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RESEARCH ARTICLE

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Tricuspid annular plane systolic excursion to pulmonary artery systolic pressure ratio in chronic thromboembolic pulmonary hypertension improves with balloon pulmonary angioplasty

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Abstract

Right ventricle (RV)-to-pulmonary artery (PA) coupling measured by the ratio of echocardiography-derived tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (PASP) is a meaningful prognostic marker in pulmonary hypertension (PH). It's unclear if balloon pulmonary angioplasty (BPA) treatment of chronic thromboembolic pulmonary hypertension (CTEPH) alters RV-PA coupling measured by TAPSE/PASP. We reviewed CTEPH patients treated with BPA at our institution who had a transthoracic echocardiogram (TTE) before BPA and a follow-up TTE at any point during BPA. TAPSE was obtained from the initial and lattermost TTE; hemodynamics were obtained before each BPA session. Between March 2015 to October 2023, there were 228 patients treated with BPA. After excluding post-PTE patients and those without PH, 67 were included. Initial TAPSE/PASP was 0.39 ± 0.21 mm/mmHg. Using previously defined TAPSE/PASP tertiles in PH (<0.19, 0.19–0.32, >0.32 mm/mmHg), there were 6 patients (9%) in low, 30 (45%) in middle, and 31 (46%) in the high tertiles at baseline. The lower TAPSE/PASP tertiles had more severe baseline hemodynamics ($p < 0.001$) compared to the high TAPSE/PASP cohort. At follow-up, TAPSE/PASP improved to 0.47 ± 0.20 mm/mmHg ($p = 0.023$), with 2 (3%), 13 (19%), and 52 (78%) patients in the low, middle, high TAPSE/PASP tertiles, respectively. As patients progress through BPA sessions, the TAPSE/PASP ratio increases, possibly reflecting improved RV mechanics and RV-PA coupling. TAPSE/PASP ratio as a marker of RV-PA coupling can improve with BPA treatment and may be an important measure to follow during treatment of CTEPH.

KEYWORDS
BPA, CTEPH, echocardiography, RV-PA coupling, TAPSE

INTRODUCTION

The ability of the right ventricle (RV) to adapt is essential in pulmonary hypertension (PH) and a major determinant of prognosis.[1,2] As PH progresses and RV afterload steadily increases, the RV undergoes homeometric remodeling to compensate and maintain contractility. This adaptive relationship between the RV contractility and afterload preserves RV-to-pulmonary artery (PA) coupling. However, when contractility fails to match the afterload, uncoupling of the RV-PA relationship occurs, resulting in a maladaptive process in which there is worsening RV dilatation and impaired RV function. This disassociation between RV contractility and afterload eventually leads to RV failure.

The gold standard method of assessing RV-PA coupling is through pressure-volume loops obtained with conductance catheters, which allow for beat-to-beat acquisition of RV volume and pressure.[3,4] However this method is invasive and expensive, and has been used mostly in a research setting. Cardiac MRI can provide information on RV contractility through noninvasive MRI-derived pressure-volume loops, but it is less widely available.[5] Echocardiography, however, is a commonly-used tool to assess cardiac function, and the tricuspid annular plane systolic excursion (TAPSE) is a routinely obtained echocardiography-derived parameter.

The ratio of TAPSE-to-pulmonary artery systolic pressure (PASP) can be used as a surrogate for RV-PA coupling, which has been shown to be a superior parameter of RV function because it is more reflective of the load-dependent status of the pulmonary circulation.[6–8] The use of TAPSE/PASP was initially studied in heart failure and was found to be a valuable measure of RV contractility, identifying impaired RV-PA coupling as a predictor of poor outcomes.[6,9–11] Given its utility in heart failure, TAPSE/PASP was also evaluated in PH and several studies have shown prognostic implications of TAPSE/PASP in pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).[8,12] Although TAPSE/PASP appears to be associated with disease severity and adverse outcomes in CTEPH,[12] it is unclear if treatment of CTEPH with balloon pulmonary angioplasty (BPA) improves TAPSE/PASP ratios and outcomes. In this study, we aim to determine the relationship between TAPSE/PASP and BPA characteristics, and if TAPSE/PASP improves with BPA treatments.

