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ORIGINAL RESEARCH

Right Ventricular Dyssynchrony Before and After Pulmonary Thromboendarterectomy in Patients with Chronic Thromboembolic Pulmonary Hypertension

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ABSTRACT

Background: Left ventricular dyssynchrony has been studied extensively, but this is not the case with right ventricular (RV) dyssynchrony. Our aim was to investigate RV dyssynchrony through 2D speckle strain imaging in patients with chronic thromboembolic pulmonary hypertension (CTEPH) before and after pulmonary thromboendarterectomy (PTE).

Methods: We measured 2D peak RV strain (%) of the RV free-wall and time to peak strain (ms) of its three freewall segments (base, mid, and apex) in 127 consecutive CTEPH patients (51 ± 14 years, 59% female) with adequate images pre- and post-PTE. RV strain was calculated using Epsilon Imaging EchoInsight® software. RV dyssynchrony was measured using two methods: the standard deviation of peak systolic strain and the standard deviation of time (ms) to peak strain (RVDT) between the three RV free-wall segments.

Results: Mean RV free wall strain did not change significantly after PTE (−11.4 ± 5.7 to −11.2 ± 5.6%, $p = 0.67$). However, RV dyssynchrony improved dramatically after surgery in RVDP and RVDT (9.4 ± 6.2 to 5.4 ± 3.8%, $p < 0.0001$; 103 ± 65 to 56 ± 65 ms, $p < 0.0001$, respectively).

Conclusions: There was a significant decrease in the standard deviation of the mean peak systolic strain and time to peak strain (dyssynchrony) of the three RV free-wall segments after PTE. The cause of this more uniform contraction of the right ventricle after PTE is unclear, but could stem from the marked change in pulmonary vascular resistance and mean pulmonary arterial pressure in this population.

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KEYWORDS Chronic thromboembolic pulmonary hypertension; dyssynchrony; pulmonary hypertension; right ventricular strain

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by a heterogeneous distribution of recurrent pulmonary arterial thromboemboli or in situ thromboses.[1–3] The resultant fibrotic transformation leads to increased pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). This increase in right ventricular (RV) afterload leads to RV hypertrophy, dilation, and eventual dysfunction and failure. CTEPH is a unique form of pulmonary hypertension because it is potentially curable by pulmonary thromboendarterectomy (PTE).[4,5]

Ventricular mechanical and electromechanical dyssynchrony has been well described in left ventricular (LV) failure in the setting of cardiac resynchronization therapy (CRT).[6] Aside from improvement in functional capacity, the success of CRT now includes echocardiographic measurements to determine the uniformity in contraction of the LV sub-segments.[7,8] RV mechanical dyssynchrony (RVD) has been less studied but has been described in the setting of heart failure and pulmonary hypertension (PH).[9,10] Furthermore, recent work by Badagliacca and colleagues and Murata and colleagues have shown that RVD may be an independent prognostic factor in patients with PH.[11,12]

Newer echocardiographic techniques such as two-dimensional (2D) speckle tracking provide an opportunity to better quantify RV function using strain analysis. The aim of this study was to assess RV dyssynchrony by 2D speckle tracking strain imaging in patients with CTEPH before and after PTE.

Materials and methods

Study population

We studied 314 consecutive patients undergoing CTEPH evaluation with right heart catheterization (RHC) and echocardiography. Of the 314 patients, 127 had adequate preoperative and postoperative strain images. All patients were referred to our center between January 1, 2012 and December 31, 2013 and had confirmed CTEPH diagnosed by pulmonary V/Q scan and pulmonary angiography. The average age of the study subjects was 51 ± 14 years (range 18–88 years); 59% were female

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

Age, yrs	51 ± 14
Sex, % female	59%
BMI, kg/m^2	31 ± 7.5
Functional Class, WHO	2.9 ± 0.5
Mean PAP, mm Hg	46 ± 12
Cardiac index, l/min/m^2	2.2 ± 0.6
PVR, dynes-sec/cm^5	717 ± 357

Note. BMI, body mass index; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance.

(Table 1). All patients were hemodynamically stable during the time of RHC and echocardiography. The study design was reviewed and approved by the UCSD Human Research Protection Program/Institutional Review Board.

