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Chapter 4

PROGNOSTIC VALUE OF RIGHT VENTRICULAR LONGITUDINAL PEAK SYSTOLIC STRAIN IN PATIENTS WITH PULMONARY HYPERTENSION

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ABSTRACT

Background

Right ventricular (RV) function is an important prognostic marker in patients with pulmonary hypertension. The present evaluation assessed the prognostic value of RV longitudinal peak systolic strain (LPSS) in patients with pulmonary hypertension.

Methods and Results

A total of 150 patients with pulmonary hypertension of different etiologies (mean age 59±15 years, 37.3% male) were evaluated. RV fractional area change and tricuspid annular plane systolic excursion index were evaluated with 2-dimensional echocardiography. RV LPSS was assessed with speckle tracking echocardiography. The patient population was categorized according to a RV LPSS value of -19%. Among several clinical and echocardiographic parameters, the significant determinants of all-cause mortality were evaluated. There were no significant differences in age, sex, pulmonary hypertension etiology and left ventricular ejection fraction between patients with RV LPSS <-19% and patients with RV LPSS ≥-19%. However, patients with RV LPSS ≥-19% had significantly worse NYHA functional class (2.7±0.6 vs. 2.3±0.8, p=0.003) and lower tricuspid annular plane systolic excursion (16±4 mm vs. 18±3 mm, p<0.001) than their counterparts. During a median follow-up of 2.6 years, 37 patients died. RV LPSS was a significant determinant of all-cause mortality (HR 3.40, 95% CI 1.19-9.72, p=0.02).

Conclusion

In patients with pulmonary hypertension, RV LPSS is significantly associated with all-cause mortality. RV LPSS may be a valuable parameter for risk stratification of these patients. Future studies are needed to confirm these results in the pulmonary hypertension subgroups.

INTRODUCTION

Pulmonary hypertension is associated with high mortality.[1] Several echocardiographic parameters have been related to all-cause mortality in this population, including pulmonary artery pressure (PAP), parameters of right ventricular (RV) function such as tricuspid annular plane systolic excursion (TAPSE), right atrial (RA) dimensions, and the presence of pericardial effusion.[2,3] Particularly, RV function has been identified as one of the main prognostic determinants in patients with pulmonary hypertension.[4-6] Therefore, accurate evaluation of RV function is relevant in the clinical management of these patients. However, the complex RV geometry may challenge the assessment of RV dimensions and function with 2-dimensional imaging modalities.[7, 8] Conventional functional parameters such as TAPSE and RV fractional area change (FAC) measured with 2-dimensional echocardiography are frequently applied in the evaluation of RV function. Current guidelines for the diagnosis and treatment of patients with pulmonary hypertension include TAPSE and RV FAC for risk stratification of these patients.[5,7,9] However, the assumption that the measurement of TAPSE at a single side represents the global function of the right ventricle is a limitation.

Two-dimensional speckle tracking is a novel technique that provides angle-independent assessment of regional myocardial deformation[10] and does not rely on geometrical assumptions. Compared with normal controls, patients with pulmonary hypertension have shown more impaired values of RV longitudinal strain as assessed with speckle tracking. In addition, RV longitudinal strain has been associated with systolic pulmonary arterial pressure (SPAP) and RV dimensions.[11,12] To date, little is known about the prognostic value of RV longitudinal strain in patients with pulmonary hypertension. Accordingly, the aim of this study was to evaluate the prognostic value of RV longitudinal peak systolic strain (LPSS) in patients with pulmonary hypertension.

METHODS

Patient population and data collection

A total of 150 patients diagnosed with pulmonary hypertension between 2004 and 2010 were retrospectively evaluated. Diagnosis of pulmonary hypertension was defined as mean PAP ≥ 25 mm Hg assessed with right heart catheterization, or SPAP ≥ 36 mm Hg estimated with echocardiography.[9] All patients were extensively screened in order to establish the diagnosis of pulmonary hypertension. According to the institutional protocol, all patients underwent a 2-dimensional transthoracic echocardiography to noninvasively quantify RV pressures, RV dimensions and function and to evaluate the cause of pulmonary hypertension.[7,13] Invasive measurement of pulmonary pressures was performed with right heart catheterization when the SPAP was ≥ 36 mm Hg as assessed with echocardiography.[9,11] However, right heart catheterization was not systematically performed when the underlying cause of pulmonary hypertension was indisputably left sided heart failure or pulmonary disease and this invasive evaluation would not have further therapeutic consequences. In addition, the underlying etiology following the Dana Point classification was determined:[9] group 1 or pulmonary arterial hypertension due to primary disease process in the pulmonary arteries, group 2 or pulmonary hypertension due to underlying left heart disease, group 3 or pulmonary hypertension due to pulmonary and hypoxic disease, group 4 or pulmonary hypertension due to chronic thromboembolic disease and group 5 or pulmonary hypertension due to multifactorial

