Pharmacology, CHU Rennes, University of Rennes, 2 Rue du Thabor, Rennes, France

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Aims

Assessing right heart function is challenging, particularly when significant tricuspid regurgitation (TR) is present. Amongst available echocardiographic techniques for assessment, literatures suggest that strain imaging may be more reliable and less susceptible to loading conditions. Thus, we aimed to assess the validity of right atrial (RA) and right ventricular (RV) strain relative to conventional metrics as well as their utility in predicting patient outcomes in TR.

Methods and results

We studied 262 consecutive patients (mean age 74 ± 11.2 years, 53% male) who underwent same-day echocardiography and right heart catheterization between 2018 and 2023. We compared right heart strain to traditional metrics of RV function and subsequently correlated RA and RV strain to heart failure (HF)-related death or hospitalization, whichever came first. Over a mean follow-up of 34 ± 15 months, there were 103 deaths and HF hospitalizations. Both RA strain and RV strain were correlated with echocardiographic and invasive measures of right heart function. Across all patients, preserved RA strain was associated with lower risk of adverse outcomes [hazard ratio (HR) 0.763, 95% confidence interval (CI) 0.618–0.943]. Similarly, preserved RV strain was correlated with better outcomes, although this was only statistically significant in patients without severe TR or pulmonary hypertension (HR 2.450, 95% CI 1.244–4.825). Moreover, abnormal ratios of RV strain to pulmonary pressures and RV size were significantly correlated with adverse outcomes ($P < 0.05$ each).

Conclusion

RA and RV strain are independently correlated with echocardiographic and invasive measures of cardiac function. Moreover, preserved RA and RV strain is likely associated with better clinical outcomes.

* Corresponding author. E-mail: erwan.donal@chu-rennes.fr

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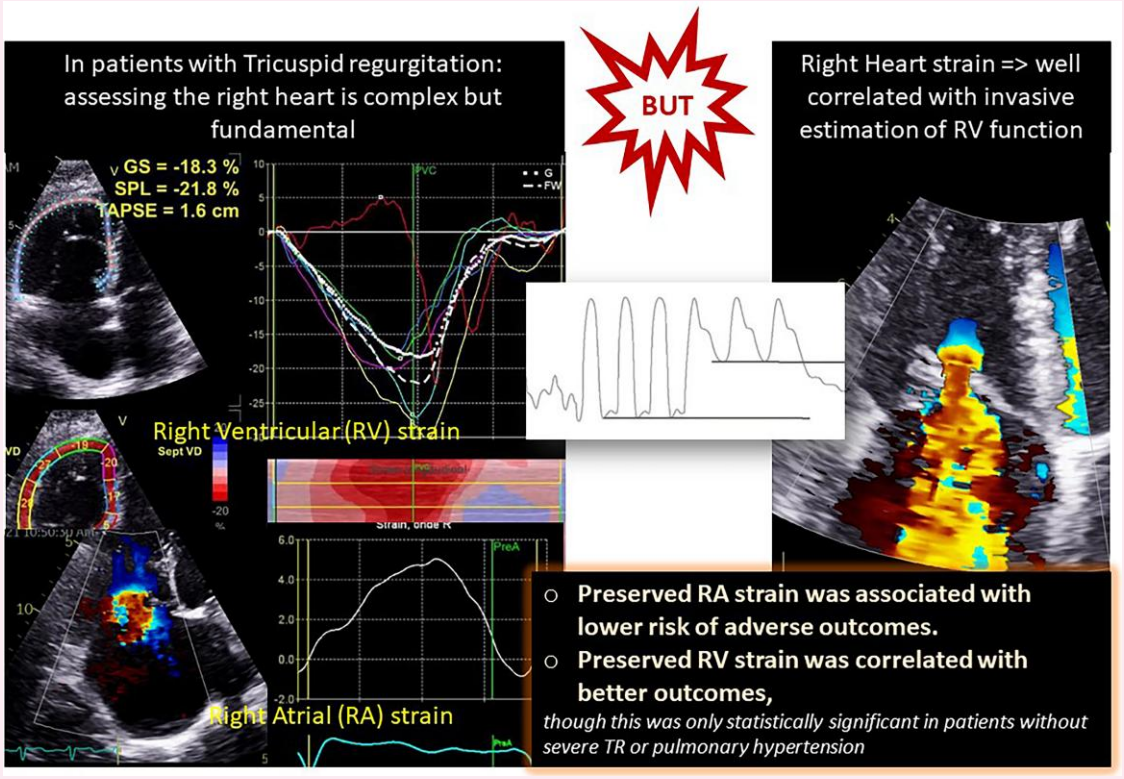
Graphical Abstract



Keywords RA strain • RV strain • tricuspid regurgitation (TR) • prognosis • right heart

Introduction

Echocardiographic assessment of right heart function is challenging due to the complex anatomy of the right ventricle (RV) and its dependence on loading conditions. RV assessment is rendered even more difficult in the presence of tricuspid regurgitation (TR), which can lead to overestimation of right heart function. Despite this fact, there are currently no reference ranges to classify 'normal' RV function [via fractional area change (FAC), tricuspid annulus plane systolic excursion (TAPSE), and S'] when significant TR is present. This lack of echocardiographic guidance often necessitates invasive or multimodal assessment of right heart function as part of clinical decision-making and risk profiling in severe TR. Even with multimodal RV assessment, there are no validated normal values for patients stratified by different loading conditions. As such, RV functional assessment is an inexact science in daily clinical practice.

