Cellular and molecular mechanism of heart failure

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Translational medicine – strategic trend in development of clinical science and practice

Basic research

Everyday clinical practice:

- **Diagnostics**
- **Treatment**
- **Primary prevention**
- **Secondary prevention and rehabilitation**
- **Cardiovascular surgery and Interventions**

Thus we should find out:

- **What specific biological events or molecular pathways play a role in certain diseases?**
- **What biomarker(s) can we monitor to assess target therapy in the clinics?**
- **How can we best use this information to discover and develop new therapeutics and associated diagnostics that will help with patient selection?**

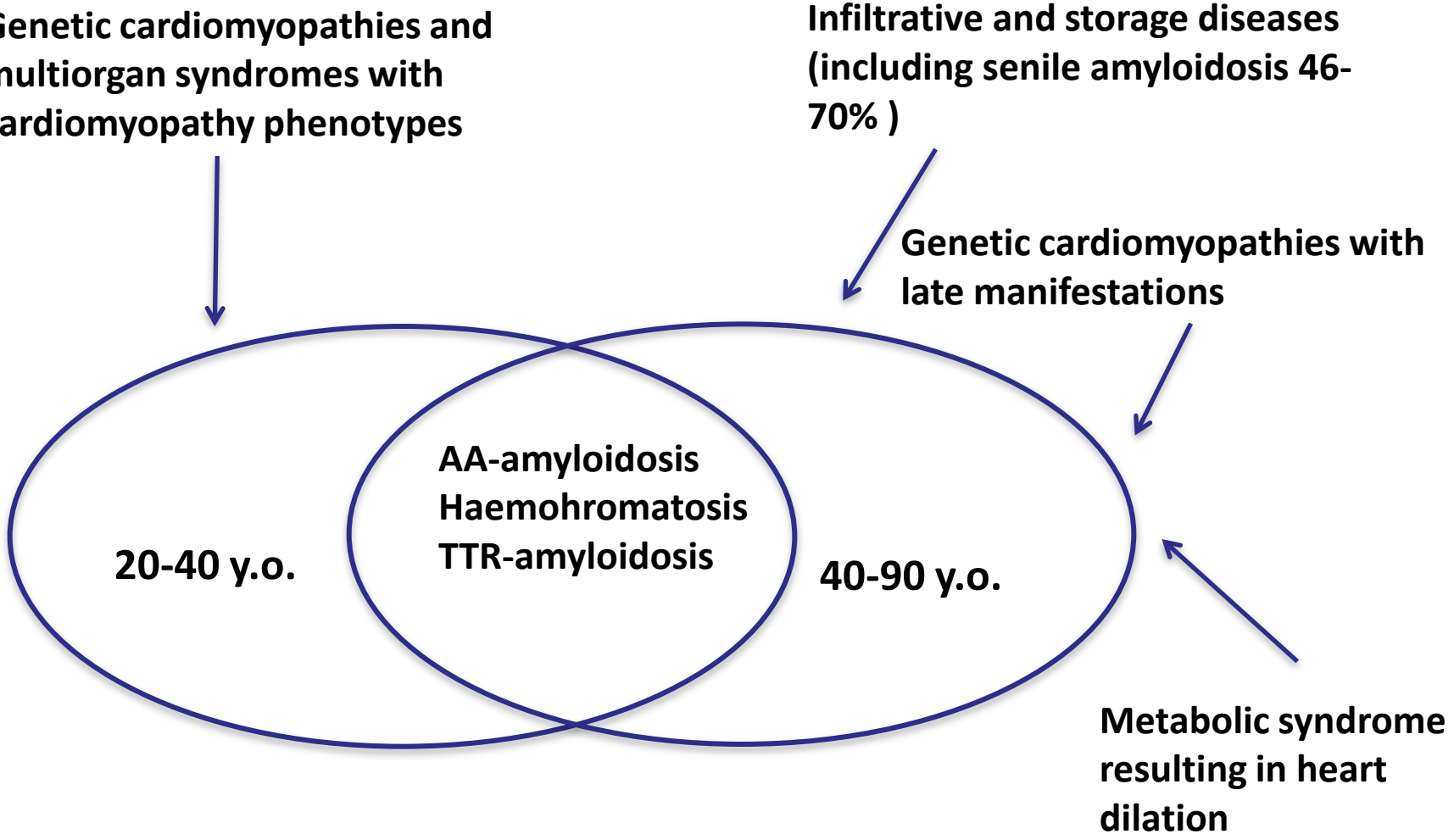
Translational research in heart failure: main projects

- Novel in etiology and pathogenesis of heart failure
- Molecular imaging modalities
- Cardiac protection against ischemia-reperfusion injury
- Targeted therapy
- Circulating stem cells and resident progenitor cells in heart failure

Etiology of heart failure

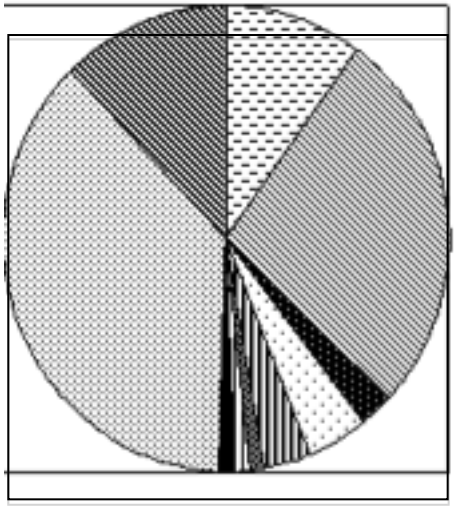
- Coronary artery disease
- Primary and secondary hypertension
- «Non-coronary heart diseases»
    - cardiomyopathies
    - myocarditis
    - infiltrative disorders (amyloidosis)
    - storage diseases
    - congenital and acquired heart diseases
- Endocrine disorders

Etiology of diastolic heart failure depending on the age of manifestation



Structure of diastolic heart failure of unknown etiology

(excluding CAD, AH, HCMP, DCMP, Myocarditis)

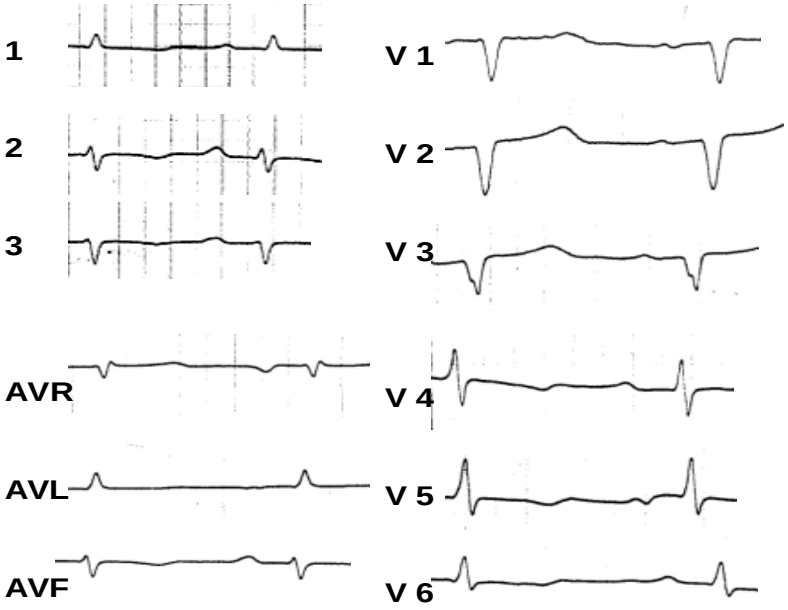


10%	Burn-out HCMP (dilated phase)
28%	AL-amyloidosis
2%	AA-amyloidosis
4%	TTR amyloidosis
3%	Haemochromatosis
1%	Wilson-Konovalov disease
1%	Syndromic HCMP
1%	Syndromic DCMP
38%	Metabolic syndrome
12%	multiorgan system disorders

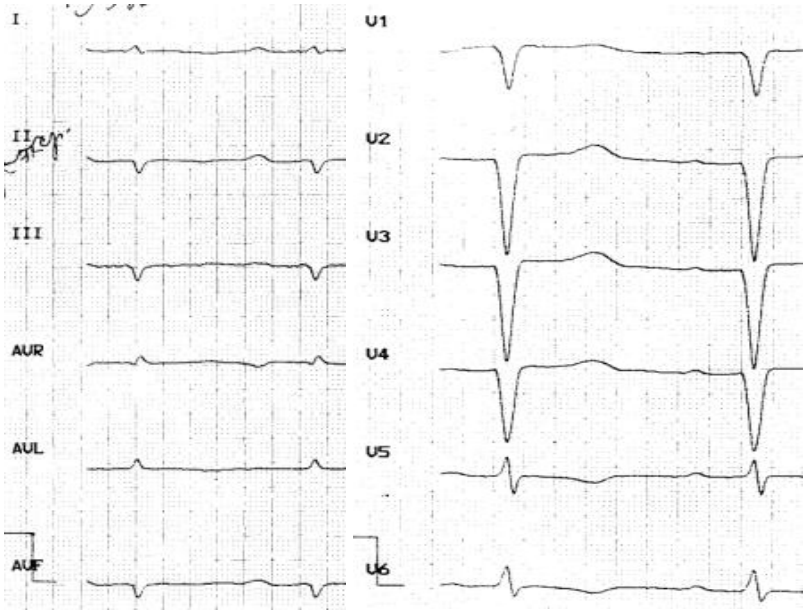
There are no rare diseases there are “rare diagnosis”

ECG in 45 y.o. patient with TTR amyloidosis. QS and ST elevation (pseudo MI) in V1-V4

23.06.2003



24.09.2004



First Russian population study on the prevalence of transthyretin mutations in patients with HF

HUMAN GENETICS

Transthyretin Gene V30M, H90N, and (del9) Mutations in Cardiomyopathy Patients from St. Petersburg

K. V. Solovyov[a, b], N. A. Grudinina[a, c], E. N. Semernin[b, c], I. V. Morozova[a], S. A. Smirnova[a], D. S. Polyakov[a], T.D. Aleynikova[a], E. V. Shliakhto[b, c], A. Ya. Gudkova[b, c], and M. M. Shavlovsky[a]

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Received June 6, 2010

Abstract—A search of transthyretin (*TTR*) gene mutations was performed in patients with cardiomyopathies from St. Petersburg. Mutations H90N, V30M and deletion (del9) of nucleotides GACTTCTCC in position 6776 from the start codon of the *TTR* gene (in position 98782 according to reference sequence AC079096 (NCBI) was found. The H90N mutation in the third exon of *TTR* gene was detected in a son of a cardiomyopathy patient and in his mother, which lacked any clinical manifestations. Mutation V30M in exon 2 of *TTR* gene was found in heterozygous in one of the probands. Deletion (del9) was revealed in a patient with cardiomyopathy and in his two daughters from different marriages, who had no clinical manifestations of the disease. All the mutations revealed in this study were previously identified in other populations.

DOI: 10.1134/S1022795411020165

TTR amyloidosis constitutes a rare (1%) but important cause of HF

- Prevalence of **AL- amyloidosis**
- were investigated in 212 patients with CMP (RCMP, HCMP, DCMP genesis) including patients with complicated biventricular predominantly right CHF by immunohistochemical methods
- Results: Cardiac form of AL-amyloidosis was diagnosed in 22 patients (10,4%)

AL- amyloidosis
is NOT a rare disease !!!