METHODS

We performed a retrospective review of consecutive patients treated with BPA at the University of California San Diego (UCSD) from March 2015 (the start of our BPA program) to October 2023. Patients were evaluated through our standard CTEPH multidisciplinary team approach.[13] Patients had a ventilation-perfusion (V/Q) scan, right heart catheterization, computed tomography angiography and/or nonselective digital subtraction pulmonary angiography to confirm the diagnosis of CTEPH and assess operability. Those who were deemed not operable candidates were then considered for BPA. Six-minute walk distance, N-terminal pro-brain natriuretic peptide (NT-pro-BNP), transthoracic echocardiography (TTE), and functional class (FC) were obtained before the initial BPA session. BPA procedure at UCSD was performed as previously described.[14] The decision to pursue additional BPA treatments was based on a combination of hemodynamics, RV function, symptoms, amenable lesions, and patient preference. During follow-up BPA sessions, repeat tests were obtained at various intervals at the discretion of providers.

Patients were included in this analysis if they had (1) a baseline TTE before BPA, and (2) a follow-up TTE at any point during BPA treatments. All included echocardiograms were performed at our institution. TAPSE was obtained from the initial and the lattermost TTE. Hemodynamics were obtained at the beginning of each BPA session. The TAPSE/PASP ratio was calculated at baseline and at follow up using the initial and lattermost TTE and BPA hemodynamics. We excluded patients who had prior PTE surgery and those without PH at rest (chronic thromboembolic pulmonary disease [CTEPD] without PH), which was defined as a resting mean pulmonary artery pressure (PAP) < 20 mmHg, pulmonary artery occlusion pressure (PAOP) ≤ 15 mmHg, and pulmonary vascular resistance (PVR) < 2 Wood units (WU) not on any PH therapies.

Patients were stratified by their initial TAPSE/PASP ratio into previously defined tertiles of TAPSE/PASP ratios in PAH: low <0.19, middle 0.19–0.32, and high >0.32 mm/mmHg.[8] ANOVA was used to compare between the three tertiles. Student's paired t test was used for analysis between baseline and follow up of continuous variables; χ^2, Fisher Exact test, and McNemar's test was used for analysis of categorical variables.

RESULTS

From March 2015 to October 2023, there were 228 patients who were treated with BPA (924 procedures). Of these 228 patients, there were 93 patients who had both a baseline TTE and at least one follow-up TTE completed at UCSD during the course of BPA treatments. Of those, we excluded 24 (30%) patients who had prior PTE surgery and 2 patients with CTEPD without PH. A total of 67 patients were included in the final analysis.

Baseline

Baseline patient demographics, comorbidities, and characteristics are shown in Tables 1 and 2. Mean age of the cohort was 57 ± 15 years and 60% were female. At baseline, 57 patients (85%) were on PH medical therapy with 60% on monotherapy, 26% on double, and 14% on triple combination therapy. The majority of patients (59/67, 88%) had a history of deep vein thrombosis (DVT) or pulmonary embolism (PE), including six patients (9%) with an upper extremity DVT. A history of splenectomy and malignancy was common, both occurring in 18% of the cohort.

The overall baseline mean TAPSE/PASP of the entire cohort was 0.39 ± 0.21 mm/mmHg. When patients were stratified by TAPSE/PASP tertile, there were 6 patients (9%) in the low, 30 patients (45%) in the middle, and 31 patients (46%) in the high tertiles. The mean TAPSE/PASP ratio for the low TAPSE/PASP cohort was 0.16 ± 0.03 mm/mmHg,

TABLE 1 Baseline demographics of patients stratified by initial TAPSE/PASP tertile.

	TAPSE/PASP <0.19 mm/mmHg (*n* = 6; 9%)	TAPSE/PASP 0.19–0.32 mm/mmHg (*n* = 30; 45%)	TAPSE/PASP >0.32 mm/mmHg (*n* = 31; 46%)
Age, years	52.2 ± 20.5	60.1 ± 13.5	55.5 ± 14.4
Female, *n* (%)	3 (50%)	20 (67%)	18 (58%)
BMI, kg/m^2	27.4 ± 11.4	29.2 ± 7.0	29.4 ± 5.7
Comorbidities, *n* (%)			
History of VTE	5 (83%)	26 (87%)	28 (90%)
Upper extremity DVT	2 (33%)	0	3 (10%)
Intravascular device	1 (17%)	4 (13%)	1 (3%)
Splenectomy	0	5 (17%)	7 (23%)
Malignancy	1 (17%)	7 (23%)	8 (26%)
BPA sessions (total)	7.0 ± 2.2	6.5 ± 1.4	5.0 ± 1.6

Abbreviations: BMI, body mass index; BPA, balloon pulmonary angioplasty; DVT, deep vein thrombosis; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion; VTE, venous thromboembolism.

TABLE 2 Patient characteristics and diagnostic testing at baseline and follow-up stratified by initial TAPSE/PASP tertile.

