“Right Ventricle Speckle Tracking in Bronchopulmonary Dysplasia: One Year Follow Up”

Marcos Clavero-Adell (m.claveroadell@gmail.com)
Hospital Universitario Miguel Servet https://orcid.org/0000-0002-3296-8070
Daniel Palanca-Arias
Hospital Universitario Miguel Servet
Marta López-Ramón
Hospital Universitario Miguel Servet
Lorenzo Jiménez-Montañés
Hospital Universitario Miguel Servet
Itziar Serrano-Viñuales
Hospital Universitario Miguel Servet
Segundo Rite-Gracia
Hospital Universitario Miguel Servet
Ariadna Ayerza-Casas
Hospital Universitario Miguel Servet

Research Article

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Abstract

Purpose: Bronchopulmonary dysplasia is still a main problem in preterm infants. The screening of secondary right ventricle (RV) failure concern neonatologist and pediatric cardiologists. Measurements of right ventricle deformation through speckle tracking analysis in echocardiography could help to early diagnosis.

Methods: A prospective longitudinal study was carried out over 28 months at a tertiary care pediatric cardiology reference center. Under 32 weeks' pre-term infants were eligible for the study. Twenty-eight days after birth, all enrolled patients were included in one group: no bronchopulmonary dysplasia (NO-BPD) or bronchopulmonary dysplasia (BPD). At 36 PMA, BPD patients were included in one group according to severity categorization (mild, moderate, severe). At three time points echocardiogram measurements were performed. Right ventricle strain was studied using speckle tracking analysis and it was compared with classical function parameters between groups and along time.

Results: Fifty patients were enrolled in the study, 22 on NO-BPD group and 28 on BPD group (16 mild, 8 moderate, 4 severe). RV strain showed no statistical differences between groups. However, BDP group showed worse RV function than NO-BPD group, both in speckle tracking analysis and in classical parameters. During de follow-up, an improvement trend is shown in RV strain.

Conclusions: RV longitudinal strain and strain rate derived by speckle tracking is feasible in preterm infants. Although it seems to be a good correlation between RV strain and BPD severity, authors cannot conclude it. More studies should be carried out to investigate the optimum echocardiographic screening model of RV dysfunction in BPD patients.

Introduction

Perinatal medicine has suffered many advances on the last two decades. Despite of that, bronchopulmonary dysplasia (BPD) is still one of the most common and worrying disease in preterm newborn (1). BPD is defined as oxygen need for ⩾28 days from birth until 36 weeks of postmenstrual age (PMA). In 2000, BPD was categorized as none, mild, moderate or severe. None BPD (NO-BPD) was defined as <28 days of oxygen therapy. Mild BPD (MI-BPD) included preterm newborn who received oxygen or mechanical respiratory support for >28 days but were on room air at 36 weeks PMA. Moderate BPD (MO-BPD) is referred to the requirement of supplemental oxygen, but <30% fraction of inspired oxygen concentration, at 36 weeks PMA. Finally, severe BPD (SE-BPD) included those patients who required >30% oxygen or positive pressure at 36 weeks PMA (2, 3). Last investigations tried to establish a more accurate definition that predict properly childhood outcomes in contemporary very preterm infants (4), but they are not widespread nowadays.

BPD implies perturbations on the lung alveolar septation and varying degrees of lung fibrosis and inflammation. BDP usually associates abnormalities in lung microvascular development, which may contribute modify of alveolar septation. Besides, lung capillary and arterioles usually suffer changes in

BPD patients, with thicker-walled pulmonary arteries. In this way, it is not difficult to think that BPD patients not only suffer from alterations on lung structure and function but also may have increased vascular resistance and pulmonary arterial pressures(5). Therefore, echocardiogram screening strategies for pulmonary hypertension (PH) and right ventricle (RV) disfunction are purposed during early childhood (6, 7).

RV myocardial deformation during the cardiac cycle can be studied through strain analysis. 2D speckle tracking (STE) is a recent application software for strain study. STE imaging provides frame-by-frame tracking of ultrasound markers, is angle independent, is less sensitive to signal noise, is not influenced by breathing movement or by the interaction with the adjacent myocardium. This technique has allowed the earlier detection of subtle RV dysfunction (8).

Materials And Methods

Study design and patients

This prospective longitudinal study was carried out over 28 months (from April 2019 to July 2021) at a tertiary care pediatric cardiology reference center. All <32 weeks pre-term infants (PTI) born before July 2020 were eligible for the study. Twenty-eight days after birth, all enrolled patients were included in one group: no bronchopulmonary dysplasia (NO-BPD) or bronchopulmonary dysplasia (BPD). At 36 PMA, BPD patients were included in one group according to severity categorization (mild, moderate, severe) (9). They were screened during routine follow-up at a tertiary care reference pediatric center, which systematically includes several cardiac evaluations. Following recommendations, there was decided to include data at three timepoints: at 36 PMA or discharge (T1), between 5 and 9 months of life (T2), and between 11 and 16 months of life (T3) (10). Anthropometrics data (weight, height), medical antecedents, and echocardiographic measurements were taken. Patients affected from congenital heart disease, major genetic disorders, cardiomyopathy or pulmonary hypertension (echocardiogram diagnosed) were excluded.

