Supplementary Material

Full Recovery of Right Ventricular Systolic Function in Children Undergoing Bilateral Lung Transplantation for Severe PAH

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ABBREVIATIONS AND ACRONYMS

BSA = body surface area
CHD = congenital heart disease
CI = cardiac index, syn. Qsi = systemic blood flow index (Qs indexed to body surface area)
CPB = cardiopulmonary bypass
HLTx = combined heart and lung transplantation
EPPVDN = European Pediatric Pulmonary Vascular Disease Network
HHT = hereditary hemorrhagic telangiectasia
IPAH/HPAH = idiopathic/heritable pulmonary arterial hypertension
LuTx = lung transplantation
LV = left ventricle
LVEDD = left ventricular end-diastolic diameter
LVEF = left ventricular ejection fraction
LVES EI = left ventricular end-systolic eccentricity index
LVESV = left ventricular end-systolic volume
LVLS = left ventricular longitudinal strain
mRAP = mean right atrial pressure
mPAP = mean pulmonary artery pressure
mSAP = mean systemic artery pressure (aorta)
NTproBNP = N-terminal prohormone of brain natriuretic peptide (NTproBNP)
PAAT = pulmonary artery acceleration time
PAH = pulmonary arterial hypertension
PCH = pulmonary capillary hemangiomatosis
PDA = persistent ductus arteriosus
PH = pulmonary hypertension
PVD = pulmonary vascular disease
PVOD = pulmonary venoocclusive disease
PVRi = pulmonary vascular resistance index (PVR indexed to body surface area)
Qsi = systemic blood flow index (Qp indexed to body surface area), syn. cardiac index
RHF = right heart failure
RV = right ventricle
RVAWD = right ventricular wall diameter (in diastole)
RVEDD = right ventricular end-diastolic diameter
RVH = right ventricular hypertrophy
RV/LV end-systolic ratio = ratios of inner diameters of RV over LV in end-systole
RV mass index = right ventricular mass index
RVEDP = right ventricular end-diastolic pressure
RVEDV index = right ventricular end-diastolic volume (indexed to body surface area)
RVEF = right ventricular ejection fraction
RVES RI = right ventricular end-systolic remodeling index
RVLS = right ventricular longitudinal strain
RVRS = right ventricular radial strain
RVCS = right ventricular circumferential strain
RVCSR = right ventricular circumferential strain rate
S/D ratio = systolic/diastolic duration ratio, CW Doppler flow of tricuspid regurgitation flow
SVRi = systemic vascular resistance (SVR indexed to body surface area)
TAPSE = tricuspid annular plane systolic excursion
TPG = transpulmonary pressure gradient
TR = tricuspid regurgitation
TRV = tricuspid regurgitation velocity (m/s)
SVR = systemic vascular resistance
VA-ECMO = veno-arterial extracorporeal membrane oxygenation

SUPPLEMENTARY TEXT

SUPPLEMENTARY METHODS

Non-Invasive Imaging (Echocardiography, Cardiac MRI)

Echocardiographic function and diameters were assessed using B-mode, M-Mode, Doppler and ventricular strain analysis (1, 2). All examinations were performed on Philipps IE33 or EPIQ CVx ultrasound machines. Images were recorded digitally and analyzed at a workstation using Intellispace Echo software (Philips Medical Systems, The Netherlands) by a single experienced investigator. To judge cardiac remodeling and function pre- and post-LuTx, we assessed at least 10 conventional and 2D-speckle tracking echocardiographic variables. For strain analysis, the TomTec RV/LV-AutoStrain software was used (TomTec Imaging Systems 2.41.00, Unterschleissheim, Germany). Every measurement was thoroughly checked by two independent, experienced cardiologists.

Cardiovascular magnetic resonance (CMR) was performed on 1.5-T Scanners (Magnetom Avanto and Magnetom Aera, both Siemens Healthineers, Erlangen, Germany) in non-sedated patients according to published PAH protocols (2, 3) (**Table S3**). Cine images were acquired during repeated breath holds; at a minimum short axis images were acquired with subsequent analysis of mass and volumes. Cardiac index (Qsi) was calculated by multiplying LV stroke volume by heart rate, divided by body surface area (BSA, m^2). Conventional CMR analysis and tissue tracking (TT; strain analysis) was conducted by a single experienced observer using CVi 42 (5.11.1) software (Circle Cardiovascular Imaging, Calgary, Canada). All MRI conventional/strain measurements were thoroughly checked by two independent, experienced investigators. CMR could not be performed in 9/15 children because they either required general anesthesia or were too sick to undergo MRI safely.

SUPPLEMENTARY RESULTS

Post-LuTx course, clinical follow up and short to midterm outcome

After LuTx, none of the 15 pediatric PH patients required re-thoracotomy for hematothorax. The mean ICU stay post-LuTx was 14±2 days (range 4-32 days). The average in-hospital stay was 54±7 days (range 21-107). There was no perioperative (30 days post-op.) mortality in this group of 15 consecutive children with end-stage PAH and RV failure undergoing bilateral LuTx. One of the 15 PAH-LuTx patients had to be re-transplanted 9 months after the initial LuTx because of acute fibrinous, organizing pneumonia with perivascular round cell infiltration consistent with cellular rejection. As of March 31, 2021, all 15 pediatric PAH-LuTx patients are alive and in clinical follow up (mean follow-up post-LuTx: 39 months; range 2 months – 7 years).

