SUPPLEMENTAL MATERIAL

Supplemental Table S1. Baseline Clinical Characteristics

		IPAH (n = 9)	SSc-PAH (n = 15)	P-value
Demographic Information				
Sex	Female (n, %)	7 (78%)	13 (87%)	0.62*
Race	Caucasian (n, %)	8 (89%)	13 (87%)	1.00*
	African-American (n, %)	1 (11%)	1 (7%)	1.00*
Age at catheterization (y)		50 ± 5	59 ± 3	0.13
Clinical Characteristics				
Body surface area (m^2)		2.0 ± 0.1	1.8 ± 0.1	0.04
Heart rate (min^{-1})		75 ± 6	72 ± 3	0.83
Mean Systemic Arterial Pressure (mm Hg)		91 ± 3	91 ± 4	0.65
PAH-targeted medications (n, %)				
	Aldosterone Antagonist	2 (22%)	3 (20%)	1.00*
	Calcium channel blocker	3 (33%)	6 (40%)	0.66*
	Prostanoid (inhaled or intravenous)	0 (0%)	0 (0%)	1.00*
	Endothelin Receptor Antagonist (ERA)	3 (33%)	4 (27%)	1.00*
	Phosphodisterase-5 Inhibitor (PDE5I)	2 (22%)	9 (60%)	0.11*
	Dual ERA/PDE5I at time of RHC	2 (22%)	4 (27%)	1.00*
	No therapy at time of RHC	3 (33%)	4 (27%)	1.00*
Creatinine (mg/dL)		0.93 ± 0.06	0.91 ± 0.05	0.86
Hemoglobin (g/dL)		13.9 ± 0.6	12.8 ± 0.4	0.13
Pro-Brain Natriuretic Peptide (pg/dl)		120 ± 33	714 ± 161	0.004

Continuous variables shown as mean ± SEM. * Fisher's exact test used to compare proportions. PAH, Pulmonary arterial hypertension; NYHA, New York Heart Association; RHC, right heart catheterization.

Supplemental Table S2. Baseline Hemodynamic and PV Loop Data

	IPAH (n = 9)	SSc-PAH (n = 15)	P-value
RHC Data			
Cardiac Output, by thermodilution (L/min)	5.0 ± 0.4	4.4 ± 0.3	0.31
Right atrial pressure (mm Hg)	7 ± 1	8 ± 1	0.70
Mean PAP (mm Hg)	42 ± 5	37 ± 3	0.47
PAWP (mm Hg)	10 ± 1	10 ± 1	0.55
PA Oxygen Saturation (%)	68 ± 1	66 ± 1	0.39
RV afterload			
Pulmonary vascular resistance (Wood units)	7.2 ± 1.8	7.1 ± 1.3	0.88
Pulmonary vascular compliance (ml·mm Hg^{-1})	2.1 ± 0.3	2.0 ± 0.3	0.70
Effective arterial elastance (E_a)	0.98 ± 0.19	0.99 ± 0.17	0.98
RV systolic function (contractility)			
RV Ejection Fraction (%)	48 ± 2	48 ± 3	0.79
End-systolic elastance (E_{es})	1.23 ± 0.15	0.47 ± 0.04	0.0002
V_0 (x-intercept of end-systolic elastance)	33.3 ± 10.7	-30.1 ± 11.9	0.003
Preload recruitable stroke work (M_{SW})	26.8 ± 1.5	22.4 ± 2.1	0.058
dP/dt_{max} (mm Hg·s^{-1})	530 ± 63	425 ± 27	0.13
RV-pulmonary arterial coupling			
E_{es}/E_a	1.42 ± 0.17	0.58 ± 0.06	0.0004
RV diastolic function			
Peak Fill Rate/EDV (s^{-1})	3.6 ± 0.5	3.0 ± 0.3	0.22
τ (Suga) (msec)	36 ± 5	29 ± 2	0.16

Continuous variables shown as mean ± SEM. RHC, right heart catheterization; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PA, pulmonary artery; RV, right ventricular; EDV, end-diastolic volume; τ, Tau, relaxation constant.

Supplemental Table S3. Cardiac Magnetic Resonance Measurements

	IPAH (n = 9)	SSc-PAH (n = 15)	P-value
Basic Measurements			
RV EDV (ml)	179 ± 24	166 ± 11	0.65
RV ESV (ml)	92 ± 15	89 ± 9	0.70
RV mass (g)	29 ± 4	30 ± 3	0.74
RV EF (%)	48 ± 2	48 ± 3	0.79
LV EDV (ml)	124 ± 9	125 ± 8	0.93
LV ESV (ml)	48 ± 4	48 ± 3	0.65
LV mass (g)	83 ± 6	91 ± 5	0.49
LV EF (%)	61 ± 2	61 ± 2	0.88
Calculated Cardiac Output (L/min)	5.0 ± 0.4	5.1 ± 0.4	0.74
RV Geometry			
RV EDVi (ml/m^2)	88 ± 11	93 ± 6	0.65
RV mass index (g/m^2)	14 ± 2	17 ± 2	0.39
RV mid-ventricular free wall thickness (mm)	3.3 ± 0.3	2.3 ± 0.2	0.01
RV mass-to-volume ratio (g/ml)	0.18 ± 0.02	0.19 ± 0.03	0.83
RV-to-LV EDV ratio	1.43 ± 0.16	1.39 ± 0.12	0.88
Ventricular mass index (VMI)	0.35 ± 0.04	0.35 ± 0.05	0.61
Late Gadolinium Enhancement			
Anterior RV-LV Insertion Point	5/7 (71%)	6/10 (60%)	1.00*
Inferior RV-LV Insertion Point	7/7 (100%)	10/10 (100%)	1.00*
Interventricular Septum	0/7 (0%)	1/10 (10%)	1.00*