Conventional Echocardiography

Echocardiographic examinations were performed using a Siemens Acuson SC2000 ultrasound system (Siemens Healthcare, Erlangen, Germany) equipped with an 8 MHz sector transducer. Two pediatric cardiologists received the same formation to perform all the echocardiographic examinations, following current guidelines (11). Image acquisition procedures were harmonized before the study started. Optimal frame rate (60 to 92 frames/sec) was used to optimize myocardial deformation analysis. ECG-guided, we systematically recorded three cardiac-cycle loops in the following views: apical classic view, apical focused on right ventricular (RV) free wall and shot-axis view focused on RV outflow tract (RVOT) and pulmonary trunk. We also used pulse-wave doppler, tissue doppler and M-mode to analyze cardiac function and heart flows. The following conventional RV function variables were measured: Right atrium area indexed by body surface (RA index), tricuspid annular plane systolic excursion (TAPSE), doppler tissue imaging tricuspid S wave velocity (SW), RV fractional shortening (RV-FS), pulmonary artery

acceleration time (PAAT), right ventricular ejection time (RVET), tricuspid regurgitation pressure gradient (TRPG) and right atrium area (RA) (12).

Speckle tracking (STE) analysis

Both sonographers performed offline strain analysis on apical loops (classic and RV-focused) by both sonographers using the software Velocity Vector Imaging (VVI) 3.0 (Siemens). A second analysis was performed on a sample of 10 randomly selected subjects to assess intra and interobserver reproducibility with no access to the results of first analysis. The investigators manually traced the endocardium in end-diastole. The software detected the movement of the entire myocardial wall (from the endocardium to the epicardium) and therefore defined the areas of interest, for which the quality was considered acceptable or not (Figure 1). VVI software automatically splits ventricular wall into 6 segments. For measuring LV strain, the whole six segments were used. For measuring RV strain, only the tree RV free wall segments were used (Figure 2). In poorly detected segments, the sonographer readjusted the endocardial contour until better detection was obtained. Whenever that was not possible two scenarios we defined: for LV, the segments in question were excluded from the analysis and the rest were used (maximum two segments); for RV, STE data were excluded. We measured the following global STE variables: global systolic LV longitudinal strain (GLS-LV) and strain rate (GLSR-LV), global systolic RV longitudinal strain (GLS-RV) and strain rate (GLSR-RV). Strain data were shown in absolute values to avoid confusion.

Formal aspects

The study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles. Approval was granted by Clinical Research Ethics Committee of Aragón (CEICA). Informed consent was obtained from all parents or legal guardians.

Statistical analysis

SPSS software version 25.0 (SPSS Inc., Chicago, IL, USA) was used for performing statistical analysis. Any difference was considered statistically significant in all tests when the P value was less than 0.05. To determine normality, the distribution of the longitudinal strain and the longitudinal strain rate of both ventricles in all subjects was assessed using the Kolmogorov–Smirnov´s and Shapiro-Wilk´s test. Summary results in the main measures were showed for different groups. Continuous variables were described by the mean and standard deviation (SD), or by median and interquartile range [Q1–Q3] if the variable didn't meet the assumption of data normality. Categorical variables were expressed by absolute frequency as well as percentage. The association between parametrical variables was measured by the Pearson correlation and for non-normal variables, the spearman correlation coefficient instead. For assessed normal samples, mean differences were tested by t-Student test. In other cases, U-Mann-Whitney test was performed. The association along time was evaluated with Friedman test.

Results

Fifty patients were enrolled on the study, 22 on NO-BPD group and 28 on BPD group (16 mild, 8 moderate, 4 severe). Characteristics are revealed in Table 1. We found some basal differences as birth weight or weeks of pregnancy at birth. As expected, BPD group required more ventilatory assistance during intensive care unit (ICU) admission. They also suffered sepsis (vertical and nosocomial) and significant arteriosus ductus more frequently. More number of patients on BPD group suffered bronchiolitis during the first year of life. Even it was observed that on BDP group, 6 patients suffered more than one acute respiratory failure along this period. No patient required home ventilation therapy.

Table 1
Sample characteristics in both groups. Escalate variables are shown as mean/median. Nominal variables are shown as the number of patients (n) and percentage.

	NO-BPD (n=22)	BPD (n=28)
Birth weigth (mean; g)	1412	840
Small for gestational age (n)	1 (4.5%)	6 (21.4%)
Weeks of pregnancy at birth (median; weeks + days)	31+4	26+3
Multiple gestation (n)	10 (45.5%)	13 (46.4%)
Complete fetal lung maduration (n)	3 (13.6%)	4 (14.3%)
Chorioamnionitis (n)	1 (4.5%)	8 (28.6%)
Advanced neonatal resucitation (n) [1]	0	3 (10.7%)
Apgar 1 (median)	9	6
Apgar 5 (median)	10	8
Surfactant (n)	2 (9.1%)	25 (83.9%)
More than one surfactant dose (n)	2 (9.1%)	14 (58%)
Significant patent ductus arteriousus (n)	3 (13.6%)	13 (46.4%)
Invasive mechanical ventilation (IMV) (n)	3 (13.6%)	18 (64.3%)
Days of IMV (median)	0	1
Nitric-oxide (n)	0	3 (10.7%)
Days of non-invasive mechanical ventilation (median)	5	35
Days of low-flow oxygen therapy before discharge (median)	0	14
Necrotizing enterocolitis (n)	2 (9.1%)	8 (28.6%)
Vertical sepsis (n)	0	6 (21.4%)
Nosocomial sepsis (n)	2 (9.1%)	18 (64.3%)
Days of diuretic treatment (median)	0	27
Days of parenteral nutrition (median)	4	14
Length of admission (mean)	43	86
Home oxygen therapy (n)	0	5 (17.9%)
Home ventilation therapy (n)	0	0

[1]More than non-invasive mechanical ventilation.