Right heart catheterization

RHC was performed 6.0 ± 5.0 days before PTE and again on the first postoperative day in all 127 patients. Standard RHC was performed using a Swan-Ganz catheter through jugular or femoral venous access. Right atrial pressure (RAP), mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) were measured. CO was determined via the thermodilution method as an average of three sequential measurements. PVR was then calculated from the equation: PVR = (mPAP – PCWP)/CO. Cardiac index was also calculated.

Echocardiography

Echocardiography was performed 9.7 ± 17.3 days before and 11.3 ± 17.0 days after PTE. All patients were hemodynamically stable and all studies were performed in the echocardiography suite. All echocardiograms were performed using a Vivid E7 cardiovascular ultrasound system (GE VingMed, Horton, Norway) by qualified sonographers with data stored digitally for off-line analysis. All sonographers were blinded to RHC data. All measurements were made in accordance with the American Society of Echocardiography recommendations.

Speckle tracking analysis

For 2D speckle tracking analysis, standard grayscale 2D images in the apical 4-chamber view were used. All images were analyzed with Epsilon Imaging EchoInsight® software. The RV free wall myocardium was separated into three standard segments. The myocardium was manually traced along the endocardial border at the single frame from end-systole. The software then employed an automated tracking algorithm to continuously trace the endocardial border throughout the cardiac cycle. Strain was calculated for each of the individual RV free wall segments—base, mid, and apex. Total strain was calculated from only the RV free wall segments to exclude interventricular interaction and postoperative septal abnormality.[13]

RVD was calculated using two methods: (1) standard deviation of peak-systolic strain between the three free wall segments (RVDP; Figure 1; and (2) standard deviation of times to peak-systolic strain between the three free wall segments corrected to the R-R interval according to Bazett's formula (RVDT; Figure 2).[10]

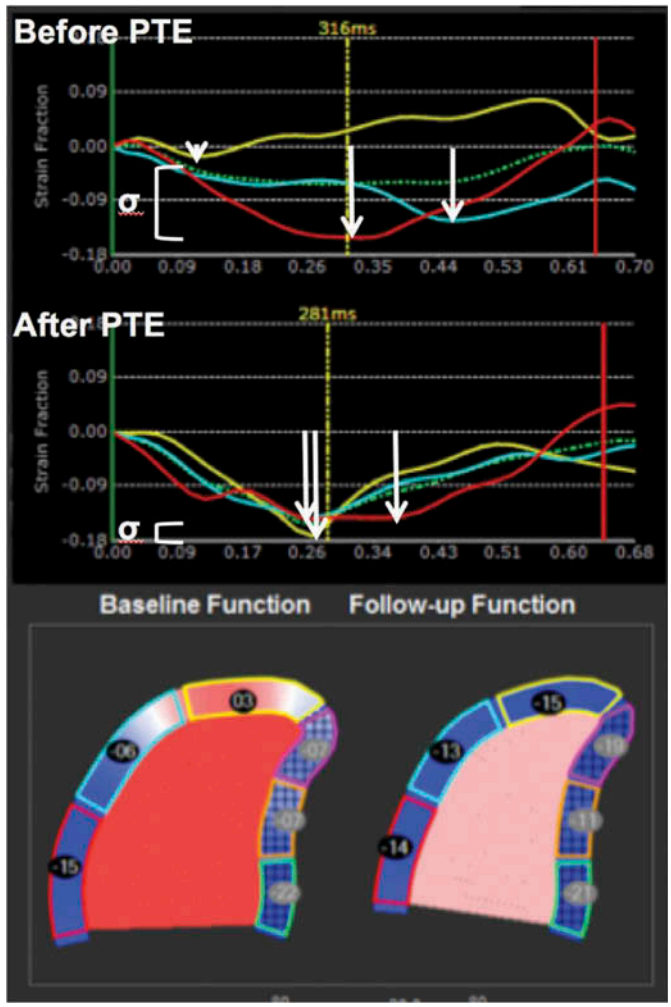

Figure 1. Representative patient showing the standard deviation (σ) of peak systolic strain between the three free-wall right ventricular free wall segments before and after PTE.

Intra-observer and inter-observer variabilities of RVD and RV segmental strain were assessed using a randomly selected subset of 10 patients. Intra-observer measurements were obtained on three separate occasions within 1 week absent of prior measurements. A second observer repeated the same measurements to obtain the inter-observer variability. Intra-class correlation coefficients (ICC) between the measurements were used to assess the intra-observer and inter-observer variabilities. An ICC > 0.8 is considered almost perfect agreement. The ICCs for intra-observer and inter-observer reproducibility were 0.90 and 0.85, respectively.