Continuous variables shown as mean ± SEM. * Fisher's exact test used to compare proportions. RV, right ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; LV, left ventricular; EDVi, EDV index; VMI, ventricular mass index (RV mass / LV mass ratio).

Supplemental Table S4. Statistical Analysis of Pacing and Exercise (NYHA I-II versus III)

Pacing	**P-values**		**Exercise**	**P-values**	
	NYHA (I-II vs. III)	Interaction Term		NYHA (I-II vs. III)	Interaction Term
Combined			**Combined**		
dP/dt_{max}	0.92	0.10	E_{es}	0.56	0.61
$dP/dt_{max}/IP$	0.38	0.69	E_a	0.86	0.42
			E_{es}/E_a	0.25	0.75
			ΔESV	0.68	0.58
			ΔEDV	0.60	0.61
IPAH			**IPAH**		
dP/dt_{max}	0.89	0.38	E_{es}	0.52	0.34
$dP/dt_{max}/IP$	0.67	0.27	E_a	0.96	0.38
			E_{es}/E_a	0.63	0.87
			ΔESV	0.57	0.67
			ΔEDV	0.78	0.77
SSc-PAH			**SSc-PAH**		
dP/dt_{max}	0.91	0.25	E_{es}	0.19	0.85
$dP/dt_{max}/IP$	0.49	0.21	E_a	0.75	0.85
			E_{es}/E_a	0.32	0.60
			ΔESV	0.88	0.86
			ΔEDV	0.77	0.80

Presented are the p-values for the comparisons of NYHA functional class group (I-II versus III) and functional class-stage effect (i.e. interaction effect) for both pacing and exercise from repeated-measures analysis of variance. Corresponding dependent variables are depicted in Supplemental Figures 4-6. NYHA, New York Heart Association; IPAH, idiopathic pulmonary arterial hypertension; SSc-PAH, systemic sclerosis-associated pulmonary arterial hypertension; dP/dt_{max}, maximum rate of change in RV pressure; $dP/dt_{max}/IP$, maximum rate of change in RV pressure normalized to instantaneous pressure; E_{es}, end-systolic elastance; E_a, effective arterial elastance; E_{es}/E_a, right ventricular-pulmonary arterial (RV-PA) coupling ratio; ESV, end-systolic volume, EDV, end-diastolic volume.

Supplemental Figures and Legends

Supplemental Figure S1. Flow sheet detailing outcomes of the 43 patients prospectively enrolled in the study. Of the 28 patients that met diagnostic criteria for IPAH or SSc-PAH, PV catheter data were obtained from 24. Of the remaining 15 with alternate diagnoses, data were obtained from 13. Six patients were excluded for technical reasons or changes in clinical condition prior to or during the research study. Primary comparisons were made between IPAH and SSc-PAH (n=24). A larger cohort used for regression analyses also included the 9/13 subjects with alternate diagnoses that successfully completed exercise (total n=33).

Supplemental Figure S2. Exercise RV Pressure-Volume loops presented for all patients in the IPAH (S2A) and SSc-PAH cohorts (S2B) from rest (stage 0) and exercise stages 1-2.

Supplemental Figure S3. (A) Stage 2 (25W workload) Heart rate (HR), Stroke Volume (SV), Cardiac Output (CO), and RV Ejection Fraction (EF) for IPAH and SSc-PAH subjects. Dot and box plots presented. There were no significant differences in HR, SV, or CO between IPAH and SSc-PAH. EF tended to be lower in SSc-PAH when compared to IPAH at stage 2 ($p=0.056$). (B) Scatter-plot and linear predictions of CO determined by $SV \cdot HR$ versus CO by direct Fick, for both IPAH and SSc-PAH. There was no significant difference between the regression coefficients of each disease group. (C) Bland-Altman plot comparing CO determined by PV loop versus Fick.