Amongst the new imaging tools for assessing right heart function, speckle-tracking echocardiography appears to be a more sensitive marker of early cardiac dysfunction and is less sensitive to loading conditions. Within speckle-tracking techniques, the measurement of right atrial (RA) strain has shown prognostic relevance in cohorts with pulmonary hypertension and heart failure (HF).[1–4] Similarly, RV free wall strain (FWS) carries prognostic importance across a broad range of conditions, including aortic stenosis (AS), acute HF, and chronic HF.[1–4]

Given these preliminary data, we aimed to correlate RA and RV strain with right heart chamber sizes, invasive and non-invasive measures of RV systolic function, and clinical outcomes (death and HF hospitalization) in a heterogeneous group of patients with varying degrees of TR.

Methods

Population

We studied 262 consecutive patients who presented to Rennes University Hospital between January 2018 and January 2023 and underwent same-day transthoracic echocardiography (TTE) and right heart catheterization (RHC). This population was heterogeneous, with the most common reasons for evaluation being TR (112 patients, 42.7%), mitral regurgitation (MR) (75 patients, 28.6%), dilated cardiomyopathy (DCM) (25 patients, 9.5%), and AS (24 patients, 9.2%). Additional reasons for evaluation included hypertrophic cardiomyopathy (HCM) ($n = 6$), atrial septal defect (ASD) ($n = 4$), pulmonary artery hypertension (PAH) ($n = 5$), and others (mitral stenosis, respiratory failure, aortic regurgitation, and breathlessness, $n = 11$). Patients who did not undergo cardiac catheterization in the same admission as their echocardiogram were excluded. The study was conducted following the 'Good Clinical Practice' Guidelines in the Declaration of Helsinki.

Echocardiography

All echocardiographic examinations were performed on commercially available GE ultrasound machines. Data were stored on a dedicated workstation for offline analysis (EchoPAC v112.99, GE Healthcare, Chicago, IL, USA). All exams were analysed in a Cardiovascular Imaging Core Laboratory per current guidelines (CIC-IT 1414 Iso9001).

RV function was assessed per current guidelines and recommendations, with normal values including FAC ≥ 35%, TAPSE ≥ 17 mm, and RV S' ≥ 9.5 cm/s. TR severity was graded on a scale of 0–5 using a combination of quantitative and qualitative methods.[5] Given that severe TR affects RV

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functional assessment, we stratified patients by TR grade for our *post hoc* analyses. Those with grade ≥ 3 TR were defined as the 'severe TR group, and those with grade < 3 TR were defined as the 'non-severe TR group'.

RA strain was manually measured by two trained, blinded reviewers using a single, RA-focused apical four-chamber image (*Figure 1*; see 'Statistical analysis' section). Per convention, the 0 point for RA strain was established as peak RA strain minus conduit and booster strain. The value for RA reservoir strain (an approximation of peak strain) was recorded for analysis. RV FWS was measured with EchoPAC's automated RV strain tool, using dedicated RV views when possible. We did not include RV global longitudinal strain in our analysis given the dependence of the interventricular septum on left ventricular (LV) function.

Right heart catheterization

All RHC were performed via femoral approach using a multi-lumen floating catheter (Swan–Ganz catheter). Standard measured and derived parameters were recorded for each patient (6), including RA pressure (RAP), pulmonary artery systolic, diastolic, and mean pressures (sPAP, dPAP, and mPAP), cardiac output, and cardiac index. Where TR was present, the Fick method was the method used to estimate cardiac output. RV stroke work index (RVSWi) was calculated according to Equation (1), where the cut-off for severe RV dysfunction was <300 mmHg/mL/m^2, borderline RV dysfunction was 300–600 mmHg/mL/m^2, and normal RV function was >600 mmHg/mL/m^2. Pulmonary artery pulsatility index (PAPi) was calculated per Equation (2) below, where values ≥ 3 were considered normal and values < 3 were considered abnormal (9).

$$\text{RVSWi} = (\text{mPAP} - \text{RAP}) \times (\text{CI (mL/m}^2)/\text{heart rate (bpm)}), \quad (1)$$

$$\text{PAPi} = (\text{sPAP} - \text{dPAP})/\text{RAP}. \quad (2)$$

Clinical outcomes

Clinical outcomes (deaths and HF hospitalizations) were obtained from the hospital's electronic medical record. All outcomes were verified with the patient's general practitioner, identifying the date of death and the reason for HF hospitalization, where applicable.

Statistical analysis

Firstly, we assessed the inter-observer reliability of RA strain measurements. Two trained, blinded observers analysed RA strain in 40 patients, and their measurements were compared using Bland–Altman analysis and Pearson correlation.

Across all patients, we conducted linear regression analyses considering invasive RV functional parameters (RAP, mPAP, CI, RVSWi, and PAPi), non-invasive RV functional parameters (RA surface area, RV FAC, TAPSE, and TAPSE/sPAP), LV functional parameters [LV ejection fraction (LVEF) and mean *E*/*e*'], and left atrial volume index (LAVi) as the dependent variables and RA and RV strain as the independent variables. Missing data were added via multiple imputation. Normality of variable distribution was assessed graphically and through skewness or kurtosis metrics. Log transformation was used to restore normality and to allow for the use of parametric tests. Outliers were reviewed, although no corrections were necessary.

Next, univariate linear regression models were fitted, and any parameters with $P < 0.15$ were considered for a multivariate model. Ultimately, we retained only parameters with $P < 0.05$ (MIANALYZE procedure in SAS v15.1).

Across all patients, we correlated RA strain, RV strain, RV strain/sPAP, and RV strain/RV end-diastolic volume to event-free survival (defined as freedom from death or unplanned HF hospitalization) using proportional hazard Cox regression models. To assess the functional form of continuous covariates and check the proportional hazard assumption for each covariate in the Cox models, we used the graphical and numerical methods from cumulative sums of Martingale residuals over follow-up times.

