STATISTICAL ANALYSIS

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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1. Assessment of variable distribution

Variable	Number of Observations	Kolmogorov-Smirnov Test	Shapiro-Wilk Test	DISTRIBUTION
Height [cm]	72	0.001	<0.001	NOT NORMAL
Weight [Kg]	72	<0.001	<0.001	NOT NORMAL
Heart Rate [bpm]	72	0.040	0.082	NOT NORMAL
R-R [ms]	72	0.070	0.001	NOT NORMAL
LVM [mL]	72	0.134	0.117	NORMAL
LVM [g]	72	0.138	0.117	NORMAL
LVEDV [mL]	72	0.076	0.113	NORMAL
LVESV [mL]	72	0.200	0.374	NORMAL
LVSV [mL]	72	0.074	0.053	NORMAL
LVEF [%]	72	0.003	0.020	NOT NORMAL
CO [L/min]	72	0.200	0.721	NORMAL
RVEDV [mL]	72	0.200	0.634	NORMAL
RVESV [mL]	72	0.084	0.200	NORMAL
RVSV [mL]	72	0.200	0.488	NORMAL
RVEF [mL]	72	0.200	0.549	NORMAL
Scar [%]	58	0.200	0.624	NORMAL
Scar [mL]	58	0.072	0.297	NORMAL
MO region [%]	24	0.005	0.006	NOT NORMAL
MAAR [%]	24	0.200	0.218	NORMAL

Kolmogorov-Smirnov and Shapiro-Wilk tests have been used to assess variable distribution using all available observations (regardless treatments and time-points). Normally distributed variables were expressed as mean ± standard deviation and analyzed by parametric tests. Not normally distributed variables were expressed as median [interquartile range] and analyzed by non-parametric tests.

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	**0.043**	0.832	**0.043**	0.421
LVM [g]	98.3 ± 9.25	87.9 ± 16.19	78.3 ± 13.01	0.090	-	-	-
LVEDV [mL]	78.3 ± 16.42	73.4 ± 14.23	73.9 ± 8.80	0.829	-	-	-
LVESV [mL]	34.0 ± 6.89	32.0 ± 6.82	31.6 ± 3.60	0.787	-	-	-
LVSV [mL]	44.2 ± 9.52	41.4 ± 7.64	42.3 ± 5.21	0.856	-	-	-
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	0.738	-	-	-
RVEDV [mL]	70.2 ± 10.58	70.6 ± 7.36	72.4 ± 9.90	0.929	-	-	-
RVESV [mL]	30.4 ± 4.63	31.4 ± 6.45	29.8 ± 5.63	0.913	-	-	-
RVSV [mL]	39.9 ± 6.79	39.2 ± 4.46	38.6 ± 10.10	0.967	-	-	-
RVEF [mL]	56.7 ± 3.05	55.7 ± 6.54	56.1 ± 2.29	0.939	-	-	-

Data from IM-sEV and IC-sEV delivery study have been analyzed at baseline with Kruskal-Wallis test (not-normally distributed variables) or ANOVA with post-hoc Bonferroni test (normally distributed 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	0.194	-	-	-
LVM [g]	110.1 ± 17.83	102.4 ± 28.36	86.1 ± 12.59	0.196	-	-	-
LVEDV [mL]	92.1 ± 5.28	79.8 ± 20.07	76.8 ± 8.64	0.156	-	-	-
LVESV [mL]	54.3 ± 9.01	46.3 ± 10.07	50.6 ± 5.47	0.383	-	-	-
LVSV [mL]	37.8 ± 8.99	33.5 ± 10.36	26.2 ± 3.25	0.107	-	-	-
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	**0.036**	1.000	**0.046**	0.120
RVEDV [mL]	74.1 ± 12.20	71.4 ± 3.15	74.8 ± 10.10	0.863	-	-	-
RVESV [mL]	40.1 ± 13.85	36.8 ± 2.45	54.6 ± 2.11	**0.019**	1.000	0.064	**0.030**
RVSV [mL]	32.0 ± 4.64	34.6 ± 3.56	20.2 ± 8.11	**0.008**	1.000	**0.028**	**0.012**
RVEF [mL]	46.4 ± 11.16	48.5 ± 3.61	26.2 ± 8.01	**0.003**	1.000	**0.009**	**0.007**
Scar [%]	28.3 ± 5.30	25.9 ± 12.27	23.5 ± 9.30	0.713	-	-	-
Scar [mL]	25.5 ± 4.10	22.2 ± 10.52	17.3 ± 5.75	0.216	-	-	-
MO region [%]	0.2 [0.2; 0.4]	0.3 [0.2; 0.6]	0.1 [0.1; 0.2]	**0.029**	1.000	0.231	**0.029**
MAAR [%]	39.1 ± 3.19	39.8 ± 6.49	43.4 ± 11.78	0.677	-	-	-

