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ORIGINAL RESEARCH

Multi-Beat Right Ventricular-Arterial Coupling Predicts Clinical Worsening in Pulmonary Arterial Hypertension

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BACKGROUND: Although right ventricular (RV) to pulmonary arterial (RV-PA) coupling is considered the gold standard in assessing RV dysfunction, its ability to predict clinically significant outcomes is poorly understood. We assessed the ability of RV-PA coupling, determined by the ratio of multi-beat (MB) end-systolic elastance (Ees) to effective arterial elastance (Ea), to predict clinical outcomes.

METHODS AND RESULTS: Twenty-six subjects with pulmonary arterial hypertension (PAH) underwent same-day cardiac magnetic resonance imaging, right heart catheterization, and RV pressure-volume assessment with MB determination of Ees/Ea. RV ejection fraction (RVEF), stroke volume/end-systolic volume, and single beat-estimated Ees/Ea were also determined. Patients were treated with standard therapies and followed prospectively until they met criteria of clinical worsening (CW), as defined by ≥10% decline in 6-minute walk distance, worsening World Health Organization (WHO) functional class, PAH therapy escalation, RV failure hospitalization, or transplant/death. Subjects were 57±14 years, largely WHO class III (50%) at enrollment, with preserved average RV ejection fraction (RVEF) (47±11%). Mean follow-up was 3.2±1.3 years. Sixteen (62%) subjects met CW criteria. MB Ees/Ea was significantly lower in CW subjects (0.7±0.5 versus 1.3±0.8, P=0.02). The optimal MB Ees/Ea cut-point predictive of CW was 0.65, defined by ROC (AUC 0.78, P=0.01). MB Ees/Ea below this cut-point was significantly associated with time to CW (hazard ratio 5.1, P=0.001). MB Ees/Ea remained predictive of outcomes following multivariate adjustment for timing of PAH diagnosis and PAH diagnosis subtype.

CONCLUSIONS: RV-PA coupling as measured by MB Ees/Ea has prognostic significance in human PAH, even in a cohort with preserved RVEF.

Key Words: outcome ■ pressure-volume relationship ■ pulmonary hypertension ■ right ventricular dysfunction

The principal determinant of clinical worsening in pulmonary arterial hypertension (PAH) is dysfunction of the right ventricle (RV).[1] Assessment of RV function, however, can be challenging in PAH. RV function depends on the complex interplay between intrinsic myocardial contractility and pulmonary vascular afterload. Because the RV is quite afterload dependent,[2,3] commonly used load-dependent metrics like RV fractional area change, tricuspid annular plane systolic excursion (TAPSE), and even RV ejection fraction (RVEF) may not fully capture intrinsic RV dysfunction.

The gold standard for assessment of ventricular-arterial function requires simultaneous measures

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CLINICAL PERSPECTIVE

What Is New?

- Multi-beat right ventricular-pulmonary arterial (RV-PA) coupling is considered a gold standard assessment of right ventricular function and used often in experimental studies of RV function in pulmonary arterial hypertension.
- However, its ability to predict clinical outcomes in human pulmonary arterial hypertension has not been well established.
- The present study shows that the multi-beat RV-PA coupling ratio does indeed predict clinical outcomes in a prospective cohort study of human pulmonary arterial hypertension.

What Are the Clinical Implications?

- This study helps to validate the predictive capacity and overall utility of multi-beat RV-PA coupling in studies of human pulmonary arterial hypertension.
- The predictive capacity of other RV metrics known to predict clinical worsening—RV ejection fraction and the RV stroke volume/end systolic volume ratio—were validated in this cohort.
- The single-beat estimate of RV-PA coupling, on the other hand, was not shown to predict clinical worsening, and multi-beat RV-PA coupling contributed additional predictive power even when added to a model of RV ejection fraction alone.

Nonstandard abbreviations and acronyms

PAH	pulmonary arterial hypertension
CTD-PAH	connective tissue disease-associated PAH
RV	right ventricle
RVEF	RV ejection fraction
MB	multi-beat
SB	single-beat
Ees	end-systolic elastance
Ea	effective arterial elastance
RV-PA coupling	right ventricular-pulmonary arterial coupling

of pressure and volume at different loading conditions.[4–6] This allows generation of multi-beat (MB) pressure-volume loops, which then facilitate the direct measurement of end-systolic elastance (Ees), a load-independent measure of contractility, and effective arterial elastance (Ea), a lumped measure of total ventricular afterload. The ratio of both elastances, Ees/Ea, describes the coupling of right ventricular systolic function to pulmonary arterial afterload. Ees can also be estimated from a single-beat using assumptions based on a measured pressure waveform, and these too have been used to estimate Ees/Ea.[7]

Measurement of multi-beat RV Ees and coupling metrics such as Ees/Ea have demonstrated superior sensitivity in detecting occult RV dysfunction,[8,9] and multi-beat RV Ees has even been shown to correlate with intrinsic RV myocyte maximal force generation in humans.[10] However, only one report has assessed the correlation between directly measured Ees/Ea and clinical outcomes in humans with PAH.[11] Furthermore, no study has assessed the predictive capacity of MB Ees/Ea in a cohort in which other clinical metrics of RV dysfunction, such as RVEF, remain relatively preserved. The aim of the present study is to assess the ability of multi-beat Ees/Ea to predict clinical outcomes in human subjects with PAH. The predictive capacity of single-beat coupling metrics such as stroke volume/end-systolic volume (SV/ESV) and the single-beat estimate of Ees/Ea are also assessed.

METHODS

Study Subjects

Patients referred to our institution between 2013 and 2016 for right heart catheterization (RHC) for the diagnosis or evaluation of PAH were eligible for this prospective study. All subjects gave informed consent to a protocol approved by the Johns Hopkins Medicine Institutional Review Board. Subjects underwent same-day resting cardiac magnetic resonance (CMR) imaging, followed by RHC with concomitant pressure-volume loop catheterization of the RV. Baseline 6-minute walk distance and functional capacity assessment were prospectively obtained from the day of RHC or that same week. Pulmonary hypertension (PH) was diagnosed if mean pulmonary artery pressure (mPAP) ≥25 mm Hg. Subjects met diagnostic criteria for World Health Organization (WHO) Group I PAH if mPAP ≥25 mm Hg, pulmonary arterial wedge pressure (PAWP) ≤15 mm Hg, pulmonary vascular resistance (PVR) ≥3 Wood units, and secondary causes of PH were excluded. PH subtypes and Group I PAH subtypes were adjudicated as previously described.[9] Clinical events were prospectively adjudicated from date of RHC onward. Data will not be available to other researchers given the small cohort and its relatively specific and potentially identifiable nature. Analytic methods and study materials will be available upon request.

