CHEST Online Supplement

The Right Ventricular-Pulmonary Arterial Coupling and Diastolic Function Response to Therapy in Pulmonary Arterial Hypertension

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Variable		Non-Responders	Responders		
			All	Super-responders	Partial Responders
Age (yr)		57±19	53 ± 13	**48 ± 11†**	59 ± 12
Sex (Female)		7 (78)	34 (79)	18 (81)	16 (76)
BMI (kg/m^2)		34.1 ± 14.1	30.0 ± 6.7	29.8 ± 5.2	30.3 ± 8.0
WSPH Category	CTD	2 (22.2)	10 (2.3)	3 (13.6)	7 (33.3)
	Drugs/Toxins	2 (22.2)	6 (23.3)	5 (22.7)	1 (4.8)
	HIV	0 (0.0)	1 (14.0)	1 (4.5)	0 (0)
	iPAH	4 (44.4)	21 (2.3)	10 (45.5)	11 (52.4)
	Portal Hypertension	0 (0.0)	4 (48.8)	2 (9.1)	2 (9.5)
	PVOD	1 (11.1)	0 (9.3)	0 (0)	0 (0)
Diabetes	Diabetes	0 (0.0)	1 (2.3)	1 (4.5)	0 (0)
BNP	BNP (pg/mL)	**1278 ± 1170***	604.1 ± 476	481.9 ± 444	732.2 ± 485
6 Minute Walk Distance (M)		**152 ± 124***	298 ± 91	328 ± 91	254 ± 75
Risk Scores	ERS Low Risk	0 (0)	1 (2.3)	1 (4.5)	0 (0)
	ERS Intermediate Risk	0 (0)	24 (55.8)	14 (63.6)	10 (47.6)
	ERS High Risk	9 (100)	18 (41.9)	7 (31.8)	11 (52.4)
	REVEAL Risk Score	11.9 ± 0.8	9.6 ±1.5	9.3 ± 1.5	9.9 ± 1.4
	REVEAL 2 Risk Score	11.0 ± 0.5	10.0 ± 2.1	**9.2 ± 1.5†**	10.9 ± 2.3
Hemodynamics	Mean PAP (mmHg)	58.4 ± 14	55.4 ± 10.3	55.6 ± 11.4	55.1 ± 9.3
	Cardiac Output (L/min)	3.7 ± 1.5	4.1 ± 1.3	4.1 ± 1.2	4.1 ± 1.4
	PCWP (mmHg)	9.1 ± 4.1	8.6 ± 4.6	8.6 ± 4.0	9.7 ± 4.2
	RAP (mmHg)	13 ± 7	12 ± 7	11 ± 5	14 ± 7
	PVR (WU)	15.7 ± 7.8	12.1 ± 4.2	12.5 ± 4.4	11.8 ± 4.0
	Compliance (mL/mmHg)	0.8 ± 0.4	1.1 ± 0.4	1.0 ± 0.4	1.1 ± 0.4
	PAO2 sat (%)	**52 ± 12***	60.4 ± 8.3	60 ± 9.0	62 ± 7.5
Cardiac Imaging	Echo RA area (cm^2)	27.7 ± 5.2	20.0 ± 3.8	17.3	22.7
	Echo TAPSE (cm)	1.43 ± 0.41	1.45 ± 0.38	1.45 ± 0.4	1.46 ± 0.4
	Echo FAC (%)	15.7 ± 9.4	20.1 ± 8.2	22.3 ± 7.2	17.8 ± 6.6
	MRI RVESVi (mL/m^2)		87.5 ± 43.7	79.4 ± 22.2	96.4 ± 60.8