Data from IM-sEV and IC-sEV delivery study have been analyzed at 2-3 Days with Kruskal-Wallis test (not-normally distributed variables) or ANOVA with post-hoc Bonferroni test (normally distributed 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	0.629	-	-	-
LVM [g]	99.7 ± 15.15	103.8 ± 20.01	93.6 ± 12.63	0.630	-	-	-
LVEDV [mL]	79.3 ± 7.63	85.9 ± 17.61	89.9 ± 11.97	0.432	-	-	-
LVESV [mL]	47.7 ± 8.16	44.9 ± 6.43	54.6 ± 9.16	0.221	-	-	-
LVSV [mL]	31.6 ± 5.13	40.9 ± 13.08	35.3 ± 7.12	0.314	-	-	-
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	0.326	-	-	-
RVEDV [mL]	76.0 ± 15.43	71.8 ± 13.22	72.0 ± 21.35	0.912	-	-	-
RVESV [mL]	45.3 ± 11.03	38.9 ± 4.89	47.8 ± 11.97	0.439	-	-	-
RVSV [mL]	30.7 ± 6.81	32.9 ± 9.21	24.2 ± 10.53	0.343	-	-	-
RVEF [mL]	40.6 ± 6.61	45.4 ± 4.37	32.9 ± 5.60	**0.022**	0.712	0.174	**0.023**
Scar [%]	29.3 ± 12.12	15.3 ± 3.28	20.0 ± 8.41	0.100	-	-	-
Scar [mL]	29.1 ± 10.69	13.5 ± 2.48	17.6 ± 8.54	**0.040**	**0.044**	0.153	1.000

Data from IM-sEV and IC-sEV delivery study have been analyzed at 1 Month with Kruskal-Wallis test (not-normally distributed variables) or ANOVA with post-hoc Bonferroni test (normally distributed 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	0.070	-	-	-
LVM [g]	98.3 ± 9.25	110.1 ± 17.83	99.7 ± 15.15	0.107	-	-	-
LVEDV [mL]	78.3 ± 16.42	92.1 ± 5.28	79.3 ± 7.63	**0.032**	0.156	0.901	**0.018**
LVESV [mL]	34.0 ± 6.89	54.3 ± 9.01	47.7 ± 8.16	**0.012**	**0.038**	0.067	**0.049**
LVSV [mL]	44.2 ± 9.52	37.8 ± 8.99	31.6 ± 5.13	**0.015**	0.156	**0.025**	0.063
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	0.156	-	-	-
RVEDV [mL]	70.2 ± 10.58	74.1 ± 12.20	76.0 ± 15.43	0.776	-	-	-
RVESV [mL]	30.4 ± 4.63	40.1 ± 13.85	45.3 ± 11.03	0.137	-	-	-
RVSV [mL]	39.9 ± 6.79	32.0 ± 4.64	30.7 ± 6.81	**0.049**	0.597	0.078	0.109
RVEF [mL]	56.7 ± 3.05	46.4 ± 11.16	40.6 ± 6.61	**0.035**	0.149	**0.008**	0.363
Scar [%]	N.A.	28.3 ± 5.30	29.3 ± 12.12	0.846	-	-	-
Scar [mL]	N.A.	25.5 ± 4.10	29.1 ± 10.69	0.482	-	-	-
MO region [%]	N.A.	0.2 [0.2; 0.4]	N.A.	-	-	-	-
MAAR [%]	N.A.	39.1 ± 3.19	N.A.	-	-	-	-