Echocardiographic 2D-Speckle Tracking (longitudinal RV and LV strain; Figure 3, Table S5).

Our echocardiographic 2D-speckle tracking findings are consistent with reversal of the underlying pathophysiology, i.e., RV pressure overload and RV failure associated with LV underfilling and compression via end-systolic septal shift pre-LuTx, and immediate RV pressure unloading and increased filling of the LV post-LuTx. Consistent changes in the segmental and average RV longitudinal strain are shown in **Figure S3**.

RV pressure unloading after LuTx decreases the heart failure biomarker NTproBNP

In addition to the aforementioned comprehensive imaging analysis, we also conducted a heart failure biomarker comparison at both time points. Of note, serum NTproBNP concentrations are dependent on renal excretion efficiency, and some patients underwent

hemodialysis post-LuTx. Nevertheless, we found a marked reduction of serum NTproBNP concentration from an average of 3094 to 946 pg/ml 3-8 weeks after LuTx (n=7), indicating greatly decreased myocardial stress post-LuTx.

SUPPLEMENTARY DISCUSSION

The current data confirm our previous observations that moderate to severe RV hypertrophy persists for months after LuTx for PAH in childhood (RVAWD ~4-8mm; **Figure 1A, B**). For that reason, we frequently prescribe mineralocorticoid receptor antagonists (spironolactone, eplerenone) and beta-blockers to support ventricular reverse-remodeling and diastolic function after LuTx.

The RV/LV end-systolic dimension ratio is derived to combine a measure of RV size with interventricular septal shift secondary to elevated RV pressure, in the parasternal short axis view (Echo).

Among other right heart metrics, the RV end-systolic remodeling index (RVES RI) has excellent test–retest characteristics and strongly predicted outcome in adults with PAH (4).

Similarly to TAPSE, cardiac index, when estimated by MRI-derived stroke volume and heart rate, was not a good indicator of clinical status or improvement after LuTx.

In a prospective study on 54 treatment naïve adults with PAH, 2D 4CSL tracked clinical improvement with vasodilator therapy and had better receiver operating curves (ROC) for the probability of adverse clinical outcomes than circumferential strain(5). Importantly, adult PAH patients had better event-free survival when 2D 4CSL was greater than -16.6%(5).

SUPPLEMENTARY FIGURES

Figure S1. Right ventricular end-systolic remodeling index (RVES RI) decreases in pediatric patients with pulmonary arterial hypertension (PAH) after bilateral lung transplantation

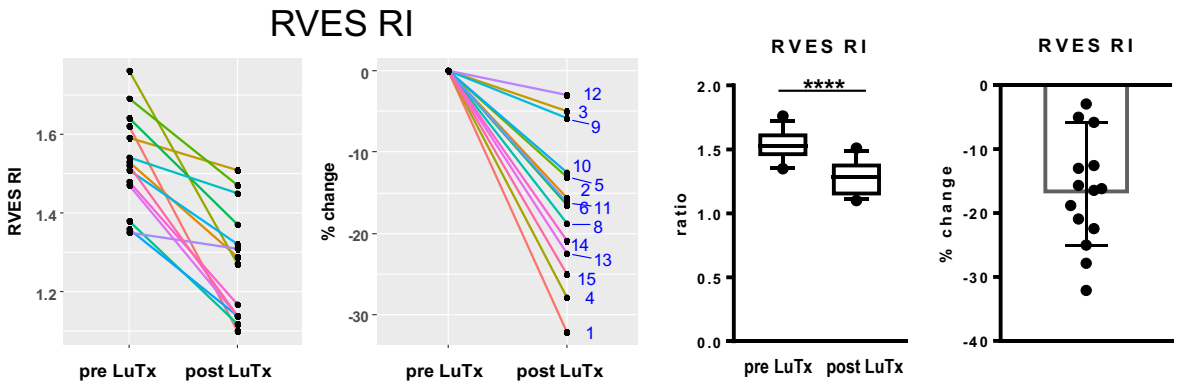

Figure S1. *Right ventricular end-systolic remodeling index (RVES RI) decreases in pediatric patients with pulmonary arterial hypertension (PAH) after bilateral lung transplantation.* The RVES RI was calculated as described in Koestenberger M et al. Pediatr Res. 2020; 88: 285-292. doi: 10.1038/s41390-020-0748-2. Normal values are below 1.2. All patients with RVES RI data pre-LuTx and post-LuTx (N=14) are shown. One patient had insufficient echocardiographic 4-chamber view windows. The paired two-tailed t-test was used. ****$p <$ 0.0001, n=14. The box and whisker plots (third column) show the median, IQR, and 10-90th percentile. The scatter plots (fourth column) show the 95% confidence interval for the median. Abbreviations: RVES RI, right ventricular end-systolic remodeling index.

