Chapter 5

IMPACT OF RIGHT VENTRICULAR DYSSYNCHRONY ON LEFT VENTRICULAR PERFORMANCE IN PATIENTS WITH PULMONARY HYPERTENSION

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ABSTRACT

Pulmonary hypertension has been associated with right ventricular (RV) dyssynchrony which may induce left ventricular (LV) dysfunction and dyssynchrony through ventricular interdependence. The present study evaluated the influence of RV dyssynchrony on LV performance in patients with pulmonary hypertension. One hundred and seven patients with pulmonary hypertension (age 63 ± 14 years, systolic pulmonary arterial pressure 60 ± 19 mm Hg) and LV ejection fraction (EF) >35 % were evaluated. Ventricular dyssynchrony was assessed with speckle tracking echocardiography and defined as the standard deviation of the time to peak longitudinal strain of six segments of the RV (RV-SD) and the LV (LV-SD) in the apical four-chamber view. Mean RV-SD and LV-SD assessed with longitudinal strain speckle tracking echocardiography were 51 ± 28 ms and 47 ± 21 ms, respectively. The patient population was divided according to the median RV-SD value of 49 ms. Patients with RV-SD ≥49 ms had significantly worse NYHA functional class (2.7 ± 0.7 vs. 2.3 ± 0.7, p = 0.004), RV function (tricuspid annular plane systolic excursion: 16 ± 4 mm vs. 19 ± 4 mm, p <0.001), LVEF (50 ± 10 % vs. 55 ± 8 %, p = 0.001), and larger LV-SD (57 ± 18 ms vs. 36 ± 18 ms, p < 0.001). RV-SD significantly correlated with LV-SD (r = 0.55, p < 0.001) and LVEF (r = -0.23, p = 0.02). Multiple linear regression analysis showed an independent association between RV-SD and LV-SD (β = 0.35, 95 %CI 0.21–0.49, p < 0.001). RV dyssynchrony is significantly associated with LV dyssynchrony and reduced LVEF in patients with pulmonary hypertension.

INTRODUCTION

Pulmonary hypertension (PH) is a serious disease with high morbidity and mortality in which increased pulmonary pressures lead to right ventricular (RV) dilatation and dysfunction.[1] RV dysfunction is one of the main determinants of long-term outcome of patients with PH.[2-4] Importantly, the effects of chronically increased pulmonary pressures are not limited to the RV but also to the left ventricle (LV), causing LV dysfunction and further impairing the outcome of patients with PH. RV remodeling with dilatation, hypertrophy and leftward deviation of the interventricular septum leads to reduced diastolic compliance and contractility and impairs LV filling.[5] Furthermore, electrophysiological remodeling of the RV has been described in patients with PH.[6] Slow conduction and prolonged action potential duration cause a delayed RV peak myocardial shortening of the lateral free wall relative to the septum and lateral LV wall.[5-7] This interventricular dyssynchrony leads to reduced LV filling and stroke volume. The assessment of RV and LV dyssynchrony in patients with PH is still debated. RV pacing has recently shown to improve stroke volume in patients with chronic thromboembolic pumonary hypertension.[8] However, it remains unclear if these beneficial effects may also be observed in other groups of patients with PH. Further knowledge on the presence of RV and LV dyssynchrony and their interdependence may result in novel pacing strategies that correct the interventricular and intraventricular mechanical dyssynchrony in patients with PH of varying pathophysiology.

Two-dimensional speckle tracking echocardiography allows for angle-independent evaluation of myocardial deformation and can provide comprehensive information on intraventricular mechanics, including RV and LV dyssynchrony.[9] The purpose of this evaluation was to assess the influence of RV dyssynchrony, measured with speckle tracking echocardiography, on LV performance in two different patients groups with PH: pulmonary arterial hypertension and PH caused by left heart disease with LV ejection fraction (EF) >35%.

