STATISTICAL ANALYSIS

NON-PARAMETRIC TESTS

Intracoronary delivery of extracellular vesicles from human cardiac-derived progenitor cells reduces infarct size and improves cardiac function in porcine acute myocardial infarction

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List of abbreviations
LVM: Left Ventricular Mass; LVEDV: Left Ventricular End-Diastolic Volume; LVESV: Left Ventricular End-Systolic Volume; LVSV: Left Ventricular Stroke Volume; LVEF: Left Ventricular Ejection Fraction; CO: Cardiac Output; RVEDV: Right Ventricular End-Diastolic Volume; RVESV: Right Ventricular End-Systolic Volume; RVSV: Right Ventricular Stroke Volume; RVEF: Right Ventricular Ejection Fraction; IS: Infarct Size; IV: Infarct Volume.

2. IM-sEV and IC-sEV delivery study

2.1 Comparison of treatments at each time-point

2.1.1 Evaluation at Baseline: Ctrl vs. IC-sEV vs. IM-sEV

Baseline Evaluation	Ctrl [n=5]	IC [n=4]	IM [n=5]	Overall *P*-value	Pairwise comparisons		
					Ctrl *vs.* IC	Ctrl *vs.* IM	IC vs. IM
Height [cm]	83 [79; 87]	76 [71; 80]	75 [72; 78]	**0.038**	0.140	0.055	1.000
Weight [Kg]	32 [31; 35]	34 [31; 35]	31 [30; 36]	0.851	-	-	-
Heart Rate [bpm]	80 [68; 95]	97 [91; 103]	89 [76; 95]	0.170	-	-	-
R-R [ms]	753 [642; 882]	619 [582; 664]	676 [633; 791]	0.170	-	-	-
LVM [mL]	91.2 ± 6.91	83.0 ± 14.39	71.5 ± 10.65	**0.038**	1.000	**0.038**	0.282
LVM [g]	98.3 ± 9.25	87.9 ± 16.19	78.3 ± 13.01	0.097	-	-	-
LVEDV [mL]	78.3 ± 16.42	73.4 ± 14.23	73.9 ± 8.80	0.656	-	-	-
LVESV [mL]	34.0 ± 6.89	32.0 ± 6.82	31.6 ± 3.60	0.593	-	-	-
LVSV [mL]	44.2 ± 9.52	41.4 ± 7.64	42.3 ± 5.21	0.603	-	-	-
LVEF [%]	56.3 [55.6; 57.2]	56.8 [54.8; 57.9]	57.2 [56.9; 57.6]	0.413	-	-	-
CO [L/min]	3.6 ± 1.17	4.1 ± 0.97	3.6 ± 0.50	0.744	-	-	-
RVEDV [mL]	70.2 ± 10.58	70.6 ± 7.36	72.4 ± 9.90	0.946	-	-	-
RVESV [mL]	30.4 ± 4.63	31.4 ± 6.45	29.8 ± 5.63	0.762	-	-	-
RVSV [mL]	39.9 ± 6.79	39.2 ± 4.46	38.6 ± 10.10	0.941	-	-	-
RVEF [%]	56.7 ± 3.05	55.7 ± 6.54	56.1 ± 2.29	0.643	-	-	-

Data from IM-sEV and IC-sEV delivery study have been analyzed at baseline with Kruskal-Wallis (all variables). Groups were treated as independent samples.

2.1.2 Evaluation at 2/3 Days: Ctrl vs. IC-sEV vs. IM-sEV

2-3 Days Evaluation	Ctrl [n=5]	IC [n=4]	IM [n=5]	Overall *P*-value	Pairwise comparisons Ctrl *vs.* IC	Ctrl *vs.* IM	IC vs. IM
Height [cm]	83 [79; 87]	78 [72; 88]	77 [74; 80]	0.227	-	-	-
Weight [Kg]	33 [32; 38]	36 [32; 37]	32 [29; 36]	0.628	-	-	-
Heart Rate [bpm]	80 [65; 89]	89 [70; 93]	83 [51; 92]	0.606	-	-	-
R-R [ms]	754 [675; 919]	678 [647; 874]	721 [653; 1200]	0.606	-	-	-
LVM [mL]	104.9 ± 16.97	97.5 ± 26.97	82.0 ± 12.01	0.105	-	-	-
LVM [g]	110.1 ± 17.83	102.4 ± 28.36	86.1 ± 12.59	0.105	-	-	-
LVEDV [mL]	92.1 ± 5.28	79.8 ± 20.07	76.8 ± 8.64	0.143	-	-	-
LVESV [mL]	54.3 ± 9.01	46.3 ± 10.07	50.6 ± 5.47	0.418	-	-	-
LVSV [mL]	37.8 ± 8.99	33.5 ± 10.36	26.2 ± 3.25	0.105	-	-	-
LVEF [%]	44.4 [31.3; 49.2]	42.5 [37.6; 44.5]	34.3 [33.3; 34.8]	0.214	-	-	-
CO [L/min]	2.9 ± 0.40	2.8 ± 0.73	1.9 ± 0.50	**0.047**	1.000	**0.048**	0.456
RVEDV [mL]	74.1 ± 12.20	71.4 ± 3.15	74.8 ± 10.10	0.613	-	-	-
RVESV [mL]	40.1 ± 13.85	36.8 ± 2.45	54.6 ± 2.11	0.059	-	-	-
RVSV [mL]	32.0 ± 4.64	34.6 ± 3.56	20.2 ± 8.11	**0.021**	1.000	0.085	**0.034**
RVEF [%]	46.4 ± 11.16	48.5 ± 3.61	26.2 ± 8.01	**0.016**	1.000	**0.030**	0.059
IS [%]	28.3 ± 5.30	25.9 ± 12.27	23.5 ± 9.30	0.526	-	-	-
IV [mL]	25.5 ± 4.10	22.2 ± 10.52	17.3 ± 5.75	0.114	-	-	-

