Overexpression of GATA4, TGF-ß3, MEF2C and HIF1-α contributes to improvement of infarct size in porcine model of chronic myocardial infarction, treated with percutaneous intramyocardial delivery of secretome of apoptotic white blood cells (APOSEC)

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A) Background

Although tremendous efforts have been made to replace infarcted myocardium with regenerative cells, the currently available methods has proven marginal efficacy in clinical application. Secretome of apoptotic peripheral white blood cells (APOSEC), derived from easily obtainable large amount of peripheral blood mononuclear cells (PBMC) regenerates the myocardium after acute ischemic injury. We hypothesized that catheter-based delivery of APOSEC would be effective in a clinically relevant porcine model of chronic left ventricular (LV) dysfunction after AMI.

B) Preparation of APOSEC

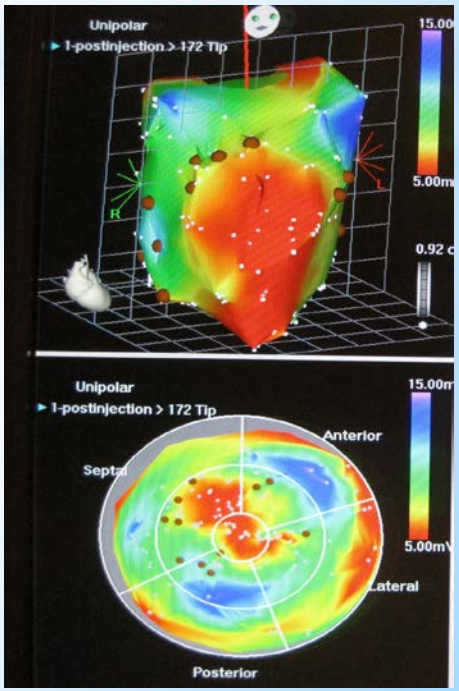
C) Study design

Day 0
Closed chest reperfused AMI
Haemodynamic measurements

Day 3
Cardiac MRI
LV function
Late enhancement

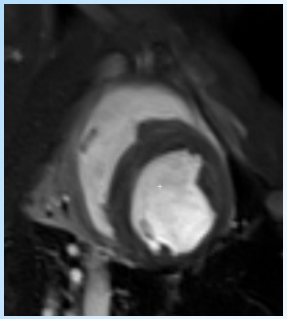
Day 30
Percutaneous intramyocardial injection of APOSEC or Medium

Day 60
Cardiac MRI
LV function
Late enhancement
Control angiography
Haemodynamic measurements



Cardiac MRI and NOGA-mapping

APOSEC



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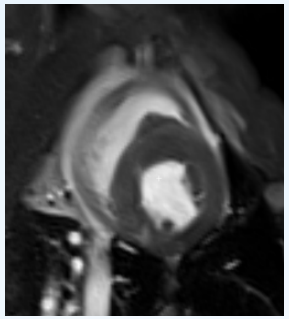

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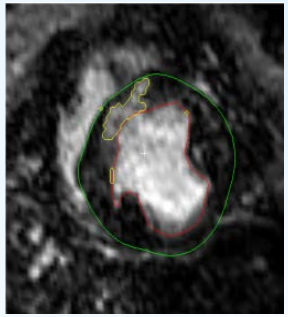
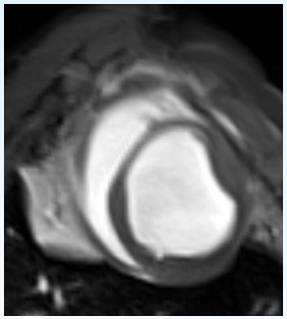


FUP LE

Medium



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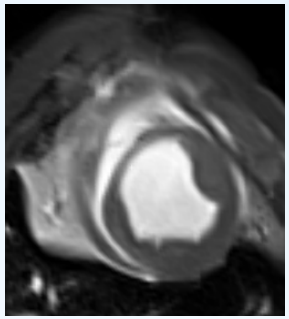