Given that more severe TR and higher pulmonary pressures reflect more advanced disease states with differential patient outcomes, we further divided patients in the severe and non-severe TR groups by mean pulmonary pressures. Considering mPAP ≥ 25 mmHg as a cut-off, we stratified the 'severe TR group' into Group A (TR grade ≥ 3 and mPAP ≥ 25 mmHg) and Group B (TR grade ≥ 3 and mPAP < 25 mmHg). Similarly, we divided patients in the 'non-severe TR group' into Groups C (TR grade < 3 and mPAP ≥ 25 mmHg) and D (TR grade < 3 and mPAP < 25 mmHg). We then evaluated the homogeneity of regression estimators amongst the four groups by using an interaction term in the regression model (REG procedure, SAS v15.1).

All statistical analyses were performed using SAS v15.1 software (SAS Institute, Cary, NC, USA). All *P*-values were two-sided and statistical significance was set at 0.05.

Results

Clinical characteristics

A total of 262 patients were included in this study, of whom 139/262 (53.1%) were male. Mean age was 72.3 ± 11.2 years, and most patients (219/262, 83.6%) had New York Heart Association (NYHA) Class II and III symptoms. When dividing patients by TR severity, 138/262 (52.6%) were in the severe TR group (grade ≥ 3) and 124/262 (47.3%) were in the non-severe TR group (grade < 3). Mean age was significantly older in the severe TR group (75.7 ± 7.9 vs. 68.6 ± 13.0 years, $P < 0.0001$); however, there were no differences in the percentage of males vs. females ($P = 0.20$). The most common indications for TTE and RHC evaluation were TR (120/138 patients, 87.0%) in the severe TR group, compared with MR (56/124 patients, 45.2%) and DCM (23/124 patients, 18.5%) in the non-severe TR group ($P < 0.01$ for each). Notably, there was no difference in baseline NYHA class ($P = 0.43$) or baseline presence of PAPs ≥ 25 mmHg (for sure a pulmonary hypertension according to European Society of Cardiology (ESC) 2022 guidelines[6] defining the cut-off ≥ 20 mmHg) between the groups (76.6% vs. 71.0%, $P = 0.30$). However, patients in the non-severe TR group had higher rates of lung disease (21.0% vs. 10.9%) and lower rates of atrial fibrillation/atrial flutter (35.5% vs. 74.6%) ($P < 0.05$ each). There were no significant differences in the presence of comorbidities such as hypertension, diabetes, obesity, tobacco use, or renal impairment between the two groups ($P > 0.05$ each). Similarly, the rates of prior cardiac interventions (e.g. pacemaker insertion, coronary revascularization, or valvular intervention) did not differ between the groups ($P > 0.05$ each). Additional demographic data can be found in *Table 1*.

Baseline echocardiographic and invasive data

Baseline echocardiographic and invasive data from same-day TTE and RHC are shown in *Table 2*. Amongst the invasive measurements, patients in the severe TR group had mean RAP 11.5 ± 6.2 mmHg, mean mPAP 26.2 ± 8.8 mmHg, median PAPi 2.46 [1.43; 3.80] and mean RVSWi 561 ± 304 mmHg/mL/m^2. Patients in the non-severe TR group had mean RAP 8.1 ± 4.5 mmHg, mean mPAP 28.6 ± 9.6 mmHg, median PAPi 3.54 [2.20; 5.37], and mean RVSWi 835 ± 383 mmHg/mL/m^2 ($P < 0.05$ each). There was no significant difference in mean CI between the groups ($P > 0.05$). Amongst the echocardiographic measurements, patients in the severe TR group had mean TR V_{max} 2.77 ± 0.61 m/s, median RA surface 15.6 [13.3; 21.2] cm^2, median *E*/*e*' 11.2 [7.72; 14.7], and mean TAPSE 18.4 ± 4.77 cm. Patients in the non-severe TR group had mean TR V_{max} 3.01 ± 0.56 m/s, median RA surface 10.3 [8.52; 13.6] cm^2, median *E*/*e*' 13.2 [9.05; 16.0], and mean TAPSE

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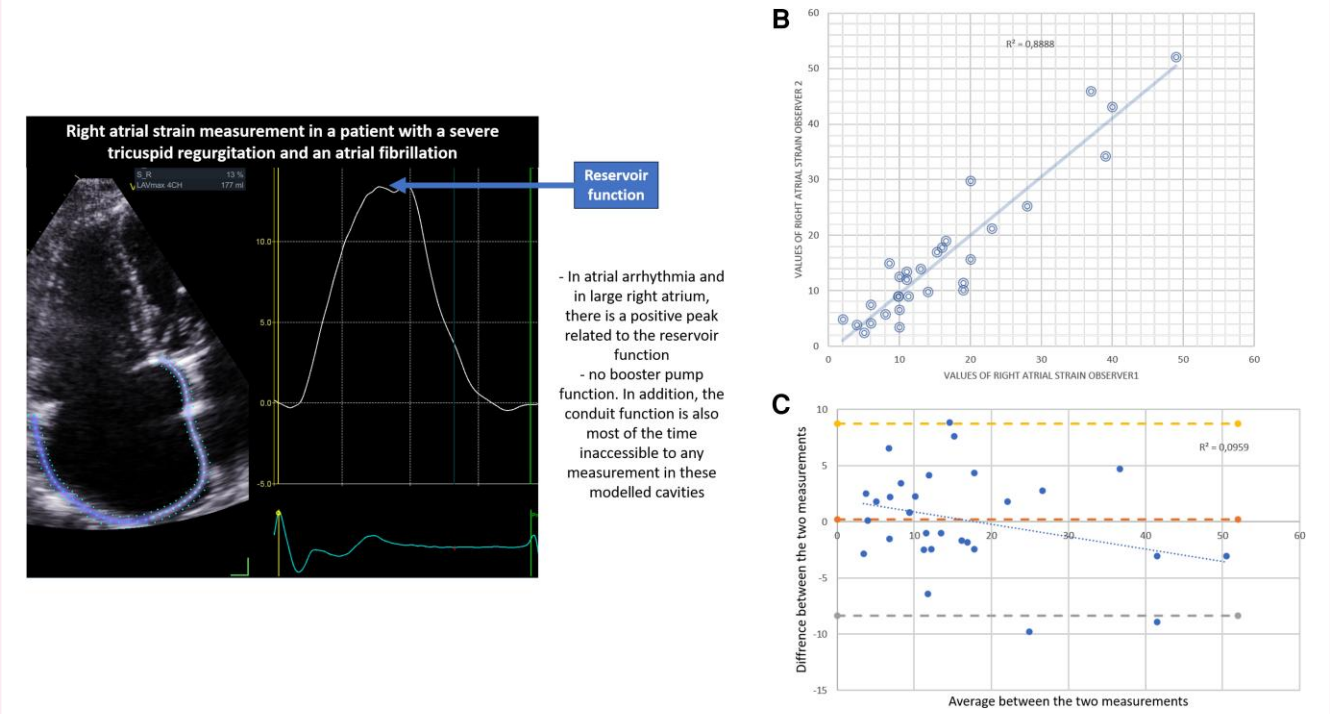

