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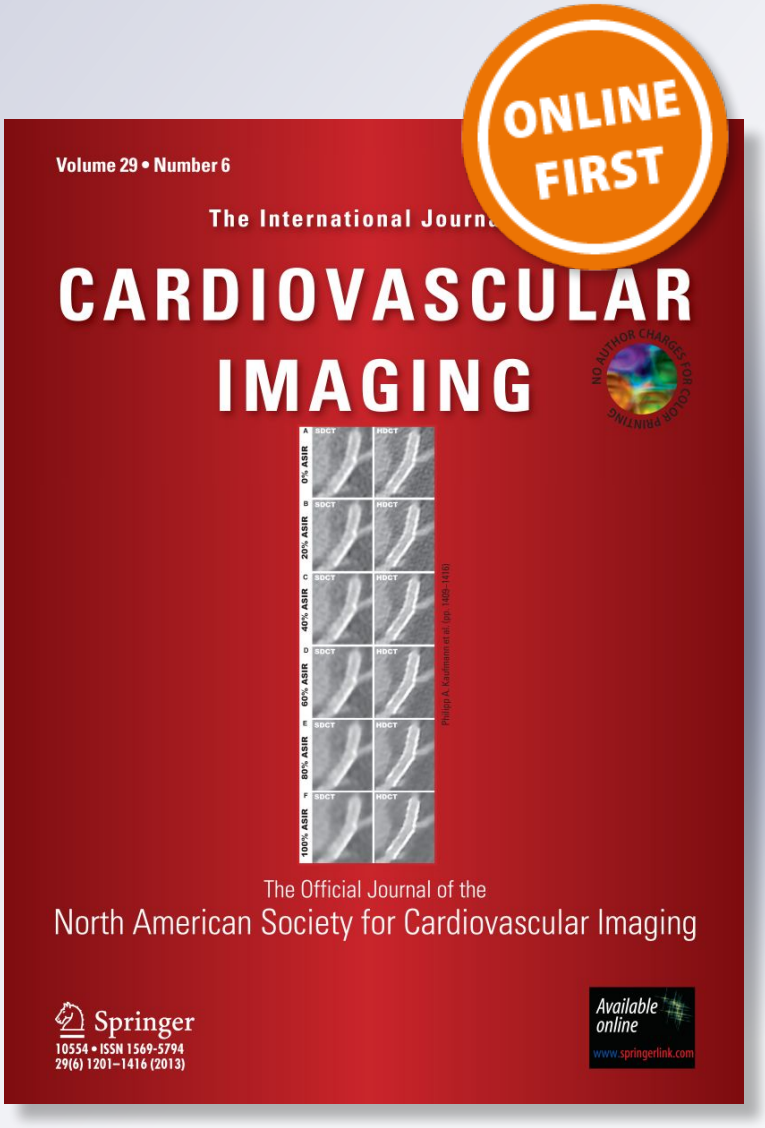

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ORIGINAL PAPER

Altered synchrony of right ventricular contraction in borderline pulmonary hypertension

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Abstract Imaging studies have shown that pulmonary hypertension (PH) is associated with inhomogenous right ventricular (RV) regional contraction, or dyssynchrony, and that this is of prognostic relevance. This study aimed at the identification and functional significance of RV dyssynchrony in borderline PH defined by a mean pulmonary artery pressure between (mPAP) 20 and 25 mmHg. RV dyssynchrony was measured by 2-dimensional speckle tracking echocardiography in 17 patients with pulmonary arterial hypertension (PAH), 13 patients with borderline PH and 14 controls. Dyssynchrony was defined as the R-R interval-corrected standard deviation of the times to peak-systolic strain for the basal and medium segments of the RV. All the PH patients underwent a right heart catheterization. RV dyssynchrony amounted to 69 ± 34 ms in PAH, 47 ± 23 ms in borderline PH and 8 ± 6 ms in controls, all different from each other ($p < 0.05$). RV dyssynchrony in borderline PH was the only parameter of RV systolic dysfunction in 11 of 13 (85%) of the patients. RV dyssynchrony was accompanied by postsystolic shortening and correlated to RV fractional area change, not to mPAP or pulmonary vascular resistance. RV dyssynchrony occurs in borderline PH and may reflect early RV-arterial uncoupling.

