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## The Coronary Arteriogenesis with combined Heparin and Exercise therapy in chronic refractory Angina (CARHEXA) trial: a double-blind randomized placebo-controlled stress echocardiographic study

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**Background:** Coronary collateral circulation exerts protective effects on myocardial ischemia due to coronary artery disease (CAD) and can be promoted by exercise (E) with heparin (H) co-administration. Whether this arteriogenic effects is accompanied by functional improvement of left ventricle (LV) during stress remains unknown.

**Purpose:** To establish the stress-induced functional effects on LV regional and global function of 2-week cycle of H+E in patients with "no-option" CAD.

**Methods:** In a prospective, single-center, double-blind, randomized, parallel-group study we recruited 32 "no-option" patients (27 males; mean age of 61±8 years), with stable angina and CTO, refractory to OMT, not suitable for revascularization and with E-induced ischemia. All underwent 2-week cycle of E (2 E test per day, 5 days a week) and were pre-treated with i.v. 0.9% saline or unfractionated H (100 IU/kg up to maximum of 5.000IU, 10 min prior to E). Canadian Class Score (CCS) and 12-lead E-ECG for time-to-1 mm ST-segment depression were assessed at entry and after treatment. LV function was evaluated during treadmill exercise

with conventional and advanced imaging indices: Wall Motion Score Index (WMSI); Ejection Fraction (EF); Force (systolic blood pressure/end-systolic volume); Global Longitudinal Strain (GLS).

**Results:** Post-treatment exercise-time and CCS improved in both groups. In H+E patients exercise-time improved from 369.8±107.8 sec to 475.3±114.6 sec (p=0.001) while in E patients improved from 384±152.7 sec to 464.8±134.1 sec (p=0.019). CCS score changed in H+E from 2.6±0.7 to 1.9±0.7 (p=0.000), and in E group from 2.4±0.7 to 2.1±0.9 (p=0.046). At peak exercise, H+E was different from E group for EF and GLS (see Table).

**Conclusion:** A 2-week, H+E cycle is associated with improvement in regional and global LV function during exercise, concordantly shown by conventional (WMSI, EF) and advanced (GLS) echocardiographic indices of LV function. This integrates and supplements the classical objective index based on ST-segment depression, unable to localize and quantify the functional consequences of therapy on myocardial ischemia.

Effects of H+E on SE parameters

	H+E	p	P+E	p	*H+E vs P+E
STRESS	Time 0 vs Time 1		Time 0 vs Time 1		Time 0 Time 1
WMSI	1.377 vs 1.279	0.005	1.404 vs 1.376	0.290	0.626 0.255
EF (%)	60.9 vs 64.8	0.016	61.2 vs 57.8	0.284	0.943 0.016
Force (mmHg/mL)	6.36 vs 6.5	0.158	5.82 vs 4.68	0.209	0.760 0.098
GLS (%)	-16.96 vs -18.50	0.001	-15.79 vs -15.60	0.380	0.325 0.027

SE = stress echocardiography; H+E = heparin+exercise; P+E = placebo+exercise; Time 0 = before randomization; Time 1 = after 2-week therapy cycle. \*p values.