Cardiologia Hungarica
2022; 52: 14–22.

Original article

DOI: 10.26430/CHUNGARICA.2022.52.5.14

Tricuspid regurgitation and right ventricular contraction pattern in heart failure with reduced ejection fraction: a 3D echocardiography study

Kai Shiida*, Adrienn Ujvári*, Bálint Károly Lakatos, Márton Tokodi, Annamária Kosztin, Boglárka Veres, Walter Schwertner, Attila Kovács, Alexandra Fábián*, Béla Merkely*

Heart and Vascular Center, Semmelweis University, Budapest, Hungary

Corresponding Author:
Dr. Alexandra Fábián, Heart and Vascular Center, Semmelweis University, Városmajor str. 68, 1122 Budapest, Hungary
E-mail: fabian.alexandra@med.semmelweis-univ.hu

The development of secondary tricuspid regurgitation (TR) is associated with poor outcomes in patients with heart failure and reduced left ventricular (LV) ejection fraction (HFrEF). Data are scarce concerning the right ventricular (RV) morphological and functional remodeling in HFrEF in relation to the severity of TR.

Accordingly, we aimed to characterize RV remodeling in HFrEF patients with and without significant TR using three-dimensional (3D) echocardiography.

We retrospectively identified 138 patients with HFrEF. In this cohort, we graded TR severity according to current guidelines and compared patients with no to mild TR (non-significant TR, n=78) versus patients with moderate to severe TR (significant TR, n=60). All patients underwent clinically indicated 3D transthoracic echocardiography. 3D LV and RV end-diastolic volumes (EDVi) and ejection fractions (EF) were measured. To characterize RV mechanical pattern, the ReVISION method was used to quantify the contribution of the longitudinal, radial, and anteroposterior motion components to total RV EF.

Patients with significant TR had higher LV EDVi and lower LV EF compared with patients with non-significant TR (LV EDVi: 117.2±34.9 vs. 102.6±39.6 ml/m^2; LV EF: 27.0±6.6 vs. 30.2±7.7%, both $p<0.05$). Concerning the right heart, RV EDVi was significantly higher in patients with significant TR compared with those without (92.1±32.4 vs. 74.1±26.9 ml/m^2; $p<0.01$). RV EF was lower in patients with significant TR (36±10.3 vs. 42.5±9.3%, $p<0.05$). Regarding RV mechanics, anteroposterior and longitudinal components were significantly decreased in patients with significant TR compared with patients with non-significant TR (anteroposterior relative contribution: 10.0±4.5 vs. 11.7±3.7%; longitudinal: 8.2±3.8 vs. 11.1±3.8%; both $p<0.05$). On the other hand, the radial component did not show a difference between patients with or without significant TR (17.8±6.9 vs. 19.8±6.2%; p=NS).

By assessing RV mechanics using 3D echocardiography, we have shown that HFrEF patients with significant TR presented with reduced RV global function, mainly attributable to the deterioration of the longitudinal and anteroposterior motion components. Identification of the turning point where RV plasticity diminishes, and significant TR develops would be of high clinical interest for more tailored therapeutic decisions.

Keywords: tricuspid regurgitation, 3D echocardiography, right ventricle

*Kai Shiida, Adrienn Ujvári, Alexandra Fábián and Béla Merkely contributed equally to this work.

Received 04. 02. 2022, accepted 09. 03. 2022.

A jobb kamra mechanikájának összefüggése a tricuspidalis regurgitáció mértékével csökkent bal kamrai ejekciós frakciójú, szívelégtelen betegeknél: 3D echokardiográfiás vizsgálat

A funkcionális tricuspidalis regurgitáció (TR) kialakulása csökkent ejekciós frakcióval járó szívelégtelenségben (HFrEF) a betegek kiemelten rossz prognózisával hozható összefüggésbe. Ugyanakkor kevés adat áll rendelkezésünkre HFrEF-betegekben a TR hatására vagy éppen következményeként bekövetkező jobb kamrai (JK) morfológiai és funkcionális változásokról.

Célunk a JK-remodelláció jellemzése volt 3D-echokardiográfia segítségével, HFrEF-alapbetegség mellett diagnosztizált szignifikáns TR-rel rendelkező és nem rendelkező betegek összehasonlítása által.

Retrospektív vizsgálatunkban 138 szívelégtelenségben szenvedő beteget azonosítottunk. A jelenlegi irányelvek alapján meghatároztuk a TR súlyosságát a teljes betegpopulációban, és összehasonlítottuk a TR-rel egyáltalán nem vagy enyhe TR-rel rendelkező betegeket (nem szignifikáns TR, n=78) és a közepes vagy súlyos TR-rel rendelkező betegeket (szignifikáns TR, n=60). Minden beteg 3D-echokardiográfiás vizsgálaton vett részt, ahol meghatároztuk a 3D bal (BK) és jobb kamrai végdiasztolés térfogatokat (EDVi) és ejekciós frakciókat (EF). A JK mechanikai mintázatának jellemzésére a ReVISION szoftvert alkalmaztuk. A szoftver segítségével számszerűsítettük a longitudinális (LEF), radiális (REF), és anteroposzterior (AEF) mozgáskomponensek hozzájárulását a teljes JK pumpafunkcióhoz.

A szignifikáns TR-rel rendelkező betegek nagyobb BK EDVi, valamint alacsonyabb BK EF-értékeket mutattak (BK EDVi: 117,2±34,9 vs. 102,6±39,6 ml/m^2, BK EF: 27,0±6,6 vs. 30,2±7,7%; p<0,05). A jobb szívfél tekintetében a JK EDVi jelentősen nagyobb, míg a JK EF alacsonyabb volt a szignifikáns TR-rel rendelkező betegekben, mint a TR-rel nem rendelkező betegekben (JK EDVi: 92,1±32,4 vs. 74,1±26,9 ml/m^2; p<0,01, JK EF: 36±10,3 vs. 42,5±9,3%, p<0,05). A JK mechanikát vizsgálva az anteroposzterior és a longitudinális mozgáskomponens jelentős csökkenést mutatott a szignifikáns TR-rel rendelkező betegekben (AEF: 10,0±4,5 vs. 11,7±3,7%; LEF: 8,2±3,8 vs. 11,1±3,8%; p<0,05). Ezzel szemben a radiális mozgáskomponens nem különbözött a két csoportban (REF: 17,8±6,9 vs. 19,8±6,2%; p=ns).