Keywords Pulmonary hypertension · Pulmonary circulation · Right ventricle · Dyssynchrony · Postsystolic shortening · Speckle tracking echocardiography

Bouchra Lamia and Robert Naeije take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Introduction

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) ≥25 mmHg measured during a right heart catheterization [1, 2]. There is still uncertainty about the clinical significance of a mPAP between its normal value and PH, sometimes referred to as borderline pulmonary hypertension [1, 3]. Yet only mild increases in mPAP have been reported to be associated with a decreased exercise capacity [4, 5]. Borderline pulmonary hypertension defined as a mPAP between 19 and 24 mmHg in a large cohort has been recently shown to be associated with increased mortality and hospitalization [6]. In addition borderline pulmonary hypertension may represent early stage pulmonary arterial hypertension (PAH) in high-risk patients [7–9].

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Right ventricular (RV) function is a major determinant of symptomatology and outcome in PH [10]. Whether RV function is altered in early or borderline PH is not exactly known. Hilde et al. recently reported an echocardiographic demonstration of increased RV wall thickness and dimensions, and depressed indices of systolic function in patients with chronic obstructive pulmonary disease (COPD) and mPAP only mildly increased or at the upper limit of normal [11]. The authors speculated on the effects of intra-thoracic pressure changes, hypoxemia and hypercapnia, so that it is not known if their findings are generally relevant to borderline PH. On the other hand, echocardiography generates many measurements of RV structure and function of prognostic relevance in PH [12], but one does not know which one might be informative in early stage pulmonary vascular disease.

Magnetic resonance imaging (MRI), tissue Doppler imaging and speckle tracking echocardiography studies have demonstrated that severe PH may be associated with a prolonged RV contraction until into left ventricular (LV) diastole, resulting in "postsystolic shortening" or inter-ventricular "asynchrony" [13–15]. These studies also disclosed a considerable regional heterogeneity of RV contraction, or "dyssynchrony" and showed it to be of both functional and prognostic relevance [16–20].

We tested the hypothesis that RV dyssynchrony is universal in the presence of increased PAP, thus already detectable in mild or borderline PH, and that it is associated with altered RV pump function.

Methods

Patients

The study population included 44 subjects. 17 therapy naïve patients with idiopathic and anorexigen-induced PAH and 13 patients with borderline PH defined as mPAP between 19 and 24 mmHg and confirmed on right heart catheterization were studied. Fourteen healthy subjects matched for age sex and body mass index to the borderline PH patients served as controls. None of the patients had electrocardiographic signs of intraventricular conduction delay to avoid confounding factors of RV evaluation. All the patients had been referred for a suspicion of PAH, and thus had undergone a diagnostic work-up including echocardiography and right heart catheterization [21]. The echocardiography was done within an hour of the right heart catheterization. The Board for human studies of the University of Rouen approved the study. Written informed consent was obtained from all patients prior to enrollment.

Hemodynamics

All patients underwent a standard right heart catheterization with measurements of systolic, diastolic and mean PAP (sPAP, dPAP, mPAP), right atrial pressure (RAP), mean pulmonary artery wedge pressure (PAWP), stroke volume (SV), cardiac index (CI) and pulmonary vascular resistance (PVR).

Echocardiography

An echocardiographic system (Vivid 7 dimension, General electric, Fairfield, Connecticut, USA) was used to obtain images with a 4.5 MHz transducer. Digital routine gray-scale 2-D and tissue Doppler cine loops from three consecutives beats were obtained at functional residual capacity, with a brief relaxed end-expiratory breath hold.

Offline analysis was then performed on digitally stored images (EchoPac, General electric, Fairfield, Connecticut, USA) .

Conventional measurements of right ventricular function

Standard M-mode, 2-dimensional (2D) and Doppler images were acquired. Measurements were performed in accordance with American Society of Echocardiography guidelines [22]. Parameters of RV structure and function were measured: right atrial area (RA area), RV end-diastolic area (EDA), RV end-systolic area (ESA), RV fractional area change (FAC) %, tricuspid annular plane systolic excursion (TAPSE), RV wall thickness and presence of pericardial effusion.

