

**Supplemental Table 1.** Baseline characteristics of patients with HFrEF and controls.

	<b>HFrEF (N=148)</b>	<b>Control (N=36)</b>	<b>p-value</b>
<b>Clinical characteristics</b>			
Age, years	54 ± 12	54 ± 10	0.923
Male, n (%)	127 (84)	22 (61)	0.004
Body mass index, kg/m <sup>2</sup>	27.4 ± 4.5	28.3 ± 4.8	0.282
NYHA class, n (%): I-II; III-IV	34 (23); 114 (77)	NA	NA
Ischemic HF aetiology, n (%)	65 (44)	NA	NA
Diabetes mellitus, n (%)	50 (33)	3 (8)	0.002
Ischemic heart disease, n (%)	69 (46)	4 (11)	0.002
Haemoglobin, mg/L	137.0 ± 18.3	139.1 ± 17.3	0.525
BNP, ng/L	1019 [509; 1824]	29 [9; 46]	<0.001
<b>Echocardiography*</b>			
LV end-diastolic diameter, mm	69.7 ± 8.5	46.7 ± 4.1	<0.001
LV mass index, gr/m <sup>2</sup>	128.5 ± 31.7	75.9 ± 14.2	<0.001
LV ejection fraction, %	22.0 ± 6.7	60.0 ± 5.0	<0.001
Mitral regurgitation, n (%): 0-2 grade; 3-4 grade	72 (48); 78 (52)	36 (100); 0 (0)	<0.001
Tricuspid regurgitation, n (%): 0-2 grade; 3-4 grade	98 (65); 52 (35)	34 (97); 1 (3)	<0.001
Right ventricular basal dimensions, mm	45.0 ± 3.4	36.0 ± 4.2	<0.001
Tricuspid annular plane systolic excursion, mm	15.2 ± 4.2	23.8 ± 4.8	<0.001
<b>Electrocardiography</b>			
Heart rate, bpm	80 ± 16	68 ± 12	<0.001
Atrial rhythm, n (%): Sinus; Paced; AFib or AFlu	128 (85); 3 (2); 19 (13)	36 (0); 0 (0); 0 (0)	<0.001
QRS morphology, n (%): LBBB; RBBB; normal; other alterations*	31 (21); 13 (9); 36 (24); 68 (45)	1 (3); 2 (5); 30 (83); 3 (8)	<0.001
QRS duration, ms	120.4 ± 24.8	93.2 ± 18.3	<0.001
<b>Therapy</b>			
Furosemide, n (%)	143 (97)	4 (12)	<0.001
ACE, ARB or ARNI, n (%)	103 (70)	13 (36)	<0.001
MRA, n (%)	128 (86)	4 (11)	<0.001
Betablocker, n (%)	124 (84)	9 (25)	<0.001
Devices, n (%): ICD; CRT; none	111 (75); 12 (8); 25 (17)	NA	NA

\*Mitral and tricuspid regurgitation were assessed semiquantitatively and reported using a 4-stage grading (i.e., 0) none-trace; 1) mild; 2) moderate; 3) severe).

**Abbreviations:** ACE – Angiotensin Converting Enzyme Inhibitor; AFlu – Atrial Flutter; AFib – Atrial Fibrillation; ARB – Angiotensin Receptor Blocker; ARNI – Angiotensin Receptor Neprilysin Inhibitor; BNP – Brain Natriuretic Peptide; CRT – Cardiac Resynchronization Therapy; HFrEF – Heart Failure with Reduced Ejection Fraction; ICD – Implantable Cardioverter-Defibrillator; LBBB – Left Bundle Branch Block; MRA – Mineralocorticoid Receptor Antagonist; NA – Not Applicable; NYHA – New York Heart Association; RBBB – Right Bundle Branch Block. \*Other alterations include: left anterior fascicular block, left posterior fascicular block, incomplete LBBB and nonspecific intraventricular conduction delay.