	Low TAPSE/PASP Tertile (<0.19 mm/mmHg) *n* = 6			Middle TAPSE/PASP tertile (0.19–0.32 mm/mmHg) *n* = 30			High TAPSE/PASP tertile (>0.32 mm/mmHg) *n* = 31		
	Baseline	Follow-up	*p* Value	Baseline	Follow-up	*p* Value	Baseline	Follow-up	*p* Value
BPA session number	1	6.3 ± 2.3	—	1	5.3 ± 1.5	—	1	4.0 ± 1.6	—
Functional class, I/II/III/IV, *n* (%)	0/2/4/0 (0/33/67/0%)	1/4/1/0 (17/67/17/0%)	0.325	0/3/24/3 (0/10/80/10%)	3/17/10/0 (10/57/33/0%)	<0.001	0/10/21/0 (0/32/68/0%)	5/13/12/0[a] (17/43/40/0%)	0.050
PH therapies, *n* (%)	6 (100%)	5 (83%)	—	27 (91%)	28 (93%)	—	24 (77%)	20 (65%)	—
NT-proBNP, pg/mL	673 ± 516	83 ± 69	0.036	745 ± 1086	597 ± 1622	0.644	137 ± 117	129 ± 83	0.561
6MWD,[b] meters	404 ± 127	500 ± 78	0.724	355 ± 146	395 ± 126	0.376	446 ± 145	468 ± 133	0.611
TAPSE/PASP, mm/mmHg	0.16 ± 0.03	0.32 ± 0.11	0.006	0.27 ± 0.04	0.38 ± 0.13	<0.001	0.55 ± 0.22	0.59 ± 0.37	0.596
TAPSE, cm	1.35 ± 0.29	1.83 ± 0.37	0.026	2.03 ± 0.33	2.28 ± 0.86	0.165	2.50 ± 1.06	2.43 ± 1.19	0.810
PASP, mmHg	82.7 ± 11.0	59.8 ± 12.7	0.020	75.6 ± 9.1	62.4 ± 14.5	<0.001	47.5 ± 12.9	44.1 ± 10.3	0.006

Abbreviations: 6MWD, 6 min walk distance; BPA, balloon pulmonary angioplasty; NT-proBNP, N-terminal pro-brain natriuretic peptide; PASP, pulmonary artery systolic pressure; PH, pulmonary hypertension; TAPSE, tricuspid annular plane systolic excursion.

[a]One missing functional class data at follow-up.

[b]6MWD data available for low tertile baseline/follow-up in *n* = 5/5; middle tertile baseline/follow-up in *n* = 17/23; high tertile baseline/follow-up in *n* = 22/20.

as compared to 0.27 ± 0.04 mm/mmHg in the middle and 0.55 ± 0.22 mm/mmHg in the high tertiles ($p < 0.001$) (Table 2). The initial TAPSE (1.35 ± 2.91 cm in the low vs. 2.03 ± 3.29 cm in the middle vs. 2.50 ± 1.06 cm in the high, $p = 0.002$) and NT-proBNP (673 ± 516 pg/nL in the low vs. 730 ± 1166 pg/nL in the middle vs. 137 ± 117 pg/nL in the high tertile, $p = 0.02$) were also significantly different between tertiles. Difference in 6-min walk distance was not significantly different between groups ($p = 0.161$). Patients in the low TAPSE/PASP tertile were more likely to be on combination PH therapies at baseline compared to the middle and high groups, with an average number of PH therapies of 1.8 versus 1.5 versus 1.0 ($p = 0.033$), respectively.

BPA session characteristics and invasive hemodynamics as stratified by TAPSE/PASP tertiles are shown in Table 3. Between the low versus middle versus high TAPSE/PASP cohorts, there was a significant difference in the systolic PAP (82.7 ± 11.0 vs. 75.6 ± 9.1 vs. 47.5 ± 12.9 mmHg, $p < 0.001$), diastolic PAP (29.3 ± 1.6 vs. 24.9 ± 3.3 vs. 17.8 ± 5.3 mmHg, $p < 0.001$), mean PAP (48.3 ± 4.4 vs. 43.7 ± 3.9 vs. 29.2 ± 7.3 mmHg, $p < 0.001$), and PVR (7.8 ± 2.8 vs. 6.7 ± 2.6 vs. 3.0 ± 1.1 WU, $p < 0.001$). There was no significant difference in right atrial pressure (RA), PAOP, cardiac output, or cardiac index between groups. The number of complications during the initial BPA were not significantly different across the three tertiles; there were one (20%), seven (30%), and three (11%) complications in the low, middle, and high tertiles ($p = 0.283$).