	MRI RVEDVi (mL/m^2)		116.2 ± 44.6	110.4 ± 26.2	122.8 ± 59.4
	MRI RVEF (%)		26.2 ± 10.3	**23.8 ± 7.2†**	19.0 ± 8.06
	MRI SV/ESV		0.39 ± 0.23	0.43 ± 0.2	0.34 ± 0.1
	MRI RV mass (gm/m2)		45.0 ± 18.5	41.4 ± 12.5	48.9 ± 23.0
	RV Mass/Volume (gm/mL)		0.4 ± 0.11	0.4 ± 0.12	0.4 ± 0.10
RVPA Coupling and Diastolic Function	Right ventricular elastance, (Ees) (mmHg/mL)	1.5 ± 1.1	1.5 ± 0.7	1.6 ± 0.7	1.4 ± 0.7
	Arterial elastance (Ea) (mmHg/mL)	**2.8 ± 1.8***	1.9 ± 0.7	1.9 ± 0.8	1.8 ± 0.6
	RVPA coupling ratio	0.6 ± 0.4	0.9 ± 0.4	0.9 ± 0.4	0.8 ± 0.4
	RV end-diastolic elastance (mmHg/mL)		1.2 ± 0.7	1.4 ± 0.8	1.1 ± 0.6
	$Ed_{corrected}$		3.4 ± 2.1	3.8 ± 2.1	2.9 ± 2.0

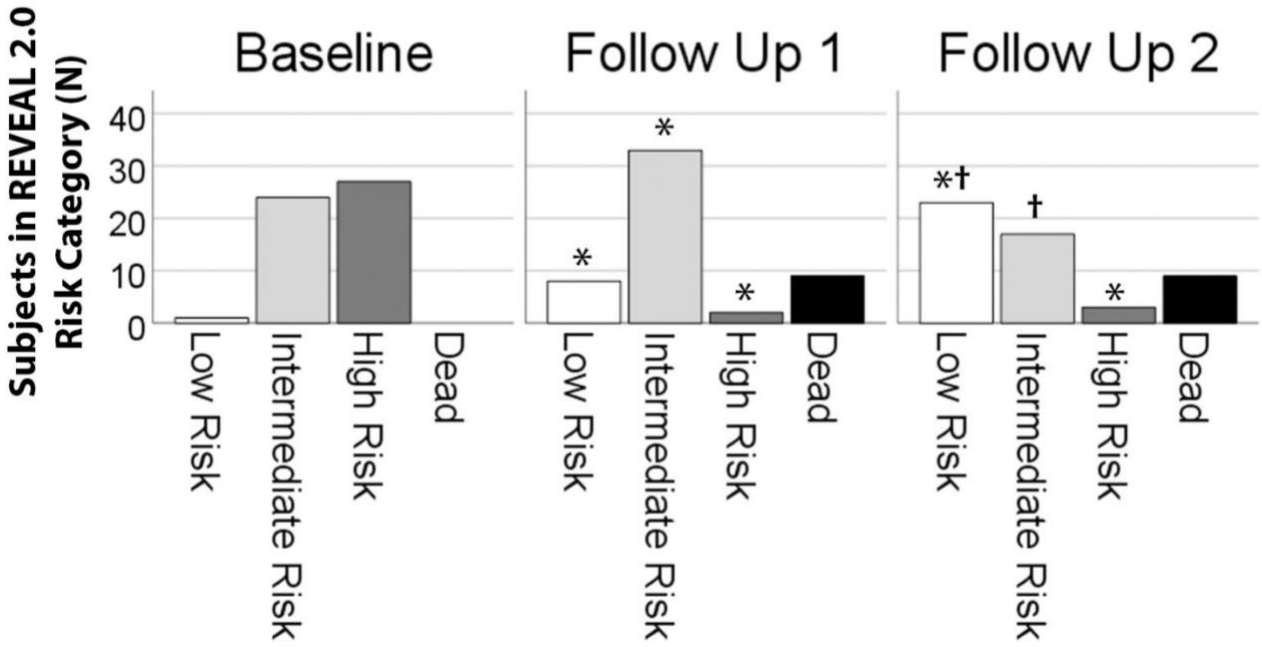
e-Table 1. Baseline demographics and clinical data, multiparametric risk scores, resting hemodynamics, cardiac imaging, and coupling/diastolic function by therapeutic response. Therapeutic response is classified by follow up 1 (responders versus non-responders) and at follow-up 2 (super-responders and partial-responders). Baseline two-group comparisons were done with unpaired, two-tailed t tests for continuous variables or Pearson's chi-square test for categorical variables. See Table 1 of the main manuscript for abbreviations. *p<0.05 for non-responders versus responders; † p<0.05 for super-responders versus partial-responders. Data are represented by N (%) or mean ± SD.

