

# Grading right ventricular dysfunction in left ventricular disease using echocardiography: a proof of concept using a novel multiparameter strategy

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## Abstract

**Aims** Grading right ventricular dysfunction (RVD) in patients with left ventricular (LV) disease has earned little attention. In the present study, we established an echocardiographic RVD score and investigated how increments of the score correspond to RVD at right heart catheterization.

**Methods and results** We included 95 patients with LV disease consecutively referred for heart transplant or heart failure work-up with catheterization and echocardiography within 48 h. The RVD score (5 points) included well-known characteristics of the development from compensated to decompensated right ventricular (RV) function: pulmonary hypertension, reduced RV strain, RV area dilatation, moderate/severe tricuspid regurgitation, and increased right atrial pressure (RAP) by echocardiography. Comparing three groups with increments of RVD score [1 (mild), 2–3 (moderate), and 4–5 (severe)] showed more advanced RVD with increasing RV end-diastolic pressure ( $P < 0.001$ ) and signs of uncoupling to load (reduced ratio between RV and pulmonary artery elastance,  $P < 0.001$ ) and more spherical RV shape (RV area/length,  $P < 0.001$ ). Receiver operating characteristic curve analysis for detection of severe RV (RAP  $\geq 10$  mmHg) showed for the RVD score an area under the curve of 0.88 compared with 0.69, 0.68, and 0.64 for RV strain, tricuspid annular plane systolic excursion, and fractional area change, respectively. A patient with RVD score  $\geq 4$  had a 6.7-fold increase in likelihood of severe RVD, and no patient with RVD score  $\leq 1$  had severe RVD.

**Conclusions** In this proof of concept study, a novel RVD score outperformed the widely used longitudinal parameters regarding grading of RVD severity, with a potential role for refined diagnosis, follow-up, and prognosis assessment in heart failure patients.

**Keywords** Right ventricle; Right ventricular dysfunction; Echocardiography; Right heart catheterization; Left ventricular disease

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## Introduction

Grading right ventricular dysfunction (RVD) in patients with left ventricular (LV) disease has earned little attention. RVD is present when there is echocardiographic evidence of abnormal values of functional parameters. RV failure is a complex clinical syndrome resulting from RVD characterized by the inability of the RV to support optimal circulation in

the presence of normal right atrial pressure (RAP) and with fluid retention (peripheral oedema & ascites) as clinical manifestation.<sup>1,2</sup> The functional echocardiographic parameters used during the last 20 years have been related to the longitudinal contraction of the RV free wall, and their prognostic impact has been documented.<sup>3–6</sup> Historically, the assessment of longitudinal function started with the M-mode measurement of the tricuspid annular plane systolic

excursion (TAPSE),<sup>7</sup> followed by measuring the annular plane velocity (S')<sup>8</sup> and more recently measuring the RV deformation (RV strain,  $RV_{Str}$ )<sup>9</sup> and rate of deformation (RV strain rate,  $RV_{SR}$ ) with speckle tracking imaging.

The development towards RV failure in patients with LV disease is typically initiated by pulmonary hypertension and increased RV afterload. Hypertrophic remodelling enables the RV to adapt and stay coupled to increased pressure load with preserved stroke volume and without dilatation or changes in geometry.<sup>10</sup> Parameters related to the longitudinal contraction of the RV free wall are surrogates for myocardial performance, but they have inherent limitations. The longitudinal contraction can be reduced due to myocardial dysfunction but also due to loading conditions (reduced preload or increased afterload),<sup>11</sup> and assessment of contraction cannot tell if the RV is coupled or uncoupled to its load. RV dilatation is the most important finding indicating RV-pulmonary artery uncoupling.<sup>12</sup> The RV volume is difficult to assess using standard echocardiography and dilatation can pass unrecognized. An indirect sign indicating RV uncoupling is a moderate or severe tricuspid regurgitation due to a more spherical shape and annular remodelling.<sup>13</sup> In the present study, we hypothesized that grading severity of RVD in patients with LV disease in a standardized and reproducible manner require a multiparameter approach. Grading RVD is important for several reasons. Firstly, to recognize severe RVD is important because it will have direct impact on the heart failure treatment strategy and in patients considered candidates for LV assist, it increases the risk of RV failure following implantation.<sup>14,15</sup> Secondly, in patients with LV disease, occurrence of mild or moderate RVD often indicates LV haemodynamic decompensation calling for optimization of heart failure therapy. Thirdly, RVD is often reversible and in that case, it is a marker of good therapy response, LV reverse remodelling, and improved outcome.<sup>16</sup> In the present study, we established a multiparameter 5-point RVD score with the aim to investigate how increments of the score correspond to RVD at right heart catheterization.

## Methods

### Study population

In this single-centre observational study, we screened 108 patients with LV disease consecutively referred between July 2015 and July 2019 for heart transplant or heart failure work-up with right heart catheterization and echocardiography within 48 h. The echocardiographic investigation was performed the same day as right heart catheterization in 15 patients, within 24 h in 61 patients, and within 48 h in 19 patients. The patients did not have acute decompensated heart failure. Thirteen patients did not have assessment of

pulmonary artery systolic pressure (PASP) by Doppler, and they were excluded. The study population then comprise 95 patients. Samples for laboratory tests for renal, liver, and cardiac function were obtained during the hospital stay. Seventy-three per cent performed a cardiopulmonary exercise test. Patients with active myocarditis or diseases involving both ventricles (amyloidosis & sarcoidosis) were not included as well as patients with advanced pulmonary disease. The study was conducted according to the Declaration of Helsinki. The Regional Ethics Review Board in Gothenburg gave ethical approval (Dnr. 286-18).

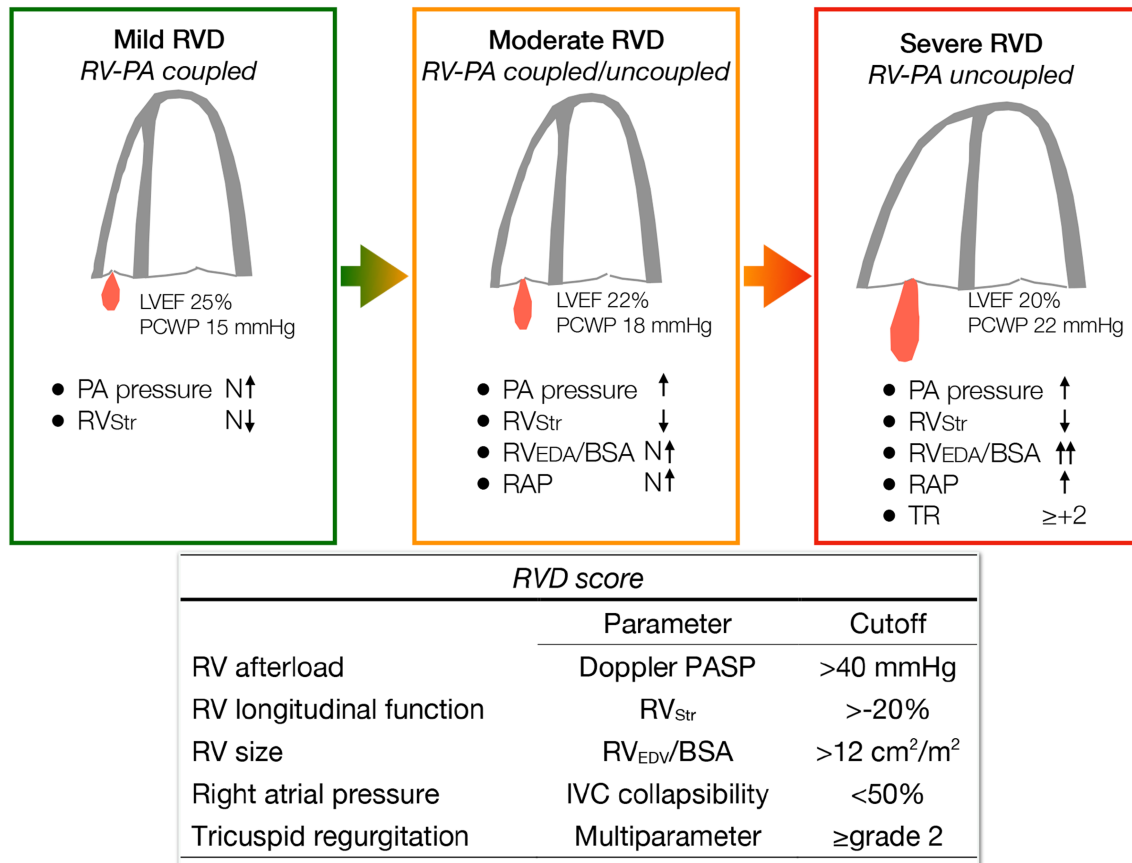
### The right ventricular dysfunction score