Clinical, Imaging, and Catheterization Measurements

The full protocol has been previously outlined.[9] In short, baseline clinical characteristics were prospectively obtained as described. Patients underwent a

clinical RHC via right internal jugular venous approach. After the clinical RHC, the 8F introducer sheath was exchanged for a dual-entry 9F sheath to facilitate simultaneous placement of a 4F balloon-tipped pulmonary artery wedge catheter and 5F pressure-volume catheter (SPC-570-2 or RP-CA-41103-PN, Millar, Houston, TX), with the latter guided to the RV apex using fluoroscopy. Signals were analyzed to determine the electrode pairs needed to summate the total volume signal. Steady-state data were acquired during gentle end-expiratory breath hold to generate resting pressure-volume loops. Preload was then reduced via Valsalva maneuver and, if needed, manual external inferior vena cava compression, to create of a family of pressure-volume loops, using a previously validated method.[8,9] Two experienced investigators reviewed real-time data acquisition to ensure adequate preload reduction such that the end-systolic pressure-volume relationship could be determined. Multiple loops from both steady state and preload measurements were averaged.

In blinded fashion, the following measurements were calculated: effective arterial elastance (Ea) was calculated from end-systolic pressure divided by stroke volume. The multi-beat end-systolic elastance (Ees) was generated from the perpendicular regression line of multiple end-systolic points during preload reduction. The single-beat estimate was calculated using the method described by Brimouille and colleagues: a sine wave was fit to the isovolumic portions of the RV pressure-time tracing to determine maximum pressure (Pmax) at RV end-diastolic volume (Vmax), and Ees was calculated based on the slope between this calculated point (Pmax, Vmax) and the end-systolic pressure-volume point (end-systolic pressure, end-systolic volume).[7] RVEF and SV/ESV were derived directly from CMR data.

Patients were prospectively followed. Clinical worsening (CW) was defined when subjects first met any 1 of 5 clinical end points: (1) ≥10% reduction in 6-minute walk distance,[12,13] (2) worsening WHO functional class, (3) escalation of PAH-specific therapy >3 months after index RHC, (4) hospitalization for RV failure or PAH, or (5) death or lung transplantation (Table 1).

Table 1. Criteria Constituting Clinical Worsening

Criteria	Number Meeting Criteria, n
Decrease in 6MWD by ≥10%	7
Worsening WHO functional class	4
Escalation of PAH-specific therapy	8
Hospitalization for PAH/RVF	6
Death or transplant	0
Meeting more than 1 criteria	16

The 5 criteria that constituted clinical worsening (CW) were (1) any decrease in 6-minute walk distance (6MWD) by ≥10%, (2) a worsening in World Health Organization (WHO) Functional Class, (3) an escalation of pulmonary arterial hypertension (PAH)-specific therapy, (4) a hospitalization for PAH or right ventricular failure (RVF), or (5) death or lung transplantation. Number of subjects meeting each criteria noted above. Sixteen patients met more than 1 criteria; if so, time to first CW event was used for survival analysis.

Statistical Analysis

Standard comparisons were made using Student *t* tests to compare means and chi-square analyses to compare proportions; Cohen's *d* was used to compare effect sizes. Univariable logistic regressions were performed to examine associations between clinical variables of interest and CW. Receiver operator curves were generated to determine the ability of (1) multi-beat Ees/Ea, (2) single-beat Ees/Ea, (3) SV/ESV, and (4) RVEF to predict CW. An area under the curve was calculated for each, and if significant, the Youden index used to determine the value that achieved maximal sensitivity and specificity in this cohort. Kaplan-Meier survival analyses were performed to determine associations between the 4 aforementioned metrics (each dichotomized at its respective Youden index) and time to CW. Sensitivity analyses were repeated in the connective tissue disease-associated PAH (CTD-PAH) subset of subjects. Cox proportional hazard models were conducted to examine relationships between multi-beat Ees/Ea and time to CW. Subjects were prospectively followed for CW events; they were censored if no event occurred by the end of the study (ie, right-censored). Multivariable Cox models were adjusted for biologically important clinical covariates. Improvements in model fit and predictive capacity resulting from addition of clinical covariates to Cox models were assessed with likelihood ratio tests and Akaike's information criteria. Throughout, a 2-sided $P<0.05$ denoted statistical significance.

RESULTS

A total of 51 subjects were enrolled into the study between 2013 and 2016. Seven patients had incomplete CMR or pressure-volume data, due either to inability to tolerate CMR or insufficient pressure-volume loop recordings. Eighteen patients did not meet diagnostic criteria for Group I PAH (9 did not have PH, while 9 had PH due to secondary causes). These 25 subjects were excluded from analysis. The 26 subjects with Group I PAH and complete CMR and pressure-volume loop data were ultimately studied. These 26 subjects were prospectively followed from date of RHC for a mean follow up of 3.2±1.3 years. Out of the 26 subjects, a total of 16 subjects eventually met criteria for CW (Table 1). Seven subjects experienced