Variable		Super-responders N=23	Partial responders N=20
Risk Score (s)	ERS Low Risk	8 (36)	0 (0)
	ERS Intermediate Risk	14 (64)	19 (91)
	ERS High Risk	0 (0)	2 (9)
ERS Risk Score Elements	Functional Class		
	II	8 (36)	0 (0)
	III	14 (64)	18 (86)
	IV	0 (0)	3 (14)
	6 MWD (m)	**409 ± 115***	281 ± 95
	BNP (pg/mL)	169 ± 179	276 ± 95
	RAP (mmHg)	5 ± 4	7 ± 5
	Cardiac Index (L/min/m^2)	3.1 ± 0.8	2.7 ± 0.8
	PA $O2_{sat}$ (%)	66.5 ± 7.4	64 ± 6.3
Treatment	Treprostinil Dose	46.1 ± 6.8	42.6 ± 11.1
	Diuretics (Loop)	16 (73)	18 (86)
	Diuretics (Combination)	5 (23)	8 (38)
Hemodynamics	mPAP (mmHg)	44.8 ± 11.0	46.0 ± 8.4
	PCWP	6.3 ± 3.1	7.3 ± 4.1
	PVR (WU)	7.4 ± 3.2	8.1 ± 2.8
	Compliance (mL/mmHg)	1.8 ± 0.8	1.5 ± 0.5
Cardiac Imaging	RA area (cm^2)	22.8 ± 5.0	25.6 ± 8.2
	TAPSE (cm)	2.7 ± 3.3	1.7 ± 0.43
	FAC (%)	24.7 ±9.3	23 ± 10.0
	RV ESVi (mL/m^2)	70.4 ± 25.3	90.7 ± 58.7
	RV EDVi (mL/m^2)	104 ± 29.4	123 ± 60.5
	RVEF (%)	33.0 ± 9.2	30.4 ± 11.0
	SV/ESV	0.52 ± 0.2	0.47 ± 0.3
	MRI RV mass (gm/m2)	42.1 ± 12.5	51.5 ± 25.3
	RV Mass/Volume (gm/mL)	0.44 ± 0.16	0.41 ± 0.10
RVPA Coupling	Ees (mL/mmHg)	1.1 ± 0.6	1.4 ± 0.8
	Ea (mL/mmHg)	1.2 ± 0.5	1.3 ± 0.5
	Ees/Ea	1.1 ± 0.5	1.1 ± 0.5
	Eed (mL/mmHg)	0.7 ± 0.5	0.9 ± 0.6
	$Eed_{corrected}$	1.8 ± 1.4	2.18 ± 1.41

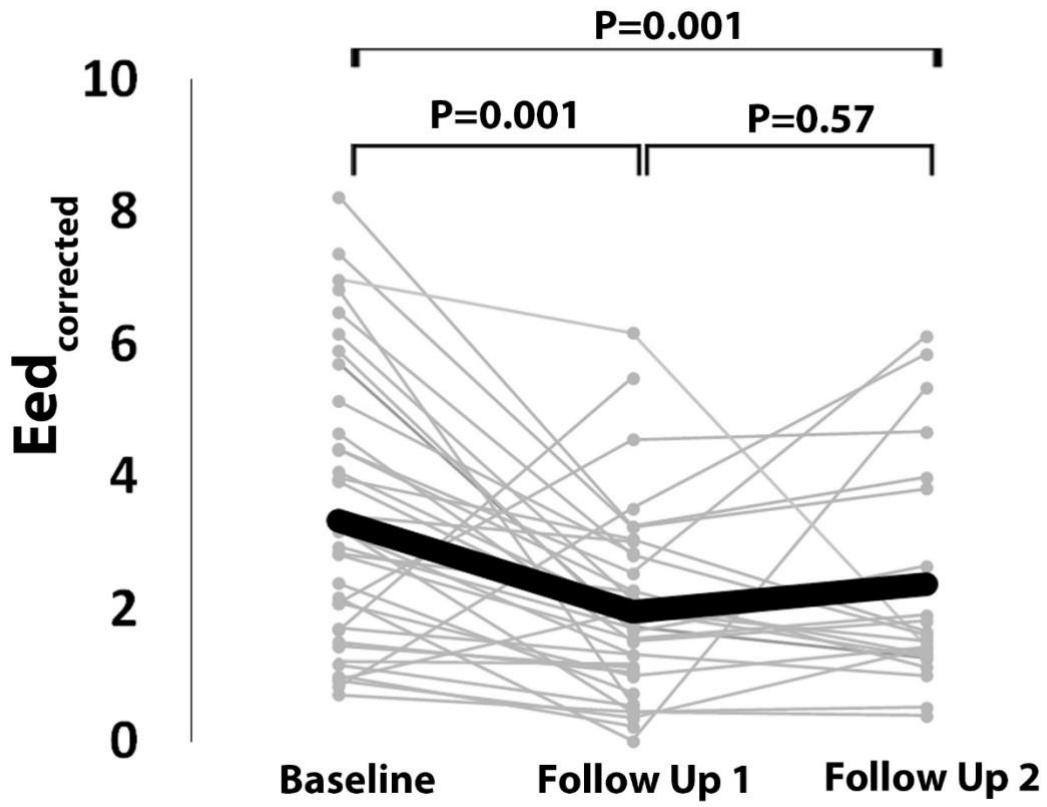
e-Table 2. Follow Up 1 Demographics and clinical data, multiparametric risk scores, resting hemodynamics, cardiac imaging, and coupling/diastolic function classified therapeutic response at follow up 2. Therapeutic response is classified by achievement of ERS risk score 1 (low risk) as super-responders or ERS risk score 2/3 (intermediate or high risk) at follow up 2. See Table 1 of the main manuscript for abbreviations. Two-group comparisons were done with unpaired, two-tailed t tests for continuous variables or Pearson's chi-square test for categorical variables. * $p<0.05$ for super-responders versus partial-responders. Data are represented by N (%) or mean ± SD.