METHODS

One hundred and seven patients with PH and LVEF >35 % were evaluated. PH was defined by the presence of systolic pulmonary arterial pressure (SPAP) ≥36 mm Hg on echocardiography or mean PAP ≥25 mm Hg at right heart catheterization. Fifty patients were diagnosed with pulmonary arterial hypertension (group 1 of Dana Point Classification) and the remaining 57 patients had PH caused by left heart disease (group 2 of Dana Point Classification).[10] Patients with complex congenital heart disease, ventricular septal defect and patients with pacemaker were excluded. Furthermore, patients from group 3 (pulmonary disease), group 4 (chronic thrombo-embolic PH) and group 5 (miscellaneous) of the Dana Point classification were excluded.[10] The diagnosis of PH was established by an extensive screening protocol according to the institutional PH protocol based on the current guidelines for diagnosis and management of patients with PH.[10] In this screening protocol two-dimensional transthoracic echocardiography, electrocardiography and right heart catheterization were included. However, right heart catheterization was not always performed in patients with left-sided heart disease in whom the results of the right heart catheterization would not influence the decision making. Clinical and echocardiographic data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University

Medical Center) and the echocardiography database and were retrospectively analysed. Clinical parameters included New York Heart Association (NYHA) functional class, cardiovascular risk factors, and medications. Two-dimensional echocardiography was performed to assess RV and LV dimensions and function and to estimate SPAP. Additionally, RV and LV dyssychrony were evaluated with two-dimensional longitudinal strain speckle tracking echocardiography.

Echocardiography

Echocardiographic data were acquired using a commercially available ultrasound system (Vivid 7 and E9, General Electric-Vingmed, Milwaukee, Wisconsin) equipped with a 3.5 MHz transducer and with the patient in left lateral decubitus position. During breath-hold, standard two-dimensional, color, pulsed and continuous wave Doppler data were obtained and saved in cine-loop format. All images were analyzed offline using dedicated software (EchoPac 111.0.0, General Electric-Vingmed, Horten, Norway).

First, LV end-systolic volume and end-diastolic volume were measured in the apical two- and four-chamber views and LVEF was calculated using the biplane Simpson`s method.[11] Diastolic LV function was assessed by obtaining deceleration time and peak early (E) and late (A) diastolic velocities using pulsed wave Doppler of the mitral valve inflow. Early diastolic mitral annulus velocity (E`) was measured using tissue Doppler imaging at the septal and lateral parts of the mitral annulus. The E/A and E/E` ratio were calculated as a measure of LV filling pressures.[12] The presence of valvular heart disease was evaluated according to the current guidelines.[11,13,14]

RV dimensions were evaluated by measuring RV end-diastolic area, RV end-systolic area, tricuspid annulus diameter and the RV base to apex diameter, as described in the current guidelines.[15] RV function was assessed measuring the tricuspid annular plane systolic excursion (TAPSE) in the apical four-chamber view.[15] The RV pressure was estimated by calculating the maximum velocity of the tricuspid regurgitant jet using the modified Bernoulli equation and the SPAP was estimated by adding the right atrial pressure to the RV pressure. The right atrial pressure was assumed based on the diameter and inspiratory collapse of the vena cava inferior.[15] Other echocardiographic signs of PH included the measurement of the LV eccentricity index, assessed in the parasternal short axis at the level of the papillary muscles as a measure of abnormal motion of the interventricular septum.[16]

Two-dimensional longitudinal strain speckle tracking analysis of the RV and LV was performed in the apical four-chamber view. As previously described, speckle tracking echocardiography allows angle-independent assessment of myocardial deformation by tracking frame-to-frame the movement of natural acoustic markers, or speckles, distributed within the myocardium on two-dimensional gray-scale images.[17] The endocardial border was manually traced at end-systole and the automatically displayed region of interest was manually adjusted to the thickness of the myocardium to ensure proper tracking.[17] The RV and LV were divided into a 6-segment model, sharing the interventricular septum, in the apical four-chamber view (Figure 1). Time to peak strain was calculated from QRS onset to the negative peak strain of each of the 6 segments of the LV and RV.[9] RV and LV dyssynchrony (RV-SD and LV-SD) were derived by calculating the standard deviation of the time to peak strain of six segments.