A 3D-echokardiográfia lehetővé tette a JK mechanika részletes jellemzését. Eredményeink alapján a szignifikáns TR-rel rendelkező HFrEF-betegek csökkent globális JK-funkciót mutatnak, amit elsősorban a longitudinális és az anteroposzterior mozgáskomponensek markáns csökkenése határoz meg.

Kulcsszavak: tricuspidalis regurgitáció, 3D echokardiográfia, jobb kamra

Introduction

In patients with heart failure with reduced left ventricular ejection fraction (HFrEF) the impaired left ventricular (LV) systolic function and subsequent adverse remodeling have a significant influence on the right ventricular (RV) morphology and function (1). The potential development of right ventricular (RV) dysfunction in patients with left-sided heart diseases is a well-established adverse clinical and prognostic factor (2). Therefore, it is of paramount importance to recognize those HFrEF patients in whom right heart failure may develop during the disease course (3).

The development of severe tricuspid regurgitation (TR) is nearly entirely secondary in HFrEF. It is associated with poor outcomes and more severe signs and symptoms (4). Nevertheless, the prognosis of patients with significant TR is strongly influenced by the adverse RV remodeling; however, longitudinal data are scarce on RV adaptation to this increased load. Compared to the LV, whose anatomy and function have been a subject of intensive research, RV morphology and mechanics were traditionally less studied due to its complex anatomical structure. However, several studies have recently shown the strong prognostic role of RV involvement in numerous cardiovascular diseases (5). Therefore, despite the shortcomings of its assessment, a thorough RV quantification could help to recognize RV dysfunction in HFrEF patients induced by (or accompanied by) significant TR.

The advancements in transducer and software technologies in three-dimensional (3D) echocardiography offer a more accurate and detailed ventricular structure and function quantification with good feasibility and close correlation with gold standard cardiac magnetic resonance imaging (6). Although the 3D assessment of RV function allows the quantification of global RV pump function, right ventricular ejection fraction (RV EF) is the cumulative result of the complex interplay among distinct mechanical components. Thus, it may not be able to capture subtle changes in RV performance (7). Notably, three main mechanisms contribute to the global RV pump function: shortening along the longitudinal, radial, and anteroposterior directions, which could be separately analyzed using a 3D echocardiographic pipeline (8). The quantification of the above-mentioned

mechanical components of the RV could aid in further clarifying RV plasticity in HFrEF patients and potentially identify the turning point where RV function diminishes and results in tricuspid valve incompetency and, ultimately, right heart failure.
Accordingly, our pilot study aimed to characterize RV remodeling in HFrEF patients with and without significant (moderate +) functional TR using 3D echocardiography.

Methods

Study design and population

Clinically and hemodynamically stable patients with established diagnosis of heart failure with reduced left ventricular ejection fraction who underwent clinically indicated 2D and 3D transthoracic echocardiography at our Center were retrospectively identified. Using this cohort, we have divided patients into two subgroups:

1. those who presented with significant TR (patients with moderate or severe TR) and
2. those who presented with no or mild TR (patients with non-significant TR).

Exclusion criteria were:

1. presence of any primary cause of TR revealed at the first report or during the review process of the previously acquired datasets and
2. suboptimal LV and RV 3D dataset image quality for the respective 3D analysis.

Protocol 2D and 3D echocardiography was performed in all patients. Demographic and clinical data (age, weight, height, body surface area, body mass index, cardiovascular risk factors, and comorbidities) were retrieved from the electronic clinical records of the hospital database. Obtaining written informed consent was waived because of the retrospective nature of the analysis. Our study protocol is in accordance with the Declaration of Helsinki.

Two- and Three-dimensional echocardiography

Transthoracic echocardiographic examinations were performed on commercially available ultrasound systems (E95, 4Vc-D probe, GE Vingmed Ultrasound, Horten, Norway and EPIQ 7, X5-1 probe, Philips Medical Systems, Best, the Netherlands). A standard acquisition protocol consisting of 2D loops from parasternal, apical, and subxiphoid views was applied. Left ventricular internal diameters, wall thicknesses, and relative wall thickness; left atrial (LA) 2D end-systolic volume; mitral inflow velocities such as early (E) and late diastolic (A) peak velocities, their ratio, and E wave deceleration time; systolic (s′), early diastolic (e′), and atrial (a′) velocities of the mitral lateral and septal annulus; average E/e′; right ventricular basal short-axis diameter, tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC); right ventricular systolic pressure (RVSP) and right atrial (RA) 2D end-systolic volume were measured according to current guidelines (9).
TR was graded based on integrating multiple parameters as per current guidelines (10). TR jet was established either on apical four-chamber or parasternal right ventricular (RV) inflow views. Lack of TR was defined as an absolutely not or just barely detectable jet, no flow convergence, and not having measurable effective regurgitant orifice area (EROA) along with a faint, incomplete, or no continuous-wave Doppler signal. Mild TR was defined as a small jet but with measurable EROA (<0.20 cm^2). Therefore, our 'non-significant TR' subgroup consisted of patients presented with non-detectable or mild TR. Our patients with a significant TR subgroup consisted of moderate to severe TR patients. Significant TR was defined as at least a moderate or large central jet with dense continuous-wave Doppler signal. Additionally, quantitative measurements were applied to characterize TR severity further. Therefore, we quantified EROA and regurgitant volume (RVol) preferably on zoomed color apical four-chamber views, aligning the direction of flow with insonation beam and changing the baseline in the direction of the jet. Thus, significant TR was defined as EROA ≥0.20 cm^2 and RVol ≥30 ml.
Beyond conventional echocardiographic examination, ECG-gated full-volume 3D datasets reconstructed from four cardiac cycles optimized for the left or the right heart were obtained for further analysis on a separate workstation. 3D datasets focused on the left heart were processed using semiautomated, commercially available software (4D LV-Analysis 3, TomTec Imaging, Unterschleissheim, Germany). We determined LV end-diastolic volume index (EDVi), end-systolic volume index (ESVi), and stroke volume index (SVi). To assess global LV function, ejection fraction (EF), 3D global longitudinal strain (GLS), and 3D global circumferential strain (GCS) were also calculated. Concerning the right heart, we quantified 3D RV EDVi, ESVi, and SVi, EF, and septal and free wall two-dimensional longitudinal strain as well (4D RV-Function 2, TomTec Imaging).