	NO-BPD (n=22)	BPD (n=28)
Suffered bronchiolitis during first year of life (n)	2 (9%)	11 (39.2%)
Suffered more than one acute respiratory failure (n)	1 (4.5%)	6 (21.4%)
[1]More than non-invasive mechanical ventilation.		

Ultrasound parameters of cardiac function were measured. Results are exposed as mean and standard deviation, or median and interquartile range (Table 2). At T1, fifty measures of each variable were achieved. At T2, 4 patients didn't attend to the medical appointment (2 moved to a different city and 2 refused because of COVID pandemic). At T3, 11 more patients weren´t able to performance a quality echography examination because of bad quality images. T-Student or U-Mann-Whitney test were performed to analyze differences between groups. No statistical differences were found. However, at the three timepoints, BPD group had some data of worse RV function, with lower TAPSE, SW, RV-FS and RV strain and. At T1, these differences were more remarkable after making a new group distribution; severe BPD group presented lower values of SW, RV-FS and GLS-RV than none/mild BPD or moderate BPD. These contrasts were not found at T2 or T3. BPD group also showed lower LV strain values at T1 than NO-BPD group (no statistical significance). This finding was not associated with the presence of significant patent ductus arteriosus. These differences disappeared at T2 and T3.

Table 2
Echocardiographic measurements at the three timepoints. Classification in NO-BPD and BPD. Mean (Standard Deviation) for parametric variables and T-Student test for comparison between groups (p value). Median [interquartile range Q1; Q3] for non-parametric variables and U-Mann-Whitney test for comparison between groups (p value).

		Mean (SD) or Median [Q1; Q3]		p value
		NO-BPD (n = 22)	BPD (n = 28)	
T1	HR (bpm)	164.5 (13.6)	164.8 (12.5)	0.942
	RA index (cm2/m2)	9.1 (1.6)	9.4 (2.1)	0.493
	TAPSE (mm)	10.1 (1.7)	9.7 (1.7)	0.378
	SW (cm/s)	9.8 [9; 11.7]	9.9 [9; 11.7]	0.537
	PAAT / RVET ratio	0.34 (0.09)	0.33 (0.08)	0.714
	GLS-RV (%)	23.9 (4.6)	22 (6.3)	0.215
	GLSR-RV (%)	2.62 [2.26; 3.16]	2.33 [1.92; 2.67]	0.062
	RV-FS (%)	47.3 [39.4; 51.5]	46.3 [34; 49.8]	0.226
	GLS-LV (%)	22 (3.2)	20.4 (3.3)	0.094
	GLSR-LV (%)	2.23 (0.51)	2.07 (0.41)	0.224
		NO-BPD (n = 21)	BPD (n = 25)	
T2	HR (bpm)	138.9 (18.1)	145.7 (14.2)	0.176
	RA index (cm2 / m2)	8.8 [7.6; 9.5]	8.8 [7.5; 9.5]	0.384
	TAPSE (mm)	14.8 (2.1)	13.4 (2.4)	0.039
	SW (cm/s)	12.2 (1.7)	11.2 (1.6)	0.064
	PAAT / RVET ratio	0.38 (0.07)	0.39 (0.08)	0.401
	GLS-RV (%)	26 [21.2; 28.2]	24.1 [18.9; 27.9]	0.349
	GLSR-RV (%)	2.57 (0.88)	2.43 (0.82)	0.594
	RV-FS (%)	39.3 (13.7)	42.1 (13.5)	0.500
	GLS-LV (%)	22.8 (3.5)	22.8 (3.5%)	0.995
	GLSR-LV (%)	2.3 (0.49)	2.07 (0.55)	0.157
		NO-BPD (n = 15)	BPD (n = 16)	

HR: heart rate. BPM: beats per minute.

		Mean (SD) or Median [Q1; Q3]		p value
T3	HR (bpm)	131 (16.6)	128.7 (17.6)	0.699
	RA index (cm2/m2)	8.3 (1.6)	9.9 (1.7)	0.007
	TAPSE (mm)	15.7 [13.8; 16.7]	14.7 [14.5; 15.9]	0.717
	SW (cm/s)	12.3 (2.1)	12.1 (1.6)	0.806
	PAAT / RVET ratio	0.37 (0.06)	0.41 (0.07)	0.05
	GLS-RV (%)	28 (6.1)	26 (4.1)	0.315
	GLSR-RV (%)	2.88 (0.85)	2.60 (0.75)	0.335
	RV-FS (%)	43.6 [35.6; 56.9]	41.7 [32.5; 46.4]	0.166
	GLS-LV (%)	23.8 (4.5)	24.4 (3.1)	0.671
	GLSR-LV (%)	2.28 [1.96; 2.57]	2.07 [1.76; 2.38]	0.349

HR: heart rate. BPM: beats per minute.

Table 3
Echocardiographic measurements at T1. Classification in none/mild BPD, moderate BPD (MO-BPD) and severe BPD (SE-BPD). Mean (Standard Deviation) for parametric variables and T-Student test for comparison between groups (p value). Median [interquartile range Q1; Q3] for non-parametric variables and U-Mann-Whitney test for comparison between groups (p value).