Table 2. Baseline Demographic and Imaging Characteristics

Characteristic	Full Cohort (n=26)	CW (+) (n=16)	CW (–) (n=10)	*P* Value	Effect Size
Baseline demographics					
Sex (female/male)	22/4	13/3	9/1	0.9	0.26
Age, y	57±14	61±14	63±9	0.9	0.10
White/Non-white	23/3	14/2	9/1	0.6	0.10
IPAH/CTD-PAH	8/18	2/14	6/4	0.03	1.39
BSA, m^2	1.8±0.3	1.8±0.2	1.9±0.3	0.5	0.29
WHO-FC (I/II/III)	1/12/13	1/7/7	0/5/5	0.2	0.25
6MWD, m	375±131	371±143	381±118	0.9	0.21
Creatinine, mg/dL	0.9±0.2	0.9±0.2	0.9±0.2	0.4	0.29
NT pro-BNP, pg/mL	614±738	720±594	443±933	0.4	0.39
Cardiac MRI					
RVEDV, mL	169±51	158±56	176±50	0.4	0.61
RVESV, mL	91±39	78±33	98±41	0.2	0.52
RV mass, g	28±12	31±17	27±9	0.4	0.31
RVEF, %	47±11	49±9	46±13	0.4	0.52
RV SV/ESV	1.0±0.4	1.1±0.4	0.9±0.5	0.4	0.61
LVEDV, mL	123±27	120±32	125±25	0.7	0.19
LVESV, mL	48±12	46±13	49±12	0.6	0.26
LV mass, g	86±20	80±17	90±22	0.2	0.61
LVEF, %	61±6	62±5	61±6	0.8	0.17

Values represent mean±SD unless otherwise specified. *P* values reflect the significance of the difference in means/proportions in subjects with vs without CW. 6MWD indicates 6-minute walk distance; BSA, body surface area; CW, Clinical worsening; CTD-PAH, connective tissue disease-associated PAH; IPAH, Idiopathic pulmonary arterial hypertension; LVEF, LV ejection fraction; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; NT pro-BNP, N-terminal pro-B natriuretic peptide; RVEF, RV ejection fraction; RVEDV, RV end-diastolic volume; RVESV, RV end-systolic volume; SV/ESV, stroke volume/end-systolic volume; and WHO-FC, World Health Organization Functional Class.

a ≥10% decrease in 6MWD, 4 experienced a worsening in WHO functional capacity, 8 saw an escalation in PAH-specific therapy, and 6 were hospitalized for PAH or right ventricular failure. None died or underwent lung transplant during the prospective monitoring period. Of the 16 subjects who clinically worsened, 7 subjects eventually met multiple criteria; in these cases, the time to the first CW event was used for time-to-event analyses.

The baseline characteristics of the full 26-subject cohort are outlined in Tables 2 and 3. Subjects were on average 57±14 years old, and predominantly female (22/26) and Caucasian (23/26). Eight patients had idiopathic PAH (IPAH) while 18 had CTD-PAH. The vast majority were WHO functional capacity class II or III (25/26); 1 subject was WHO class I. On CMR, average RVEF was 47±11% and 18/26 (69%) had RVEF ≥40%. The cohort had a mean right atrial (RA) pressure 7±4 mm Hg, mPAP 39±13 mm Hg, PVR 7±5 Wood units, and PAWP of 10±4 mm Hg. Multi-beat Ees, Ea, and Ees/Ea for the full cohort were 0.76±0.5 mm Hg/mL, 0.96±0.5 mm Hg/mL, and 0.95±0.7, respectively. Single-beat estimate of Ees was 0.76±0.5 mm Hg/mL, making the mean single-beat Ees/Ea 0.85±0.3. A Bland-Altman plot compared agreement between multi-beat Ees/Ea and the single-beat estimate of Ees/Ea (Figure S1A). There was reasonable agreement between the 2 measures when mean Ees/Ea was <1.0; at Ees/Ea ratios >1.0, a ratio considered normal, the single-beat estimate of Ees/Ea underestimated the multi-beat Ees/Ea ratio. Similarly, single-beat (SB) Ees/Ea tended to underestimate coupling most prominently in those with RVEF >40% (Figure S1B).

The 16 subjects with CW were more likely to have CTD-PAH (88% versus 40%, *P*=0.03) and lower mPAP (32±10 versus 42±14 mm Hg, *P*=0.05) compared with subjects without CW. They were also more likely to have a lower MB Ees/Ea ratio (0.7±0.5 versus 1.3±0.8, *P*=0.02). Notably, RVEF, SV/ESV, and the single-beat Ees/Ea were not significantly different between CTD-PAH and IPAH. Other baseline demographics were also not significantly different between groups.

In univariable logistic regression analysis (Table 4), MB Ees/Ea was significantly predictive of CW, with hazard ratio (HR) of 0.26 per unit of Ees/Ea (95% CI, 0.07, 0.91; *P*=0.04). Lower RVEF (HR, 0.95 per 1% in RVEF; 95% CI, 0.91, 0.99; *P*=0.03) and lower SV/ESV (HR, 0.23 per unit of SV/ESV; 95% CI, 0.06,

Table 3. Baseline Hemodynamic Characteristics

Characteristic	Full Cohort (n=26)	CW (+) (n=16)	CW (–) (n=10)	*P* Value	Effect Size
Right heart catheterization					
HR, bpm	73±12	75±15	72±12	0.7	0.12
SBP, mm Hg	128±19	126±14	129±21	0.8	0.05
DBP, mm Hg	71±10	66±9	74±9	0.03	0.90
RAP, mm Hg	7±4	6±3	8±5	0.2	0.55
RVSP, mm Hg	62±22	52±18	69±22	0.05	0.90
RVDP, mm Hg	10±5	8±6	10±5	0.3	0.48
MPAP, mm Hg	39±13	32±10	42±14	0.05	0.91
PCWP, mm Hg	10±4	9±3	10±4	0.8	0.13
CI, L/min per m^2	2.5±0.5	2.6±0.6	2.4±0.5	0.5	0.33
PVR, W.U.	7±5	5±4	8±5	0.2	0.70
PA O_2 Sat, %	67±5	68±4	66±6	0.4	0.36
SV/PP	2.4±1.4	3.0±1.8	2.0±1.3	0.6	0.77
Pressure-volume loop					
Multi-beat Ea	0.96±0.5	0.8±0.5	1.1±0.5	0.3	0.46
Multi-beat Ees	0.76±0.5	0.9±0.5	0.7±0.5	0.2	0.57
Multi-beat Ees/Ea	0.95±0.7	0.7±0.5	1.3±0.8	0.02	1.07
Single-beat Ees	0.72±0.3	0.6±0.2	0.8±0.4	0.4	0.40
Single-beat Ees/Ea	0.85±0.3	0.9±0.4	0.8±0.3	0.3	0.41

Values represent mean±SD unless otherwise specified. *P* values reflect the significance of the difference in means/proportions in subjects with vs without CW. CI indicates Cardiac index; CW, Clinical worsening; DBP, Diastolic blood pressure; Ea, Effective arterial elastance; Ees, End-systolic elastance; HR, Heart rate; MPAP, Mean pulmonary arterial pressure; PA O_2 Sat, Pulmonary arterial oxygen saturation; PCWP, Pulmonary capillary wedge pressure; PVR, Pulmonary vascular resistance; RAP, Right atrial pressure; RVDP, RV diastolic pressure; RVSP, RV systolic pressure; SV/PP, Stroke volume/pulse pressure; SBP, Systolic blood pressure; and W.U., Wood units.