Data from IM-sEV and IC-sEV delivery study have been analyzed at 2-3 Days with Kruskal-Wallis test (all variables). Groups were treated as independent samples.

2.1.3 Evaluation at 1 Month: Ctrl vs. IC-sEV vs. IM-sEV

1 Month Evaluation	Ctrl [n=5]	IC [n=4]	IM [n=5]	Overall *P*-value	Pairwise comparisons Ctrl *vs.* IC	Ctrl *vs.* IM	IC vs. IM
Height [cm]	87 [83; 89]	89 [87; 91]	85 [83; 87]	0.120	-	-	-
Weight [Kg]	39 [36; 42]	41 [34; 42]	43 [39; 43]	0.433	-	-	-
Heart Rate [bpm]	86 [73; 106]	90 [76; 103]	92 [84; 99]	0.893	-	-	-
R-R [ms]	699 [565; 824]	670 [586; 788]	649 [605; 711]	0.893	-	-	-
LVM [mL]	95.0 ± 14.40	98.9 ± 19.01	89.1 ± 12.06	0.761	-	-	-
LVM [g]	99.7 ± 15.15	103.8 ± 20.01	93.6 ± 12.63	0.761	-	-	-
LVEDV [mL]	79.3 ± 7.63	85.9 ± 17.61	89.9 ± 11.97	0.392	-	-	-
LVESV [mL]	47.7 ± 8.16	44.9 ± 6.43	54.6 ± 9.16	0.231	-	-	-
LVSV [mL]	31.6 ± 5.13	40.9 ± 13.08	35.3 ± 7.12	0.553	-	-	-
LVEF [%]	43.6 [33.0; 45.3]	47.7 [39.4; 53.4]	39.6 [34.0; 44.5]	0.137	-	-	-
CO [L/min]	2.8 ± 0.22	3.7 ± 1.22	3.3 ± 0.92	0.273	-	-	-
RVEDV [mL]	76.0 ± 15.43	71.8 ± 13.22	72.0 ± 21.35	0.744	-	-	-
RVESV [mL]	45.3 ± 11.03	38.9 ± 4.89	47.8 ± 11.97	0.525	-	-	-
RVSV [mL]	30.7 ± 6.81	32.9 ± 9.21	24.2 ± 10.53	0.309	-	-	-
RVEF [%]	40.6 ± 6.61	45.4 ± 4.37	32.9 ± 5.60	**0.030**	0.783	0.336	**0.026**
IS [%]	29.3 ± 12.12	15.3 ± 3.28	20.0 ± 8.41	0.170	-	-	-
IV [mL]	29.1 ± 10.69	13.5 ± 2.48	17.6 ± 8.54	**0.045**	**0.047**	0.631	1.000

Data from IM-sEV and IC-sEV delivery study have been analyzed at 1 Month with Kruskal-Wallis test (all variables). Groups were treated as independent samples.