mechanisms.[9] Patients with complex congenital heart disease, poor acoustic echocardiographic windows or with significant pericardial effusion were excluded.

Clinical evaluation included the assessment of New York Heart Association (NYHA) functional class and comprehensive evaluation of demographics, cardiovascular risk factors and medical treatment. Coronary artery disease was defined by history of prior myocardial infarction, coronary revascularization or significant coronary artery lesions as assessed with anatomic (computed tomography coronary angiography or invasive coronary angiography) tests. RV LPSS was measured with speckle tracking strain echocardiography.[11,12,14]

Clinical and echocardiographic data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands) and the echocardiography database and were retrospectively analyzed. All patients were followed-up for the occurrence of all-cause mortality. The significant determinants of all-cause mortality were derived from the various clinical and echocardiographic variables. The Institutional Review Board of the Leiden University Medical Center approved this retrospective evaluation of clinically collected data, and waived the need for written informed consent.

Echocardiography

Images were obtained with the patient in the left lateral decubitus position using a commercially available system (Vivid 7 and E9, General Electric-Vingmed, Milwaukee, Wisconsin). All data were acquired in the parasternal, apical and subcostal views using 3.5 MHz and M5S transducers. Conventional 2-dimensional, color, pulsed, and continuous wave Doppler data were obtained during breath-hold and 3 consecutive beats were stored in cine-loop format. In order to obtain accurate 2-dimensional speckle tracking analysis of myocardial deformation, depth, image sector and frame rate (>40 fps) were adjusted. Analysis of the images was performed offline using dedicated software (EchoPac 110.0.0, General Electric-Vingmed, Horten, Norway).

Left ventricular (LV) volumes and function were evaluated measuring the end-diastolic and end-systolic volumes and ejection fraction (EF) by the Simpson's method.[13] RV dimensions and function were evaluated by measuring the RV FAC and the TAPSE index, as recommended by current guidelines.[7] RA area was traced in the apical 4-chamber view at the end of ventricular systole.[7] The RV pressure was estimated by calculating the maximum velocity of the tricuspid regurgitant jet using the modified Bernoulli equation. The RA pressure was estimated by measuring the diameter and the inspiratory collapse of the vena cava inferior. Right atrial pressure was estimated as 3 mm Hg if the inferior vena cava (IVC) diameter was ≤ 2.1 cm and did collapse >50% with a sniff, 15 mm Hg if the IVC diameter was >2.1 cm and collapsed <50% with a sniff, and 8 mm Hg if the IVC diameter and collapse did not fit this paradigm.[7] By adding the RV pressure to the RA pressure, the SPAP was estimated. Pericardial effusion was evaluated in the parasternal long-axis and short-axis.[15] Patients with significant pericardial effusion were excluded from further analysis, as previously mentioned.

Two-dimensional speckle tracking analysis

Speckle tracking analysis of the RV was performed from the apical 4-chamber view images, using commercially available software (EchoPac 110.0.0, General Electric-Vingmed, Horten, Norway). Although this methodology has been primary and extensively tested to assess left ventricular

performance, several reports have shown its feasibility and accuracy to evaluate RV function.[16,17] As previously described, the endocardial border of the RV free wall was manually traced at end-systole and automatically adjusted to include the entire myocardium.[18] Subsequently, the region of interest was manually adjusted to the thickness of the myocardium to ensure proper tracking.[10,19] As previously reported, the inter- and intra-observer variabilities of our laboratory for the measurement of longitudinal strain were 0.9±1.0% and 1.2±0.5%, respectively.[10,18,20] RV LPSS was measured in the basal, mid-ventricular and apical segments of the RV free wall and calculated as the average of the three segments (Figure 1). RV LPSS is defined as the percentage of myocardial shortening relative to the original length and is conventionally presented as a negative value. Therefore, the more negative the value of RV LPSS is, the more preserved is the shortening.

