Supplement/Table S1. PAH-specific medications among study groups

PAH-specific therapies	Placebo	Low-fixed dose Carvedilol	Escalating-dose Carvedilol
Phosphodiesterase type 5 inhibitor (PDE-5i) only	**0**	**2**	**1**
Soluble guanylate cyclase stimulator (sGC) only	**0**	**0**	**0**
Endothelin receptor antagonist (ERA) only	**0**	**0**	**0**
PDE-5i/sGC + ERA	**2**	**5**	**3**
IV/SC prostacyclin only	**2**	**0**	**1**
Inhaled prostacyclin only	**0**	**0**	**0**
IV/SC prostacyclin + ERA	**0**	**1**	**1**
IV/SC prostacyclin + PDE-5i/sGC	**2**	**1**	**1**
IV/SC prostacyclin + PDE-5i/sGC + ERA	**3**	**0**	**2**
Inhaled prostacyclin +ERA	**0**	**0**	**0**
Inhaled prostacyclin + PDE-5i/sGC	**0**	**0**	**0**
Inhaled prostacyclin + PDE-5i/sGC + ERA	**0**	**1**	**1**

Supplement/Table S2. Comparison of PH subjects and Controls

Variable	PH N = 30	Controls N=12	p-value[A]
Baseline			
Age (years)	44 ± 12	42 ± 12	0.3
Race			0.5
Caucasian- n (%)	23 (77%)	11 (72%)	
African American- n (%)	6 (20%)	1 (8%)	
Asian- n (%)	1 (3%)	0 (0%)	
Gender			0.4
Female- n (%)	21 (70%)	10 (83%)	
Male- n (%)	9 (30%)	2 (17%)	
Height (cm)	167 ± 10	167 ± 6	0.5
Weight (kg)	83 ± 20	71 ± 15	0.02
Temperature (F)	97.3 ± 0.8	97.4 ± 0.7	0.3
Heart rate at rest (beats/min)	78 ± 7	69 ± 12	0.01
Echocardiogram			
LA area (cm^2)	17 ± 3	16 ± 3	0.1
LVEF (%)	59 ± 6	60 ± 5	0.4
RA area (cm^2)	20 ± 6	15 ± 6	<0.01
RAP (mmHg)	7 ± 4	6 ± 3	0.3
RVED area (cm^2)	29 ± 9	18 ± 5	<0.001
RVES area (cm^2)	21 ± 8	10 ± 3	<0.001
RVSP (mmHg)	67 ± 27	26 ± 6	<0.001
RVFAC (%)	29 ± 10	46 ± 7	<0.001
LV SV (ml)	63 ± 18	63 ± 11	0.5
LV cardiac output (l/min)	4.8 ± 1.6	3.8 ± 0.7	<0.01
RV peak global longitudinal strain (%)	-16 ± 4	-23 ± 4	<0.001
LV peak global longitudinal strain (%)	-18 ± 3	-18 ± 2	0.4
NT-proBNP (pg/ml)	90 (25, 498)	44 (22, 64)	<0.01
Urinary cAMP/creatinine (umol/g)	1.0 (0.5, 1.5)	1.2 (0.7, 1.4)	0.1
Hypoxia-Inducible Pathways			
Erythropoietin (mIU/ml)	6.8 (4.2, 12.9)	2.6 (1.8, 4.6)	0.02
Heart Glucose Uptake by FDG-PET scan			
RV/LV ratio (SUV)	0.8 (0.5,1.4)	0.2 (0.2, 0.6)	<0.01
RV (SUV)	3.8 (2.3, 6.0)	1.7 (1.3, 1.9)	<0.001

Numerical variables are presented as mean ± standard deviation, or alternatively as median (25^{th} percentile, 75^{th} percentile) when distributions are substantially skewed.