The five standard echocardiographic parameters included in the RVD score represent either the most common cause of RVD (pulmonary hypertension), a measure of RVD ( $RV_{Str}$ ) or relate to findings when the RV-PA is uncoupled (RV dilatation, increased RA pressure,  $\geq$ moderate tricuspid regurgitation). The maximum RVD score is 5. *Figure 1* (upper panel) is a schematic drawing showing the findings we can expect in a patient with LV disease that migrate from having mild RVD to moderate RVD and finally severe RVD. It is conceivable that increased score implies more severe RVD. Grading pathology is often done using three levels (mild, moderate, and severe). We defined three groups with incremental rise in RVD score (RVDS), namely  $RVDS_1$  (mild),  $RVDS_{2-3}$  (moderate), and  $RVDS_{4-5}$  (severe). The cut-off values indicating RVD (*Figure 1*, lower panel) were chosen from reference populations.<sup>17</sup> The cut-off value for Doppler PASP  $> 40$  mmHg was chosen because this threshold is known to identify patients with pulmonary artery mean pressure (PAMP)  $> 25$  mmHg<sup>18</sup> and correspond to a threshold with increased risk for all-cause death.<sup>19</sup> The grading of tricuspid regurgitation was based on the density and shape of the regurgitant jet, the colour Doppler jet area, and presence of systolic hepatic vein flow reversal.<sup>20</sup>

### Echocardiography

The echocardiographic examination was performed using a commercially available imaging system (Vivid E9 or E95, GE Healthcare, Milwaukee, Wisconsin, USA). Image analysis was performed using EchoPAC (GE Healthcare, Milwaukee, Wisconsin, USA). The LV systolic function was assessed using the LV ejection fraction and volumes by the biplane Simpsons method. Global longitudinal strain was determined using speckle tracking imaging from three apical projections. Left atrial size was determined in end-systole from biplane projections and the left atrial volume was indexed to BSA. Valvular regurgitation was graded using the recommended multiparameter approach.<sup>20</sup> In the present

**Figure 1** Schematic drawing (upper panel) showing how the development in a patient with LV disease, from mild RVD to moderate RVD and finally severe RVD, recruits more of the parameters included in the RVD score. Patients with mild RVD (upper panel, left) might have reduced longitudinal function or pulmonary hypertension but normal RV size indicating normal RV-PA coupling.<sup>10</sup> As RV function deteriorates, the RV-PA is uncoupled, and we can expect to find enlargement of the RV in patients with moderate RVD (upper panel, middle). With severe RVD there will be signs of increased RAP and often greater than or equal to moderate tricuspid regurgitation (upper panel, right). The lower panel shows a table with the cut-off values used. LVEF, left ventricular ejection fraction; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; RV, right ventricular; RVD, right ventricular dysfunction.



study, echocardiographic assessment of RAP had two different purposes: firstly, to be used in the assessment of Doppler PASP and, secondly, as a part of the RVD score and assessment of RV function. The RAP by echocardiography was obtained using the inferior vena cava dimension and collapsibility.<sup>21</sup> Increased RAP (15 mmHg) was defined as collapsibility < 50% with dilated inferior vena cava ( $\geq 21$  mm), and normal RAP (3 mmHg) was defined as collapsibility  $\geq 50\%$  and cava inferior diameter < 21 mm. Patients that fell outside this paradigm were classified as having increased RAP (10 mmHg) if the inferior vena cava diameter was normal but collapsibility < 50%, and upper normal (8 mmHg) RAP if the inferior vena cava was dilated but with collapsibility  $\geq 50\%$ . For the RVD score, patients with reduced inferior vena cava collapsibility rendered one point regardless of vessel dimension.

Right ventricular end-diastolic and end-systolic areas were traced in either standard ( $n = 28$ ), focused ( $n = 61$ ), or modified ( $n = 19$ ) apical four-chamber projections and RV

fractional area change (FAC) was calculated. Assessment of TAPSE by M-mode and tissue Doppler imaging were performed, both at the lateral tricuspid annulus. From the tissue Doppler curve, peak systolic velocity ( $S'$ ) was measured. The basal RV linear dimension was determined in the apical projection as the maximal transversal dimension in the basal third of the RV in end-diastole. The length of the RV long-axis was measured from the mid-position of the annular diameter to apex. From the parasternal long-axis view, we measured the end-diastolic proximal RV outflow tract diameter.<sup>17</sup> The RV geometry was described using the ratio between RV end-diastolic area and RV length.<sup>14</sup>

Speckle tracking was performed on the RV free wall by manual tracing and with the region of interest adjusted to lowest possible thickness (frame rate 44–60 Hz). Longitudinal RV<sub>Str</sub> and RV<sub>SR</sub> were recorded as the mean of their peak points in systole in the medial and basal segments. We omitted the apical segment due to often occurring problems with

the visual assessment of tracking and that the apical segment was only partly included in the sector.

The RV-PA coupling was estimated using the TAPSE/Doppler PASP ratio as proposed by Guazzi *et al.*<sup>22</sup>

## Right heart catheterization

A Swan–Ganz catheter (7Fr; Baxter Healthcare, Edwards Critical Care Division, Deerfield, IL) was introduced through the right internal jugular vein under fluoroscopic guidance using the Seldinger technique and measurements performed during free-breathing. The following variables were measured or derived: mean RAP, RV end-diastolic pressure, PAMP, pulmonary capillary wedge pressure (PCWP), cardiac output, pulmonary vascular resistance, and total pulmonary resistance. Cardiac output was determined by the thermodilution method as the mean of three to five consecutive measurements not varying by more than 10%. Stroke volume and cardiac output was indexed to BSA yielding stroke volume index and cardiac index. Pulmonary vascular resistance was calculated as (PAMP-PCWP)/cardiac output and total pulmonary resistance as PAMP/cardiac output. The pulmonary artery elastance was calculated as PAMP/stroke volume. The systolic RV elastance was calculated as PASP/end-systolic area ratio.<sup>23</sup> A supine exercise test was performed with measurement of RAP, PCWP, and cardiac index at steady state ( $n = 56$ ). The upper normal value for RAP is 8 mmHg. Severe RVD was defined from invasive data as  $\text{RAP} \geq 10$  mmHg. The stroke work index was calculated as (PAMP-RAP)\*indexed stroke volume.