**Supplemental Table 2.** Imaging and hemodynamic data in patients with HFrEF and controls

	<b>HF patients (N=148)</b>	<b>Controls (N=36)</b>	<b>p-value</b>
<b>GSPECT</b>			
RV phase SD, %	11.2 ± 4.9	7.6 ± 2.5	<0.001
RV end-diastolic volume – mL	256.4 ± 97.9	204.4 ± 61.1	<0.001
RV end-diastolic volume index – mL/m <sup>2</sup>	138.0 ± 47.9	103.1 ± 24.3	<0.001
RV end-systolic volume – mL	165.5 ± 82.1	96.5 ± 32.1	<0.001
RV end-systolic volume index – mL/m <sup>2</sup>	85.8 ± 41.9	48.1 ± 14.0	<0.001
RV ejection fraction - %	37.7 ± 14.9	53.1 ± 5.4	<0.001
<b>Right heart catheterization</b>			
RA mean pressure - mmHg	9.6 ± 5.8	5.0 ± 2.9	<0.001
RV systolic elastance (Ees) - mmHg/mL	0.32 [0.23; 0.49]	0.32 [0.23; 0.47]	0.177
RV diastolic compliance - mL/mmHg	0.03 [0.02; 0.05]	0.04 [0.03; 0.06]	0.003
Cardiac output, L/m	3.8 ± 0.9	5.6 ± 1.4	<0.001
Stroke volume, mL	48.8 ± 14.7	76.9 ± 23.8	<0.001
PA mean pressure - mmHg	34.3 ± 10.8	16.3 ± 6.5	<0.001
PA compliance - mL/mmHg	1.8 [2.3; 2.6]	4.8 [3.5; 6.5]	<0.001
PA elastance (E <sub>apA</sub> ) - mmHg/mL	1.00 [0.73; 1.53]	0.36 [0.26; 0.44]	<0.001
PA wedge pressure - mmHg	22.8 ± 8.5	8.2 ± 4.2	<0.001
PVR - WU	2.9 [1.9; 4.2]	1.4 [1.0; 2.1]	<0.001
RV ventricular-arterial coupling ratio	0.29 [0.21; 0.51]	0.92 [0.61; 1.37]	<0.001
Systolic blood pressure - mmHg	109.4 ± 16.2	128.5 ± 20.9	<0.001
Diastolic blood pressure - mmHg	75.0 ± 10.0	77.1 ± 9.9	0.258