	Variable	Super-responders N=23	Partial responders N=20
Risk Score (s)	ERS Low Risk	22 (100)	0 (0)
	ERS Intermediate Risk	0 (0)	18 (90%)
	ERS High Risk	0 (0)	2 (10)
ERS Risk Score Elements	Functional Class		
	II	**17 (36)**	2 (10)
	III	4 (64)	17 (85)
	IV	0 (0)	1 (5)
	6 MWD (m)	**449 ± 107***	314 ± 115
	BNP (pg/mL)	**38.4 ± 28.6***	191.0 ± 157.2
	RAP (mmHg)	3 ± 2	**7 ± 5**
	Cardiac Index (L/min/m^2)	3.0 ± 0.5	2.7 ± 0.6
	PA $O2_{sat}$ (%)	**70.5 ± 5.0***	62.0 ± 6.8
Treatment	Treprostinil Dose (ng/kg/min)	64.5 ± 20.1	66.4 ± 19.1
	Combination Therapy?	17 (74)	20 (100)
	Diuretics (Loop)	16 (72)	18 (90)
	Diuretics (Combination)	5 (23)	8 (40)
Hemodynamics	mPAP (mmHg)	**35.3 ± 8.5***	43.2 ± 8.7
	PCWP	6.6 ± 2.5	7.5 ± 3.4
	PVR (WU)	**5.5 ± 1.9***	7.3 ± 2.7
	Compliance (mL/mmHg)	**2.4 ± 1.0***	1.6 ± 0.5
Cardiac Imaging	RA area (cm^2)	**20.6 ± 5.1***	28.8 ± 10.0
	TAPSE (cm)	2.1 ± 0.34	1.9 ± 0.5
	FAC (%)	27.3 ± 11.2	19.7 ± 9.6
	RV ESVi (mL/m^2)	**57.3 ± 18.0***	104.0 ± 73.4
	RV EDVi (mL/m^2)	98.3 ± 29.5	141.5 ± 6.3
	RVEF (%)	**42.0 ± 5.1***	28.7 ± 10.0
	SV/ESV	**0.73 ± 0.2***	0.43 ± 0.21
	MRI RV mass (gm/m^2)	39.8 ± 7.9	55.0 ± 50.7
	RV Mass/Volume (gm/mL)	0.43 ± 0.16	0.37 ± 0.14
RVPA Coupling	Ees (mL/mmHg)	1.2 ± 1.0	1.2 ± 0.7
	Ea (mL/mmHg)	**0.8 ± 0.2***	1.2 ± 0.4
	Ees/Ea	1.5 ± 0.9	1.0 ± 0.5
	Eed (mL/mmHg)	**0.6 ± 0.3***	0.9 ± 0.4
	$Eed_{corrected}$	**1.6 ± 0.95***	3.2 ± 2.0