## Statistical analysis

Continuous variables are expressed as the mean  $\pm$  SD, medians with interquartile ranges or as numbers with percentages. The degree of the linear relationship was assessed by the Spearman correlation coefficient ( $R_s$ ). To compare multiple groups, we used one-way ANOVA test when the distribution was normal or Kruskal–Wallis test when the distribution was not normal. In cases where the null-hypothesis was rejected ( $P$  value  $< 0.05$  considered statistically significant), we continued with a post-hoc analysis of intergroup comparisons using the independent-sample  $t$ -test or Mann–Whitney test when appropriate. Using the Bonferroni correction for multiple testing, the null hypothesis was rejected if the  $P$  value was  $< 0.016$ . Regarding the ability to detect patients with severe RVD, we performed receiver operator characteristic curve analysis. The diagnostic ability of the longitudinal and global RV function parameters as well as the 5-point but also a 4-point RVD score, omitting the Doppler assessment of systolic pulmonary artery pressure, were included in the analysis. Diagnostic performance was

described using sensitivity, specificity, positive likelihood ratio [sensitivity/(1-specificity)] and negative likelihood ratio [(1-sensitivity)/specificity]. To evaluate the interindividual variability of the RVD score the measurements and assessments included were made by two investigators (OBH & MA) on the same investigation ( $n = 20$ ). The variability for continuous variables ( $\text{RV}_{\text{Str}}$ ,  $\text{RV}_{\text{EDA}}$ , & Doppler PASP) was described by the coefficient of variation, which was expressed as the SD of differences divided by the mean value of two measurements. For categorical parameters (normal vs. increased  $\text{RAP}_{\text{Echo}}$ , TR grade  $< 2$  or  $\geq 2$ ,  $\text{RVDS}_1$ ,  $\text{RVD}_{2-3}$  vs.  $\text{RVDS}_{4-5}$ ), we used kappa statistics. The statistical analysis was performed using SPSS for Macintosh, Version 26.

## Results

### Baseline characteristics

The mean  $\pm$  SD age of the study group was  $53 \pm 14$  years, and 78% were male participants. Dilated cardiomyopathy was diagnosed in 73%, ischemic heart disease in 18%, and other cardiac disorders in 9%. Eighty-one per cent were heart transplant work-up. Eighty-eight per cent had a LV ejection fraction  $< 40\%$ , and 9% had atrial fibrillation. Ninety-four per cent received a beta-blocker, 75% loop-diuretics, and 49% an aldosterone inhibitor. All patients were treated with either an angiotensin 2 inhibitor (37%), an angiotensin-converting-enzyme inhibitor (35%), or angiotensin receptor-neprilysin inhibitor (32%). Sixty-three patients (66%) had either an implantable cardioverter defibrillator ( $n = 31$ ), cardiac resynchronization therapy ( $n = 24$ ), or both ( $n = 8$ ). The proportion of patients with tricuspid regurgitation  $\geq$  Grade 2 and a lead going through the tricuspid valve was 32% compared with 22% in patients without a lead ( $P = 0.35$ ). Among the heart transplant work-up patients ( $n = 77$ ), 43% were listed for transplantation, and 23% were considered not candidates due to comorbidities, age, or compliance issues. Thirty-four per cent did not fulfil the inclusion requirements for heart transplantation. The median follow-up time was 40 months (range 13 to 60 months). Ten patients (11%) died during the study period, and 44 patients (46%) were transplanted. Eight patients (8%) received a left ventricular assist device as a bridge to transplantation.

### Longitudinal function and right ventricular dysfunction score vs. right ventricular dysfunction severity

The correlations between longitudinal and global RV function parameters ( $S'$ , TAPSE,  $\text{RV}_{\text{Str}}$  & FAC) and different markers related to increasing severity of RVD were for RAP, RV

**Table 1** Clinical, demographic, laboratory, functional capacity, LV echocardiographic and right heart catheterization data in patients with RVDS<sub>1</sub>, RVDS<sub>2-3</sub> and RVDS<sub>4-5</sub>

	Variable			Overall P value	Post-hoc analysis*		
	RVDS <sub>1</sub> n = 21	RVDS <sub>2-3</sub> n = 33	RVDS <sub>4-5</sub> n = 19		RVDS <sub>1</sub> vs. RVDS <sub>2-3</sub>	RVDS <sub>1</sub> vs. RVDS <sub>4-5</sub>	RVDS <sub>2-3</sub> vs. RVDS <sub>4-5</sub>
<b>Demographic and clinical characteristics</b>							
Age (years)	52 ± 16	53 ± 15	57 ± 10	0.88	—	—	—
Male gender (n/%)	14/67	27/82	16/84	0.78	—	—	—
<b>Aetiology (n/%)</b>							
DCM	15/71	26/79	12/63	0.82	—	—	—
IHD	3/14	4/12	5/26	**	—	—	—
Other	3/14	3/9	2/11	**	—	—	—
<b>Comorbidities (n/%)</b>							
Hypertension	4/19	3/9	9/32	**	—	—	—
Diabetes	5/24	5/15	4/21	**	—	—	—
Cerebrovascular disease	1/5	3/9	0	**	—	—	—
COPD	1/5	5/15	2/11	**	—	—	—
CABG	0/0	3/9	2/11	**	—	—	—
Htx work-up (n/%)	19/90	24/73	16/84	0.76	—	—	—
Listed for Htx (n/%)	5/24	11/33	10/53	0.28	—	—	—
ICD and/or CRT (n/%)	14/67	21/64	15/79	0.81	—	—	—
ICD (n/%)	7/33	14/42	7/37	0.87	—	—	—
CRT (n/%)	7/33	4/12	7/37	**	—	—	—
ICD + CRT (n/%)	2/10	3/9	1/5	**	—	—	—
Mortality	3/14	4/12	2/11	**	—	—	—
<b>Laboratory</b>							
Creatinine (μmol/L)	93 (84; 128)	103 (93; 143)	132 (124; 149)	0.023	0.3	0.02	0.5
Bilirubin (μmol/L)	9.2 (6.3; 15)	13 (12; 20)	16 (11; 28)	0.015	0.10	0.02	0.93
NT-proBNP (ng/L)	1280 (916; 2125)	4055 (2272; 5988)	4735 (2978; 11 725)	<0.001	<0.001	<0.001	1.0
<b>Functional capacity</b>							
NYHA group 3–4 (n/%)	16/76	23/72	18/100	0.63	—	—	—
VO <sub>2</sub> (mL/kg/min)	14.9 ± 3.4	13.2 ± 3.7	9.5 ± 2.5	0.001	0.61	0.001	0.014
<b>Echocardiography</b>							
LVEF (%)	27 (21; 35)	22 (18; 28)	22 (17; 27)	0.04	0.053	0.14	1.0
LV <sub>EDVI</sub> (mL/m <sup>2</sup> )	90 (64; 124)	112 (83; 136)	104 (73; 126)	0.22	—	—	—
LV <sub>GIS</sub> (%)	-7.6 (-9.8; -5.9)	-5.7 (-6.7; -3.9)	-5.3 (-7.6; -2.6)	0.051	—	—	—
LAVI (mL/m <sup>2</sup> )	51 (44; 63)	61 (43; 77)	67 (54; 83)	0.08	—	—	—
E/E'	12.9 ± 4.3	16.2 ± 5.5	17.3 ± 6.3	0.03	0.10	0.05	1.0
MR ≥ moderate (n/%)	7/33	16/50	8/40	0.71	—	—	—
<b>Right heart catheterization</b>							
Heart rate (bpm)	71 ± 11	72 ± 17	76 ± 14	0.17	—	—	—
RAP ≥ 10 mmHg (n/%)	0/0	14/42	14/74	<0.001	<0.001	<0.001	0.12
SAMP (mmHg)	69 ± 10	71 ± 10	71 ± 9	0.61	—	—	—
CI (L/min/m <sup>2</sup> )	2.5 ± 0.4	2.3 ± 0.7	2.2 ± 0.5	0.031	0.10	0.043	1.0
PAMP (mmHg)	21 ± 9	29 ± 8	32 ± 8	<0.001	0.02	<0.001	0.24
PVR (wood units)	1.9 (1.3; 2.6)	2.1 (1.5; 2.9)	2.4 (1.2; 3.8)	0.42	—	—	—
E <sub>a</sub> (mmHg/mL)	0.28 (0.19; 0.49)	0.56 (0.41; 0.65)	0.68 (0.35; 1.06)	<0.001	0.007	0.001	0.72
E <sub>es</sub>	2.8 (1.4; 4.2)	2.5 (1.7; 3.7)	2.3 (1.7; 2.6)	0.24	—	—	—
E <sub>es</sub> /E <sub>a</sub>	8.5 (6.4; 11.4)	5.2 (3.5; 7.0)	3.0 (2.2; 4.5)	<0.001	0.004	<0.001	0.02
SWI (mmHg × mL/m <sup>2</sup> )	0.51 (0.36; 0.80)	0.56 (0.41; 0.78)	0.42 (0.25; 0.63)	0.13	—	—	—
RV size							

