ONLINE SUPPLEMENT MATERIAL

Dynamic Right Ventricular – Pulmonary Arterial Uncoupling During Maximum Incremental Exercise in Exercise Pulmonary Hypertension and Pulmonary Arterial Hypertension

METHODS

Invasive Cardiopulmonary Exercise Testing (iCPET)

Briefly, RHC was performed in the supine position with a 5-port pacing PA catheter (Edwards LifeSciences, Irvine, CA, USA) inserted percutaneously under fluoroscopic and ultrasound guidance into the internal jugular vein and a radial artery catheter concurrently placed in the radial artery. Patients underwent a symptom-limited incremental CPET using an upright cycle ergometer with a breath-by-breath assessment of gas exchange (ULTIMA CPX; Medical Graphics Corporation, St Paul, MN, USA). Patients undergo two minutes of rest are followed by 2 min of unloaded cycling at 40-60 RPM. Work rate is continuously increased using a ramp protocol at 5, 10, 15 or 20 W/min depending on the patient's functional status until peak exercise is achieved as evident either by peak RER >1.10 or peak heart rate >85% predicted or partial pressure of venous oxygen level >27 mmHg. Pulmonary and systemic hemodynamics were continuously and simultaneously monitored during exercise (Xper Cardio Physiomonitoring System; Phillips, Melborne, FL, USA). Pulmonary pressures were recorded at the end of passive exhalation. When respirophasic changes persisted, an electronic average over three respiratory cycles was used. Arterial and mixed venous blood gases and pH were collected during each minute

of exercise, and the arterial-mixed venous oxygen content difference ($Ca\text{-}vO_2$) was calculated. Oxygen extraction was calculated as CaO_2 minus CvO_2 divided by CaO_2. Fick CO was determined every minute. Oxygen delivery (DO_2) was calculated by multiplying cardiac output by the arterial oxygen content (CaO_2).

Table S1: Functional and physiological determinants of exercise pulmonary hypertension (ePH) during upright incremental invasive cardiopulmonary exercise testing in patients with (+) and without (-) beta-adrenergic blocker use.

	B-blocker (+)	B-blocker (-)	p-value
Subjects	3	9	

Age, years	73 (66 – 81)	72 (64 – 76)	0.320
Female, n (%)	1 (33)	6 (67)	0.839
BMI, kg/m^2	32 (24 – 36)	29 (25 – 36)	0.905
Exercise Capacity			
Max work rate, watts	84 (76 – 97)	99 (66 – 108)	0.853
Peak $V0_2$, % predicted	13.1 (11.9 – 13.7)	16.2 (11.4 – 18.1)	0.712
Peak $Ca\text{-}v0_{2,\text{ corrected for Hgb}}$	89.4 (81.6 – 99.2)	77.8 (73.8 – 87.0)	0.355
Peak CI, $L/min/m^2$	4.4 (4.3 – 4.9)	5.1 (4.3 – 6.4)	0.459
Peak SVI mL/m^2	48.3 (35.5 – 52.4)	43.5 (40.9 – 54.3)	0.853
Peak heart rate, % predicted	67 (66 -85)	79 (74 – 86)	0.517
Peak heart rate (bpm)	105 (102 – 121)	122 (105 – 129)	0.405
Delta heart rate (bpm)	52 (43 – 54)	47 (37 – 59)	0.853
Peak DO_2, mL/kg/min	19.9 (14.9 – 21.7)	21.1 (16.6 – 28.9)	0.579
Pulmonary hemodynamics			
Peak mPAP, mmHg	35 (34 – 37)	36 (34 – 37)	0.925
Peak RAP, mmHg	6 (3 – 10)	8 (6 -10)	0.577
Peal TPR, WU	3.8 (3.6 – 4.3)	3.8 (2.6 – 4.0)	0.579
Peak PVRI, WU	410 (356 – 512)	388 (276 – 434)	0.459
Peak PAC, mL/mmHg	2.6 (2.4 – 3.1)	2.9 (2.1 – 3.5)	0.853
Load independent RV function			
Rest Ees ($mmHg/mL/m^2$)	0.71 (0.88 – 1.16)	0.71 (0.45 – 0.94)	0.539
Peak Ees ($mmHg/mL/m^2$)	1.09 (0.86 – 1.18)	1.32 (0.92 – 1.97)	0.609
Contractile reserve ($mmHg/mL/m^2$)	0.45 (-0.65 – 0.46)	0.57 (0.19 – 1.20)	0.475

