

SUPPLEMENTAL MATERIAL

Right atrial function is associated with RV diastolic stiffness: RA-RV interaction in pulmonary arterial hypertension

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Supplemental table S1. Comparison of patients with 30 CMR phases and patients with follow-up to the overall cohort

	All PAH patients (n=97)	Baseline PAH with 30 CMR phases (n=56)	Patients with follow-up (n=62)
Age, y	57.5 ± 17.9	57.4 ± 16.8	54.1 ± 18.1
Female, n (%)	63 (65%)	33 (59%)	41 (66%)
NYHA 1/2/3/4	4/33/53/7	2/22/29/3	4/27/29/2
NTproBNP, pg/ml	1367 [360-2809]	1122 [372-2368]	1290 [396-2327]
Right heart catheterization			
Heart rate, bpm	80 ± 14	76 ± 11	79 ± 12
mPAP, mmHg	51 ± 15	51 ± 15	53 ± 14
PAWP, mmHg	9 ± 3	9 ± 3	9 ± 3
CI, L/min/m ²	2.6 ± 0.9	2.7 ± 0.9	2.5 ± 0.8
PVR, mmHg/L/min	8.9 [6.1-11.9]	8.3 [5.8-11.2]	9.5 [6.9-12.6]
mRAP, mmHg	6 [4-10]	6 [4-9]	6 [4-10]
SvO ₂ , %	62 ± 10	63 ± 11	63 ± 9
Cardiac magnetic resonance			
RV EDV index, ml/m ²	82 ± 22	83 ± 21	82 ± 20
RV ESV index, ml/m ²	54 ± 21	53 ± 20	53 ± 19
RV ejection fraction, %	37 ± 12	38 ± 12	36 ± 11
RV mass index, g/m ²	49 ± 16	50 ± 15	50 ± 15
Pressure-volume analysis			
Ees, mmHg/ml	0.48 [0.35-0.77]	0.47 [0.34-0.73]	0.51 [0.38-0.82]
Ea, mmHg/ml	1.57 [1.14-2.11]	1.52 [1.11-2.05]	1.69 [1.23-2.15]
Ees/Ea	0.35 [0.24-0.54]	0.31 [0.25-0.54]	0.31 [0.23-0.52]
Eed, mmHg/ml	0.63 [0.40-0.99]	0.64 [0.42-1.02]	0.64 [0.42-1.02]
Strain and RV filling			
RA reservoir strain, %	14.3 ± 5.1	15.2 ± 5.2	14.5 ± 5.0
RA passive strain, %*	-5.6 ± 3.4	-5.8 ± 3.5	-5.8 ± 3.6
RA active strain, %	-9.0 ± 4.0	-9.7 ± 4.1	-9.1 ± 3.8
RV global longitudinal strain, %	-15.1 ± 4.7	-15.5 ± 4.7	-15.0 ± 4.9
RV passive strain, %	7.3 ± 3.6	7.6 ± 4.0	7.4 ± 3.7
RV active strain, %	8.0 ± 3.5	8.0 ± 3.7	7.9 ± 3.7
RV passive filling volume, ml	33 ± 19	36 ± 20	34 ± 19
RV active filling volume, ml	22 ± 17	22 ± 14	20 ± 16

There are no differences between baseline patients with 30 CMR phases or patients with follow-up measurements and the overall cohort. PAH indicates pulmonary arterial hypertension; CMR, cardiac magnetic resonance; NYHA, New York Heart Association functional class; NTproBNP, Nterminal pro brain natriuretic peptide; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; mRAP, mean right atrial pressure; SvO₂, mixed venous oxygen saturation; EDV, end-diastolic volume; ESV, end-systolic volume; RV, right ventricular; Ees, end-systolic elastance; Ea, arterial elastance; Eed, end-diastolic elastance; RA, right atrial

Supplemental table S2: Longitudinal strain, right atrial emptying and right ventricular filling