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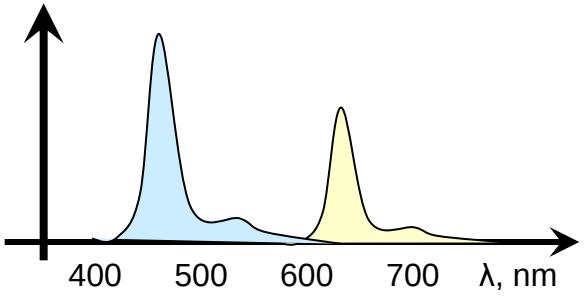
Molecular imaging:
advantages and state-of-the-art

- Early detection of biochemical and metabolic processes underlying the disease;
- Combination of diagnostics and therapeutic effect (teranostics);
- Individual characteristics of the disease course at the molecular level (personalized therapy);
- Understanding molecular pathogenesis of the disease

Diagnostic fluorescent systems

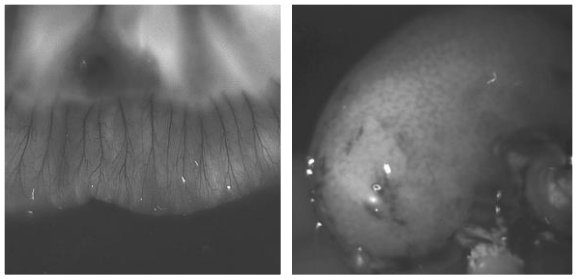
Single-dot spectral

Evaluation of the metabolism of certain substances



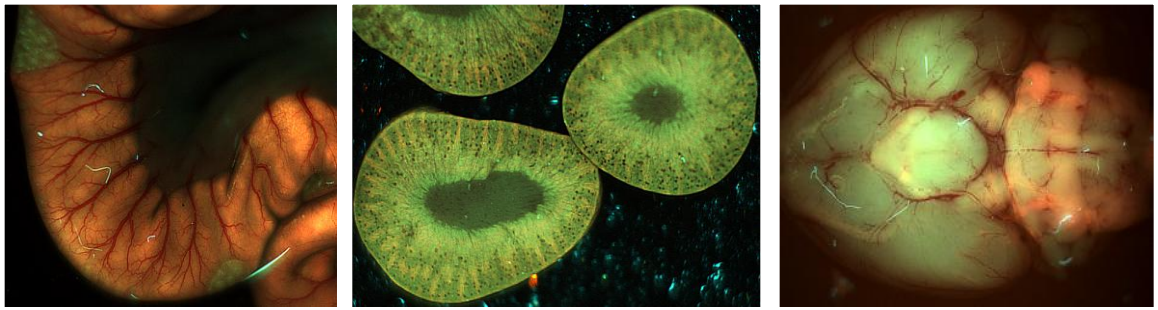
Monochromatic

Evaluation of structure (anatomical imaging)

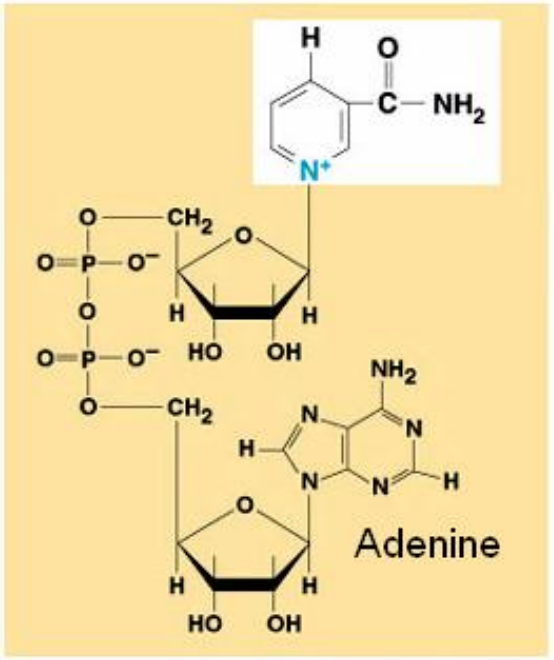


Multispectral

Evaluation of metabolism + structure



Ischemia-induced imbalance between NAD and NADH can affect the intensity of autofluorescence



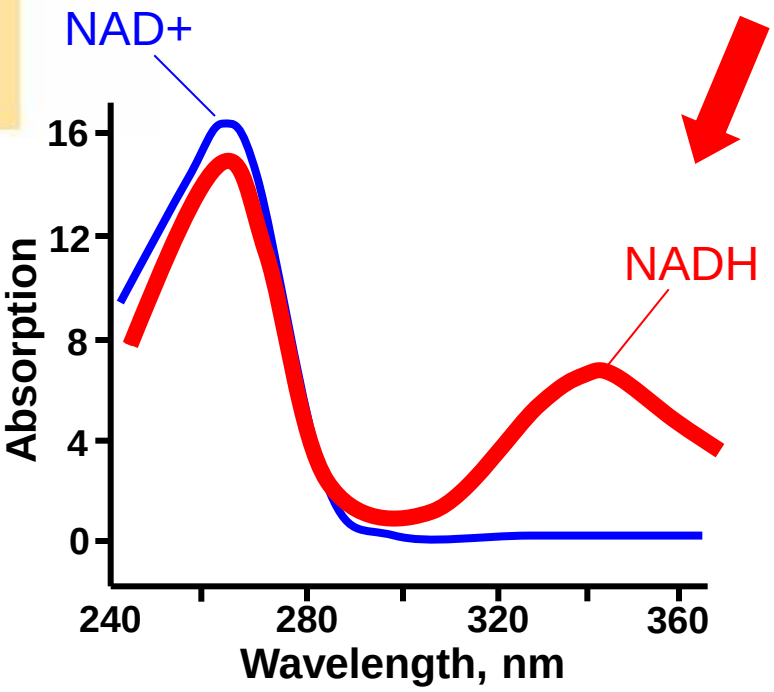
Oxidized form: NAD+

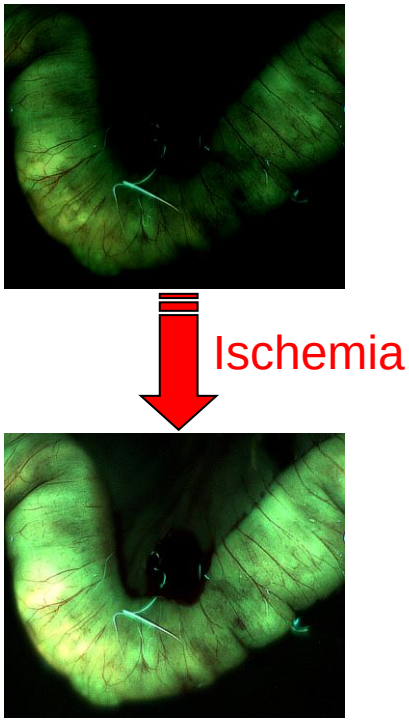
+ 2[H]

Ischemia

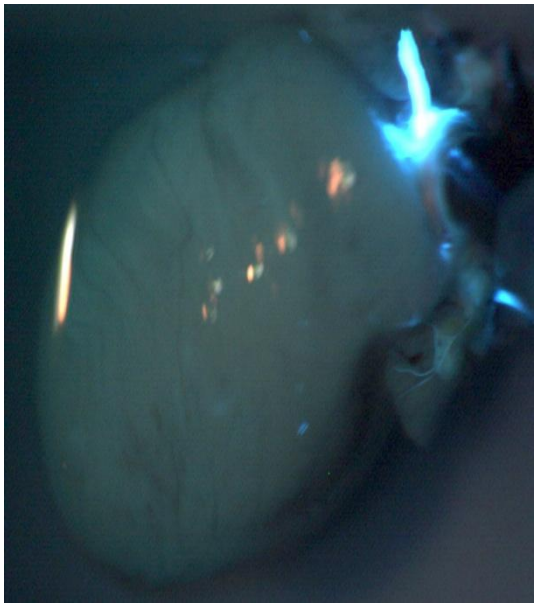
+ H+

Reduced of the oxidized form: NADH

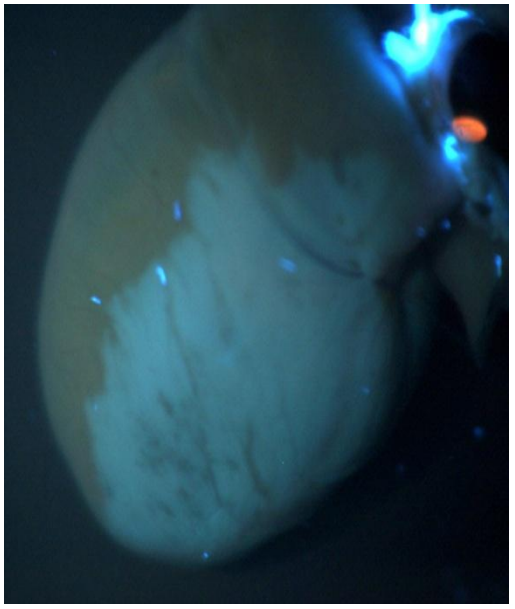




Intraoperative imaging of tissue viability. Autofluorescence method

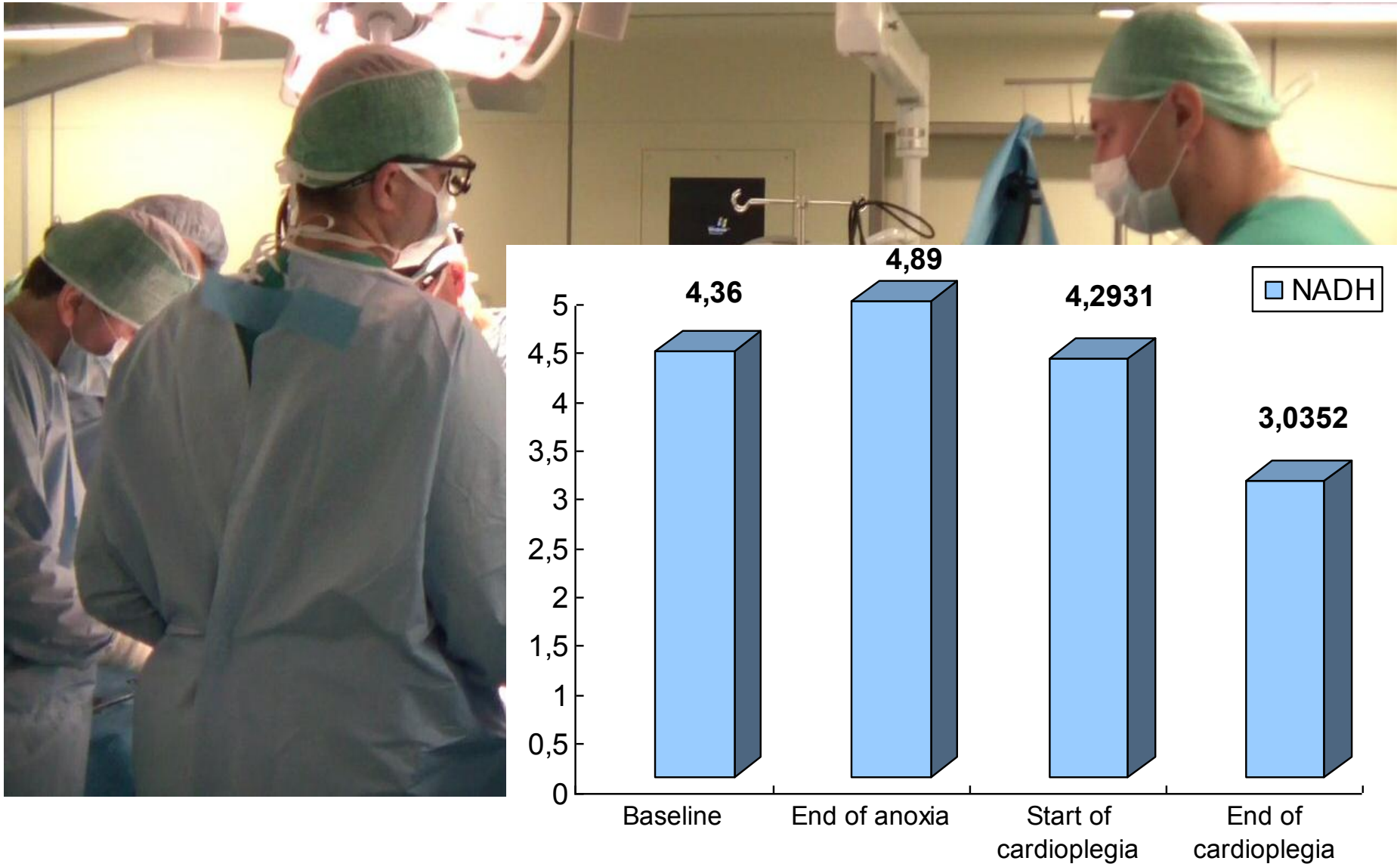


Before ischemia



30 sec after coronary occlusion

Intraoperative evaluation of myocardial metabolism in cardiac surgery with use of fluorescent spectroscopy