Controls from IM-sEV and IC-sEV delivery study have been analyzed at all time points with Friedman test for paired samples (not-normally distributed variables) or ANOVA for repeated measures (normally distributed 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	0.177	-	-	-
LVM [g]	87.9 ± 16.19	102.4 ± 28.36	103.8 ± 20.01	0.176	-	-	-
LVEDV [mL]	73.4 ± 14.23	79.8 ± 20.07	85.9 ± 17.61	**0.047**	0.243	0.068	0.061
LVESV [mL]	32.0 ± 6.82	46.3 ± 10.07	44.9 ± 6.43	**0.011**	**0.023**	**0.048**	0.679
LVSV [mL]	41.4 ± 7.64	33.5 ± 10.36	40.9 ± 13.08	**0.013**	**0.012**	0.876	**0.014**
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	**0.004**	**0.009**	0.177	**0.039**
RVEDV [mL]	70.6 ± 7.36	71.4 ± 3.15	71.8 ± 13.22	0.974	-	-	-
RVESV [mL]	31.4 ± 6.45	36.8 ± 2.45	38.9 ± 4.89	0.156	-	-	-
RVSV [mL]	39.2 ± 4.46	34.6 ± 3.56	32.9 ± 9.21	0.304	-	-	-
RVEF [mL]	55.7 ± 6.54	48.5 ± 3.61	45.4 ± 4.37	0.065	-	-	-
Scar [%]	N.A.	25.9 ± 12.27	15.3 ± 3.28	0.106	-	-	-
Scar [mL]	N.A.	22.2 ± 10.52	13.5 ± 2.48	0.140	-	-	-
MO region [%]	N.A.	0.3 [0.2; 0.6]	N.A.	-	-	-	-
MAAR [%]	N.A.	39.8 ± 6.49	N.A.	-	-	-	-

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 (not-normally distributed variables) or ANOVA for repeated measures (normally distributed 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	0.088	-	-	-
LVM [g]	78.3 ± 13.01	86.1 ± 12.59	93.6 ± 12.63	0.154	-	-	-
LVEDV [mL]	73.9 ± 8.80	76.8 ± 8.64	89.9 ± 11.97	**0.009**	**0.035**	**0.022**	0.066
LVESV [mL]	31.6 ± 3.60	50.6 ± 5.47	54.6 ± 9.16	**0.001**	**<0.001**	**0.005**	0.469
LVSV [mL]	42.3 ± 5.21	26.2 ± 3.25	35.3 ± 7.12	**<0.001**	**<0.001**	**0.009**	**0.011**
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	**0.014**	**0.016**	0.506	0.052
RVEDV [mL]	72.4 ± 9.90	74.8 ± 10.10	72.0 ± 21.35	0.914	-	-	-
RVESV [mL]	29.8 ± 5.63	54.6 ± 2.11	47.8 ± 11.97	**0.001**	**<0.001**	**0.014**	0.237
RVSV [mL]	38.6 ± 10.10	20.2 ± 8.11	24.2 ± 10.53	**0.006**	**0.006**	**0.045**	0.398
RVEF [mL]	56.1 ± 2.29	26.2 ± 8.01	32.9 ± 5.60	**<0.001**	**0.001**	**0.001**	0.055
Scar [%]	N.A.	23.5 ± 9.30	20.0 ± 8.41	0.351	-	-	-
Scar [mL]	N.A.	17.3 ± 5.75	17.6 ± 8.54	0.914	-	-	-
MO region [%]	N.A.	0.1 [0.1; 0.2]	N.A.	-	-	-	-
MAAR [%]	N.A.	43.4 ± 11.78	N.A.	-	-	-	-

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 (not-normally distributed variables) or ANOVA for repeated measures (normally distributed 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	0.987	-	-	-
Delta LVM [g]	11.6 ± 7.84	15.1 ± 13.61	11.3 ± 18.69	0.908	-	-	-
Delta LVEDV [mL]	23.8 ± 37.02	8.1 ± 10.24	4.0 ± 3.05	0.392	-	-	-
Delta LVESV [mL]	71.0 ± 73.20	45.7 ± 18.58	60.4 ± 5.42	0.714	-	-	-
Delta LVSV [mL]	-12.9 ± 17.20	-20.5 ± 10.71	-38.1 ± 2.61	**0.018**	1.000	**0.019**	0.148
Delta LVEF [%]	-27.2 ± 16.41	-26.4 ± 7.66	-40.5 ± 1.42	0.119	-	-	-
Delta CO [L/min]	-14.9 ± 26.21	-32.2 ± 5.92	-45.8 ± 18.17	0.082	-	-	-
Delta RVEDV [mL]	5.6 ± 10.78	2.0 ± 10.95	3.4 ± 5.11	0.835	-	-	-
Delta RVESV [mL]	29.9 ± 30.51	22.8 ± 38.2	88.5 ± 36.3	**0.027**	1.000	0.067	0.051
Delta RVSV [mL]	-17.1 ± 21.19	-10.6 ± 13.9	-47.0 ± 19.77	**0.029**	1.000	0.089	**0.046**
Delta RVEF [mL]	-17.6 ± 21.98	-11.9 ± 13.74	-53.5 ± 13.36	**0.006**	1.000	**0.020**	**0.012**