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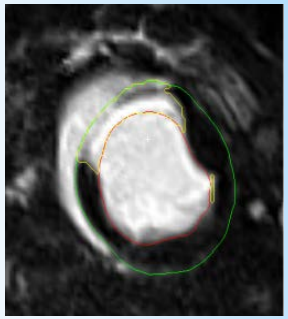
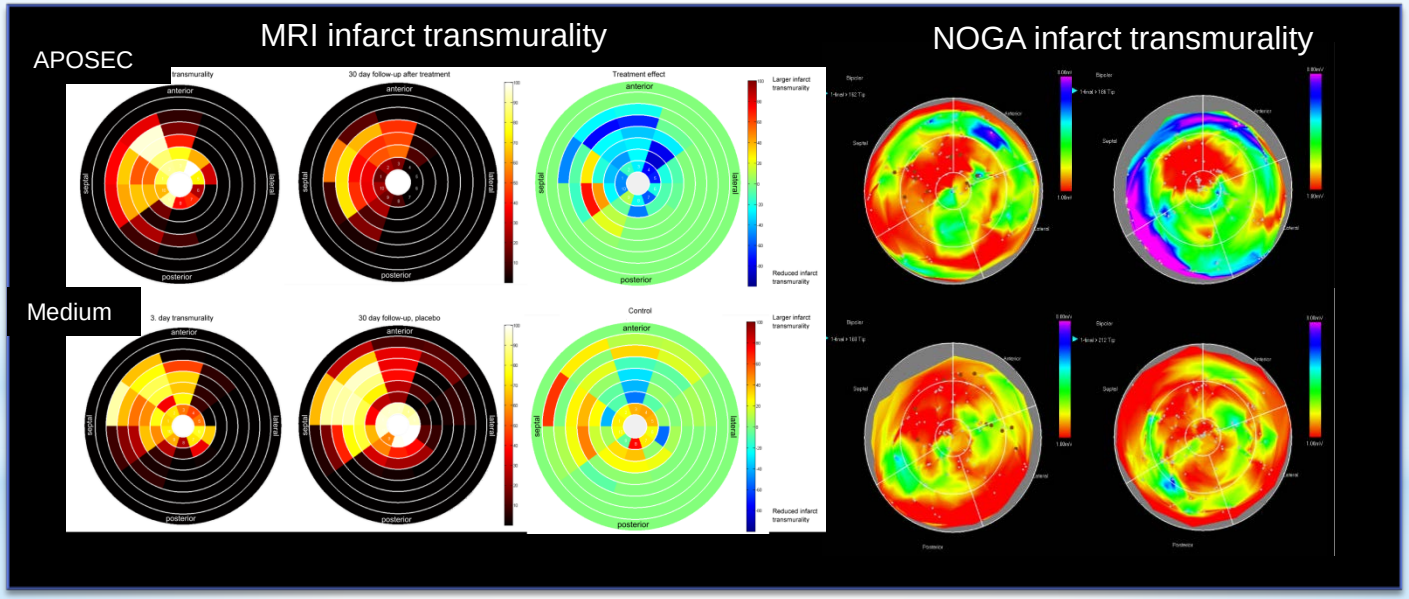


FUP LE

C)