Figure S2. Normalization of right ventricular volumes after lung transplantation (LuTx) in an adolescent with severe idiopathic pulmonary arterial hypertension, RV hypertrophy and dilation.

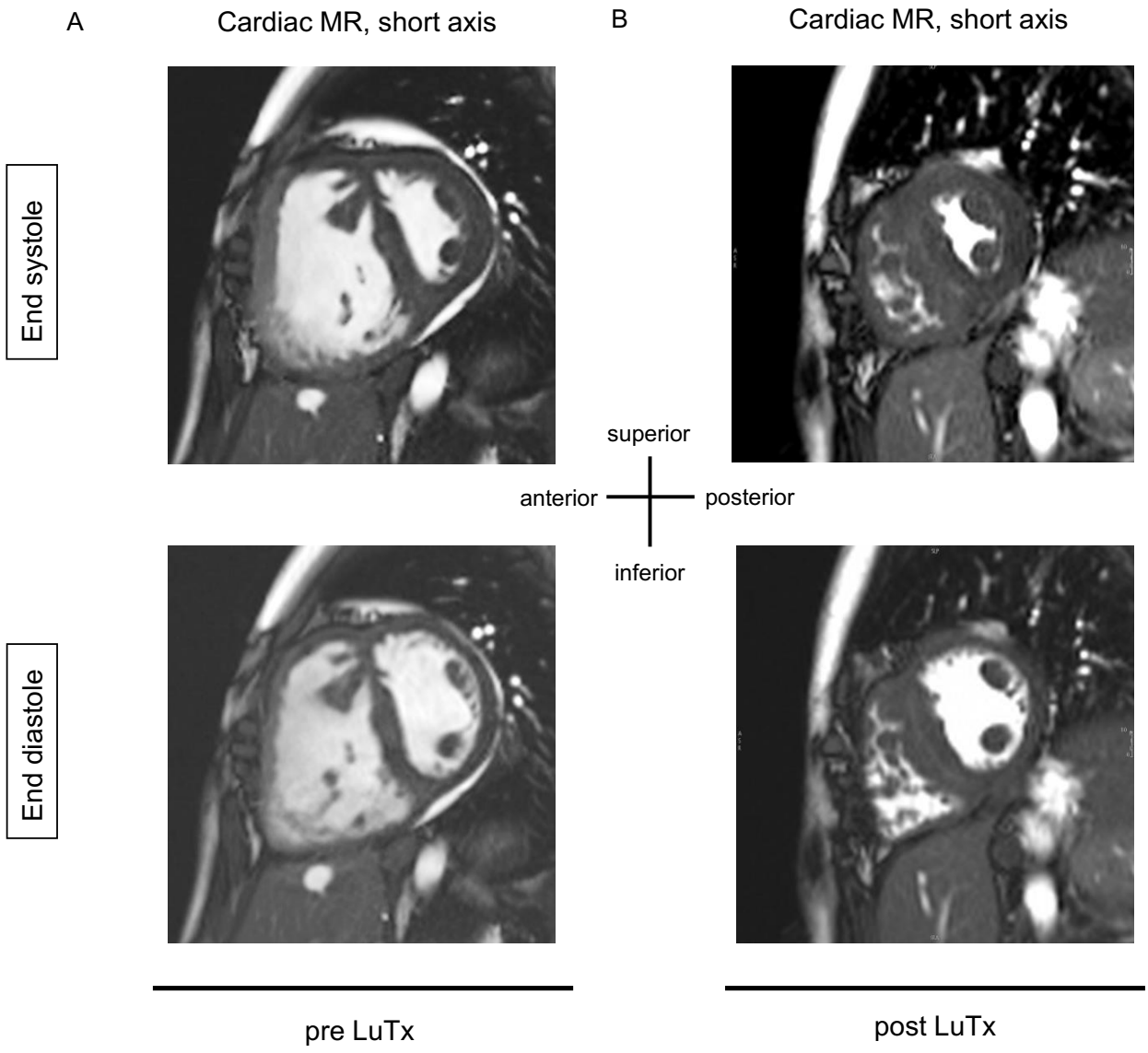

Figure S2. *Normalization of right ventricular volumes after lung transplantation (LuTx) in a 13-year-old female with severe idiopathic pulmonary arterial hypertension, RV hypertrophy and dilation.* Standard end-systolic and end-diastolic single images in the short axis view pre- (**Figure S2 A**) and post-LuTx (**Figure S2 B**; 8mm slices) are shown. See also Supplementary Movies 1A and 1B.