		Mean (SD) or Median [Q1; Q3]			p value
		None/mild-BPD (n = 38)	MO-BPD (n = 8)	SE-BPD (n = 4)	
T1	HR (bpm)	166.3 (13.7)	160.5 (9.3)	158 (7.1)	0.290
	RA index (cm2/m2)	9.1 (1.8)	9.9 (2.7)	9.9 (1.4)	0.447
	TAPSE (mm)	9.8 (1.7)	9.7 (1.8)	10.5 (2.1)	0.939
	SW (cm/s)	10 [9; 12]	9.7 [8.1; 12]	8.9 [7.4; 9.6]	0.121
	PAAT / RVET ratio	0.33 (0.09)	0.34 (0.09)	0.38 (0.09)	0.510
	GLS-RV (%)	23.1 (5.3)	23.8 (7.6)	18.8 (4.6)	0.321
	GLSR-RV (%)	2.38 [1.99; 2.78]	2.36 [2; 3-09]	2.52 [1.1; 4.85]	0.958
	RV-FS (%)	46.7 [35.8; 51.1]	46.7 [35.4; 52.1]	40.3 [30; 47]	0.566
	GLS-LV (%)	21 (3.7)	20.7 (2.2)	22.3 (1.8)	0.729
	GLSR-LV (%)	2.15 (0.5)	2.1 (0.34)	2.2 (0.33)	0.946

HR: heart rate. BPM: beats per minute.

Pearson test was used to study association between variables at the three timepoints. It showed significant good positive correlation between GLS-RV vs. RV-FS (R = 0.617) and between GLS-RV vs. GLS-LV (R = 0.403). It was found mild positive correlation between GLS-RV vs. TAPSE (R = + 0.303). No correlation was found between GLS-RV and SW (Figure 1).

Friedman test was used to study cardiac function variables along time (T1, T2, T3). No differences were found in strain variables of both ventricles (GLS, GLSR), RV-FS, RA index or PAAT / RVET ratio. However, an improvement trend is shown in GLS-RV (Figure 2) and GLSR-RV. Other variables of RV function, like RV-FS didn't show it (Figure 3). RV strain measurements didn´t either showed relation with the number of bronchiolitis along the first year of life.

Ultrasound measurements reproducibility were assessed using intra and interobserver reliability on 10 blindly images randomly sampled from the study. Intraobserver reliability was good, with an intraclass correlation coefficient (ICC) above 0.77. Interobserver reliability was relatively good, with an ICC above 0.69.

Discussion

BPD is a chronic lung disease that, throughout the influence of multiple factors, generates lung alterations, not only in the airway but also on the pulmonary vessels, leading to a variable worsening on the cardiopulmonary function. Last advances on perinatal medicine have allowed to decrease its incidence, but BPD is still the responsible for significant morbidity on preterm infants (3). PH is a rare complication after suffering from BPD, but it is known that it the appearance PH worsens the clinical course, morbidity and mortality of BPD (13). The gold standard technique for the diagnosis of PH y cardiac catheterization, an invasive procedure requiring general anesthesia in young children. It allows a direct measurement of the pulmonary arterial pressure (PAP). However, transthoracic echocardiography is more commonly used in children for its ability to estimate PAP and its consequences on RV (14). Mourani et al. did a retrospective review of data from 25 infants who underwent echocardiography and subsequent cardiac catheterization for the evaluation of pulmonary hypertension. Compared with cardiac catheterization, echocardiography had 79% sensitivity for the presence of pulmonary hypertension (15).

Several traditional echocardiographic measurements are usually used on PH screening. Tricuspid regurgitation pressure gradient (TRPG) represents the most common and reliable method to evaluate the presence and severity of PH (6). In our study, TRPG was used to exclude patients with PH. Other echocardiographic methods have been studied to analyze RV function in preterm infants. Sehgal et al. assessed RV function using tissue Doppler imaging (TDI), 2D RV-FS, TAPSE, and myocardial performance index (MPI) using echocardiography. They found that higher E/E and lower RV-FS showed strong correlations with the subsequent duration of respiratory support during hospitalization. The rest of parameters had no relevance. Although in normal values (16), our sample showed lower RV-FS in BPD group at T1, with correlate with their results. However, there is lack of evidence in the literature about the echocardiographic management of these patients.

It´s known that RV strain is a feasible technique (8, 17). RV strain predicts mortality in a population of stable patients with chronic heart failure with reduced LV ejection fraction independent (18), predicts the prognosis after acute myocardial infarction in adults (19) or mortality in patients with COVID-19 (20). RV strain has also been exposed as an useful tool in the evaluation of RV in PH patients of several etiologies (21, 22).That´s why authors decided to study GLS, in order to inquire if added value was shown. Xie et al. evaluated strain in children between 3-5 years old. They found some differences in RV strain between preterm BDP patients and term infants and also that duration of invasive ventilation was as an independent determinant of GLS-RV (23). Our cohort compare BDP with NO-BDP patients, but all of them are PTI. Perhaps, GLS impairment is associated not only with BPD, but also with prematurity.

Haque et al. also studied RV function in BPD patients. They didn´t found differences in traditional echocardiographic parameters, but using speckle tracking they discovered that infants with severe BPD had lower peak global systolic strain than did infants with moderate BPD or mild/none BPD (24). However, other authors did not found differences between BPD and NO-BPD group neither traditional echocardiographic parameters or through myocardial deformation analysis (25).

Blanca et al. designed a similar study to ours (26). They included BPD patients, with and without PH. At 6 months of PMA, they found differences in RV fractional shortening and GLS-RV between non-PH and PH patients (all of them suffered from BPD). In our investigation, we excluded PH, hoping that GLS-RV would contribute to detect subclinical changes in RV myocardial damage. However, it´s probable that larger alterations in clinical situation are needed to find significant differences in GLS. Our cohort also shows an improvement along time, which suggest the theory that patients with non-severe clinical situation (non-PH patients) demonstrate a total recovery of myocardial alterations.