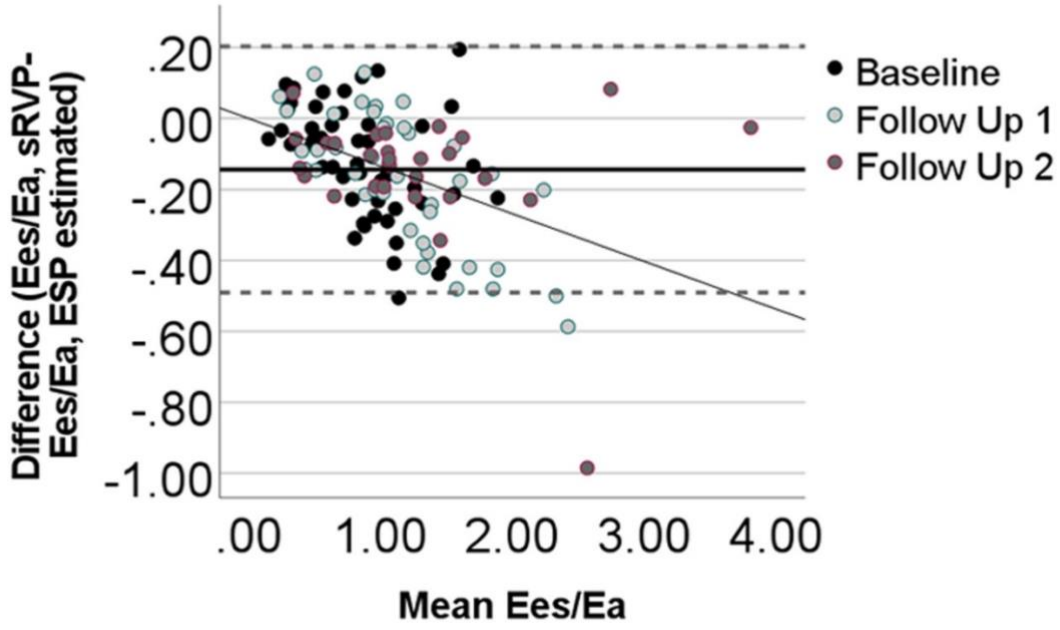
e-Table 3. Follow Up 2 Demographics and clinical data, multiparametric risk scores, resting hemodynamics, cardiac imaging, and coupling/diastolic function classified therapeutic response at follow up 2. Therapeutic response is classified by achievement of ERS risk score 1 (low risk) as super-responders or ERS risk score 2/3 (intermediate or high risk) at follow up 2. See Table 1 of the main manuscript for abbreviations. Two-group comparisons were done with unpaired, two-tailed t tests for continuous variables or Pearson's chi-square test for categorical variables. See table S2 for abbreviations. * $p<0.05$ for super-responders versus partial-responders. Data are represented by N (%) or mean ± SD.



e-Figure 1. Therapeutic changes in REVEAL 2.0 risk score. There is an improvement from high and intermediate risk at baseline to low and intermediate risk at follow-up 1. Subjects dead before follow-up 1 were non-responders with irreversible RV failure. Patients in low risk continued at follow-up 2 indicating further improvement. Changes are like ERS risk score changes. REVEAL within group differences tested with Persons's chi-square test. * P<0.05 versus baseline; † P<0.05 versus follow up 1



e-Figure 2. Figure 4. Longitudinal Assessment of $Eed_{corrected}$ among treatment responders. Spaghetti plots demonstrating changes in Eed corrected ($Eed_{corrected}$) for RV mass/volume (relative wall thickness) over time. $Eed_{corrected}$ tested with repeated measures ANOVA. Large bracket indicates overall model P-value; small brackets indicate pairwise comparisons.



e-Figure 3. Accuracy and precision of Ees/Ea based on two methods of estimation of end-systolic pressure. Bland-Altman plot representing the accuracy of Ees/Ea calculated from ESP estimated from systolic right ventricular pressure (sRVP) versus mean pulmonary artery pressure (mPAP). There is considerable bias -0.143 which was proportional (beta -0.13, $p<0.0001$ for this relationship). Limits of agreement were also large 0.18 to -0.49. Ees/Ea and Eed tested with repeated measures ANOVA..