Figure S3. Echocardiographic 2D speckle tracking demonstrates full recovery of segmental and average RV longitudinal strain pre- and post-Lung transplantation in children with pulmonary arterial hypertension

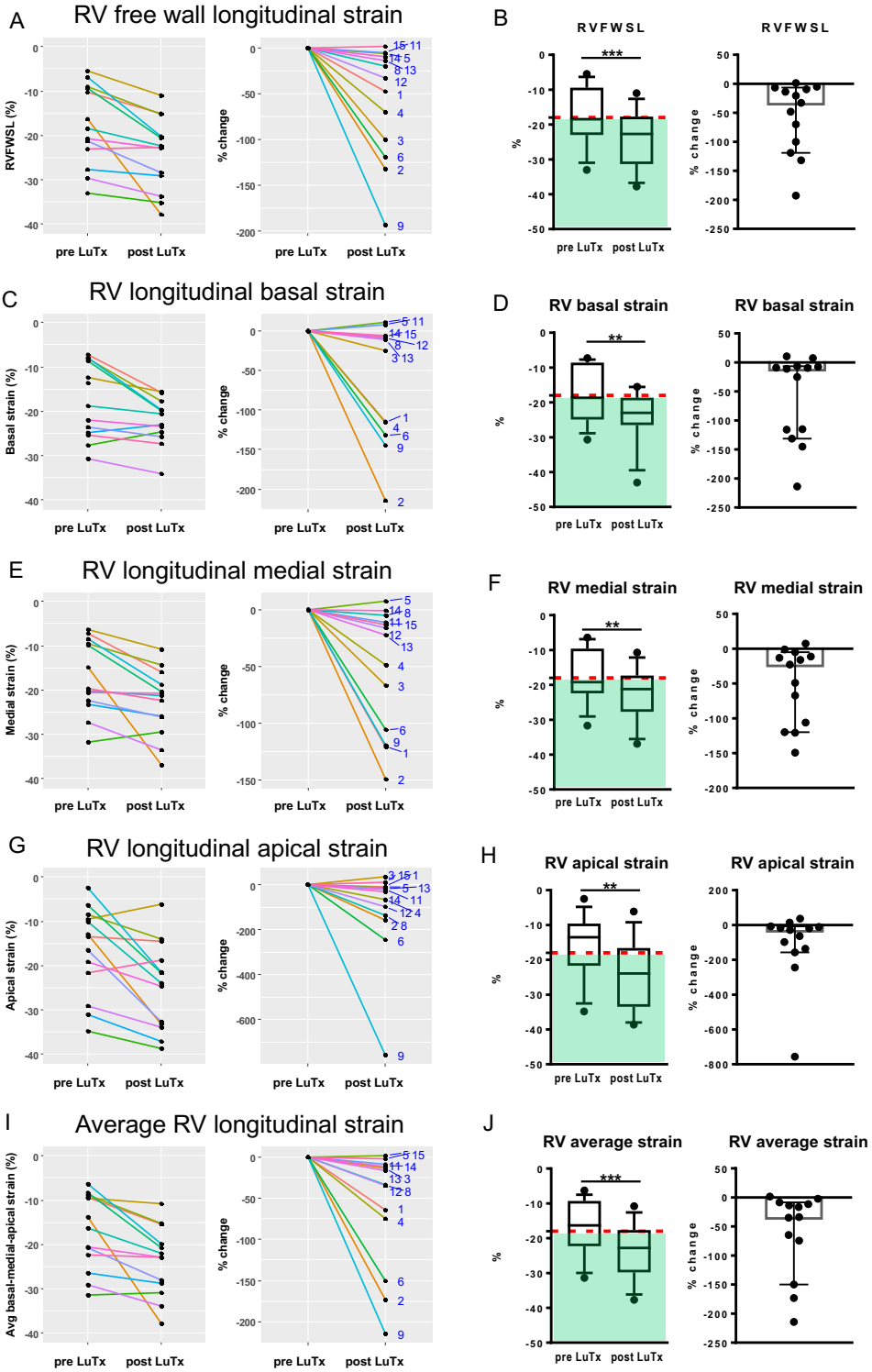

Figure S3. *Echocardiographic 2D speckle tracking demonstrates full recovery of segmental and average RV longitudinal strain pre- and post-Lung transplantation in children with pulmonary arterial hypertension.* **Figures S3 A-J** show the results of the 2 D strain analysis of the 13 patients with accessible cardiac strain data pre- and post-LuTx. The RV free wall longitudinal strain (RVFWSL, **Figure S3 A,B**), RV longitudinal basal strain (**Figure S3 C,D**), RV longitudinal medial strain (**Figure S3 E,F**) and RV longitudinal apical strain (**Figure S3 G,H**) were abnormal in almost all PAH patients pre-LuTx and recovered within 2 months post-LuTx. **Figure S3 A, C, E, G, I** show the individual changes of each of the thirteen patients pre- and post-LuTx (percentage change). The box and whisker plots (**Figure S3 B, D, F, H, J**) show the median, IQR, and 10-90th percentile. ** $p < 0.01$, ***$p < 0.001$, n=13. Abbreviations: RV, right ventricle.