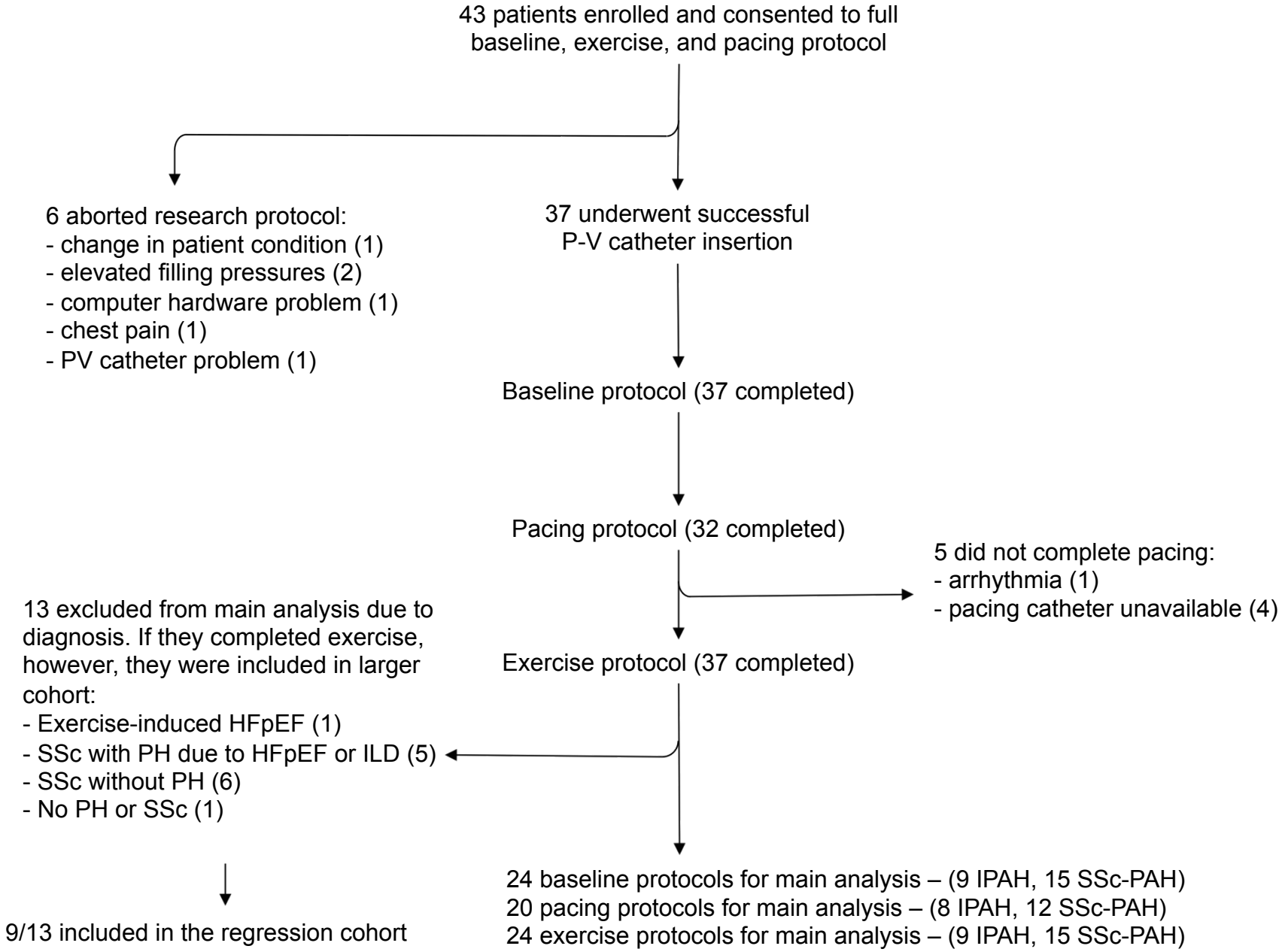
Supplemental Figure S4. (A) Force-frequency response comparing NYHA class III to NYHA class I-II patients in the combined, IPAH, and SSc-PAH cohorts. Contractility was assessed by dP/dt_{max} and dP/dt_{max} normalized to instantaneous pressure developed ($dP/dt_{max}/IP$) with escalating pacing rates. See supplemental Table S4 for corresponding p-values. There were no statistically significant differences between NYHA class III patients and their less symptomatic counterparts in any cohort. (B) Recirculation fraction (RF) between NYHA functional class groups. Data presented as dot and box plots. There were no significant differences in RF between NYHA III and NYHA I-II patients in the combined, IPAH, or SSc-PAH cohort.

Supplemental Figure S5. Exercise change in E_{es}, E_a, and E_{es}/E_a comparing NYHA class III to NYHA class I-II patients in the combined, IPAH, and SSc-PAH cohorts. See supplemental Table S4 for corresponding p-values. There were no statistically significant differences between NYHA III and NYHA I-II patient groups.