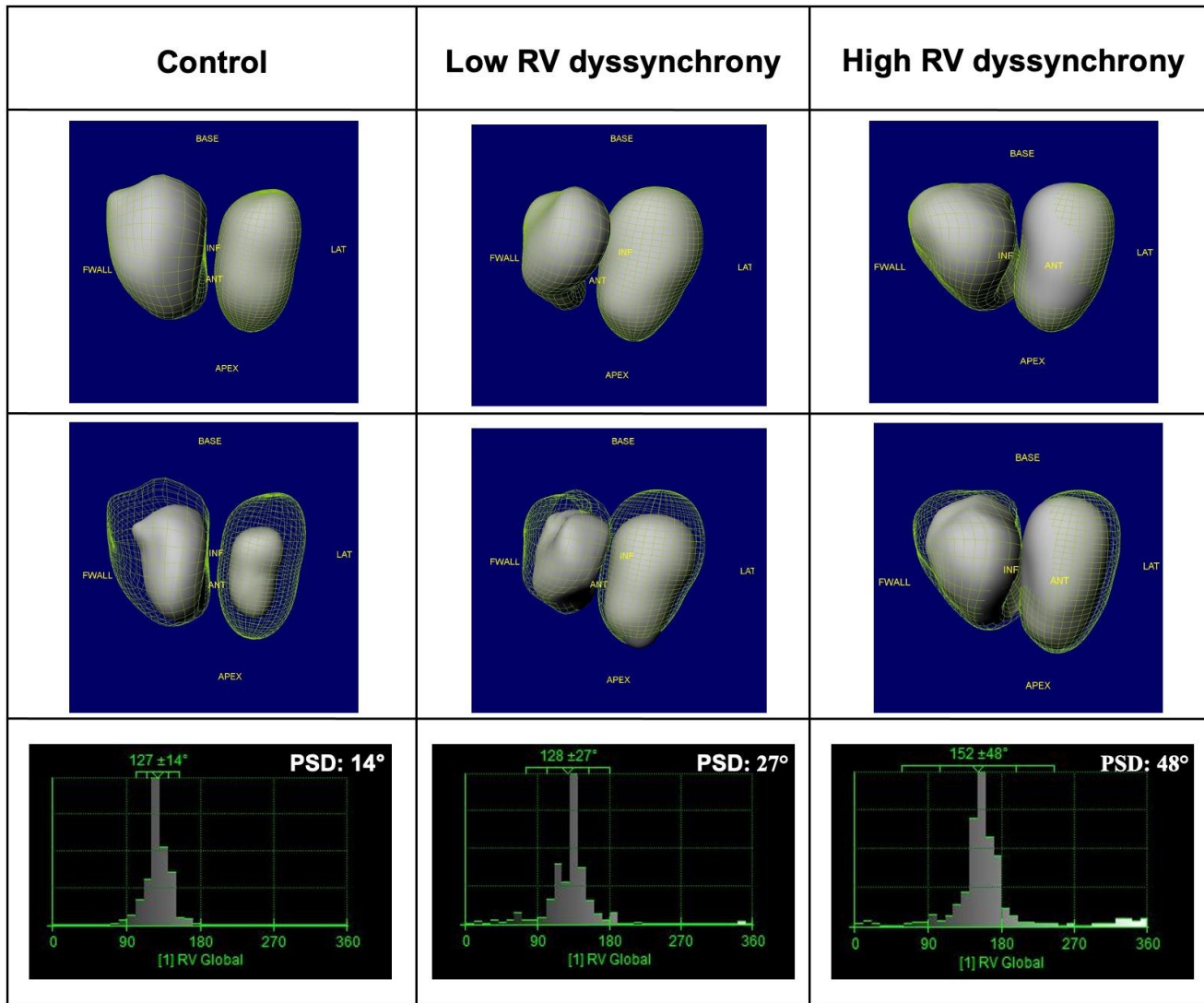
**Abbreviations:** GSPECT - Gated Single-Photon Emission Computed Tomography; HFrEF – Heart Failure with Reduced Ejection Fraction; PA – Pulmonary Artery; PVR – Pulmonary Vascular Resistance; RA – Right Atrial; RV – Right Ventricular; SD – Standard deviation; SVR – Systemic Vascular Resistance; WU - Wood Units

**Supplemental Table 3** Effect of afterload reduction (sildenafil) and preload increase (leg rise) on right ventricular dyssynchrony, hemodynamics and cardiac volumes derived from SPECT

