Angioplasty Summit
TCTAP2010
4/29/2010

#5 Atherosclerosis "From Basic to Translational Research"

Angiogenic and Cardioprotective Therapy for PAD and MI

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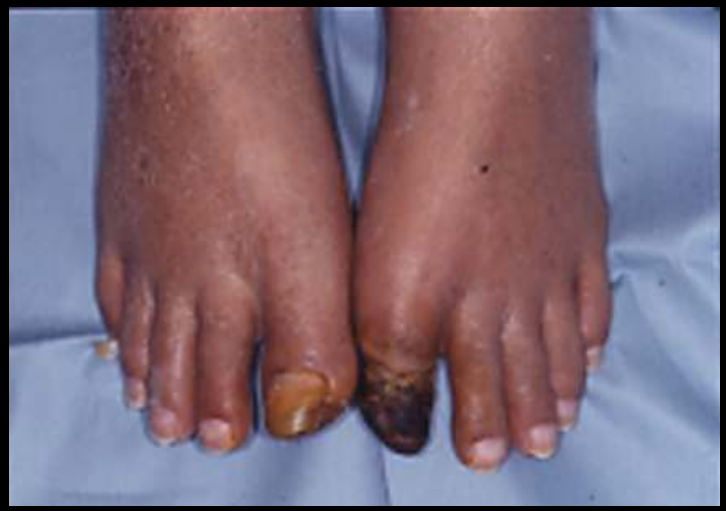
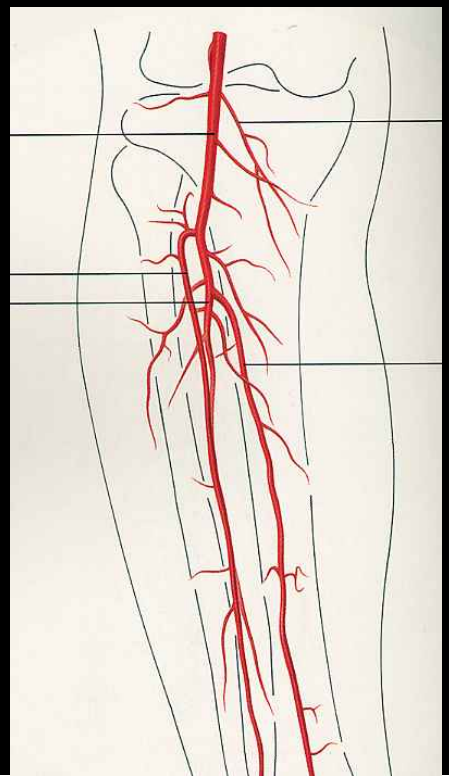
Osaka University Graduate School of Medicine
Suita, Japan

Angiogenic Therapy for PAD

Arteriosclerosis Obliterance (ASO)

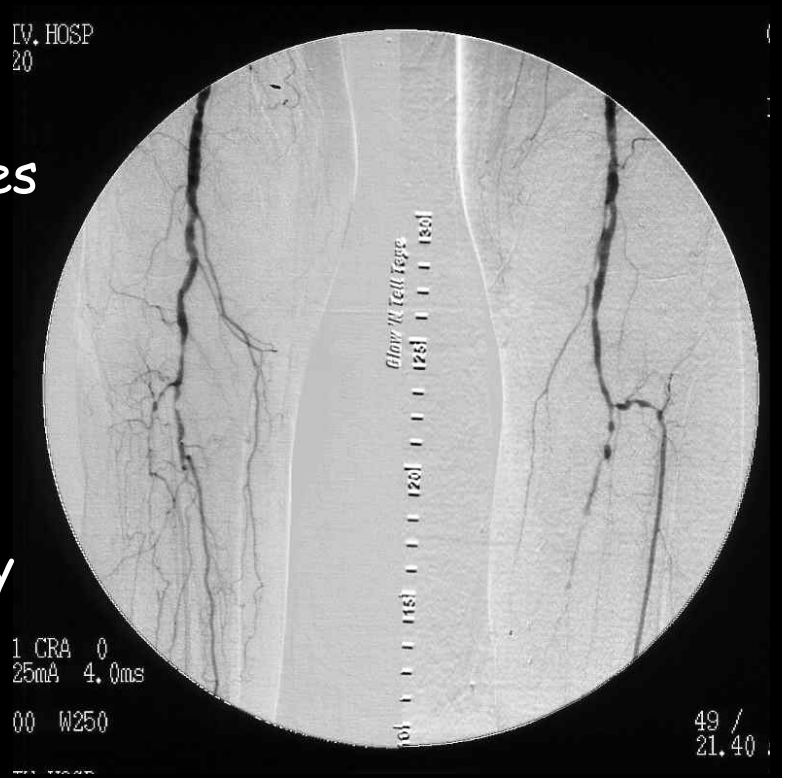


etiology - atherosclerosis
more than 2% in people
older than 65 yr
~1/2 million in Japan