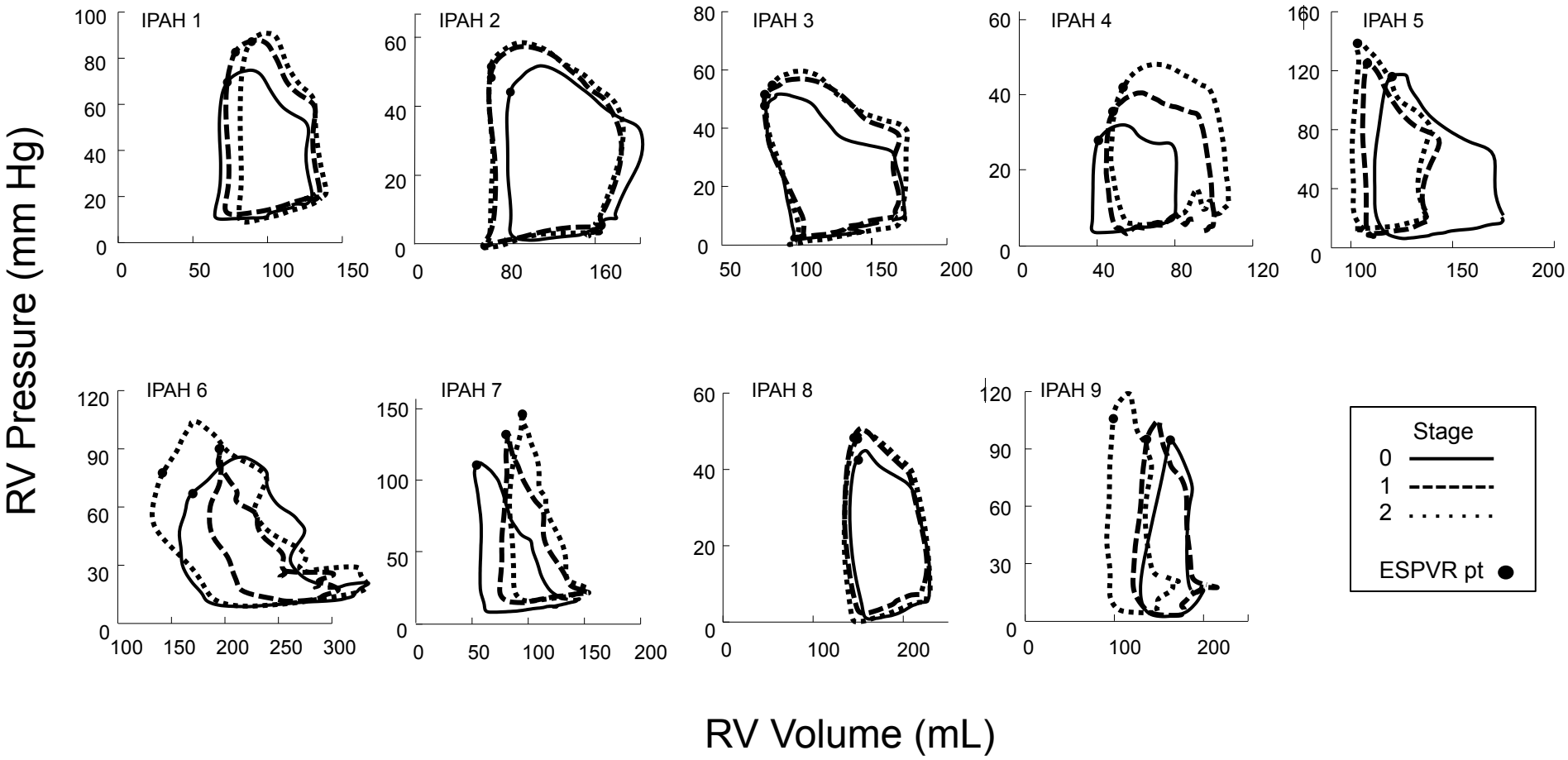
Supplemental Figure S6. Exercise change in RV volumes comparing NYHA class III to NYHA I-II patients in the combined, IPAH, and SSc-PAH cohorts. See supplemental Table S4 for corresponding p-values. There were no statistically significant differences between NYHA III and NYHA I-II patient groups.

Supplemental Figure S7. Correlations between V_E/V_{CO2} and RV-PA and LV functional indices. (A) V_E/VCO_2 was compared to several measures of right ventricular-pulmonary vascular load in a cohort consisting of IPAH and SSc-PAH patients, SSc patients with secondary PH, and SSc and normal patients without PH. V_E/VCO_2 correlated with mean pulmonary artery pressure (mean PAP), resting and peak exercise pulmonary vascular resistance (PVR), pulmonary vascular compliance (C_{PA}), and effective arterial elastance (E_a); there was also a trend towards correlation with right ventricular ejection fraction (RVEF). (B) On the other hand, V_E/VCO_2 did not correlate with left ventricular ejection fraction (LVEF) or pulmonary artery wedge pressure (PAWP). (C) Among PH subjects, change in RVSP at peak exercise did not correlate with resting Ees/Ea (log transformed).