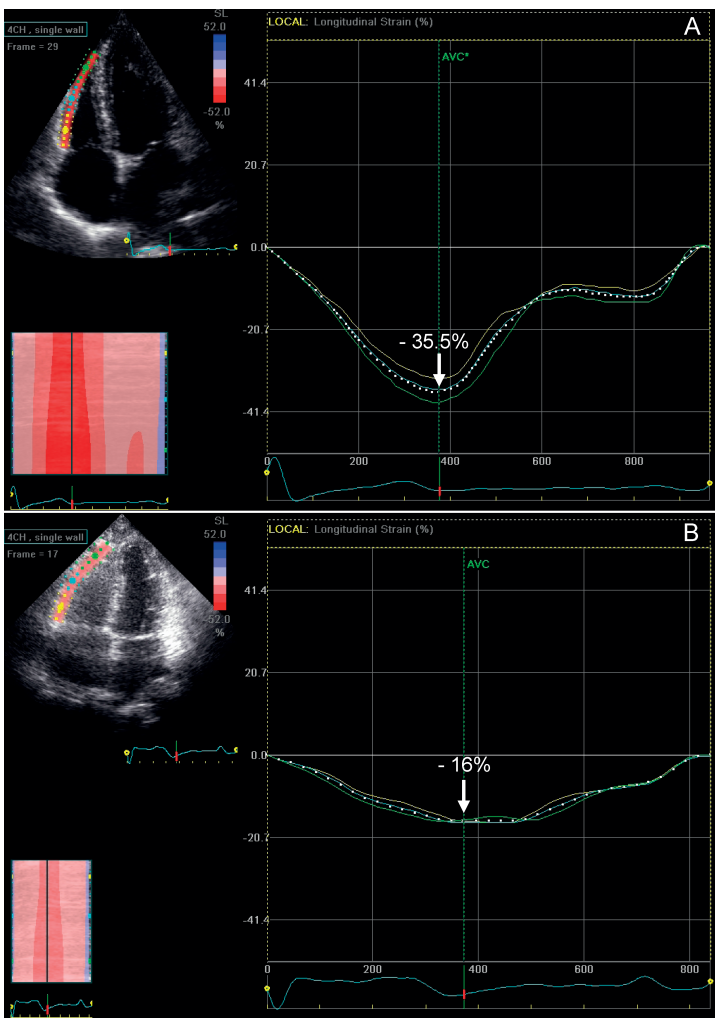

Figure 1. Right ventricular strain assessment of the right ventricular free wall in the apical 4-chamber view in a patients with RV LPSS value of < -19% (panel A) and in a patient with RV LPSS value of ≥ -19% (panel B).

Follow-up

All patients received optimal treatment according to current recommendations[9] and were regularly evaluated at the outpatient clinic and followed-up for the occurrence of the primary end point, all-cause mortality.

Statistical analysis

Continuous data are presented as mean ± standard deviation and categorical data are presented as percentages or frequencies. Baseline characteristics were compared between groups using the Student t test or the χ^2 test. The patient population was categorized according to the RV LPSS cut-off value of -19 %.[12] Cumulative survival estimates of the two patient groups were calculated with the Kaplan-Meier method, considering the date of the first echocardiography as onset of follow-up. The significant determinants of all-cause mortality were assessed with the Cox proportional hazard model. Clinical and echocardiographic relevant variables, including age, sex, NYHA class, LVEF, RA area and SPAP were analyzed in a multivariable model. Variables with a p-value <0.1 in this multivariable analysis were then included in non-nested multivariable Cox proportional hazard models to test the prognostic value of RVFAC, TAPSE and RV LPSS separately. RVFAC was introduced as continuous variable whereas TAPSE and RV LPSS were introduced both as continuous and as dichotomous variables based on previous reports (≤1.8 cm and ≥-19%, respectively).[5,12] The incremental value of each parameter of RV function (RVFAC, TAPSE, and RV LPSS) over the baseline model that included age, NYHA functional class, LVEF, and SPAP was assessed by calculating the change in χ^2. RV FAC, TAPSE and RV LPSS were introduced in a conditional forward stepwise method. The relative fit of the models was calculated with the -2 log likelihood. Finally, survival analyses, using the Kaplan-Meier method and univariable Cox proportional hazard model with RV LPSS as continuous variable and as dichotomous variable (≥-19%), were performed in the patient population after exclusion of patients in Dana Point group 2 and within the Dana Point group 2. A p-value <0.05 was considered statistically significant. All data were analyzed using the package SPSS (SPSS® 17.0 for windows, SPSS Inc, Chicago, USA). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

RESULTS

Patient characteristics

Eight patients were excluded because of poor echocardiographic image quality, leading to a feasibility of RV LPSS measurement of 94.7%. Table 1 summarizes the clinical and echocardiographic characteristics of the remaining 142 patients.