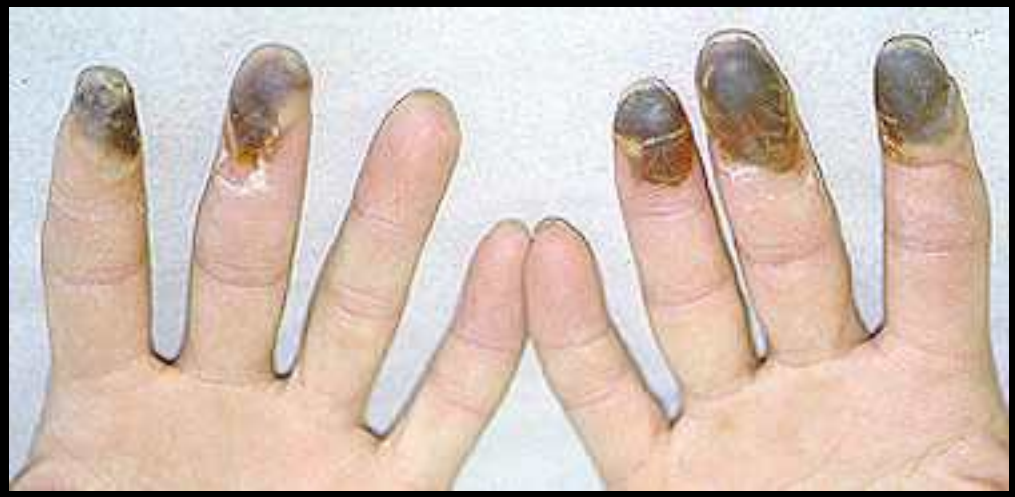


schema of leg arteries

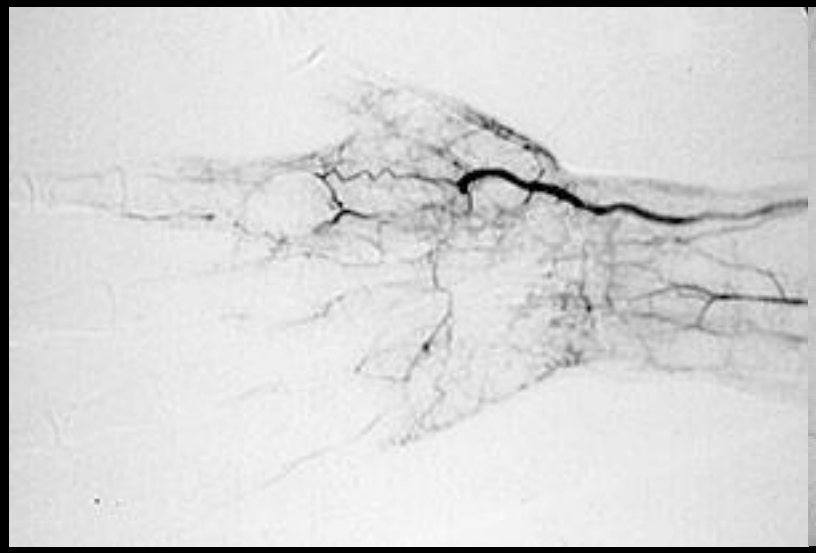
angiography



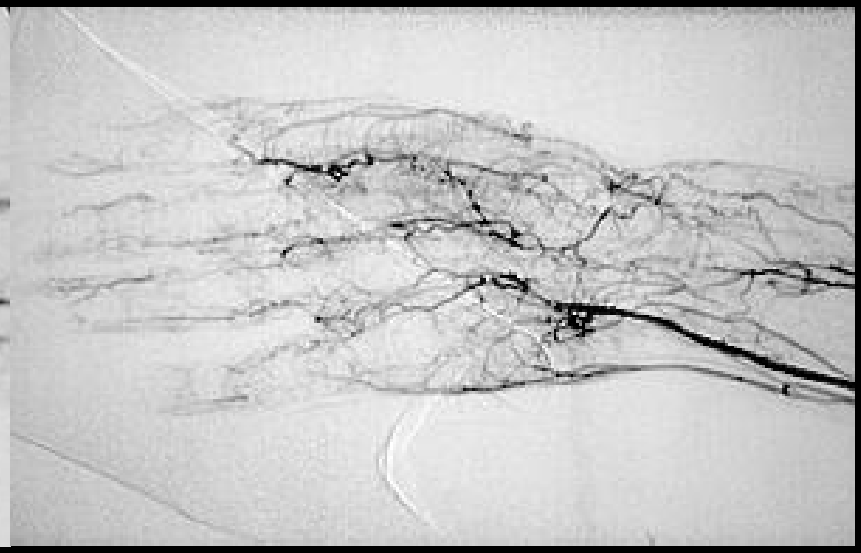
Buerger Disease (TAO)



etiology is unknown
male, smoking
several thousands patients in Japan



TAO



normal

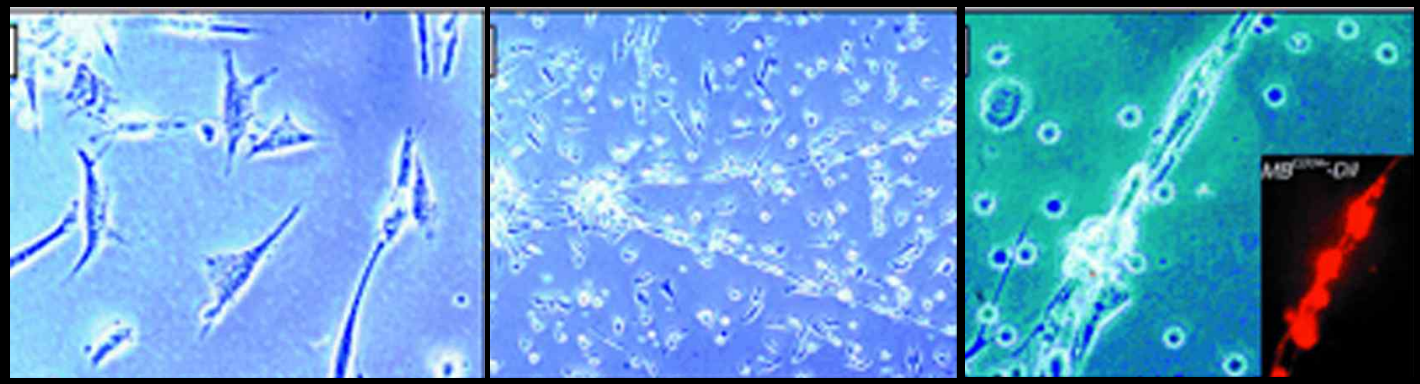
Therapeutic Angiogenesis

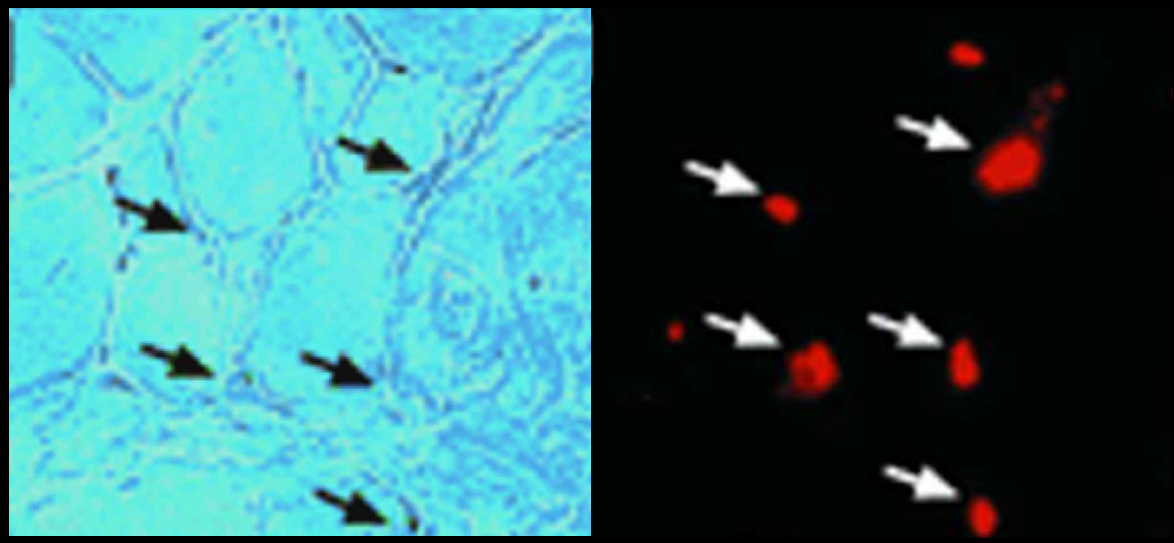
Table 2 Phase 2 and 3 angiogenesis trials

Trial	Therapeutic agent	Disease target	n	Endpoint	Results[a]	Reference
VIVA trial	Recombinant VEGF protein	CHD	178	ETT[b] at 60 d	Negative	97
FIRST trial	Recombinant FGF-2 protein	CHD	337	ETT at 90 d	Negative	98
TRAFFIC trial	Recombinant FGF-2 protein	PAOD	190	ETT at 90 d	Positive	99
GM-CSF trial	Recombinant GM-CSF protein	CHD	21	Invasive collateral flow index at 2 weeks	Positive	100
AGENT trial	Adenovirus-FGF-4	CHD	79	ETT at 4 weeks	Positive[c]	101
VEGF peripheral vascular disease trial	Adenovirus-$VEGF_{165}$ Plasmid/liposome $VEGF_{165}$	PAOD	54	Increased vascularity in angiography at 3 months	Positive	102
KAT trial	Adenovirus-$VEGF_{165}$ Plasmid/liposome$VEGF_{165}$	CHD	103	Improved myocardial perfusion at 6 months	Positive (adenovirus group only)	103
REVASC trial (Biobypass-CAD)	Adenovirus-$VEGF_{121}$	CHD	67	Time to 1 mm ST segment depression on ETT at 26 weeks	Positive	104
RAVE trial (Biobypass-PAD)	Adenovirus $VEGF_{121}$	PAOD	105	Peak walking time at 12 weeks	Negative	105
Euroinject One Trial	Plasmid $VEGF_{165}$	CHD	74	Improved myocardial perfusion at 3 months	Negative[d]	106

CHD, coronary heart disease; PAOD, peripheral vascular disease. [a]Efficacy measured as the study protocol–defined primary or secondary endpoint. [b]ETT, exercise tolerance test. [c]Only one dose-group showed positive results. [d]Positive results were obtained after excluding results from two of the six study centers where patient recruitment might have been a confounding issue.