(Continues)

Table 1 (continued)

	Variable				Overall P value	Post-hoc analysis*	
	RVDS <sub>1</sub> n = 21	RVDS <sub>2-3</sub> n = 33	RVDS <sub>4-5</sub> n = 19	RVDS <sub>1</sub> vs. RVDS <sub>2-3</sub>		RVDS <sub>1</sub> vs. RVDS <sub>4-5</sub>	RVDS <sub>2-3</sub> vs. RVDS <sub>4-5</sub>
RV D1 (mm)	43 ± 7	48 ± 7	54 ± 7	<0.001	0.08	<0.001	0.07
RVOT <sub>prox</sub> (mm)	33 ± 6	36 ± 5	42 ± 4	<0.001	0.17	<0.001	0.002
RV function by echocardiography							
TR ≥ moderate (n/%)	1/5	11/33	15/79	<0.001	0.054	<0.001	0.01
RV <sub>SR</sub> (1/s)	-1.0 ± 0.3	-1.0 ± 0.3	-0.9 ± 0.2	0.14	—	—	—
FAC (%)	35 ± 11	25 ± 9	24 ± 9	0.002	0.005	0.005	1.0
TAPSE/Doppler PASP	0.49 (0.39; 0.56)	0.30 (0.24; 0.41)	0.25 (0.21; 0.35)	<0.001	0.001	<0.001	1.0

Values are mean ± standard deviation, median (IQR 25%; 75%), or numbers and percent. BSA, body surface area; CABG, coronary artery bypass grafting; CI, cardiac index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; DCM, dilated cardiomyopathy; E/E', ratio between mitral early inflow velocity and the annular plane tissue velocity;  $E_{es}$ , right ventricular elastance;  $E_{pa}$ , pulmonary artery elastance; FAC, fractional area change; ICD, implantable cardioverter defibrillator; IHD, ischemic heart disease; Htx, heart transplant; LAVI, indexed left atrial area; LV<sub>GLS</sub>, left ventricular global longitudinal strain; LV<sub>EDVI</sub>, indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association class; PAMP, pulmonary artery mean pressure; PVR, pulmonary vascular resistance; RV, right ventricle; RVD1, right ventricle inflow diameter; RVD3, length of the right ventricle from annular plane to apex; RV<sub>EDA</sub>, right ventricle area in diastole; TR, tricuspid regurgitation; RV<sub>SR</sub>, right ventricle strain rate; SAMP, systemic arterial mean pressure; SWI, stroke work index; VO<sub>2</sub>, maximum oxygen consumption; WU, wood units.

\*Significance values have been adjusted by the Bonferroni correction for multiple tests.

\*\*Too small number to allow statistical testing

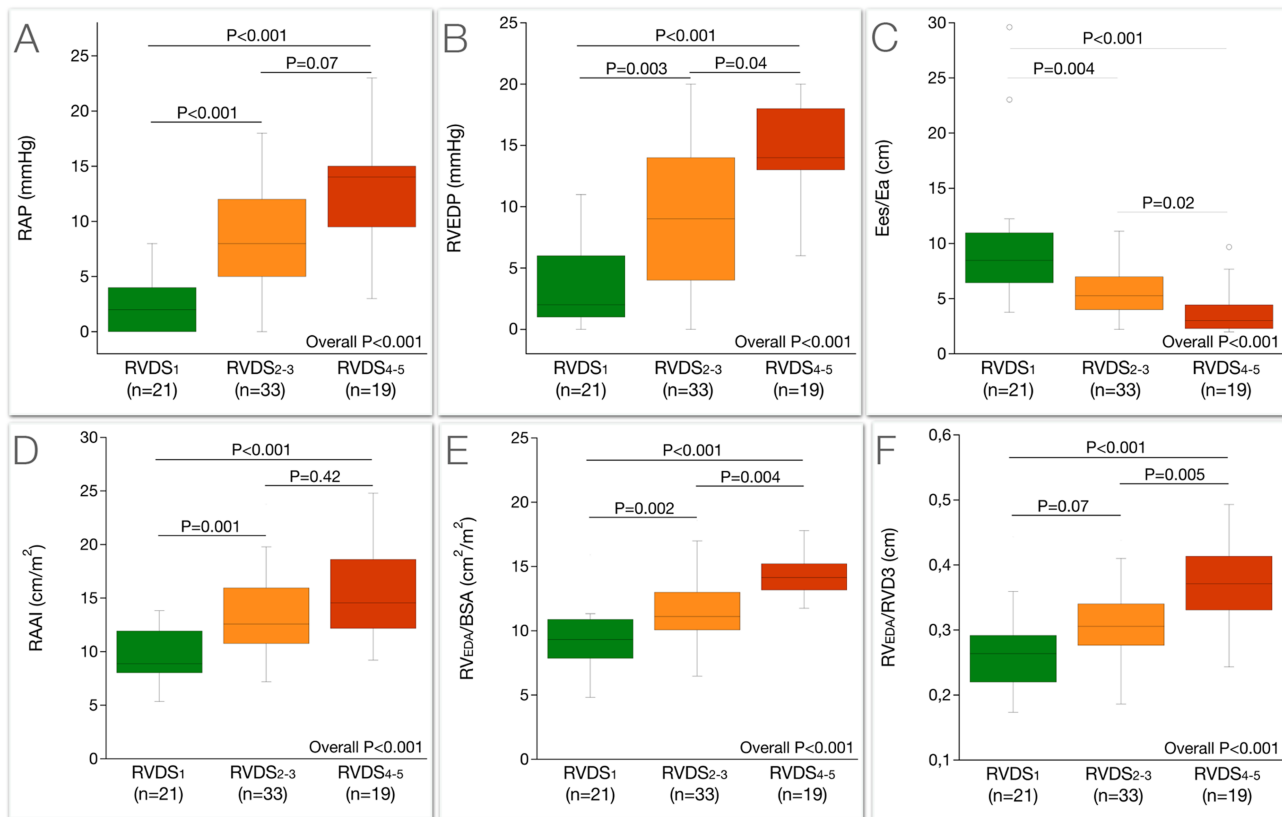
outflow diameter, size of the right atrium, and total pulmonary vascular resistance weak or not significant with  $R_s$  range 0.24–0.34 (Table S1). The corresponding correlation for the RVD score was moderate with  $R_s$  range 0.52–0.67. The correlations between longitudinal and global RV function parameters and the ratio between RV elastance and PA elastance ( $E_{es}/E_{pa}$ ) were weak to moderate with  $R_s$  range (0.32–0.69). The corresponding correlation for the RVD score was strong with  $R_s$  0.71.