[A]: *Fisher exact for categorical values and T-test (one-sided) for quantitative values and in cases of skewed distributions, T-test was applied to log-transformed values.*

Supplement/Table S3. Adverse events in PAHTCH

Adverse event	Group	Study week at which event occurred	Carvedilol Dose at time of event	Dose de-escalation	Final dose
Fatigue/toe discoloration/vivid dreams	Low-fixed	12 weeks	3.125 mg	Yes	0 mg
Dyspnea/wheezing	Dose-escalating	4 weeks	25 mg	Yes	12.5 mg
Cough/leg swelling	Dose-escalating	3 weeks	12.5 mg	Yes	6.25 mg
Site infection/acute bronchitis	Dose-escalating	8 weeks	6.25 mg	Yes	3.125 mg
Leg swelling	Dose-escalating	8 weeks	25 mg	Yes	12.5 mg
Chest pain	Low-fixed	18 weeks	3.125 mg	No	3.125 mg
Bronchitis	Placebo	8 weeks	Placebo	No	Placebo
Blurry vision	Dose-escalating	8 weeks	25 mg	No	25 mg
Cholecystitis	Dose-escalating	12 weeks	25 mg	No	25 mg
Dyspnea	Placebo	1 week	Placebo	No	Placebo
Bloating	Low-fixed	Run-in week	3.125 mg	No	3.125 mg
Nausea/vomiting	Dose-escalating	16 weeks	25 mg	No	25 mg
Broken arm	Dose-escalating	10 weeks	25 mg	No	25 mg
Leg swelling	Dose-escalating	Run-in week	3.125 mg	No	3.125 mg
Dizziness	Dose-escalating	18 weeks	3.125 mg	No	3.125 mg

Supplement/Table S4. Differences in outcomes measured among the three study groups at baseline, 3-month, and 6-month visits excluding subjects with functional class I

Variable	Placebo N = 9	Low-fixed Dose Carvedilol N = 7	Escalating-dose Carvedilol N = 9	p-value[A]
Baseline				
Age (years)	40 ± 13	43 ± 5	54 ± 9	0.02
Weight (kg)	81 ± 13	83 ± 14	92 ± 24	0.4
Temperature (F)	97.6 ± 0.5	97.3 ± 0.6	97.5 ± 0.6	0.5
Race (Caucasian/African American/Asian)	6/3/0	5/2/0	9/0/0	0.2
Gender (M/F)	2/7	4/3	6/3	0.9
Classification of pulmonary hypertension				0.6
Pulmonary arterial hypertension – n (%)				
Idiopathic	2 (22%)	2 (29%)	4 (44%)	
Heritable	4 (44%)	4 (57%)	2 (22%)	
Associated	2 (22%)	0	2 (22%)	
Pulmonary hypertension due to lung diseases and/or hypoxia– n (%)	0	1 (14%)	0	
Chronic thromboembolic pulmonary hypertension – n (%)	1 (11%)	0	1 (11%)	
6-minute walk test				
Distance walked (m)	437 ± 83	469 ± 98	419 ± 153	0.7
Oxygen saturation at 6 min (%)	89 ± 6	93 ± 4	89 ± 6	0.2
Heart rate at rest (beats/min)	83 ± 8	78 ± 5	80 ± 8	0.4
Heart rate at 6 min (beats/min)	110 ± 18	116 ± 26	123 ± 13	0.4
Heart rate 1 min post exercise (beats/min)	100 ± 13	89 ± 11	103 ± 15	0.1
Heart rate recovery (beats/min)	9 ± 15	26 ± 22	20 ± 15	0.2
Echocardiogram				
LA area (cm^2)	17 ± 2	17 ± 3	19 ± 4	0.3
LVEF (%)	61 ± 6	57 ± 9	58 ± 6	0.5
RA area (cm^2)	18 ± 5	21 ± 8	21 ± 7	0.6
RAP (mmHg)	6 ± 2	6 ± 4	8 ± 6	0.5
RVED area (cm^2)	31 ± 7	26 ± 4	31 ± 14	0.6
RVES area (cm^2)	22 ± 7	18 ± 6	23 ± 12	0.5
RVSP (mmHg)	76 ± 23	51 ± 13	66 ± 31	0.1
RVFAC (%)	28 ± 10	33 ± 12	28 ± 9	0.6
LV SV (ml)	70 ± 19	66 ± 18	57 ± 17	0.3
LV cardiac output (l/min)	4.9 ± 1.8	5.8 ± 2.3	4.5 ± 1.0	0.4
RV peak global longitudinal strain (%)	-15 ± 5	-17 ± 4	-16 ± 5	0.8
LV peak global longitudinal strain (%)	-17 ± 3	-18 ± 2	-18 ± 4	0.9
NT-proBNP (pg/ml)	170 (35, 498)	57 (22, 169)	163 (19, 825)	0.8
Heart glucose uptake by FDG-PET scan RV/LV ratio (SUV)	1.1 (0.9, 1.4)	0.6 (0.5, 0.8)	0.9 (0.5, 1.6)	0.6
At 3-month follow up				
Weight (kg)	80.9 ± 12.2	82.7 ± 13.9	92.0 ± 21.8	0.4
Temperature (F)	97.6 ± 0.7	96.9 ± 1.1	96.9 ± 1	0.2
6-minute walk test				
Distance walked (m)	415 ± 88	490 ± 94	415 ± 151	0.4
Oxygen saturation at 6 min (%)	88 ± 6	94 ± 5	90 ± 5	0.1
Heart rate at rest (beats/min)	78 ± 10	69 ± 10	69 ± 8[B]	0.1
Heart rate at 6 min (beats/min)	103 ± 28	119 ± 29	106 ± 17	0.4
Heart rate 1 min post exercise (beats/min)	92 ± 24	84 ± 11	79 ± 13[B]	0.3
Heart rate recovery (beats/min)	10 ± 23	35 ± 20	27 ± 16	0.05
Echocardiogram				
LA area (cm^2)	16 ± 3	17 ± 3	21 ± 5	0.05
LVEF (%)	60 ± 5	62 ± 5	63 ± 7	0.7
RA area (cm^2)	17 ± 5	21 ± 8	21 ± 6	0.4
RAP (mmHg)	5 ± 0	6 ± 2	9 ± 5	0.08
RVED area (cm^2)	31 ± 7	26 ± 5	31 ± 14	0.6
RVES area (cm^2)	23 ± 8	17 ± 4	23 ± 8	0.2
RVSP (mmHg)	76 ± 21	54 ± 7	58 ± 23	0.06