Detailed Quantification of 3D RV Mechanics

To quantify the three major functional components contributing to total RV performance, we used the ReVISION software (Argus Cognitive, Inc, Lebanon, NH, USA). First, the 3D mesh model exported from the 4D RV-Function software package was re-oriented by a standard, automated method to identify the longitudinal (from the tricuspid annulus to the apex), radial (perpendicular to the interventricular septum), and anteroposterior (parallel to the interventricular septum) axes. Then, motion decomposition was performed along these directions in a vertex-based manner to quantify component values generated by each motion component [i.e., longitudinal EF (LEF), radial EF (REF), and anteroposterior EF (AEF)], as previously described (11). The to-

TABLE 1. Demographic and clinical characteristics of study samples

	Overall (n=138)	Patients with non-significant TR (n=78)	Patients with significant TR (n=60)	p
Baseline demographic characteristics				
Age (years)	68.5±11.1	67±10.8	70.5±11.2	0.062
Male, n (%)	113 (82)	65 (83)	48 (80)	0.617
BSA (m^2)	2.01±0.24	2.05±0.25	1.97±0.21	0.053
BMI, kg/m^2	28.1±4.7	28.3±4.7	27.9±4.7	0.636
Systolic blood pressure, mmHg	124.0±19.5	127.8±18.5	120.2±19.9	0.100
Diastolic blood pressure, mmHg	76.2±13.1	78.4±11.6	73.9±14.4	0.158
Heart rate, bpm	78.6±16.3	77.3±13.6	79.6±18.4	0.603
Risk factors and medical history				
Smoking (%)	8 (6)	7 (9)	1 (2)	0.069
COPD (%)	12 (9)	8 (10)	4 (7)	0.458
Diabetes (%)	44 (32)	25 (32)	19 (32)	0.962
Atrial fibrillation (%)	67 (49)	31 (40)	36 (60)	0.018
PM (%)	65 (47)	37 (47)	28 (47)	0.929
ICD (%)	39 (28)	16 (21)	23 (38)	0.021
CRT (%)	15 (11)	9 (12)	6 (10)	0.774
Hypertension (%)	98 (71)	53 (68)	45 (75)	0.365
Previous CABG (%)	24 (17)	11 (14)	13 (22)	0.245
Previous PCI (%)	53 (38)	32 (41)	21 (35)	0.471
Significant mitral valve disease (%)	5 (4)	0 (0)	5 (8)	0.009
Significant aortic valve disease (%)	7 (5)	2 (3)	5 (8)	0.126
Previous AVR (%)	1 (1)	1 (1)	0	0.379

Continuous variables are presented as means ± SD; categorical variables are reported as frequencies (%). AVR: aortic valve replacement or repair, BMI: body mass index, BSA: body surface area, CABG: coronary artery bypass grafting, COPD: chronic obstructive pulmonary disease, CRT: cardiac resynchronization therapy, ICD: implantable cardioverter defibrillator, MVR: mitral valve replacement or repair, PCI: percutaneous coronary intervention, PM: pacemaker

tal RV stroke volume is generated by the aggregated contribution of the motion components, however, due to the non-linear RV deformation pattern, summing the decomposed EFs does not add up to the value of total RVEF (LEF + AEF + REF ≠ RVEF). After applying rescaling, i.e., LEF' = LEF/(LEF + AEF + REF) × RVEF, then LEF' + AEF' + REF' = total RVEF will hold. In our current study, we used the rescaled values to enhance interpretability further. 3D RV GLS, GCS and global area strain (GAS) were also calculated using the ReVISION software (8).

Statistical analysis

Statistical analysis was performed using dedicated software (StatSoft Statistica, v12, Tulsa, OK, USA). Continuous variables are presented as mean ± standard deviation (SD), whereas categorical variables are reported as frequencies and percentages. After verifying the normal distribution of each variable using the Shapiro–Wilk test, groups were compared with unpaired Student's t-test or Mann–Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables, as appropriate. The Pearson or Spearman test was computed to assess the correlation between continuous variables. A two-sided p-value of <0.05 was considered statistically significant.