	<b>Baseline</b>	<b>Afterload reduction (N=15)</b>	<b>p-value</b>	<b>Baseline</b>	<b>Preload modulation (N=135)</b>	<b>p-value</b>
RV dyssynchrony, degrees	44.9 ± 19.2	29.6 ± 13.9	0.004	40.5 ± 17.6	37.7 ± 16.4	0.080
<b><i>Right heart catheterization</i></b>						
RA mean pressure, mmHg	7.9 ± 3.5	4.3 ± 2.5	<0.001	9.3 ± 5.7	11.7 ± 6.4	<0.001
RV end-diastolic pressure, mmHg	12.0 ± 4.3	6.3 ± 3.7	<0.001	11.5 ± 6.1	14.4 ± 6.0	<0.001
PA mean pressure, mmHg	44.0 ± 8.6	31.2 ± 9.9	<0.001	33.6 ± 10.4	38.5 ± 9.7	<0.001
PA wedge pressure mean, mmHg	25.3 ± 5.9	19.6 ± 8.7	0.005	22.3 ± 8.1	26.3 ± 7.8	<0.001
PA elastance, mmHg/mL	1.7 [1.1; 1.9]	0.9 [0.6; 1.1]	<0.001	1.0 [0.7; 1.5]	1.2 [0.8; 1.6]	<0.001
RV systolic elastance (Ees) - mmHg/mL	0.48 [0.29; 0.79]	0.50 [0.25; 0.90]	0.889	0.31 [0.22; 0.49]	0.31 [0.22; 0.49]	0.489
RV ventricular-arterial coupling ratio	0.43 [0.15; 0.54]	0.57 [0.34; 0.90]	0.002	0.29 [0.20; 0.51]	0.28 [0.17; 0.47]	0.001
Pulmonary vascular resistance - WU	4.9 [4.3; 6.6]	2.7 [1.8; 3.8]	<0.001	2.8 [1.8; 3.9]	3.1 [2.1; 4.4]	0.031
Cardiac output, L/min	3.7 ± 0.8	4.4 ± 0.8	0.003	3.8 ± 0.9	3.7 ± 0.9	0.411
<b><i>SPECT-derived data</i></b>						
RV end-diastolic volume, mL	256.1 ± 77.7	214.3 ± 75.4	0.002	278.2 ± 98.4	289.8 ± 94.1	0.001
RV end-systolic volume, mL	152.7 ± 75.5	107.1 ± 66.1	<0.001	173.1 ± 86.9	178.9 ± 84.0	0.023
RV ejection fraction, %	43.1 ± 12.6	54.1 ± 14.1	<0.001	40.8 ± 14.9	41.0 ± 14.0	0.867

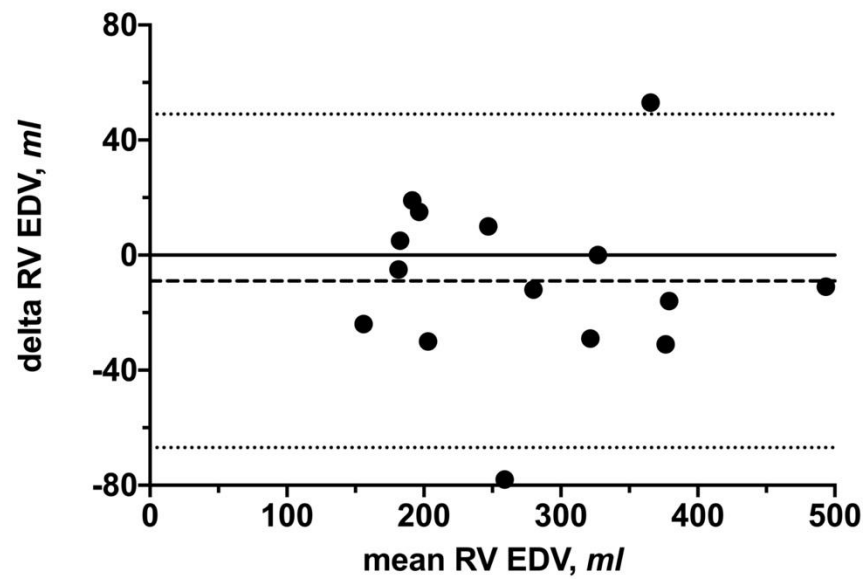
**Abbreviations:** PA – Pulmonary Artery; PVR – Pulmonary Vascular Resistance; RA – Right Atrial; RV – Right Ventricular; WU - Wood Units.