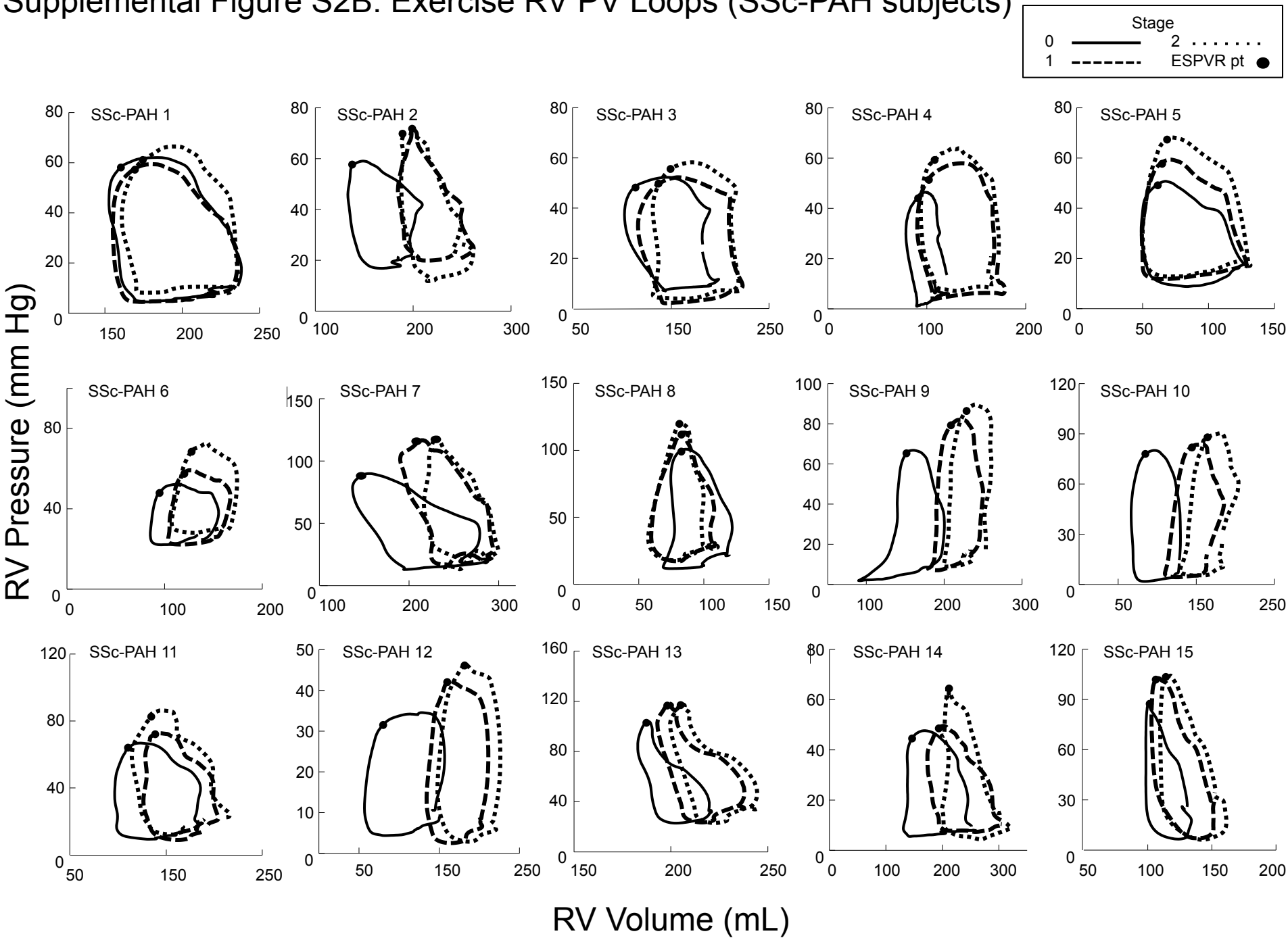
Supplemental Figure S1. Flow Diagram of Patient Recruitment



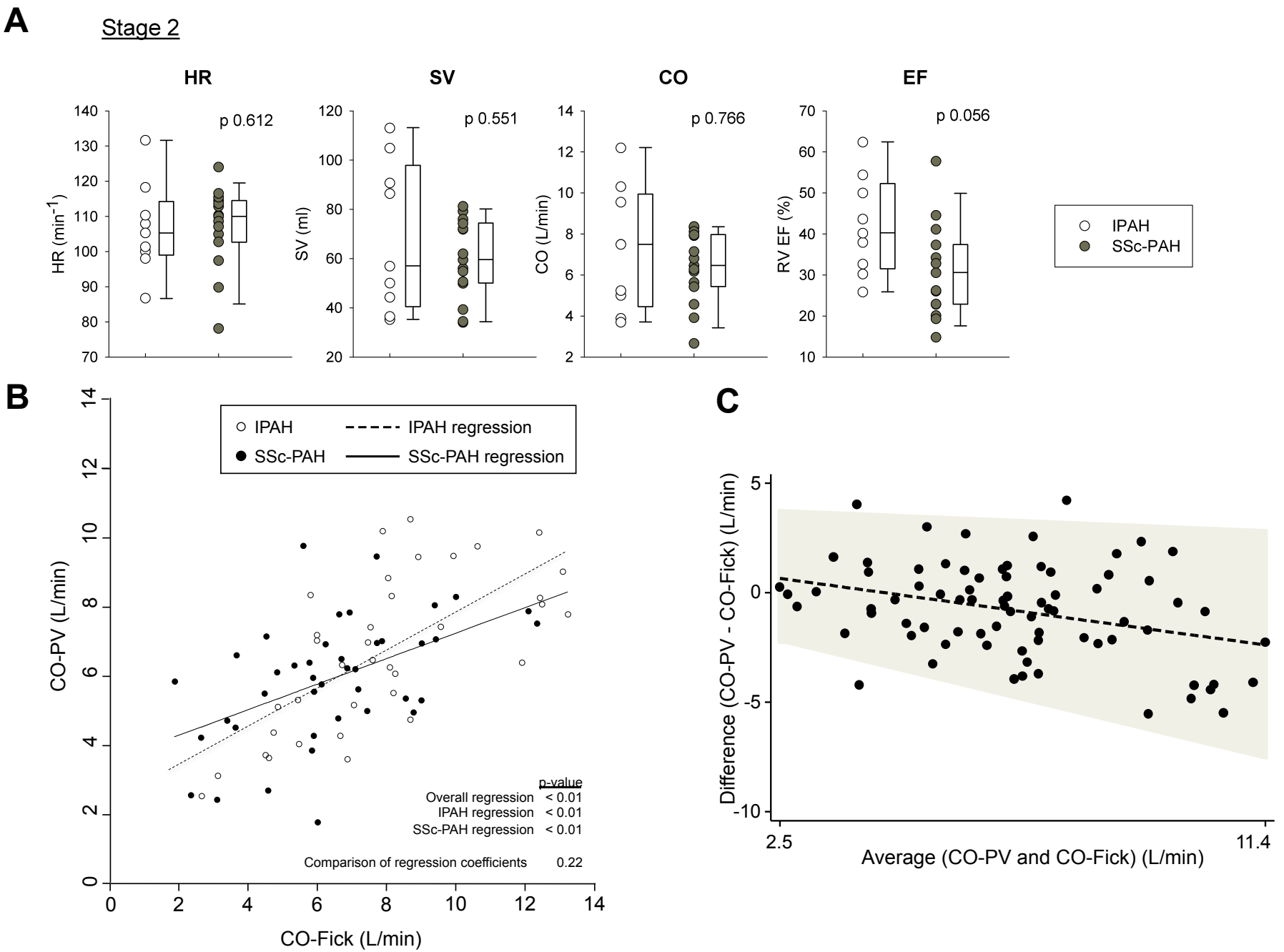
Supplemental Figure S2A. Exercise RV PV Loops (IPAH subjects)