Variable	Control (n=31)	PAH patients (n=97)	p-Value
RA reservoir strain, %	19.1 ± 4.3	14.3 ± 5.1	< 0.001
RA passive strain, %	-12.4 ± 3.3	-5.6 ± 3.4	< 0.001
RA active strain, %	-7.5 ± 2.8	-9.0 ± 4.0	0.019
RV GLS, %	-23.6 ± 3.6	-15.1 ± 4.7	< 0.001
RV passive strain, %	15.1 ± 3.2	7.3 ± 3.6	< 0.001
RV active strain, %	8.9 ± 3.2	8.0 ± 3.5	0.16
RA passive emptying volume, ml	25 ± 9	23 ± 10	0.39
RA active emptying volume, ml	22 ± 8	38 ± 14	< 0.001
RV passive filling volume, ml	48 ± 19	33 ± 19	< 0.001
RV active filling volume, ml	24 ± 13	22 ± 17	0.38
Vena cava backflow, ml	-2 ± 14	17 ± 19	< 0.001

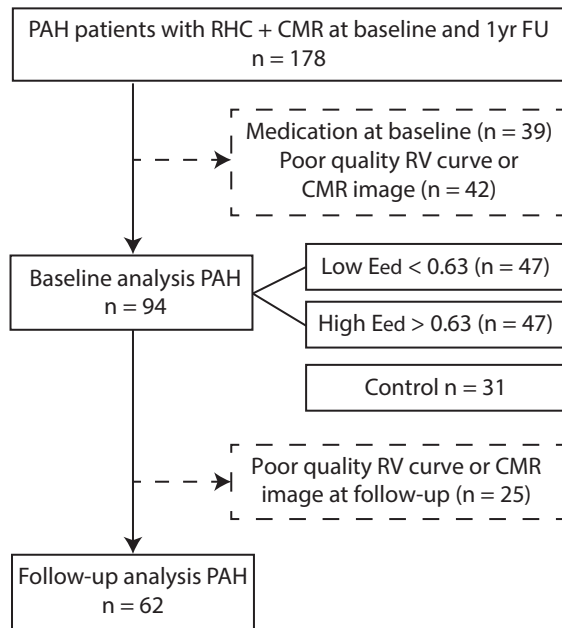
Data presented as mean ± SD. PAH indicates pulmonary arterial hypertension; RA, right atrial; RV, right ventricular; GLS, global longitudinal strain.