Figure 1 Manual RA strain assessment in EchoPAC. (*A*) Example of manual RA strain imaging in EchoPAC software. (*B*) Pearson's correlation coefficient for inter-observer reliability of RA strain. (*C*) Bland–Altman analysis for inter-observer of RA strain.

20.2 ± 5.12 cm ($P < 0.05$ each). There were no differences in RV FAC, LVEF, or LAVi between the groups ($P > 0.05$ each) (*Table 2*).

RA strain

Both Pearson correlation and Bland–Altman analysis showed minimal inter-observer variability for manually measured RA strain (*Figure 1*). Plotting Observer 1 and Observer 2's results together, Pearson's correlation coefficient (*r*) was 0.88 ($P = 0.04$) (*Figure 1B*). Similarly, Bland–Altman analysis showed a bias of 0.206% and limits of agreement ±8.3% (*Figure 1C*).

Utilizing these manually derived measurements, median RA reservoir strain was 9.0% (6.0; 15.0%) in the severe TR group compared with 17.8% (9.8; 26.3%) in the non-severe TR group ($P < 0.0001$). Per univariate linear regression, RA strain was significantly correlated with the invasive measures of RAP, CI, PAPi, and RVSWi ($P < 0.05$ each) and echocardiographic measures of RA surface area, FAC, TAPSE, TAPSE/sPAP, RV FWS, LVEF, *E*/*e*′, and LAVi ($P < 0.05$ each). These variables were hence included in the multivariate linear regression, which showed that RA strain was positively correlated with TAPSE, FAC, CI, and RVSWi (i.e. larger absolute RA strain value correlates with larger TAPSE, FAC, CI, and RVSWi) and negatively correlated with RA surface area (i.e. absolute RA strain value decreases with increasing RA size) ($P < 0.05$ each). The other correlations were not statistically significant; thus, TAPSE, FAC, RA surface area, CI, and RVSWi were all included in the final, parsimonious multivariate analysis (*Table 3*).

RV free wall strain

Mean RV FWS was −19.0 ± 5.6% in the severe TR group and −19.0 ± 5.9% in the non-severe TR group ($P > 0.05$). Per univariate linear regression of invasive RV functional measures, RV FWS was significantly correlated with RAP and CI ($P < 0.05$ each) but was not correlated with PAPi and RVSWi ($P > 0.05$ each). Per univariate linear regression of echocardiographic measures, RV FWS was significantly correlated with RA strain, FAC, TAPSE, TAPSE/sPAP, RA strain, LVEF, *E*/*e*′, and LAVi. As such, these parameters (with the addition of RA surface area, which was nearly statistically significant) were included in the multivariate linear regression. Multivariate regression showed that RV FWS was negatively correlated with FAC, TAPSE, and LVEF (i.e. increasingly negative value of RV FWS correlates with increasing FAC, TAPSE, and LVEF) ($P < 0.05$ each). Moreover, RV FWS was correlated *E*/*e*′ and CI; thus, these were also included in the final, parsimonious multivariate analysis (*Table 4*). All other inter-modality correlations were not statistically significant.

Clinical outcomes

Over a median follow-up of 34 ± 15 months, there were 103 events recorded, including 56 HF hospitalizations and 47 deaths. In the severe TR group, there were 33 HF hospitalizations and 24 deaths, giving an event rate of 57/138 (41.3%). In the non-severe TR group, there were 23 HF hospitalizations and 23 deaths, giving an event rate of 46/124 (37.1%) ($P = 0.49$).

Across all cohorts, greater absolute value of RA reservoir strain was associated with reduced rates of death and HF hospitalization (HR 0.763 for a 10-point change, 95% CI 0.618–0.943). Abnormal RV strain was correlated with adverse clinical outcomes, although this result was not statistically significant (HR 1.209 for a 6-unit change, 95% CI 0.981–1.490). However, when indexing RV strain to sPAP and RV end-diastolic area, abnormal RV strain ratios were significantly associated with adverse clinical outcomes (HR for RV strain/sPAP 1.235 for a 0.2-unit change, 95% CI 1.005–1.518; HR for RV strain/RV end-diastolic area 1.549 for a 0.6-unit change, 95% CI 1.175–2.041) (*Figure 2*).