As to GLS-LV data in BPD group at T1, authors purpose its correlation with RV function. When echocardiographic measurements were taken, septum took part of LV strain so RV movement may be related with these results. Czernik et al. studied LV strain for the first month of life in BPD patients. They found higher values of LV strain in BPD group during the first two weeks of life, which disappear at month of life. They explain that findings with the hemodynamic changes that appear within the first days of life and the volume overload that generates a patent ductus permeable (27). In our cohort, first analysis was made at 36 PMA and no relationship was found with the presence of PDA. At this timepoint, PDA-associated problems are usually resolved.

This study has several strengths and limitations. The main strengths include the longitudinal follow-up over 1 year of life. We used the same equipment and protocol for all patients and echocardiographic images and measurements were made by the same investigators. The study was limited by offline speckle tracking analysis. The dependence of 2D-STE imaging on the frame-by-frame tracking of the myocardial pattern means it is influenced by image factors, including reverberation artefacts and attenuation. Thus, we lost to many cases at T3, due to the requirement of a very good loop imagen to complete a reliable strain analysis. Our study was also limited by the small sample size which makes difficult to find significant differences and generates large variances. After statistical analysis, we realize we should include PH patients, given that more variability in clinical situation is needed to find differences.

In conclusion, our study demonstrates that, although challenging, measuring RV longitudinal strain and strain rate derived by speckle tracking is feasible in preterm infants. Although it seems to be a good correlation between RV strain and BPD severity, authors cannot conclude it in our study. More studies should be carried out to investigate the optimum echocardiographic screening model of RV dysfunction in BPD patients (whether including strain measurements or not) and to confirm that non-PH patients who suffered from BPD keep a normal RV function over the years.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose

Author Contributions

All authors contributed to the study conception and design. Recruiting patients and material preparation was done by Marcos Clavero-Adell, Itziar Serrano-Viñuales, Segundo Rite-Gracia. Echocardiogram images and STE analysis were performed by Marcos Clavero-Adell and Ariadna Ayerza-Casas. Data collection was performed by Daniel Palanca-Arias, Marta López-Ramón and Lorenzo Jiménez-Montañés. Analysis was performed by Marcos Clavero-Adell, Daniel Palanca-Arias and Ariadna Ayerza-Casas. The first draft of the manuscript was written by Ariadna Ayerza-Casas and Marcos Clavero-Adell and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

Ethics in publishing

The study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles. Approval was granted by Clinical Research Ethics Committee of Aragón (CEICA).

Consent to participate

Written informed consent was obtained from the parents.

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Figures

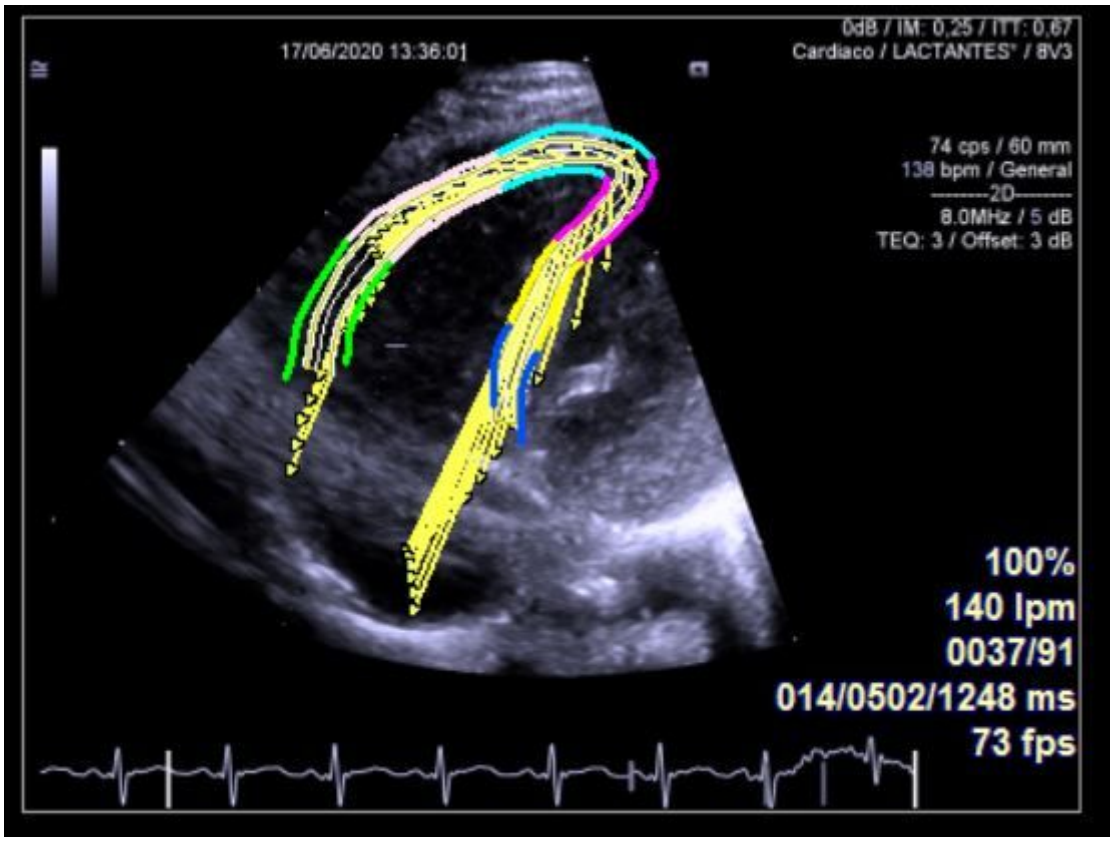

Figure 1

Right ventricle-focused four chamber view. Strain analysis of right ventricle with speckle tracking software. The endocardial and epicardial borders were manually delineated to perform a semiautomatic trace of the myocardial movement. The magnitude and direction of each vector reflect the corresponding myocardial movement towards the reference point.