Supplemental table S3. Change in hemodynamics and CMR variables after treatment

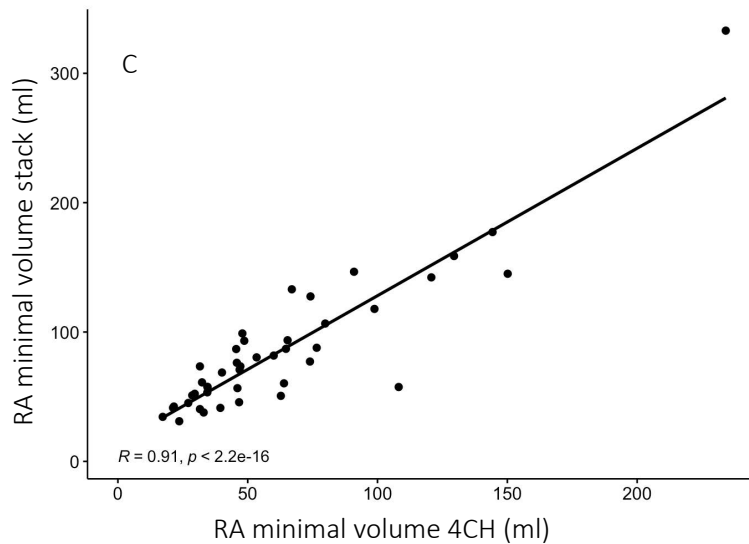
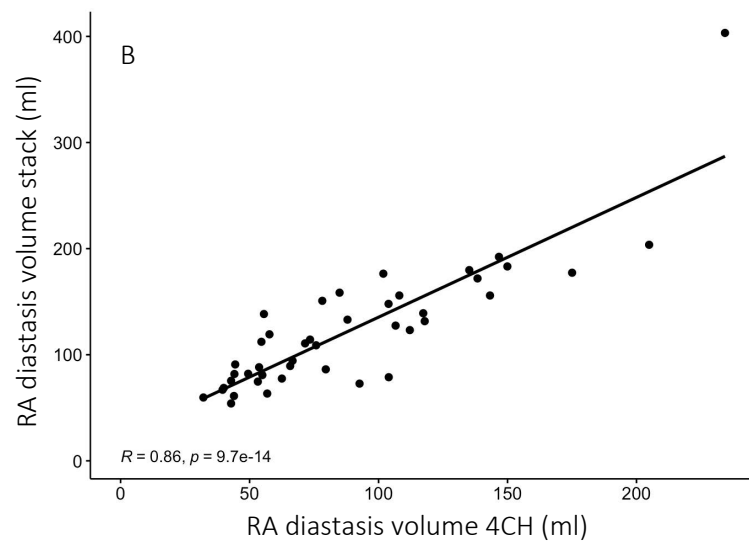
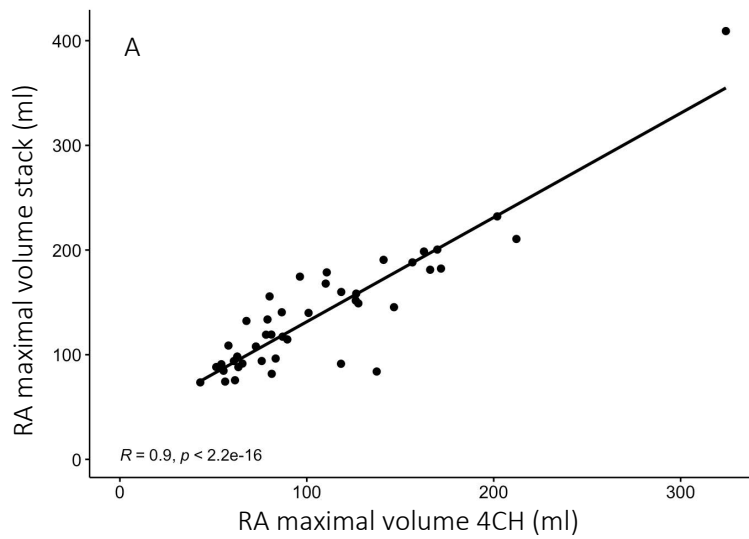
	Baseline PAH (n=62)	Follow-up PAH (n=62)	p-Value
ERA	na	10 (16%)	
PDE5i	na	6 (10%)	
ERA + PDE5i	na	39 (63%)	
Triple therapy	na	4 (6%)	
Calcium channel blocker	na	3 (5%)	
Right heart catheterization			
Heart rate, bpm	79 ± 13	75 ± 11	0.015
mPAP, mmHg	53 ± 14	43 ± 12	< 0.001
PAWP, mmHg	9 ± 3	9 ± 3	0.187
CI, L/min/m ²	2.5 ± 0.8	3.2 ± 0.9	< 0.001
PVR, mmHg/L/min	9.6 [6.8-12.9]	4.7 [3.7-7.1]	< 0.001*
mRAP, mmHg	6 [4-11]	6 [4-8]	0.001
SvO ₂ , %	63 ± 9	70 ± 7	< 0.001
E _{es} , mmHg/ml (n=53)	0.48 [0.37-0.82]	0.41 [0.21-0.75]	<0.053*
E _a , mmHg/ml (n=58)	1.73 [1.23-2.16]	0.92 [0.76-1.46]	<0.001*
E _{es} /E _a (n=53)	0.31 [0.23-0.48]	0.42 [0.22-0.66]	0.32*
E _{ed} , mmHg/ml (n=53)	0.64 [0.38-0.95]	0.39 [0.28-0.71]	0.004*
Cardiac magnetic resonance			
RVEDV index, ml/m ²	82 ± 20	76 ± 19	0.003
RVESV index, ml/m ²	54 ± 19	42 ± 17	< 0.001
Stroke volume index, ml/m ²	28 ± 9	34 ± 9	< 0.001
RVEF, %	36 ± 11	47 ± 11	< 0.001
RV mass index, g/m ²	50 ± 15	42 ± 12	< 0.001
RA max volume index, ml/m ²	74 [64-89]	67 [56-79]	0.002*
RA passive emptying, ml	22.9 ± 9.1	21.1 ± 9.9	0.13
RA active emptying, ml	40.0 ± 11.4	35.9 ± 12.9	0.009
RV passive filling, ml	34.1 ± 19.1	37.9 ± 21.2	0.10
RV active filling, ml	19.7 ± 15.5	27.2 ± 14.9	0.002
Vena cava backflow, ml	20.1 ± 15.5	8.0 ± 17.1	<0.001