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Table 1 Baseline demographic data of patients undergoing same-day TTE and RHC ($n = 262$)

Parameter	All Patients ($n = 262$)	Non-severe TR group ($n = 124$)	Severe TR group ($n = 138$)	Difference (95% CI)
Age (years)	72.3 ± 11.2	68.6 ± 13.0	75.7 ± 7.9	−7.10 (−9.75 to −4.45)
Sex, female	123 (46.9%)	53 (42.7%)	70 (50.7%)	0.08 (−0.04 to 0.20)
Indication for evaluation				
TR	112 (42.7%)	8 (6.45%)	104 (75.4%)	0.59 (0.60–0.77)
MR	75 (28.6%)	56 (45.2%)	19 (13.8%)	−0.31 (−0.42 to −0.21)
DCM	25 (9.5%)	23 (18.5%)	2 (1.45%)	−0.17 (−0.24 to −0.10)
AS	24 (9.2%)	16 (12.9%)	8 (5.80%)	−0.07 (−0.04 to 0.00)
HCM	6 (2.3%)	6 (4.8%)	0 (0%)	
PAH	5 (1.9%)	4 (3.2%)	1 (0.7%)	
ASD	4 (1.5%)	3 (2.4%)	1 (0.7%)	
Other	11 (4.2%)	8 (6.5%)	3 (2.2%)	
NYHA class				
I	26 (9.9%)	15 (12.1%)	11 (7.97%)	−0.04 (−0.11 to 0.03)
II	160 (61.1%)	75 (60.5%)	85 (61.6%)	0.01 (−0.11 to 0.13)
III	59 (22.5%)	24 (19.4%)	35 (25.4%)	0.06 (−0.04 to 0.16)
IV	14 (5.3%)	8 (6.45%)	6 (4.35%)	−0.02 (−0.08 to 0.03)
Unknown	3 (1.1%)	2 (1.6%)	1 (0.7%)	
Pulmonary hypertension	202 (73.7%)	98 (79.0%)	104 (75.4%)	−0.04 (−0.14 to 0.06)
Lung disease	41 (15.6%)	26 (21.0%)	15 (10.9%)	−0.10 (−0.19 to −0.01)
AF/atrial flutter	147 (56.1%)	44 (35.5%)	103 (74.6%)	0.39 (0.28–0.51)
Hypertension	134 (51.1%)	56 (45.2%)	78 (56.5%)	0.11 (−0.01 to 0.23)
Diabetes	34 (13.0%)	11 (8.87%)	23 (16.7%)	0.08 (0.00–0.16)
BMI ≥ 25 kg/m^2	138 (52.7%)	68 (54.8%)	70 (50.7%)	−0.04 (−0.16 to0.08)
Tobacco use	78 (29.8%)	43 (34.7%)	35 (25.4%)	−0.09 (−0.20 to 0.02)
Renal impairment	61 (23.3%)	25 (20.2%)	36 (26.1%)	0.06 (−0.04 to 0.16)
Previous cardiac intervention				
Pacemaker/ICD insertion	38 (14.5%)	16 (12.9%)	22 (15.9%)	0.03 (−0.05 to 0.11)
Valvular intervention	41 (15.6%)	20 (16.1%)	21 (15.2%)	−0.01 (−0.10 to 0.08)
PCI	32 (12.2%)	15 (12.1%)	17 (12.3%)	0.00 (−0.08 to 0.08)
CABG	12 (4.6%)	5 (4.03%)	7 (5.07%)	0.01 (−0.04 to 0.06)

AF, atrial fibrillation; CABG, coronary artery bypass graft; ICD, intra cardiac defibrillator; PCI, percutaneous coronary intervention.

When further dividing patients based on TR grade and mPAP, there were 74 patients in Group A (grade ≥ 3 TR and mPAP ≥ 25 mmHg), 64 in Group B (grade ≥ 3 TR and mPAP < 25 mmHg), 73 in Group C (grade < 3 TR and mPAP ≥ 25 mmHg), and 51 in Group D (grade < 3 TR and mPAP < 25 mmHg). The homogeneity of regression estimators was rejected across the four groups ($P < 0.05$). Across the individual subgroups, RA strain was not predictive of clinical outcomes ($P > 0.05$ each; *Figure 2*, Panel 1). Abnormal RV strain was predictive of adverse clinical outcomes but only in patients without severe TR or pulmonary hypertension (Group D). The hazard ratio (HR) for combined events in this group was 2.450 (95% CI 1.244–4.825) for a 6-point decrease in the absolute value of RV FWS (*Figure 2*, Panel 2). Additionally, the ratio of RV strain/sPAP was predictive of adverse outcomes in this group (HR 2.141, 95% CI 1.110–4.130) (*Figure 2*, Panel 3).

Interestingly, in patients with severe TR or PAPs ≥ 25 mmHg (Group A), the ratio of RV strain/RV end-diastolic area was also predictive of worse outcomes (HR 2.056, 95% CI 1.074–3.937) (*Figure 2*, Panel 4).

Discussion

In our heterogeneous cohort of 262 patients, both RA and RV strain were correlated with invasive and echocardiographic markers of RV function across univariate analyses. Beyond these inter-modality measurement correlations, preserved RA strain was correlated with lower rates of HF death and hospitalization in our overall cohort. Abnormal RV FWS was also correlated with adverse patient outcomes in our overall cohort, and this result was nearly statistically significant (HR 1.209 for a 6-point change, 95% CI 0.981–1.490). However, in *post hoc* analyses, abnormal RV FWS was a statistically significant predictor of adverse outcomes in patients with early stages of TR (i.e. those without severe TR or PAPs ≥ 25 mmHg). In addition, abnormal RV FWS/sPAP—an emerging metric of RV–PA uncoupling—was predictive of adverse outcomes in this subgroup as well as in the overall population. Lastly, RV FWS/RV end-diastolic area was correlated with adverse patient outcomes in the overall population as well as in patients with advanced disease (severe TR and PAPs ≥ 25 mmHg).