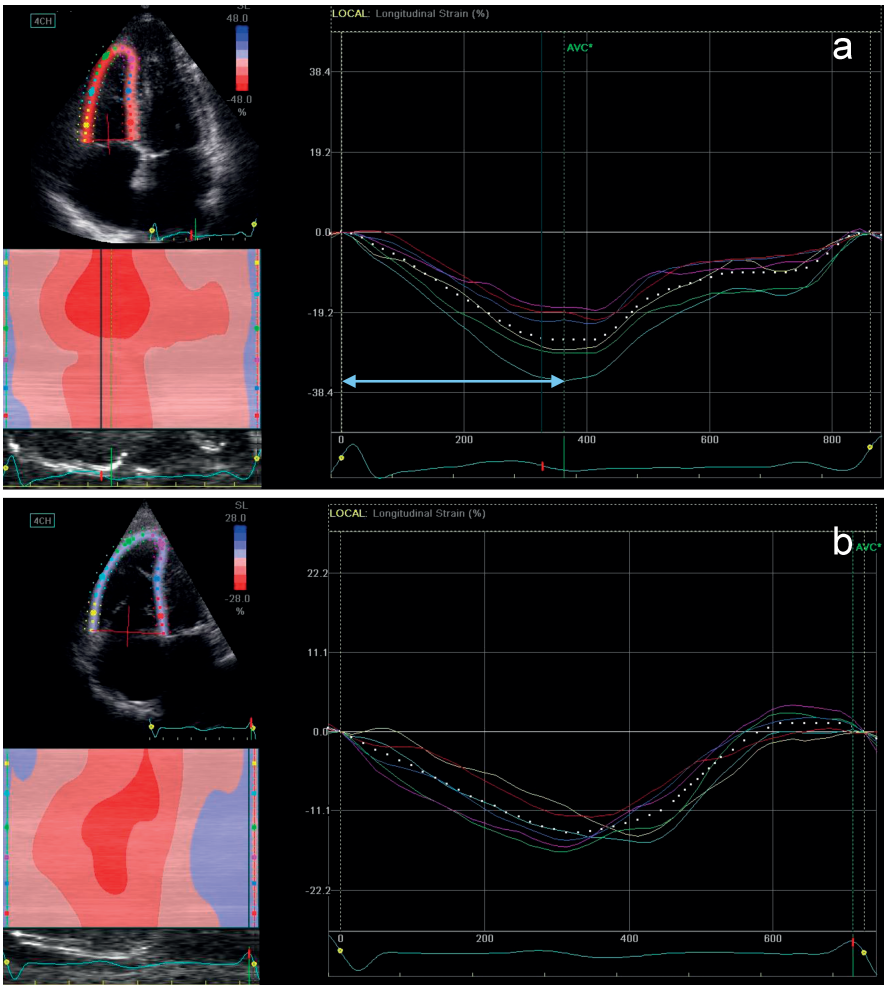

Figure 1. Assessment of right and left ventricular dyssynchrony by two-dimensional speckle-tracking echocardiography. The right and left ventricle were divided into 6-segment model in the apical 4-chamber view. The blue line in panel a represents the time from QRS onset to the maximal shortening of the myocardium, displayed by the negative peak strain of one of the six segments (light blue curve in panel a) of the right ventricle. The same method was used in the left ventricle (not shown in figure). Panel a represents a patient with pulmonary hypertension (SPAP 50 mm Hg) with a RV-SD of 17 ms. Panel b represents a patient with pulmonary hypertension (SPAP 95 mm Hg) with RV dyssynchrony (RV-SD of 70 ms).

Statistical analysis

Continuous data are presented as mean ± standard deviation and categorical data are presented as frequencies or percentages. Clinical and echocardiographic characteristics were compared using the unpaired Student *t* test and the χ^2 test. Correlations between variables were assessed by calculating the Pearson correlation coefficients and performing linear regression analyses. Multivariable linear regression analysis was performed to evaluate the independent effect of RV-SD

on LV performance parameters. The coefficient of correlation and the 95% confidence interval was calculated and corrected for clinically relevant parameters, including age, sex, QRS duration, Dana Point group, LV eccentricity index and SPAP. Finally, 20 patients were randomly selected to test the intra- and interobserver reproducibility of RV-SD measurement. Subsequently, Bland-Altman analysis was performed and the mean bias and two standard deviations were calculated. All data were analyzed using the package SPSS (SPSS® 17.0, SPSS Inc, Chicago, USA). A $p < 0.05$ was considered statistically significant.

RESULTS

A total of 107 patients were evaluated. The clinical and echocardiographic characteristics of the overall patient population are summarized in Table 1. The mean age was 63 ± 14 years, 41% of the patient population was male, mean NYHA functional class was 2.5 ± 0.7 and mean QRS duration was 100 ± 20 ms. Furthermore, 57 patients (53 %) were diagnosed with PH caused by left heart disease (Dana Point group 2) while the remaining 50 (47 %) patients were diagnosed with pulmonary arterial hypertension (Dana Point group 1) (Supplemental table 1). The overall population had a mean LVEF of 53 ± 9 %, a mean tricuspid annulus diameter of 4.2 ± 0.7 cm and TAPSE of 18 ± 4 mm. The mean estimated SPAP and mean pulmonary arterial pressure (MPAP) were 60 ± 19mm Hg and 39 ± 11.