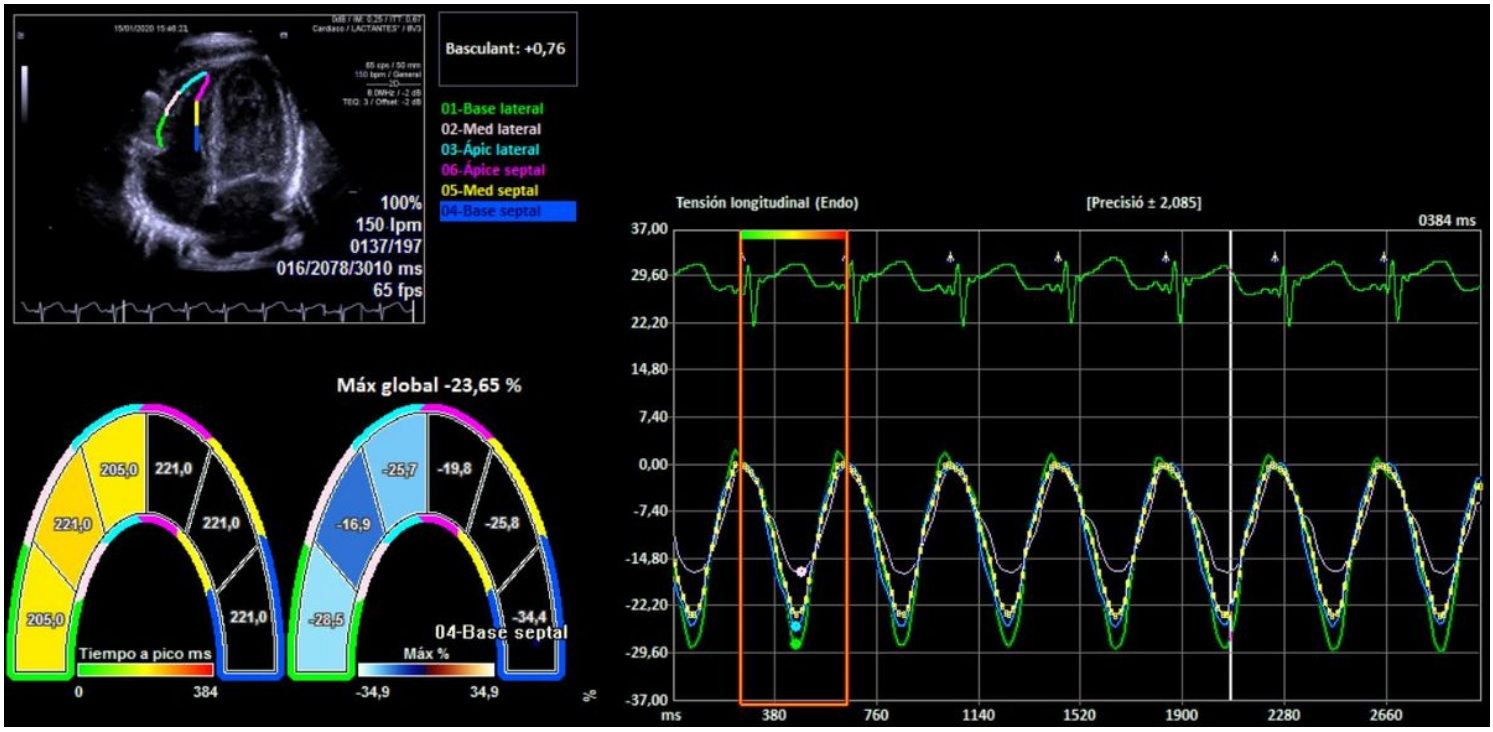

Figure 2

Strain measurement of the right ventricle using speckle tracking. The software analyses the regional values of strain rate of the six segments in which it divides. Investigators selected the three right free wall segments and an average value was obtained.