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Table 2 Baseline invasive and echocardiographic RV functional parameters in patients undergoing same-day RHC and TTE ($n = 262$)

Parameter	n*	All Patients ($n = 262$)	Non-severe TR group ($n = 124$)	Severe TR group ($n = 138$)	Difference mean (95% CI)
Traditional invasive measurements					
Heart rate (bpm)	246	70.8 ± 14.6	73.7 ± 14.9	68.3 ± 13.8	5.41 (1.79 to 9.02)
RAP (mmHg)	262	9.88 ± 5.71	8.07 ± 4.54	11.5 ± 6.16	−3.4 (−4.8 to −2.1)
mPAP (mmHg)	262	27.3 ± 9.24	28.6 ± 9.62	26.2 ± 8.77	2.39 (0.15 to 4.63)
CI (L/min/m^2)	223	2.40 [1.92; 2.97]	2.50 [1.93; 3.21]	2.30 [1.89; 2.75]	0.32 (0.14 to 0.51)
PAPi (unitless)	262	2.90 [1.87; 4.60]	3.54 [2.20; 5.37]	2.46 [1.43; 3.80]	1.48 (0.77 to 2.19)
RVSWi (mmHg/mL/m^2)	209	684 ± 368	835 ± 383	561 ± 304	275 (181 to 368)
Traditional echocardiographic measurements					
TR V_{max} (m/s)	262	2.88 ± 0.60	3.01 ± 0.56	2.77 ± 0.61	0.23 (0.09 to 0.38)
RA area (cm^2/m^2)	262	13.5 [9.97; 18.0]	10.3 [8.52; 13.6]	15.6 [13.3; 21.2]	−5.6 (−7.0 to −4.3)
RV FAC (%)	259	42.1 ± 11.7	42.6 ± 12.7	41.6 ± 10.7	1.02 (−1.9 to 3.90)
TAPSE (mm)	262	19.2 ± 5.01	20.2 ± 5.12	18.4 ± 4.77	1.81 (0.60 to 3.01)
TAPSE/sPAP (mm/mmHg)	262	0.46 [0.33; 0.60]	0.47 [0.33; 0.67]	0.44 [0.33; 0.56]	0.05 (−0.00 to 0.11)
LVEF (%)	262	53.9 ± 15.1	53.0 ± 17.9	54.7 ± 12.1	−1.7 (−5.4 to 1.95)
E/e′ (unitless)	167	12.3 [8.34; 15.9]	13.2 [9.05; 16.0]	11.2 [7.72; 14.7]	2.29 (0.08 to 4.49)
LAVi (mL/m^2)	262	61.0 [45.0; 78.0]	58.0 [42.0; 74.5]	63.0 [46.0; 82.0]	−3.6 (−11 to 3.95)
New echocardiographic measurements					
RA strain (%)	256	11.9 [7.5; 20.6]	17.8 [9.8; 26.3]	9.0 [6.0; 15.0]	7.61 (5.17 to 10.1)
RV FWS (%)	252	−18.8 ± 5.7	−18.4 ± 5.9	−19.1 ± 5.5	0.37 (−1.1 to 1.86)
RV FWS/RVED area (%/cm^2)	252	−0.85 [−1.2; −0.60]	−1.1 [−1.4; −0.64]	−0.72 [−1.0; −0.59]	−0.60 (−0.86 to −0.33)
RV FWS/sPAP (%/mmHg)	252	−0.48 ± 0.21	−0.46 ± 0.24	−0.48 ± 0.19	0.02 (−0.04 to 0.08)

Variables with normal distributions were listed as mean ± standard deviation; variables with non-normal distributions were listed as median [interquartile range] (see Methods).
Standardized differences with absolute values greater than 0.10 indicate likely clinical relevance, particularly when the absolute value of the CI's lower limit exceeds 0.10.
*$n < 262$ reflects that not all invasive and non-invasive measurements were available for each patient.

These data are important, as the roles of RA and RV strain have not yet been fully clarified in clinical practice.[3] While the field of cardiology has historically neglected the importance of right heart function, it is now increasingly studied due to its prognostic importance in cardiovascular and pulmonary diseases.[3] Amongst left-sided parameters, strain imaging has been incorporated into guidelines due to its enhanced sensitivity for detecting cardiac dysfunction. Similarly, strain imaging appears to have a promising role in the assessment of right heart function.[3,7] In this study, we showed that RA and RV strain was closely associated with both invasive measures of right heart function (pulmonary pressures, RVSWi, and PAPi) and echocardiographic measures of cardiac function (FAC, TAPSE, RV/PA coupling, LVEF, and LV diastolic function). This is consistent with other literature[8,9] and may therefore help to complement future assessment of right heart function. Additionally, the importance of these correlations with invasive measurements cannot be understated, as this may help to limit future invasive testing (i.e. RHC).[10]

Identifying RV dysfunction is important in the management of patients with cardiac disease, as the presence of RV dysfunction has prognostic implications and affects the risks associated with cardiac surgery.[11] Patients with advanced RV dysfunction may be considered ineligible for cardiac surgery given the morbidity associated with this condition. At present, echocardiography is our primary means for assessing the RV. However, due to the complex geometry of the RV and high load dependency of RV echocardiographic measures, the utilization of catheter-derived measurements and cardiac magnetic resonance imaging have been necessary to best quantify RV function.[12] With the emergence of speckle-tracking technology as a more sensitive technique to assess cardiac dysfunction, right heart strain assessment may help to better characterize right heart function. Namely, it has already been shown to predict patient outcomes post-cardiac surgery.[4,13]

In patients with severe TR, echocardiographic assessment of the RV is further challenged by increased TR regurgitant volumes that 'flatter' the RV. Given that haemodynamically significant TR reduces cardiac afterload, RV dysfunction may still be present even when FAC, TAPSE, and RV S' are normal. Despite this fact, there are currently no reference ranges that account for this pseudo-normalization of values; future guidelines may need to be adjusted to avoid classifying abnormal RV function as normal in the setting of reduced afterload.[2,14]

While strain imaging has been shown to have increased sensitivity in the detection of subtle cardiac dysfunction, it is also subject to loading conditions.[15] As such, normal RA and RV strain values need to be defined in different loading conditions. In our cohort, this may have led to an apparent lack of relationship between severe TR and RV FWS, as the 'normal' range for strain may include patients with early RV dysfunction.