Baseline vor injection

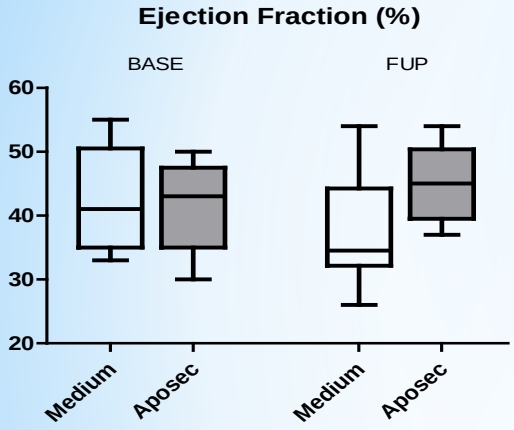
FUP

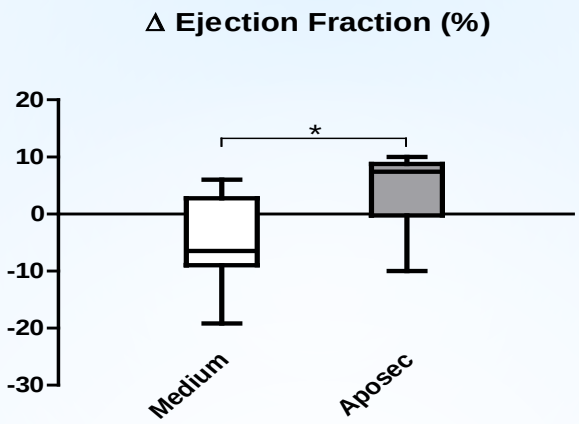
Difference between baseline and FUP

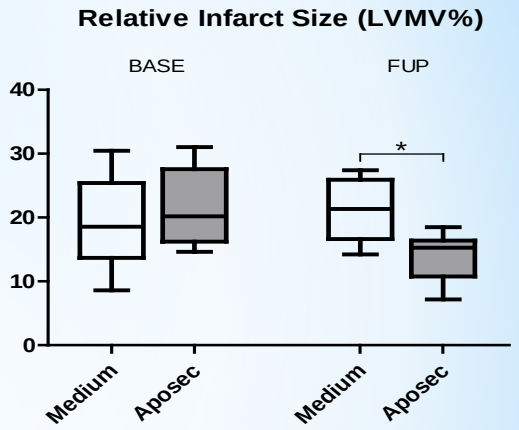
Baseline vor injection

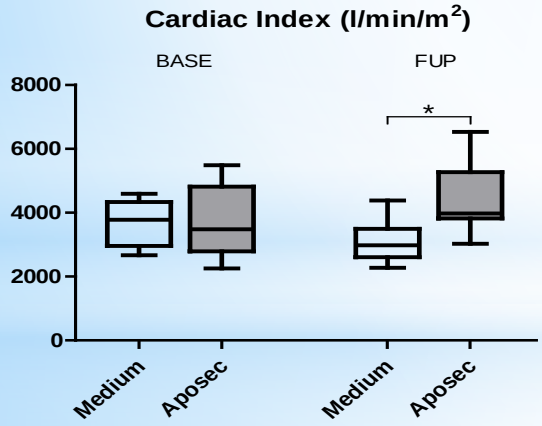
FUP

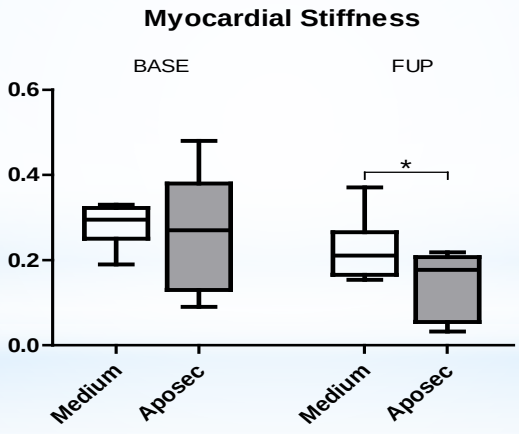
Results of myocardial function, infarct size and heamodynamics