Delta 2-3 Days *minus* Baseline from data of the IM-sEV and IC-sEV delivery study have been analyzed with ANOVA with post-hoc Bonferroni test (all delta variables were normally distributed). 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	0.287	-	-	-
Delta LVEDV [mL]	-13.8 ± 7.65	8.6 ± 6.86	17.8 ± 16.29	**0.003**	**0.041**	**0.003**	0.764
Delta LVESV [mL]	-11.8 ± 8.36	-1.3 ± 12.91	9.2 ± 23.19	0.171	-	-	-
Delta LVSV [mL]	-14.9 ± 10.14	21.7 ± 4.68	34.2 ± 13.70	**<0.001**	**0.001**	**<0.001**	0.317
Delta LVEF [%]	-1.3 ± 8.90	12.3 ± 7.98	15.2 ± 17.72	0.105	-	-	-
Delta CO [L/min]	-2.0 ± 20.28	31.4 ± 17.1	83.5 ± 72.49	**0.041**	0.916	**0.041**	0.362
Delta RVEDV [mL]	6.4 ± 35.96	0.2 ± 15.60	-3.4 ± 26.40	0.857	-	-	-
Delta RVESV [mL]	26.7 ± 61.21	6.5 ± 18.17	-12.8 ± 20.34	0.333	-	-	-
Delta RVSV [mL]	-1.8 ± 26.89	-6.2 ± 15.75	34.3 ± 66.30	0.331	-	-	-
Delta RVEF [mL]	-8.0 ± 27.59	-6.4 ± 6.96	34.4 ± 37.70	0.068	-	-	-
Delta Scar [%]	3.4 ± 42.17	-32.1 ± 25.86	-13.1 ± 31.47	0.344	-	-	-
Delta Scar [mL]	15.1 ± 44.84	-21.3 ± 50.13	-0.5 ± 29.56	0.453	-	-	-

Delta 1 Month *minus* 2-3 Days from data of the IM-sEV and IC-sEV delivery study have been analyzed with ANOVA with post-hoc Bonferroni test (all delta variables were normally distributed). 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	0.644
LVM [g]	67.7 ± 8.25	69.9 ± 6.52	0.642
LVEDV [mL]	81.5 ± 10.47	87.4 ± 3.87	0.232
LVESV [mL]	52.0 ± 8.74	56.7 ± 4.45	0.287
LVSV [mL]	29.5 ± 5.38	30.7 ± 3.66	0.685
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	0.920
RVEDV [mL]	76.7 ± 6.75	72.9 ± 8.17	0.466
RVESV [mL]	38.1 ± 7.44	38.5 ± 5.76	0.927
RVSV [mL]	38.7 ± 6.60	34.5 ± 8.75	0.440
RVEF [mL]	50.4 ± 8.09	46.9 ± 8.21	0.523
Scar [%]	23.4 ± 0.90	24.6 ± 3.33	0.509
Scar [mL]	21.0 ± 1.16	20.0 ± 3.57	0.612
MO region [%]	0.3 [0.1; 0.8]	0.6 [0.5; 0.9]	0.257
MAAR [%]	46.3 ± 8.70	44.8 ± 4.07	0.714

Data from Placebo-controlled IC-sEV-delivery study have been analyzed at 2-3 days with Mann-Whitney test (not-normally distributed variables) or T-student test (normally distributed 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	0.199
LVM [g]	85.2 ± 4.97	90.8 ± 13.69	0.456
LVEDV [mL]	110.7 ± 9.17	100.8 ± 8.19	0.112
LVESV [mL]	73.9 ± 8.04	65.8 ± 6.28	0.110
LVSV [mL]	36.8 ± 2.93	35.0 ± 3.93	0.467
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	0.751
RVEDV [mL]	76.4 ± 4.59	73.3 ± 9.56	0.566
RVESV [mL]	36.2 ± 9.03	39.4 ± 7.16	0.549
RVSV [mL]	40.2 ± 4.51	33.9 ± 5.43	0.092
RVEF [mL]	53.1 ± 9.30	46.4 ± 5.64	0.193
Scar [%]	20.9 ± 0.85	22.3 ± 2.95	0.393
Scar [mL]	16.2 ± 0.29	16.2 ± 9.40	0.993