2.2 Comparison of time-points for each treatment

2.2.1 Paired evaluation of Ctrl group

Controls	Baseline [n=5]	2-3 Days [n=5]	1 Month [n=5]	Overall P-value	Pairwise comparisons		
					B vs. 2-3 D	B vs. 1 M	2-3 D vs. 1 M
Height [cm]	83 [79; 87]	83 [79; 87]	87 [83; 89]	0.165	-	-	-
Weight [Kg]	32 [31; 35]	33 [32; 38]	39 [36; 42]	**0.015**	1.000	**0.013**	0.173
Heart Rate [bpm]	80 [68; 95]	80 [65; 89]	86 [73; 106]	0.549	-	-	-
R-R [ms]	753 [642; 882]	754 [675; 919]	699 [565; 824]	0.549	-	-	-
LVM [mL]	91.2 ± 6.91	104.9 ± 16.97	95.0 ± 14.40	0.104	-	-	-
LVM [g]	98.3 ± 9.25	110.1 ± 17.83	99.7 ± 15.15	**0.049**	0.053	0.464	1.000
LVEDV [mL]	78.3 ± 16.42	92.1 ± 5.28	79.3 ± 7.63	0.091	-	-	-
LVESV [mL]	34.0 ± 6.89	54.3 ± 9.01	47.7 ± 8.16	**0.007**	**0.005**	0.342	0.342
LVSV [mL]	44.2 ± 9.52	37.8 ± 8.99	31.6 ± 5.13	**0.015**	1.000	**0.013**	0.173
LVEF [%]	56.3 [55.6; 57.2]	44.4 [31.3; 49.2]	43.6 [33.0; 45.3]	**0.015**	0.173	**0.013**	1.000
CO [L/min]	3.6 ± 1.17	2.9 ± 0.40	2.8 ± 0.22	0.368	-	-	-
RVEDV [mL]	70.2 ± 10.58	74.1 ± 12.20	76.0 ± 15.43	0.549	-	-	-
RVESV [mL]	30.4 ± 4.63	40.1 ± 13.85	45.3 ± 11.03	0.091	-	-	-
RVSV [mL]	39.9 ± 6.79	32.0 ± 4.64	30.7 ± 6.81	0.247	-	-	-
RVEF [%]	56.7 ± 3.05	46.4 ± 11.16	40.6 ± 6.61	0.074	-	-	-
IS [%]	N.A.	28.3 ± 5.30	29.3 ± 12.12	0.893	-	-	-
IV [mL]	N.A.	25.5 ± 4.10	29.1 ± 10.69	0.500	-	-	-

Controls from IM-sEV and IC-sEV delivery study have been analyzed at all time points with Friedman test for paired samples (all variables). Groups were treated as related samples.

2.2.2 Paired evaluation of IC-sEV

Intracoronary Infusion	Baseline [n=4]	2-3 Days [n=4]	1 Month [n=4]	Overall P-value	Pairwise comparisons		
					B vs. 2-3 D	B vs. 1 M	2-3 D vs. 1 M
Height [cm]	76 [71; 80]	78 [72; 88]	89 [87; 91]	**0.022**	0.874	**0.027**	0.339
Weight [Kg]	34 [31; 35]	36 [32; 37]	41 [34; 42]	**0.021**	0.867	**0.024**	0.335
Heart Rate [bpm]	97 [91; 103]	89 [70; 93]	90 [76; 103]	0.368	-	-	-
R-R [ms]	619 [582; 664]	678 [647; 874]	670 [586; 788]	0.368	-	-	-
LVM [mL]	83.0 ± 14.39	97.5 ± 26.97	98.9 ± 19.01	0.057	-	-	-
LVM [g]	87.9 ± 16.19	102.4 ± 28.36	103.8 ± 20.01	**0.039**	0.231	**0.040**	1.000
LVEDV [mL]	73.4 ± 14.23	79.8 ± 20.07	85.9 ± 17.61	**0.018**	0.472	**0.014**	0.472
LVESV [mL]	32.0 ± 6.82	46.3 ± 10.07	44.9 ± 6.43	**0.049**	0.102	0.102	1.000
LVSV [mL]	41.4 ± 7.64	33.5 ± 10.36	40.9 ± 13.08	**0.048**	0.102	1.000	0.102
LVEF [%]	56.8 [54.8; 57.9]	42.5 [37.6; 44.5]	47.7 [39.4; 53.4]	**0.039**	**0.040**	0.231	1.000
CO [L/min]	4.1 ± 0.97	2.8 ± 0.73	3.7 ± 1.22	**0.038**	**0.039**	1.000	0.231
RVEDV [mL]	70.6 ± 7.36	71.4 ± 3.15	71.8 ± 13.22	0.779	-	-	-
RVESV [mL]	31.4 ± 6.45	36.8 ± 2.45	38.9 ± 4.89	0.105	-	-	-
RVSV [mL]	39.2 ± 4.46	34.6 ± 3.56	32.9 ± 9.21	0.368	-	-	-
RVEF [%]	55.7 ± 6.54	48.5 ± 3.61	45.4 ± 4.37	**0.039**	0.231	**0.040**	1.000
IS [%]	N.A.	25.9 ± 12.27	15.3 ± 3.28	0.144	-	-	-
IV [mL]	N.A.	22.2 ± 10.52	13.5 ± 2.48	0.145	-	-	-

Animals underwent Intracoronary infusion from IM-sEV and IC-sEV delivery study have been analyzed at all time points with Friedman test for paired samples (all variables). Groups were treated as related samples.