Follow-up

Follow-up assessment occurred at an average of BPA session number 4.8 ± 1.8. The overall population mean TAPSE/PASP improved from 0.39 ± 0.21 to 0.47 ± 0.29 mm/mmHg ($p = 0.023$).

In the baseline low TAPSE/PASP group ($n = 6$), there was significantly improved TAPSE/PASP, from 0.16 ± 0.03 mm/mmHg at baseline to 0.32 ± 0.11 mm/mmHg at follow-up ($p = 0.006$) (Figure 1, Table 2). There was also significant improvement in systolic PAP (82.7 ± 11.0 vs. 59.8 ± 12.7 mmHg, $p = 0.02$), diastolic PAP (29.3 ± 1.6 vs. 19.5 ± 6.7 mmHg, $p = 0.02$), mean PAP (48.3 ± 4.4 vs. 35.0 ± 8.8 mmHg, $p = 0.033$), and PVR (7.8 ± 2.8 vs. 4.1 ± 0.8 WU, $p = 0.02$) at follow-up. There was a trend toward higher cardiac output ($p = 0.083$) and cardiac

TABLE 3 BPA characteristics and invasive hemodynamics from initial BPA to follow-up stratified by initial TAPSE/PASP tertile.

	Low TAPSE/PASP tertile (<0.19 mm/mmHg), $n = 6$			Middle TAPSE/PASP tertile (0.19–0.32 mm/mmHg), $n = 30$			High TAPSE/PASP tertile (>0.32 mm/mmHg), $n = 31$		
	Initial BPA	Follow-up	*p* Value	Initial BPA	Follow-up	*p* Value	Initial BPA	Follow-up	*p* Value
BPA session number	1	6.3 ± 2.3	—	1	5.3 ± 1.5	—	1	4.0 ± 1.6	—
Contrast, mL	203 ± 60	316 ± 127	—	222 ± 71	207 ± 85	—	232 ± 79	221 ± 73	—
Fluoroscopy time, min	35.7 ± 10.2	39.5 ± 11.9	—	36.3 ± 9.2	33.8 ± 10.3	—	36.5 ± 10.4	35.4 ± 10.6	—
Segments treated, *n*	3.2 ± 0.8	3.8 ± 0.8	—	3.1 ± 0.9	4.0 ± 1.3	—	3.5 ± 1.1	4.0 ± 1.3	—
Complications during session	1 (17%)	0	1.0	7 (23%)	2 (7%)	0.06	3 (10%)	2 (6%)	1.0
RA, mmHg	9.0 ± 4.8	6.2 ± 5.2	0.236	7.2 ± 3.1	7.0 ± 2.7	0.786	6.5 ± 2.9	6.6 ± 2.4	0.805
Sys PAP, mmHg	82.7 ± 11.0	59.8 ± 12.7	0.020	75.6 ± 9.1	62.4 ± 14.5	<0.001	47.5 ± 12.9	44.1 ± 10.3	0.006
Dia PAP, mmHg	29.3 ± 1.6	19.5 ± 6.7	0.021	24.9 ± 3.3	20.4 ± 5.4	<0.001	17.8 ± 5.3	16.7 ± 4.4	0.121
Mean PAP, mmHg	48.3 ± 4.4	35.0 ± 8.8	0.033	43.7 ± 3.9	36.0 ± 7.7	<0.001	29.2 ± 7.3	27.3 ± 5.9	0.013
PAOP, mmHg	11.2 ± 4.5	10.0 ± 3.9	0.514	11.6 ± 4.5	12.0 ± 4.1	0.492	11.9 ± 4.0	11.9 ± 2.8	0.959
CO, L/min	5.2 ± 1.2	6.3 ± 2.1	0.083	5.1 ± 1.4	5.2 ± 1.2	0.859	5.6 ± 1.3	5.5 ± 1.4	0.555
CI, L/min/m^2	2.7 ± 0.3	3.1 ± 0.4	0.057	2.7 ± 0.7	2.7 ± 0.5	0.956	2.8 ± 0.6	2.7 ± 0.6	0.505
PVR, dynes × sec × cm^{-5}	620 ± 228	331 ± 66	0.021	538 ± 208	386 ± 186	<0.001	244 ± 87	223 ± 69	0.09

Abbreviations: BPA, balloon pulmonary angioplasty; CI, cardiac index; CO, cardiac output; Dia, diastolic; PAOP, pulmonary artery occlusion pressure; PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; RA, right atrial pressure; Sys, systolic; TAPSE, tricuspid annular plane systolic excursion.