The median value of RV-SD was 49 ms. Based on this cut-off value, the patient population was dichotomized into two groups: 54 patients with a RV-SD value <49 ms and 53 patients with a RV-SD value ≥49 ms. The two study groups were comparable in age, gender, distribution of PH etiology and heart rate (Table 1). NYHA functional class was more impaired in the patient group with RV-SD ≥49 ms compared to the patient group with RV-SD <49 ms (2.7 ± 0.7 vs. 2.3 ± 0.7, p = 0.004). Interestingly, there was a significant difference in QRS duration between the patient group with more RV dyssynchrony (RV-SD ≥ 49 ms), and the patient group with less RV dyssynchrony (RV-SD < 49 ms), even though the mean value of both groups remained <120 ms (106 ± 22 ms vs. 95 ± 15 ms, p = 0.005). There was no significant difference in cardiovascular risk factors or use of medication.

Patients with more pronounced RV dyssynchrony (RV-SD ≥ 49 ms) had significantly larger RV dimensions and worse RV function in comparison to patients with less dyssynchrony (RV-SD < 49 ms) (tricuspid annulus diameter: 4.5 ± 0.8 cm vs. 3.9 ± 0.6 cm; RV end-diastolic area; 23.8 ± 6.3 mm^2 vs. 19.1 ± 4.5 mm^2; TAPSE: 16 ± 4 mm vs. 19 ± 4 mm, p < 0.001). Although the LV volumes were comparable between the two groups, LVEF was significantly lower in the group of patients with RV-SD ≥ 49 ms compared with the group of patients with RV-SD < 49 ms (50 ± 10 % vs. 55 ± 8 %, p = 0.001). Diastolic function was comparable between the two groups. Finally, patients with a RV-SD ≥ 49 ms had significantly more LV dyssynchrony assessed with speckle tracking echocardiography (LV-SD: 57 ± 18 ms vs. 36 ± 18ms, respectively; p < 0.001). According to Bland-Altman analysis, the intra- and inter-observer variability of RV-SD measurement was 5 ± 24 ms and 5 ± 26 ms, respectively. The intra- and inter-observer variability of our laboratory for the measurement of LV-SD has previously been reported as 7 ± 22 ms and -7 ± 13 ms, respectively.[18]

Correlation between RV-SD and clinical and echocardiographic characteristics

Table 2 demonstrates the correlation coefficients between RV-SD and LV parameters. RV-SD was significantly correlated with SPAP (r = 0.65, p < 0.001). In addition, there was a modest but significant