Endothelial progenitor cells (EPC)

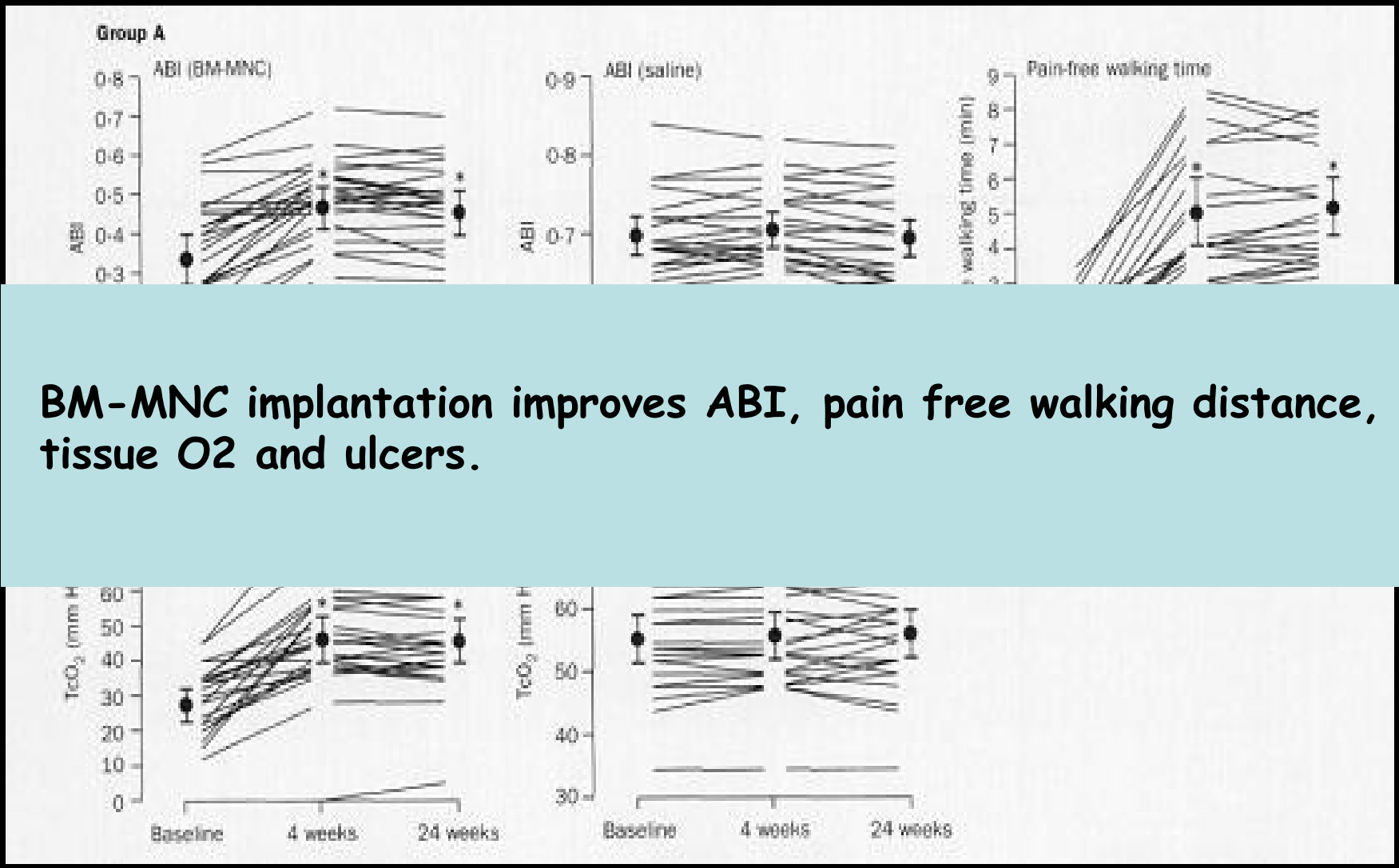




EPC is produced in bone marrow

Asahara et al Science 1997

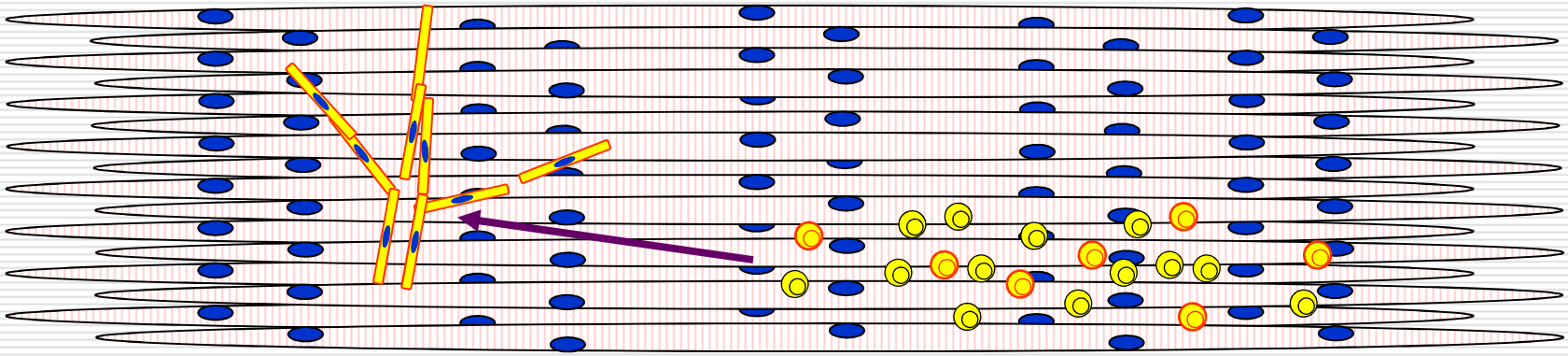
Results of clinical trial using BM-MNC



BM-MNC implantation improves ABI, pain free walking distance, tissue O2 and ulcers.