Results

One hundred and thirty-eight HFrEF patients with local 3D echocardiography performed were retrospectively identified. After the guideline-based assessment of TR severity, 60 patients were presented with at least moderate TR, while 78 patients had only mild or no TR.
Baseline demographic and clinical characteristics are summarized in *Table 1*. There were no significant differences in age, sex, blood pressure, and heart rate in patients with or without TR. Our overall patient population had a male predominance, as 80% of study subjects were males. Concerning cardiovascular risk factors, 32% of the study population was diagnosed with diabetes, and 9% had chronic obstructive pulmonary disease (COPD) in medical history. In the overall study population, eight patients (6%) were reported as smokers. History of atrial fibrillation was significantly more

TABLE 2. Conventional 2D echocardiographic parameters of study population

	Overall (n=138)	Patients with non-significant TR (n=78)	Patients with significant TR (n=60)	P
LVIDd (mm)	63.1±7.9	62.4±7.4	63.8±8.3	0.306
IVSd (mm)	11.2±2.6	11.6±2.5	10.7±2.6	0.045
PWd (mm)	9.2±1.7	9.5±1.7	8.8±1.6	0.014
RWT (%)	0.30±0.07	0.31±0.07	0.28±0.07	0.025
LV Mi (g/m^2)	138.6±33.7	139.3±32.1	137.8±35.8	0.816
E (cm/s)	85.0±33.7	73.7±29.3	99.2±33.7	0.008
A (cm/s)	69.8±32.2	76.9±32.4	58.2±28.7	<0.001
E/A	1.46±0.90	1.15±0.83	1.96±0.79	<0.001
DT (ms)	175.7±64.5	186.9±67.7	161.9±57.9	0.041
Mitral lateral s′ (cm/s)	5.8±1.5	6.0±1.7	5.5±1.3	0.113
Mitral lateral e′ (cm/s)	8.3±2.7	8.4±2.6	8.1±2.8	0.665
Mitral lateral a′ (cm/s)	6.2±2.9	6.7±3.1	5.6±2.7	0.307
Mitral medial s′ (cm/s)	4.7±1.2	4.9±1.2	4.4±1.2	0.072
Mitral medial e′ (cm/s)	5.3±1.7	5.7±1.9	4.8±1.2	0.008
Mitral medial a′ (cm/s)	5.3±2.0	5.6±2.1	5.1±2.0	0.335
E/e′ average	14.7±7.4	11.8±5.3	17.8±8.0	<0.001
LAVi (ml/m^2)	50.8±17.0	46.5±15.5	56.8±17.3	0.001
RVd (mm)	40.0±7.0	39.1±6.5	41.1±7.5	0.113
RVSP (mmHg)	30.2±12.3	24.1±9.7	37.4±11.1	<0.001
TAPSE (mm)	17.4±4.2	17.9±4.2	16.7±4.0	0.118
FAC (%)	37.4±10.8	39.3±9.6	34.7±11.9	0.028
RVSLS (%)	–10.2±5.6	–11.5±6.1	–8.3±4.3	0.003
RVFWLS (%)	–20.0±7.4	–21.9±6.6	–17.3±7.6	0.001
RAVi (ml/m^2)	41.6±17.8	35.9±15.1	49.4±18.4	<0.001

Continuous variables are presented as means±SD, categorical variables are reported as frequencies (%). A: mitral inflow velocity during atrial contraction, a': peak late (atrial) diastolic annular velocity, DT: deceleration time, E: early diastolic mitral inflow velocity, e': early diastolic annular velocity, FAC: fractional area change, IVSd: interventricular septal thickness at end-diastole, LAVi: left atrial volume index, LV: left ventricle, LVIDd: LV internal diameter at end-diastole, Mi: mass index, PWd: posterior wall thickness at end-diastole, RAVi: right atrial volume index, RV: right ventricle, RVd: RV basal diameter, RVFWLS: RV free wall longitudinal strain, RVSLS: RV septal longitudinal strain, RVSP: RV systolic pressure, RWT: relative wall thickness, s': systolic annular velocity, TAPSE: tricuspid annular plane systolic excursion

frequent in patients with significant TR (diagnosed in 36 patients, 60%) than those without (31 patients, 40%). Among patients with significant TR, 23 patients (38%) had implantable cardioverter-defibrillator (ICD), whereas in patients with non-significant TR, only 16 patients (21%) had ICD. Heart failure was mainly of ischemic etiology, which was represented by the number of patients who underwent previous percutaneous coronary intervention (PCI) or previous coronary artery bypass grafting (CABG) procedures in the overall patient population (PCI: 53 patients, 38%; CABG: 24 patients, 17%). Significant mitral valve disease was more common in patients with significant TR (diagnosed in 5 patients, 8%). None of the patients in our study cohort had previous mitral valve replacement or repair, whereas one patient with non-significant TR had previous aortic valve replacement *(Table 1)*.

Conventional 2D echocardiographic parameters of the study population are shown in *Table 2*. Wall thicknesses and relative wall thickness (RWT) values were significantly lower in patients with significant TR, whereas LV end-diastolic internal diameter and calculated LV mass index did not differ between the two groups. Concerning diastolic function, patients presented with significant TR demonstrated higher transmitral E-wave velocity along with significantly higher E/A ratio, whereas transmitral A-wave velocity and deceleration time were lower. Furthermore, the early diastolic velocity of the mitral septal annulus was significantly lower in patients with significant TR, whereas the average E/e′ ratio was higher compared to patients without significant TR. 2D LA volume index was significantly higher among patients with significant TR. Regarding the right heart, RV basal diameter did not show any difference between the study groups, whereas RV systolic pressure was significantly higher in patients with significant TR. In