Table 1. Patient characteristics

Clinical characteristics	Total population (n=107)	RV-SD < 49 ms (n=54)	RV-SD ≥ 49 ms (n=53)	p-value
Age (years)	63 ± 14	65 ± 13	61 ± 14	0.12
Male, n (%)	44 (41)	18 (33)	26 (49)	0.10
Group 2 PH, n (%)	57 (53)	28 (52)	29 (55)	0.77
NYHA functional class	2.5 ± 0.7	2.3 ± 0.7	2.7 ± 0.7	0.004
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.83
QRS duration (ms)	100 ± 20	95 ± 15	106 ± 22	0.005
Heart rate (beats/min)	75 ± 15	75 ± 14	75 ± 16	0.88
Coronary artery disease, n (%)	30 (28)	14 (26)	16 (30)	0.62
Hypercholesterolemia, n (%)	17 (16)	7 (13)	10 (19)	0.40
Smoker, n (%)	10 (9)	4 (7)	6 (11)	0.53
Hypertension, n (%)	44 (41)	23 (43)	21 (40)	0.76
Diabetes mellitus, n (%)	20 (19)	13 (24)	7 (13)	0.15
Medical treatment, n (%)[a]				
Oral endothelin receptor antagonist	5 (5)	3 (6)	2 (4)	1.00
Phosphodiesterase-5 inhibitor	4 (4)	1 (2)	3 (6)	0.36
Diuretics	57 (53)	27 (50)	30 (57)	0.49
ACE/AT II	61 (57)	31 (57)	30 (57)	0.93
Beta blockers	44 (41)	21 (39)	23 (43)	0.64
Anticoagulation	46 (43)	21 (39)	25 (47)	0.39
Echocardiographic characteristics				
LVEDV (ml)	91 ± 35	91 ± 27	92 ± 42	0.84
LVESV (ml)	44 ± 21	40 ± 14	47 ± 26	0.09
LVEF (%)	53 ± 9	55 ± 8	50 ± 10	0.001
Deceleration time (ms)	193 ± 77	199 ± 62	186 ± 89	0.38
E`-velocity (m/s)	0.06 ± 0.02	0.07 ± 0.03	0.06 ± 0.02	0.65
E/A ratio	1.1 ± 0.6	1.1 ± 0.5	1.1 ± 0.6	0.68
E/E` ratio	17.8 ± 12.2	19.1 ± 11.4	16.4 ± 13.0	0.25
LV eccentricity index	1.20 ± 0.3	1.14 ± 0.3	1.25 ± 0.3	0.05
Significant left-sided valvular heart disease, n (%)				
Mitral regurgitation	8 (8)	4 (7)	4 (8)	1.00
Mitral stenosis	3 (3)	0 (0)	3 (6)	0.12
Aortic regurgitation	1 (1)	0 (0)	1 (2)	0.50
Aortic stenosis	3 (3)	2 (4)	1 (2)	1.00
Tricuspid annulus diameter (cm)	4.2 ± 0.7	3.9 ± 0.6	4.5 ± 0.8	<0.001
RV base-apex diameter (cm)	7.5 ± 1.0	7.4 ± 0.9	7.7 ± 1.0	0.08
RVEDA (mm^2)	21.4 ± 5.9	19.1 ± 4.5	23.8 ± 6.3	<0.001
RVESA (mm^2)	13.9 ± 5.0	12.1 ± 3.6	15.7 ± 5.5	<0.001
TAPSE (mm)	18 ± 4	19 ± 4	16 ± 4	<0.001
SPAP (mm Hg)	60 ± 19	54 ± 17	65 ± 19	0.003
LV-SD (ms)	46.7 ± 21.0	36.1 ± 18.1	57.4 ± 18.2	<0.001
RV-SD (ms)	51.0 ± 27.7	29.7 ± 13.1	72.6 ± 21.0	<0.001[b]

Table 1. (continued)

	Total population (n=107)	RV-SD < 49 ms (n=54)	RV-SD ≥ 49 ms (n=53)	p-value
Right heart catheterisation				
MPAP (mm Hg)	39 ± 11	37 ± 11	41 ± 12	0.13
PCWP (mm Hg)	19 ± 9	18 ± 8	19 ± 9	0.63
TPG (mm Hg)	20 ± 13	18 ± 11	22 ± 14	0.22
PVR (dynes·s·cm^{-5})	348 ± 267	303 ± 214	395 ± 303	0.19

[a]At the time of first presentation at the pulmonary hypertension outpatient clinic
[b]By definition.
ACE: angiotensin-converting-enzyme inhibitor; AT II: angiotensin II receptor antagonist; BSA: body surface area; EF: ejection fraction; FAC: fractional area change; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LV-SD: left ventricular standard deviation; MPAP: mean pulmonary pressure; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PCWP: pulmonary capillary wedge pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RVEDA: right ventricular end diastolic area; RVESA: right ventricular end systolic area; RV-SD: right ventricular standard deviation; SPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TPG: trans pulmonary gradient

Table 2. Pearson correlation coefficients for right ventricular dyssynchrony and left ventricular variables and hemodynamic parameters

Variable	r-value for RV-SD	p-value
QRS (ms)	0.30	0.002
LVEDV (ml)	0.07	0.50
LVESV (ml)	0.18	0.06
LV EF (%)	- 0.23	0.02
Deceleration time (ms)	- 0.20	0.04
E`-velocity (m/s)	- 0.10	0.29
E/E` ratio	- 0.12	0.23
E/A ratio	- 0.14	0.23
Eccentricity index	0.22	0.03
LV-SD (ms)	0.55	<0.001
SPAP (mm Hg)	0.65	<0.001
MPAP (mm Hg)	0.28	0.02
PCWP (mm Hg)	0.05	0.67
TPG (mm Hg)	0.23	0.07
PVR (dynes·s·cm^{-5})	0.18	0.18