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Pre- and postconditioning in open heart surgery: main benefits

1. Reduced myocardial ATP breakdown
2. Lower troponin T in the postoperative period – **lower myocardial injury**
3. Hemodynamic benefit and **improved cardiac performance**: greater LV and RV ejection fraction, higher cardiac index
4. Reduced duration of mechanical ventilation
5. Less need for inotropic support
6. Fewer ventricular tachyarrhythmias

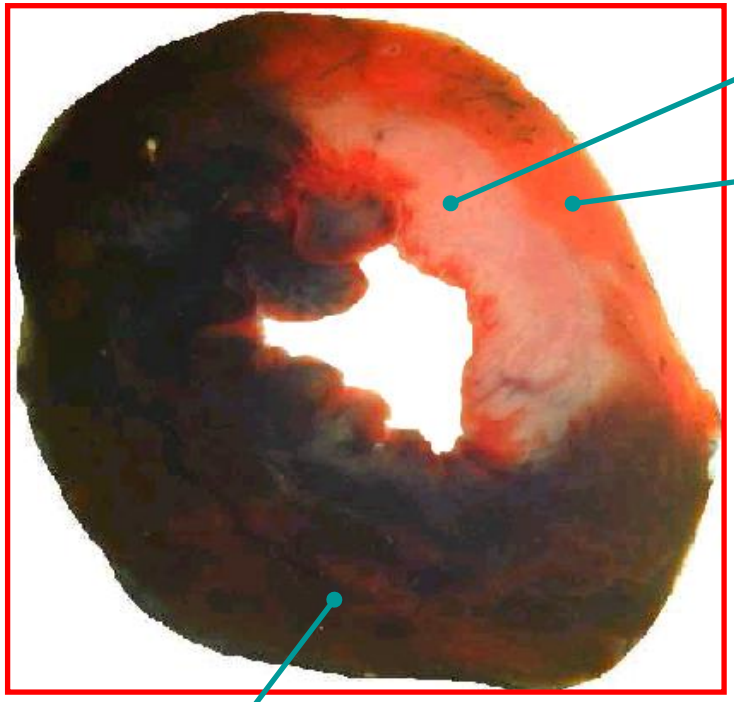
Current concept of preconditioning: *cardioprotective phenotype can be elicited by a wide spectrum of mildly noxious stimuli applied either locally or systemically*

Ischemic preconditioning: local and remote

Non-ischemic preconditioning:

- Pharmacological preconditioning
- Preconditioning with physical factors
- Metabolic preconditioning

Local ischemic preconditioning (LPC): significant infarct limitation occurs when preconditioning stimulus is strong enough

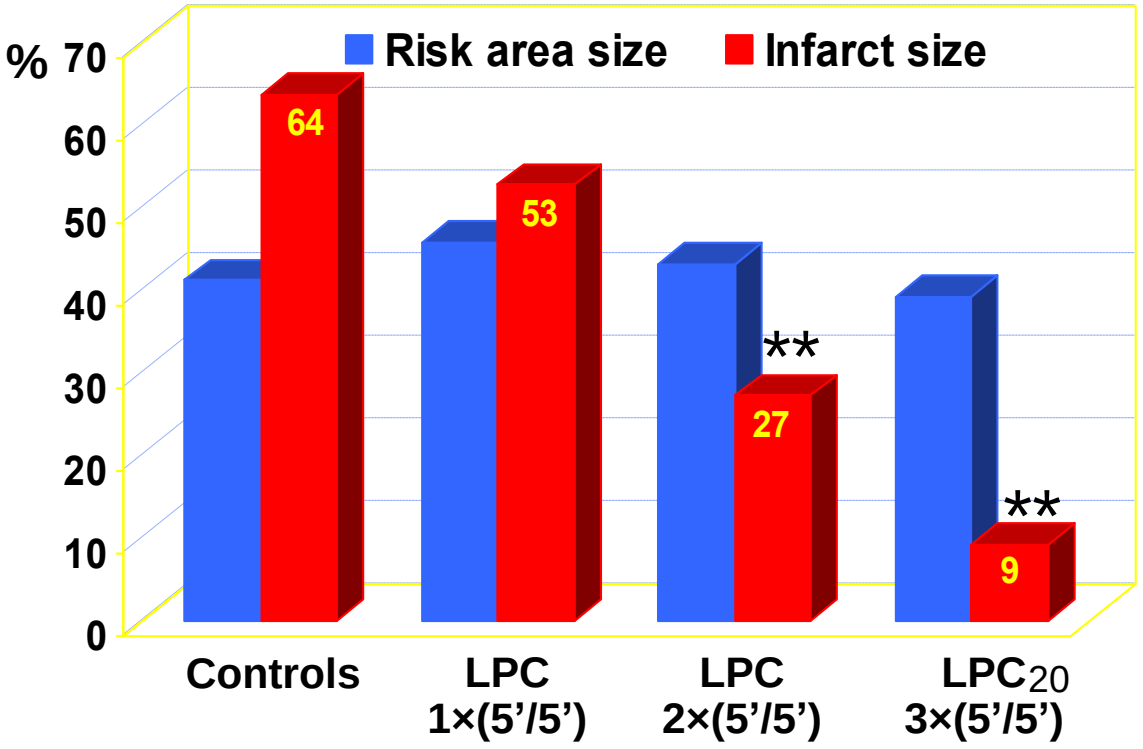


Necrotic area

Viable myocardium within the risk area

Normal perfusion

** - p<0.01 vs. controls



Personal communication, 2001

First description of antiarrhythmic effect of ischemic postconditioning

ELSEVIER

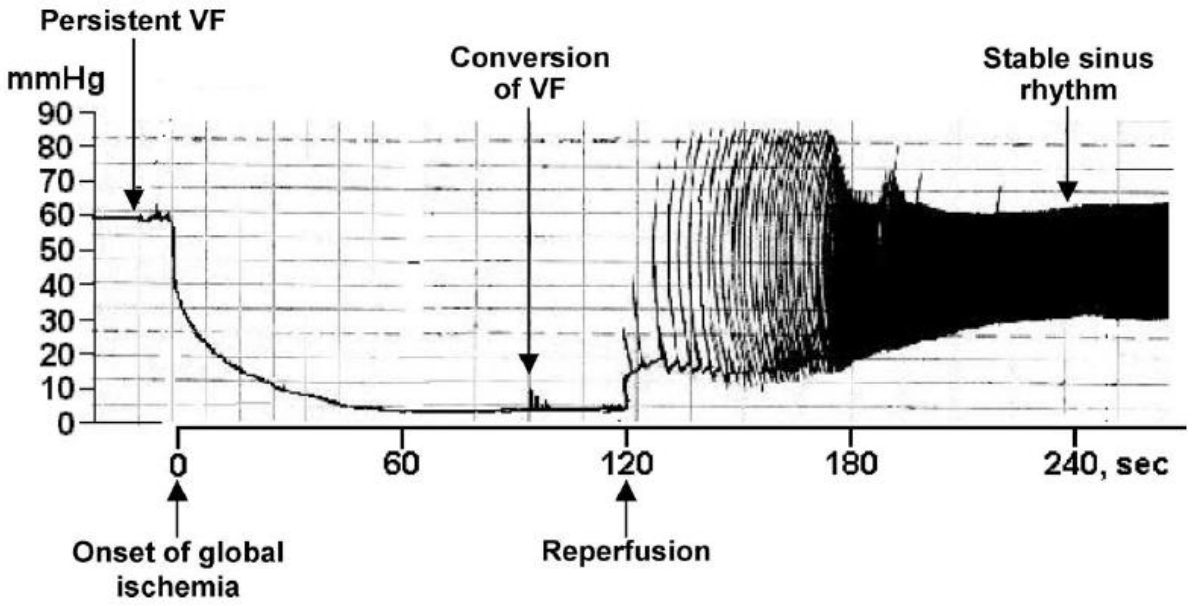
European Journal of Cardio-thoracic Surgery 25 (2004) 1006–1010

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

Ischemic postconditioning: brief ischemia during reperfusion converts persistent ventricular fibrillation into regular rhythm

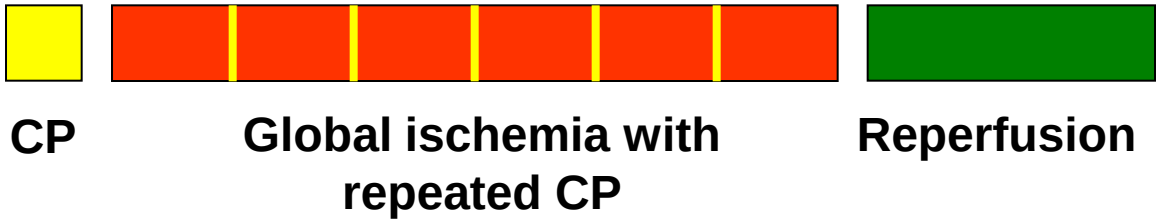
Michael Galagudza[a,c], Dmitry Kurapeev[b], Sarkis Minasian[a], Guro Valen[c], Jarle Vaage[d,*]



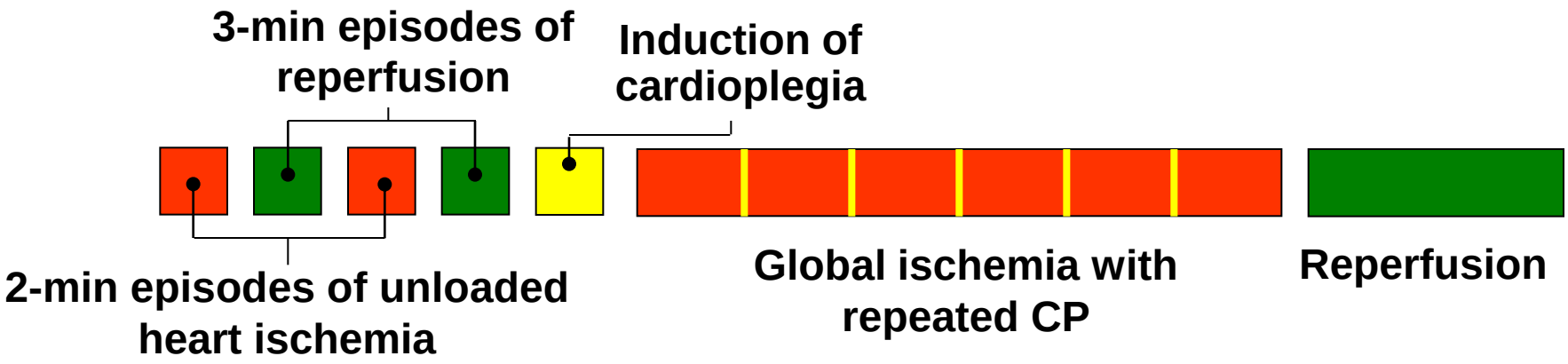
Restoration of ischemic environment for 2 min resulted in 100% reversal of persistent VF in the isolated rat heart

New method of preconditioning induction in open heart surgery

Standard CPB and cardioplegia scheme



CPB and cardioplegia scheme with preconditioning

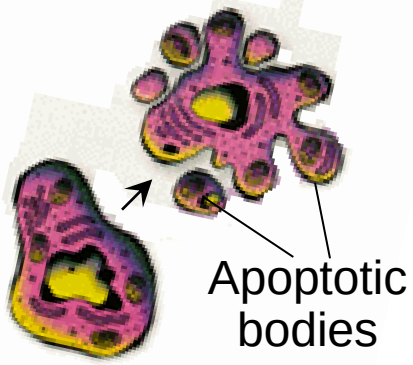


Clinical trial on the effectiveness of ischemic preconditioning in cardiac surgery

