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MYOCARDIAL ISCHEMIA AND INFARCTION

EXTRACARDIAC INJECTION OF PLASMID VEGF165 IMPROVES MYOCARDIAL FUNCTION BY STIMULATING MYOCYTES TO RE-ENTER THE CELL CYCLE IN SWINE WITH HIBERNATING MYOCARDIUM

ACC Poster Contributions
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Session Title: Novel Strategies To Limit Ischemic LV Dysfunction
Abstract Category: Myocardial Ischemia/Infarction--Basic
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Background: Over-expressing VEGF improves function in chronic myocardial ischemia but the mechanism is unknown and the relative role of paracrine vs. direct myocardial effects has not been established

Methods: Swine with hibernating myocardium from a chronic LAD occlusion received extracardiac plasmid VEGF165 (500μg) at 4 skeletal muscle sites. We assessed flow (microspheres) and function (echo) 4 weeks (n=8) after VEGF165 vs. untreated hibernating myocardium (n=6) and sham controls (n=5). Histological analysis was performed to quantify myocyte size and nuclear density. Proliferating cardiomyocytes in the growth phase of the cell cycle (Ki-67) and mitosis (phospho-Histone H3, pHH3) were quantified with immunofluorescence.

Results: Extracardiac VEGF165 increased LAD wall thickening from 3.0 ± 0.5 mm in untreated to 5.1 ± 0.6 mm after 4 weeks ($p<0.05$). Vasodilated flow did not change after VEGF (LAD/remote 0.27 ± .03 in untreated vs. 0.25 ± .02 after VEGF165, p-ns). Extracardiac VEGF165 increased Ki-67 and pHH3 positive myocytes (Table) in parallel with an increase in myocyte nuclei (713 ± 46 to 827 ± 23 nuclei/mm2, $p<0.05$) and reversed cellular hypertrophy.

Conclusions: These data indicate that extracardiac VEGF165 improves function by increasing myocyte proliferation independently of perfusion. The use of peripheral skeletal muscle VEGF165 injection supports a paracrine action and may provide a noninvasive approach to improve viable dysfunctional myocardium.

Quantitative Histology / Immunohistochemistry			
	Hibernating LAD		
	Sham (n=5)	Untreated(n=6)	VEGF165(n=8)
LAD ΔWT (ESWT-EDWT) (mm)	6.4 ± 0.5	3.0 ± 0.5*	5.1 ± 0.6†
Myocyte Nuclear Density (number/mm2)	1212 ± 36	713 ± 46*	827 ± 23*†
Ki67+ Myocytes (nuclei/106 myocytes)	284 ± 69	410 ± 82*	675 ± 81*†
pHH3+ Myocytes (nuclei/106 myocytes)	2 ± 2	9 ± 5	126 ± 31*†
Myocyte Diameter (μm)	13.8 ± 0.4	18.4 ± 1.0*	15.8 ±0.4*†
Mean ± SEM, *p<0.05 vs. Sham, †p<0.05 Untreated vs.VEGF165			