Based on a prespecified cut-off value of RV LPSS, the patient population was categorized into two groups: patients with RV LPSS <-19% (more preserved RV myocardial shortening) (n = 46) and patients with RV LPSS ≥-19% (more impaired RV myocardial shortening) (n = 96).[12] Both groups of patients were comparable in terms of age, sex, body surface area, and distribution of pulmonary hypertension etiology according to the Dana point classification.[9] There was no difference in cardiovascular risk factors between the two groups. However, patients with RV LPSS ≥-19% tended to show higher prevalence of coronary artery disease compared with patients with RV LPSS < -19% (25%

Table 1. Patient characteristics

Clinical characteristics	RV LPSS<-19% (n=46)	RV LPSS≥-19% (n=96)	*P* value
Age, y	59.8 ± 16.2	58.5 ± 15.3	0.64
Male, n (%)	16 (35)	37 (39)	0.67
BSA, m^2	1.8 ± 0.2	1.8 ± 0.3	0.55
BMI, kg/ m^2	25.0 ± 4.9	26.1 ± 5.4	0.23
NYHA	2.3 ± 0.8	2.7 ± 0.6	0.003
Pulmonary hypertension group, n (%)	46	96	0.17
I, PAH	18 (39)	35 (37)	
II, heart disease	13 (28)	33 (34)	
III, pulmonary disease	8 (17)	24 (25)	
IV, CTEPH	4 (9)	3 (3)	
V, miscellaneous	3 (7)	1 (1)	
Coronary artery disease, n (%)	5 (11)	24 (25)	0.051
Hypercholesterolemia, n (%)	9 (20)	25 (26)	0.40
Diabetes mellitus, n (%)	6 (13)	22 (23)	0.17
Smoker, n (%)	7 (15)	10 (10)	0.41
Hypertension, n (%)	11 (24)	29 (30)	0.43
Medical treatment, n (%)			
Oral endothelin receptor antagonist	11 (24)	26 (27)	0.69
Phosphodiesterase-5 inhibitor	7 (15)	12 (13)	0.66
Beta-blockers	14 (30)	30 (31)	0.92
ACE/AT II	14 (30)	44 (46)	0.08
Diuretics	24 (52)	67 (70)	0.04
Anticoagulation	16 (35)	48 (50)	0.09
Echocardiographic characteristics			
LVEDV, ml	95.3 ± 37	97.1 ± 32	0.77
LVESV, ml	44.0 ± 22	46.5 ± 21	0.52
LVEF, %	54.7 ± 10	52.8 ± 10	0.30
RVEDA, mm^2	19.7 ± 5.3	23.0 ± 7.0	0.006
RVESA, mm^2	12.6 ± 4.3	15.6 ± 5.9	0.003
RVFAC, %	37 ± 9	33 ± 10	0.03
TAPSE, mm	18 ± 3	16 ± 4	<0.001
SPAP, mm Hg	59 ± 20	64 ± 21	0.14
RV LPSS, %	- 23.5 ± 3.7	- 14 ± 3.5	-

ACE: angiotensin-converting-enzyme inhibitor; AT II: angiotensin II receptor antagonist; BSA: body surface area; CTEPH: chronic thromboembolic pulmonary hypertension; DM: diabetes mellitus; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; RVEDA: right ventricular end-diastolic area; RVFAC: right ventricular fractional area change; RV LPSS: right ventricular longitudinal peak systolic strain; RVESA: right ventricular end-systolic area; SPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion

vs. 11%, respectively; p=0.051). The patient group with RV LPSS value ≥-19% had a significantly worse NYHA functional class compared with patients with RV LPSS <-19% (2.7±0.6 versus 2.3±0.8, p=0.003). There were no significant differences in LV ejection fraction, LV dimensions or SPAP between both groups of patients. The mean values of TAPSE and RVFAC were significantly lower in the group of

patients with RV LPSS ≥-19% as compared to the group of patients with RV LPSS <-19% (TAPSE: 16 ± 4 mm versus 18 ± 3 mm, p<0.001; RVFAC: 33 ± 10% versus 37 ± 9%, p=0.03, respectively).