EF: ejection fraction; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LV-SD: left ventricular standard deviation; MPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RV-SD: right ventricular standard deviation; SPAP: systolic pulmonary arterial pressure; TPG: trans pulmonary gradient

correlation between RV-SD and QRS duration (r = 0.30, p = 0.002), and eccentricity index (r = 0.22, p = 0.03). Deceleration time was also significantly correlated with RV-SD (r = -0.20, p = 0.04), however other parameters of diastolic function did not show a significant correlation. RV-SD did not correlate with LV volumes. However, RV-SD significantly correlated with LVEF (r = -0.23, p = 0.02) (Figure 2a) and LV-SD (r = 0.55, p < 0.001) (Figure 2b).

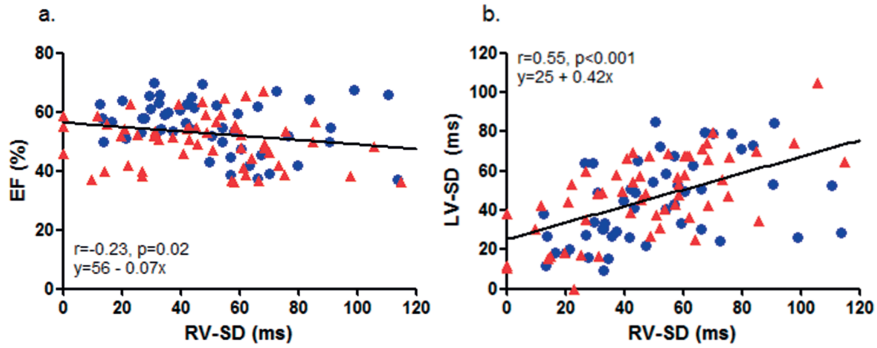

Figure 2. Correlation between right ventricular dyssynchrony and left ventricular performance. The scatter plots demonstrate the correlation between RV-SD and LV ejection fraction (a) and RV-SD and LV-SD (b). Patients with pulmonary arterial hypertension (group 1) are represented by the blue dots; patients with pulmonary hypertension due to left-sided heart disease (group 2) are represented by red triangles.

Influence of RV-SD on LV performance

Multivariate linear regression analysis was performed to evaluate the effect of RV dyssynchrony on LV performance, particularly on LVEDV, LV EF and LV-SD. After correction for age, sex, PH etiology, QRS duration, LV eccentricity index, and SPAP as independent variables in each of the three models, RV-SD remained independently related to LVEF (β = -0.07, 95% CI -0.14 – 0.00, p = 0.05) and LV-SD (β = 0.35, 95% CI 0.21 – 0.49, p < 0.001) (Table 3). RV-SD was not significantly associated to LVEDV.

Table 3. Multivariate linear regression analysis

Independent	Dependent		
	LVEDV (ml) **β (95% CI)**	**LV EF (%)** **β (95% CI)**	**LV-SD (ms)** **β (95% CI)**
Male[a]	-14.28 (-27.32 to -1.18) P=0.03	2.65 (-1.38 to 6.67) P=0.20	6.34 (-1.56 to 14.23) P=0.11
Age[a]	-0.19 (-0.64 to 0.26) P=0.41	0.06 (-0.81 to 0.20) P=0.41	-0.10 (-0.371 to 0.17) P=0.47
DP group[a]	12.89 (0.68 to 25.11) P=0.04	-5.17 (-8.93 to -1.40) P=0.008	4.40 (-2.97 to 11.78) P=0.24
QRS duration (ms)[a]	0.25 (-0.13 to 0.62) P=0.19	-0.05 (-0.17 to 0.07) P=0.40	-0.06 (-0.29 to 0.17) P=0.60
LV Eccentricity index[a]	-29.20 (-53.35 to -5.04) P=0.02	-0.41 (-7.85 to 7.04) P=0.91	-5.09 (-19.68 to 9.50) P=0.49
SPAP (mm Hg)[a]	-0.29 (-0.63 to 0.05) P=0.10	0.06 (-0.05 to 0.16) P=0.29	0.32 (0.11 to 0.52) P=0.003
RV-SD (ms)[a]	0.14 (-0.09 to 0.37) P=0.23	-0.07 (-0.14 to 0.00) P=0.05	0.35 (0.21 to 0.49) P<0.001

[a]All independent variables were forced simultaneously in the multivariable model.
DP: Dana Point classification; LV: left ventricle; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LV-SD: left ventricular standard deviation

DISCUSSION

The present evaluation demonstrated that RV dyssynchrony is significantly associated with LV dyssynchrony and reduced LVEF in patients with pulmonary arterial hypertension (group 1 of Dana Point classification) and PH due to left sided heart disease (group 2 of Dana Point classification).