Regarding the clinical importance of these metrics, previous literature has suggested that RA and RV strain may carry prognostic importance.[16–18] In our complete population of patients ($n = 262$) with and without severe TR, preserved RA reservoir strain was predictive of favourable clinical outcomes. However, when stratifying patients

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Table 3 Univariate and multivariate linear regression modelling with RA strain as dependent variable ($n = 256$)

Parameter	Standardized estimated regression coefficient [95% CI]		
	Univariate analysis	Full multivariate analysis	Parsimonious multivariate analysis (final model)
TAPSE	0.53 [0.43–0.64]	0.28 [0.16–0.39]	0.33 [0.23–0.44]
RA surface area (log)	−0.45 [−0.56 – −0.34]	−0.24 [−0.35 – −0.12]	−0.29 [−0.39 – −0.19]
RAP	−0.36 [−0.47 – −0.24]	−0.02 [−0.15–0.11]	
RVSWi	0.31 [0.18–0.43]	0.10 [−0.02–0.23]	
PAPi (log)	0.28 [0.17–0.40]	0.12 [−0.02–0.25]	0.17 [0.07–0.27]
TAPSE/sPAP (log)	0.39 [0.28–0.51]		
RV FWS	−0.36 [−0.48 – −0.24]	−0.09 [−0.21–0.04]	
RV FAC	0.33 [0.21–0.45]	0.11 [0–0.22]	0.14 [0.04–0.24]
LAVi (log)	−0.34 [−0.46 – −0.23]	−0.10 [−0.21–0.01]	
CI (log)	0.29 [0.17–0.41]	0.09 [−0.02–0.21]	0.12 [0.01–0.22]
LVEF	0.22 [0.10–0.34]	−0.02 [−0.12–0.09]	
E/*e*′ (log)	−0.10 [−0.23–0.03]	−0.03 [−0.14–0.08]	

TAPSE/sPAP was not entered in multivariable model as it was highly correlated with TAPSE.

Table 4 Univariate and multivariate linear regression modelling with RV FWS as dependent variable ($n = 252$)

Parameter	Standardized estimated regression coefficient [95% CI]		
	Univariate analysis	Full multivariate analysis	Parsimonious multivariate analysis (final model)
TAPSE	−0.44 [−0.55 to −0.32]	−0.18 [−0.32 to −0.05]	−0.21 [−0.33 to −0.10]
LVEF	−0.38 [−0.50 to −0.26]	−0.15 [−0.28 to −0.03]	−0.15 [−0.27 to −0.03]
E/*e*′ (log)	0.20 [0.07–0.33]	0.08 [−0.04 to 0.20]	0.10 [−0.01 to 0.21]
RA strain	−0.35 [−0.47 to −0.23]	−0.09 [−0.23 to 0.05]	
RA surface area (log)	0.11 [−0.01 to 0.23]	−0.02 [−0.15 to 0.11]	
RAP	0.21 [0.09–0.33]	0.05 [−0.09 to 0.20]	
RVSWi	−0.04 [−0.17 to 0.09]	0.09 [−0.05 to 0.22]	
PAPi (log)	−0.09 [−0.21 to 0.04]	−0.02 [−0.16 to 0.13]	
TAPSE/sPAP (log)	−0.32 [−0.44 to −0.19]		
RV FAC	−0.50 [−0.61 to −0.39]	−0.31 [−0.43 to −0.19]	−0.33 [−0.45 to −0.21]
LAVi (log)	0.18 [0.06–0.31]	0.01 [−0.12 to 0.13]	
CI (log)	−0.33 [−0.45 to −0.20]	−0.11 [−0.23 to 0.01]	−0.11 [−0.23 to 0.01]

TAPSE/sPAP was not entered in multivariable model as it was highly correlated with TAPSE.

by TR grade and mPAP, RA reservoir strain was not related to patient outcomes. The latter result was likely due to smaller sample sizes in subgroup comparisons, which reduced our statistical power to define subgroup regression estimators. Moreover, although RV FWS was not predictive of adverse clinical events our overall population, there was a trend towards a significant relationship. When stratifying patients by TR grade and mPAP, we found that abnormal RV FWS was significantly correlated with adverse outcomes in patients with early stages of disease (non-severe TR and no pulmonary hypertension). This finding is intuitive, given RV strain may detect subclinical RV dysfunction before FAC, TAPSE, and S' become abnormal, and it corroborates existing literature.[1,19]

Beyond RV FWS, we showed that increasing (less negative) ratios of RV FWS/sPAP were associated with higher rates of HF hospitalization and death.[19,20] In a recent cohort of 171 patients with severe TR, Ancona *et al.*[21] similarly demonstrated that abnormal RV FWS/sPAP was associated with higher rates of all-cause mortality (HR 0.004, $P = 0.02$). In subsequent Kaplan–Meier analysis, RV FWS > 14% and RV FWS/sPAP > 0.26%/mmHg in Ancona's cohort had the highest rates of event-free survival.[20] Combined with our results, these findings suggest that RV–PA coupling (as estimated by RV FWs/sPAP) is an important predictor of survival in TR. This is likely because as TR progresses, the RV inevitably dilates to maintain forward stroke volume. After marked dilatation occurs, the RV lacks sufficient contractility to overcome its afterload, leading to RV–PA 'uncoupling'.