Tateishi-Y E et al. Lancet 2002

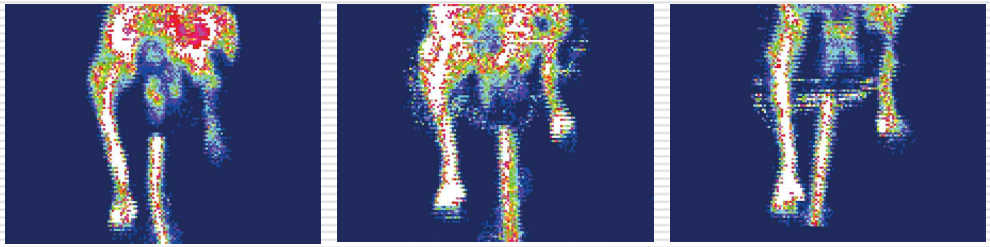
Hypothesis 1
Vasculogenesis by EPC



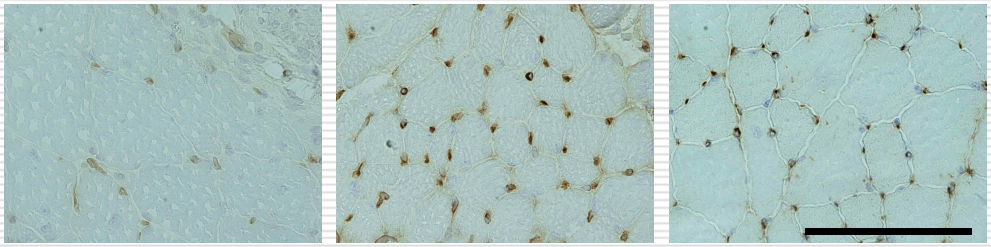
EPC
(Vasculogenesis)

Neovascular formation is induced by PB-MNC as well as BM-MNC

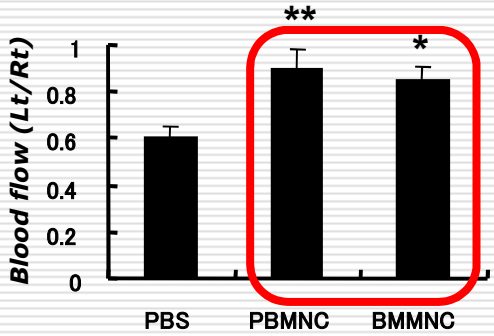
PBS PB-MNC BM-MNC

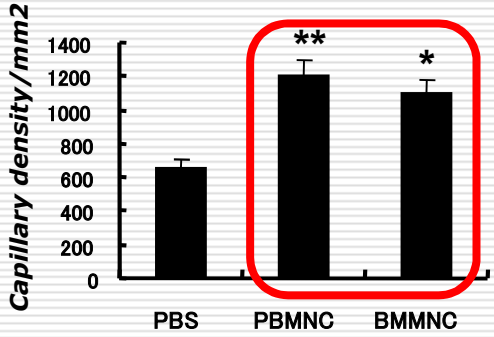


Laser doppler imagings



Immunohistochemistry (CD31, brown)





Although # of EPC is 1/100 in PB compared with in BM, the effects are same!

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Chiba University Graduate School of Medicine