Data from Placebo-controlled IC-sEV-delivery study have been analyzed at 1 Month with Mann-Whitney test (not-normally distributed variables) or T-student test (normally distributed 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	0.174
LVM [g]	98.9 ± 14.84	116.8 ± 20.4	0.172
LVEDV [mL]	119.7 ± 6.62	114.5 ± 16.3	0.565
LVESV [mL]	79.6 ± 4.09	71.4 ± 11.52	0.215
LVSV [mL]	40.2 ± 3.32	41.5 ± 6.38	0.716
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	0.778
RVEDV [mL]	80.4 ± 3.66	77.1 ± 10.9	0.578
RVESV [mL]	43.6 ± 8.86	41.7 ± 7.59	0.735
RVSV [mL]	36.9 ± 5.66	35.4 ± 7.61	0.751
RVEF [mL]	46.1 ± 9.09	45.8 ± 6.90	0.948
Scar [%]	23.9 ± 2.45	18.0 ± 2.45	**0.005**
Scar [mL]	24.3 ± 3.74	18.0 ± 4.4	**0.046**

Data from Placebo-controlled IC-sEV-delivery study have been analyzed at 3 Months with Mann-Whitney test (not-normally distributed variables) or T-student test (normally distributed 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	**0.036**	0.118	0.068	0.138
LVM [g]	67.7 ± 8.25	85.2 ± 4.97	98.9 ± 14.84	**0.030**	**0.003**	**0.068**	0.248
LVEDV [mL]	81.5 ± 10.47	110.7 ± 9.17	119.7 ± 6.62	**0.004**	**0.013**	**0.015**	0.322
LVESV [mL]	52.0 ± 8.74	73.9 ± 8.04	79.6 ± 4.09	**0.004**	**0.009**	**0.020**	0.398
LVSV [mL]	29.5 ± 5.38	36.8 ± 2.93	40.2 ± 3.32	**0.020**	0.054	**0.036**	0.323
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	0.203	-	-	-
RVEDV [mL]	76.7 ± 6.75	76.4 ± 4.59	80.4 ± 3.66	0.598	-	-	-
RVESV [mL]	38.1 ± 7.44	36.2 ± 9.03	43.6 ± 8.86	0.471	-	-	-
RVSV [mL]	38.7 ± 6.60	40.2 ± 4.51	36.9 ± 5.66	0.653	-	-	-
RVEF [mL]	50.4 ± 8.09	53.1 ± 9.30	46.1 ± 9.09	0.507	-	-	-
Scar [%]	23.4 ± 0.90	20.9 ± 0.85	23.9 ± 2.45	0.053	-	-	-
Scar [mL]	21.0 ± 1.16	16.2 ± 0.29	24.3 ± 3.74	**0.010**	**0.005**	0.256	**0.020**
MO region [%]	0.3 [0.1; 0.8]	N.A.	N.A.	-	-	-	-
MAAR [%]	46.3 ± 8.70	N.A.	N.A.	-	-	-	-

Controls from Placebo-controlled IC-sEV-delivery study have been analyzed at all time points with Friedman test for paired samples (not-normally distributed variables) or ANOVA for repeated measures (normally distributed 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	**<0.001**	**0.010**	**0.001**	**0.030**
LVM [g]	69.9 ± 6.52	90.8 ± 13.69	116.8 ± 20.4	**<0.001**	**0.012**	**0.001**	**0.027**
LVEDV [mL]	87.4 ± 3.87	100.8 ± 8.19	114.5 ± 16.3	**0.007**	**0.007**	**0.020**	0.136
LVESV [mL]	56.7 ± 4.45	65.8 ± 6.28	71.4 ± 11.52	**0.046**	**0.012**	0.064	0.407
LVSV [mL]	30.7 ± 3.66	35.0 ± 3.93	41.5 ± 6.38	**0.005**	0.055	**0.013**	0.061
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	**0.016**	0.121	0.266	**0.002**
RVEDV [mL]	72.9 ± 8.17	73.3 ± 9.56	77.1 ± 10.9	0.736	-	-	-
RVESV [mL]	38.5 ± 5.76	39.4 ± 7.16	41.7 ± 7.59	0.714	-	-	-
RVSV [mL]	34.5 ± 8.75	33.9 ± 5.43	35.4 ± 7.61	0.956	-	-	-
RVEF [mL]	46.9 ± 8.21	46.4 ± 5.64	45.8 ± 6.90	0.972	-	-	-
Scar [%]	24.6 ± 3.33	22.3 ± 2.95	18.0 ± 2.45	**0.002**	0.183	**0.002**	**0.039**
Scar [mL]	20.0 ± 3.57	16.2 ± 9.40	18.0 ± 4.4	0.647	**-**	**-**	-
MO region [%]	0.6 [0.5; 0.9]	N.A.	N.A.	-	-	-	-
MAAR [%]	44.8 ± 4.07	N.A.	N.A.	-	-	-	-