SUPPLEMENTARY TABLES

Table S1. Classification of Pulmonary Hypertension (6th World Symposium on Pulmonary Hypertension, Nice 2018)

Group 1-5 Pulmonary Hypertension	
1. Pulmonary arterial hypertension (PAH)	
1.1 Idiopathic PAH	
1.2 Heritable PAH	Causal gene mutations, e.g. BMPR2, ACVRL1, TBX4, EIF2AK4, ATP13A3, GFD2, SOX17, AQP1, SMAD9, ENG, KCNK3, CAV1, …
1.3 Drug and toxin induced	e.g., amphetamines/ methamphetamines, dasatinib
1.4 Associated with:	1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers	Reduction of mPAP ⩾10 mmHg to reach an absolute value of mPAP ⩽40 mmHg. Increased or unchanged cardiac output Long-term response to CCBs
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement	Pulmonary function tests (Decreased DLCO (frequently <50%) Chest HRCT (e.g. septal lines; centrilobular ground-glass opacities/nodules) Response to PAH therapy (possible pulmonary edema)
1.7 Persistent PH of the newborn syndrome	
2. Pulmonary hypertension due to left heart disease	2.1 PH due to heart failure with preserved LVEF 2.2 PH due to heart failure with reduced LVEF 2.3 Valvular heart disease 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH
3. Pulmonary hypertension due to lung diseases and/or hypoxia	3.1 Obstructive lung disease 3.2 Restrictive lung disease 3.3 Other lung disease with mixed restrictive/obstructive pattern 3.4 Hypoxia without lung disease 3.5 Developmental lung disorders
4. PH due to pulmonary artery obstructions	4.1 Chronic thromboembolic PH 4.2 Other pulmonary artery obstructions
5. Pulmonary hypertension with unclear multifactorial mechanisms	5.1 Hematological disorders 5.2 Systemic and metabolic disorders 5.3 Others 5.4 Complex congenital heart disease

From: Simonneau G et al. Eur Resp J 2019; 53: 1801913; DOI: 10.1183/13993003.01913-2018

Table S2. Individual patient characteristics and medication pre-LuTx

ID	Age (years)	Gender (M/F)	Weight (kg)	BSA (m^2)	FC (1-4)	NTproBNP (pg/mL)	Diagnosis	PH relevant medication pre-LuTx	Medical condition and ECLS status pre-LuTx	ECLS status during and post-LuTx, complications post-LuTx
1	15.0	F	43.0 (4^{th} Perc.)	1.40	4	5203	PCH/PAH (group 1.6 PH)	ILO, SIL, BOS, SPI, FUR, 15 L O_2/min	Acute RHF, alveolar diffusion impairment, VA-ECMO-CPR pre-LuTx, 1 day on VA-ECMO pre-LuTx	pre-LuTx ECMO cannula dislocation/ hematothorax/thoracotomy, LuTx on VA-ECMO, 7 days on ECMO after LuTx, critical illness neuropathy
2	13.0	F	45.0 (31^{st} Perc.)	1.50	4	4436	IPAH (group 1.1 PH), type 1 diabetes	EPIV, SIL, BOS, FUR	Acute RHF, VA-ECMO-CPR pre-LuTx, 12 days on VA-ECMO pre-LuTx	LuTx on VA-ECMO, 12 days on ECMO after LuTx
3	10.7	M	35.0 (44^{th} Perc.)	1.30	4	1482	IPAH (group 1.1 PH)	TREP i.v., SIL, MAC, SPI, ASA	Progression of PH, RHF	LuTx on VA-ECMO, 7 days on VA-ECMO after LuTx
4	14.1	F	47.0 (23^{rd} Perc.)	1.50	4	10972	PAH-CHD (group 1.4.4 PH) s/p d-TGA repair, vWS type 2	TREP i.v., RIO, BOS, 2 L O_2/min	Progression of PH, acute RHF	LuTx on VA-ECMO, 8 days on ECMO after LuTx
5	1.9	M	8.2 (< 1^{st} Perc.)	0.42	3-4	8384	PAH-CHD (group 1.4.4 PH), Preterm 29 + 2 GW, IRDS, prothrombin mutation, severe RPA hypoplasia, ASD II, s/p PDA closure	SIL, MAC, CLO, SPI, 0.75 L O_2/min	Progression of PH, RHF	LuTx on VA-ECMO, 5 days on VA-ECMO after LuTx, post-LuTx subtotal middle cerebral artery infarction on VA-ECMO
6	2.3	F	8.9 (< 1^{st} Perc.)	0.43	4	9720	IPAH (group 1.1 PH), ASD II	ILO inhal., SIL, MAC, SEL, SPI, 2-3 L O_2/min	Progression of PH, RHF	LuTx on CPB, no VA-ECMO after LuTx
7	17.4	F	39.0 (< 1^{st} Perc.)	1.30	3	743	HPAH, BMPR2 mutation (group 1.2 PH), M. Osler (HHT), small PFO	ILO inhal., SIL, MAC, SPI	Progression of PH	LuTx on VA-ECMO, 15 days on ECMO after LuTx