- 200 patients with ischemic heart disease and valvular pathology;
- Randomization into the groups of preconditioning, controls, and parallel circulatory support;
- Main end points: troponin I, CK-MB prior to cardiopulmonary bypass, and 12, 24, and 48 h after surgery;
- Transmyocardial oxygen gradient (paired blood samples from the cardioplegic cannula);
- Myocardial biopsies for electron microscopy and molecular studies (Western blot analysis);
- Secondary end points: hemodynamic and clinical parameters

Myocardial protection and regeneration with product of apoptosis: *hypothesis*

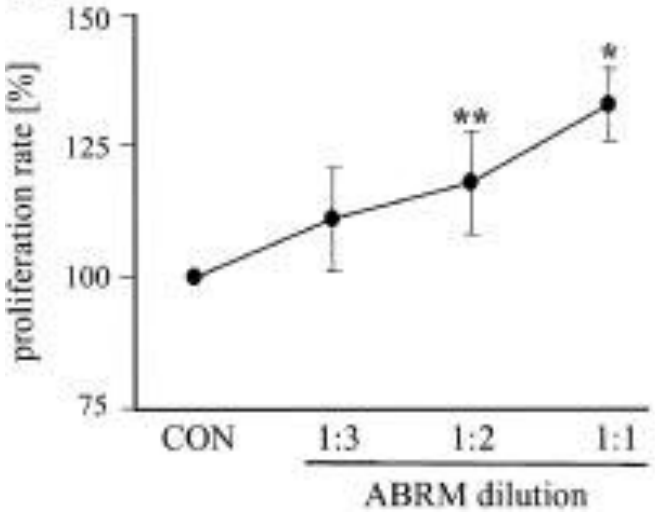
Cardiac myocyte apoptosis



Cardiac injury

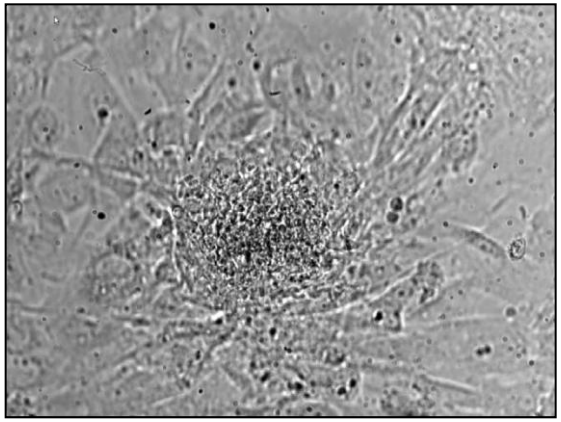
Our hypothesis: products of apoptosis might be a *"rescue signals"* for cardiac resident stem cells and circulating bone marrow stem cells thereby promoting cardiac regeneration after injury

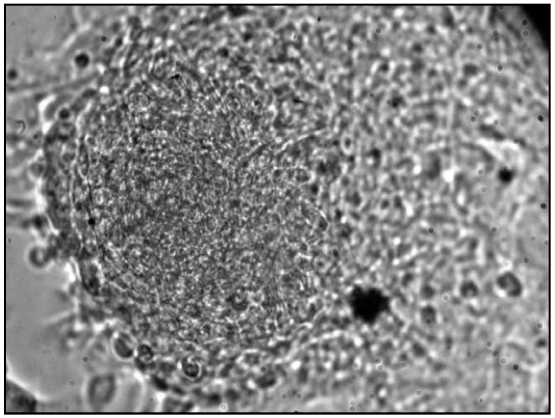
Genesis of the hypothesis: endothelial apoptotic bodies dose-dependently stimulate proliferation of endothelial progenitor cells (Hristov et al., 2004)



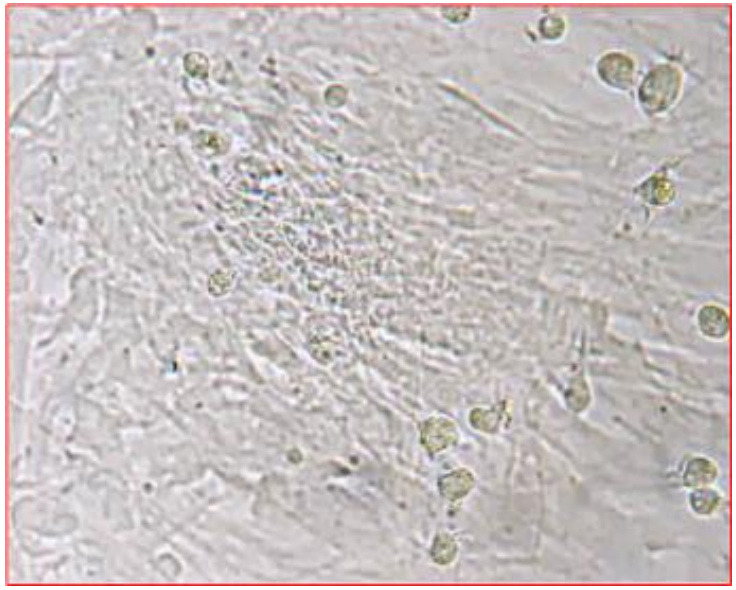
Apoptotic body-enhanced proliferation and maturation of cardiac myocyte colonies

Controls
(10th day of culture)

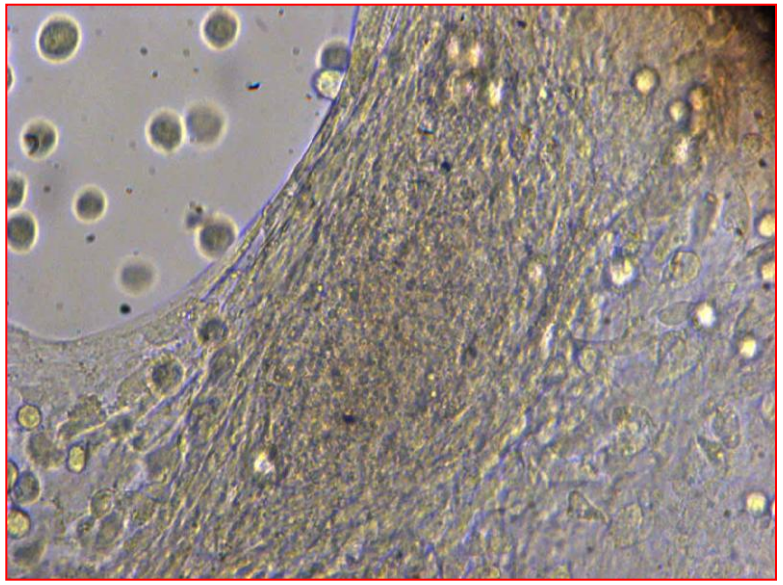




Apoptotic bodies
(10th day of culture)



25th day, 46 beats/min

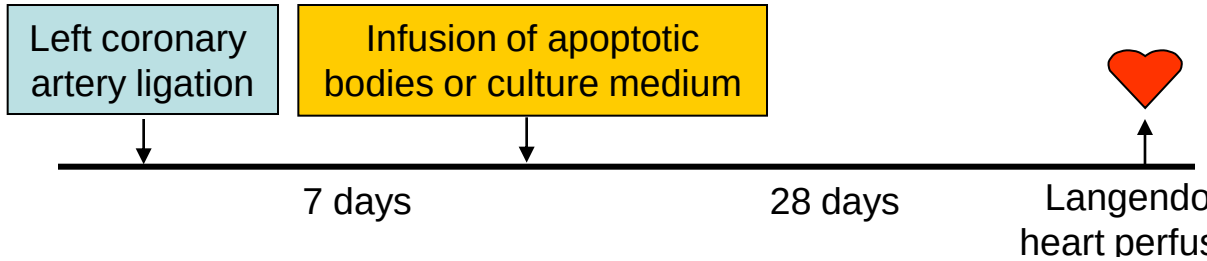


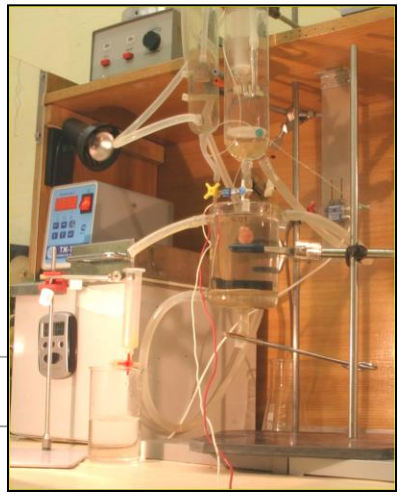
25th day, 99 beats/min

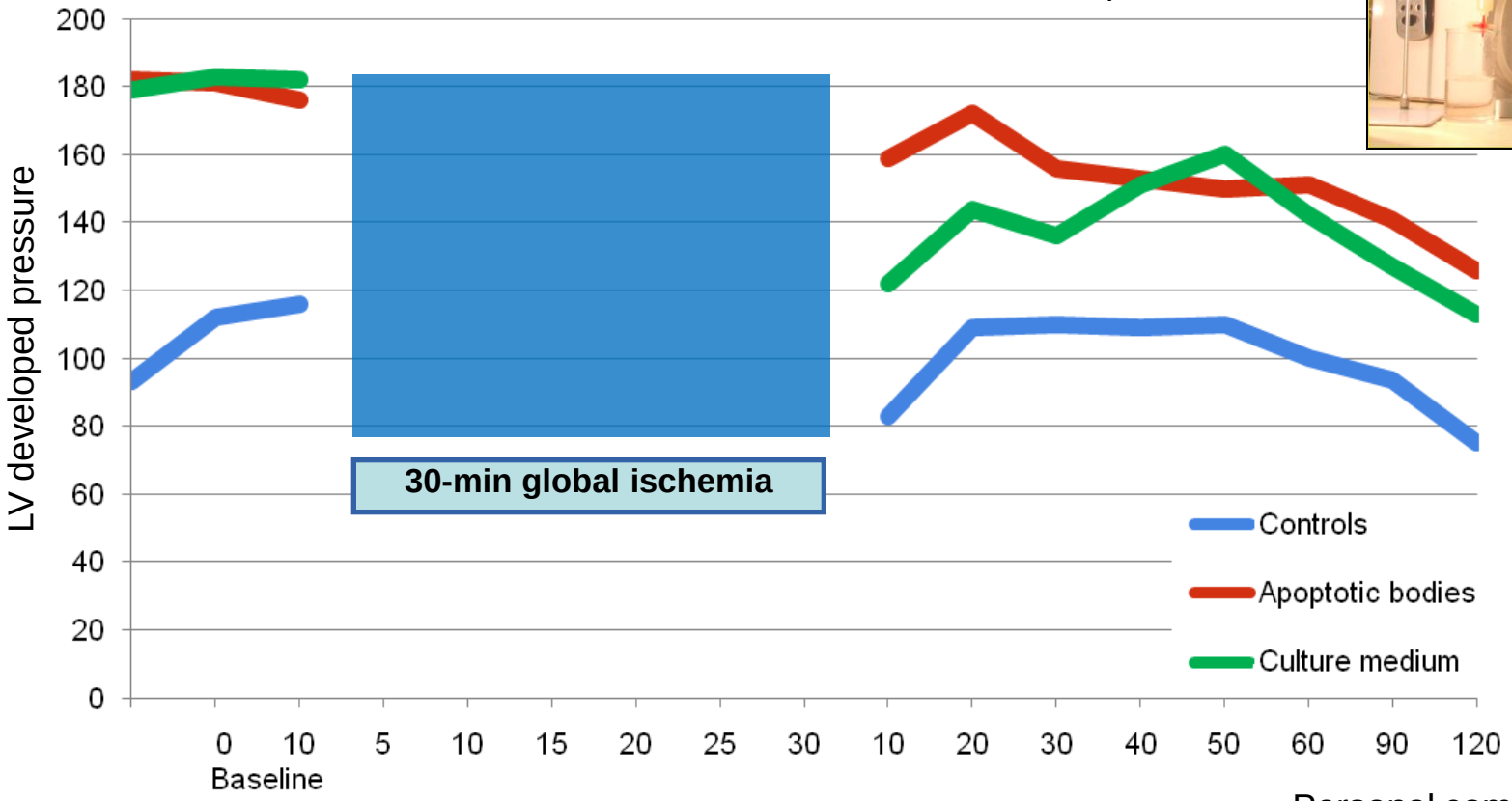
G. Belostotskaya et al., 2011

Apoptotic products-mediated amelioration of LV function

Experimental design:







Personal communication, 2011

Perspectives and applications apoptotic bodies

- Additional proof-of-concept experiments in different models of cardiac injury;
- Identification of the molecular pattern of the “rescue signal” from the apoptotic bodies may contribute to the development of novel drugs for heart failure;
- The payload of the apoptotic body can vary depending on the cell source, type and severity of injury, etc.
  Molecular profiling of these natural “cocktails” may provide unique opportunity of tissue- and cell-targeted repair.