0.91; *P*=0.04) were also predictive of CW. The single-beat estimate of Ees/Ea was not predictive of CW (HR, 0.32 per unit of Ees/Ea, *P*=0.22), though the HR was numerically similar to that of MB Ees/Ea. A forest plot comparison of RVEF, MB Ees/Ea, SB Ees/Ea, and SV/ESV is shown in Figure 1. CTD-PAH was a significant predictor of CW, with HR 5.6 (*P*=0.02). There was a trend towards incident PAH (ie, newly diagnosed PAH at time of RHC versus assessment of a prevalent PAH subject) predicting CW (HR, 2.28, *P*=0.11).

Receiver operator curve (ROC) analyses were next determined. ROC of the multi-beat Ees/Ea ratio as a predictor of CW (Figure 2) demonstrated an area under the curve (AUC) of 0.78 (95% CI, 0.57, 0.92; *P*=0.01). Based on the Youden index, the optimal multi-beat Ees/Ea cutoff was <0.65, which yielded a 73% sensitivity and 90% specificity for predicting CW. On the other hand, ROC analyses utilizing RVEF, SV/ESV, and the single-beat estimate of Ees/Ea did not demonstrate a significant ability to predict CW (*P*>0.05 for all 3 AUC). The AUC for MB Ees/Ea was the greatest of the 4 metrics tested, but this difference was not statistically significant based on pairwise ROC comparisons (AUC for MB Ees/Ea versus SB Ees/Ea chi-square statistic 1.48, *P*=0.22; MB Ees/Ea versus RVEF chi-square 0.93, *P*=0.34; MB Ees/Ea versus SV/ESV chi-square 0.43, *P*=0.51). That said, sample size limited the power of pairwise ROC comparisons.

In Kaplan-Meier survival analysis, MB Ees/Ea proved predictive of time to CW, using the optimally determined cutoff of MB Ees/Ea <0.65 (HR, 5.1, log rank *P*=0.001) (Figure 3). Reduced RVEF and SV/ESV also predicted time to CW (HR, 3.3, *P*=0.004 and HR 3.3, *P*=0.028, respectively), whereas SB Ees/Ea again did not (*P*=0.5) (Figure 4).

Since CTD-PAH and incident PAH were associated with CW in univariable analyses, we performed multivariable modeling adjusting for disease subgroup (CTD-PAH versus IPAH) and incident versus prevalent disease in order to address possible confounding. MB Ees/Ea <0.65 remained predictive of CW after adjustment for incident PAH and CTD-PAH (HR, 7.66 [95% CI, 1.35, 43.60], *P*=0.023) (Figure S2, Table S1). The relationship between MB Ees/Ea and time to CW did not differ in subjects with CTD-PAH versus those with IPAH (interaction term *P*=0.215; Table S2) or in subjects with incident versus prevalent PAH (interaction term *P*=0.876; Table S3). In a sensitivity analysis of MB Ees/Ea in the CTD-PAH sub-cohort, MB Ees/Ea remained predictive of CW (HR, 0.16, *P*=0.038). ROC analysis of MB Ees/Ea among CTD-PAH sub-cohort generated an AUC of 0.897 (*P*<0.001), with the same optimal cut point as the larger cohort (Figure S3A).

Table 4. Univariable Predictors of Clinical Worsening

Characteristic	Hazard Ratio	95% CI	*P* Value
Age	1.00	1.00 to 1.04	0.88
Male sex	2.80	0.73 to 10.47	0.13
CTD-PAH (vs IPAH)	5.60	1.26 to 24.88	0.02
Incident PAH (vs prevalent)	2.28	0.83 to 6.27	0.11
6MWD, m	1.00	1.00 to 1.00	0.60
WHO FC (I/II vs III)	1.06	0.38 to 2.91	0.91
NT pro-BNP	1.00	1.00 to 1.00	0.23
RVEDV	1.01	1.00 to 1.02	0.18
RV mass	0.97	0.92 to 1.02	0.25
RVEF	0.95	0.91 to 0.99	0.03
RV SV/ESV	0.23	0.06 to 0.91	0.04
RAP	1.03	0.91 to 1.17	0.60
Mean pulmonary arterial pressure	1.02	0.98 to 1.05	0.33
Cardiac index	0.55	0.21 to 1.44	0.23
Pulmonary vascular resistance	1.07	0.98 to 1.18	0.15
Multi-beat Ea	1.45	0.58 to 3.68	0.43
Multi-beat Ees	0.38	0.10 to 1.42	0.15
Multi-beat Ees/Ea	0.26	0.07 to 0.91	0.04
Single-beat Ees	1.05	0.26 to 4.17	0.94
Single-beat Ees/Ea	0.32	0.05 to 2.0	0.22

CTD-PAH diagnosis, RVEF, RV SV/ESV, and Multi-beat Ees/Ea were significant predictors of clinical worsening. 6MWD indicates 6-minute walk distance; CTD-PAH, Connective tissue disease-associated PAH; Ea, Effective arterial elastance; Ees, End-systolic elastance; NT pro-BNP, N terminal pro-brain natriuretic peptide; RAP, Right atrial pressure; RVEF, RV ejection fraction; RVEDV, RV end-diastolic volume; and SV/ESV, stroke volume/end-systolic volume.