2.2.3 Paired evaluation of IM-sEV

Intramyocardial Infusion	Baseline [n=5]	2-3 Days [n=5]	1 Month [n=5]	Overall *P*-value	Pairwise comparisons B *vs.* 2-3 D	B *vs.* 1 M	2-3 D *vs.* 1 M
Height [cm]	75 [72; 78]	77 [74; 80]	85 [83; 87]	**0.007**	0.342	**0.005**	0.342
Weight [Kg]	31 [30; 36]	32 [29; 36]	43 [39; 43]	0.022	1.000	**0.034**	0.081
Heart Rate [bpm]	89 [76; 95]	83 [51; 92]	92 [84; 99]	0.247	-	-	-
R-R [ms]	676 [633; 791]	721 [653; 1200]	649 [605; 711]	0.247	-	-	-
LVM [mL]	71.5 ± 10.65	82.0 ± 12.01	89.1 ± 12.06	0.165	-	-	-
LVM [g]	78.3 ± 13.01	86.1 ± 12.59	93.6 ± 12.63	0.074	-	-	-
LVEDV [mL]	73.9 ± 8.80	76.8 ± 8.64	89.9 ± 11.97	**0.015**	0.173	**0.013**	1.000
LVESV [mL]	31.6 ± 3.60	50.6 ± 5.47	54.6 ± 9.16	**0.014**	0.175	**0.013**	1.000
LVSV [mL]	42.3 ± 5.21	26.2 ± 3.25	35.3 ± 7.12	**0.007**	**0.005**	0.342	0.342
LVEF [%]	57.2 [56.9; 57.6]	34.3 [33.3; 34.8]	39.6 [34.0; 44.5]	**0.015**	**0.013**	0.173	1.000
CO [L/min]	3.6 ± 0.50	1.9 ± 0.50	3.3 ± 0.92	**0.013**	**0.011**	1.000	0.151
RVEDV [mL]	72.4 ± 9.90	74.8 ± 10.10	72.0 ± 21.35	0.549	-	-	-
RVESV [mL]	29.8 ± 5.63	54.6 ± 2.11	47.8 ± 11.97	**0.022**	**0.034**	0.081	1.000
RVSV [mL]	38.6 ± 10.10	20.2 ± 8.11	24.2 ± 10.53	**0.023**	**0.036**	0.077	1.000
RVEF [%]	56.1 ± 2.29	26.2 ± 8.01	32.9 ± 5.60	**0.015**	**0.013**	0.174	1.000
IS [%]	N.A.	23.5 ± 9.30	20.0 ± 8.41	0.225	-	-	-
IV [mL]	N.A.	17.3 ± 5.75	17.6 ± 8.54	0.893	-	-	-

Animals underwent Intramyocardial infusion from IM-sEV and IC-sEV delivery study have been analyzed at all time points with Friedman test for paired samples (all variables). Groups were treated as related samples.

2.3. Comparison of delta values

2.3.1 Evaluation of 2/3 Days *minus* Baseline

2/3 Days *minus* Baseline [%]	Ctrl [n=5]	IC [n=4]	IM [n=5]	Overall *P*-value	Pairwise comparisons		
					Ctrl *vs.* IC	Ctrl *vs.* IM	IC *vs.* IM
Delta LVM [mL]	14.6 ± 11.68	16.2 ± 16.20	15.7 ± 17.54	0.936	-	-	-
Delta LVM [g]	11.6 ± 7.84	15.1 ± 13.61	11.3 ± 18.69	0.606	-	-	-
Delta LVEDV [mL]	23.8 ± 37.02	8.1 ± 10.24	4.0 ± 3.05	0.421	-	-	-
Delta LVESV [mL]	71.0 ± 73.20	45.7 ± 18.58	60.4 ± 5.42	0.460	-	-	-
Delta LVSV [mL]	-12.9 ± 17.20	-20.5 ± 10.71	-38.1 ± 2.61	**0.023**	1.000	**0.030**	0.111
Delta LVEF [%]	-27.2 ± 16.41	-26.4 ± 7.66	-40.5 ± 1.42	0.214	-	-	-
Delta CO [L/min]	-14.9 ± 26.21	-32.2 ± 5.92	-45.8 ± 18.17	0.064	-	-	-
Delta RVEDV [mL]	5.6 ± 10.78	2.0 ± 10.95	3.4 ± 5.11	0.897	-	-	-
Delta RVESV [mL]	29.9 ± 30.51	22.8 ± 38.2	88.5 ± 36.3	0.086	-	-	-
Delta RVSV [mL]	-17.1 ± 21.19	-10.6 ± 13.9	-47.0 ± 19.77	0.062	-	-	-
Delta RVEF [%]	-17.6 ± 21.98	-11.9 ± 13.74	-53.5 ± 13.36	**0.023**	1.000	0.070	**0.044**

Delta 2-3 Days *minus* Baseline from data of the IM-sEV and IC-sEV delivery study have been analyzed with Kruskal-Wallis test (all variables). Groups were treated as independent samples.