RVFAC (%)	20 ± 7[B]	32 ± 9	28 ± 6	<0.01
LV SV (ml)	67 ± 13	75 ± 20	69 ± 12	0.6
LV cardiac output (l/min)	4.9 ± 1.2	4.8 ± 1.2	4.8 ± 1.2	>0.9
RV peak global longitudinal strain (%)	-14 ± 4	-18 ± 4	-17 ± 4	0.3
LV peak global longitudinal strain (%)	-19 ± 3	-18 ± 4	-18 ± 2	0.9
NT-proBNP (pg/ml)	245 (42, 571)	37 (30, 143)	195 (47, 1033)	0.3
At 6-month follow up				
Weight (kg)	79.7 ± 11.5	83.5 ± 14.0	89.6 ± 19.6	0.4
Temperature (F)	97.6 ± 0.4	97.4 ± 0.8	97.1 ± 1.1	0.5
6-minute walk test				
Distance walked (m)	453 ± 59	469 ± 106	427 ± 142	0.8
Oxygen saturation at 6 min (%)	90 ± 3	91 ± 7	85 ± 8	0.2
Heart rate at rest (beats/min)	73 ± 10	73 ± 5[B]	73 ± 9	0.9
Heart rate at 6 min (beats/min)	116 ± 35	116 ± 18	114 ± 20	0.9
Heart rate 1 min post exercise (beats/min)	93 ± 24	96 ± 14	84 ± 16	0.4
Heart rate recovery (beats/min)	23 ± 19	20 ± 23	30 ± 12[B]	0.6
Echocardiogram				
LA area (cm^2)	18 ± 3	17 ± 3	20 ± 3	0.06
LVEF (%)	58 ± 6	61 ± 7	62 ± 6	0.5
RA area (cm^2)	19 ± 4	19 ± 7	22 ± 5	0.5
RAP (mmHg)	6 ± 2	6 ± 2	8 ± 4	0.1
RVED area (cm^2)	29 ± 7	25 ± 5	31 ± 10	0.4
RVES area (cm^2)	23 ± 5	17 ± 4	24 ± 9	0.2
RVSP (mmHg)	66 ± 23	44 ± 17	64 ± 32	0.2
RVFAC (%)	25 ± 9	30 ± 11	27 ± 11	0.6
LV SV (ml)	63 ± 12	67 ± 21	70 ± 20	0.7
LV cardiac output (l/min)	4.5 ± 0.9	4.6 ± 1.7	5.0 ± 1.8	0.7
RV peak global longitudinal strain (%)	-15 ± 4	-18 ± 4	-16 ± 4	0.4
LV peak global longitudinal strain (%)	-14 ± 12	-18 ± 3	-19 ± 3	0.4
NT-proBNP (pg/ml)	292 (58, 497)	55 (28, 127)	175 (54, 589)	0.4
Heart glucose uptake by FDG-PET scan RV/LV ratio (SUV)	0.8 (0.7, 1.1)	0.5 (0.3, 0.7)	0.8 (0.4, 1.0)	0.3