Rest Ea (mmHg/mL/m^2)	0.51 (0.37 – 0.53)	0.46 (0.45 – 0.51)	0.918
Peak Ea (mmHg/mL/m^2)	0.77 (0.71 – 0.84)	0.86 (0.78 – 0.90)	0.219
Rest Ees/Ea	1.70 (1.34 – 3.00)	1.42 (1.00 – 1.86)	0.475
Peak Ees/Ea	1.30 (1.24 – 1.51)	1.60 (1.06 – 2.36)	0.800

Data presented as n or median (interquartile range). BMI – body mass index; VO_2 – oxygen consumption; CaO_2 – arterial oxygen content; Ca-vO_2 – arterial-mixed venous oxygen content difference; CO – cardiac output; CI – cardiac index; SV – stroke volume; SVI – stroke volume index; bpm – beats per minute; DO_2 – oxygen delivery; mPAP – mean pulmonary arterial pressure; RAP – right atrial pressure; TPR – total pulmonary resistance; PVR – pulmonary vascular resistance; PAC – pulmonary arterial compliance

Table S2: Univariate and bivariate model for predicting Peak VO_2 (% predicted) in all patients with ePH and PAH (n=20)

Variable	**ß-Coefficient**	**p-value**	**95% Confidence Interval**
Measures of RV afterload			
Rest PA Compliance (mL/mmHg)	2.82	0.47	-5.27 – 10.92
Peak PA Compliance (mL/mmHg)	1.99	0.61	-6.16 – 10.14
Rest PVR (WU)	-5.99	0.12	-13.65 – 1.67

Peak PVR (WU)	-4.98	0.20	-12.82 – 2.85
Peak TPR (mmHg.min.L^{-1})	-5.96	0.12	-13.63 – 1.70
Rest Ea (mmHg/mL/m^2)	-6.42	0.09	-13.99 – 1.16
Peak Ea (mmHg/mL/m^2)	-2.09	0.60	-10.24 – 6.06
Measures of RV performance			
Rest cardiac index (L/min^2)	4.03	0.30	-3.94 – 11.99
Peak cardiac index (L/min^2)	4.56	0.24	-3.34 – 12.46
Maximum HR (% predicted)	7.72	0.04	0.45 – 14.99
Rest SV index (mL/m^2)	6.20	0.10	-1.42 – 13.82
Peak SV index (mL/m^2)	0.62	0.88	-7.59 – 8.82
Rest Ees (mmHg/mL/m^2)	-7.76	0.04	-15.02 – -0.50
Peak Ees (mmHg/mL/m^2)	-0.61	0.88	-8.82 – 7.60
Contractile reserve (mmHg/mL/m^2)	6.71	0.08	-0.80 – 14.22
Rest RV coupling (Ees/Ea)	-0.06	0.99	-8.27 – 8.16
Peak RV-PA coupling (Ees/Ea)	0.32	0.94	-7.89 – 8.53
Systemic oxygen extraction			
Systemic O_2 extraction (Ca-vO_2)	2.58	0.51	-5.54 – 10.69
Baseline characteristics and hemodynamics			
Age (years)	3.45	0.38	-4.59 – 11.48
Baseline Hgb (g/dL)	6.01	0.12	-1.65 – 13.67
B-blocker therapy	0.69	0.86	-7.52 – 8.89
Pulmonary Hemodynamics			
Rest mPAP (mmHg)	-4.27	0.27	-12.20 – 3.67
Peak mPAP (mmHg)	-1.97	0.62	-10.12 – 6.19
Rest PAWP (mmHg)	-1.14	0.77	-9.34 – 7.05

Peak PAWP (mmHg)	-6.68	0.08	-14.20 – 0.84
Bivariate model			
Maximum HR (%predicted)	6.69	0.05	-0.09 – 13.46
Rest Ees (mmHg/mL/m^2)	-6.73	0.05	-13.51 – 0.04

PA – pulmonary artery; PVR – pulmonary vascular resistance; TPR - total pulmonary resistance; Ea: arterial elastance; SV – stroke volume; RV- right ventricle; Ees – end systolic elastance; Ca-vO_2 – arterial and venous oxygen content difference; Hgb – hemoglobin; mPAP – mean pulmonary artery pressure; PAWP – pulmonary arterial wedge pressure; HR – heart rate.

