Supplemental Table 1 – 2D echography, Doppler, tissue Doppler- and Speckle tracking-derived parameters of systolic and diastolic function at rest and during the cardiopulmonary test.

	Empagliflozin (n = 22)			**Sitagliptin (n = 22)**				
	Baseline	Follow-up	*p value*	Baseline	Follow-up	*p value*	*p value B*	*p value T*
SV rest (mL)	74.8 ± 15.9	73.5 ± 17.0	*ns*	65.7 ± 15.7	74.6 ± 22.3	*ns*	*ns*	*ns*
SV 4 min	94.1 ± 22.2	92.5 ± 22.9	*ns*	81.5 ± 18.2	88.6 ± 23.7	*ns*	*ns*	*ns*
SV AT	100.7 ± 24.1	97.6 ± 20.8	*ns*	93.8 ± 22.0	96.7 ± 25.9	*ns*	*ns*	*ns*
SV peak (mL)	109.1 ± 24.7	106.9 ± 25.2	*ns*	101.6 ± 26.9	104.8 ± 27.8	*ns*	*ns*	*ns*
CO rest, L/min	5.7 ± 1.6	5.7 ± 1.2	*ns*	5.2 ± 1.2	6.0 ± 2.0	*ns*	*ns*	*ns*
CO at 4 min, L/min	8.8 ± 2.1	8.5 ± 1.9	*ns*	8.1 ± 2.2	8.6 ± 2.4	*ns*	*ns*	*ns*
CO at AT, L/min	11.9 ± 3.7	11.3 ± 3.1	*ns*	11.6 ± 3.0	11.6 ± 3.9	*ns*	*ns*	*ns*
CO peak, L/min	14.3 ± 4.2	14.2 ± 3.8	*ns*	13.6 ± 4.3	14.0 ± 4.4	*ns*	*ns*	*ns*
LVEF rest (%)	60.5 ± 3.6	60.6 ± 4.1	*ns*	58.1 ± 5.1	60.7 ± 5.7	*ns*	*ns*	*ns*
LVEF at 4 min (%)	64.2 ± 3.7	63.8 ± 4.1	*ns*	61.0 ± 5.6	64.0 ± 5.6	*ns*	*ns*	*ns*
LVEF at AT (%)	66.9 ± 3.8	66.4 ± 5.2	*ns*	63.8 ± 6.1	67.0 ± 5.7	*ns*	*ns*	*ns*
LVEF peak (%)	69.1 ± 4.7	68.6 ± 5.2	*ns*	66.3 ± 6.9	70.4 ± 5.8	*ns*	*ns*	*ns*
ΔLVEF	8.6 ± 3.1	7.9 ± 4.1	*ns*	8.2 ± 4.0	9.4 ± 2.6	*ns*	*ns*	*ns*
Contractility res (n, %)	15 (52)	14 (48)	*ns*	14 (48)	18 (56)	*ns*	*ns*	*ns*
S' mean rest (cm/sec)	8.8. ± 1.7	9.0 ± 1.9	*ns*	9.8 ± 2.0	9.7 ± 1.7	*ns*	*ns*	*ns*
S' mean 4 min	10.9 ± 1.8	10.9 ± 2.0	*ns*	11.5 ± 2.1	10.7 ± 1.4	*ns*	*ns*	*ns*
S' mean AT	12.7 ± 2.3	13.0 ± 2.6	*ns*	13.4 ± 2.4	12.6 ± 1.5	*ns*	*ns*	*ns*
S' mean peak (cm/sec)	13.9 ± 2.9	14.1 ± 2.9	*ns*	14.5 ± 2.5	14.4 ± 2.2	*ns*	*ns*	*ns*
ΔS' mean	5.2 ± 2.3	5.2 ± 2.2	*ns*	4.7 ± 1.7	4.7 ± 1.4	*ns*	*ns*	*ns*
E/A ratio rest	0.94 ± 0.26	0.92 ± 0.18	*ns*	0.86 ± 0.23	0.84 ± 0.22	*ns*	*ns*	*ns*
E/e' rest (cm/sec)	8.3 ± 2.2	7.7 ± 2.0	*ns*	8.7 ± 2.7	7.8 ± 2.3	*ns*	*ns*	*ns*
E/e' 4 min	9.2 ± 1.9	7.9 ± 2.0	*ns*	9.3 ± 2.2	8.9 ± 2.1	*ns*	*ns*	*ns*
E/e' AT	8.5 ± 1.5	8.2 ± 1.9	*ns*	8.9 ± 1.9	8.6 ± 1.5	*ns*	*ns*	*ns*
E/e' peak (cm/sec)	8.7 ± 1.8	8.2 ± 2.3	*ns*	9.0 ± 2.4	8.6 ± 1.5	*ns*	*ns*	*ns*
Elastance rest	6.2 ± 1.4	5.7 ± 1.6	*ns*	6.0 ± 1.4	6.0 ± 2.0	*ns*	*ns*	*ns*
Elastance peak	12.5 ± 3.7	11.8 ± 3.7	*ns*	12.0 ± 3.6	12.6 ± 4.6	*ns*	*ns*	*ns*
Δ elastance	6.3 ± 2.7	6.1 ± 2.5	*ns*	5.9 ± 2.6	6.6 ± 3.4	*ns*	*ns*	*ns*
TAPSE rest	20.9 ± 2.9	20.6 ± 2.6	*ns*	21.3 ± 2.7	20.1 ± 2.6	*ns*	*ns*	*ns*
TAPSE 4 min	24.5 ± 3.6	24.1 ± 3.0	*ns*	25.8 ± 3.5	22.3 ± 3.2	*ns*	*ns*	*ns*
TAPSE AT	26.7 ± 3.1	26.7 ± 3.3	*ns*	28.0 ± 3.8	24.5 ± 3.5	*ns*	*ns*	*ns*
TAPSE peak	28.5 ± 3.6	28.2 ± 3.2	*ns*	30.1 ± 3.6	27.1 ± 3.8	*ns*	*ns*	*ns*
sPAP rest	24.2 ± 4.3	24.0 ± 3.0	*ns*	23.4 ± 3.9	23.1 ± 2.5	*ns*	*ns*	*ns*
sPAP 4 min	29.2 ± 7.2	27.2 ± 6.2	*ns*	24.5 ± 4.3	25.2 ± 5.6	*ns*	*ns*	*ns*
sPAP AT	34.1 ± 11.9	32.8 ± 8.1	*ns*	30.6 ± 6.2	30.5 ± 8.0	*ns*	*ns*	*ns*
sPAP peak	35.0 ± 12.1	33.8 ± 8.2	*ns*	31.7 ± 7.2	32.0 ± 10.6	*ns*	*ns*	*ns*
CPO rest (W)	1.31 ± 0.39	1.23 ± 0.33	*ns*	1.19 ± 1.36	1.26 ± 0.56	*ns*	*ns*	*ns*
CPO 4 min (W)	2.34 ± 0.73	2.10 ± 0.59	*ns*	2.19 ± 0.71	2.17 ± 0.78	*ns*	*ns*	*ns*
CPO AT (W)	3.71 ± 1.42	3.36 ± 1.13	*ns*	3.66 ± 1.22	3.59 ± 1.67	*ns*	*ns*	*ns*
CPO peak (W)	4.72 ± 1.76	4.80 ± 1.63	*ns*	4.55 ± 1.77	4.71 ± 1.95	*ns*	*ns*	*ns*
CPOM rest (W/100g)	0.77 ± 0.29	0.71 ± 0.26	*ns*	0.68 ± 0.19	0.70 ± 0.27	*ns*	*ns*	*ns*
CPOM 4 min (W/100g)	1.35 ± 0.56	1.19 ± 0.42	*ns*	1.25 ± 0.41	1.22 ± 0.37	*ns*	*ns*	*ns*
CPOM AT (W/100g)	2.11 ± 0.83	1.93 ± 0.76	*ns*	2.08 ± 0.66	2.07 ± 0.89	*ns*	*ns*	*ns*
CPOM peak (W/100g)	2.73 ± 1.03	2.78 ± 1.08	*ns*	2.57 ± 0.89	2.65 ± 1.04	*ns*	*ns*	*ns*
TAPSE/sPAP rest (mm/mmHg)	0.88 ± 0.17	0.86 ± 0.12	*ns*	0.93 ± 0.14	0.88 ± 0.13	*ns*	*ns*	*ns*