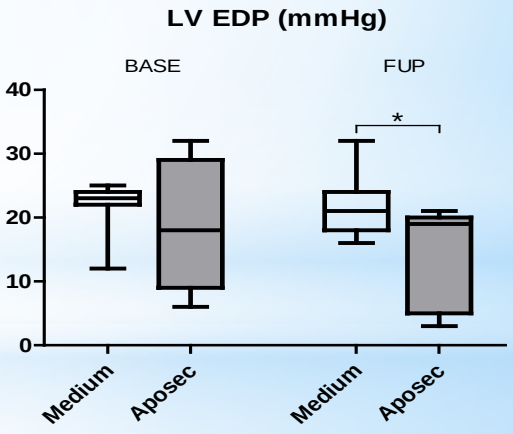




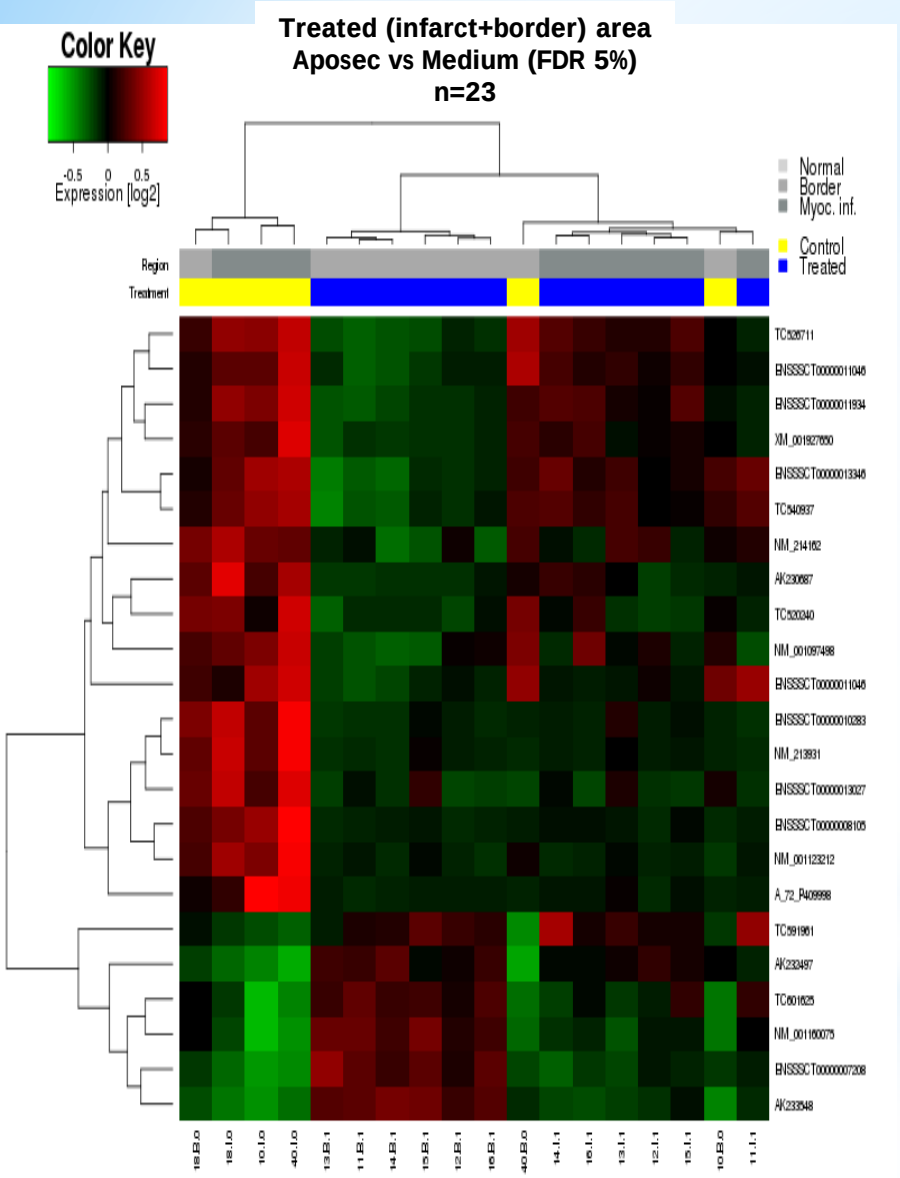








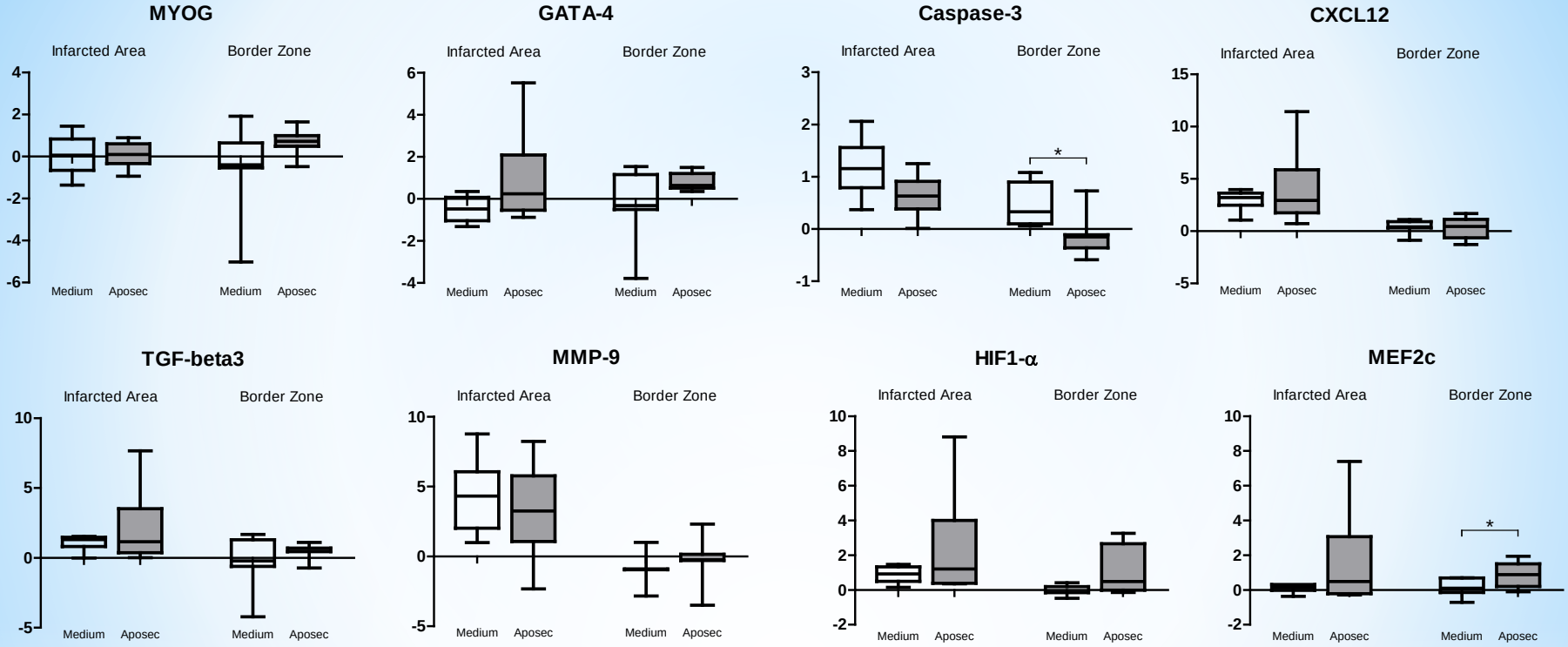
Differences in gene expression profile in the treated area