Collect PB-MNC by cell sorter

PB-MNC therapy is better than BM-MNC therapy

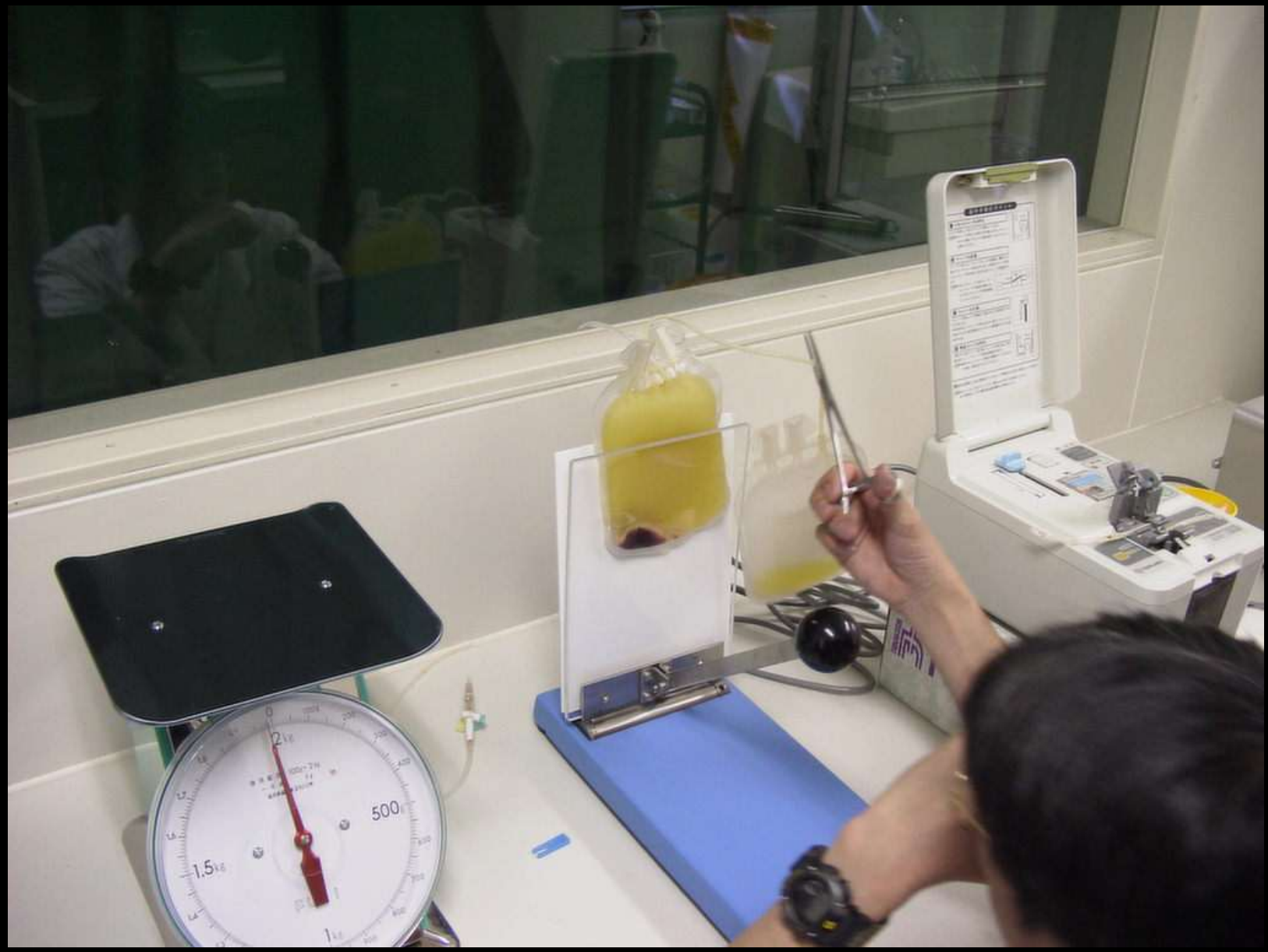
1 less risk
1/2 ASO Pts have CAD

no general anesthesia
no bone marrow aspiration

2 no anemia
  800ml BM vs 10ml blood

3 less expensive
  $5000 vs $0

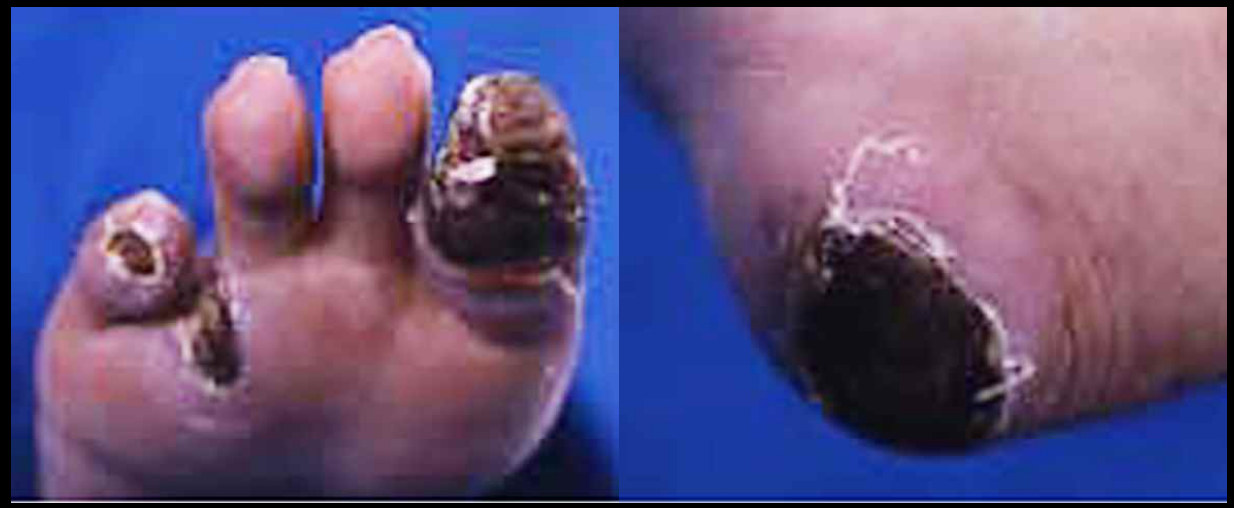
Collect PB-MNC by centrifugation



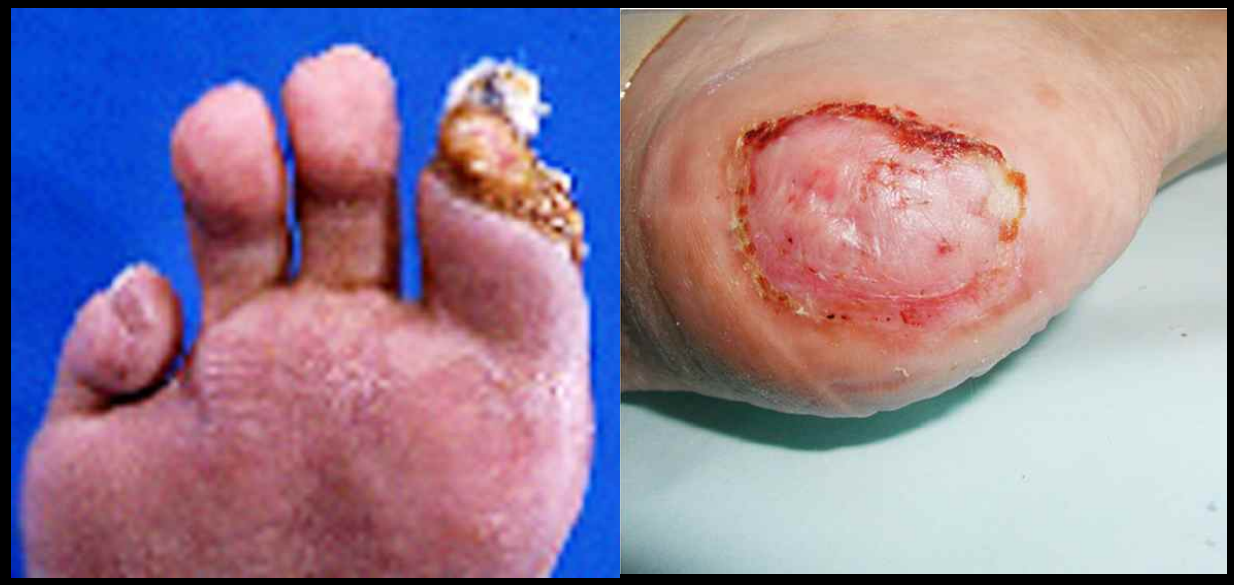
Injection of PB-MNC into ischemic skeletal muscle