PH is associated with functional and structural changes of the RV, characterized by RV dilatation and hypertrophy, abnormal RV geometry with leftward deviation of the interventricular septum, and dyssynchronous RV contraction that lead to systolic dysfunction.[1,5,19] Previous reports demonstrated that patients with PH show RV dyssynchrony with abnormal RV deformation and mechanical delay between the RV free wall and interventricular septum measured with tissue Doppler imaging techniques.[7,20,21] Additionally, the studies demonstrated an association between the presence of RV dyssynchrony and impaired RV function and enlarged dimensions of the RV. The present evaluation provides additional data showing that specifically patients with PH and significant RV dyssynchrony (RV-SD ≥ 49 ms) had significantly larger RV dimensions and worse RV function measured by TAPSE as compared with patients who did show a synchronous contraction of the RV. However, in contrast to previous studies, the assessment of RV dyssynchrony was performed with two-dimensional speckle tracking echocardiography. Unlike tissue Doppler imaging techniques, two-dimensional speckle tracking echocardiography permits angle-independent assessment of myocardial deformation.[17] To date, the gold standard for non-invasive assessment of RV dyssynchrony has not been established and, accordingly, the cut-off value to define significant RV dyssynchrony remains unknown. In the present evaluation, the patient population was dichotomized according to the median value of RV-SD. Whether this cut-off value may have prognostic implications should be evaluated in prospective studies.

Kalogeropoulos et al have reported a high feasibility and good reproducibility of RV dyssynchrony assessment with two-dimensional speckle tracking echocardiography in patients with PH.[9] Using this technique, the authors reported a prevalence of RV dyssynchrony of 69.4% in their patient population and the presence of RV dyssynchrony was strongly correlated with RV dysfunction.

Several studies have demonstrated the presence of RV dyssynchrony in patients with PH and how this RV dyssynchrony may distort LV geometry and impair diastolic filling.[5,6,22,23] Using tagged magnetic resonance imaging, Marcus et al[5] showed significantly more prolonged time to peak shortening of the RV than the interventricular septum and the LV free wall in patients with PH. This resulted in significant interventricular dyssynchrony with a time difference between RV and LV peak shortening of 94 ± 41ms. Interestingly, this interventricular dyssynchrony was not associated with the QRS duration but was negatively correlated with LVEDV and stroke volume. Therefore, interventricular dyssynchrony due to a delayed time to peak RV shortening may impair LV performance. The present evaluation confirms and extends these results by showing that RV dyssynchrony is significantly associated with LV dyssynchrony independently of QRS duration and etiology of PH. Patients with larger RV dyssynchrony as assessed with two-dimensional speckle tracking showed larger LV dyssynchrony and more impaired LVEF.

The independent deleterious effects of RV dyssynchrony on LV performance in patients with PH observed in the present evaluation raise the question on whether pacing strategies aiming at resynchronizing the RV may improve the LV performance, clinical symptoms and outcomes. To date, the effects of RV pacing alone or cardiac resynchronization therapy on RV, LV and interventricular

dyssynchrony in patients with PH remain unclear. In a recent study, RV pacing improved LV stroke volume, diastolic filling and global RV contractility in patients with chronic thromboembolic PH.[8] Whether these beneficial effects may also be observed in other groups of patients with PH remains unknown. The present evaluation included patients with PH of different underlying pathophysiologies; patients with pulmonary arterial hypertension and patients with PH secondary to left sided heart disease and preserved LVEF. According to the current guidelines these two groups are not eligible for cardiac resynchronization therapy CRT, since LVEF is >35 % and the mean QRS duration is <120ms.[24] Further studies in a broad spectrum of patients with PH will be needed to establish the potential of pacing therapies in PH.