Statistical analysis

Data are presented as means ± standard deviation. A paired two-tailed Student's *t*-test was used to evaluate differences in longitudinal RV free wall strain, RV basal strain, RV mid strain, RV apical strain, and RV dyssynchrony following PTE. 95% confidence intervals and *p*-values were calculated to establish significance. Longitudinal RV free wall strain, RV basal strain, RV mid strain, RV apical strain, and RV dyssynchrony were compared to RHC parameters using linear regression software

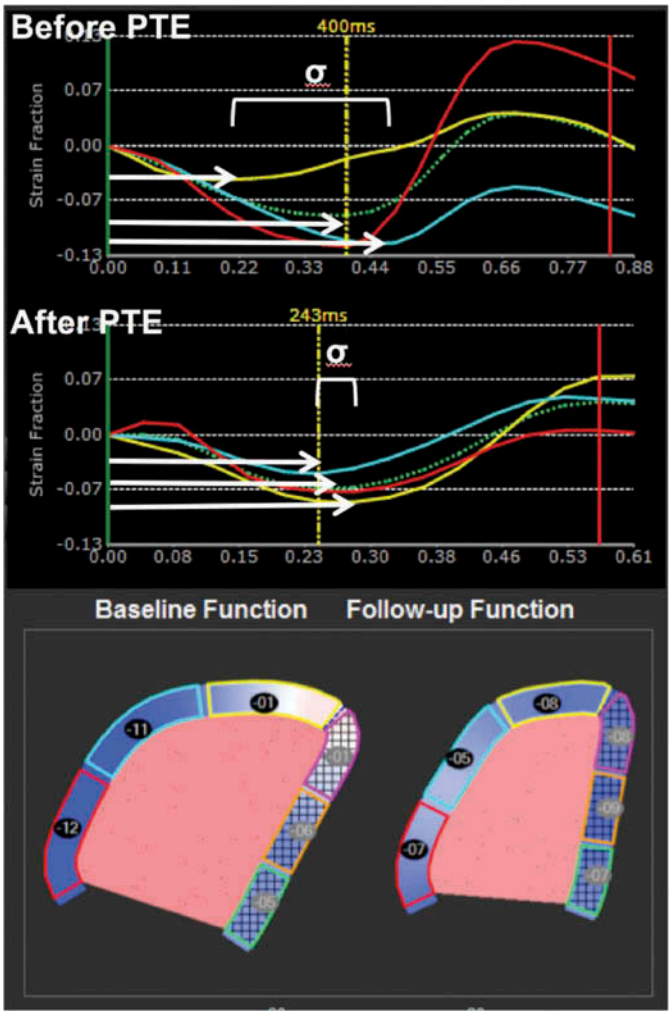

Figure 2. Representative patient showing the standard deviation (σ) of time to peak systolic strain between the three free-wall right ventricular free wall segments before and after PTE.

[Excel (Microsoft, Redmond, WA, USA) and Stata (StataCorp LP, College Station, TX, USA)]. ANCOVA was performed to adjust for independent variables and covariates using MedCalc Statistical Software version 17.5.3 (MedCalc Software bvba, Ostend, Belgium).

Results

Data from pre- and post-PTE transthoracic echocardiograms and RHCs are presented in Table 2. There were statistically significant reductions in both mPAP (46 ± 12 to 23 ± 7 mmHg, $p < 0.001$) and PVR (723 ± 358 to 238 ± 133 [dynes-sec]/cm^5, $p < 0.001$) following PTE. Furthermore, CO significantly increased (4.4 ± 1.3 to 5.6 ± 1.2 L/min, $p < 0.001$) following PTE.

Echocardiographic data for RV function and strain are presented in Table 2. The total longitudinal RV free wall strain remained the same before and after PTE (−11.4 ± 5.7 to −11.2 ± 5.6%, $p = 0.68$). Basal and mid RV free wall strain worsened (i.e. became less negative): −17.1 ± 10 to −14.1 ± 8.3% ($p = 0.003$) and −12.8 ± 8.4 to −10.1 ± 7.1% ($p = 0.001$) respectively after PTE, but apical free wall strain improved (−3.7 ± 8.9 to −9.2 ± 6.9%, $p < 0.001$). Tricuspid annular plane systolic excursion (TAPSE) decreased after PTE (1.5 ± 0.6 to 0.7 ± 0.4 cm, $p < 0.001$). Tricuspid annular systolic velocity (S') decreased after PTE (8.2 ± 3.5 to 5.4 ± 2.8 cm/sec, $p < 0.001$) (these TAPSE and S' results are similar to previously published data[14,15]).