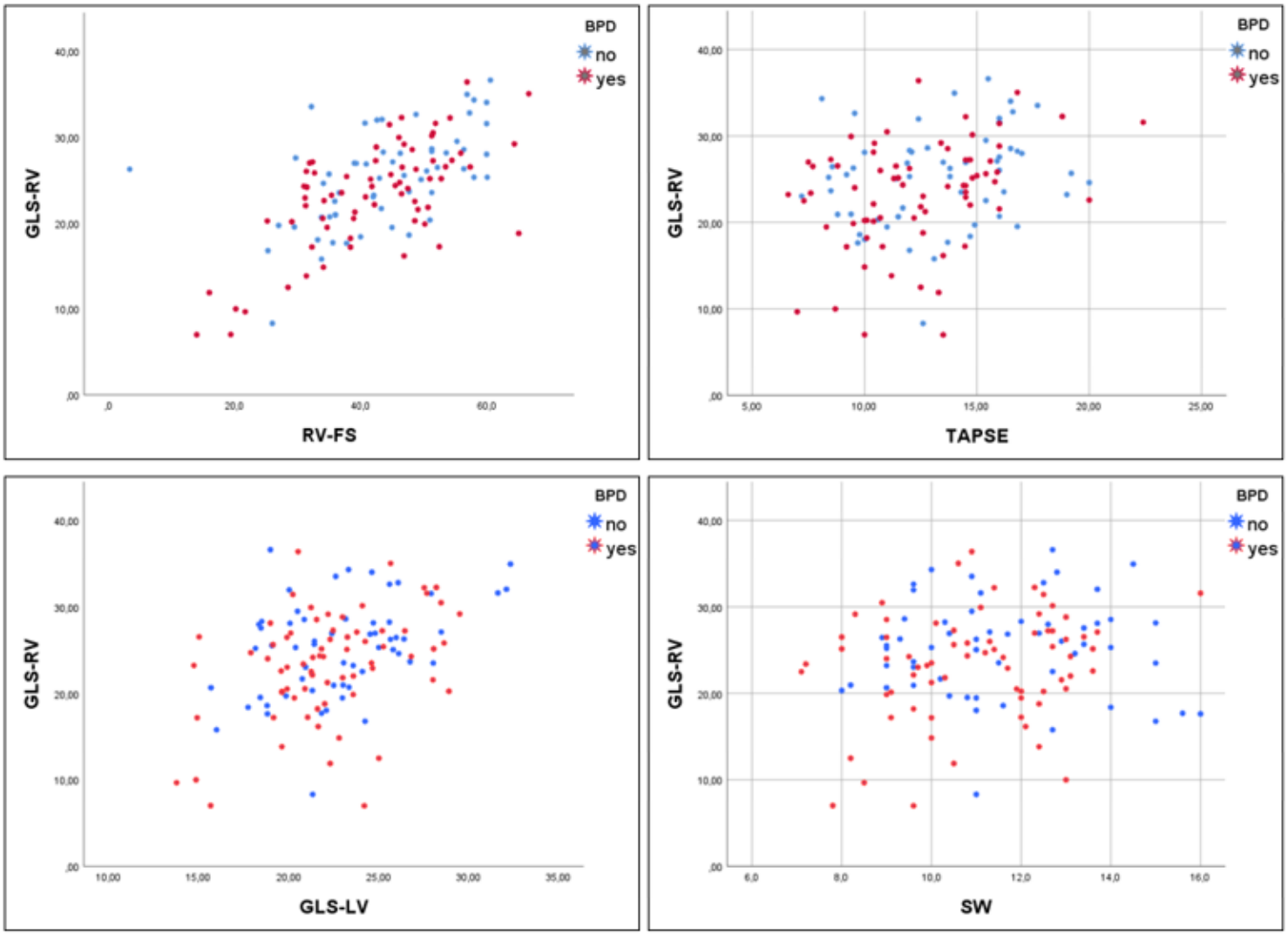

Figure 3

Scatter plot relating GLS-RV with RV-FS, TAPSE, GLS-LV and SW. It´s shown clear positive correlation between GLS-RV and RV-FS or GLS-LV. It´s seems there is also positive correlation between GLS-RV and TAPSE, but no so clear. There is no correlation at all between GLS-RV and SW.