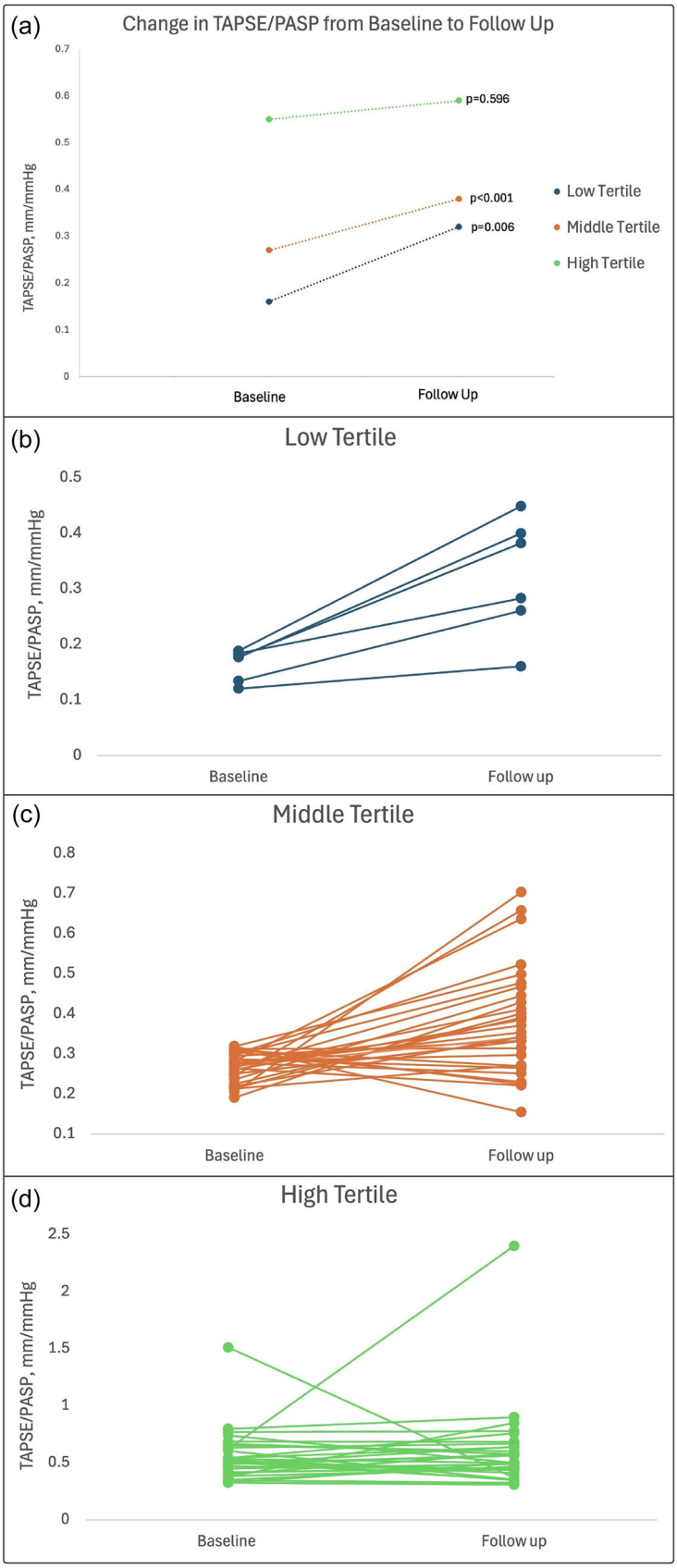

FIGURE 1 Change in TAPSE/PASP from baseline to follow-up overall (a) and in each tertile (b–d). Follow-up assessment occurred after an average of 4.8 ± 1.8 BPA sessions. There is significant improvement in TAPSE/PASP in the baseline low and middle tertiles, as compared to the baseline high tertile.

index ($p = 0.057$), and no significant change in RA or PAOP at follow up (Table 3). There was improvement in TAPSE, NT-proBNP, and functional class, with 84% of patients classified as FC I–II at follow-up as compared to 33% at baseline (Table 2). At follow-up, there were two (3%) patients remaining in the low TAPSE/PASP group (from $n = 6$) representing a decrease from baseline of 67%.