RVD data are presented in Table 2. RVDP (the standard deviation between peak systolic strain of the RV free wall segments) improved significantly after PTE (9.4 ± 6.2% to 5.4 ± 3.8%, $p < 0.001$). RVDT (the standard deviation of time to peak strain between the RV free wall segments) also improved significantly after PTE (103 ± 65 ms to 56 ± 65 ms, $p < 0.001$). Of note, the magnitude of improvement in RVDP or RVDT did not correlate with changes in PVR or mPAP ($r = -0.032$ [$p = 0.72$] and $r = -0.071$ [$p = 0.42$], respectively for RVDP; 0.11 [$p = 0.22$] and $r = 0.16$ [$p = 0.07$], respectively for RVDT).

We assessed whether preoperative factors could have affected postoperative RVDP or RVDT using a one-way ANCOVA. There was no significant effect of preoperative PVR, RVDP or RVDT, or RV longitudinal strain when

Table 2. Comparison of hemodynamic and echocardiographic characteristics before and after PTE.

	Before PTE	After PTE	Average difference	*p*-value
Mean PAP, mm Hg	46 ± 12 CI [44, 48]	24 ± 7 CI [23, 25]	−22 ± 10	< 0.0001
Cardiac index, l/min/m^2	2.2 ± 0.6 CI [2.1, 2.3]	2.8 ± 0.5 CI [2.7, 2.9]	0.6 ± 0.6	< 0.0001
PVR, dynes-sec/cm^5	717 ± 357 CI [654, 780]	245 ± 132 CI [222, 268]	−477 ± 310	< 0.0001
RV Basal diameter, cm	4.9 ± 0.9 CI [4.7, 5.1]	4.3 ± 0.8 CI [4.2, 4.4]	−0.6 ± 0.8	< 0.0001
RV Mid diameter, cm	4.9 ± 1.0 CI [4.7, 5.1]	4.2 ± 0.8 CI [4.1, 4.3]	−0.6 ± 0.9	< 0.0001
RV Long diameter, cm	8.2 ± 1.0 CI [7.9, 8.3]	7.6 ± 0.9 CI [7.4, 7.8]	−0.53 ± 0.7	< 0.0001
RV Area ED	34 ± 10 CI [32, 36]	28 ± 8 CI [27, 29]	−6.2 ± 6.9	< 0.0001
RV Area ES	29 ± 10 CI [27, 31]	22 ± 7 CI [21, 23]	−6.8 ± 6.0	< 0.0001
TAPSE, cm	1.5 ± 0.6 CI [1.4, 1.6]	0.7 ± 0.4 CI [0.6, 0.8]	−0.8 ± 0.6	< 0.0001
S', cm/sec	8.2 ± 3.5 CI [7.6, 8.8]	5.4 ± 3.8 CI [4.7, 6.1]	−2.8 ± 4.2	< 0.0001
RVFAC, cm^2	17 ± 9.3 CI [15.4, 18.6]	22 ± 10 CI [20, 24]	5.2 ± 8.8	< 0.0001
RV longitudinal strain, %	−11 ± 5.7 CI [−12, −10]	−11 ± 5.6 CI [−12, −10]	0.2 ± 5.51	0.68
Basal strain, %	−17 ± 10 CI [−18.8, −15.2]	−14 ± 8.3 CI [−15.5, −12.5]	3.1 ± 11	0.003
Mid strain, %	−13 ± 8.4 CI [−14.5, −11.5]	−10 ± 7.1 CI [−11.3, −8.8]	2.7 ± 9.3	0.001
Apical strain, %	−3.7 ± 8.9 CI [−5.3, −2.1]	−9.2 ± 6.9 CI [−10.4, −8.0]	−5.3 ± 9.6	< 0.0001
RV basal time to peak strain, ms	391 ± 100 CI [373, 409]	342 ± 114 CI [322, 362]	−48 ± 144	0.0003
RV mid time to peak strain, ms	371 ± 107 CI [352, 390]	319 ± 83 CI [304, 334]	−52 ± 134	< 0.0001
RV apex time to peak strain, ms	329 ± 177 CI [298, 360]	299 ± 76 CI [286, 312]	−20 ± 194	0.08
RVD, %	9.4 ± 6.2 CI [8.3, 10.5]	5.4 ± 3.8 CI [4.7, 6.1]	−3.9 ± 7.0	< 0.0001
RVD, ms	103 ± 65 CI [92, 114]	56 ± 65 CI [45, 67]	−47 ± 86	< 0.0001