Survival analysis of the CTD-PAH sub-cohort showed decreased survival time among those with MB Ees/Ea <0.65, with near significance (HR, 3.3, *P*=0.08) (Figure S3B). Lastly, in another sensitivity analysis, use of ≥15% 6MWD decline (a cutoff used in many clinical trials) rather than 10% did not appreciably change any study results.

Finally, we tested whether the addition of MB Ees/Ea to a Cox model measuring RVEF's association with time to CW would improve model fit and predictive capacity. We found that adding MB Ees/Ea to RVEF in a bivariable model, fit to time-to-event data, improved model fit (likelihood ratio test chi-square 3.89, *P*=0.049) and prediction of time to CW (by comparison of Akaike's information criteria).

DISCUSSION

The MB Ees/Ea ratio has long been considered the gold-standard measure of ventricular function. It has excellent sensitivity for detecting occult RV dysfunction

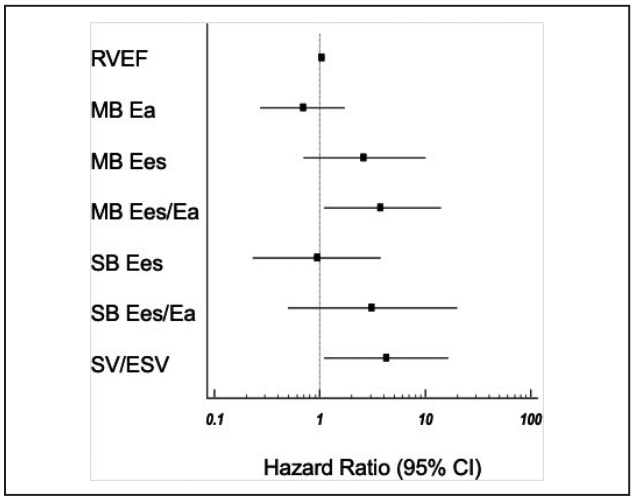

Figure 1. Forest plot comparing RVEF and coupling metrics.
Forest Plot of Hazard Ratios and 95% CIs for RV ejection fraction (RVEF), Multi-beat (MB) Effective arterial elastance (Ea), MB end-systolic elastance (Ees), MB Ees/Ea ratio, single-beat (SB) Ees, SB Ees/Ea ratio, and Stroke volume/end-systolic volume (SV/ESV).

and has been validated in both animal and human models of PAH.[8,14] Despite its utility, however, until recently there has not been any validation of its ability to predict clinical outcomes in human PAH.[11] The major findings of our current study are that: (1) MB Ees/Ea predicts time to CW in PAH, even in a cohort where RVEF was predominately preserved, (2) the predictive value of MB Ees/Ea remains true even when adjusting for PAH subtype and diagnosis timing, and (3) MB Ees/Ea proves superior to RVEF, SV/ESV, and especially the single-beat estimate of Ees/Ea in its ability to predict CW in human PAH.

The MB Ees/Ea coupling ratio is often utilized in investigational assessments of the RV[14,15]; therefore, its use would ideally be supported by a proven ability to predict clinical outcomes. The need to do so may not seem apparent, since several more readily available measures of RV function—such as RVEF, TAPSE, SV/ESV, and others[14]—have prognostic value in human PAH. However, these metrics worsen more so in late disease, during the same period that overt resting RV dilation and RV systolic dysfunction have already emerged.[16,17] Compared with these metrics, the MB Ees/Ea ratio has several key advantages: (1) it leverages multi-beat RV Ees, a load-independent, well-validated measure of RV contractile function,[4,5,8,9] and (2) it detects early, occult RV contractile dysfunction in PAH, both at rest[8] and stress[9]—dysfunction unapparent using more conventional measures of RV function such as RVEF or TAPSE. MB Ees has even been shown to correlate to sarcomere maximal contractility from RV myocardial tissue.[10] MB Ees/Ea is therefore an accurate and sensitive means of detecting RV dysfunction