Pulsed wave tissue Doppler imaging (PW-TDI) was used to measure tricuspid lateral annular peak systolic velocity and right ventricular index of myocardial performance (RIMP or Tei index).

Speckle-tracking strain analysis

The speckle-tracking analysis was used to generate regional strain from 2D images. Gray scale images were collected at frame rates of 65 Hz. Longitudinal strain was calculated as the change in length/initial length between endocardial and epicardial trace. Peak strain and time to peak strain from each of six time-strain curves were determined. Dyssynchrony was assessed excluding the apical segments for the analysis because of the high-observed variability of that segments in addition to the software manufacturer recommendations. Dyssynchrony was calculated as the standard deviation of the times to peak-systolic strain for the four mid-basal RV segments corrected to the R-R interval

between two QRS complexes, and called RV-SD4. Postsystolic shortening was defined as the time delay between pulmonary valve closure to the latest peak systolic strain.

Intra- and interobserver variabilities for RV-SD4 measurement were defined in ten randomly selected patients by the same observer and by a second independent observer respectively. The bias and limits of agreement for the two measurements of the same observer and for the measurements of two different observers were assessed using a Bland and Altman analysis [23].

Statistical analysis

Continuous variables are expressed as mean ± SD and categorical variables are expressed as counts and proportions. Two group comparisons were performed with Mann–Whitney rank-sum tests if the data were not normally distributed. Chi square or Fisher exact tests were used to analyze the categorical data. Comparisons among groups were performed using a Kruskall–Wallis test with a post-hoc analysis. Univariate analysis was applied to borderline PH and all PH populations to identify echocardiographic variables correlated to RV dyssynchrony. A multivariable analysis was not performed as the number of variables was too large with respect to the patient populations. Significance was determined as $p < 0.05$. Statistical analyses were performed using MedCalc Statistical Software version 16.1 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016).

Results

The baseline characteristics of the patients are summarized in Table 1. The patients with PAH were predominantly in WHO functional class III, with a markedly decreased 6-min walk distance, increased mPAP and decreased cardiac output with increased RAP. The patients with borderline PH were almost equally distributed between WHO functional classes II and III had a moderately decreased 6-min walk distance and an only mild increase in mPAP with preserved cardiac output and upper limit of normal RAP. These patient's symptomatology was related to a moderate COPD in 9 patients and to systemic sclerosis (SSc) in 4. The patients with COPD were GOLD stage II with a forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) of 63 ± 17%, a FEV_1 of 64 ± 4%, a residual volume of 135 ± 37%, a lung diffusing capacity of carbon monoxide (DL_{CO}) of 73 ± 27% predicted, an arterial PO_2 (PaO_2) of 10.2 ± 2.1 kPa and a $PaCO_2$ of 5.5 ± 0.9 kPa. The SSc patients had no evidence of lung fibrosis, and had a FEV_1/FVC of 77 ± 8%, a FEV_1 of 80 ± 1%, a FVC of 95 ± 1%, a DL_{CO} of 79 ± 22% predicted, a PaO_2 of 11.7 ± 0.3 kPa and a $PaCO_2$ of 5.2 ± 0.3 kPa.

Table 1 Demographic, clinical and hemodynamic characteristics of the study population

	PAH N = 17	Borderline PH n = 13
Diagnosis		
Idiopathic PAH	14 (83)	
Anorexigen-induced PAH	3 (17)	
Connectivite tissue disease		4 (31)
COPD/ Sleep disordered breathing		9 (69)
Sex, M/F	4/13	4/9
Age, yrs	67 ± 14	58 ± 19
Weight, kg	85 ± 28	81 ± 26
Height, cm	159 ± 8	164 ± 2
Functional class		
WHO II	4 (23)	7 (54)
WHO III	12 (71)	6 (46)
WHO IV	1 (6)	0
6 MWD, m	259 ± 147	427 ± 181[#]
Hemodynamics		
RAP, mmHg	11 ± 5	8 ± 2
PAP, mmHg	43 ± 11	22 ± 2[#]
Cardiac index, L/min/m^2	2.9 ± 0.9	3.9 ± 1.5
PAWP, mmHg	11 ± 3	10 ± 3
PVR, WU	8 ± 4	2± 1[#]
QRS, ms	60 ± 12	58 ± 12
First line therapy		
Calcium-channel blockers	1	
ERA	11	
PDE5i	8	
Epoprostenol	0	
Treprostinil	2	