Animals underwent Intracoronary infusion from Placebo-controlled IC-sEV-delivery study have been analyzed at all time points with Friedman test for paired samples (not-normally distributed variables) or ANOVA for repeated measures (normally distributed 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	0.419
Delta LVM [g]	26.7 ± 8.59	30.2 ± 18.88	0.735
Delta LVEDV [mL]	37.4 ± 19.00	15.4 ± 8.42	**0.035**
Delta LVESV [mL]	43.8 ± 18.96	16.2 ± 10.78	**0.018**
Delta LVSV [mL]	27.7 ± 21.75	15.1 ± 15.64	0.314
Delta LVEF [%]	-7.1 ± 8.27	-0.3 ± 10.84	0.320
Delta CO [L/min]	50.2 ± 93.67	33.0 ± 45.20	0.704
Delta RVEDV [mL]	0.3 ± 12.69	2.3 ± 21.70	0.878
Delta RVESV [mL]	-4.6 ± 19.86	4.7 ± 27.03	0.575
Delta RVSV [mL]	5.2 ± 9.90	6.4 ± 40.50	0.954
Delta RVEF [mL]	5.5 ± 10.08	2.1 ± 22.67	0.790
Delta Scar [%]	-10.6 ± 6.36	-8.4 ± 14.16	0.782
Delta Scar [mL]	-22.4 ± 5.02	-2.5 ± 26.0	0.177

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

3.3.2 Evaluation of 3 Months *minus* 2/3 Days

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	0.743
Delta LVM [g]	17.0 ± 24.06	30.1 ± 27.78	0.459
Delta LVEDV [mL]	9.0 ± 14.24	14.3 ± 20.17	0.662
Delta LVESV [mL]	8.9 ± 16.12	9.8 ± 24.94	0.949
Delta LVSV [mL]	10.1 ± 16.36	19.4 ± 19.69	0.459
Delta LVEF [%]	1.2 ± 9.73	4.8 ± 9.72	0.586
Delta CO [L/min]	23.2 ± 18.19	40.6 ± 87.96	0.712
Delta RVEDV [mL]	5.6 ± 8.60	7.5 ± 25.55	0.890
Delta RVESV [mL]	29.5 ± 57.05	9.3 ± 28.06	0.471
Delta RVSV [mL]	-7.1 ± 18.66	7.2 ± 30.97	0.435
Delta RVEF [mL]	-10.6 ± 23.85	-0.5 ± 17.89	0.460
Delta Scar [%]	14.6 ± 8.62	-18.1 ± 16.44	**0.007**
Delta Scar [mL]	49.4 ± 21.47	-1.6 ± 27.72	**0.015**

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

3.3.3 Evaluation of 3 Months *minus* 1 Month

3 Months *minus* 1 Month [%]	**Ctrl** [n=4]	**IC** [n=6]	**Overall *P*-value**
Delta LVM [mL]	49.6 ± 39.79	66.9 ± 24.27	0.412
Delta LVM [g]	49.5 ± 39.02	66.4 ± 24.75	0.475
Delta LVEDV [mL]	49.3 ± 24.25	31.9 ± 24.36	0.300
Delta LVESV [mL]	56.5 ± 28.29	27.4 ± 29.05	0.156
Delta LVSV [mL]	40.2 ± 31.24	36.6 ± 23.85	0.841
Delta LVEF [%]	-5.8 ± 13.77	3.9 ± 8.57	0.201
Delta CO [L/min]	78.7 ± 95.31	58.0 ± 26.20	0.698
Delta RVEDV [mL]	5.7 ± 13.15	6.4 ± 14.65	0.941
Delta RVESV [mL]	18.1 ± 37.79	10.6 ± 23.92	0.706
Delta RVSV [mL]	-2.5 ± 20.91	7.6 ± 29.55	0.576
Delta RVEF [mL]	-7.1 ± 19.59	0.7 ± 26.44	0.630
Delta Scar [%]	2.5 ± 11.37	-26.5 ± 8.80	**0.002**
Delta Scar [mL]	16.8 ± 24.08	-8.7 ± 21.53	0.119

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