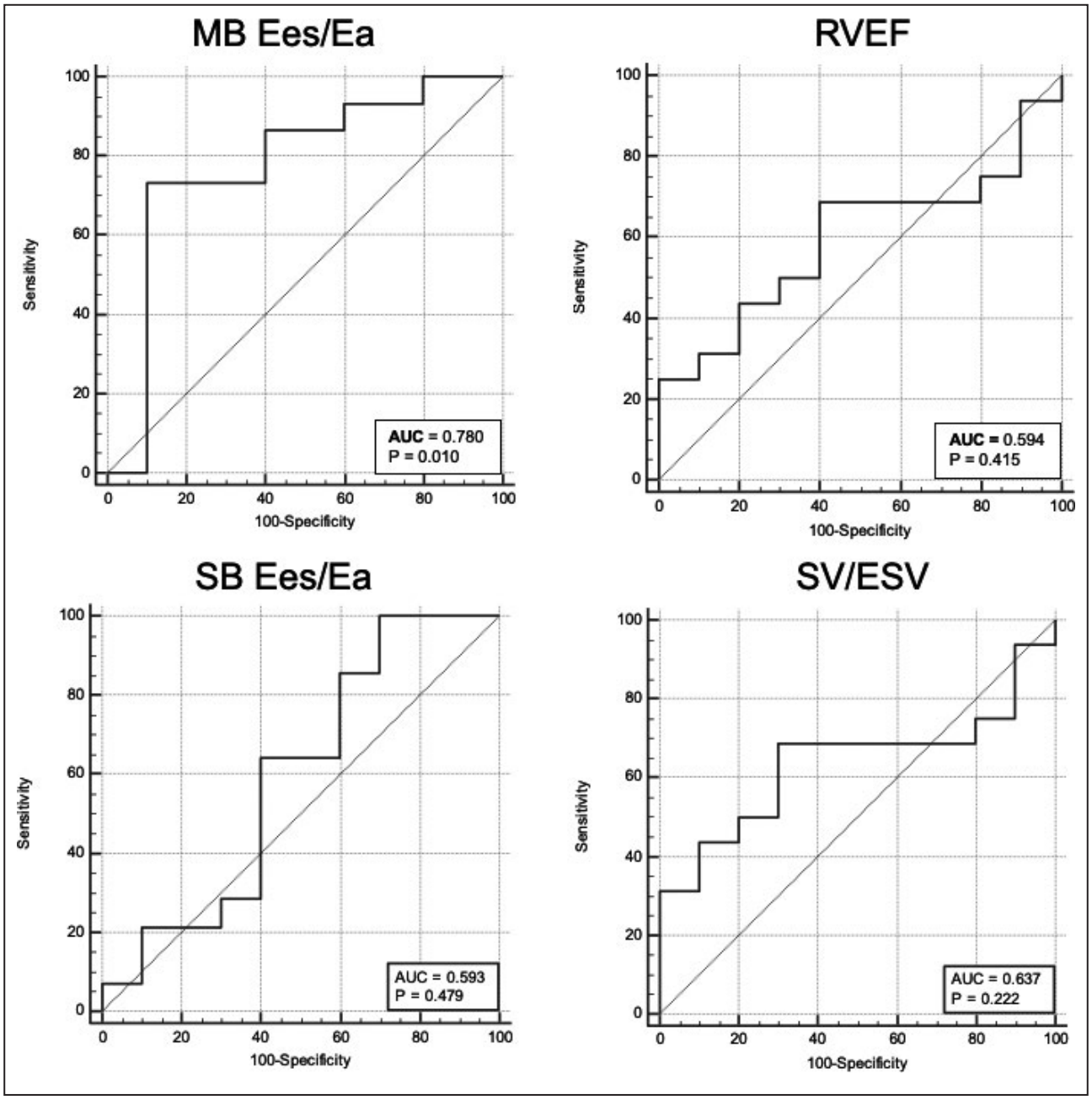

Figure 2. Multi-beat Ees/Ea best predicts clinical worsening (CW) by receiver operator curve (ROC) analysis.
Multi-beat Ees/Ea significantly predicted CW with an Area Under the Curve (AUC) of 0.780. By ROC analysis, right ventricle (RV) ejection fraction, single-beat Ees/Ea, and stroke volume/end-systolic volume (SV/ESV) were not able to predict CW.

and early RV-PA uncoupling. To date, one of the key missing pieces regarding the validity of MB Ees/Ea has been evidence that this ratio predicts clinical outcomes in human PAH.[15] A recent report by Richter and colleagues is the first published report to demonstrate that MB Ees/Ea predicts clinical outcomes in human PAH.[11] The present study adds to the literature by not only independently arriving to a similar conclusion, but importantly, doing so in a distinct human PAH cohort, with preserved baseline RV function, as indexed by RVEF.

There are important similarities and differences between the Richter study and the present one.[11] Both use a similar definition of CW and find that similar multi-beat Ees/Ea cutoffs (0.65 in this study, 0.70 in the Richter study) predict worsening in human PAH. There are differences in demographics and PAH subtypes between groups (more women and more CTD-PAH in the present study), which help to strengthen generalizability. Perhaps most importantly, though, the present study investigates a

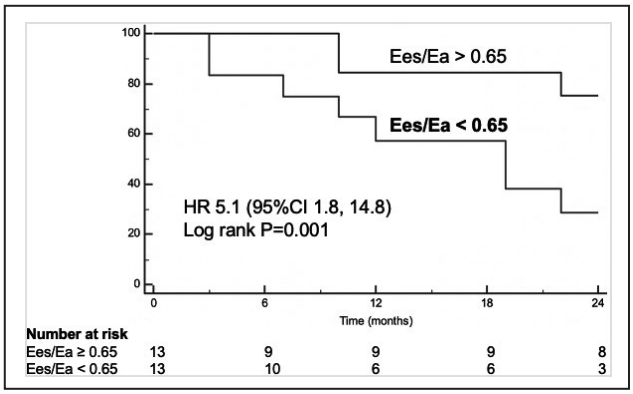

Figure 3. Multi-beat Ees/Ea Predicts Time to Clinical Worsening (CW).
Multi-beat Ees/Ea, using a cut off of <0.65, was also able to significantly predict time to CW in Kaplan–Meier Survival Analysis.

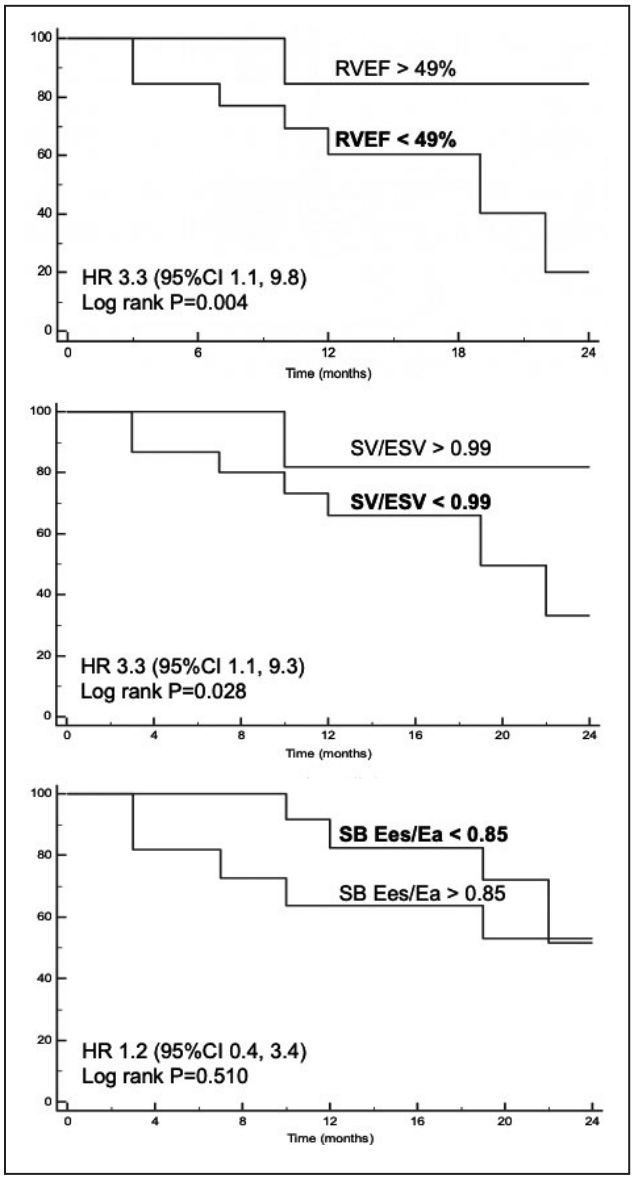

Figure 4. Other metrics vary in predicting time to clinical worsening (CW).
RV ejection fraction (RVEF) and Stroke Volume/End-diastolic Volume (SV/ESV) were also able to predict time to CW in Kaplan–Meier Survival Analysis. Single-beat Ees/Ea did not significantly predict time to CW. Since Area Under the Curve (AUC) analysis was non-significant for all 3, median values for all 3 variables were used as the cutoff.