Supplemental Figure 1

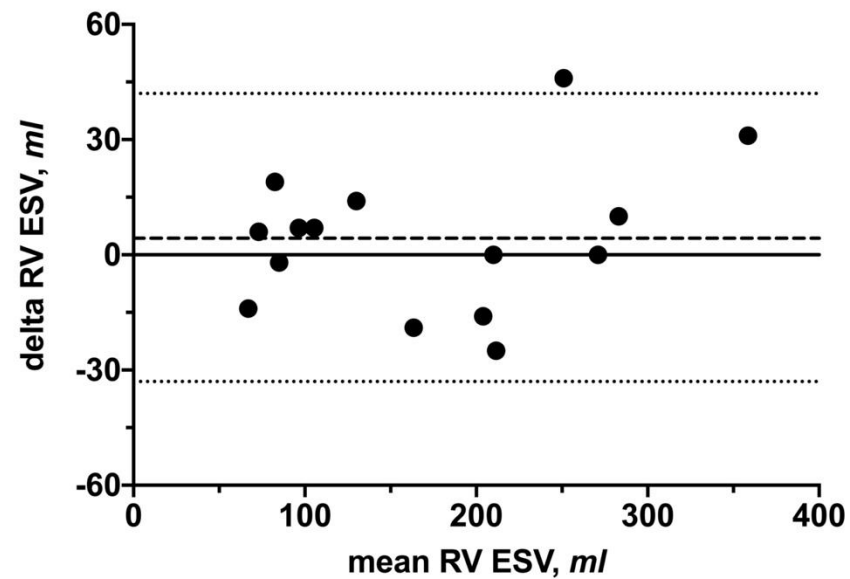


Supplemental Figure 2

**A**

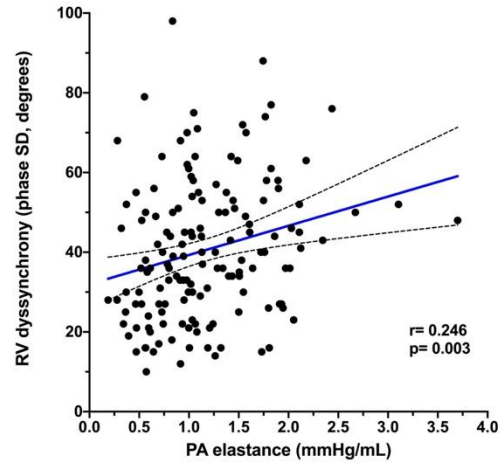


**B**

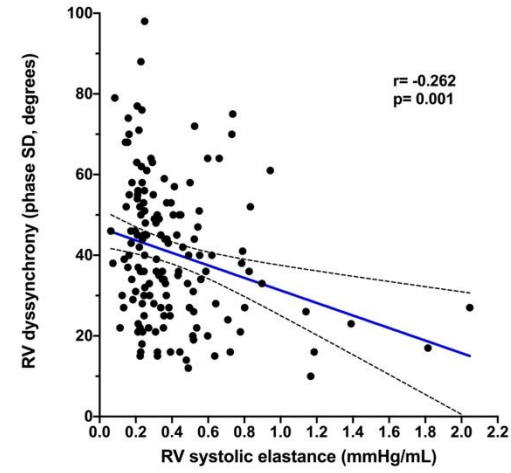


### Supplemental Figure 3

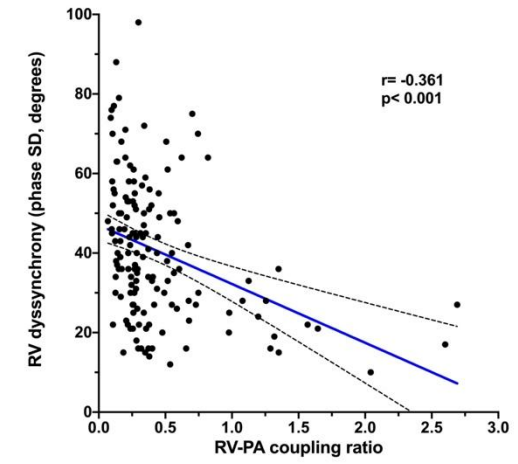
**A**



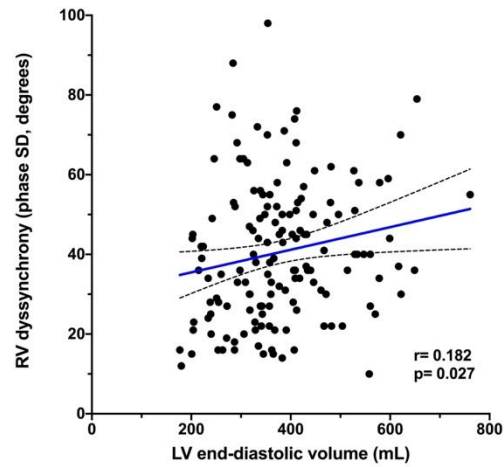