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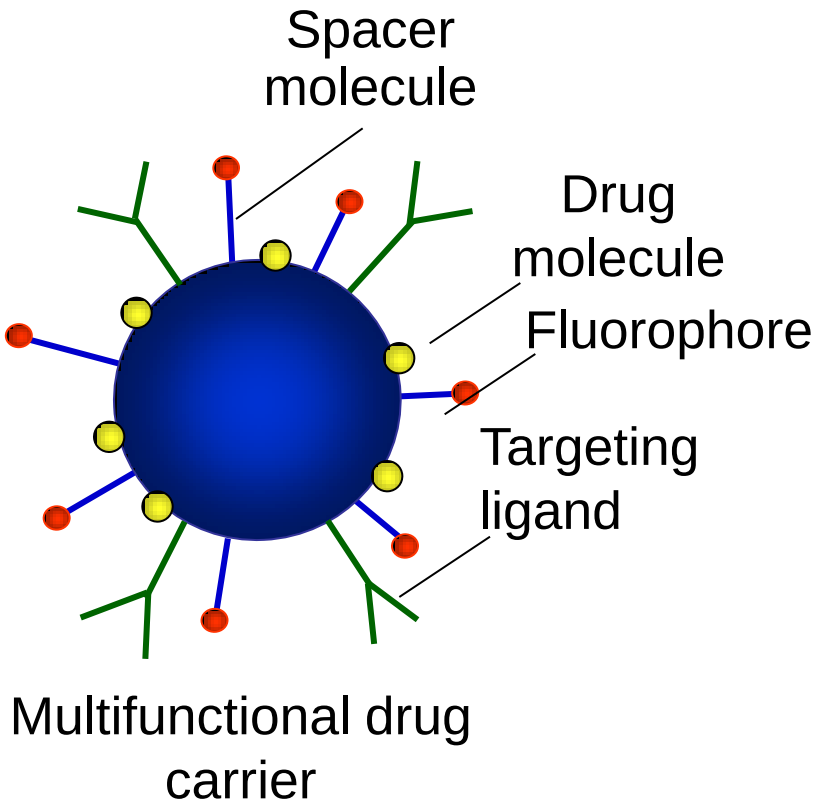
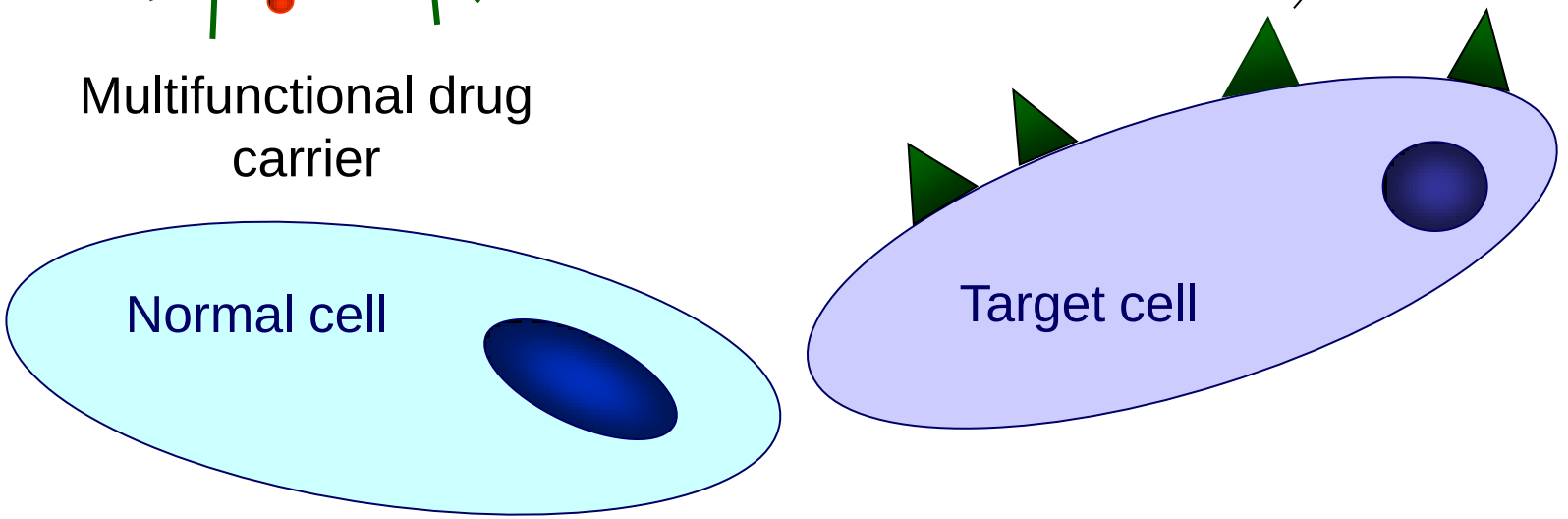
Targeted drug delivery to the ischemic heart: *advantages*

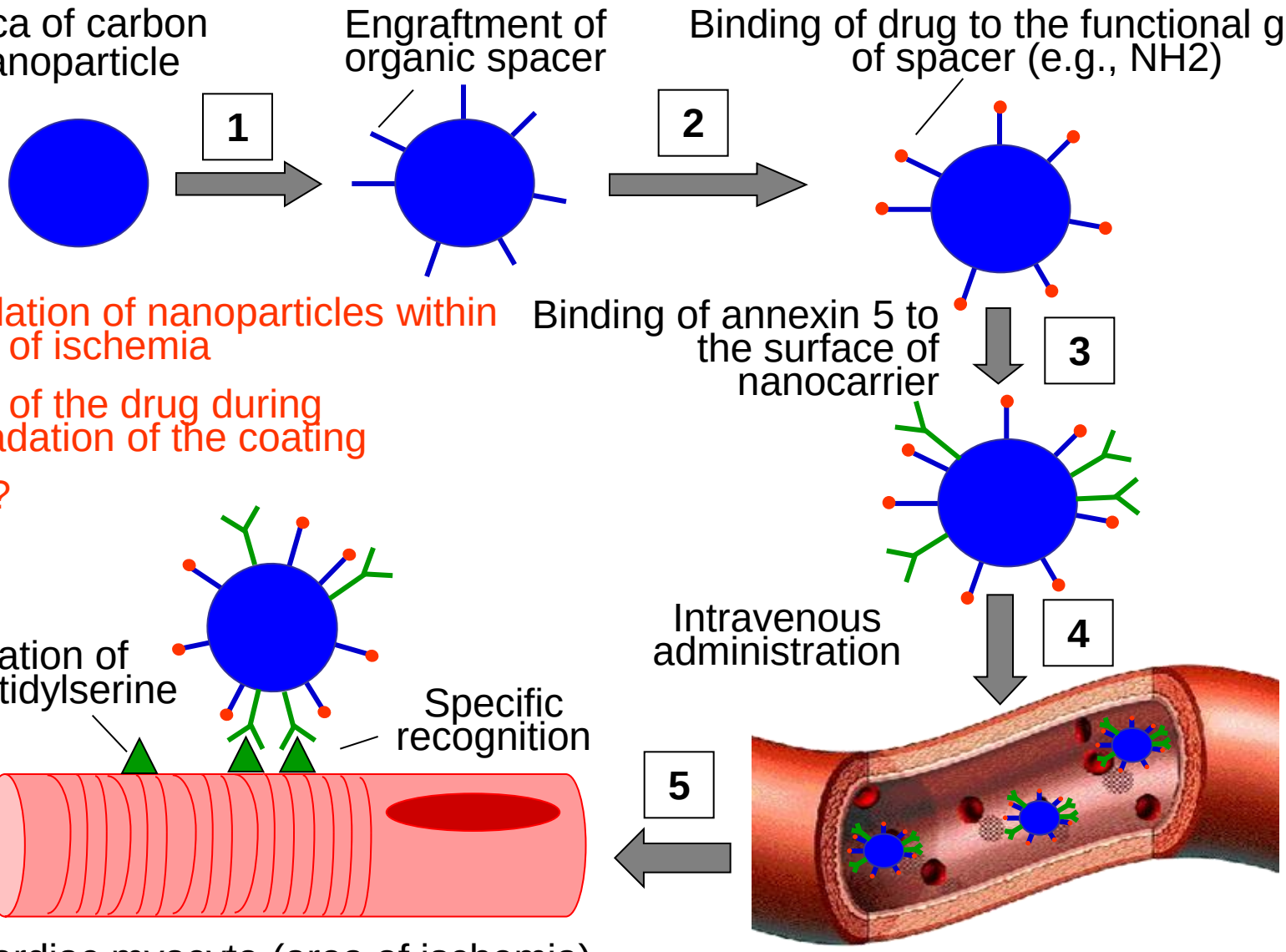
- Decreased volume of drug distribution
- Reduced drug toxicity
- Increase in the solubility of hydrophobic drugs
- Improvement in the stability of the drugs (proteins, peptides, oligonucleotides)
- Increased biocompatibility
- Increased patient adherence to treatment

Active nanoparticle-based heart targeting: *use of targeting ligands ("anchors")*