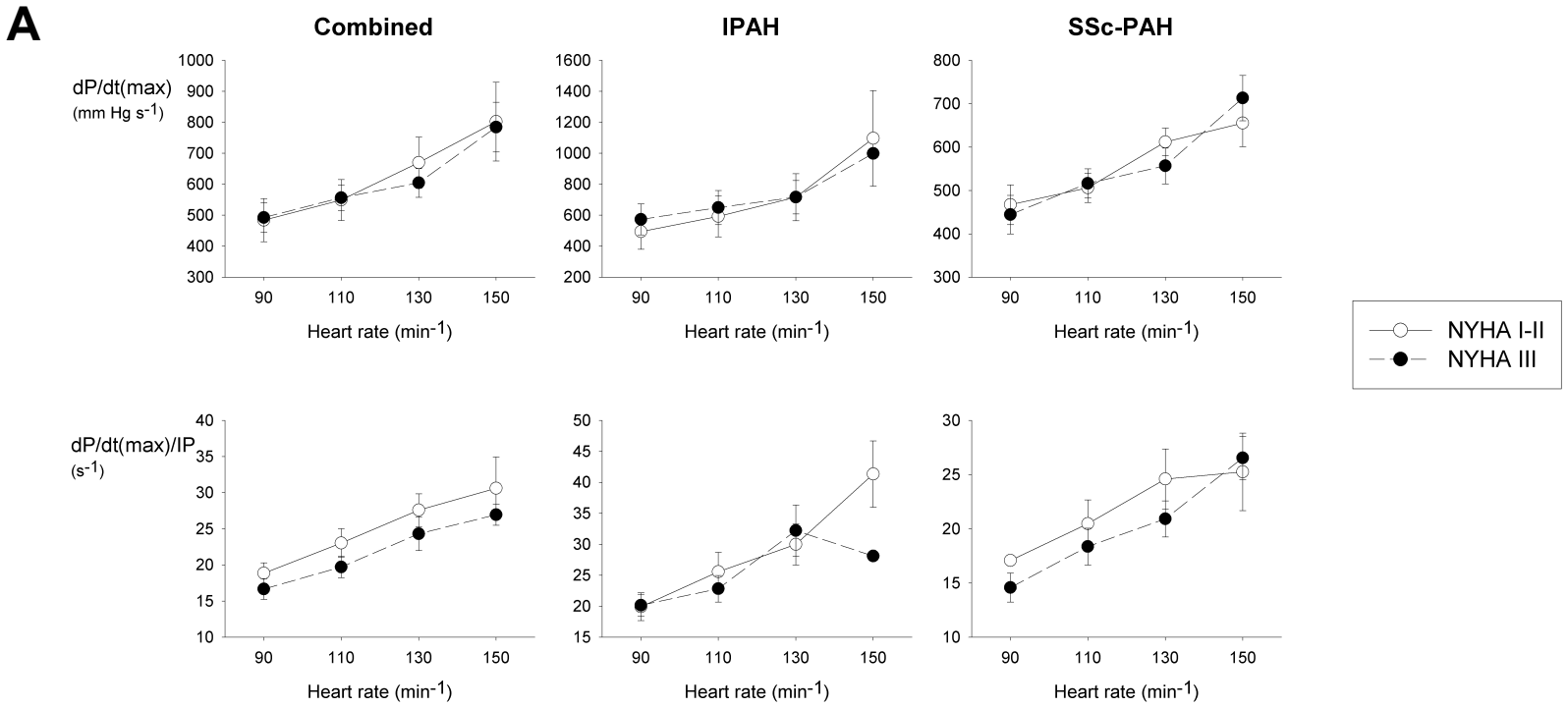
Supplemental Figure S2B. Exercise RV PV Loops (SSc-PAH subjects)