2.3.2 Evaluation of 1 Month *minus* 2/3 Days

1 Month *minus* 2/3 Days [%]	Ctrl [n=5]	IC [n=4]	IM [n=5]	Overall P-value	Pairwise comparisons Ctrl *vs.* IC	Ctrl *vs.* IM	IC vs. IM
Delta LVM [mL]	-8.7 ± 12.61	4.8 ± 20.98	10.9 ± 22.54	0.291	-	-	-
Delta LVM [g]	-8.9 ± 12.73	4.7 ± 20.96	11.1 ± 22.48	0.291	-	-	-
Delta LVEDV [mL]	-13.8 ± 7.65	8.6 ± 6.86	17.8 ± 16.29	**0.010**	0.078	**0.012**	1.000
Delta LVESV [mL]	-11.8 ± 8.36	-1.3 ± 12.91	9.2 ± 23.19	0.195	-	-	-
Delta LVSV [mL]	-14.9 ± 10.14	21.7 ± 4.68	34.2 ± 13.70	**0.006**	0.184	**0.004**	0.785
Delta LVEF [%]	-1.3 ± 8.90	12.3 ± 7.98	15.2 ± 17.72	0.089	-	-	-
Delta CO [L/min]	-2.0 ± 20.28	31.4 ± 17.1	83.5 ± 72.49	**0.026**	0.242	**0.024**	1.000
Delta RVEDV [mL]	6.4 ± 35.96	0.2 ± 15.60	-3.4 ± 26.40	0.946	-	-	-
Delta RVESV [mL]	26.7 ± 61.21	6.5 ± 18.17	-12.8 ± 20.34	0.526	-	-	-
Delta RVSV [mL]	-1.8 ± 26.89	-6.2 ± 15.75	34.3 ± 66.30	0.650	-	-	-
Delta RVEF [%]	-8.0 ± 27.59	-6.4 ± 6.96	34.4 ± 37.70	0.065	-	-	-
Delta IS [%]	3.4 ± 42.17	-32.1 ± 25.86	-13.1 ± 31.47	0.248	-	-	-
Delta IV [mL]	15.1 ± 44.84	-21.3 ± 50.13	-0.5 ± 29.56	0.206	-	-	-

Delta 1 Month *minus* 2-3 Days from data of the IM-sEV and IC-sEV delivery study have been analyzed with Kruskal-Wallis test (all variables). Groups were treated as independent samples.

3. Placebo-controlled IC-sEV-delivery study

3.1 Comparison of treatments at each time-point

3.1.1 Evaluation at 2/3 Days: Ctrl vs. IC-sEV

2-3 Days Evaluation	Ctrl [n=4]	IC [n=6]	*P*-value
Height [cm]	83 [82; 83]	78 [67; 80]	0.071
Weight [Kg]	42 [37; 42]	39 [36; 50]	0.548
Heart Rate [bpm]	95 [50; 108]	76 [70; 85]	0.352
R-R [ms]	631 [556; 1424]	788 [706; 852]	0.352
LVM [mL]	64.4 ± 7.82	66.6 ± 6.20	0.762
LVM [g]	67.7 ± 8.25	69.9 ± 6.52	1.000
LVEDV [mL]	81.5 ± 10.47	87.4 ± 3.87	0.476
LVESV [mL]	52.0 ± 8.74	56.7 ± 4.45	0.257
LVSV [mL]	29.5 ± 5.38	30.7 ± 3.66	0.762
LVEF [%]	36.6 [31.0; 41.1]	34.1 [32.3; 39.4]	0.762
CO [L/min]	2.5 ± 1.06	2.4 ± 0.47	0.914
RVEDV [mL]	76.7 ± 6.75	72.9 ± 8.17	0.610
RVESV [mL]	38.1 ± 7.44	38.5 ± 5.76	1.000
RVSV [mL]	38.7 ± 6.60	34.5 ± 8.75	0.576
RVEF [%]	50.4 ± 8.09	46.9 ± 8.21	0.476
IS [%]	23.4 ± 0.90	24.6 ± 3.33	1.000
IV [mL]	21.0 ± 1.16	20.0 ± 3.57	0.914

Data from Placebo-controlled IC-sEV-delivery study have been analyzed at 2-3 days with Mann-Whitney test (all variables). Groups were treated as independent samples.