Several limitations should be acknowledged. First, the cut-off value to define RV dyssynchrony was based on the median value of RV-SD measured in the patient population. Therefore, the present results may not be generalizable. Moreover, the present evaluation was observational. Prospective evaluation of the prognostic implications of this definition of RV dyssynchrony (RV-SD ≥ 49 ms) would help to clarify its clinical value. Finally, other groups of the Dana Point classification were not included in the present evaluation.

CONCLUSION

RV dyssynchrony is significantly associated with LV dyssynchrony and reduced LV ejection fraction in patients with PH.

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SUPPLEMENTARY TABLE

Supplemental table 1. Comparison group 1 (PAH) and group 2 (left heart disease)

Clinical characteristics	Group 1 (PAH) (n=50)	Group 2 (LV disease) (n=57)	p-value
Age (years)	60 ± 14	66 ± 13	0.02
Male , n (%)	14 (28)	30 (53)	0.01
NYHA functional class	2.4 ± 0.9	2.5 ± 0.6	0.63
BSA (m^2)	1.8 ± 0.20	1.9 ± 0.24	0.05
QRS duration (ms)	97 ± 18	104 ± 20	0.06
Heart rate (beats/min)	76 ± 15	75 ± 15	0.71
Coronary artery disease, n (%)	7 (14)	23 (40)	0.002
Hypercholesterolemia, n (%)	4 (8)	13 (23)	0.04
Smoker, n (%)	4 (8)	6 (11)	0.75
Hypertension, n (%)	17 (34)	27 (47)	0.16
Diabetes mellitus, n (%)	6 (12)	14 (25)	0.10
Medical treatment, n (%)[a]			
Oral endothelin receptor antagonist	5 (10)	0 (0)	0.02
Phosphodiesterase-5 inhibitor	2 (4)	2 (4)	1.00
Diuretics	19 (38)	38 (67)	0.003
ACE/AT II	24 (48)	37 (65)	0.08
Beta blockers	14 (28)	30 (53)	0.01
Anticoagulation	14 (28)	32 (56)	0.003
Echocardiographic characteristics			
LVEDV (ml)	81 ± 30	101 ± 37	0.003
LVESV (ml)	36 ± 14	51 ± 24	<0.001
LVEF (%)	56 ± 9	50 ± 8	0.005
Deceleration time (ms)	183 ± 48	202 ± 94	0.18
E'-velocity (m/s)	0.07 ± 0.03	0.06 ± 0.02	0.12
E/A ratio	0.97 ± 0.3	1.3 ± 0.7	0.04
E/E'-ratio	12.3 ± 5.3	22.5 ± 14.3	<0.001
LV eccentricity index	1.26 ± 0.3	1.13 ± 0.3	0.02
Tricuspid annulus diameter (cm)	4.1 ± 0.7	4.2 ± 0.8	0.52
RV base-apex diameter (cm)	7.6 ± 0.9	7.5 ± 1.0	0.55
RVEDA (mm^2)	21.8 ± 6.3	21.1 ± 5.6	0.54
RVESA (mm^2)	14.7 ± 5.7	13.2 ±4.1	0.12
TAPSE (mm)	18 ± 4	18 ± 4	0.49
SPAP (mm Hg)	60 ± 21	59 ± 17	0.77
LV-SD (ms)	44 ± 21	49 ± 21	0.27
RV-SD (ms)	50 ± 25	52 ± 30	0.82
Right heart catheterisation			
MPAP (mm Hg)	42 ± 13	37 ± 10	0.08

Supplemental table 1. (continued)

Clinical characteristics	Group 1 (PAH) (n=50)	Group 2 (LV disease) (n=57)	p-value
PCWP (mm Hg)	12 ± 6	24 ± 7	<0.001
TPG (mm Hg)	30 ± 12	12 ± 8	<0.001
PVR (dynes·s·cm^{-5})	531 ± 272	204 ± 149	<0.001

ACE: angiotensin-converting-enzyme inhibitor; AT II: angiotensin II receptor antagonist; BSA: body surface area; EF: ejection fraction; FAC: fractional area change; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LV-SD: left ventricular standard deviation; MPAP: mean pulmonary artery pressure; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PCWP: pulmonary capillary wedge pressure; PH: pulmonary hypertension; RVEDA: right ventricular end diastolic area; RVESA: right ventricular end systolic area; PVR: pulmonary vascular restistance; RV-SD: right ventricular standard deviation; SPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TPG: trans pulmonary gradient

[a]At the time of first presentation at the pulmonary hypertension outpatient clinic