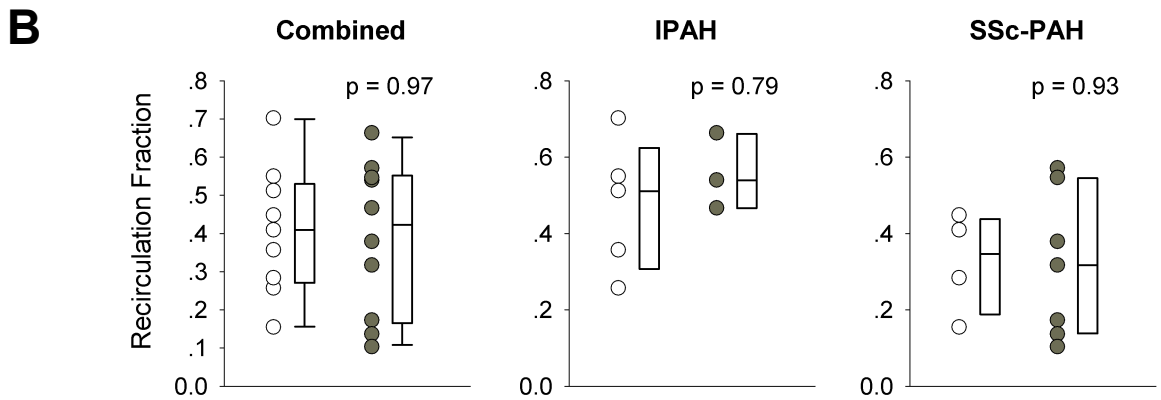


Supplemental Figure S3. Heart rate, Stroke Volume, and Cardiac Output



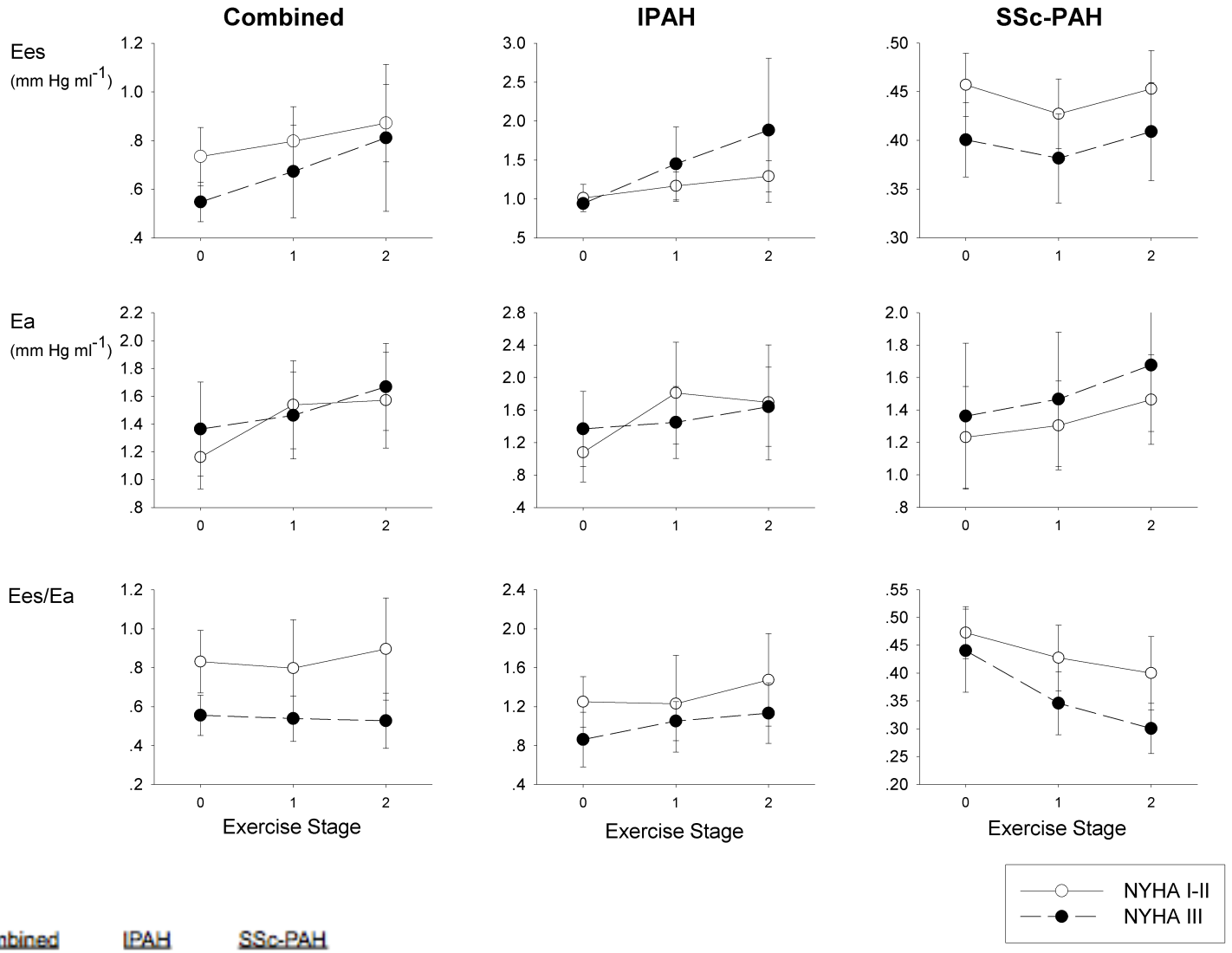
Supplemental Figure S4. Pacing Analysis and Recirculation Fraction (NYHA I-II versus III)