There were no significant differences in terms of pulmonary hypertension specific treatment with oral endothelin receptor antagonists or phosphodiesterase-5 inhibitors between the two groups of patients. Both groups of patients were also comparable in use of beta-blockers and angiotensin-converting enzyme inhibitors or angiontensin II receptor antagonists. However, the group of patients with RV LPSS ≥-19% received significantly more diuretics compared with the patients with RV LPSS <-19% (70% versus 52%, p=0.04).

Clinical Outcome

During a median follow-up of 31.2 months (interquartile range of 10 – 50 months), 37 (26%) patients with pulmonary hypertension died. There were no patients lost at follow-up. In the group of patients with RV LPSS <-19%, the cumulative survival rates at 1, 3 and 5 years follow-up were 93%, 90%, and 90%, respectively. In contrast, the group of patients with RV LPSS ≥-19% showed worse long-term outcome with survival rates of 77% at 1 year, 66% at 3 years and 55% at 5 years follow-up (log-rank p=0.002) (Figure 2). After exclusion of patients from the Dana Point group 2, patients with RV LPSS ≥-19% had significantly worse survival in comparison to patients with RV LPSS <-19% (log-rank p=0.001) (Figure 3). In contrast, within the Dana Point group 2, categorization of patients based on RV LPSS <-19% or ≥-19% did not result in significant survival rates differences (log-rank p=0.46).

Prognostic value of RVLPSS in patients with pulmonary hypertension

Table 2 shows the univariable and multivariable analyses to identify the significant determinants of all-cause mortality among various clinical and echocardiographic variables. Age, NYHA functional class, and LVEF and SPAP (all with a p<0.1) were introduced in non-nested multivariable models

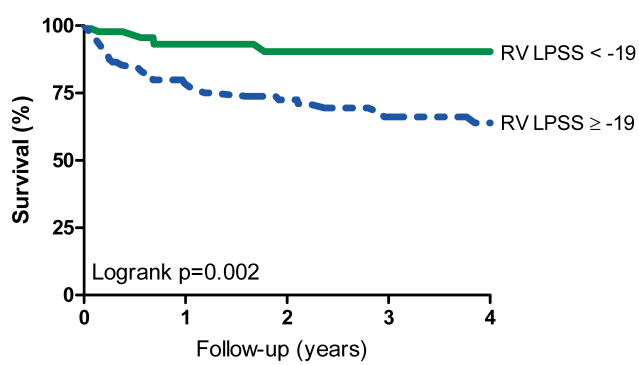

Figure 2. Kaplan Meier survival curves of total patient population. Kaplan Meier survival curve for patients with a right ventricular longitudinal peak systolic strain (RV LPSS) < -19% (solid line) and patients with a RV LPSS ≥ -19% (dotted line). During a median follow-up of 31.2 months (interquartile range of 10 – 50 months) 37 (26%) patients had died. Patients with RV LPSS ≥ -19% had significant worse survival than patients with RV LPSS < -19%.

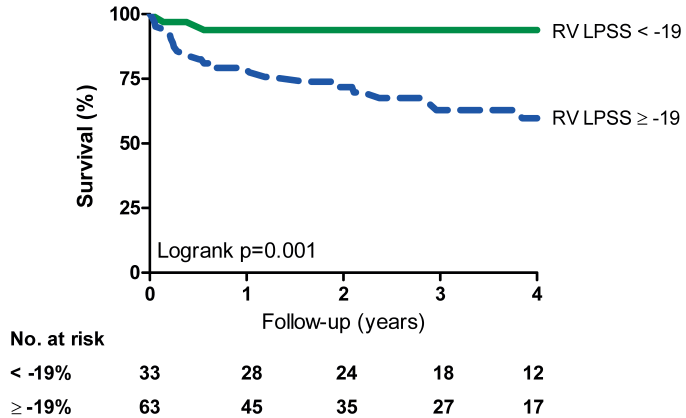

Figure 3. Kaplan Meier survival curves of patient population after exclusion of patients with left heart disease (Dana Point group 2). Kaplan Meier survival curve for patients with a right ventricular longitudinal peak systolic strain (RV LPSS) < -19% (solid line) and patients with a RV LPSS ≥ -19% (dotted line). Patients with RV LPSS ≥ -19% had significant worse survival than patients with RV LPSS < -19%.