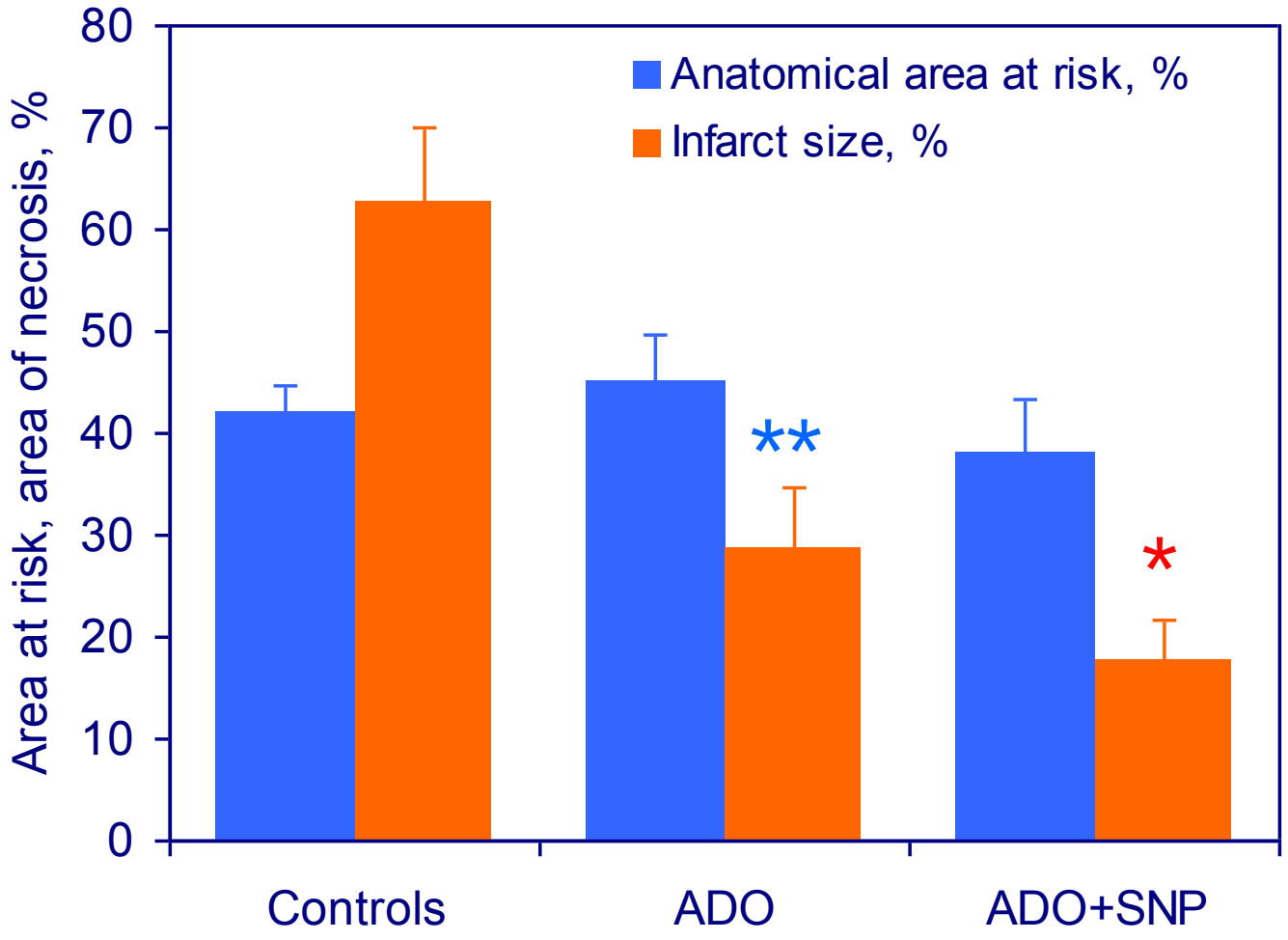




The algorithm of heart targeting with nanoparticles



Augmentation of infarct-limiting effect of adenosine after its adsorption on the surface of silica nanoparticles



** - p<0,01 versus control; * - p<0,05 in comparison to free adenosine

Our publications on targeted drug delivery

International Journal of Nanomedicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Targeted drug delivery into reversibly injured myocardium with silica nanoparticles: surface functionalization, natural biodistribution, and acute toxicity

JMTM
21,8

930

Received February 2009
Revised July 2009
Accepted January 2010

Targeted drug delivery to ischemic heart with use of nanoparticulate carriers

Concepts, pitfalls and perspectives

Michael Galagudza
V.A. Almazov Federal Heart, Blood and Endocrinology Center, Institute of Experimental Medicine, St-Petersburg, Russia and

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SICA-HF

Studies Investigating Co-morbidities Aggravating Heart Failure

МИНИСТЕРСТВО ОБРАЗОВАНИЯ И НАУКИ РОССИЙСКОЙ ФЕДЕРАЦИИ
ФЕДЕРАЛЬНОЕ АГЕНТСТВО ПО НАУКЕ И ИННОВАЦИЯМ

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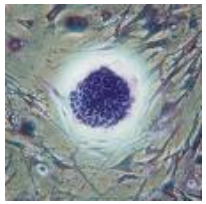
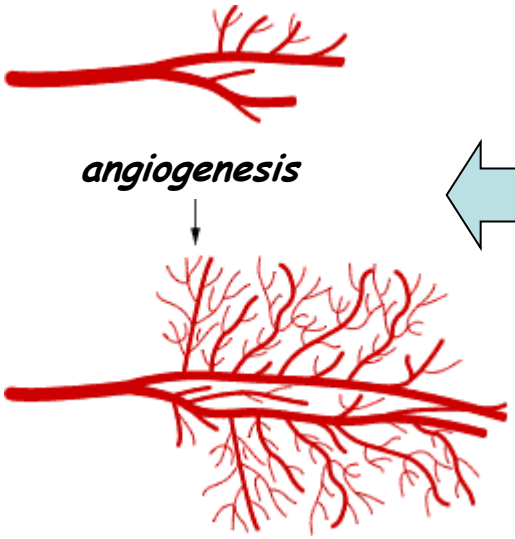
"R&D in priority fields of the S&T complex of Russia
2007 – 2012"

Stem cells and progenitor cells in angiogenesis



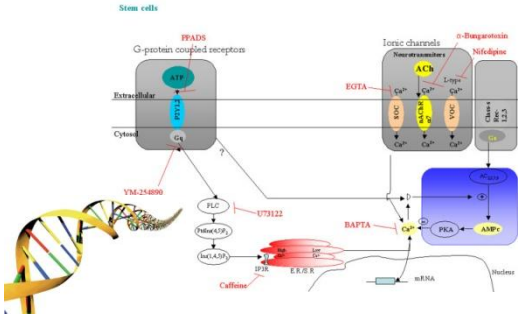
Stem cells and progenitor cells



Various extracellular factors

We hypothesize that estimation of angiogenic potential of the patient's own stem cells and progenitor cells can serve as a novel valuable diagnostic and prognostic criteria/markers for heart failure (also in combination with diabetes and body mass disorders), and potentially constitute therapeutic targets.

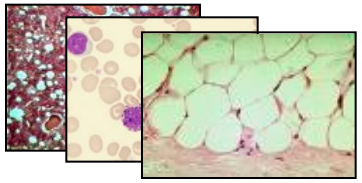
Material and Approaches



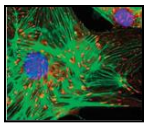
Study participants

(HF / DM / Obesity & Healthy controls)

Biosamples



Bone marrow, blood, fat tissue



DNA
Serum, Plasma, etc.
Cells:

MSC BM
MSC FT
EPC

Clinical Data (Complete evaluation)

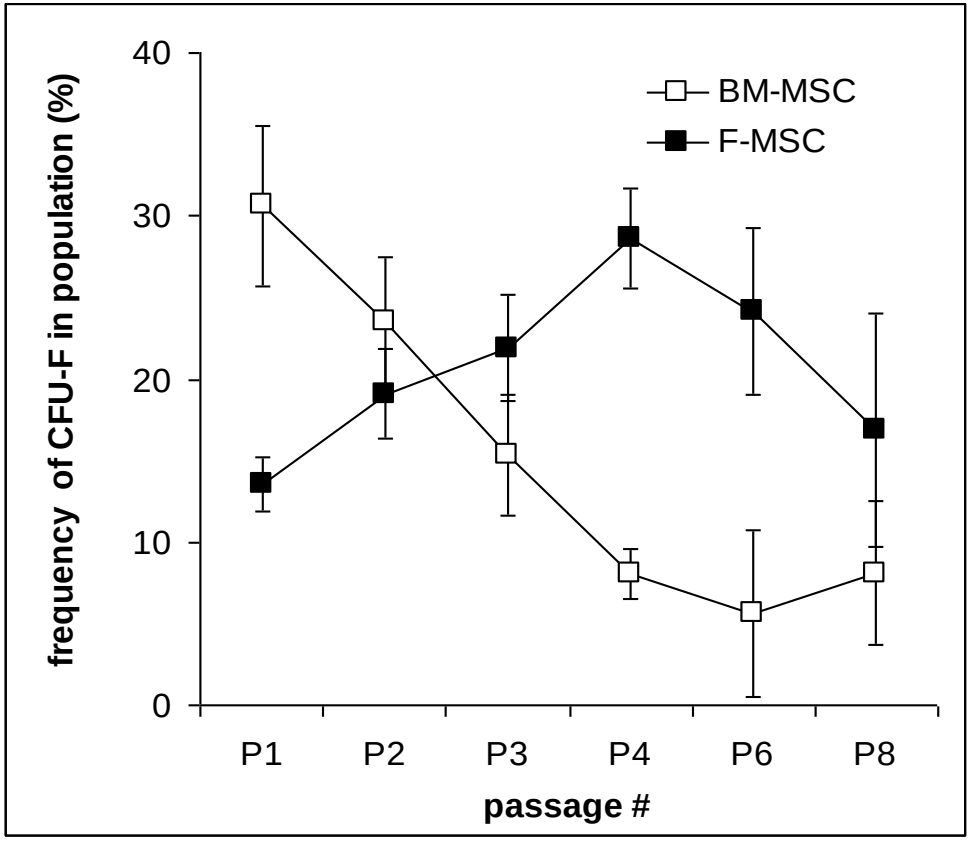
Laboratory Data (Blood biochemistry, SNP assay, etc.)

+

Cell Properties (Proliferation, differentiation, interactions)

Merging a volume of clinical and laboratory data promises identifying candidate targets for diagnostics and prognostics

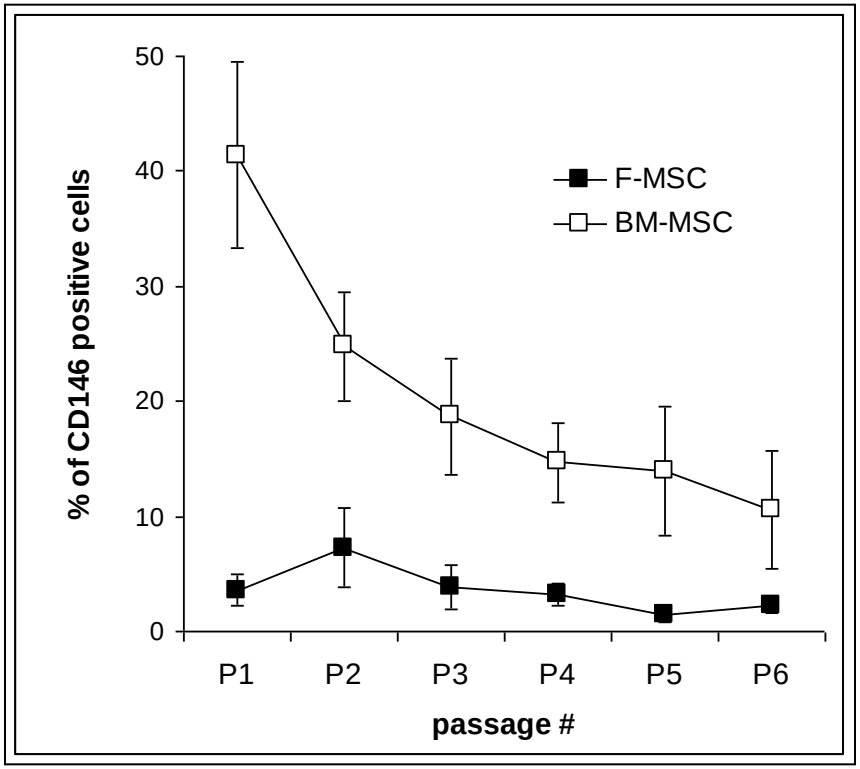
Comparative study of two patient-derived MSC populations