cohort with preserved RVEF, which further extends generalizability into a range of more compensated PAH patients. With the recent inclusion of lower pulmonary pressures in the new definition of PAH,[18] MB Ees/Ea may prove a more sensitive way to detect occult RV dysfunction in this population.

Another important distinction is that the present study does not find as strong of agreement between multi-beat and single-beat estimates of Ees/Ea. This is likely due to the more compensated RVEF in our PAH cohort. Like in the Richter cohort, a Bland-Altman analysis of our cohort shows reasonable agreement when Ees/Ea <1.0.[11] However, in the present study, bias increased when Ees/Ea >1.0 and when RVEF >40%, with the single-beat estimate generally underestimating the multi-beat ratio. Compared with the Richter cohort, the present cohort had a higher proportion of subjects with Ees/Ea >1.0, which further skewed the disagreement between both measures. Similar concerns about SB underestimation of RV-PA coupling have been reported in animal models of PH,[19] and a recent systematic review.[20] This led to an inability of the SB estimate of Ees/Ea in predicting CW in the present study. Differences in agreement between SB and MB assessments, especially among those with preserved RVEF, likely hindered the predictive ability of the SB Ees/Ea ratio. Our data suggest difficulty in approximating Pmax at higher pulmonary pressures, which then skew the single-beat estimate of Ees/Ea at coupling ratios. That said, the directionality of the single-beat results mirror those of the multi-beat findings in this cohort. Therefore, it is also possible that differences in measurement technique or cohort size may have limited our ability to detect a relationship between SB Ees/Ea and outcomes. Other SB methods have also been proposed.[21,22] Further validation of SB and MB estimates of Ees/Ea in human PAH, and especially in subjects with more preserved RV function, will help reconcile differences between these metrics.

Not surprisingly, RVEF measured by CMR proved predictive of CW and also predicted time to CW in the present study. RV dilation and RVEF are known to deteriorate as RV dysfunction ensues in PAH.[14] RVEF is a reliable and well-established predictor of clinical outcomes in human PAH as well as PH regardless of etiology,[14] and the present study further supports the predictive capacity of RVEF. Perhaps more importantly, RVEF prediction

in the present study essentially serves as a "positive control" for our cohort, thus helping to validate our main findings about MB Ees/Ea and clinical outcomes. Additionally, MB Ees/Ea was not simply a more onerous alternative to RVEF in this cohort. Instead, MB Ees/Ea showed added value when added to a prediction model of RVEF alone. MB Ees/Ea has already been shown to detect occult RV dysfunction undetected by RVEF alone,[8,9] and the superiority of a bivariable model of multi-beat Ees/Ea and RVEF lend weight to this finding.

SV/ESV was also found to be predictive of time to CW. This mirrors a study by Vanderpool and colleagues that showed SV/ESV predicts outcomes in PAH.[23] Other studies have replicated the predictive capacity of SV/ESV in both adult and pediatric PH.[24,25] SV/ESV has several potential advantages itself. It is readily reproducible and attainable from multiple modalities like CMR. It has a better discriminatory range than RVEF in patients with moderate RV dysfunction.[26] The Vanderpool study found additional advantages to SV/ESV that were not seen in our cohort. However, cohort size or the relatively well-preserved baseline RVEF may have limited our ability to come to the same full conclusion as the Vanderpool study.[23]

The present study has several important limitations. PAH is a rare disease, and thus enrollment occurred at a single tertiary-care center. This limits generalizability and leads to referral biases inherent to our center. For example, CTD-PAH is heavily represented in our PAH population. But sensitivity analyses and adjustments for CTD-PAH status did not change our overall conclusion that the multi-beat Ees/Ea is predictive of outcomes. MB Ees/Ea requires invasive RV pressure-volume loop analysis, which by its nature is invasive and difficult. This limits cohort size and thus statistical power. Therefore, type II error was possible throughout. The size of our cohort also limited any complex multivariable analyses. Future, larger single-center studies, or collaborations with other centers that perform pressure-volume catheterizations of the RV, will hopefully overcome limitations in sample size. Achieving appropriate preload reduction during pressure-volume loop data acquisition required operator experience that admittedly can be challenging to achieve; future standardization efforts will be beneficial for the field. Finally, attainment of MB Ees/Ea remains costly and technically intricate, and therefore clinical surrogates to the MB Ees/Ea ratio are still needed. The current study does not address this issue.[27]

In conclusion, we demonstrate that the multi-beat Ees/Ea does indeed predict CW in a prospective study of a human PAH cohort with relatively preserved RVEF, and remained predictive even after key adjustments. These findings suggest that assessing RV-PA coupling may be particularly relevant in detecting early and occult RV dysfunction. The single-beat estimate of Ees/Ea was not predictive of outcomes, and further work is likely needed to refine this metric in higher ranges of Ees/Ea and RVEF. These findings add support to the investigational and clinical utility of the MB Ees/Ea ratio in human PAH.

ARTICLE INFORMATION

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Disclosures

Dr Tedford reports no direct conflicts pertinent to the development of this manuscript. Other general conflicts include consulting relationships with Medtronic, Arena Pharmaceuticals and United Therapeutics. Dr Tedford is on a steering committee for Medtronic and the research advisory board for Abiomed. He also does hemodynamic core lab work for Actelion and Merck. The remaining authors have no disclosures to report.