Values are n (%), n, or mean ± SD

6MWD 6-min walk distance distance, *ERA* endothelin receptor antagonist, *PAH* pulmonary arterial hypertension, *PAP* mean pulmonary arterial pressure, *PDE5i* phosphodiesterase 5 inhibitor, *PVR* pulmonary vascular resistance, *PAWP* mean pulmonary artery wedge pressure, *RAP* mean right arterial pressure, *WHO* World Health Organization, *WU* Wood unit

[#] $p < 0.05$

The echocardiographic measurements are shown in Table 2. As compared to controls, patients with borderline PH had increased RV dimensions and wall thickness, with a trend to increased RA surface area. The only other abnormal features were an increased 2D strain value of the medium segment of the RV free wall and dyssynchrony. Patients with pulmonary hypertension had more important increase in RV dimensions, depression of several indices of RV systolic function and enhanced dyssynchrony.

Table 2 Comparison of echocardiographic features between pah patients, borderline ph patients and normal subjects

	Normal subjects (n = 14)	Borderline PH (n = 13)	PAH group (n = 17)
Right heart structure			
RA area, cm^2	10 ± 3	12 ± 3	16 ± 7*,#
RVEDA, cm^2	13 ± 3	17 ± 5§	22 ± 7*,#
RVESA, cm^2	7 ± 2	9 ± 3§	15 ± 6*,#
RVEDA/LVEDA	0.4 ± 0.06	0.6 ± 0.3§	1.0 ± 0.5*
RV wall thickness, mm	2.0 ± 0.1	4.0 ± 0.6§	5.0 ± 1*
Pericardial effusion	0	0	5*,#
RV systolic function			
TAPSE, mm	23 ± 2	23 ± 3	17 ± 5*,#
RVFAC, %	51 ± 6	45 ± 14	31 ± 16*,#
PDP velocity RVFW, cm/s	11 ± 1	11 ± 2	9 ± 2
Pulsed Doppler MPI	0.35 ± 0.06	0.40 ± 0.08	0.50 ± 0.21*
Peak 2DS mid RVFW, %	24 ± 7	19 ± 11§	12 ± 8*,#
Peak 2 DS base RVFW, %	23 ± 8	22 ± 15	15 ± 12
Peak 2DS mid septum, %	17 ± 3	17 ± 2	16 ± 7
Peak 2DS base septum, %	17 ± 4	19 ± 4	17 ± 7
Systolic shortening, ms	355 ± 31	361 ± 53	309 ± 84
Post systolic shortening, ms	1 ± 4	19 ± 15§	52 ± 52*,#
Post systolic shortening, %	0 ± 1	5 ± 4 §	18 ± 20*,#
Intraventricular dyssynchrony			
RV-SD4, ms	8 ± 6	47 ± 23§	69 ± 34*,#

MPI myocardial performance index, Pulsed tissue Doppler peak systolic velocity at the basal RVFW

RA right atrium area, *RV* right ventricular, *RVFW* Right ventricular free wall, *RVFAC* right ventricular fractional area change, *RVESA* right ventricular end systolic area, *RVEDA* right ventricular end diastolic area, *Peak 2DS mid RVFW* Peak 2D strain of the mid segment of the RVFW, *Peak 2 DS base RVFW* peak 2D strain of the basal segment of the RVFW, *Peak 2DS mid septum* Peak 2D strain of the mid segment of the septum, *Peak 2DS base septum* Peak 2D strain of the basal segment of the septum, *PDP velocity RVFW* pulsed tissue Doppler peak velocity at the basal RVFW segment, *RV-SD4* standard deviation of the times to peak strain for the 4 mid and basal segments of the right ventricle, similar to dyssynchrony index, *TAPSE* tricuspid annular plane systolic excursion

*$p < 0.05$: PAH patients versus normal subjects

#$p < 0.05$: PAH versus borderline PH patients

§$p < 0.05$: borderline PH patients versus normal subjects

An example of segmental strain curves in a normal subject, a patient with borderline PH and a patient with PAH is represented in Fig. 1. The figure also illustrated how dyssynchrony was determined. Figure 2 presents box and whisker plots of RV SD4 in controls, patients with borderline PH and patients with PAH.