ID	Age (years)	Gender (M/F)	Weight (kg)	BSA (m^2)	FC (1-4)	NTproBNP (pg/mL)	Diagnosis	PH relevant medication pre-LuTx	Medical condition and ECLS status pre-LuTx	ECLS status during and post-LuTx; complications post-LuTx
8	10.2	F	25.0 (3^{rd} Perc.)	0.91	4	110	HPAH, TBX4 mutation (group 1.2 PH), IRDS, chILD, PFO, small patella syndrome	ILO inhal., SIL, MAC, SPI, 1.5-2.5 L O_2/min	Progression of PH	LuTx on VA-ECMO, 9 days on VA-ECMO after LuTx
9	11.7	M	32.0 (11^{th} Perc.)	1.10	4	7596	PVOD/PAH (group 1.6 PH), Preterm 32 + 5 GW, s/p gastroschisis, double aortic arch with atresia of the left arch, type 2 vWD, intervent. rASD 09/2017	TREP i.v., TAD, BOS, AML, SPI, ASA	Progression of PH, acute RHF, VA-ECMO-CPR pre-LuTx, 2 days on VA-ECMO pre-LuTx	LuTx on VA-ECMO, 6 days on VA-ECMO after LuTx
10	17.6	F	57.0 (42^{nd} Perc.)	1.70	3	566	IPAH (group 1.1 PH), type 2 vWD, migraine	TREP i.v. infusion pump, SIL, MAC, DIG, SPI	Progression of PH	LuTx on VA-ECMO, 4 days on VA-ECMO after LuTx
11	16.1	F	51.0 (20^{th} Perc.)	1.50	4	444	IPAH (group 1.1 PH), intervent. rASD 01/2019	ILO inhal., SIL, MAC, AML, ASA, SPI, 2L O_2/min	Progression of PH	LuTx on VA-ECMO, 9 days on VA-ECMO after LuTx
12	11.1	F	40.0 (59^{th} Perc.)	1.30	4	243	PVOD/PCH/PAH with plexiform lesions (group 1.6 PH), partial anomalous pulmonary venous connection, type 2 vWD	Levosimendan, Milrinone, SIL, MAC	Newly diagnosed, treatment resistant PH, acute RHF	LuTx on VA-ECMO, 5 days on VA-ECMO after LuTx, re-transplantation 9 months after initial LuTx because of cellular rejection
13	5.5	F	16.8 (9^{th} Perc.)	0.74	3	359	HPAH, BMPR2 mutation (group 1.2 PH)	EPIV, SIL, BOS, AML	Progression of PH, RHF	LuTx on CPB, 6 days on VA-ECMO after LuTx,
14	8.1	F	22.2 (9^{th} Perc.)	0.91	3-4	273	HPAH, BMPR2 mutation (group 1.2 PH), s/p VSD repair, type 2 vWD	Levosimendan (repetitive), SIL, MAC, SEL, SPI	Progression of PH, acute RHF	LuTx on VA-ECMO, 7 days on VA-ECMO after LuTx
15	6.1	F	14.7 (< 1^{st} Perc.)	0.66	3	408	IPAH, heterozygous EIF2AK4 mutation of unclear significance (group 1.1 PH), ASD II, type 2 vWD	RIO, MAC, SEL, SPI	Progression of PH, RHF	LuTx on CPB, 6 days on VA-ECMO after LuTx

Table S2. *Individual PAH patient characteristics undergoing bilateral lung transplantation (LuTx).* The indicated serum N-terminal prohormone of brain natriuretic peptide (NTproBNP) concentrations are the last measurements prior to LuTx. Of note, several patients were admitted to the hospital in critical condition with several fold higher NTproBNP levels which then improved under therapy (e.g., patient 14 had an initial serum NTproBNP level of 2293 pg/ml). Abbreviations: AML, amlodipine; ASA, acetylsalicylic acid (P.O.); BSA, body surface area; CHD, congenital heart disease; CLO, clopidogrel; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; digoxin (P.O.); EPIV; epoprostenol i.v.; FUR, furosemide (P.O.); HPAH, heritable PAH; ILO, iloprost; IPAH, idiopathic PAH; intervent. rASD, interventional creation of a restrictive atrial septal defect; LuTx, lung transplantation; NT-proBNP, N-terminal pro b-type natriuretic peptide; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PVOD, pulmonary venoocclusive disease; RHF, right heart failure; SEL, selexipag (P.O.); SIL, sildenafil (P.O.); SPI, spironolactone (P.O.); TAD, Tadalafil; TREP, treprostinil; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Table S3. Characteristics of six patients undergoing bilateral lung transplantation (LuTx) who had cardiac magnetic resonance imaging (MRI) pre- and post-LuTx