Systematic Name	logFC	adj. P value	Name of gene	Regulation in Aposec group
NM_214162	-1.887	0.029	caspase 1. apoptosis-related cysteine peptidase (interleukin 1. beta. convertase)	down
NM_001097498	-0.753	0.015	tumor necrosis factor (ligand) superfamily. member 13b	down
ENSSSCT00000010283	-0.815	0.003	similar to LOC513955 protein	down
NM_001160075	-0.949	0.005	claudin 3	down
ENSSSCT00000013346	-1.18	0.007	similar to Uncharacterized protein CXorf21 homolog	down
NM_001123212	-1.287	0.01	uroplakin 1B	down
ENSSSCT00000011046	-1.623	0.014	similar to Stromal cell-derived factor 2-like protein 1 precursor (SDF2-like protein 1) (PWP1-interacting protein 8)	down
ENSSSCT00000007208	-2.936	0.015	similar to Protein S100-A2 (S100 calcium-binding protein A2) (Protein S-100L)	down
ENSSSCT00000008105	-1.249	0.016	epididymal secretory protein	down
XM_001927650	-0.908	0.022	similar to trichohyalin	down
NM_213931	-3.367	0.038	arachidonate 15-lipoxygenase	down
TC520240	-1.61	0.047	n.i.	down
ENSSSCT00000013027	-2.617	0.013	n.i.	down
AK233548	-1.097	0.015	n.i.	down
ENSSSCT00000011046	-1.297	0.015	n.i.	down
AK230687	-2.509	0.015	n.i.	down
ENSSSCT00000011934	-1.895	0.016	n.i.	down
A_72_P409998	0.929	0.007	n.i.	up
TC601625	1.154	0.013	n.i.	up
TC591961	0.592	0.015	n.i.	up
TC540937	2.522	0.015	n.i.	up
TC526711	3.032	0.029	n.i.	up
AK232497	2.857	0.04	n.i.	up

RT-qPCR of selected genes of interest

B)



Comments

1. RT-qPCR analyses confirmed the significant overexpression of cardiac myogenesis and vascular development gene, MEF2c and the repression of apoptosis regulator caspase-3 in the border zone of infarction in the APOSEC–-treated animals.

2. Trend towards higher expression ($p<0.1$) of angiogenic regulatory factor, hypoxia inducible factor 1alpha (HIF-1α) and transcription factor, GATA-4 was seen in the border zone of the APOSEC group ~~as~~ compared with the medium group.

3. No statistical difference between the groups was observed regarding the expressions of genes involved in stem cell homing (CXCR12), transcription factor myogenin, extracellular matrix proteins MMP-9, and TGFß-3.

Summary

1. The present study demonstrated that the 3D-guided NOGA injection approach of APOSEC is safe and effective in chronic myocardial ischemia.

1. Percutaneous intramyocardial injection of APOSEC was associated with reduction in infarct size and significant increase in LV EF, which are accompanied by improvement in contractile function and haemodynamics.

2. Gene profiling analysis of the APOSEC-treated myocardial areas revealed downregulation of inflammatory and apoptotic genes.

3. Post-hoc validation of gene expression by RT-qPCR showed higher levels of expression of myogenic factor, MEF2C and a robust downregulation of apoptosis regulator, caspase-3.

In summary, we could show that catheter-based 3D-NOGA guided intramyocardial application of APOSEC attenuates myocardial remodeling after AMI, mitigating apoptosis and inflammation and alters gene expression related to enhanced myocyte function.