Treatment modalities consisted of mono-, double- or triple therapy or calcium channel blocker. PAH indicates pulmonary arterial hypertension; ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase-5 inhibitor; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; mRAP, mean right atrial pressure; SvO₂, mixed venous oxygen saturation; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular endsystolic volume; RVEF, right ventricular ejection fraction; RV, right ventricular.

*paired t test after logarithmic transformation

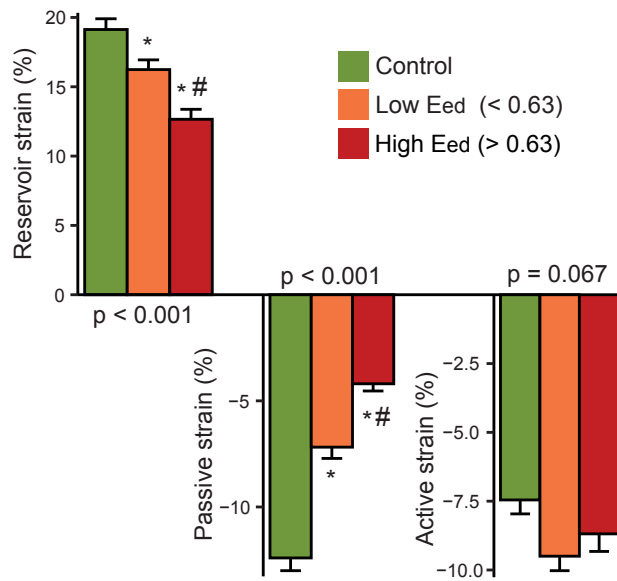


Supplemental figure S1. Flowchart of patient selection PAH indicates pulmonary arterial hypertension; RHC, right heart catheterization; CMR, cardiac magnetic resonance imaging; FU, follow-up; RV, right ventricular; Eed, end-diastolic elastance.

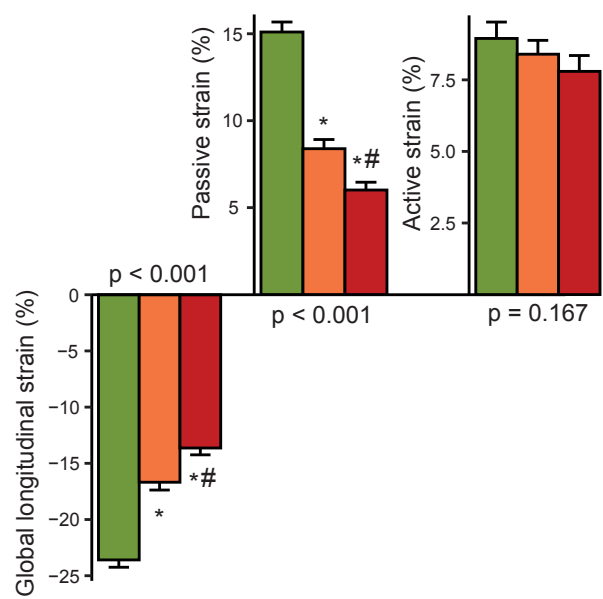


Supplemental figure S2. Correlations of RA volume determined on the four-chamber view or transverse stack slices
 RA volumes were lower when determined on the four-chamber view, but correlated excellent with the volumes determined on a stack of slices. RA indicates right atrium; 4CH, four-chamber