Table 2. Uni- and multivariable Cox regression proportional hazard ratio analyses to identify determinants of all-cause mortality in patients with pulmonary hypertension

	Univariable			Multivariable		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age, y	1.03	1.01 – 1.06	0.009	1.04	1.01 – 1.08	0.007
Sex	0.58	0.30 – 1.12	0.105	0.60	0.29 – 1.22	0.16
BMI, kg/m^2	0.96	0.90 – 1.032	0.291			
NYHA class	2.76	1.56 – 4.88	<0.001	3.10	1.60 – 5.99	0.001
LVEF, %	1.03	0.99 – 1.06	0.141	1.05	1.01 – 1.09	0.015
RA area, cm^2	1.06	1.02 – 1.10	0.006	1.02	0.98 – 1.07	0.410
SPAP, mm Hg	1.01	0.99 – 1.02	0.356	1.02	0.99 – 1.03	0.098
Coronary artery disease	0.75	0.31 – 1.79	0.513			
PH etiology*			0.654			
Group I	Reference					
Group II	0.97	0.43 – 2.19	0.945			
Group III	1.63	0.71 – 3.71	0.248			
Group IV	0.48	0.06 – 3.64	0.476			
Group V	1.09	0.14 – 8.28	0.935			

BMI: body mass index; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PH: pulmonary hypertension; RA area: right atrial area; SPAP: systolic pulmonary arterial pressure. *According to Dana Point classification[9]

to test the multivariable-adjusted associations between RVFAC, TAPSE and RV LPSS and all-cause mortality (Table 3). RVFAC and TAPSE, introduced as continuous variables, were not significant determinants of all-cause mortality. However, when TAPSE was introduced as dichotomous variable, using the cut-off value of 18 mm as previously reported,[5] patients with TAPSE ≤ 18 mm had a trend

Table 3. Cox multivariable regression analysis to test the prognostic value of RV FAC, TAPSE and RV LPSS.

	HR	95% CI	p-value	Model χ^2	Significance from baseline	-2 log likelihood
Baseline model + RVFAC				27.8	0.56	281
Age, y	1.05	1.02 – 1.08	0.001			
NYHA class	3.37	1.78 – 6.37	<0.001			
LVEF, %	1.03	0.99 – 1.07	0.09			
SPAP, mm Hg	1.02	0.99 – 1.03	0.09			
RVFAC, %	0.99	0.95 – 1.03	0.56			
Baseline model + TAPSE (mm)				28.6	0.23	280
Age, y	1.05	1.02 – 1.07	0.001			
NYHA class	2.93	1.59 – 5.39	0.001			
LVEF, %	1.04	1.00 – 1.09	0.04			
SPAP, mm Hg	1.02	0.99 – 1.03	0.07			
TAPSE, mm	1.06	0.96 – 1.15	0.23			
Baseline model + TAPSE ≤ 18 mm				30.2	0.07	278
Age, y	1.05	1.02 – 1.08	0.001			
NYHA class	2.92	1.60 – 5.32	<0.001			
LVEF, %	1.04	1.002 – 1.08	0.04			
SPAP, mm Hg	1.02	1.001 – 1.04	0.04			
TAPSE ≤ 18mm	2.14	0.89 – 5.13	0.09			
Baseline model + RV LPSS (%)				33.4	0.001	283
Age. y	1.04	1.01 – 1.07	0.002			
NYHA class	2.69	1.43 – 5.07	0.002			
LVEF, %	1.03	0.99 – 1.07	0.09			
SPAP, mm Hg	1.01	0.99 – 1.03	0.21			
RV LPSS, %	1.13	1.05 – 1.22	0.001			
Baseline model + RV LPSS ≥ -19 %	30.6	0.008	287			
Age, y	1.04	1.02 – 1.07	0.001			
NYHA class	2.63	1.43 – 4.84	0.002			
LVEF, %	1.03	0.99 – 1.07	0.09			
SPAP, mm Hg	1.01	0.99 – 1.03	0.12			
RV LPSS ≥ 19 %	3.40	1.19 – 9.72	0.02			