We defined a cutoff value of 20 ms as criterion of RV dyssynchrony (upper 95% limit of normal of the control group = mean + 2SD). According to this criterion, RV dyssynchrony was present in 100% of PAH patients and in 85% of patients (11/13) with borderline PH.

All the patients with an increased dyssynchrony also presented with prolonged systole and postsystolic shortening.

In patients with borderline PH, RV-SD4 was only correlated to RVFAC, not to PAP, PVR, pulmonary arterial compliance (Ca), SV, ESA, EDA, TAPSE, sPAP/ESA (taken as an index of end-systolic elastance), or SV/ESA (taken as an index of RV-arterial coupling). (Table 3).

When all the PH patients were pooled, RV-SD4 remained correlated to FAC, and was otherwise more tightly correlated to sPAP/ESA, SV/ESA or ESA. SD4 was not correlated to PAP, PVR or Ca (Table 4).

The RV-SD4 intraobserver and interobserver variabilities assessed using a Bland and Altman analysis showed biases of 0.1 and 0.16 ms and limits of agreement of −1.9 to +2.1 and −3.0 to +3.3 ms respectively.

Discussion

The present results show that borderline PH is associated with a moderate increase in RV dimensions and wall thickness and with a striking heterogeneity of regional RV

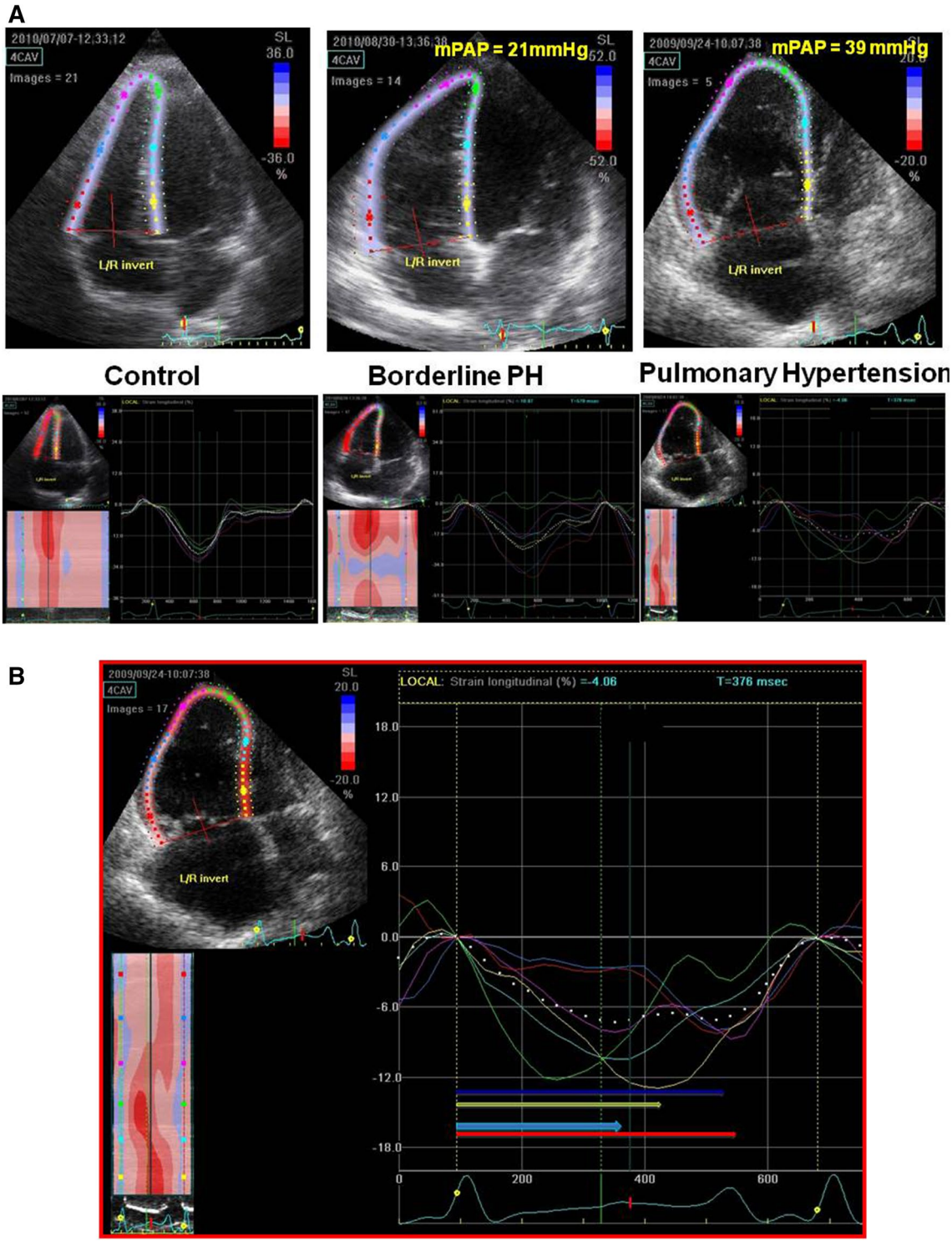

Fig. 1 **a** Right ventricular (RV) dyssynchrony evaluation in a normal subject, in a patient with borderline pulmonary hypertension (PH) and in a patient with pulmonary arterial hypertension (PAH). Dyssynchrony was calculated as the