Interestingly, in our patients with TR grade ≥ 3 and mPAP ≥ 25 mmHg, the ratio RV strain/RV end-diastolic area was also associated with higher rates of HF death and hospitalization. This is in partial concordance with other recent literature, which has suggested that larger

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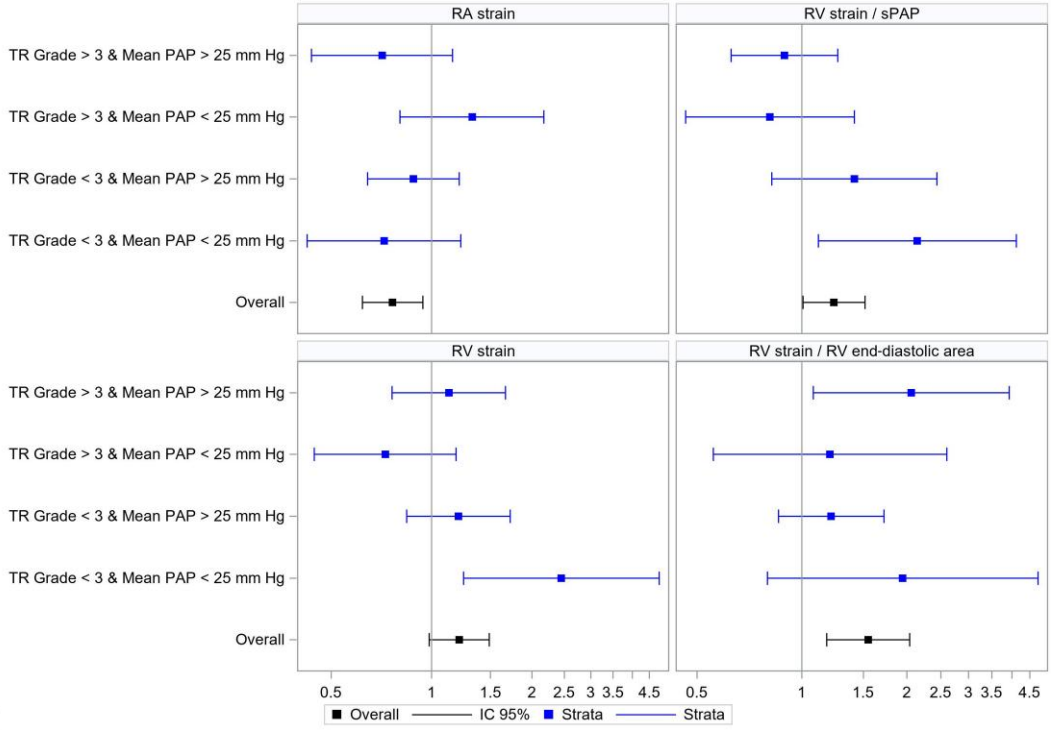

Figure 2 HRs with 95% CIs for combined endpoint (HF hospitalization or cardiovascular mortality) across all population and subgroups A–D divided based on TR grade and mean PAP. (Panel 1) HR and 95% CI for 10-point change in RA strain. (Panel 2) HR and 95% CI for 6-point change in RV FWS. (Panel 3) HR and 95% CI for 0.2-point change in RV FWS/sPAP. (Panel 4) HR and 95% CI for 0.6-point change in RV FWS/RV end-diastolic area.

baseline RV volume may be predictive of poor prognosis in TR. In a prospective cohort of 43 patients undergoing tricuspid valve surgery, Rodríguez-Palomares *et al.*[22] showed that RV end-diastolic volume index was the best predictor of HF hospitalization and mortality (HR = 1.1, $P = 0.02$).[23] Although we measured RV end-diastolic area rather than end-diastolic volume in our cohort, both indices are similar in that they provide multidimensional information about the RV (compared with unidimensional indices such as TAPSE, RV S', and RV diameters). As such, the ratio of RV FWS indexed to RV end-diastolic area likely provides key information about the function of the RV relative to its degree of dilation. This ratio is perhaps most important in patients with severe TR (grade ≥ 3) and pulmonary hypertension, as both conditions exacerbate RV dilation and contribute to RV dysfunction and RV–PA uncoupling.

Overall, we purport that RA strain and RV strain are both an accurate and impactful means of assessing RV function in TR. Other indices such as RV FWS/sPAP and RV FWS/RV end-diastolic area may also hold utility in characterizing the degree of RV–PA uncoupling, which is a key mechanism of RV dysfunction in TR.

Limitations

Our work is subject to several key limitations. First, this was a retrospective, observational study; thus, all findings must be confirmed in larger, prospective, and preferably multi-centre cohort. Although we verified the dates of hospitalization and/or death for the 103 clinical events that occurred, it is highly possible that we 'undercounted' the number events that occurred in other healthcare systems in France and across Europe. Due to inability to access other electronic health records, this may have biased our results (e.g. 'undercounting' of events in our non-severe TR group).

Second, all strain analyses were performed using GE EchoPAC software. As such, our values relate to this vendor and limit their generalizability. When measuring RA strain, we analysed only the reservoir strain value. The omission of RA conduit and pump strain values may have missed dysfunction in these phases. Additionally, the threshold we used to define abnormal RV FWS (>−23%) is still a matter of debate, and clarification of the true abnormal range in a vendor-dependent fashion is required. Normal strain values also need to be clarified by RV loading conditions.

Lastly, although RV–PA coupling has been highlighted via the TAPSE/sPAP-ratio, others have suggested alternate ratio(s). It has been considered important to acknowledge that ratios considering geometry and loading conditions are relevant for better assessing RV function (geometry and load are impacting and then are important to recognize for assessing RV function).

Conclusions

RA strain and RV strain are exciting tools that complement and refine our assessment of right heart function. Enabling the early detection of right heart dysfunction is important to better risk profile patients and determine their candidacy for future cardiac interventions.

Conflict of interest: GE Healthcare has provided research facilities to Rennes University Hospital through a contract with Erwan Donal and CHU Rennes.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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