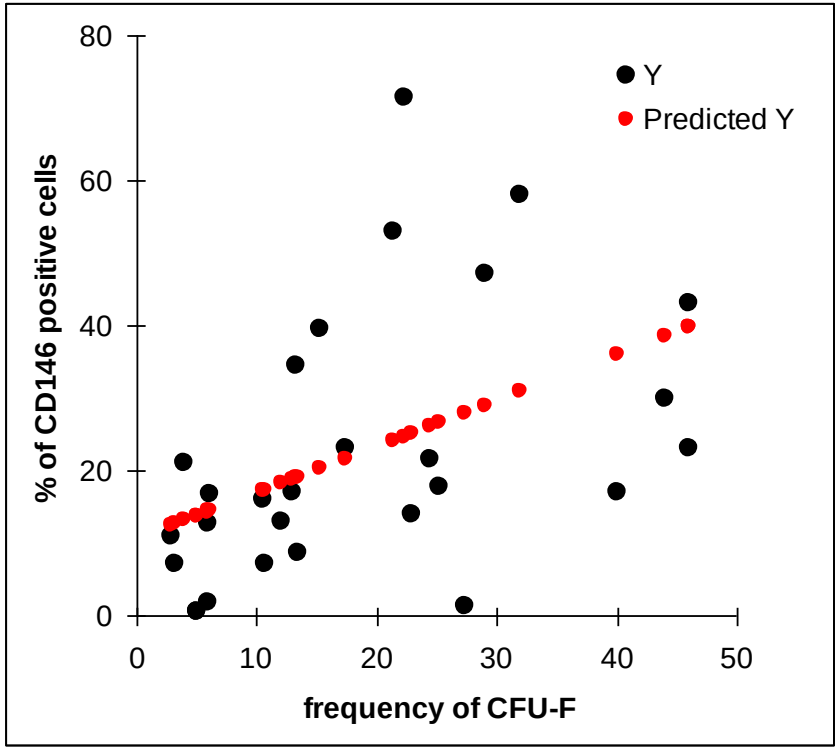


The study compares MSC derived from bone marrow (BM-MSC) and subcutaneous adipose tissue (F-MSC) of the same patient

Frequency of Colony Forming Units (CFU) changes with successive passages in MSC derived from bone marrow (BM-MSC) and adipose tissue (F-MSC)

Identification of CD146 as a candidate MSC subpopulation-specific marker



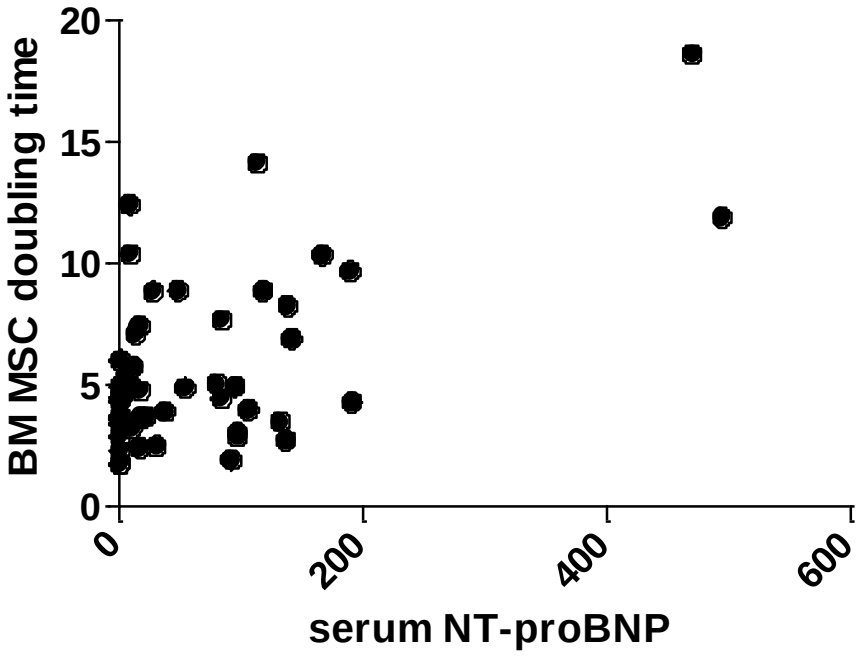


The population of CD146+ cells was more abundant in BM-MSC than in F-MSC at early passages and declined dramatically by P4.

Correlation of HF patient's stem cell functional properties with clinical laboratory parameters

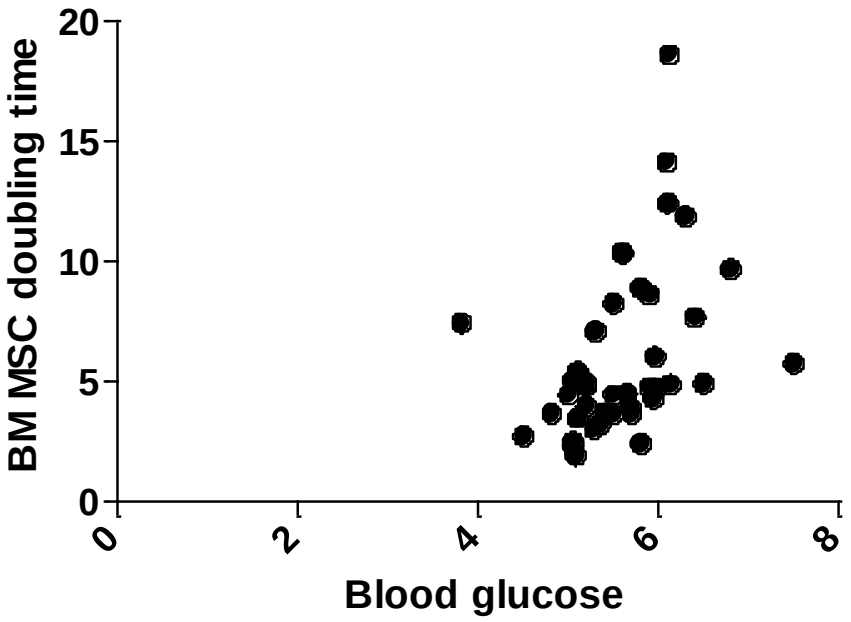
Serum NTproBNP and population doubling time of BM MSC

r=0.35; p=0.01



Blood glucose and population doubling time of BM MSC

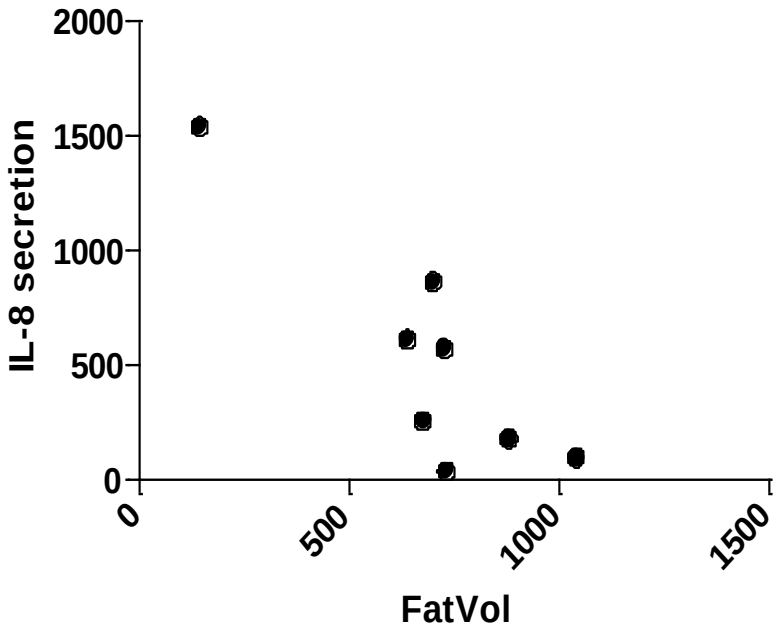
r=0.51; p=0.0005



Correlation of HF patient's stem cell functional properties with clinical laboratory parameters

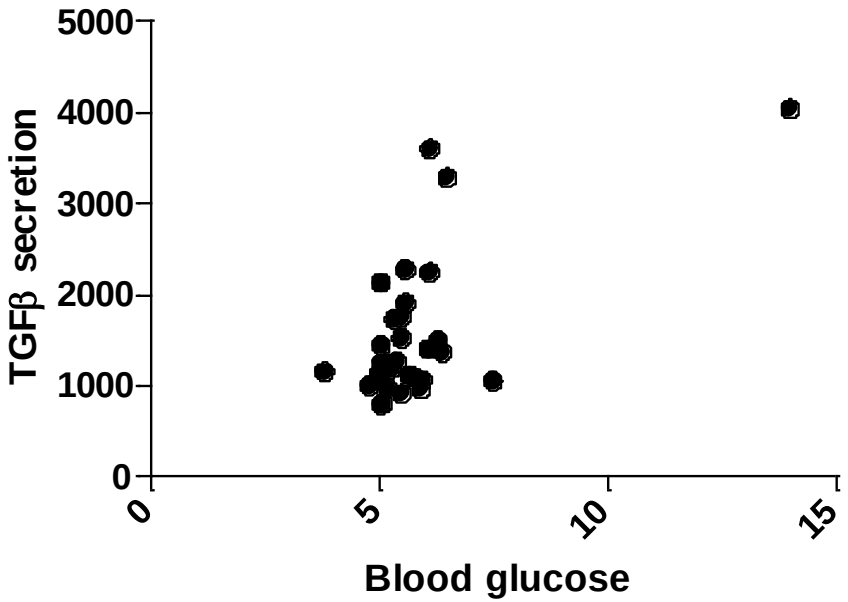
Abdominal fat volume and IL-8 secretion by F MSC