Note. CI = 95% confidence interval; ED, end-diastolic; ES, end-systolic; PAP, pulmonary artery pressure; PTE, pulmonary thromboendarterectomy; PVR, pulmonary vascular resistance; RV, right ventricular; RVD, right ventricular dyssynchrony; S', tricuspid annular velocity; TAPSE, Tricuspid annular plane systolic excursion.

controlling for age, BMI, sex, and the use of pulmonary hypertension medications prior to PTE. There was a significant effect of preoperative TAPSE on postoperative RVDT [$F(25,93) = 3.72$, $p = <0.001$], with an R^2-adjusted of 0.36, but not postoperative RVDP [$F(25,95) = 1.43$, $p = 0.11$]. In other words, patients with a higher preoperative TAPSE tended to have more postoperative improvement in RVDT.

We also assessed for independent preoperative factors that could affect the percent change in RVDP and RVDT. There was a significant effect of preoperative RVDP on percent change in RVDP from baseline when controlling for age, BMI, sex, PVR, mPAP, and use of pulmonary hypertension medications [$F(24,96) = 3.32$, $p = < 0.001$] with an R^2-adjusted of 0.31. There was no significant effect of preoperative PVR, TAPSE, or RV longitudinal strain on percent change in RVDP from baseline. There was a significant effect of preoperative RVDT and TAPSE on percent change in RVDT from baseline when controlling for age, BMI, sex, PVR, mPAP, and use of pulmonary hypertension medications [$F(4,112) = 6.37$, $p = <0.001$ and $F(24,92) = 2.57$, $p = 0.001$, respectively] with R^2-adjusted values of 0.14 and 0.23. There was no significant effect of preoperative PVR or longitudinal strain on percent change in RVDT from baseline.

Discussion

Mechanical dyssynchrony of the LV has been previously described as an important component of LV systolic dysfunction. Furthermore, improvement of mechanical LV dyssynchrony is often seen with clinically successful resynchronization therapy.[6] More recently, RVD has been described in pulmonary arterial hypertension. In PH, RVD is an independent prognostic factor directly related to afterload, which is reversible with large reductions in PVR.[10] The current study is the first to show that RVD improves essentially immediately after PTE.

We sought to evaluate RV dyssynchrony using previously described methods that measure the standard deviation of time to peak negative strain (Figure 2).[10,11,16] We evaluated dyssynchrony of the three RV free-wall segments and excluded the interventricular septum. Some previous studies of RV dyssynchrony have evaluated all wall segments including the apex (e.g., Murata and colleagues[12]), while others have focused on the basal and mid wall segments (e.g. Bradagliacca and colleagues[11]). In this study, we included basal, mid, and apical RV free wall segments. Patients who underwent PTE had an improvement in dyssynchrony by an average of 47 ms (46% decrease from baseline, $p < 0.0001$). When only including the basal and mid free wall segments, dyssynchrony improved by an average of 27 ms ($p = 0.026$). We excluded strain analysis of the interventricular septum for several reasons. First, the twisting motion of the LV may influence RV function via the septum.[13] Second, RV free wall strain has been shown to correlate most with RV performance in the setting of PH.[17] Finally, PTE patients undergo cardiopulmonary bypass, which is associated with paradoxical septal motion and changes in both postoperative translation and strain measurements.[18]

In addition to calculating RVD using time to peak negative strain, we used a novel method by measuring the standard deviation of peak strain between the free wall segments (Figure 1). Patients with normal RV function show minimal difference in the magnitude of peak strain.[19] In our cohort of patients, RV basal and mid free wall strain worsened after PTE (−17.1 ± 10 to −14 ± 8.3% [$p = 0.003$] and −12.8 ± 8.1 to −10.1 ± 7.1% [$p = 0.001$], respectively) while RV apical strain improved (−3.7 ± 8.8 to −9.2 ± 6.9%, $p < 0.0001$). Total longitudinal strain remained unchanged after PTE (−11.4 ± 5.7 to −11.2 ± 5.6%, $p = 0.68$). However, the standard deviation of peak strain between the three free wall segments decreased after PTE (9.4 ± 6.2 to 5.4 ± 3.8%, $p < 0.0001$). Thus, the magnitude of strain between the three segments became more uniform after PTE and RV dyssynchrony lessened.