TABLE 3. Three-dimensional echocardiographic data of all study groups

	Overall (n=138)	Patients with non-significant TR (n=78)	Patients with significant TR (n=60)	P
LEFT VENTRICLE				
LV EDVi (ml/m^2)	108.8±38.3	102.6±39.5	117.2±34.9	0.030
LV ESVi (ml/m^2)	78.7±32.3	72.9±32.8	86.5±30.2	0.018
LV SVi (ml/m^2)	30.1±9.8	29.6±9.9	30.8±9.7	0.523
LV EF (%)	28.8±7.4	30.2±7.7	27.0±6.6	0.012
LV GLS (%)	–8.4±3.1	–9.3±3.1	–7.2±2.7	<0.001
LV GCS (%)	–12.2±3.7	–12.8±3.9	–11.6±3.1	0.052
RIGHT VENTRICLE				
RV EDVi (ml/m^2)	81.2±30.3	74.1±26.9	92.1±32.4	0.005
RV ESVi (ml/m^2)	50.3±25.6	44.1±21.9	59.9±28.1	0.004
RV SVi (ml/m^2)	30.9±8.4	29.9±8.2	32.3±8.6	0.214
RV EF (%)	39.8±10.2	42.5±9.3	36.0±10.3	0.002
RV GLS (%)	–12.1±4.1	–13.4±3.6	–10.2±3.9	<0.001
RV GCS (%)	–12.9±4.8	–14.2±3.9	–11.3±5.3	0.003
RV GAS (%)	–22.7±6.7	–24.8±5.9	–19.8±6.7	<0.001
RV LEF (%)	9.9±4.0	11.1±3.8	8.3±3.8	<0.001
RV REF (%)	18.9±6.6	19.8±6.2	17.8±6.9	0.154
RV AEF (%)	10.9±4.1	11.7±3.7	10.0±4.5	0.049

Continuous variables are presented as means ± SD, categorical variables are reported as frequencies (%). AEF: anteroposterior ejection fraction, EDVi: end-diastolic volume index, EF: ejection fraction, ESVi: end-systolic volume index, GAS: global area strain, GCS: global circumferential strain, GLS: global longitudinal strain, LEF: longitudinal ejection fraction, LV: left ventricle, REF: radial ejection fraction, RV: right ventricle, SVi: stroke volume index

patients with significant TR, FAC, RV septal longitudinal strain, and RV free wall longitudinal strain showed significantly decreased values, in contrast to TAPSE, which did not differ between the two groups. 2D RA volume index was significantly higher in patients presented with significant TR *(Table 2)*.

We have compared patients with significant TR and patients without TR based on 3D echocardiographic data. The results are shown in *Table 3*. As expected, there were significant differences between patients with vs. without significant TR concerning LV and RV morphological and functional parameters. Patients with significant TR had higher LV and RV EDVi and ESVi values than patients without TR, whereas LV and RV SVi values did not differ between the two groups. In patients with significant TR, LV EF, LV GLS along with RV EF, RV GLS, GCS, and RV GAS showed significantly decreased values, in contrast to LV GCS which did not show a difference compared to patients without TR. Concerning the contraction pattern of the RV, values of RV LEF and RV AEF were significantly lower in patients with significant TR compared to those without. In contrast, RV REF did not differ among the study groups *(Table 3)*.

Univariable correlations between 3D echocardiography-derived parameters and TR severity grade (trace, gr. I, II, III, IV) were assessed using our entire study population. LV volumes such as LV EDVi (r=0.210, p=0.018) and LV ESVi (r=0.235, p=0.008) correlated significantly with TR severity, whereas LV SVi (r=0.046, p=0.611) did not. LV functional parameters, namely, LV EF (r=–0.241, p=0.005), LV GLS (r=0.371, p<0.001) and LV GCS (r=0.183, p=0.035) showed a weaker inverse correlation with TR severity. Concerning the right heart, RV EDVi (r=0.409, p<0.001), RV ESVi (r=0.415, p<0.001) and RV SVi (r=0.213, p=0.048) showed significant correlations with TR grade. RV EF (r= –0.395, p<0.001), RV GLS (r=0.470, p<0.001), and RV GCS (r=0.302, p=0.003) had also inverse correlations with TR severity. Regarding the different components of RV mechanics, RV LEF (r= –0.401, p<0.001), RV AEF (r= –0.250, p=0.016) and RV REF (r= –0.214, p=0.039) as well had significant inverse correlations with TR severity grade *(Figure 1)*.

Discussion

To the best of our knowledge, our study is the first that investigated RV remodeling and contraction patterns in HFrEF patients presented with versus without significant TR using 3D echocardiography. HFrEF patients with severe TR have shown significant cardiac changes comprising a significant dilation of both the left and the right ventricle along with decreased biventricular systolic function. Concerning the RV mechanical pattern, the RV pump function's longitudinal and anteroposterior components decreased significantly in patients with

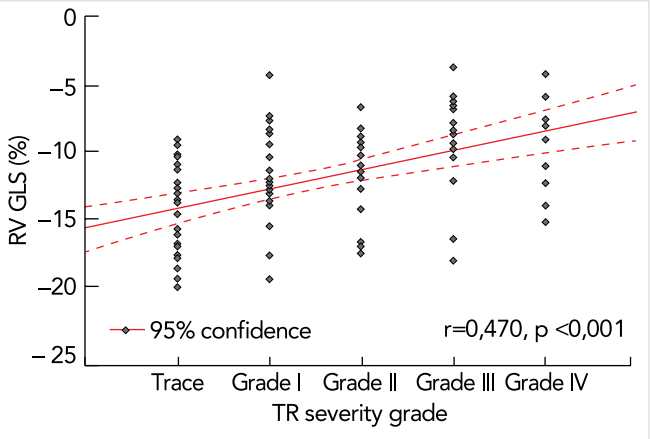

FIGURE 1. Graphical representation of the association between functional tricuspid regurgitation (TR) and right ventricular mechanics. Concerning RV mechanics, global longitudinal strain (RV GLS) showed a significant inverse correlation with TR severity

significant TR. In contrast, the radial component was maintained. Therefore, the markedly reduced RV global function in patients with significant TR was mainly attributable to the deterioration of the longitudinal and anteroposterior motion components *(Figure 2)*.

While significant progress has been made in the management of HFrEF, the prognosis still remains particularly poor (12). Adverse right ventricular remodeling further contributes to the unfavorable outcome (13). LV systolic dysfunction significantly influences the RV function directly due to the mechanical interdependence between the two ventricles, and the effect of the LV backward failure with consequentially increasing RV pressures is also far from negligible (1). In heart failure with preserved ejection fraction (HFpEF), it has been previously shown that more than 50% of total deaths are attributable to right heart failure (13). Thus, the development of RV dysfunction, irrespective of heart failure etiology and also the LVEF has been identified persistently as an independent predictor of poor survival and a primary determinant of functional limitations (2).