standard deviation of the times to peak strain for the four mid and basal segments of the right ventricle. Individual segment strain is color-coded. *Colored lines* represent the time interval between QRS onset and peak systolic strain for each mid segments and basal segments of the RV free wall and septum. RV dyssynchrony was minimal in a normal subject (picture on the *left*) RV dyssynchrony was significant in a patient with elevated mean pulmonary artery pressure (MPAP) (picture in the *middle*). RV was maximal in a PAH patient (picture on the *right*) **b** RV dyssynchrony evaluation in a patient with PAH Individual segment strain is color-coded. *Colored lines* represent the time interval between QRS onset and peak systolic strain for each mid segments and basal segments of the RV free wall and septum

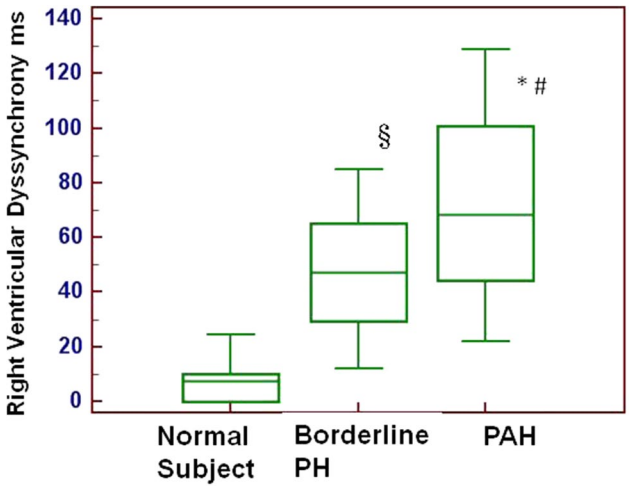

Fig. 2 Comparison of right ventricular dyssynchrony measured as the standard deviation of the times to peak strain of 4 regions (SD4) in normal subjects, in patients with borderline pulmonary hypertension (PH) and in patients with pulmonary arterial hypertension (PAH). RV dyssynchrony was significantly increased in borderline PH and in PAH patients compared to controls. *$p < 0.05$: PAH patients versus normal subjects. #$p < 0.05$: PAH patients versus borderline PH patients. §$p < 0.05$: Borderline PH patients versus normal subjects

Table 3 Univariate analysis of hemodynamic variables associated with RV dyssynchrony in Borderline PH patients