In the baseline middle TAPSE/PASP tertile ($n = 30$), there was significant improvement in TAPSE/PASP (0.27 ± 0.04 vs. 0.38 ± 0.13 mm/mmHg, $p < 0.001$) (Figure 1, Table 2), systolic PAP (75.6 ± 9.1 vs. 62.4 ± 14.5 mmHg, $p < 0.001$), diastolic PAP (24.9 ± 3.3 vs. 20.4 ± 5.4 mmHg, $p < 0.001$), mean PAP (43.7 ± 3.9 vs. 36.0 ± 7.7 mmHg, $p < 0.001$), and PVR (6.7 ± 2.6 vs. 4.8 ± 2.3 WU, $p < 0.001$) at follow-up. There was no difference in cardiac output, cardiac index, RA, or PAOP; TAPSE and NT-proBNP were also not significantly changed at follow-up (Tables 2 and 3). Functional class improved, with 67% of patients at FC I–II at follow-up compared to 23% at baseline. At follow-up, there were 13 (19%) patients remaining in the middle TAPSE/PASP tertile (from $n = 30$) representing a decrease from baseline of 57%.

In the baseline high TAPSE/PASP group ($n = 31$), there was significant improvement in systolic PAP (47.5 ± 12.9 vs. 44.1 ± 10.3 mmHg, $p = 0.006$) and mean PAP (29.2 ± 7.3 vs. 27.3 ± 5.9 mmHg, $p = 0.012$) only (Table 3). There was no significant change in TAPSE/PASP at follow-up ($p = 0.596$) (Figure 1, Table 2). The PVR, cardiac output, cardiac index, RA, PAOP, TAPSE, and NT-proBNP were also not significantly changed (Tables 2 and 3). Functional class improved at follow-up, with 58% patients to FC I–II as compared to 32% at baseline. At follow-up, there were now 52 (78%) patients in the high TAPSE/PASP tertile (from $n = 31$) representing an increase from baseline of 68%.

Similar to during the initial BPA, the number of complications were low in all the groups during follow-up BPA sessions as well. The low tertile had no complications, while the middle and high tertiles each had two complications at follow-up (Table 3). There were no statistically significant differences in rates of complications between groups or from baseline to follow-up.

DISCUSSION

TAPSE/PASP has emerged as a valuable tool in evaluating RV-PA coupling in pulmonary vascular disease.[8,15] As PAH progresses, there is subsequent worsening of pulmonary artery pressures, RV afterload, and RV function which results in RV failure and death. Impaired RV-PA coupling indicates a poor prognosis, and prior studies have established a significant association between TAPSE/PASP and hemodynamics, functional status, as well as mortality.[8,16] However, TAPSE/PASP ratio is a dynamic parameter. Prior studies have shown that with optimization of PAH-targeted therapies, TAPSE/PASP can improve in PAH patients and is associated with achieving low risk status and reduced PVR.[17] Compared to PAH though, the main pathophysiological mechanism of CTEPH is obstructive fibrotic thromboembolic material, so the primary treatments are interventional therapies aimed at relieving this obstruction (PTE and BPA). In this study, we show that in patients with CTEPH, (1) low TAPSE/PASP ratios are associated with more severe hemodynamics, and (2) TAPSE/PASP can improve with sequential BPA treatments.

After an average of 4.8 BPA sessions, the TAPSE/PASP ratio of the overall cohort improved from 0.39 ± 0.21 mm/mmHg to 0.47 ± 0.29 mm/mmHg. This is further highlighted when patients were stratified into tertiles, as patients with the lowest baseline TAPSE/PASP (<0.19 mm/mmHg) had the most improvement, while those who started with a baseline high TAPSE/PASP did not have significant changes. This resulted in a decrease in the absolute number of patients in the low and middle tertiles between baseline and follow-up, from 6 to 2 and 30 to 13 patients, respectively, and an increase in those in the high tertile from 31 to 52 patients. Furthermore, only 16 out of 67 patients (24%) had completed all BPA treatments at the time of echocardiography for TAPSE evaluation. This represented 2 (33%) patients in the low, 6 (20%) in the middle, and 8 (26%) in the high tertiles. The remaining 51 patients proceeded to receive an additional 1.4 ± 0.7 BPA sessions (range 1–3). Despite less than a quarter of patients in our study being deemed complete with BPA treatments, there were already significant improvements in TAPSE/PASP observed.

The ideal TAPSE/PASP threshold to identify patients at high risk of deterioration is variable based on the patient population. TAPSE/PASP has been studied in heart failure with preserved and reduced ejection fraction, acute pulmonary embolism (PE), and various forms of PH. In heart failure with preserved ejection fraction (HFpEF) patients, TAPSE/PASP has been useful for identifying patients with combined pre- and postcapillary PH (cpc-PH) and therefore, at higher risk of adverse outcomes. One study found a TAPSE/PASP ratio of <0.36 mm/mmHg had high accuracy in identifying cpc-PH patients;[18] similarly, Guazzi and colleagues noted a TAPSE/PASP < 0.35 mm/mmHg as an independent predictor of worse outcomes in HFpEF.[11] In acute PE patients, a higher TAPSE/PASP ratio of <0.4 mm/mmHg was determined to the optimal value for predicting adverse events, including 7- and 30-day mortality,[19] while in CTEPH, a TAPSE/PASP ratio of