Severe secondary TR is a well-established complication of primary left-sided cardiac diseases and is classically attributed to pulmonary hypertension as a result of left-sided heart failure (14). Although secondary TR is a common finding, its influence on RV remodeling in the context of HFrEF is poorly understood. Nevertheless, in a pilot study conducted by *Topilsky et al.*, and later by Benfari and colleagues on a larger sample size, severe TR was associated with a higher mortality rate and more frequent adverse cardiac events (4, 15). The latter study also provided evidence that each increment in the grade of secondary TR is associated with gradually worse survival in HFrEF, independent of baseline clinical characteristics. These results support the theory that secondary TR is not just an innocent bystander but rather a significant condition affecting the underlying cardiac disease (4). Nevertheless, the subsequent development of RV remodeling and dysfunction plays a pivotal role in the pathophysiology of secondary TR, inducing a vicious circle of increased volume overload of the RV, leading to further RV dysfunction and worsening of TR (16–18). This high prevalence of RV systolic dysfunction in patients with significant TR was further supported by a study examining a multicenter registry including 106 patients with severe TR referred for novel tricuspid transcatheter devices (TriValve registry) (19). Still, compared to its left counterpart, data are still scarce regarding RV remodeling exacerbated by TR in a heart failure patient population. This could be mainly attributable to the more complex anatomical and mechanical structure of the RV and the subsequent imaging difficulties in RV assessment using conventional echocardiographic techniques.

The emergence of advanced techniques, such as deformation imaging and 3D echocardiography, helped to overcome the limitations of conventional 2D echocardiography by offering a more accurate and detailed quantification of ventricular structure and function with good feasibility and close correlation with gold standard cardiac magnetic resonance imaging (6). While accurate detection of RV dysfunction with conventional 2D echocardiography is challenging in patients with severe TR, speckle-tracking echocardiography-derived RV free wall longitudinal strain has been proposed as a more sensitive and predictive measurement. A recent study showed that in severe secondary TR, impaired RV free wall longitudinal strain identifies higher RV dysfunction rates than TAPSE and FAC (20). Similarly, in our cohort, patients with significant TR showed markedly decreased RV FWLS and RV septal longitudinal strain; however, TAPSE was not able to capture these differences and remained similar in the two groups. On the other hand, speckle-tracking refers only to the longitudinal shortening of the RV using a single apical four-chamber cut and neglects the two other motion directions of the ventricular contraction. Thus, the use of 3D echocardiography is essential for a comprehensive assessment of RV volumes and function that goes beyond the importance of longitudinal shortening (21). Therefore, in our study, we utilized 3D evaluation of the RV, and as anticipated, patients with significant TR showed larger RV volumes. RV EF gained momentous scientific attention as it seems to have an independent, added prognostic value on top of left ventricular LV EF quantification (22). Accordingly, we assessed 3D global function and found that patients with severe TR had significantly lower RV EF along with markedly decreased RV GLS and GCS compared to those without. Interestingly, several studies have shown that global RV EF could remain preserved at the first stages in patients with severe TR and left-sided heart diseases despite the significant decline in longitudinal function (5, 23). The maintained RV plasticity could explain this at the