	Spearman's coefficient (rho)	95% CI	p value
Hemodynamics			
Mean PAP, mmHg	0.14	−0.44 to 0.64	0.69
Systolic PAP, mmHg	−0.11	−0.62 to 0.46	0.72
PVR, WU	0.15	−0.43 to 0.64	0.62
Compliance (SV/PAPP)	−0.30	−0.73 to 0.29	0.31
Contractility (MPAP/RVESA)	0.11	−0.47 to 0.62	0.72
Contractility (SPAP/RVESA)	−0.09	−0.61 to 0.48	0.75
Elastance (MPAP/SV)	0.33	−0.27 to 0.74	0.27
Elastance (SPAP/SV)	0.35	−0.24 to 0.75	0.23
Coupling (SV/RVESA)	−0.21	−0.68 to 0.38	0.48
RVEDA, cm2	−0.51	−0.83 to 0.06	0.07
RVESA, cm2	−0.06	0.59 to 0.50	0.83
TAPSE	−0.18	−0.66 to 0.41	0.55
RVFAC	−0.59	−0.86 to -0.07	0.03

CI confidence interval, *PAP* pulmonary artery pressure, *PAPP* pulmonary artery pulse pressure, *PVR* pulmonary vascular resistance, *RVFAC* right ventricular fractional area change, *RVEDA* right ventricular end-diastolic area, *RVESA* right ventricular end-systolic area, *SV* stroke volume, *TAPSE* tricuspid annular plane systolic excursion, WU wood unit

Table 4 Univariate analysis of hemodynamic variables associated with RV dyssynchrony in PAH and Borderline PH patients

	Spearman's coefficient (rho)	95% CI	p value
Hemodynamics			
Mean PAP, mmHg	0.28	−0.09 to 0.58	0.13
Systolic PAP, mmHg	0.20	−0.17 to 0.52	0.28
PVR, WU	0.25	−0.136 to 0.570	0.20
Compliance (SV/PAPP)	−0.18	−0.51 to 0.18	0.32
Contractility (MPAP/RVESA)	−0.31	−0.61 to 0.046	0.08
Contractility (SPAP/RVESA)	−0.38	−0.65 to −0.02	0.03
Elastance (MPAP/SV)	0.31	−0.04 to 0.60	0.08
Elastance (SPAP/SV)	0.30	−0.06 to 0.59	0.10
Coupling (SV/RVESA)	−0.47	−0.71 to −0.13	0.008
RVEDA, cm2	0.11	−0.256 to 0.456	0.54
RVESA, cm2	0.39	0.038 to 0.66	0.03
TAPSE	−0.25	−0.56 to −0.126	0.18
RVFAC	−0.58	−0.77 to −0.27	0.0009

CI confidence interval, *PAP* pulmonary artery pressure, *PAPP* pulmonary artery pulse pressure, *PVR* pulmonary vascular resistance, *RVFAC* right ventricular fractional area change, *RVEDA* right ventricular end-diastolic area, *RVESA* right ventricular end-systolic area, *SV* stroke volume, *TAPSE* tricuspid annular plane systolic excursion, *WU* wood unit

contraction. They also show that RV dyssynchrony at all levels of increased mPAP is inversely related to indices of systolic function rather than directly to indices of afterload, which suggests a negative effect on RV pump function.

There has been little data reported until now on the imaging of RV function in borderline PH, and all are by echocardiography. Most recently Hilde et al. reported on altered RV function in 72 patients with COPD and "no PH", of whom 21 actually had a borderline PH [11]. Their "no PH" patients had upper limit of normal mPAP or mPAP between 20 and 25 mmHg, with PVR on average of 2 WU, which is the same as in the present study. The results showed the "no PH" patients had an increased RV wall thickness, dilatation and altered indices of systolic function including strain, TAPSE, acceleration of isovolumic contraction, FAC, tricuspid annulus S' wave and MPI. The authors explained these results by the fact that upper limit of normal mPAP corresponds to an already advanced pulmonary vascular remodeling, with hypoxemia, hypercapnia and altered lung mechanics contributing to increased pulmonary vascular stiffness and thus increased RV afterload [11]. These patients would also present with steep increases in MPAP at exercise as a cause of repetitive increases in afterload remodeling the RV [24]. The COPD patients in the present study were GOLD II with quasi preserved

DL_{CO} and arterial blood gases, thus no major alterations in lung mechanics or gas exchange as identifiable causes of RV dysfunction.