<0.154 mm/mmHg was associated with more severe hemodynamics and higher incidence of pericardial effusion.[12] In PAH patients, TAPSE/PASP ratios as low as 0.14 mm/mmHg have been observed;[10] Tello et al validated a TAPSE/PASP threshold of <0.31 mm/mmHg as a marker of worse prognosis in PAH. Lower TAPSE/PASP values in PAH patients were associated with significantly worse hemodynamics and functional status compared to those with higher ratios; there was also better overall survival in the higher TAPSE/PASP cohorts.[8] The association between TAPSE/PASP and mortality was maintained even when specific high-risk PAH populations were selected for, such as severe PAH awaiting lung transplant and systemic sclerosis-associated PAH.[16,20] Regardless of the population, TAPSE/PASP is an important prognostic marker, highlighting the importance of RV-PA coupling.

The varying TAPSE/PASP thresholds between different populations highlight the ability of the RV to adapt in different disease states. In a cohort of CTEPH and PAH patients who had similar 6-min walk distance and functional class, there was a lower mean PAP and PVR in the CTEPH cohort;[21] furthermore, CTEPH patients were also found to have a more dilated and less hypertrophic RV at diagnosis compared to PAH. This is all suggestive of poorer RV adaptation in CTEPH as compared to PAH.[22] Even within CTEPH, there are differences in RV adaptation between proximal and distal CTEPH, with more RV dilatation and a lower RV ejection fraction seen in proximal disease.[23] BPA is usually reserved for distal inoperable CTEPH and was the most common reason for BPA in our cohort;[14] there are multiple risk factors for developing distal CTEPH (Table 1) and it is not clear if specific risk factors are associated with differing RV adaptation. While the numbers of each risk factor were too low to make any strong conclusions about TAPSE/PASP in relation to these risk factors, it may be worth exploring in the future.

In contrast to PAH and heart failure, TAPSE/PASP in the CTEPH population is not as well described. In the study by Tello and colleagues, there were a small proportion (12%) of CTEPH patients included in the study cohort but the vast majority were PAH.[24] Duan and colleagues specifically evaluated TAPSE/PASP in CTEPH and observed that TAPSE/PASP correlated with hemodynamic severity and served as a predictor for clinical worsening.[12] However, the role of treatment was incompletely evaluated as there were a mix of patients who received PTE, BPA, medical therapy, or no intervention. Compared to Duan's study, our cohort of CTEPH patients was preselected for BPA based on a multidisciplinary CTEPH team discussion. To minimize BPA-related complications, these patients are typically not in overt RV failure at the time of BPA and may require initiation of PH medical therapies before starting BPA treatments.[25,26] In our study cohort, 57 out of 67 patients (85%) were on PH medical therapies before the start of BPA treatments (Table 2). During the course of BPAs, there were changes in the number of PH medical therapies in 14 patients (21%); 5 patients had an increase in number of medications required while 9 patients had a decrease in PH medical therapies (Supporting Information S1: Figure 1). Even in a highly selected population of CTEPH patients, our study showed patients in the lowest TAPSE/PASP tertile had the most severe hemodynamics. Although severity of hemodynamics, specifically PVR and mean PAP, is associated with higher incidence of lung injury complications in BPA,[26,27] we did not observe this in our study. The main complication in our cohort was hemoptysis, which represented all the complications except for one case of access site hematoma in the high TAPSE/PASP tertile. All the cases of hemoptysis were successfully controlled locally in the cardiac catheterization lab with a combination of balloon occlusion and/or anticoagulation reversal. Between the initial and follow-up BPAs, the rate of complications in the low tertile went from 16.7% to zero; from 23.3% to 6.7% in the middle tertile; and from 9.7% to 6.5% in the high tertile (Table 3). However, the overall absolute numbers of complications in the entire cohort were very low, and differences in complication rates between tertiles and between initial and follow-up BPA did not meet statistical significance in the analysis, so we cannot conclude there is an association of TAPSE/PASP with BPA-related complications. The overall minimal complications in this cohort may be due to our efforts to minimize that risk through patient selection, initiation of medical therapy when necessary, and institutional BPA experience.[14]