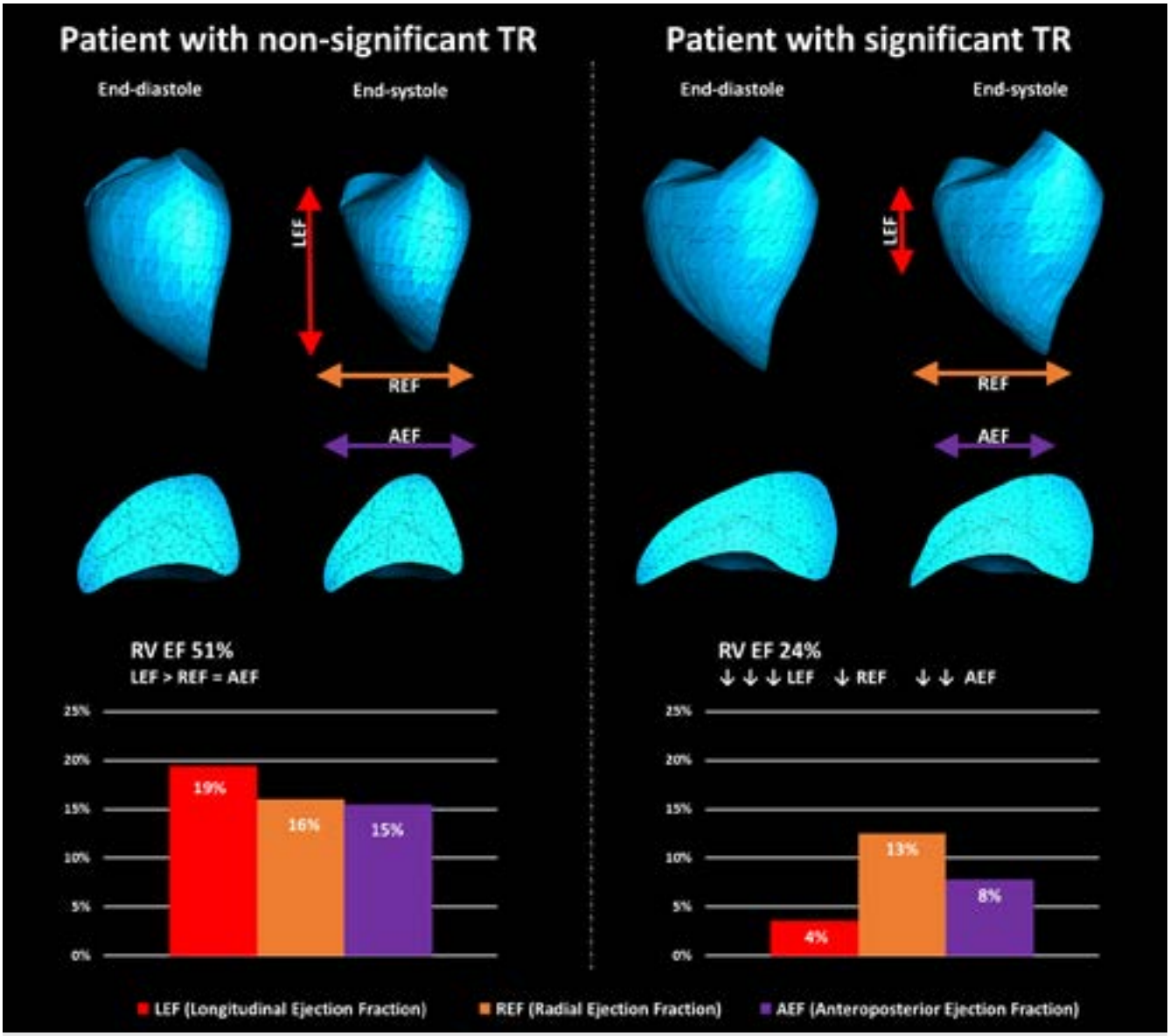

FIGURE 2. Representative cases of right ventricular (RV) mechanical adaptation in a patient with non-significant versus a patient with significant tricuspid regurgitation and heart failure with reduced ejection fraction. Three-dimensional schematic representation of the 3 major components contributing to total RV pump function: (i) longitudinal shortening along the long-axis (red) contributing to RV longitudinal ejection fraction (LEF), (ii) inward (radial) motion of the RV free wall (orange) contributing to radial ejection fraction (REF), and (iii) short-axis shortening in the anteroposterior direction (purple) contributing to anteroposterior ejection fraction (AEF). Blue surfaces represent RV end-diastolic and end-systolic volumes, respectively. In case of the patient without significant TR (left), all three components show a balanced contribution. However, in the patient with significant TR, AEF and particularly, LEF show a significant decrease, whereas REF remains maintained

compensatory stage, where the RV increases its transverse function in relation to the decreased longitudinal shortening (24). However, if the accompanying cardiac disease and overload persists, RV function inevitably transitions into a decompensated stage, where the global pump function will start to decline (25). Therefore, it is essential to characterize the other two main mechanisms that contribute to the global RV function beyond the longitudinal component, before severe RV dysfunction could manifest. In our study, we assessed RV longitudinal, radial, and anteroposterior ejection fraction using 3D vertex-based motion decomposition (8). We found that RV LEF and RV AEF were significantly decreased in patients with significant TR, while RV REF remained similar to those who did not develop significant TR. We may suggest that in patients with significant TR the reduced global RV function was mainly attributable to the deterioration of the longitudinal and anteroposterior motion components. The markedly lower LV functional measures of patients with severe TR also underpin these findings: previous studies suggest that RV AEF may reflect the influence of LV contrac-

tion in RV function by quantifying the traction of the LV free wall to the RV insertion points (5). Moreover, the significantly elevated pulmonary arterial pressures of patients with severe TR may result in decreased longitudinal shortening (26). According to these findings, RV plasticity is characterized by a compensation provided by the radial shortening, and when this compensation is depleted that will finally result in manifest right heart failure. Furthermore, we analyzed the associations between 3D echocardiography-derived parameters and TR severity. Although LV parameters correlated with TR severity, enlarged RV volumes and decreasing functions (RV GLS and RV LEF in particular) correlated the most with TR severity, underscoring the importance of TR in the development of adverse RV remodeling.

Limitations

There are several limitations of our pilot study that have to be acknowledged. First, the case number is relatively limited, and a selection bias may apply as the study participants were identified based on the availability of 3D echocardiography. Second, to answer the main questions of our study, a longitudinal follow-up of these patients is needed to describe the dynamics of the disease course. However, our study was rather cross-sectional. Lastly, no gold standard modality is available to validate our findings considering the RV mechanical pattern.

Conclusions

With the comprehensive assessment of RV mechanics using 3D echocardiography, we have shown that HFrEF patients with severe TR had undergone adverse RV remodeling comprising a significant dilation of both the left and the right ventricles along with decreased biventricular systolic function. Furthermore, we demonstrated that these patients had significantly reduced RV global function, which was mainly attributable to the deterioration of the longitudinal and anteroposterior motion components. Further studies are warranted to identify the turning point where RV plasticity diminishes, and significant TR develops.

Declaration of interest

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

References

1. Haddad F, Hunt SA, Rosenthal DN, et al. Right ventricular function in cardiovascular disease, part I: Anatomy, physiology, aging, and functional assessment of the right ventricle. Circulation 2008; 117: 1436–48. https://doi.org/10.1161/CIRCULATIONAHA.107.653576

2. Padang R, Chandrashekar N, Indrabhinduwat M, et al. Aetiology and outcomes of severe right ventricular dysfunction. Eur Heart J 2020; 41: 1273–1282. https://doi.org/10.1093/eurheartj/ehaa037

3. Mandoli GE, Pastore MC, Benfari G, et al. New echocardiographic indices of shift to biventricular failure to optimize risk stratification of chronic heart failure. Esc Heart Fail 2022; 9: 476–485. https://doi.org/10.1002/ehf2.13722

4. Benfari G, Antoine C, Miller WL, et al. Excess Mortality Associated With Functional Tricuspid Regurgitation Complicating Heart Failure With Reduced Ejection Fraction. Circulation 2019; 140: 196–206. https://doi.org/10.1161/CIRCULATIONAHA.118.038946