A) Right atrial strain



B) Right ventricular strain



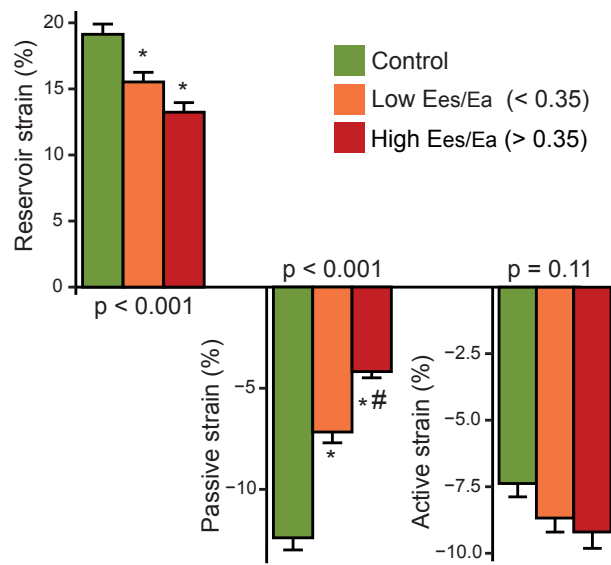
Supplemental figure S3. Quantification of RA and RV strain in the three cardiac phases

A) RA strain (mean \pm SEM) divided in three phases. B) RV strain (mean \pm SEM) divided in three phases. p values represent ANOVA test. RA indicates right atrial; RV, right ventricular; ANOVA, analysis of variance; Eed, end-diastolic elastance.