**B**



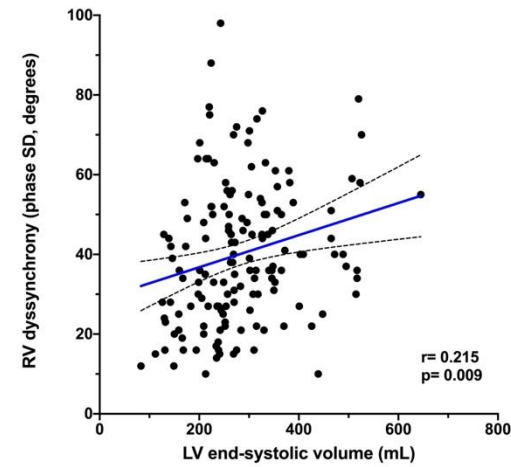
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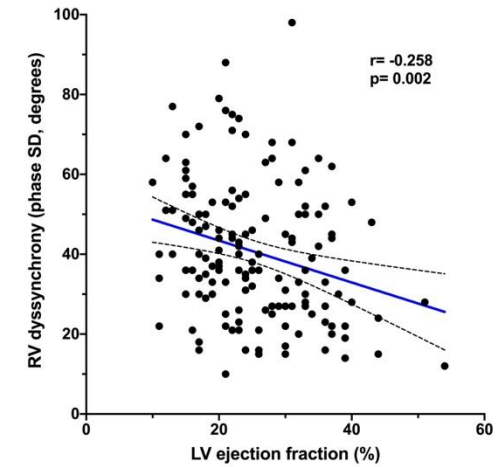
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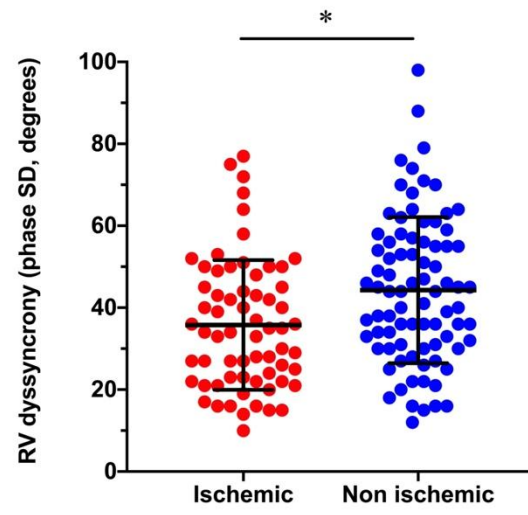
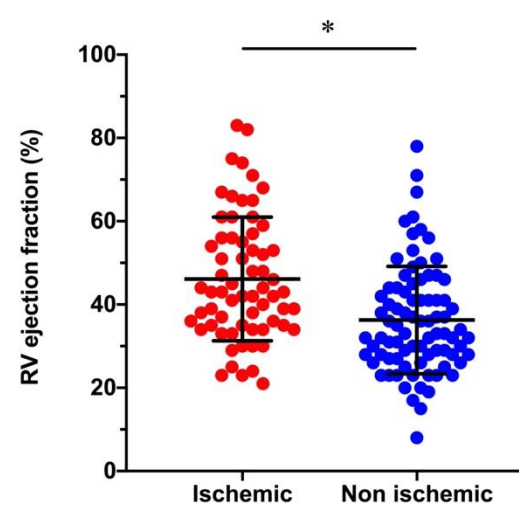