Case1 70F, ASO

Before



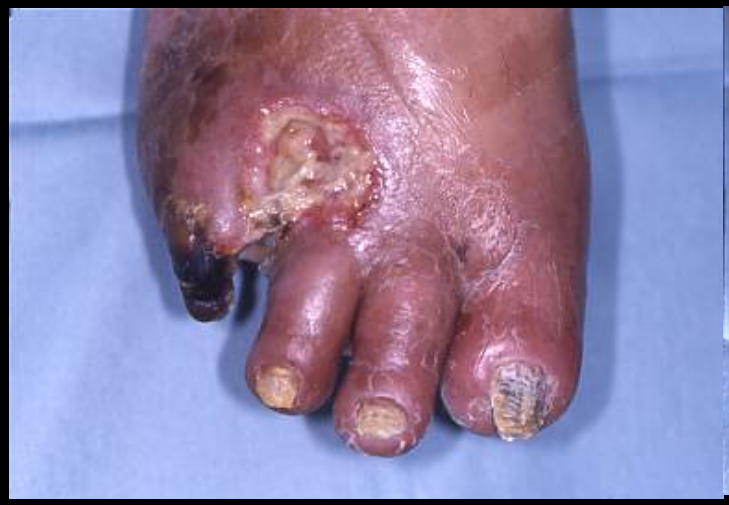
After PB-MNC implant

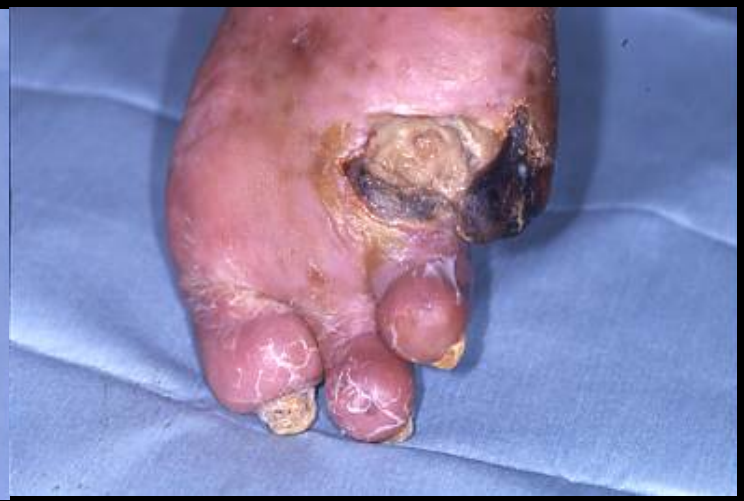


Minamino et al. Lancet 2002

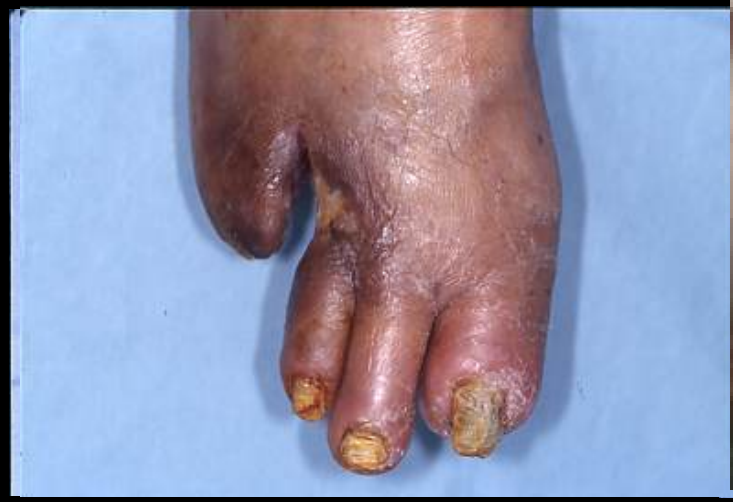
Case2 67M,TAO

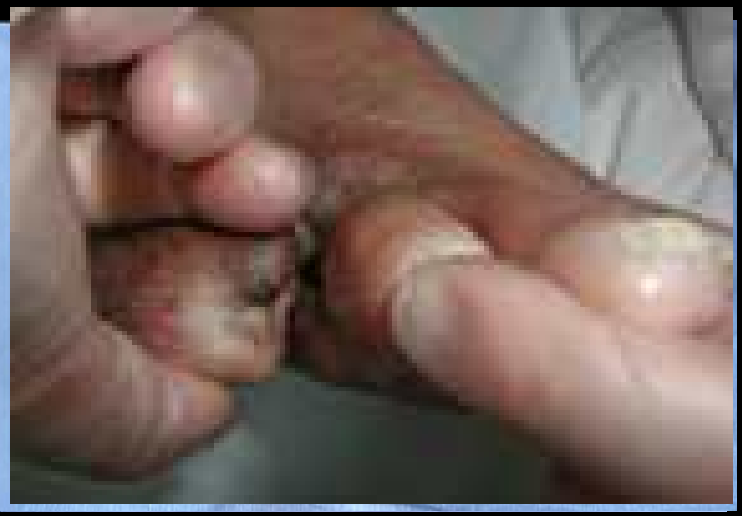
Before





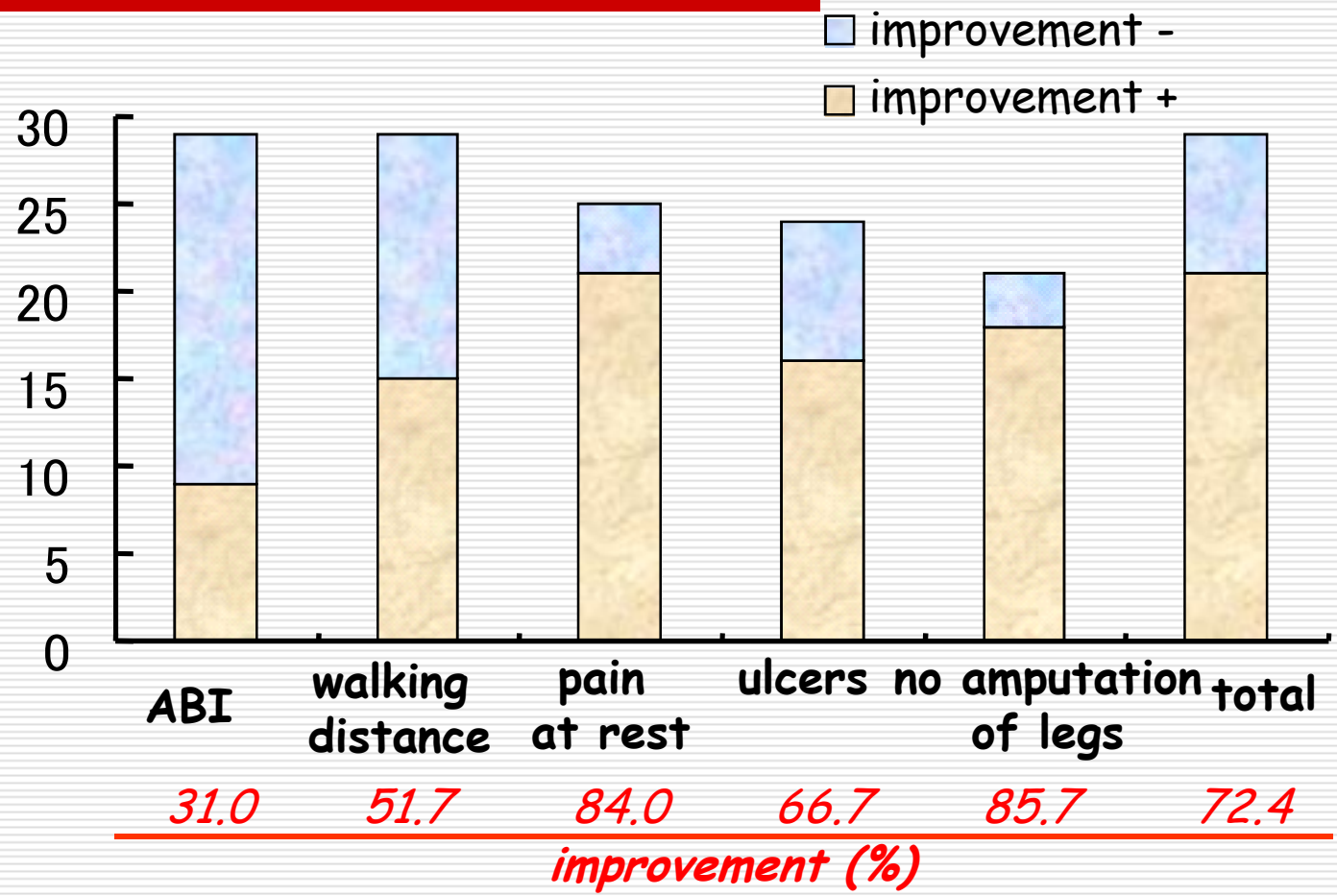
After Implant of PB-MNC





Minamino et al. Lancet 2002

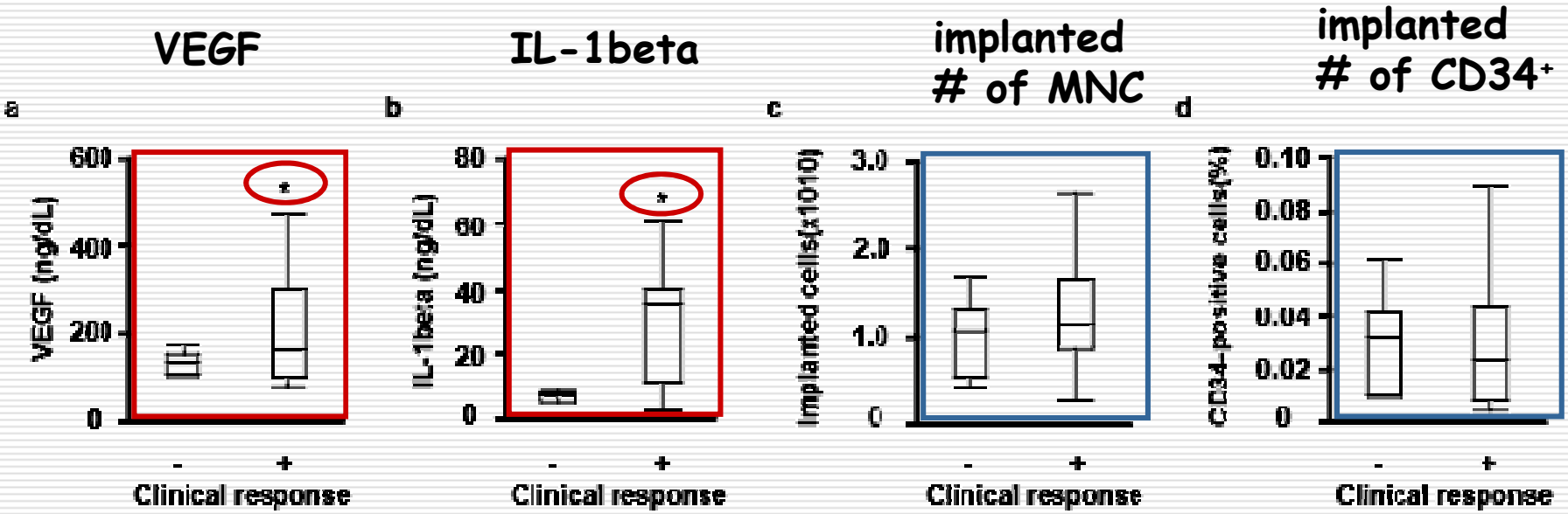
Results of PB-MNC implantation