TAPSE/sPAP 4 min (mm/mmHg)	0.87 ± 0.17	0.93 ± 0.24	*ns*	1.08 ± 0.22	0.91 ± 0.20	*ns*	*ns*	*ns*
TAPSE/sPAP AT (mm/mmHg)	0.85 ± 0.22	0.86 ± 0.22	*ns*	0.95 ± 0.21	0.84 ± 0.18	*ns*	*ns*	*ns*
TAPSE/sPAP peak (mm/mmHg)	0.88 ± 0.23	0.88 ± 0.25	*ns*	0.99 ± 0.22	0.90 ± 0.20	*ns*	*ns*	*ns*
TAPSE/CO rest (mm/L/min)	3.97 ± 1.37	3.76 ± 0.90	*ns*	4.32 ± 1.19	3.73 ± 1.24	*ns*	*ns*	*ns*
TAPSE/CO 4 min (mm/L/min)	2.96 ± 0.94	2.97 ± 0.77	*ns*	3.42 ± 1.03	2.78 ± 0.86	*ns*	*ns*	*ns*
TAPSE/CO AT (mm/L/min)	2.46 ± 0.85	2.55 ± 0.79	*ns*	2.57 ± 0.70	2.30 ± 0.72	*ns*	*ns*	*ns*
TAPSE/CO peak (mm/L/min)	2.17 ± 0.71	2.13 ± 0.65	*ns*	2.41 ± 0.79	2.10 ± 0.66	*ns*	*ns*	*ns*
LA reservoir strain (%)	36.7 ± 5.0	34.3 ± 38.8	*ns*	38.8 ± 2.6	38.8 ± 2.5	*ns*	*ns*	*ns*
LA reservoir/E/e' (%)	4.60 ± 1.03	4.59 ± 1.45	*ns*	4.97 ± 1.48	5.33 ± 1.52	*ns*	*ns*	*ns*
LA booster strain (%)	16.63 ± 2.81	14.39 ± 4.74	*ns*	17.75 ± 2.29	17.20 ± 0.83	*ns*	*ns*	*ns*
LA conduit strain (%)	20.05 ± 4.03	19.86 ± 6.32	*ns*	21.00 ± 3.48	21.60 ± 2.56	*ns*	*ns*	*ns*
*SVR rest (dyne*cm/sec)*	1,551 ± 442	1,404 ± 258	*ns*	1,640 ± 362	1,475 ± 404	*ns*	*ns*	*ns*
*SVR 4 min (dyne*cm/sec)*	1,105 ± 213	1,075 ± 209	*ns*	1,283 ± 388	1,116 ± 301	*ns*	*ns*	*ns*
*SVR AT (dyne*cm/sec)*	983 ± 249	998 ± 238	*ns*	1,034 ± 306	1,011 ± 275	*ns*	*ns*	*ns*
*SVR peak (dyne*cm/sec)*	873 ± 206	880 ± 185	*ns*	938 ± 273	923 ± 283	*ns*	*ns*	*ns*