Patients #2, 3, 7, 9, 14, 15	Pre-LuTx n = 6	Post-LuTx n = 6
Demographics		
Age – years	11.2 ± 1.6 (6.1 – 17.4)	11.4 ± 1.6 (6.3 – 17.7)
Sex, Female – n (%)	4 (67%)	4 (67%)
Height – m	1.4 ± 0.1	1.4 ± 0.1
Weight – kg	31.3 ± 4.5	30.9 ± 4.6
BSA – m^2	1.1 ± 0.1	1.1 ± 0.1
Clinical Diagnosis		
PH Group – n		
PH Group 1		
1.1 IPAH	3	
1.2 HPAH	2	
1.4.4 PAH-CHD	0	
1.6 PVOD/PCH	1	
Co-morbidities – n		
Hereditary thrombophilia	0	
HHT (Osler's disease)	1	
Type 1 diabetes	1	
von Willebrand disease, type 2	3 confirmed	
Functional Status		
WHO Functional Class	3.6 ± 0.2	
6 MWD (0m for ECMO) * – m, n = 6	259 ± 82	
6 MWD (last before LuTx) – m, n = 6	380 ± 29	
Biomarker		
NTproBNP – ng/l, n = 4	2439.8 ± 1739.9	1037.0 ± 288.5
Key Hemodynamics		
mRAP – mm Hg, n = 5	9.2 ± 2.3	
RVEDP – mm Hg, n = 5	12.2 ± 1.9	
mPAP/mSAP, n = 5	1.2 ± 0.02	
PVRi – WU·m^2, n = 5	25.3 ± 3.4	
PVR/SVR, n = 5	1.3 ± 0.1	
Qsi – L/min/m^2, n = 5	2.7 ± 0.2	
Risk Stratification (EPPVDN)		
Patients total – n	6	
Noninvasive Risk – n	Higher Risk – 3 Intermediate Risk – 3	
Higher Risk Score, max. 15 (decimal)	11.0/15 (0.73 ± 0.06)	
Lower Risk Score, max. 14 (decimal)	1.3/14 (0.09 ± 0.02)	
Patients with cath 0-12 months pre-LuTx – n	5	
Invasive Risk – n	Higher Risk – 3 Intermediate Risk – 2	
Higher Risk Score, max. 21 (decimal)	14.4/21 (0.68 ± 0.07)	
Lower Risk Score, max. 20 (decimal)	2.8/20 (0.14 ± 0.03)	
Pre/Post-LuTx Imaging Intervals		
Interval MRI to Tx / Tx to MRI – days (range), n = 6	61 ± 31 (15 – 203)	43 ± 4 (31 – 56)

Table S3. *Characteristics of Six Patients Undergoing Bilateral Lung Transplantation (LuTx) who had cardiac magnetic resonance imaging (MRI) pre- and post-LuTx.* Values are presented as mean ± SEM. The indicated serum N-terminal prohormone of brain natriuretic peptide (NTproBNP) concentrations were the last

measurements prior to LuTx and determined ± 14 days around the post-LuTx echo. Only catheterization data within the preceding 12 months pre-LuTx are presented and considered in the risk scores. For risk stratification, see the new 2019 EPPVDN risk score. *Two patients were supported with VA-ECMO 2 to 12 days prior to LuTx. Abbreviations: 6 MWD, 6-minute walk distance; BSA, body surface area; cath, catheterization; CHD, congenital heart disease; ECMO, extracorporeal membrane oxygenation; EPPVDN, European Pediatric Pulmonary Vascular Disease Network; HHT, hereditary hemorrhagic telangiectasia; HPAH, hereditary PAH; IPAH, idiopathic PAH; LuTx, lung transplantation; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; NT-proBNP, N-terminal pro b-type natriuretic peptide; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PVOD, pulmonary venoocclusive disease; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qsi, systemic flow index; RVEDP, right ventricular end-diastolic pressure; SVR, systemic vascular resistance; vWD, von Willebrand disease; WHO, World Health Organisation.

Table S4. Non-Invasive Imaging of PAH Patients Undergoing Bilateral Lung Transplantation

	Pre-LuTx (n=15)	Post-LuTx (n=15)	% Change	p-val
Demographics				
Age – years	10.56±1.40	10.91±1.32		
Sex, Female – n (%)	12 (80%)	12 (80%)		
Height – m	1.39±0.08	1.39±0.08		
Weight – kg	32.32±4.02	31.48±3.89		
BSA – m^2	1.11±0.11	1.11±0.10		
Echocardiography (n=15)				
Heart rate – bpm	92.67±5.50	87.73±4.06		
RVAWD – cm, M-mode, PSAX	1.10±0.09	0.72±0.06	-35%	<0.0001
RVEDD – cm, M-mode, PSAX	3.75±0.24	1.80±0.15	-52%	<0.0001
RV/LV end-systolic ratio, PSAX	2.52±0.21	0.64±0.04	-75%	<0.0001
LV eccentricity index, PSAX	2.18±0.16	1.12±0.05	-49%	<0.0001
TAPSE – cm, 4C, n = 11	1.47 (z -3.46)	1.38 (z -4.23)	-6%	n.s.(0.4551)
RVES remodeling index, 4C	1.53±0.03	1.27±0.04	-17%	<0.0001
PAAT – ms, PSAX	65.21±3.80	118.14±6.32	+81%	<0.0001
LVEDD – cm, M-mode, PSAX	2.85±0.15	3.50±0.18	+23%	0.0091
LVEF, Simpson – %	71.14±2.35	65.10±1.46	-8%	n.s.(0.1003)
LVEF, Bullet (area-length) – %	66.54±2.47	59.42±1.10	-11%	0.0154
Cardiac MRI (n=6)				
RV mass – g/m2	77.33±9.38	47.67±2.49	-35%	0.0280
LV mass – g/m2	51.50±5.16	53.50±3.58	+8%	n.s.(0.2817)
RVEDV index – ml/m2	150.67±24.19	56.00±4.16	-58%	0.0119
RVESV index – ml/m2	104.67±20.72	20.50±2.26	-78%	0.0089
LVEDV index – ml/m2	58.17±4.49	64.00±4.65	+14%	n.s.(0.4444)
LVESV index – ml/m2	24.67±2.96	26.67±3.00	+10%	n.s.(0.3876)
RVEF - %	32.83±3.62	64.00±2.46	+102%	0.0313
LVEF - %	57.67±1.93	58.67±1.93	3%	n.s.(0.8974)