Baseline model χ^2: 26.0
LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; RA area: right atrial area; RVFAC: right ventricular fractional area change; RV LPSS: right ventricular longitudinal peak systolic strain; SPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion

towards an increased risk of all-cause mortality (HR 2.14; 95% CI 0.89 – 5.13, p=0.09). In contrast, RV LPSS as continuous or dichotomous variable (<-19% vs. ≥-19%) remained a significant determinant of all-cause mortality. With every 1% increase in RV LPSS (less negative) the risk of death increased by 13% (HR 1.13; 95% CI 1.05 – 1.22, p=0.001) and patients with RV LPSS ≥-19% had a three-fold risk of all-cause mortality (HR 3.40; 95% CI 1.19 – 9.72, p=0.02) (Table 3). After exclusion of patients with left heart disease (Dana Point 2), RV LPSS remained an unadjusted significant determinant of all-cause mortality, both as continuous variable (HR 1.16; 95% CI 1.07 – 1.26, p<0.001) and as dichotomous variable (RV LPSS ≥-19%: 7.45 (95% CI 1.76 – 31.56, p=0.006).

Incremental value of RV LPSS

The addition of RV FAC and TAPSE as continuous variables to the baseline model including age, NYHA functional class, LVEF, and SPAP did not provide a significant incremental prognostic value over the baseline model (Table 3). When TAPSE was introduced as dichotomous variable, the χ^2 tended to increase (from 26 to 30.2, p=0.07). Importantly, the addition of RV LPSS to the baseline model led to a significant increment of the χ^2 value (from 26 to 33.4, p=0.001) (Table 3). Therefore, RV LPSS provides incremental prognostic value over well-known clinical variables, including NYHA functional class, and echocardiographic parameters. The relative fit of the non-nested models including RV FAC, TAPSE and RV LPSS is represented by the -2log likelihood in Table 3. These results indicate that RV LPSS may provide the model with the best fit.

DISCUSSION

The main finding of the present evaluation is that RV LPSS is a significant determinant of all-cause mortality in patients with pulmonary hypertension. Patients with RV LPSS ≥-19% had more than a three-fold mortality risk compared with patients with RV LPSS <-19%.

Conventional echocardiographic assessment of right ventricular function in pulmonary hypertension

RV function has been closely associated to survival in patients with pulmonary hypertension.[6] Several previous studies have reported the prognostic value of RV function parameters, such as TAPSE and RV FAC, in this population.[2,3,5] RV function is therefore an established parameter of relevance for risk stratification of these patients. Echocardiography is the most widely available tool to evaluate RV performance. However, conventional echocardiographic measurements of RV function are not always reliable due to the complex geometry of the right heart chamber and varying loading conditions.[21] TAPSE is a widely used measurement that evaluates longitudinal excursion of the tricuspid annulus towards the apex and it is recommended by the current guidelines as a surrogate of RV function because of its applicability in the majority of the patients.[7,9] In addition, TAPSE has been demonstrated as a prognostic marker in pulmonary hypertension patients in previous studies.[4,5] In the current evaluation, however, TAPSE was not a significant predictor of all-cause mortality, although when introduced as dichotomous variable,[5] its predictive value improved. TAPSE is measured at a single site and may not always represent adequately global RV function. Furthermore, validation studies showed varying results regarding its accuracy in measuring RV function.[22,23] It has been reported that RV FAC correlates well with MRI-derived RV EF[5,23] and the current guidelines recommend measuring RV FAC as quantitative parameter of RV function.[7] However, the measurement of this parameter has shown to be less reproducible as compared with TAPSE.[5] Furthermore, in the current study, RV FAC was not a significant predictor of all-cause mortality.