Methods.

Data collected at each stage (rest, 4 minutes, anaerobic threshold, peak exercise) included: left ventricle (LV) and atrial (LA) volumes, stroke volume (SV), peak E-wave and A-wave velocities, tissue Doppler imaging (TDI)-derived S' and e' at the septal and lateral mitral annulus, tricuspid regurgitation velocity, tricuspid annular plane systolic excursion (TAPSE) according to latest guidelines [1]. SV was measured by multiplying the LV outflow tract area at rest by the LV outflow tract (LVOT) velocity-time integral measured by pulsed-wave Doppler during each activity level. We used the simplified Bernoulli equation to measure systolic pulmonary artery pressure (PAPs) from the peak tricuspid regurgitation jet, adding the right atrial pressure estimated from imaging of the inferior vena cava at rest. LA reservoir strain was calculated at rest, using the same software, as the average of strain in six segments in the four-chamber and two-chamber. LA strain (booster, conduit) was measured using P wave and QRS as the fiducial point. We excluded poorly tracked segments and patients were not analysed if more than one segment per view was deemed unacceptable. STE-derived measurements were reported as the average of three beats. SV was calculated by multiplying the LV outflow tract area at rest by the LV outflow tract velocity-time integral measured by pulsed-wave Doppler during each activity level, as previously validated [2]. Cardiac output was calculated as the multiplication of SV and heart rate. Images were acquired concurrently with breath-by-breath gas exchange measurements at both baseline and peak of exercise. All measurements were reported as the average of three beats. Cardiac power output (CPO) was measured with the following formula: $CPO = 0.222 * CP\ \left[\frac{L}{min}\right] * mean\ BP\ [mmHg]$, while cardiac power output per mass (CPOM) was calculated as CPO divided by LV mass [g] [3]. TAPSE/sPAP and TAPSE/CO were calculated as ratios between these variables to assess right ventricle ventriculo-arterial coupling.

Abbreviations.

CO, cardiac output; CPO, cardiac power output; CPOM, cardiac power output per mass; e', tissue Doppler-derived early diastolic velocity of the mitral anulus; E/A ratio, early-to-atrial filling wave velocity ratio; EDV, end-diastolic volume; LA, left atrium; LVEF, left ventricular ejection fraction; S', tissue Doppler-derived systolic velocity of the mitral anulus; sPAP, systolic pulmonary artery pressure; SV, stroke volume; SVR, systemic vascular resistance; TAPSE, tricuspid anulus systolic excursion; Δ, rest-to-peak exercise delta.

References

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