Numerical variables are presented as mean ± standard deviation, or alternatively as median (25^{th} percentile, 75^{th} percentile) when distributions are substantially skewed

[A]*Fisher's exact or Chi-square for categorical values and ANOVA for quantitative values and in cases of skewed distributions, ANOVA was applied to log-transformed values.*

Paired t-test with Bonferroni-adjusted significance for change compared to baseline [B]$p < 0.025$

Supplemental Methods

Echocardiogram

Doppler echocardiography was performed by a single well-experienced imaging specialist using validated methods that have been previously published (1). Right ventricular function was assessed via measurement of RV fractional area change (RVFAC), myocardial performance index of the RV, tricuspid annular plane systolic excursion (TAPSE), tissue Doppler-derived systolic velocity of the lateral tricuspid annulus, and longitudinal strain by 2-dimensional speckle tracking technique. The calculation of RVFAC was based on the following formula: RVFAC (%) = (RV end-diastolic area - RV end-systolic area) / RV end-diastolic area x 100

Two Dimensional (2D) Speckle –Tracking Echocardiography (STE) was used for the evaluation of myocardial function (2-6). Strain values were determined for each segment (segmental strain) globally and regionally. Average RV peak global longitudinal strain or global strain, which refers to the average longitudinal strain value of all 6 segments of the myocardium, was assessed as a measure of right ventricular function over time of the study.

FDG-PET scan

Cardiac FDG-PET scans were conducted on fasting patients at baseline and at months 3

and 6. All subjects fasted 8 h prior to and during the study; they were then injected with 370 MBq (10 mCi) FDG, and the scan was performed 1.5 h post-injection. Finger stick blood sugar was measured to assure fasting state (blood sugar < 120 mg/dl). Patient data was acquired using a clinical PET/CT scanner (Biograph mCT 128, Siemens Molecular Imaging, Hoffman Estates, IL) having time-of-flight capable PET detectors in four-ring configuration. First, a low-dose CT scan was acquired to provide an attenuation map for PET data corrections. Then, PET data were acquired in list mode for fifteen minutes. PET images were reconstructed using iterative 3D-OSEM time-of-flight algorithm with resolution modeling. Images were analyzed in a blinded fashion by a single nuclear medicine physician using an image fusion workstation (TrueD, Syngo MultiModality Workstation, Siemens Molecular Imaging) with region-of-interest (ROI) measuring tools. Maximal standardized uptake values (SUV) were measured in the heart (right ventricle free wall, left ventricle free wall, and intraventricular septum).

Erythropoietin levels

Blood obtained from venipuncture was collected in Serum Separation Tubes (367986, Becton, Dickinson and Company, Franklin Lakes, NJ) and clotted for at least 30 minutes. Serum was isolated after centrifugation at 2000 g for 10 minutes and stored at -80°C. Human Erythropoietin Platinum ELISA Kit (BMS2035, eBioscience, San Diego, CA) was used to quantify serum erythropoietin concentrations.

Beta adrenergic receptor (βAR)

The method for measuring βAR fluorescence intensity has been previously published (7). In brief, peripheral blood cells were stained with a custom-made alprenolol-biotin probe that consists of the β-blocker alprenolol covalently linked to biotin (Cell Mosaic, Worcester, MA). The alprenolol probe binding was detected by secondary reagent Streptavidin PE (eBioscience). Samples were run on an LSR II flow cytometer (BD). Data analysis was performed using FlowJo software (vX.0.7) (Tree Star, OR), and alprenolol binding was expressed as the median fluorescence intensity (MFI) of each cell subset.

Urinary cAMP

Quantitative measures of urine samples were normalized by creatinine concentrations to account for differences in hydration and urine volume. Urinary creatinine levels were quantified on an Abbott Architect machine according to manufacturer's instructions. Urine samples were diluted 1000-fold, and cAMP was quantified using the CatchPoint cAMP Kit according to the manufacturer's protocol (Cat# R8089, Molecular Devices, Sunnyvale, CA).

NT-proBNP

NT-proBNP was measured with an electrochemiluminescence immunoassay performed on a Roche Cobas e411 analyzer. Validation studies on pooled human samples show repeatability CV of < 5% and precision CV of < 5% (Roche Diagnostics, Indianapolis, IN).

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