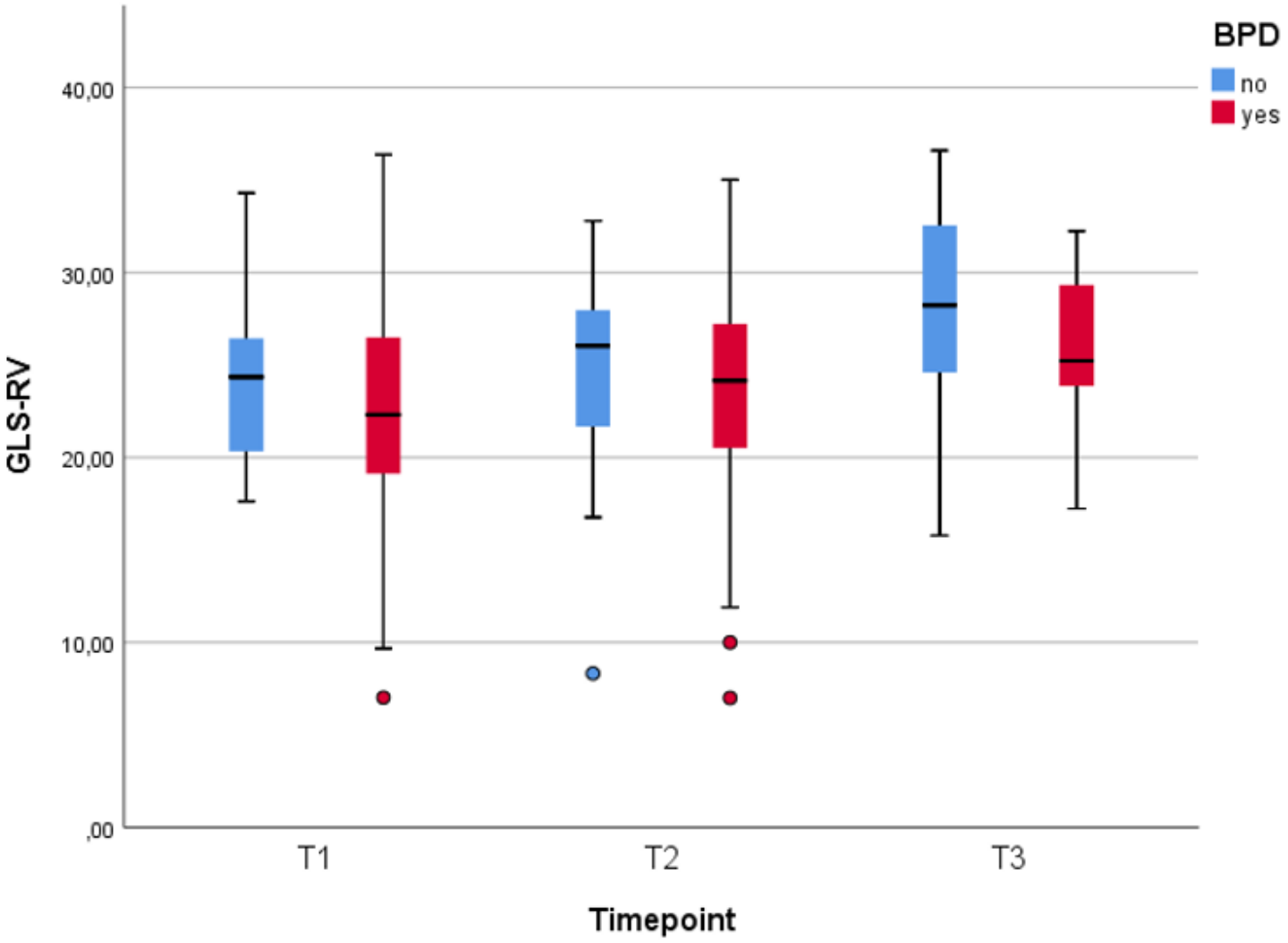

Figure 4

GLS-RV (mean and standard deviation) at different timepoints. Although it´s no significant, we can appreciate that GLS-RV tends to improve along time, which is more evident in BPD patients.

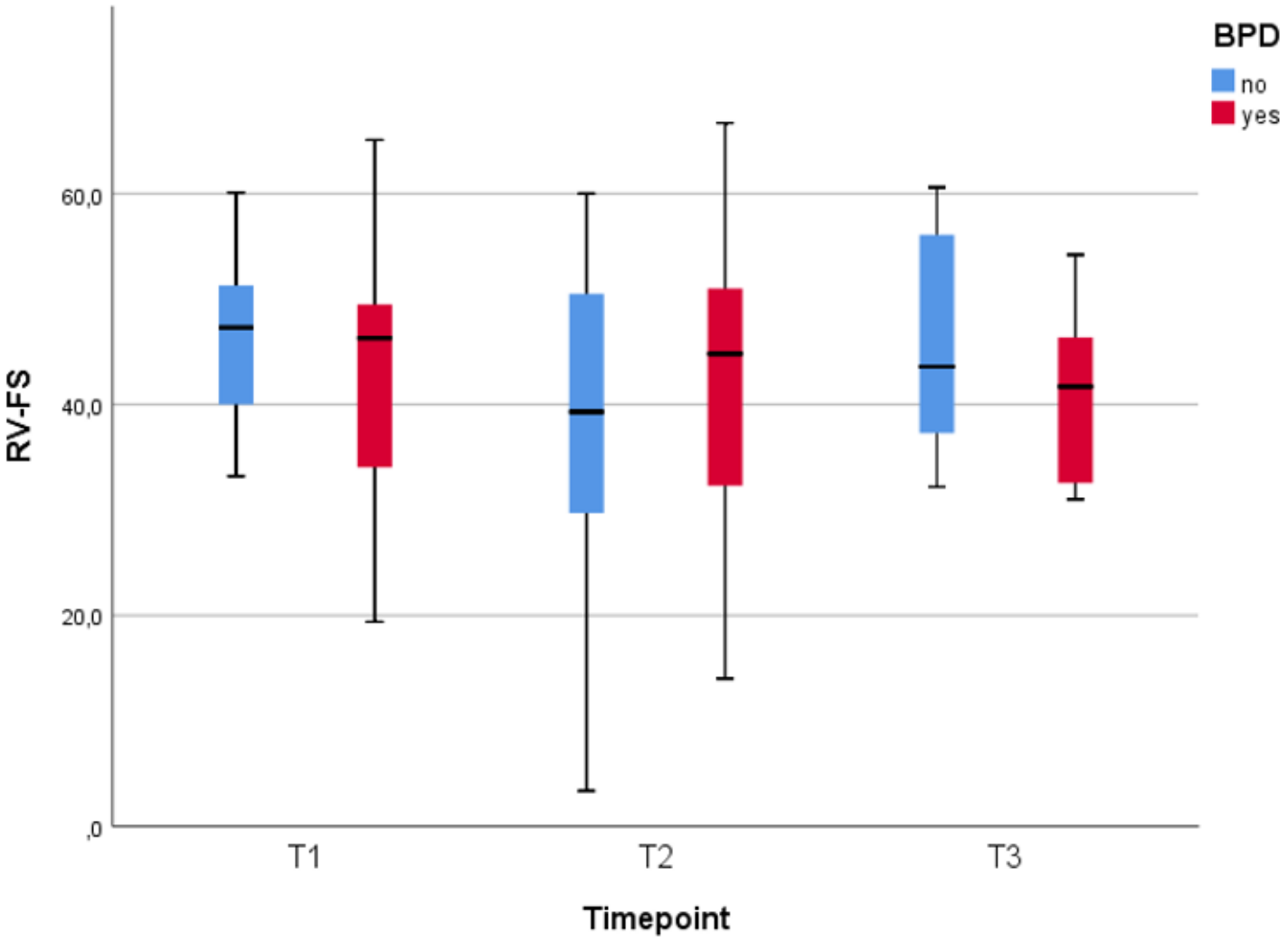

Figure 5

RV-FS (mean and standard deviation) at different timepoints. We can´t appreciate no changes in RV-FS along time, neither BPD or NO-BPD patients.