Moriya et al. Circulation 2010

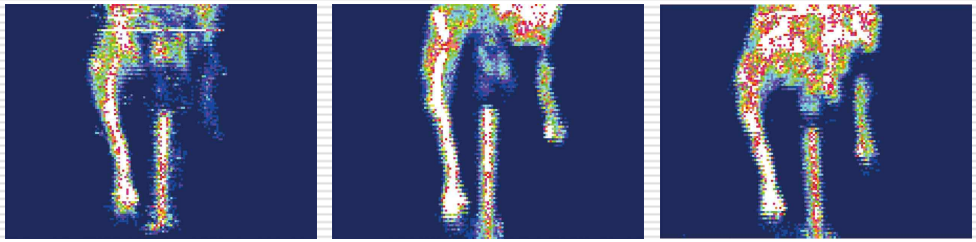
Clinical parameters

* p<0.05

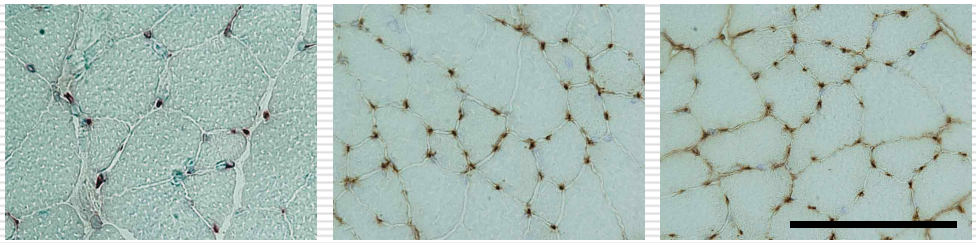


EPC may not be necessary for BM-MNC-induced neovascular formation

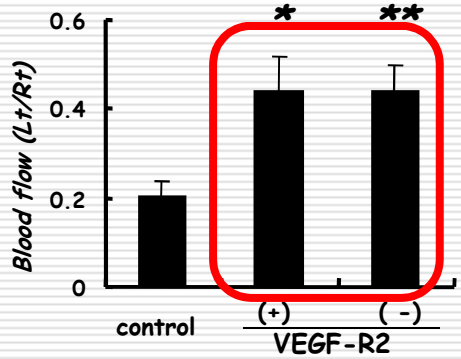
PBS VEGFR2(+) VEGFR2(-)

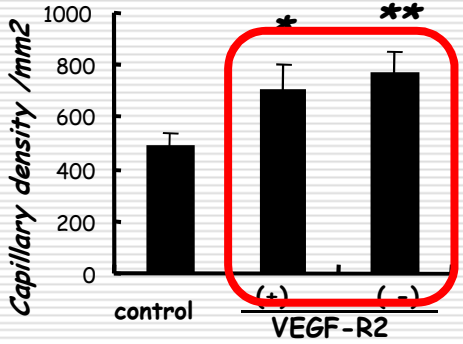


Laser doppler imagings



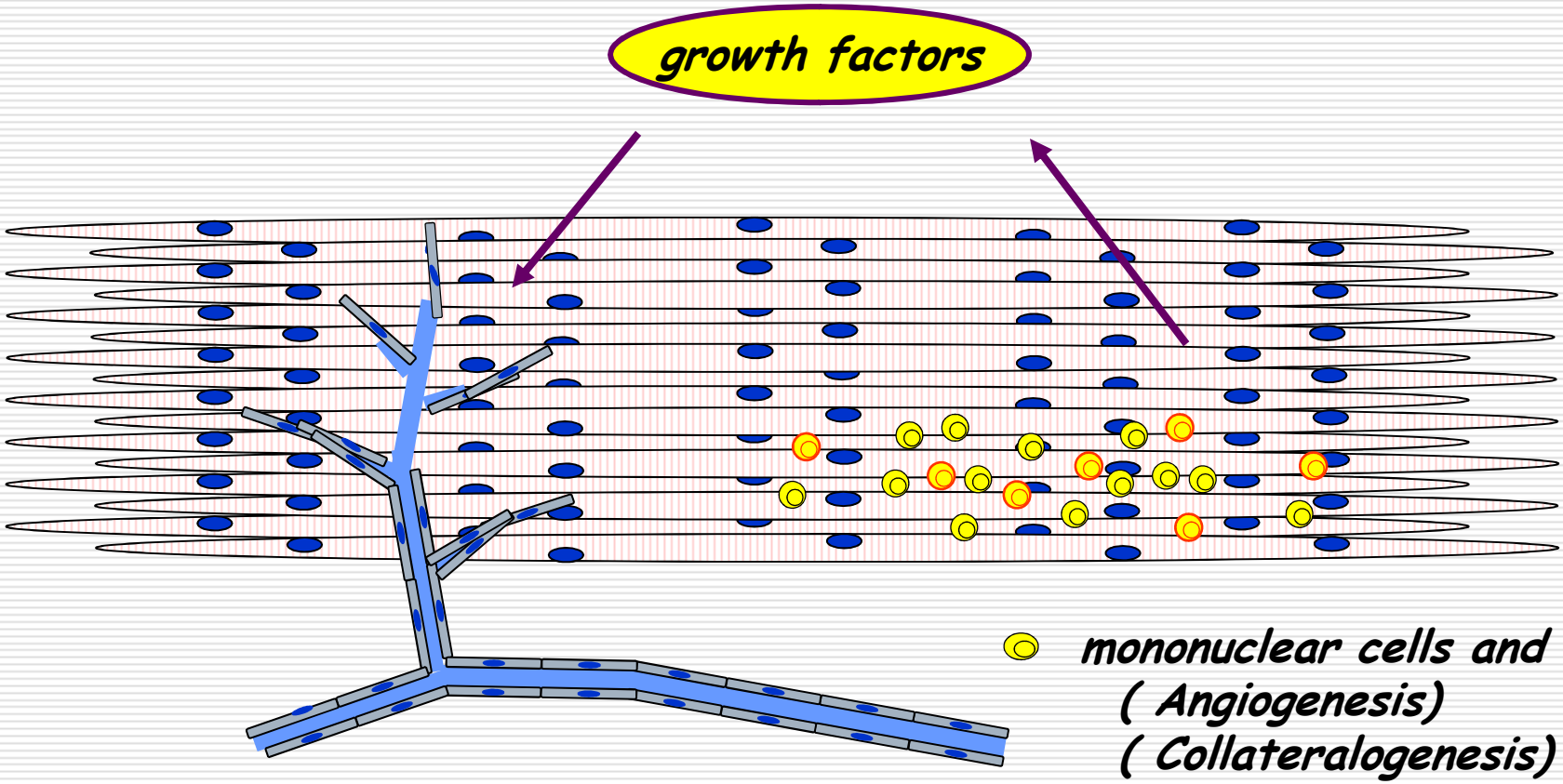
Immunohistochemistry (CD31, brown)