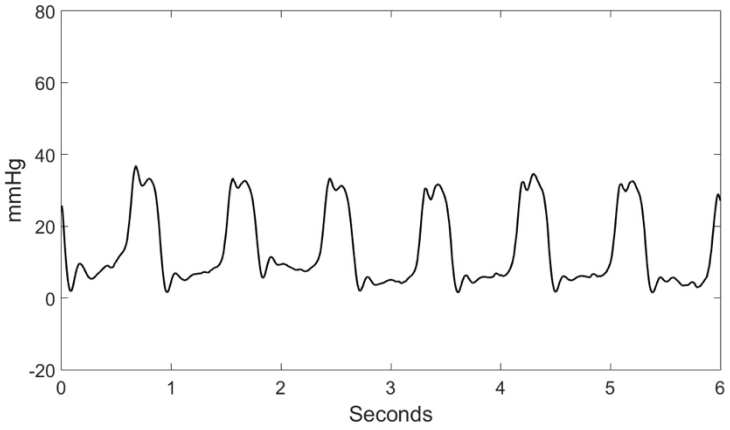
Table S3: Univariate and bivariate model for predicting peak RV-PA coupling in all patients with ePH and PAH (n=20)

Variable	**ß-Coefficient**	**p-value**	**95% Confidence Interval**
Measures of RV afterload			
Rest PA Compliance (mL/mmHg)	0.12	0.46	-0.21 – 0.48
Peak PA Compliance (mL/mmHg)	0.07	0.68	-0.28 – 0.40
Rest PVR (WU)	-0.34	0.03	-0.63 – -0.05
Peak PVR (WU)	-0.28	0.06	-0.59 – 0.02
Rest TPR (mmHg.min.L^{-1})	-0.28	0.07	-0.59 – 0.02
Peak TPR (mmHg.min.L^{-1})	-0.26	0.09	-0.57 – 0.05
Rest Ea (mmHg/mL/m^2)	-0.29	0.06	-0.59 – 0.02
Peak Ea (mmHg/mL/m^2)	-0.27	0.08	-0.56 – 0.04
Measures of RV performance			
Rest Ees (mmHg/mL/m^2)	-0.05	0.74	-0.39 – 0.28
Peak Ees (mmHg/mL/m^2)	0.32	0.04	0.03 – 0.62
Contractile reserve (mmHg/mL/m^2)	0.38	0.01	0.10 – 0.66
Baseline characteristic			
Age (years)	-0.11	0.47	-0.45 – 0.21
B-blocker therapy	-0.20	0.20	-0.52 – 0.12

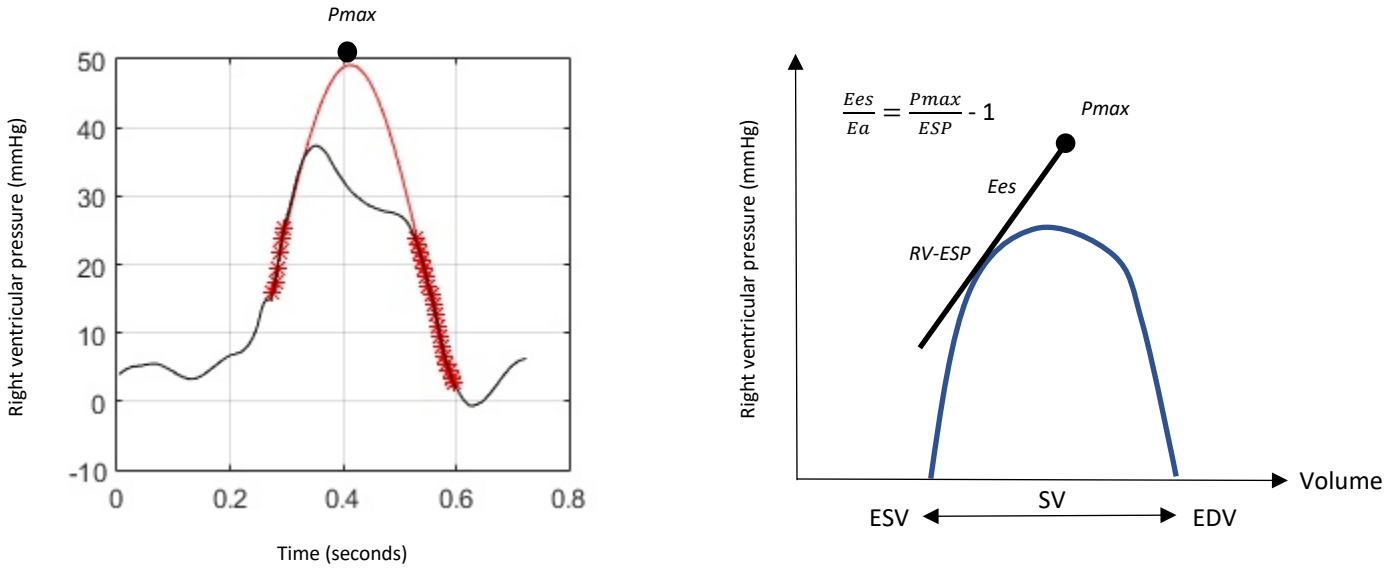
Pulmonary Hemodynamics			
Rest mPAP (mmHg)	-0.21	0.18	-0.53 – 0.10
Peak mPAP (mmHg)	-0.22	0.16	-0.54 – 0.10
Rest PAWP (mmHg)	0.37	0.01	0.10 – 0.65
Peak PAWP (mmHg)	0.17	0.27	0.15 – 0.50
Bivariate model			
Rest PVR (WU)	-0.24	0.08	-0.52 – 0.03
Contractile reserve (mmHg/mL/m^2)	0.30	0.03	0.03 – 0.58