3.1.2 Evaluation at 1 Month: Ctrl vs. IC-sEV

1 Month Evaluation	Ctrl [n=4]	IC [n=6]	P-value
Height [cm]	93 [92; 93]	91 [83; 93]	0.262
Weight [Kg]	47 [40; 47]	44 [41; 45]	0.381
Heart Rate [bpm]	84 [76; 87]	80 [63; 85]	0.476
R-R [ms]	710 [691; 791]	755 [708; 1132]	0.476
LVM [mL]	76.4 ± 7.16	86.5 ± 13.09	0.257
LVM [g]	85.2 ± 4.97	90.8 ± 13.69	0.476
LVEDV [mL]	110.7 ± 9.17	100.8 ± 8.19	0.067
LVESV [mL]	73.9 ± 8.04	65.8 ± 6.28	0.114
LVSV [mL]	36.8 ± 2.93	35.0 ± 3.93	0.576
LVEF [%]	33.2 [30.9; 35.9]	35.9 [31.1; 37.1]	0.352
CO [L/min]	3.0 ± 0.33	3.2 ± 1.11	0.476
RVEDV [mL]	76.4 ± 4.59	73.3 ± 9.56	0.762
RVESV [mL]	36.2 ± 9.03	39.4 ± 7.16	0.762
RVSV [mL]	40.2 ± 4.51	33.9 ± 5.43	0.114
RVEF [%]	53.1 ± 9.30	46.4 ± 5.64	0.352
IS [%]	20.9 ± 0.85	22.3 ± 2.95	0.610
IV [mL]	16.2 ± 0.29	16.2 ± 9.40	1.000

Data from Placebo-controlled IC-sEV-delivery study have been analyzed at 1 Month with Mann-Whitney test (all variables). Groups were treated as independent samples.

3.1.3 Evaluation at 3 Months: Ctrl *vs.* IC-sEV

3 Months Evaluation	Ctrl [n=4]	IC [n=6]	*P*-value
Height [cm]	97 [97; 98]	107 [102; 110]	**0.024**
Weight [Kg]	62 [55; 62]	67 [60; 70]	0.262
Heart Rate [bpm]	89 [82; 100]	77 [59; 87]	0.114
R-R [ms]	676 [604; 730]	780 [697; 1025]	0.114
LVM [mL]	94.2 ± 14.17	111.2 ± 19.38	0.171
LVM [g]	98.9 ± 14.84	116.8 ± 20.4	0.171
LVEDV [mL]	119.7 ± 6.62	114.5 ± 16.3	0.476
LVESV [mL]	79.6 ± 4.09	71.4 ± 11.52	0.352
LVSV [mL]	40.2 ± 3.32	41.5 ± 6.38	0.914
LVEF [%]	33.4 [32.3; 35.0]	36.2 [35.1; 37.1]	**0.019**
CO [L/min]	3.6 ± 0.50	3.7 ± 0.62	0.610
RVEDV [mL]	80.4 ± 3.66	77.1 ± 10.9	0.352
RVESV [mL]	43.6 ± 8.86	41.7 ± 7.59	0.610
RVSV [mL]	36.9 ± 5.66	35.4 ± 7.61	0.610
RVEF [%]	46.1 ± 9.09	45.8 ± 6.90	0.914
IS [%]	23.9 ± 2.45	18.0 ± 2.45	**0.010**
IV [mL]	24.3 ± 3.74	18.0 ± 4.4	0.114

Data from Placebo-controlled IC-sEV-delivery study have been analyzed at 3 Months with Mann-Whitney test (all variables). Groups were treated as independent samples.