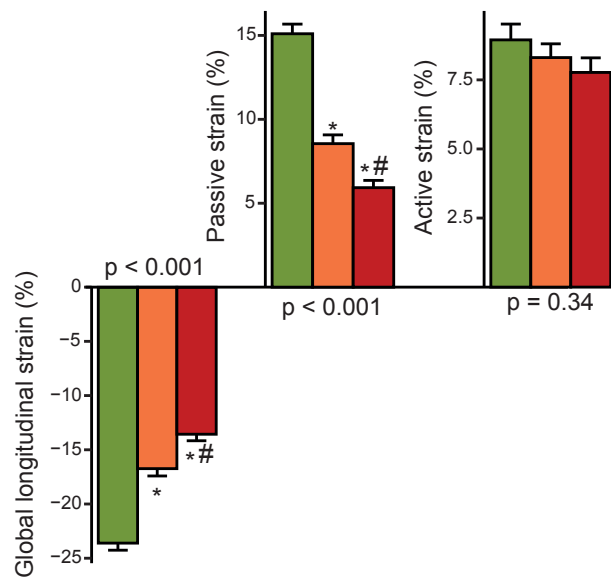
*p < 0.05 vs control

†p < 0.05 vs low Eed

A) Right atrial strain



B) Right ventricular strain

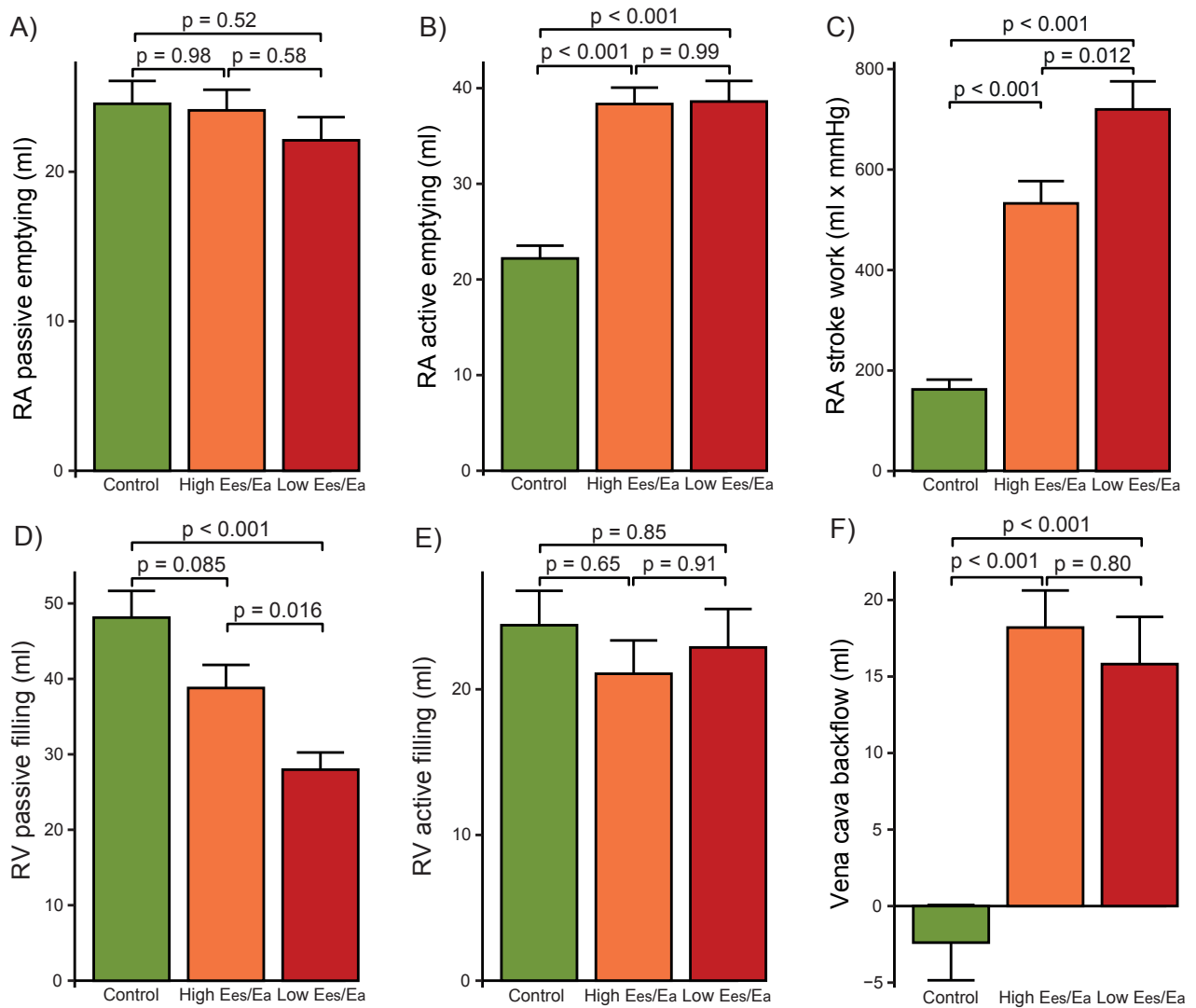


Supplemental figure S4. RA and RV strain in patients with low vs high Ees/Ea

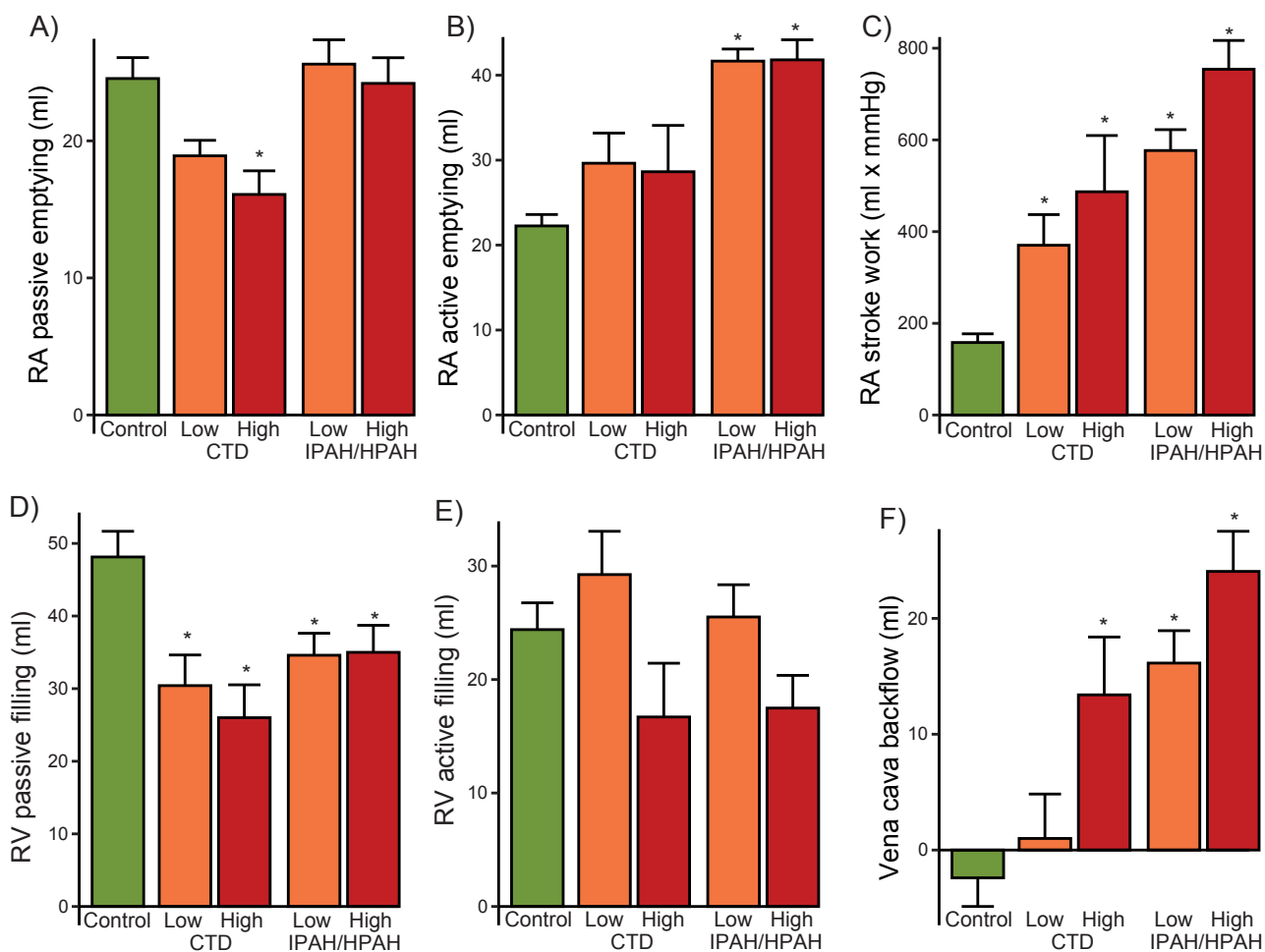
A) RA strain (mean \pm SEM) divided in three phases. B) RV strain (mean \pm SEM) divided in three phases. p values represent ANOVA test. RA indicates right atrial; RV, right ventricular; ANOVA, analysis of variance; Ees, end-systolic elastance; Ea, arterial elastance.

*p < 0.05 vs control

†p < 0.05 vs low Ees/Ea



Supplemental figure S5. RA emptying, RV filling and vena cava backflow in patients with low vs high Ees/Ea
 Data are presented as mean \pm SEM. p-values were calculated with Tukey's post-hoc analysis and family-wise correction for multiple testing. Patients were divided based on the median Ees/Ea (0.35) in a low and high Ees/Ea group. A) RA passive emptying is similar in all groups. B) RA active emptying is much higher in all patients. C) RA stroke work was estimated by multiplying RA active emptying with the end-diastolic pressure. D) RV passive filling is strongly reduced in all patients. E) RV active filling does not differ between patients with low and high Ees/Ea. F) Vena cava backflow represents the difference between RA active emptying and RV active filling. RA indicates right atrial; RV, right ventricular; Ees, end-systolic elastance; Ea, arterial elastance.



Supplemental figure S6. Comparison of RA emptying, RV filling and backflow in idiopathic/hereditary PAH and CTD-PAH with low or high Eed

RV active filling and vena cava backflow are lower in CTD-PAH patients, but show the same distribution with high vena cava backflow in high Eed patients. RA indicates right atrial; CTD, connective tissue disease; PAH, pulmonary arterial hypertension; RV, right ventricular

* $p < 0.05$ vs control