5. Surkova E, Kovacs A, Tokodi M, Lakatos BK, Merkely B, Muraru D, Ruocco A, Parati G and Badano LP. Contraction Patterns of the Right Ventricle Associated with Different Degrees of Left Ventricular Systolic Dysfunction. Circ Cardiovasc Imaging 2021: CIRCIMAGING121012774. https://doi.org/10.1161/CIRCIMAGING.121.012774

6. Muraru D, Spadotto V, Cecchetto A, et al. New speckle-tracking algorithm for right ventricular volume analysis from three-dimensional echocardiographic data sets: validation with cardiac magnetic resonance and comparison with the previous analysis tool. Eur Heart J Cardiovasc Imaging 2016; 17: 1279–1289. https://doi.org/10.1093/ehjci/jev309

7. Kovacs A, Lakatos B, Tokodi M and Merkely B. Right ventricular mechanical pattern in health and disease: beyond longitudinal shortening. Heart Fail Rev 2019; 24: 511-520. https://doi.org/10.1007/s10741-019-09778-1

8. Tokodi M, Staub L, Budai A, et al. Partitioning the Right Ventricle Into 15 Segments and Decomposing Its Motion Using 3D Echocardiography-Based Models: The Updated ReVISION Method. Front Cardiovasc Med 2021; 8: 622118. https://doi.org/10.3389/fcvm.2021.622118

9. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015; 28: 1–39 e14. https://doi.org/10.1016/j.echo.2014.10.003

10. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2017; 30: 303–371. https://doi.org/10.1016/j.echo.2017.01.007

11. Lakatos B, Toser Z, Tokodi M, et al. Quantification of the relative contribution of the different right ventricular wall motion components to right ventricular ejection fraction: the ReVISION method. Cardiovasc Ultrasound 2017; 15: 8. https://doi.org/10.1186/s12947-017-0100-0

12. Shah KS, Xu H, Matsouaka RA, et al. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. J Am Coll Cardiol. https://doi.org/10.1093/eurheartj/ehy434

13. Aschauer S, Zotter-Tufaro C, Duca F, et al. Modes of death in patients with heart failure and preserved ejection fraction. Int J Cardiol 2017; 228: 422–426. https://doi.org/10.1016/j.ijcard.2016.11.154

14. Mutlak D, Lessick J, Khalil S, et al. Tricuspid regurgitation in acute heart failure: is there any incremental risk? Eur Heart J Cardiovasc Imaging 2018; 19: 993–1001. https://doi.org/10.1093/ehjci/jex343

15. Topilsky Y, Inojosa JM, Benfari G, et al. Clinical presentation and outcome of tricuspid regurgitation in patients with systolic dysfunction. Eur Heart J 2018; 39: 3584–3592. https://doi.org/10.1093/eurheartj/ehy434

16. Dreyfus GD, Martin RP, Chan KM, et al. Functional tricuspid regurgitation: a need to revise our understanding. J Am Coll Cardiol 2015; 65: 2331–6. https://doi.org/10.1016/j.jacc.2015.04.011

17. Badano LP, Muraru D and Enriquez-Sarano M. Assessment of functional tricuspid regurgitation. Eur Heart J 2013; 34: 1875–85. https://doi.org/10.1093/eurheartj/ehs474

18. Dietz MF, Prihadi EA, van der Bijl P, et al. Prognostic Implications of Right Ventricular Remodeling and Function in Patients With Significant Secondary Tricuspid Regurgitation. Circulation 2019; 140: 836–845. https://doi.org/10.1161/CIRCULATIONAHA.119.039630

19. Taramasso M, Hahn RT, Alessandrini H, et al. The International Multicenter TriValve Registry: Which Patients Are Undergoing Transcatheter Tricuspid Repair? JACC Cardiovasc Interv 2017; 10: 1982–1990. https://doi.org/10.1016/j.jcin.2017.08.011

20. Prihadi EA, van der Bijl P, Dietz M, Abou R, Vollema EM, Marsan NA, Delgado V and Bax JJ. Prognostic Implications of Right Ventricular Free Wall Longitudinal Strain in Patients With Significant Functional Tricuspid Regurgitation. Circ Cardiovasc Imaging 2019; 12: e008666. https://doi.org/10.1161/CIRCIMAGING.118.008666

21. Tolvaj M, Tokodi M, Lakatos BK, et al. Added predictive value of right ventricular ejection fraction compared with conventional echocardiographic measurements in patients who underwent diverse cardiovascular procedures. Imaging 2021; 13: 130–137. https://doi.org/10.1556/1647.2021.00049

22. Surkova E, Muraru D, Genovese D, et al. Relative Prognostic Importance of Left and Right Ventricular Ejection Fraction in Patients With Cardiac Diseases. J Am Soc Echocardiogr 2019; 32: 1407–1415 e3. https://doi.org/10.1016/j.echo.2019.06.009

23. Kresoja KP, Rommel KP, Lucke C, et al. Right Ventricular Contraction Patterns in Patients Undergoing Transcatheter Tricuspid Valve Repair for Severe Tricuspid Regurgitation. JACC Cardiovasc Interv 2021; 14: 1551–1561. https://doi.org/10.1016/j.jcin.2021.05.005

24. Gorter TM, Hoendermis ES, van Veldhuisen DJ, et al. Right ventricular dysfunction in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Eur J Heart Fail 2016; 18: 1472–1487. https://doi.org/10.1002/ejhf.630

25. Schwarz K, Singh S, Dawson D and Frenneaux MP. Right ventricular function in left ventricular disease: pathophysiology and implications. Heart Lung Circ 2013; 22: 507–11. https://doi.org/10.1016/j.hlc.2013.03.072

26. Mostafa S. Assessment of right ventricular systolic function in heart failure with preserved, reduced and mid-range ejection fraction. Indian Heart J 2019; 71: 406–411. https://doi.org/10.1016/j.ihj.2019.11.252