The other clinical circumstance of abnormal RV function in borderline PH is SSc. Lindquist et al. reported on 36 patients with SSc and no PH an increased RV free wall thickness and right atria area with altered indices of diastolic function [25]. Similar results were reported by Huez et al. in 25 patients with SSc and no PH [26]. Their patients had an increase in RV free wall thickness as well, an increase in RVEDA, a shortened acceleration time of pulmonary flow (AcT) and a steep slope of mPAP-cardiac output relationships in keeping with the hypothesis of increased pulmonary arterial stiffness evoked by Hilde et al. in COPD patients [11, 24].

In the present study, RV dimensions, wall thickness and 2D strain value of the medium segment of the RV free wall in borderline PH were worsened and improved by some 30%, and by 60% in pulmonary hypertension patients compared to controls. On the other hand, the heterogeneity of RV contraction was increased sixfold in borderline PH for eightfold in PAH. These proportional changes indirectly suggest that RV dyssynchrony is a more sensitive albeit indirect marker of early pulmonary vascular disease, and support the notion that borderline PH is a disease entity with already significant RV-arterial uncoupling.

There has been recently an increased interest in RV function as a major determinant of PH symptomatology and outcome, so that severe PH is now understood as a disease of the RV-pulmonary circulation unit [27]. It has also been better realized that RV function adaptation to afterload is basically systolic, with increased contractility to preserve RV-arterial coupling [10, 28]. Increased RV dimension is thought to occur when systolic function fails, to preserve flow output adapted to metabolic demand, but at the price of clinical systemic congestion and worse prognosis [29]. The present results strongly suggest that the RV enlarges with altered homogeneity of contraction as soon as PAP reaches the upper limits of normal.

Prolonged contraction and dyssynchrony of the RV could be speculated to be initially of adaptative value by preserving regional excesses in wall tension. However, marked dyssynchrony like in the present study has been shown to be associated to decreased indices of RV systolic function like ejection fraction [18], cardiac output and, indirectly exercise capacity [19, 20] suggesting a negative effect on the pump function of the heart [11, 20]. This is supported by the present results showing a strong inverse correlation with FAC or indices of RV contractility (sPAP/RVESA) or RV-arterial coupling (SV/ESA) over the entire spectrum of PAP. Dyssynchrony in the present study was also associated with prolonged RV contraction and postsystolic shortening, which has been shown to impair LV filling [15]. Correction of dyssynchrony by RV pacing has been shown to restore RV function and cardiac output in rats with monocrotaline-induced PH [30]. Thus dyssynchrony at all stages of PH is associated with an alteration of RV function that can only but lead to RV-arterial uncoupling. It may be of interest that, in the present study, RV dyssynchrony was not correlated to mPAP, PVR or Ca, suggesting that it is the systolic function adaptation to afterload, not afterload per se which determines heterogeneity of RV contraction.

The addition of RV dyssynchrony to WHO functional class, 6-min walk distance and cardiac index has been shown by Badagliacca et al. to add to the prediction of clinical stability in a series of 84 patients with idiopathic, heritable or anorexigen-PAH, with a cut-off of >23 ms associated with a decreased time to clinical deterioration [20]. However, Smith et al. did not find RV dyssynchrony as measured by 3D speckle tracking echocardiography to predict survival in a cohort of 94 patients with severe PH [18]. These discrepant results might be explained that most of RV dyssynchrony is already established in early stage PH, and begs for further studies combining updated multiparametric advanced imaging techniques [31].

A limitation to the present study is in the recruitment of borderline PH patients referred for a right heart catheterization on the basis of unexplained dyspnea-fatigue symptoms, and who presented with COPD or SSc as comorbidities. One does not know if the present results are more generally applicable to borderline PH with different or without identifiable comorbidities. The second limitation is the limited study population.

In conclusion, the present results show that there is a marked heterogeneity of RV contraction in borderline PH, suggesting that it is a syndrome of early RV-arterial uncoupling.

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Compliance with ethical standards

Conflit of interest The authors declare that they have no conflit of interest.

Ethical approval Ethics in this article is approved by the Humans Research Ethics Commitee (HREC).

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