Supplementary Materials

Tables S1–S3
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Multivariate logistic regression showed MB Ees/Ea <0.65 remained predictive of clinical worsening (CW), even when adjusted for incident PAH and CTD-PAH.

Covariate	HR	95% CI	P-value
MB Ees/Ea < 0.65	7.658	1.345, 43.601	0.023
Incident PAH	3.472	0.772,15.625	0.107
CTD-PAH	4.343	0.597, 31.610	0.149

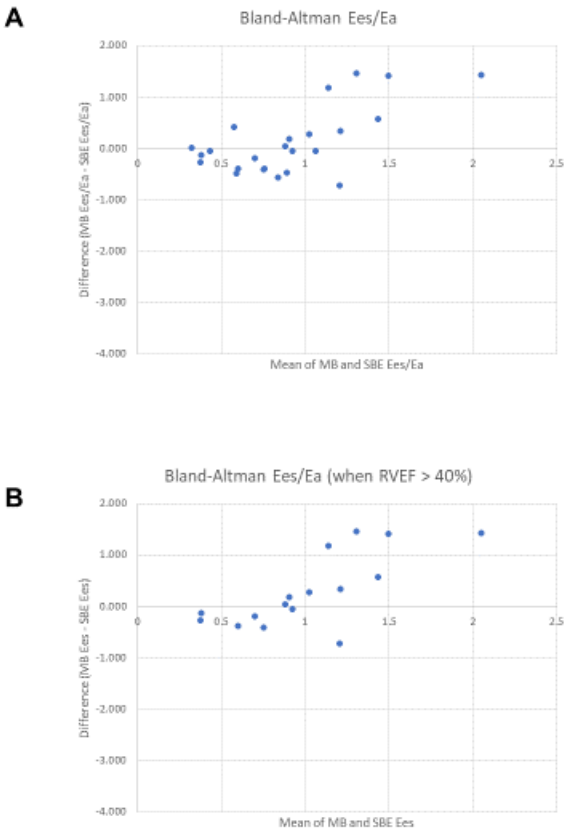
Table S2. There was no significant interaction of CTD-PAH diagnosis on MB Ees/Ea prediction of CW (interaction term P-value 0.215).

Covariate	HR	95% CI	P-value
MB Ees/Ea	11.07	0.10, 1260.63	0.320
CTD-PAH	2005	0.04, 8.8*10^7	0.163
CTD-PAH * MB Ees/Ea (Interaction Term)	0.004	6*10^-7, 24.7	0.215

Table S3. There was no significant interaction of incident PAH status on MB Ees/Ea prediction of CW (interaction term P-value 0.876).

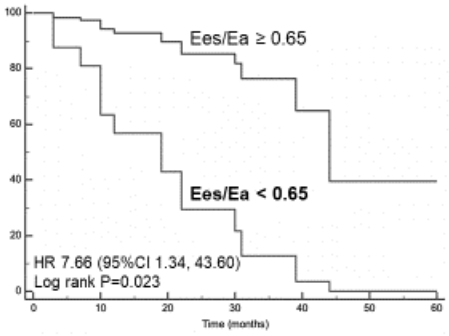
Covariate	HR	95% CI	P-value
MB Ees/Ea	0.397	0.058, 2.701	0.345
Incident PAH	1.343	0.042, 42.719	0.867
Incident PAH * MB Ees/Ea (Interaction Term)	0.737	0.016, 34.262	0.876

Figure S1. Bland-Altman Analysis comparing Single-beat (SB) and Multi-beat (MB) Ees/Ea in the (A) Overall Cohort and (B) in the Cohort with RVEF > 40%.



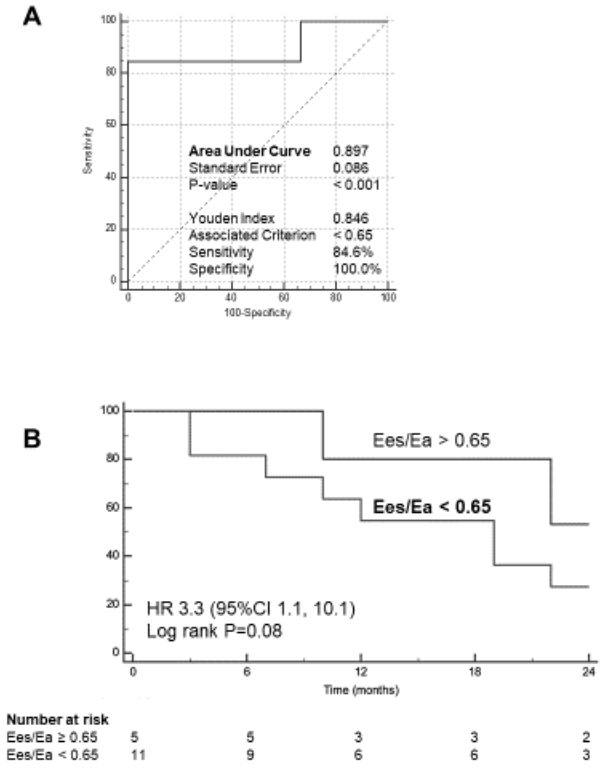
SB Ees/Ea overestimated MB Ees/Ea particularly when mean Ees/Ea > 1.0. The overestimation of SB Ees/Ea was more pronounced in the sub-cohort of RVEF > 40%.

Figure S2. Sensitivity Analysis of the Connective Tissue Disease-associated PAH (CTD-PAH) cohort only.



MB Ees/Ea remained predictive of CW in the CTD-PAH only sub-cohort by receiver operator curve analysis (AUC 0.897, P<0.001). Youden Index still predicted MB Ees/Ea <0.65 as the optimal cut off. CTD-PAH time to CW was worse in those with MB Ees/Ea < 0.65, but this did not reach statistical significance (P=0.08).

Figure S3. Multi-beat Ees/Ea adjusted for CTD-PAH and incident PAH remained predictive of time to CW.



MB Ees/Ea <0.65 remained predictive of time to CW even when adjusted for CTD-PAH and incident PAH diagnoses (HR 7.66, P=0.023).