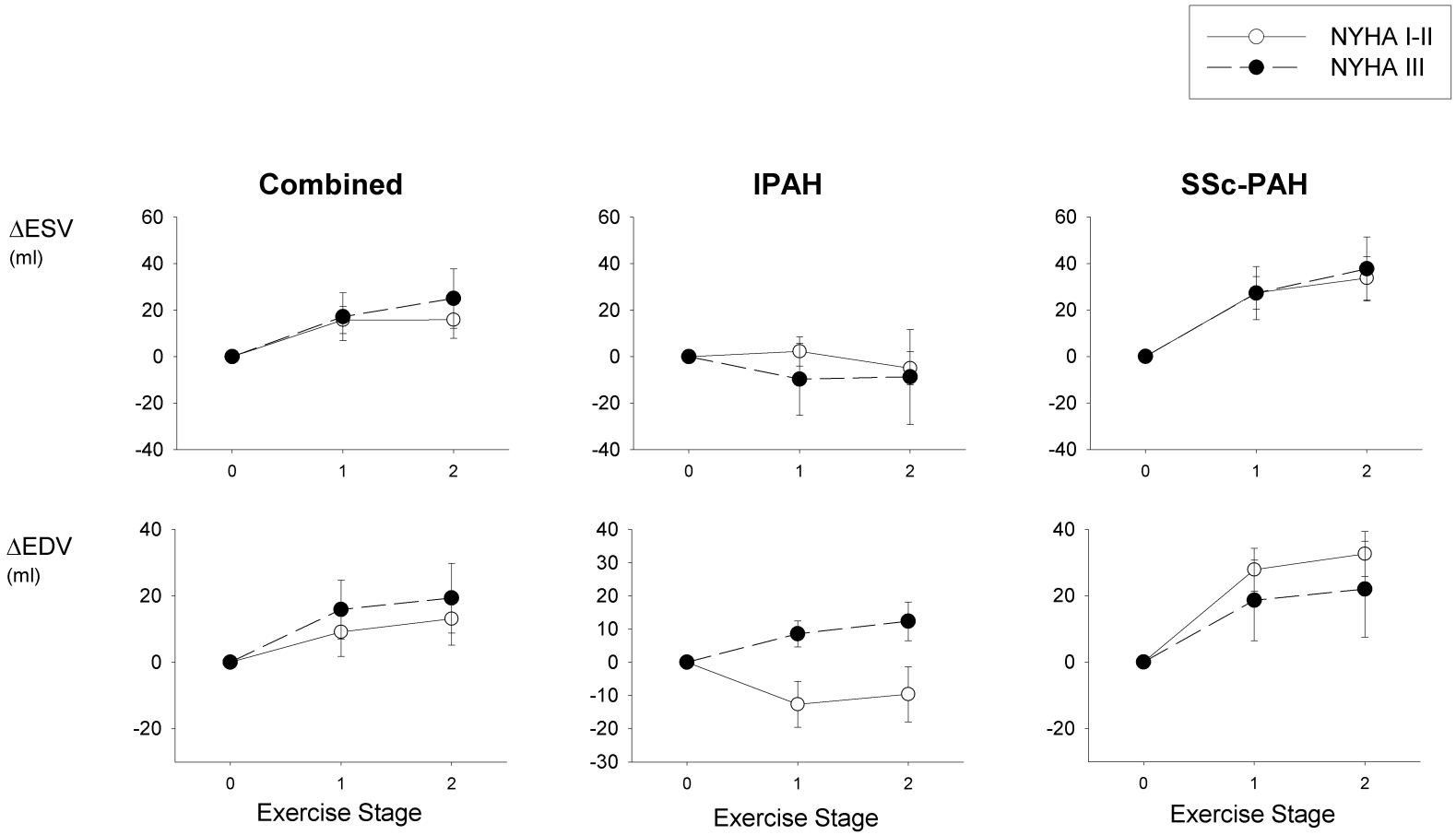
n =	Combined	IPAH	SSc-PAH
NYHA I-II	10	5	5
NYHA III	10	3	7

Supplemental Figure S5. Exercise Reserve and Coupling (NYHA I-II versus III)



n =	Combined	IPAH	SSc-PAH
NYHA I-II	13	6	7
NYHA III	11	3	8

Supplemental Figure S6. Exercise Changes in RV Chamber Size (NYHA I-II versus III)



n =	Combined	IPAH	SSc-PAH
NYHA I-II	13	6	7
NYHA III	11	3	8

Supplemental Figure S7. Correlations between V_E/V_{CO_2} and RV/LV reserve indices