3.2. Comparison of time-points for each treatment

3.2.1 Paired evaluation of Ctrl group

Controls	2-3 Days [n=4]	1 Month [n=4]	3 Months [n=4]	Overall *P*-value	Pairwise comparisons		
					2-3 D *vs.* 1 M	2-3 D *vs.* 3 M	1 M *vs.* 3 M
Height [cm]	83 [82; 83]	93 [92; 93]	97 [97; 98]	**0.018**	0.472	**0.014**	0.472
Weight [Kg]	42 [37; 42]	47 [40; 47]	62 [55; 62]	**0.019**	0.475	**0.019**	0.478
Heart Rate [bpm]	95 [50; 108]	84 [76; 87]	89 [82; 100]	0.472	-	-	-
R-R [ms]	631 [556; 1424]	710 [691; 791]	676 [604; 730]	0.472	-	-	-
LVM [mL]	64.4 ± 7.82	76.4 ± 7.16	94.2 ± 14.17	0.105	-	-	-
LVM [g]	67.7 ± 8.25	85.2 ± 4.97	98.9 ± 14.84	**0.039**	0.231	**0.040**	1.000
LVEDV [mL]	81.5 ± 10.47	110.7 ± 9.17	119.7 ± 6.62	**0.034**	0.189	**0.037**	1.000
LVESV [mL]	52.0 ± 8.74	73.9 ± 8.04	79.6 ± 4.09	**0.033**	0.185	**0.034**	1.000
LVSV [mL]	29.5 ± 5.38	36.8 ± 2.93	40.2 ± 3.32	**0.042**	0.375	**0.046**	1.000
LVEF [%]	36.6 [31.0; 41.1]	33.2 [30.9; 35.9]	33.4 [32.3; 35.0]	0.471	-	-	-
CO [L/min]	2.5 ± 1.06	3.0 ± 0.33	3.6 ± 0.50	0.174			
RVEDV [mL]	76.7 ± 6.75	76.4 ± 4.59	80.4 ± 3.66	0.472			
RVESV [mL]	38.1 ± 7.44	36.2 ± 9.03	43.6 ± 8.86	0.779			
RVSV [mL]	38.7 ± 6.60	40.2 ± 4.51	36.9 ± 5.66	0.780			
RVEF [%]	50.4 ± 8.09	53.1 ± 9.30	46.1 ± 9.09	0.627			
IS [%]	23.4 ± 0.90	20.9 ± 0.85	23.9 ± 2.45	**0.039**	**0.040**	1.000	0.231
IV [mL]	21.0 ± 1.16	16.2 ± 0.29	24.3 ± 3.74	**0.033**	0.097	1.000	**0.035**

Controls from Placebo-controlled IC-sEV-delivery study have been analyzed at all time points with Friedman test for paired samples (all variables). Groups were treated as related samples.

3.2.2 Paired evaluation of IC-sEV

Intracoronary Infusion	2-3 Days [n=6]	1 Month [n=6]	3 Months [n=6]	Overall *P*-value	Pairwise comparisons		
					2-3 D *vs.* 1 M	2-3 D *vs.* 3 M	1 M *vs.* 3 M
Height [cm]	78 [67; 80]	91 [83; 93]	107 [102; 110]	**0.002**	0.250	**0.002**	0.250
Weight [Kg]	39 [36; 50]	44 [41; 45]	67 [60; 70]	**0.030**	1.000	**0.028**	0.250
Heart Rate [bpm]	76 [70; 85]	80 [63; 85]	77 [59; 87]	1.000	-	-	-
R-R [ms]	788 [706; 852]	755 [708; 1132]	780 [697; 1025]	1.000	-	-	-
LVM [mL]	66.6 ± 6.20	86.5 ± 13.09	111.2 ± 19.38	**0.002**	0.250	**0.002**	0.250
LVM [g]	69.9 ± 6.52	90.8 ± 13.69	116.8 ± 20.4	**0.001**	0.203	**0.001**	0.203
LVEDV [mL]	87.4 ± 3.87	100.8 ± 8.19	114.5 ± 16.3	**0.011**	**0.028**	**0.028**	1.000
LVESV [mL]	56.7 ± 4.45	65.8 ± 6.28	71.4 ± 11.52	**0.042**	0.063	0.130	1.000
LVSV [mL]	30.7 ± 3.66	35.0 ± 3.93	41.5 ± 6.38	0.115	-	-	-
LVEF [%]	34.1 [32.3; 39.4]	35.9 [31.1; 37.1]	36.2 [35.1; 37.1]	0.846	-	-	-
CO [L/min]	2.4 ± 0.47	3.2 ± 1.11	3.7 ± 0.62	**0.022**	0.250	0.028	1.000
RVEDV [mL]	72.9 ± 8.17	73.3 ± 9.56	77.1 ± 10.9	0.846	-	-	-
RVESV [mL]	38.5 ± 5.76	39.4 ± 7.16	41.7 ± 7.59	0.568	-	-	-
RVSV [mL]	34.5 ± 8.75	33.9 ± 5.43	35.4 ± 7.61	0.513	-	-	-
RVEF [%]	46.9 ± 8.21	46.4 ± 5.64	45.8 ± 6.90	0.845	-	-	-
IS [%]	24.6 ± 3.33	22.3 ± 2.95	18.0 ± 2.45	**0.042**	1.000	**0.048**	0.130
IV [mL]	20.0 ± 3.57	16.2 ± 9.40	18.0 ± 4.4	0.872	-	-	-

Animals underwent Intracoronary infusion from Placebo-controlled IC-sEV-delivery study have been analyzed at all time points with Friedman test for paired samples (all variables). Groups were treated as related samples.