### The relation between right ventricular dysfunction and incremental rise in right ventricular dysfunction score

The three groups with incremental increase in RVD score showed significant differences regarding organ function, functional capacity, LV function by echocardiography, right heart catheterization findings, RV/right atrial size, RV geometry, proportion with increased pulmonary vascular resistance, RV-PA coupling, and RV function by echocardiography (Table 1, Figures 2 and 3). Patients with severe RVD (RVDS<sub>4-5</sub>) had compared with moderate RVD (RVDS<sub>2-3</sub>) lower functional capacity, higher RV end-diastolic pressure, more impaired RV-PA coupling ( $E_{es}/E_{pa}$ ), more dilated and spherical RV and more often moderate or severe tricuspid regurgitation. They did not differ significantly regarding RV longitudinal function assessed by echocardiography (Table 1, Figure 2 A–C) or LV function by echocardiography and right heart catheterization (Table 1, Figure 3D–F). Patients with moderate RVD had compared with mild RVD (RVDS<sub>1</sub>) higher RAP, higher RV end-diastolic pressure, higher PAMP, reduced pulmonary artery elastance, and RV/right atrial size and tended to have more spherical RV (Table 1, Figure 2). The RV-PA coupling ( $E_{es}/E_{pa}$  and TAPSE/Doppler PASP) was more impaired in patients with moderate compared with mild RVDS. The echocardiographic parameters related to longitudinal ( $S'$ , TAPSE, RV<sub>Str</sub> & RV<sub>SR</sub>) function did not differ between RVDS<sub>1</sub> and RVDS 2–3 (Table 1, Figure 3), but the global function (FAC) was reduced (Table 1). Patients with RVDS<sub>2-3</sub> had compared with RVDS<sub>1</sub> more pronounced LV dysfunction with higher N-terminal pro BNP level, lower LV ejection fraction, higher PCWP, and lower SvO<sub>2</sub> (Table 1, Figure 3).

Table 2 compares patients with RVDS<sub>0</sub> (normal RV function) with patients with RVDS<sub>1</sub> due to reduced RV<sub>Str</sub> (n = 13). Patients with RVDS<sub>1</sub> had higher heart rate, lower mean systemic pressure, and lower RAP and tended to have smaller stroke volume index. The median doses of loop diuretics did not differ. RA and RV size as well as RV geometry were similar while TAPSE tended to be reduced, and RV<sub>Str</sub> and RV<sub>SR</sub> were significantly reduced compared with patients with RVDS<sub>0</sub>. Eighteen patients with RVDS<sub>0</sub> and nine patients with RVDS<sub>1</sub> performed a supine bicycle exercise test during right heart catheterization. There were no differences

**Figure 2** Box plots show the relation between increments of RVD score and the right ventricular (RV) filling pressure (RAP, A), RV end-diastolic pressure (RVEDP, B), RV-PA coupling as the ratio between RV elastance and PA elastance ( $E_{es}/E_a$ , C), right atrial size (RAAI, D), the diastolic area of the RV ( $RV_{EDd}/BSA$ , E), and the RV geometry as the ratio between RV area and length ( $RV_{EDd}/RVD3$ , F). Significance values have been adjusted by the Bonferroni correction for multiple tests.



between patients with RVDS<sub>0</sub> and RVDS<sub>1</sub> regarding RAP, PCWP, and cardiac index at peak exercise (Table 2).

### Detection of severe right ventricular dysfunction

Figure 4 shows the ROC curves for the RVD 5-point score, TAPSE/Doppler PASP, longitudinal, and global function parameters for detection of patients with severe RVD ( $RAP \geq 10$  mmHg,  $n = 28$ ). The area under the curve (95% confidence interval) for the RVD score was 0.88 (0.82–0.95), for TAPSE/PASP 0.70 (0.60–0.81), for  $RV_{Str}$  0.69 (0.57–0.81), for TAPSE 0.68 (0.56–0.79), and for FAC 0.64 (0.52–0.76).  $S'$  could not detect patients with severe RVD with area under the curve 0.59 (0.45–0.72). The area under the curve for the 4-point RVD score was 0.89 (0.83–0.95). Table 3 shows the diagnostic performance using a 5-point or 4-point RVD score. Both could rule in severe RVD with high positive likelihood ratios using the threshold  $\geq 4$  or  $\geq 3$  point, respectively. Using the threshold  $\geq 2$  for both scores ruled out severe RVD. A patient with RVD score  $\geq 4$ -point in the 5-point score or  $\geq 3$  in the 4-point score had a 6.7-fold or 5.3-fold increase in

likelihood of severe RVD, respectively. On the contrary, no patient with RVD score  $\leq 1$  in the 5-point scale had severe RVD and in the 4-point scale the likelihood of severe RVD with RVD score  $\leq 1$  was reduced 20-fold.