This is the first study to show that two parameters of RV dyssynchrony improve significantly after PTE. Both time to peak strain and magnitude of peak strain become more uniform (Supplemental Video, available online). Previous studies have described these parameters in PH, but independent of each other.[20–22] In patients with CTEPH, the clinical implications of RVD before and after PTE are unclear. With ANCOVA regression analysis, the percent change in both RVDT and RVDP appear to correlate positively with lower preoperative RVDT and RVDP. Thus, those with *worse* preoperative RVD appear to show the *largest* relative improvement in RVD after PTE. In addition, better preoperative RV function as measured by TAPSE also correlated with greater improvement in RVDT, but not RVDP. Finally, preoperative PVR, RV longitudinal strain, and cardiac index had no correlation with postoperative RVDP or RVDT. One can hypothesize that improvement in RVD may be a predictor of clinical benefit after PTE. Similarly, severe post-PTE RVD could be an echocardiographic predictor of suboptimal postoperative outcomes.

Study limitations

Although we have shown good reproducibility with strain analysis, a significant proportion of eligible patients did not have adequate images for RV speckle tracking. Unfortunately, this is a common problem in recent clinical studies.[23] We are cautiously optimistic that technological developments will improve the overall applicability of RV speckle tracing.[24]

In addition, RHC and transthoracic echocardiograms were not performed simultaneously, and up to 48 hours elapsed between these procedures. This is the usual practice at our institution. All patients in the study group were hemodynamically stable during the period between echocardiography and RHC. Because of the chronicity of the disease process in patients with CTEPH, we do not believe that simultaneous measurement would have yielded significantly different results.

Right ventricular function is difficult to assess. Due to its pyramidal shape and multiple contractile movements, and sensitivity to hemodynamics and loading conditions, using a single imaging plane to assess right ventricular function is incomplete. Given the current imaging landscape and measures for RV function, both TAPSE and global longitudinal strain provide reasonably good surrogates, specifically in the setting of pulmonary hypertension.

Finally, calculation of CO via the thermodilution method (especially with severe tricuspid regurgitation) can lead to measurement errors. Severe tricuspid regurgitation occurs in only ~10% of CTEPH patients, however, and the thermodilution method remains the accepted standard measurement for CO in patients with CTEPH.

Conclusion

To our knowledge, this is the first study to evaluate RVD in patients with CTEPH prior to and following PTE. We found that two aspects of RVD improved significantly after PTE: (1) the standard deviation of time to peak strain between the three RV free wall segments, which improved from 103 ± 65 to 56 ± 65 ms ($p < 0.0001$); and (2) the standard deviation in peak strain between the three RV free wall segments, which improved from 9.4 ± 6.2 to 5.4 ± 3.8% ($p < 0.001$). However, these changes did not correlate with the reduction in mPAP or PVR, or with the increase in cardiac index. Further studies are underway to investigate whether improvement in RVD after PTE is an independent predictor of long-term RV function and clinical outcomes in CTEPH.

Supplemental video

Video 1

These are representative echocardiograms of a patient who underwent PTE.

(a) The left and right panels show four chamber views before and after surgery, respectively. The blue lines help indicate the directionality and magnitude of free wall strain. The numbers indicate the peak strain value of the individual free wall segments.

(b) The strain graphs correspond to each free-wall segment before (top panel) and after (bottom panel) PTE. These graphs show the representative improvement in RVD (splay between the function plots) by both time to peak strain (RVDT) and magnitude of peak strain (RVDP) between the three free wall segments.

(c) Figurative heat-map representation of RV free wall strain. The shades of red coincide with negative strain and shades of blue correlate with positive strain. The post-operative RV free wall shows a more uniform coloration and thus correlates with a more uniform contraction of the RV free wall.

Disclosure statement

No potential conflicts of interest were reported by the authors.

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