TAPSE/PASP may be a valuable parameter to trend as a surrogate for response to BPA treatments. In our study, patients in the middle tertile had significant improvement in TAPSE/PASP values at follow-up even though there was no significant improvement in TAPSE or PASP alone, highlighting the utility of the TAPSE/PASP ratio. This was also observed in acute PE patients in whom TAPSE/PASP ratio was predictive of mortality, but TAPSE and PASP individually were not.[19] Additionally, compared to PTE, BPA is an incremental treatment approach to CTEPH, as each BPA session can usually only accomplish treating several segments. Patients typically require on average four to six sessions for complete treatment. However, currently, there are no guidelines on optimal BPA treatment endpoints. The recently published consensus statement on BPA states that ideal BPA treatment should result in symptom relief at rest and exercise with a target goal of mean PAP less than 30 mmHg.[28] However, there

are limitations with using solely mean PAP, especially in a pulsatile system in which the RV afterload consists of resistance, compliance, and impedance.[29] The utility in TAPSE/PASP is that it allows for evaluation of both contractility and afterload together, evaluating the whole cardiopulmonary unit, rather than focusing on a single hemodynamic parameter. While complete invasive hemodynamics are done during BPA and can also provide an idea of RV function, it is not easily obtainable in all individuals. Many of our patients travel from across the country for these BPA treatments which can lead to a significant financial burden over time. However, echocardiography can more easily be done locally given its widespread availability. The echocardiography-based estimate of RV-PA coupling with TAPSE/PASP may provide adequate information on patients' response to BPA and potentially help determine if travel for additional BPA treatments is warranted. Additionally, using a standard exercise capacity measurement, such as 6-min walk distance, may not be reflective of hemodynamic improvements. This was seen in the BENEFiT trial for bosentan in CTEPH in which there was no change in 6-min walk distance despite a decrease in PVR by over 24% from baseline in the intervention group.[30] It is possible that TAPSE/PASP may be an advantageous objective measure used to assess improvement after BPA treatments, and future studies may be helpful in determining if aiming for a potential TAPSE/PASP threshold during BPA treatments is valuable.

There are some limitations to our study. First, it was single-center and retrospective with a small patient population. Although there were over 200 patients who underwent BPA, over half of the cohort did not have follow-up TTEs at our institution so were excluded. Some of these patients had follow-up testing at outside institutions but those results were not readily available. Many included patients had not completed their BPA treatments, so there may be additional improvements in TAPSE/PASP and hemodynamics that were not captured in our data; furthermore, the timing of follow-up echocardiography was not uniform amongst all patients, which may have further biased the outcomes. The sample size of the low tertile was very small compared to the middle and high tertiles, which may have skewed some of our data analyses. Additionally, there was selection bias as these patients were preselected to undergo BPA and many were already on medical therapy. The changes in PH therapies during BPA sessions were also not accounted for, and the addition or discontinuation of PH therapies may have influenced RV function as well. We also excluded patients who were post-PTE due to inaccuracies of TAPSE post-PTE surgery,[31] as well as those with CTEPD without PH to specifically select patients with resting PH. Future studies could evaluate the utility of TAPSE/PASP in highlighting specific CTEPH subgroup populations undergoing BPA, such as patients with technically operable disease or those with CTEPD without PH. Prior studies have shown that patients with CTEPD without PH can have occult RV dysfunction and impaired RV relaxation, so this is a population which may benefit from further exploration of RV-PA coupling and its potential role in determining timing of interventions.[32,33] Lastly, prospective studies with larger population sizes are needed to further evaluate the value of TAPSE/PASP in CTEPH patients receiving different treatment approaches.

CONCLUSION

RV function is critical in the evaluation of pulmonary hypertension, and RV-PA coupling is a robust surrogate of RV function. The TAPSE/PASP ratio is an easily obtainable method for gauging RV-PA coupling. In CTEPH patients, the TAPSE/PASP ratio is closely linked to disease severity and can improve with BPA treatments. As patients undergo successive BPA sessions, their hemodynamics and RV mechanics may improve, which is reflected in the higher TAPSE/PASP ratio on follow-up. Further studies are required, but TAPSE/PASP ratio may be a promising measure to follow with ongoing BPA sessions to determine response to treatment.

AUTHOR CONTRIBUTIONS

All authors have reviewed, contributed, and approved this manuscript. Jenny Z. Yang accepts responsibility for the overall integrity of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors Jenny Z. Yang served on advisory board for Janssen. Timothy M. Fernandes is a consultant for Penumbra; received research funding from Merck, United Therapeutics, Janssen. Kim M. Kerr received consulting fees from Merck. Nick H. Kim is a consultant for Bayer, Gossamer Bio, Johnson & Johnson, Merck, Pulnovo, United Therapeutics; speaker for Bayer, Johnson & Johnson, Merck; and research support from Enzyvant. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

N/A.

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