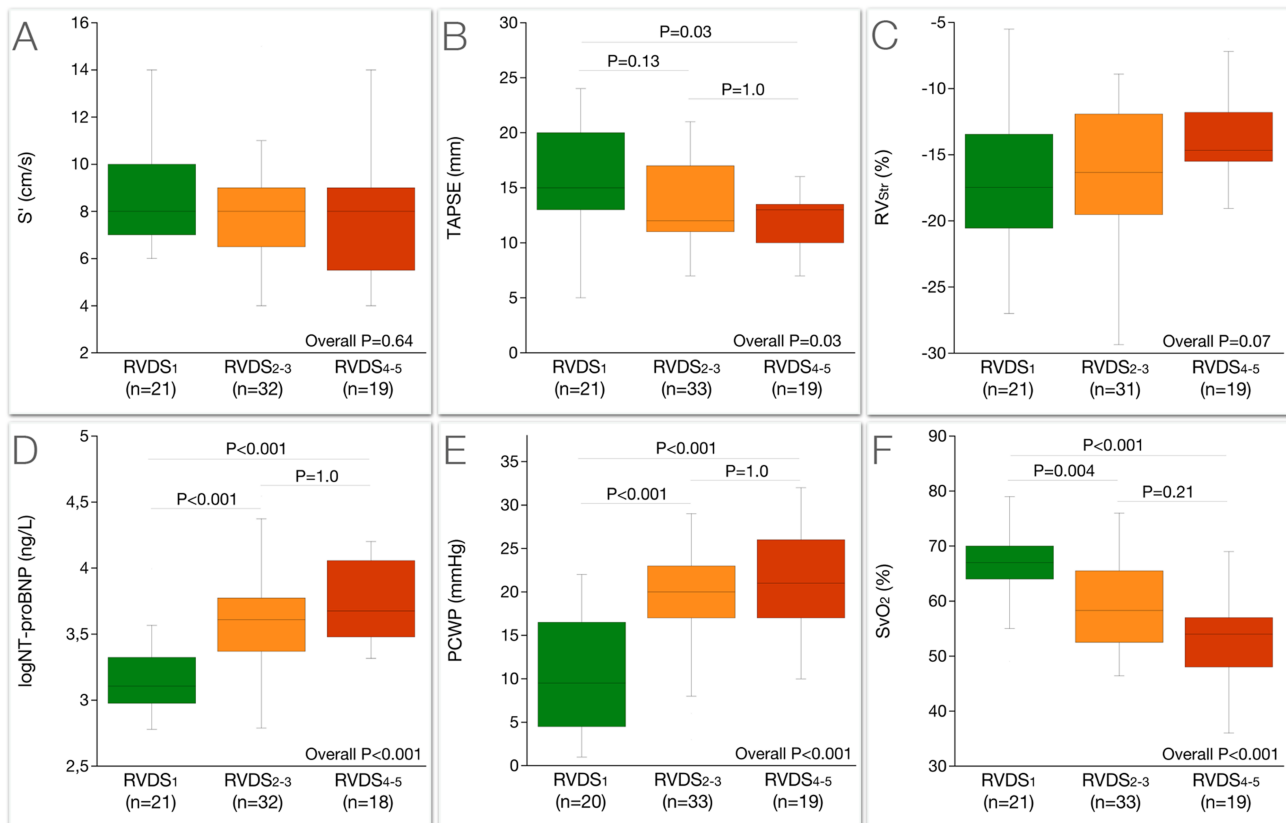
### Interobserver variability

The interobserver variability for  $RV_{EDv}$ , Doppler PASP, and  $RV_{Str}$  were 8.8%, 8.6%, and 12.2%, respectively. The agreement in assessment of  $RAP_{Echo}$ , tricuspid regurgitation, and RVD score by kappa (95% confidence interval) were 0.90 (0.71 to 1.0), 1.0, and 0.85 (0.65 to 1.0), respectively.

### Discussion

In the present study, we evaluated the diagnostic performance of a novel RVD score and the main findings are as follows: (i) incremental increase in the RVD score reflect a stepwise decline of RV function, (ii) the RVD score outperform longitudinal function parameters regarding the ability

**Figure 3** Box plots show the relation between increments of RVD score and tissue Doppler velocity ( $S'$ , A), tricuspid annular plane systolic excursion (TAPSE, B), deformation by speckle tracking ( $RV_{Str}$ , C), level of brain natriuretic peptide (log NT-proBNP, D), pulmonary capillary wedge pressure (PCWP, E), and the saturation of venous blood ( $SvO_2$ , F). Significance values have been adjusted by the Bonferroni correction for multiple tests.



to grade the severity of RVD, (iii) a 4-point RVD score omitting estimated PA pressure is as useful as the 5-point RVD score regarding ability to rule-in and rule-out severe RVD, and (iv) reduced longitudinal function as the sole sign of RVD could be due to loading conditions and should be interpreted with caution.

Grading the severity of RVD is important in patients with LV disease planned for a left ventricular assist device. The crucial question is whether or not the RV will tolerate the increased flow following implantation. No single echocardiographic parameter can be used to foresee RV failure.<sup>14,24</sup> In the present study, longitudinal or global function parameters could not differ moderate from severe RVD. Risk scores for early RV failure have been proposed, and they contain clinical, laboratory, hemodynamic, and echocardiographic parameters.<sup>25,26</sup> Assessment of severe RVD has been shown to contribute in these models; however, severe RVD is not defined. We constructed an echocardiographic score based on important components in the development from coupled to uncoupled RV function. Our proposed score is an effort to standardize the grading of RVD into three levels: mild, moderate, and severe RVD. The parameters included in the RVD

score are easily obtainable, part of standard echocardiographic examination and the grading is reproducible. *Figure 5* describes echocardiographic and invasive findings in three patients illustrating how the score system can be used. Patient A had reduced  $RV_{Str}$  as the sole finding indicating RVD. Most likely the patient does not have RVD caused by a decrease in contractility but instead a reduced  $RV_{Str}$  due to low preload. Patient B with RVD score 3 had moderate pulmonary hypertension and RV dilatation apart from reduced  $RV_{Str}$  and we suggest to describe this as moderate RVD. Patient C with RVD score 4 had reduced collapsibility of inferior vena cava indicating increased RAP together with moderate pulmonary hypertension, RV dilatation, and reduced  $RV_{Str}$  and this we suggest to describe as severe RVD. Only eight patients received treatment during the study period with a left ventricular assist device, and therefore, we cannot evaluate the ability of the RVD score to detect patients at risk for early RV failure. The causes of the early RV failure following implantation are multifactorial, but in the current risk scores, echocardiography plays a minor role that is somewhat unexpected.<sup>15,25</sup> Hopefully, by improving the assessment of RVD using a comprehensive and standardized approach as



**Table 2** Comparison between patients with RVDS<sub>0</sub> and patients with RVDS<sub>1</sub> due to reduced RV<sub>Str</sub>

Variable	RVDS <sub>0</sub> n = 22	RVDS <sub>1</sub> n = 13	P value
<b>Clinical data</b>			
Loop diuretic dose (mg)	40 (38; 80)	60 (40; 80)	0.65
NT-proBNP (ng/L)	1435 (844; 1870)	1710 (770; 2705)	0.47
VO <sub>2</sub> (mL/kg/min)	14.6 ± 4.4	13.5 ± 2.7	0.53
<b>Right heart catheterization</b>			
Heart rate (bpm)	65 ± 12	74 ± 12	0.03
SAMP (mmHg)	74 ± 11	66 ± 10	0.04
PCWP (mmHg)	9 (4; 16)	5 (4; 10)	0.13
PAMP (mmHg)	18 (12; 23)	14 (12; 17)	0.31
RAP (mmHg)	3 (1; 4)	1 (0; 2)	0.02
RVEDP (mmHg)	5 (2; 7)	2 (1; 3)	0.048
SVI (mL/m <sup>2</sup> )	39 ± 12	32 ± 7	0.03
TPR (wood units)	3.4 (2.5; 4.9)	2.5 (2.0; 4.2)	0.16
CI at stress (L/min/m <sup>2</sup> )	4.8 ± 1.1	4.9 ± 1.1	0.94
RAP at stress (mmHg)	10 (8; 12)	9 (6; 12)	0.38
PCWP at stress (mmHg)	20 (15; 32)	24 (17; 32)	0.53
<b>RA/RV size and RV geometry</b>			
RAAI (cm <sup>2</sup> /m <sup>2</sup> )	9.9 ± 3.0	8.7 ± 2.7	0.22
RV <sub>EDA</sub> /BSA (cm <sup>2</sup> /m <sup>2</sup> )	9.5 ± 1.3	9.1 ± 2.2	0.53
RV <sub>EDA</sub> /RVD3	0.27 ± 0.03	0.26 ± 0.06	0.88
<b>Global and longitudinal RV function</b>			
FAC (%)	40 ± 9	33 ± 12	0.10
TAPSE (mm)	17 ± 4	14 ± 4	0.07
S <sub>r</sub> (cm/s)	9 ± 3	8 ± 3	0.29
RV <sub>Str</sub> (%)	-25 ± 4	-15 ± 3	<0.001

CI, cardiac index; PCWP, pulmonary capillary wedge pressure; RA, right atrium; RAAI, right atrial area indexed to body surface area; RAP, right atrial pressure; RVEDP, right ventricle end-diastolic pressure; TPR, total pulmonary resistance; RVOT<sub>prox</sub>, right ventricle proximal diameter; RV<sub>Str</sub>, right ventricle strain; TAPSE, tricuspid annular plane systolic excursion; S<sub>r</sub>, tissue Doppler systolic velocity; SAMP, systemic mean artery pressure.