PA – pulmonary artery; PVR – pulmonary vascular resistance; TPR - total pulmonary resistance; Ea: arterial elastance; SV – stroke volume; RV- right ventricle; Ees – end systolic elastance; Ca-vO_2 – arterial and venous oxygen content difference; Hgb – hemoglobin; mPAP – mean pulmonary artery pressure; PAWP – pulmonary arterial wedge pressure; PVR – pulmonary vascular resistance; WU – woods unit

Figure S1

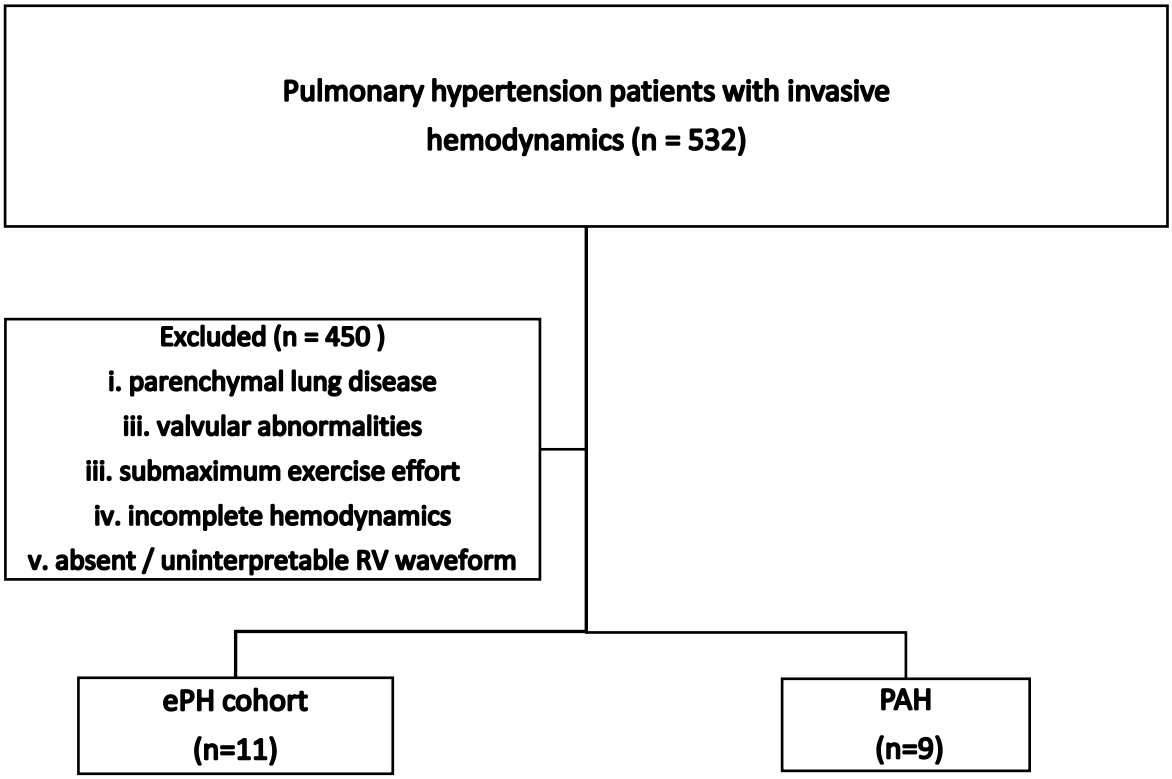


Right ventricular pressure waveform



Single beat methods to estimate right ventricle-pulmonary artery (RV-PA) coupling or Ees/Ea. Maximum right ventricular (RV) pressure generated during an isovolumic beat (Pmax) is estimated from nonlinear extrapolation of early and late isovolumic portions of an RV pressure curve from point of maximum (dp/dt max) and minimum (dp/dt min) pressure derivation. End-systolic elastance is then determined by a tangent from Pmax to the RVESP point. Ees/Ea in the pressure method is then determined by the ratio of (Pmax-RVESP) divided by SV or (Pmax/ESP – 1). Ees – end-systolic elastance; Ea – arterial elastance

Figure S2: patient selection



PAH – pulmonary arterial hypertension; ePH – exercise pulmonary hypertension; mPAP – mean pulmonary artery pressure; PAWP – pulmonary artery wedge pressure; PVR – pulmonary vascular resistance