3.3. Comparison of delta values

3.3.1 Evaluation of 1 Month *minus* 2/3 Days

1 Month *minus* 2/3 Days [%]	Ctrl [n=4]	IC [n=6]	*P*-value
Delta LVM [mL]	20.0 ± 18.56	30.3 ± 18.90	0.476
Delta LVM [g]	26.7 ± 8.59	30.2 ± 18.88	0.762
Delta LVEDV [mL]	37.4 ± 19.00	15.4 ± 8.42	**0.038**
Delta LVESV [mL]	43.8 ± 18.96	16.2 ± 10.78	**0.038**
Delta LVSV [mL]	27.7 ± 21.75	15.1 ± 15.64	0.352
Delta LVEF [%]	-7.1 ± 8.27	-0.3 ± 10.84	0.171
Delta CO [L/min]	50.2 ± 93.67	33.0 ± 45.20	1.000
Delta RVEDV [mL]	0.3 ± 12.69	2.3 ± 21.70	0.762
Delta RVESV [mL]	-4.6 ± 19.86	4.7 ± 27.03	1.000
Delta RVSV [mL]	5.2 ± 9.90	6.4 ± 40.50	0.914
Delta RVEF [%]	5.5 ± 10.08	2.1 ± 22.67	1.000
Delta IS [%]	-10.6 ± 6.36	-8.4 ± 14.16	0.352
Delta IV [mL]	-22.4 ± 5.02	-2.5 ± 26.0	0.476

Delta 1 Month *minus* 2-3 Days from data of the Placebo-controlled IC-sEV-delivery study have been analyzed with Mann-Whitney test (all variables). Groups were treated as independent samples.

3.3.2 Evaluation of 3 Months *minus* 1 Month

3 Months *minus* 1 Month [%]	Ctrl [n=4]	IC [n=6]	Overall *P*-value
Delta LVM [mL]	24.5 ± 23.78	30.3 ± 27.81	0.476
Delta LVM [g]	17.0 ± 24.06	30.1 ± 27.78	0.476
Delta LVEDV [mL]	9.0 ± 14.24	14.3 ± 20.17	0.476
Delta LVESV [mL]	8.9 ± 16.12	9.8 ± 24.94	0.171
Delta LVSV [mL]	10.1 ± 16.36	19.4 ± 19.69	0.610
Delta LVEF [%]	1.2 ± 9.73	4.8 ± 9.72	0.257
Delta CO [L/min]	23.2 ± 18.19	40.6 ± 87.96	1.000
Delta RVEDV [mL]	5.6 ± 8.60	7.5 ± 25.55	0.762
Delta RVESV [mL]	29.5 ± 57.05	9.3 ± 28.06	1.000
Delta RVSV [mL]	-7.1 ± 18.66	7.2 ± 30.97	0.476
Delta RVEF [%]	-10.6 ± 23.85	-0.5 ± 17.89	1.000
Delta IS [%]	14.6 ± 8.62	-18.1 ± 16.44	**0.010**
Delta IV [mL]	49.4 ± 21.47	-1.6 ± 27.72	0.171

Delta 3 Months *minus* 1 Month from data of the Placebo-controlled IC-sEV-delivery study have been analyzed with Mann-Whitney test (all variables). Groups were treated as independent samples.

3.3.3 Evaluation of 3 Months *minus* 2-3 Days

3 Months *minus* 2-3 Days [%]	Ctrl [n=4]	IC [n=6]	Overall *P*-value
Delta LVM [mL]	49.6 ± 39.79	66.9 ± 24.27	1.000
Delta LVM [g]	49.5 ± 39.02	66.4 ± 24.75	0.610
Delta LVEDV [mL]	49.3 ± 24.25	31.9 ± 24.36	1.000
Delta LVESV [mL]	56.5 ± 28.29	27.4 ± 29.05	0.762
Delta LVSV [mL]	40.2 ± 31.24	36.6 ± 23.85	0.476
Delta LVEF [%]	-5.8 ± 13.77	3.9 ± 8.57	0.762
Delta CO [L/min]	78.7 ± 95.31	58.0 ± 26.20	0.352
Delta RVEDV [mL]	5.7 ± 13.15	6.4 ± 14.65	0.476
Delta RVESV [mL]	18.1 ± 37.79	10.6 ± 23.92	0.914
Delta RVSV [mL]	-2.5 ± 20.91	7.6 ± 29.55	0.476
Delta RVEF [%]	-7.1 ± 19.59	0.7 ± 26.44	0.610
Delta IS [%]	2.5 ± 11.37	-26.5 ± 8.80	**0.038**
Delta IV [mL]	16.8 ± 24.08	-8.7 ± 21.53	**0.019**

Delta 3 Months *minus* 2-3 Days from data of the Placebo-controlled IC-sEV-delivery study have been analyzed with Mann-Whitney test (all variables). Groups were treated as independent samples.