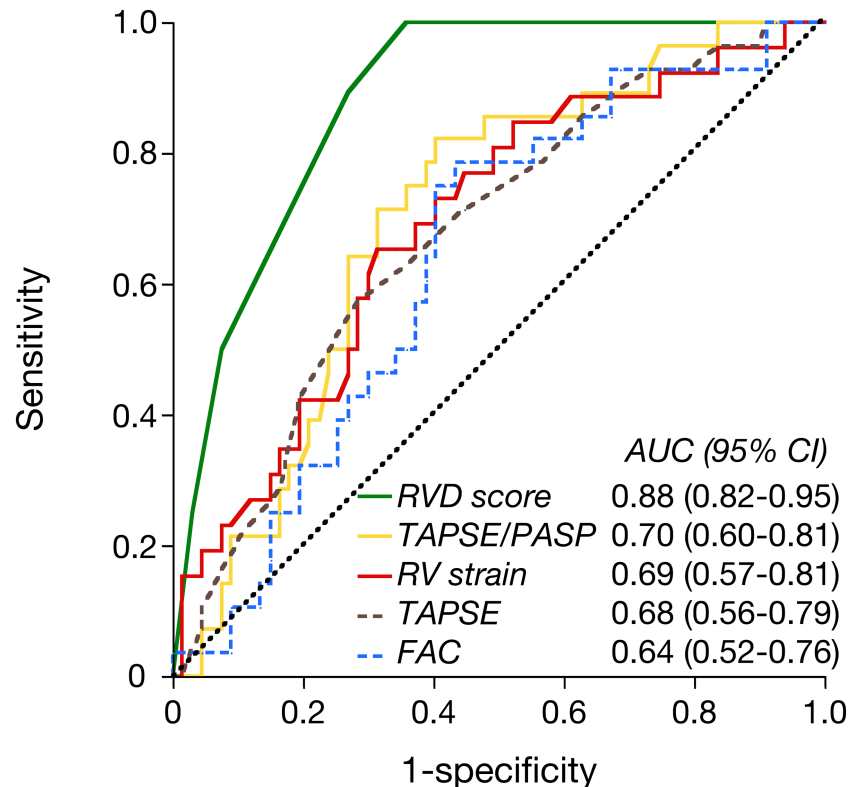
the RVD score, the contribution of echocardiography in the risk-assessment can be improved.

The principal mechanisms for the RVD in patients with LV disease are three-fold: firstly LV backward failure will cause a pressure load on the RV, secondly the underlying disease process might engage both the LV and RV myocardium,<sup>27</sup> and thirdly, LV dilatation and interventricular septal dysfunction will reduce the normally occurring LV contribution to RV systolic performance.<sup>2,10</sup> The longitudinal parameters have gained popularity because they are relatively easy to use, a moderate relation to RV ejection fraction have been documented,<sup>8,28,29</sup> and therefore, they are today commonly used alone to define RVD. We can argue against this practice for theoretical reasons that are supported by the findings in the present study. Myocardial performance, that is, the ability of the heart to generate a stroke volume, is determined by preload, afterload, and the myocardial contractility. The longitudinal parameters are surrogates for myocardial performance, which can be reduced due to intrinsic myocardial dysfunction (i.e. reduced contractility) or reduced solely due to loading conditions. The former situation with intrinsic dysfunction represents true RVD while the latter is a false positive RVD. Our results demonstrate the limitations of interpreting longitudinal function parameters in isolation from other parameters indicating RVD. Almost 20% with reduced RV<sub>Str</sub> did not have any other findings indicating RVD. These patients were characterized by low stroke volume

index and low filling pressures in both ventricles, which could be due to hypovolemia. The doses of loop diuretics did not differ between the two groups, but it could be a difference in diuretic susceptibility that explains the difference. Reduced RV<sub>Str</sub> then can be explained by a combination of a less pronounced Frank-Starling effect and for simple volumetric reasons.

Different echocardiographic parameters have been compared regarding their prognostic ability in patients with heart failure, and today deformation imaging for estimation of RV<sub>Str</sub> is regarded superior to TAPSE and tissue velocity.<sup>5,6,30</sup> These studies compare single echocardiographic longitudinal function parameters with each other. Recently, Cameli *et al.* established a prognostic echocardiographic multiparameter score in patients with LV disease and demonstrated a good predictive ability for major adverse cardiac events.<sup>31</sup> Interestingly, of the parameters that significantly differed between patients with or without major adverse cardiac events were three related to RV function (sphericity index, RV<sub>Str</sub>, and FAC) and only one to LV function (left atrium size). This is in agreement with our findings that more advanced LV dysfunction begets more advanced RVD. RVD including severe RVD in a patient with LV decompensation is often reversible, especially following the first echocardiographic assessment, due to optimization of medical therapy.<sup>10</sup> Persisting or developing RVD defined as reduced FAC, at re-evaluation, has been shown to have additive long-term prognostic importance

**Figure 4** Detection of severe RVD (RAP  $\geq 10$  mmHg) at right heart catheterization. The RVD score had the largest area under the curve compared with longitudinal parameters (RV<sub>Str</sub> & TAPSE), global FAC, and TAPSE/PASP. AUC, area under curve; CI, confidence interval; FAC, fractional area change; PASP, pulmonary artery systolic pressure; RV, right ventricular; RVD, right ventricular dysfunction; TAPSE, tricuspid annular plane systolic excursion.



**Table 3** Diagnostic performance of cut-off values indicating severe RVD using 5-point or 4-point RVD score

Variable	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)
5-point RVD score					
Rule in	$\geq 4$	50 (33–67)	93 (84–97)	6.7 (2.7–16.8)	0.54 (0.37–0.79)
Rule out	$\geq 2$	100 (87–100)	64 (52–75)	2.8 (2.0–3.8)	*
4-point RVD score					
Rule in	$\geq 3$	71 (53–85)	87 (76–93)	5.3 (2.8–10.2)	0.33 (0.18–0.60)
Rule out	$\geq 2$	96 (82–99)	67 (55–77)	2.9 (2.1–4.2)	0.05 (0.01–0.37)

CI, confidence interval; NLR, negative likelihood ratio; PLR, positive likelihood ratio.