Table S4. *Non-invasive imaging of PAH patients undergoing bilateral lung transplantation.* The pre-LuTx and post-LuTx values are shown as mean ± SEM. % Change is the relative change of the mean post-LuTx value vs. the mean pre-LuTx value. The p-values are determined either by the Wilcoxon signed-rank test or paired two-tailed t-test. Abbreviations: BSA, body surface area; LV, left ventricle; LVEDD, left-ventricular end-diastolic diameter; LVEDV, left-ventricular end-diastolic volume; LVEF, left-ventricular ejection fraction; LVESV, left-ventricular end-systolic volume; n.s., not significant; PAAT, pulmonary artery acceleration time; PSAX, parasternal short axis; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right-ventricular end-diastolic diameter; RVEDV, right-ventricular end-diastolic volume; RVEF, right-ventricular ejection fraction; RVES, right-ventricular end-systolic; RVESV, right-ventricular end-systolic volume; TAPSE, tricuspid annular plane systolic excursion.

Table S5. Echocardiographic 2D-Speckle Tracking and Cardiac Magnetic Resonance Tissue Tracking with Biventricular Strain Analysis in PAH Patients Undergoing Bilateral Lung Transplantation (Myocardial Deformation Imaging)

	Pre-LuTx (n=15)	Post-LuTx (n=15)	% Change	p-val
Demographics				
Age – years	10.56±1.40	10.91±1.32		
Sex, Female – n (%)	12 (80%)	12 (80%)		
Height – m	1.39±0.08	1.39±0.08		
Weight – kg	32.32±4.02	31.48±3.89		
BSA – m^2	1.11±0.11	1.11±0.10		
Echocardiographic 2D Strain (n=13)				
Heart rate – bpm	94.54±6.17	87.54±4.54	-7%	n.s.(0.6763)
RV FW SL, 4C, %	-17.78±2.52	-24.15±2.27	-36%	0.0005
RV FW SL basal, 4C, %	-17.78±2.34	-23.85±2.13	-34%	0.0085
RV FW SL medial, 4C, %	-17.04±2.28	-22.76±2.08	-33%	0.0012
RV FW SL apical, 4C, %	-16.58±2.78	-24.62±2.76	-48%	0.0035
RV 4C SL, %	-12.60±1.75	-22.07±2.34	-75%	0.0002
LV 4C SL, %	-20.41±2.01	-24.76±2.42	-21%	n.s.(0.0628)
Cardiac MR Strain (n=6)				
LV radial strain, %	29.92±3.25	29.55±1.78	-1%	n.s.(0.1379)
LV radial strain rate, 1/s	1.82±0.21	2.08±0.16	15%	n.s.(0.2813)
LV circumferential strain, %	-16.08±1.44	-17.28±0.85	-7%	n.s.(0.5863)
LV circumferential strain rate, 1/s	-1.07±0.14	-1.28±0.11	-20%	n.s.(0.3840)
LV longitudinal strain, %	-12.72±1.04	-12.27±1.03	4%	n.s.(0.7792)
LV longitudinal strain rate, 1/s	-0.85±0.05	-1.05±0.14	-24%	n.s.(0.1250)
RV radial strain, %	10.25±1.37	20.85±1.32	103%	0.0026
RV radial strain rate, 1/s	0.63±0.12	1.53±0.28	142%	n.s.(0.0625)
RV circumferential strain, %	-7.53±0.89	-12.88±0.70	-71%	0.0036
RV circumferential strain rate, 1/s	-0.5±0.09	-0.98±0.14	-97%	0.0334
RV longitudinal strain, %	-10.22±1.14	-17.7±3.12	-73%	0.0450
RV longitudinal strain rate, 1/s	-0.9±0.17	-1.48±0.39	-65%	n.s.(0.2049)

Table S5. *Echocardiographic 2D-speckle tracking and cardiac magnetic resonance tissue tracking with biventricular strain analysis in pediatric PAH patients undergoing bilateral lung transplantation (myocardial deformation imaging).* In two patients post-LuTx, no 4-chamber view echocardiographic images with sufficient quality were recorded. The pre-LuTx and post-LuTx values are shown as mean ± SEM. % Change is the relative change of the mean post-LuTx value vs. the mean pre-LuTx value. The p-values are determined either by the Wilcoxon signed-rank test or paired two-tailed t-test. Abbreviations: 4C, 4 chamber view; BSA, body surface area; FW, free wall; LV, left ventricle; n.s., not significant; SL, longitudinal strain.

Supplementary References

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