RV Strain

Two-dimensional strain imaging is a novel method to assess myocardial function independent of the insonation angle of the ultrasound beam.[10] Speckle tracking derived strain has been developed for the assessment of LV deformation. Nevertheless, previous studies have demonstrated the value

of measuring RV strain in order to detect changes in RV function in several populations.[16,17] Previous studies demonstrated that 2-dimensional speckle tracking strain imaging is a useful modality in the assessment of RV function.[11,14,24] RV longitudinal strain assessed with speckle tracking strain imaging is significantly impaired in patients with pulmonary hypertension and it is inversely correlated with SPAP and RV dimensions.[11,12] In a recent study, a RV LPSS cutoff value of -19% permitted discrimination between normal and impaired RV systolic function in a series of 100 healthy volunteers and in 76 patients with RV dysfunction.[12] Similarly, in the current study, patients with pulmonary hypertension and RV LPSS ≥-19% had significantly worse RV function assessed by TAPSE and RVFAC and significantly larger RV dimensions compared to patients with RV LPSS <-19%. However, the prognostic implications of RV LPSS in this specific group of patients have remained largely unknown.

Prognostic value of RV LPSS in patients with pulmonary hypertension

To date, only one study has demonstrated the prognostic value of RV LPSS in patients with pulmonary arterial hypertension. In a series of 80 patients with Dana Point classification group 1 pulmonary arterial hypertension, Sachdev and colleagues demonstrated that patients showing RV LPSS ≥-12.5% had worse 4-year survival compared with patients who had RV LPSS<-12.5%.[25] In contrast to the present study, the population evaluated by Sachdev et al comprised patients with functional class III and IV symptoms, the most severe and impaired form of pulmonary hypertension. Accordingly, the cut-off value of RV LPSS reported in the study by Sachdev et al was remarkably lower than the cut-off value proposed in the present study. Furthermore, the present study extends current evidence by assessing the prognostic value of RV LPSS measured in a broad spectrum of patients with pulmonary hypertension, according to the currently recommended Dana Point classification.[9] In addition, patients with RV LPSS ≥-19% had more than a three-fold risk of all-cause mortality, even when corrected for NYHA functional class and SPAP, established predictive parameters of mortality in patients with pulmonary hypertension. RV FAC and TASPE were included as established parameters or RV function in the multivariable models, but were not significant predictors of all-cause mortality. Similar results were observed by Sachdev and colleagues.[25] Furthermore, RV LPSS provided incremental prognostic value to a baseline model including age, NYHA functional class, LVEF, and SPAP in this study. The inclusion of group 2 (pulmonary hypertension in patients with left sided heart disease) could introduce a confounding effect. However, the presence of coronary heart disease or left sided heart disease was not a significant risk factor for all-cause mortality in this study population. RV LPSS remained as significant predictor of all-cause mortality after the exclusion of patients with left heart disease of the Dana Point group 2. In contrast, unadjusted univariate analysis performed within the Dana Point group 2 did not demonstrate the prognostic value of RV LPSS. The limited number of patients included in this group may have precluded obtaining significant differences in survival rates. Therefore, RV LPSS may be a valuable parameter for risk stratification of patients with pulmonary hypertension in addition to other clinical and echocardiographic parameters, bearing in mind that, in certain subgroups of patients, additional studies with larger populations are needed to confirm the results.

Limitations

Several limitations have to be acknowledged. First, two-dimensional speckle tracking echocardiography is dependent on image quality. In the current study 8 patients had poor acoustic window and speckle tracking analysis was not reliable. Therefore, these patients were excluded from the analysis yielding a feasibility of RV LPSS measurement of 94.7%, which is in line with other papers.[16, 26] In addition, in patients with pulmonary hypertension Dana point classification 2 and 3, right heart catheterization and invasive measurement of pulmonary pressures and pulmonary vascular resistance were not systematically performed. In the present study the follow-up time was relatively short and all-cause mortality was the only outcome available, therefore, the association between RV LPSS and other outcome measures, such as heart failure, warrant further studies. Considering the small number of patients of the different pulmonary hypertension groups, this study was underpowered to perform subgroup analyses. The different pathophysiological mechanisms underlying pulmonary hypertension in each Dana Point group should be taken into consideration. Further studies, with larger patient populations and longer follow-up, are needed to evaluate the incremental prognostic value of RV LPSS in each of the pulmonary hypertension groups of the Dana Point classification to confirm these results.

Conclusion

RV LPSS is a significant prognostic determinant in patients with pulmonary hypertension. In the present study, RV LPSS provides incremental value over other well-known clinical and echocardiographic predictors of mortality. RV LPSS may be a useful technique for risk stratification of patients with pulmonary hypertension. Future studies are needed to confirm these results across the different underlying pathophysiologies and groups of pulmonary hypertension.

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