\*Cannot be calculated due to 100% sensitivity.

compared with the baseline findings.<sup>16</sup> Importantly, it is not addressed in the present study but patients with LV disease will, most likely, change RVD score profile over time. The prognostic impact of improved, unchanged, or worsened RVD should be a topic of further studies comparing the novel RVD score with previously used single parameters<sup>3–6,30</sup> or other multiparameter scores.<sup>31</sup>

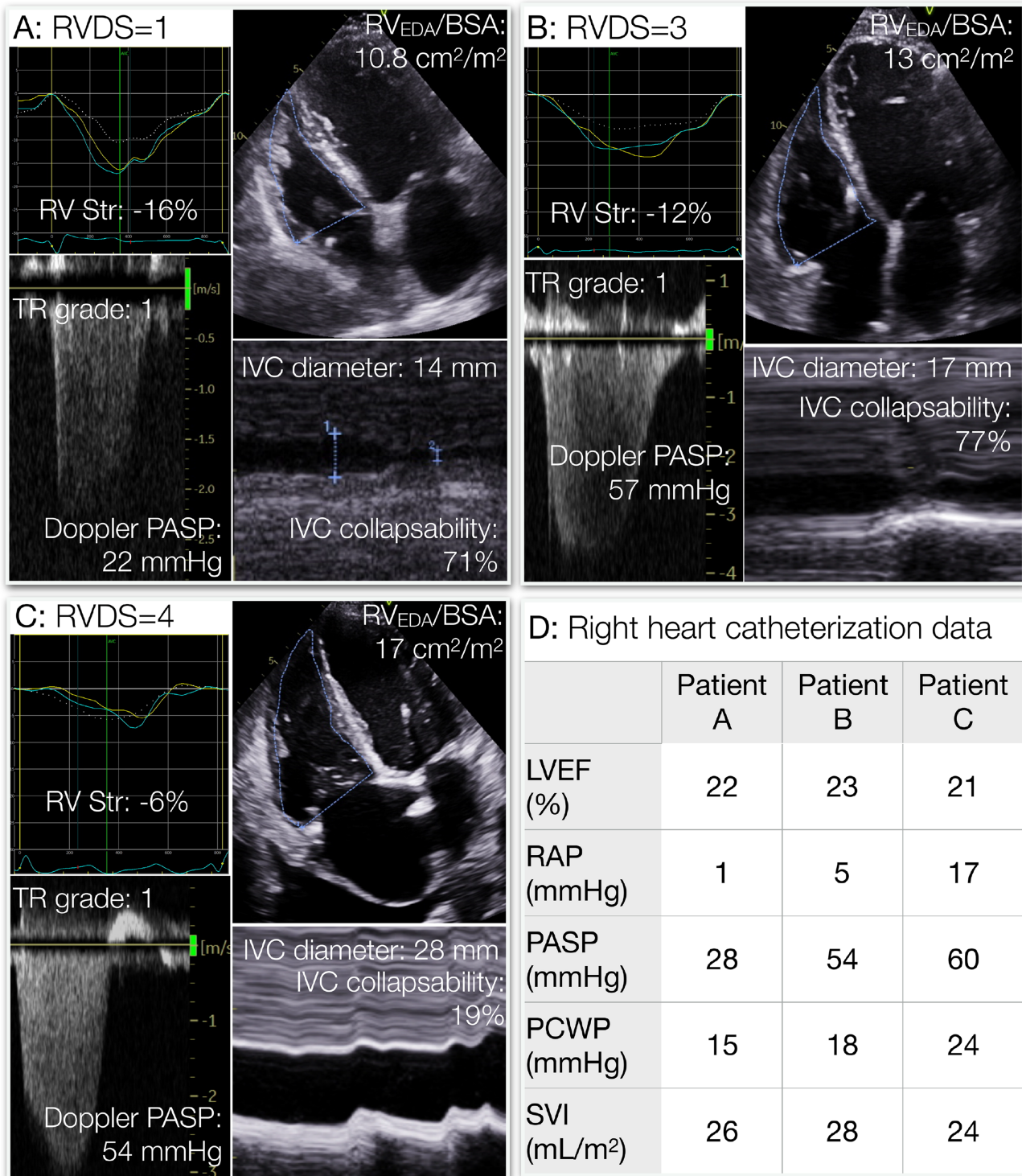
The finding of moderate or severe RVD in a patient with LV disease has therapeutic consequences. Our study results using the RVD score demonstrate how moderate or severe RVD indicate more severe LV dysfunction. On the contrary,

improved RV function has been shown to precede LV reverse remodelling.<sup>16</sup> Therefore, diagnostic tools are needed that can reliably monitor RV function as RV deterioration in a patient should raise the question if the treatment can be optimized.

### Study limitations

The study was retrospective and the population dominated by patients with advanced heart failure and dilated

**Figure 5** Echocardiographic findings and RVD score in three patients assessed as mild (A), moderate RVD (B), and severe RVD (C). Table (D) shows findings at right heart catheterization. IVC, inferior vena cava; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVD, right ventricular dysfunction; SVI, stroke volume index.



cardiomyopathy. To what extent our results can be extrapolated to patients with chronic but less symptomatic LV disease or other aetiologies is an important issue. A study should be conducted including stable patients with LV disease to investigate the ability of the RVD score and the longitudinal parameters to predict future events. Nine patients (9%) had chronic obstructive pulmonary disease but not of advanced stage. Importantly, the RVD score should be interpreted with caution in patients with comorbidities such as lung fibrosis, chronic obstructive pulmonary disease and connective tissue diseases due to possible pulmonary vascular disease. Enlargement of the RV is an important sign indicating RV uncoupling. Although a moderate relation has been documented between linear RV dimensions and RV volume by cardiac magnetic resonance,<sup>32</sup> it is well known that due to the complex RV anatomy, dilatation can pass unnoticed by echocardiography. It is conceivable that future use of 3D-based echocardiography can improve the detection of RV dilatation and allow assessment of RV ejection fraction.<sup>33</sup> The RV ejection fraction assessed by cardiac magnetic resonance provides independent prognostic information in patients with non-ischemic cardiomyopathy,<sup>34</sup> and with 3D echocardiography in patients with diverse cardiac disorders.<sup>35</sup> Further studies are needed to compare the prognostic impact of 3D RV ejection fraction with a multiparameter approach such as the RVD score. Tricuspid regurgitation  $\geq$  Grade 2 is one of the parameters included in the RVD score. Patients with more advanced LV disease often have a lead going through the tricuspid orifice. In the present study, there was no significant difference in tricuspid regurgitation severity comparing those who had a lead with those who did not. Still, the possibility that the lead causes significant regurgitation should be considered, and an effort made to visualize the lead trajectory, preferably using 3D echocardiography. Echocardiography and right heart catheterization were not performed simultaneously. It is therefore possible that especially the actual RAP was different at echocardiography and right heart catheterization. Furthermore, invasive measurements were performed during free-breathing that might introduce an underestimation of filling pressures. These errors can, however, not favour our results. In clinical practice, assessment of PASP by Doppler

is not possible in a substantial proportion of patients. However, the 4-point RVD score, excluding assessment of Doppler PASP, had comparable ability to rule-in and rule-out severe RVD as the 5-point score.

## Conclusions

Our new RVD score is based on the pathophysiology of RV decompensation and provides grading of RVD severity (mild, moderate, & severe) in a systematic and reproducible manner. The RVD score is a new diagnostic tool with better discriminative ability compared with longitudinal function parameters, with the potential to refine the diagnosis, improve follow-up of both RV and LV function, and assessment of prognosis in patients with heart failure. The study is a proof of concept based on a single-centre experience and calls for external validation.

## Conflict of interest

The authors have no conflict of interest to declare.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Correlation between parameters related to RVD and echocardiographic RVD score, longitudinal and global RV function parameters.

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