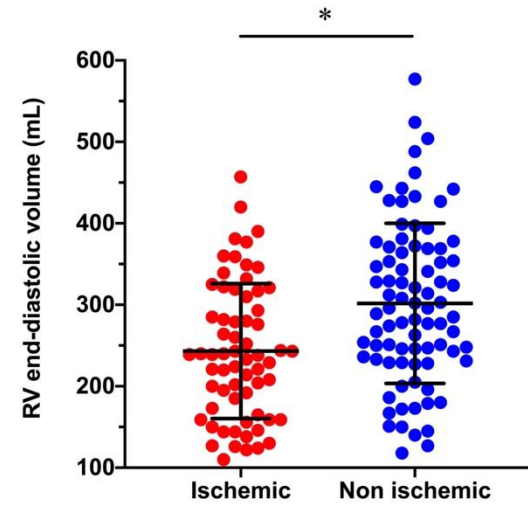
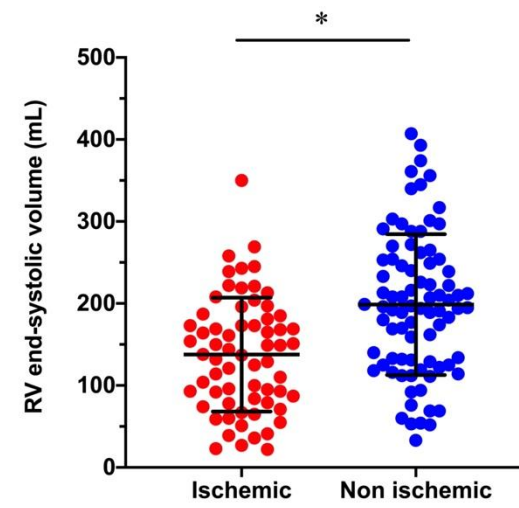
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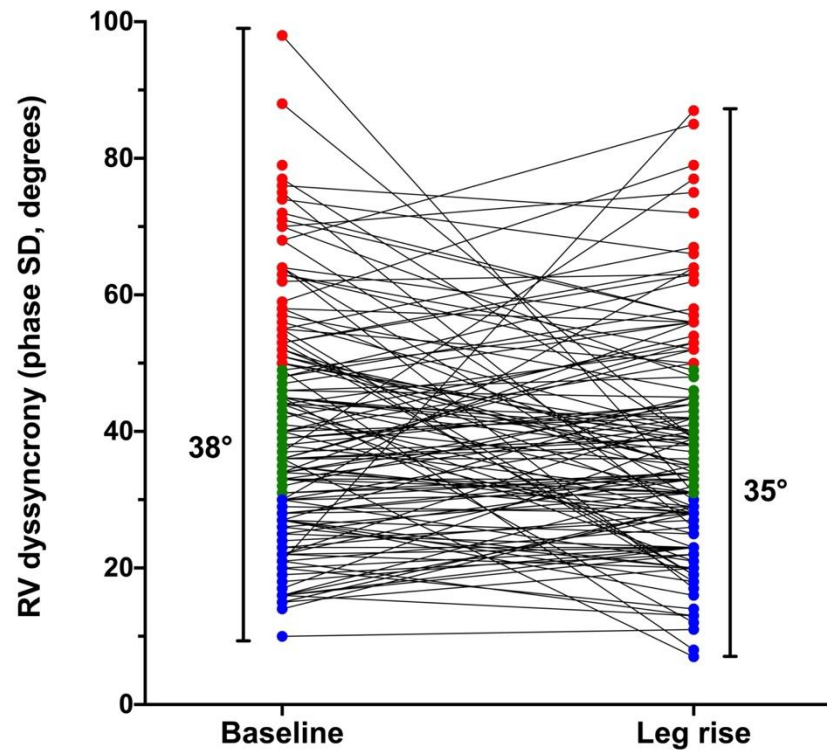


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**A****B****C****D****Supplemental Figure 5**

**A****B**