r=-0.81; p=0.02

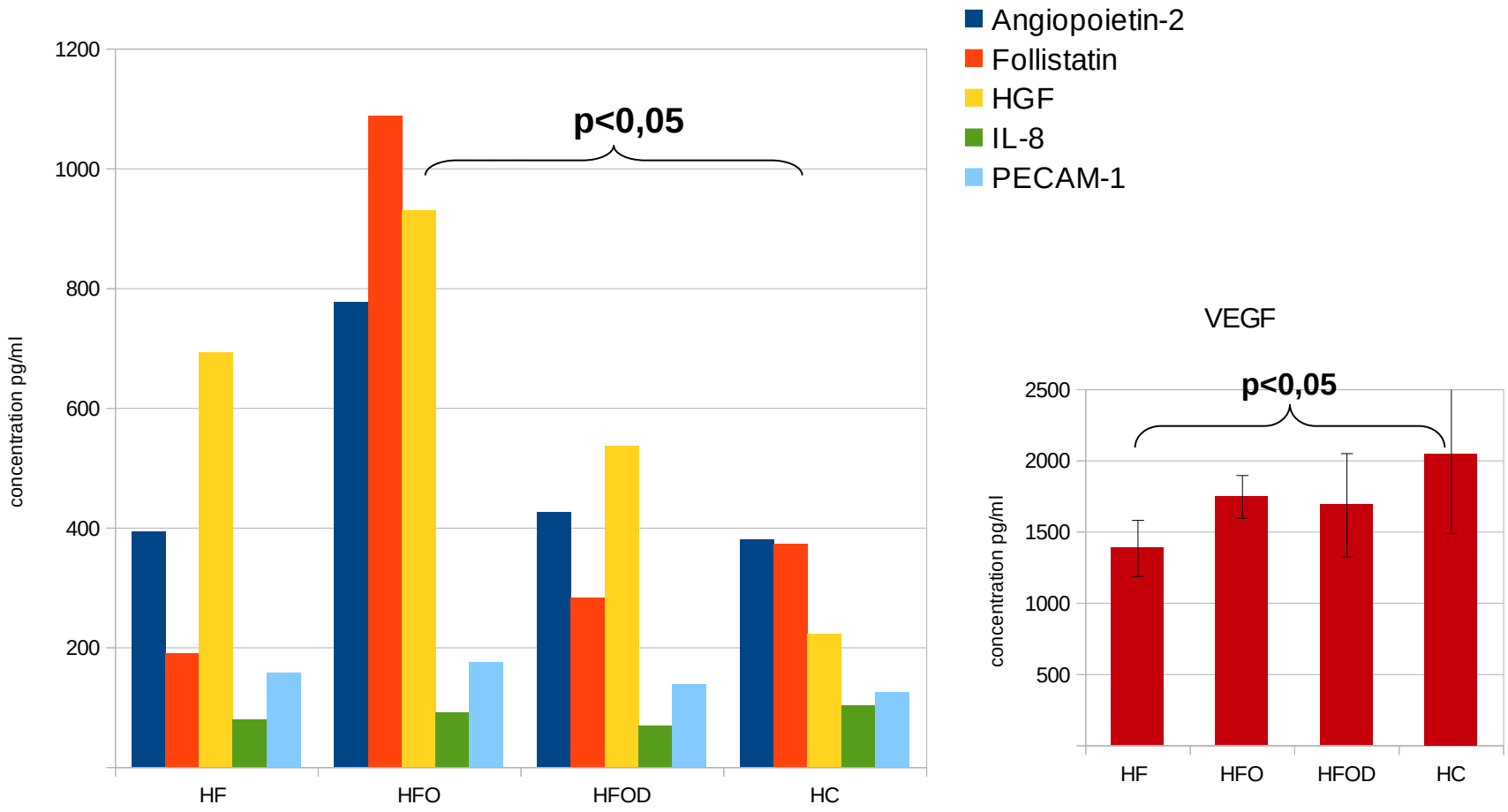


Correlation of blood glucose and TGFβ secretion by F MSC

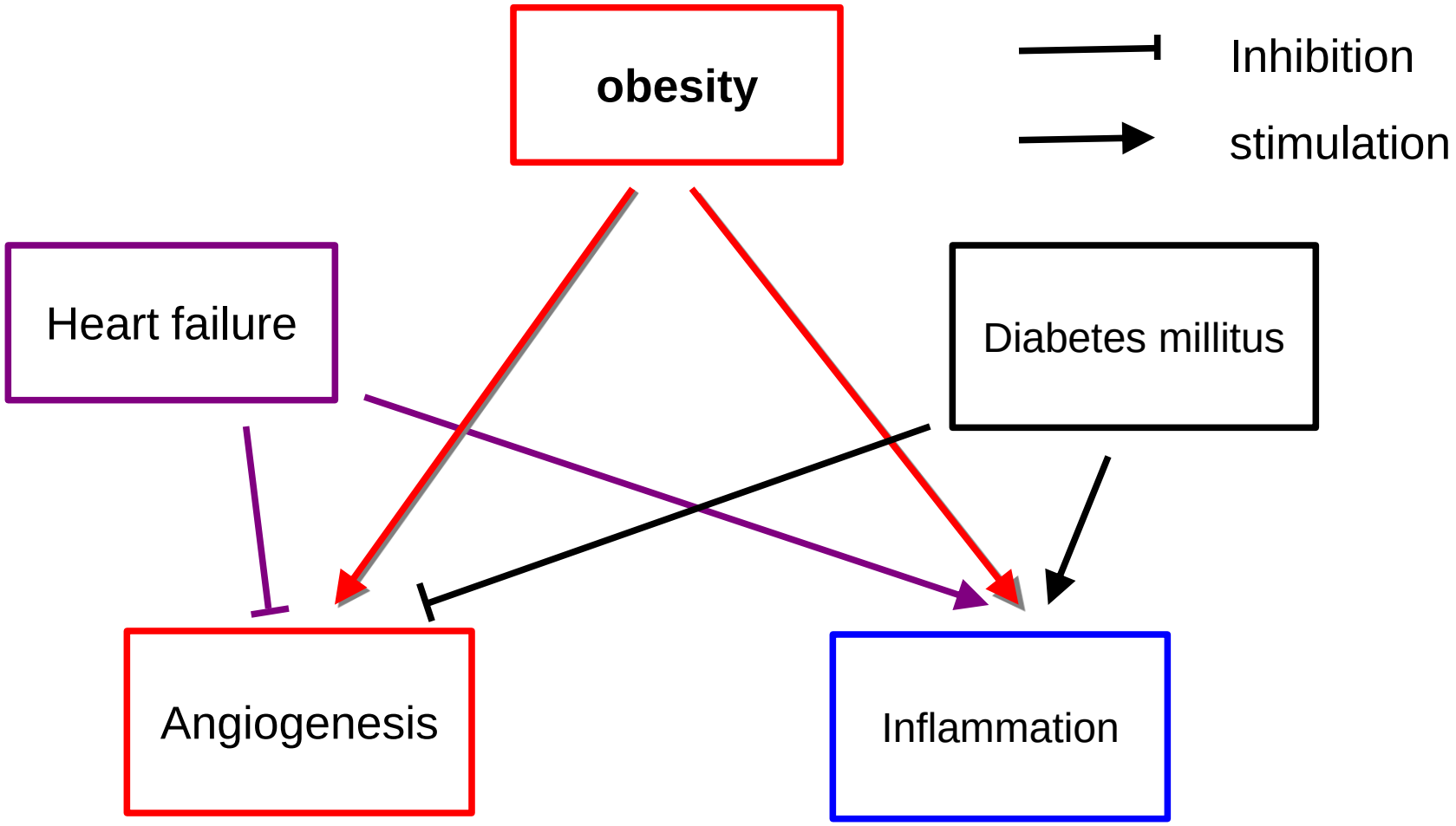
r=0.51; p=0.04



BM MSC from HF obesity patients secrete greater amount of angiogenic factors but not VEGF



HF Patient-derived MSC stimulated EC growth



- MSC derived from HF and HF&Cm are altered between the groups when cultured in vitro.
- BM MSC have greater capacity to produce some proangiogenic and proinflammatory factors comparing to FMSC
- MSC from HF patients with obesity are more potent in producing angiogenic factors comparing both to patients with isolated HF and healthy subjects.

Clinical trial
“Intramyocardial Multiple Precision Injection of Bone Marrow Mononuclear Cells in Myocardial Ischemia” (acronim: IMPI)

Goal: investigation of the effect of mononuclear bone marrow cell transplantation after precise intramyocardial injection for treatment of coronary artery disease and heart failure

Trial characteristics: Double-blind randomized placebo-controlled trial

Dates: Total duration of the study: September 2010 – September 2014. Patient enrollment: 18 months after beginning of the study. Follow up period – 36 months.

Trial registration

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Intramyocardial Multiple Precision Injection of Bone Marrow Mononuclear Cells in Myocardial Ischemia (IMPI)

This study is currently recruiting participants.

Verified on May 2011 by Almazov Federal Center of Heart, Blood and Endocrinology

First Received on May 13, 2011. Last Updated on May 16, 2011 History of Changes

Sponsor:	Almazov Federal Center of Heart, Blood and Endocrinology
Information provided by:	Almazov Federal Center of Heart, Blood and Endocrinology
ClinicalTrials.gov Identifier:	NCT01354678

Purpose

Randomised placebo-controlled study of efficiency and safety of bone marrow mononuclear cells transplantation by intramyocardial multiple precision injection in ischemic heart failure patients.

Condition	Intervention	Phase
Heart Failure	Procedure: NOGA XP Cardiac Navigation System	Phase I

Clinical data of the patient NM-01

Age: 62 years

Diagnosis

Main: CAD, effort angina

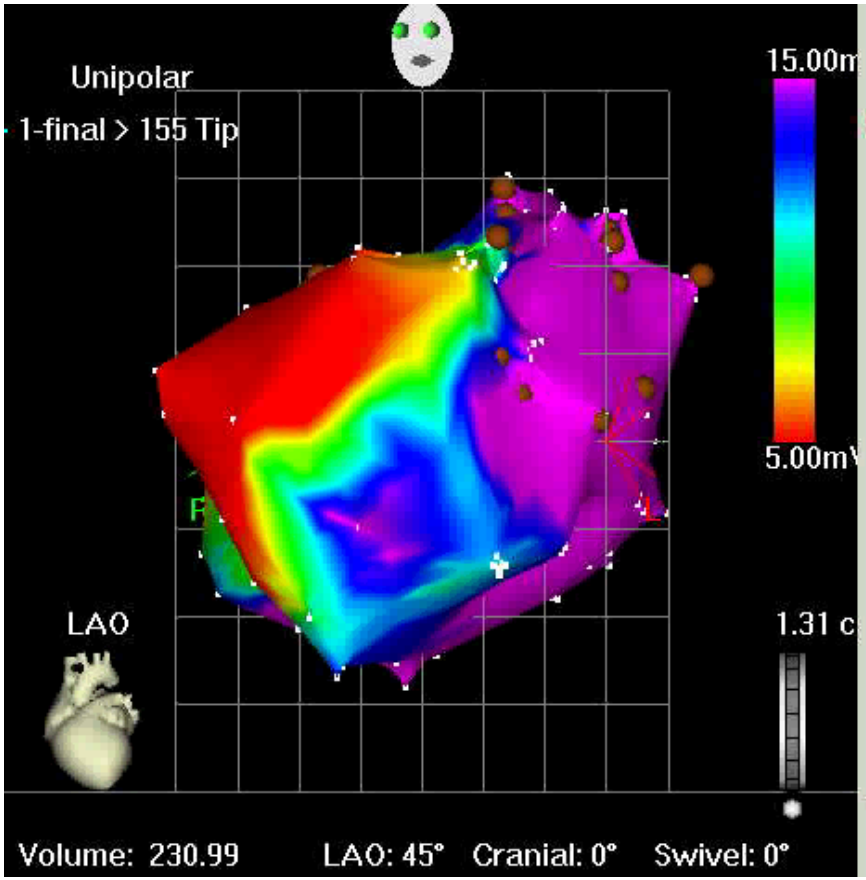
Postinfarction cardiosclerosis (STEMI in 1996)

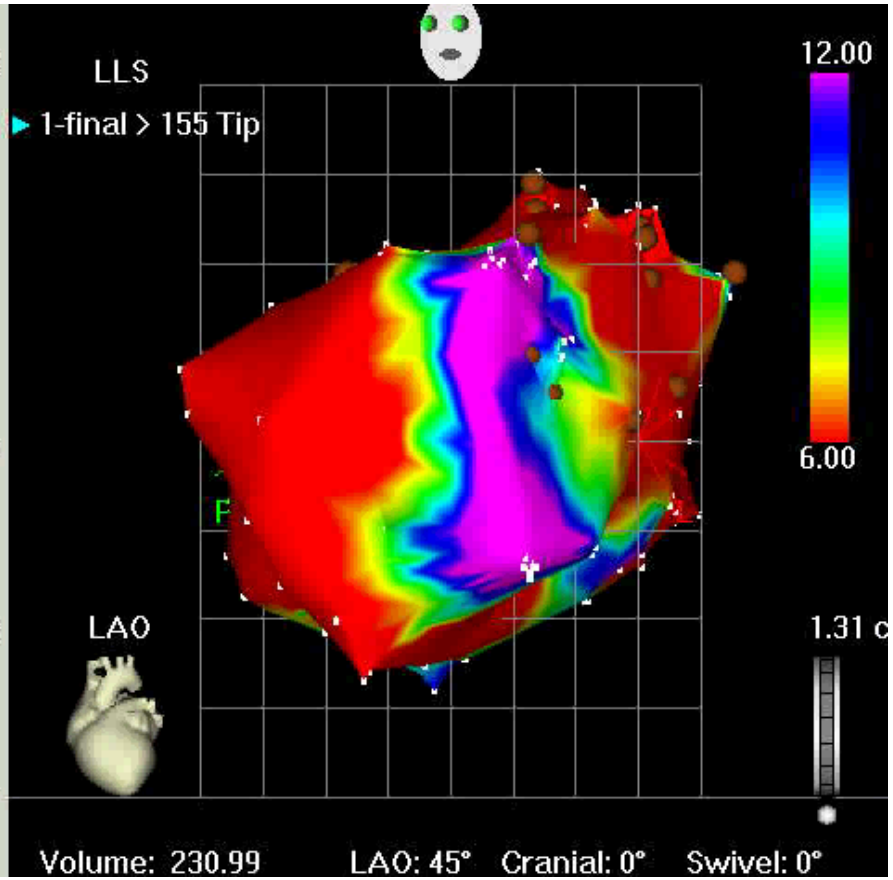
CABG, LV aneurism surgery in 1997

Arterial hypertension

Complications: Atrial fibrillation with impaired AV conduction. LBBB. Ventricular premature beats. Paroxysmal ventricular tachycardia. Implantation of CRT-device. CHF II (NYHA)

Patient NM-01 data





Voltage **Contractility**

● = sites of injection of cells

13 injections 200 microL each