Scale bar: 100μm * p<0.05 vs control ** p<0.01 vs control

Hypothesis 2
Angiogenesis by growth factors from MNC



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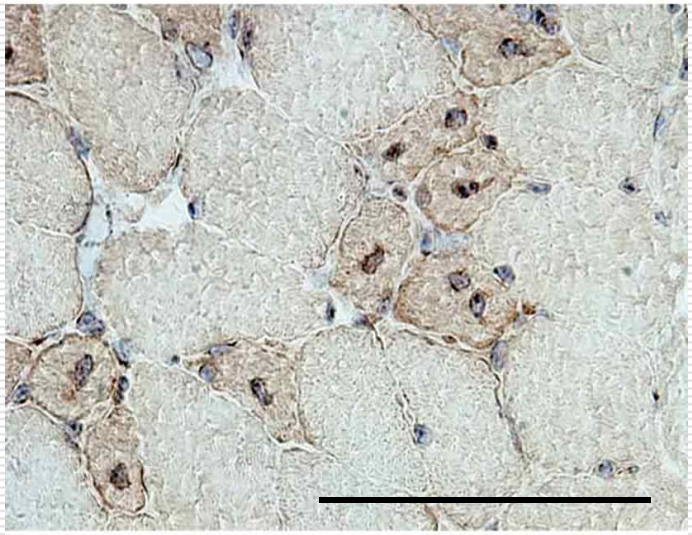
Regenerated skeletal muscle produces IL-1β and VEGF

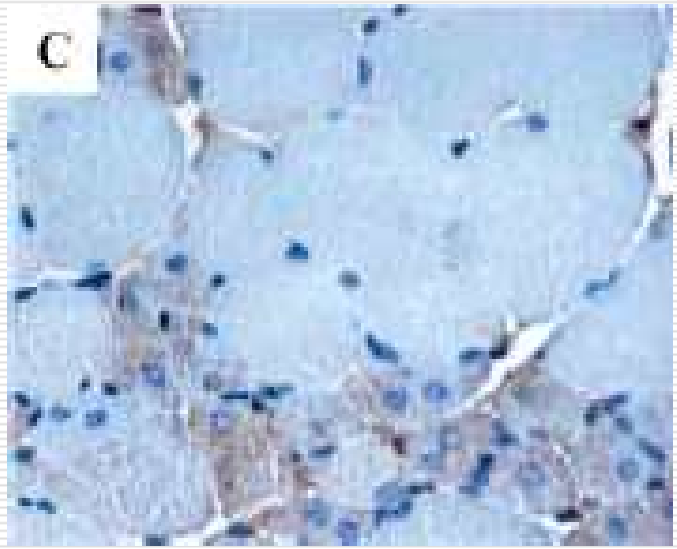
Immunohistochemistry

IL-1beta



Scale bar: 100μm

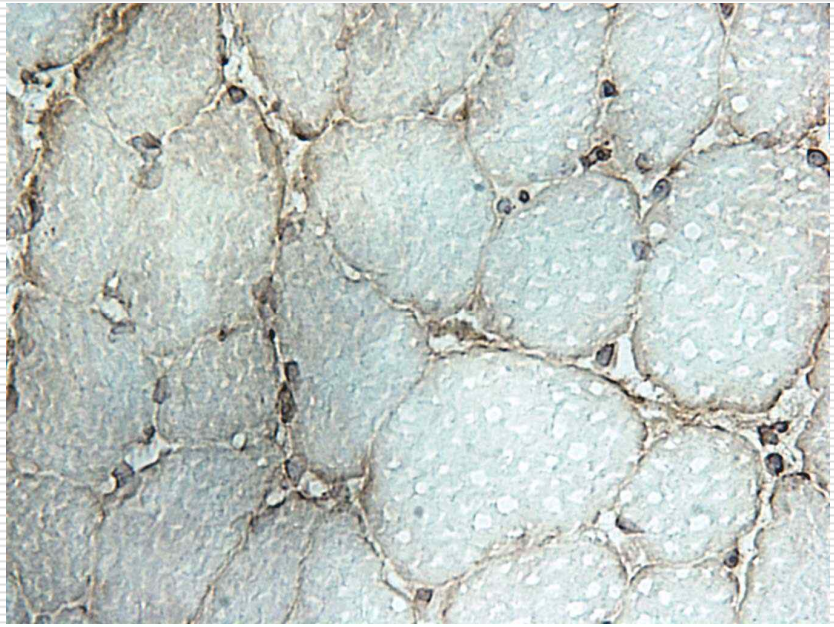
VEGF



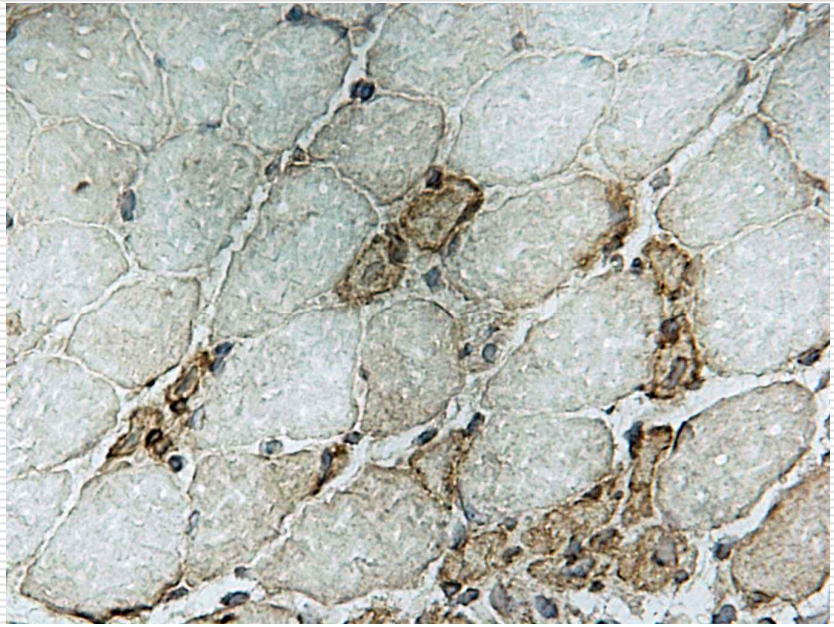
AJP 2003,163:1417

PB-MNC activate satellite cells

Immunohistochemistry, N-CAM



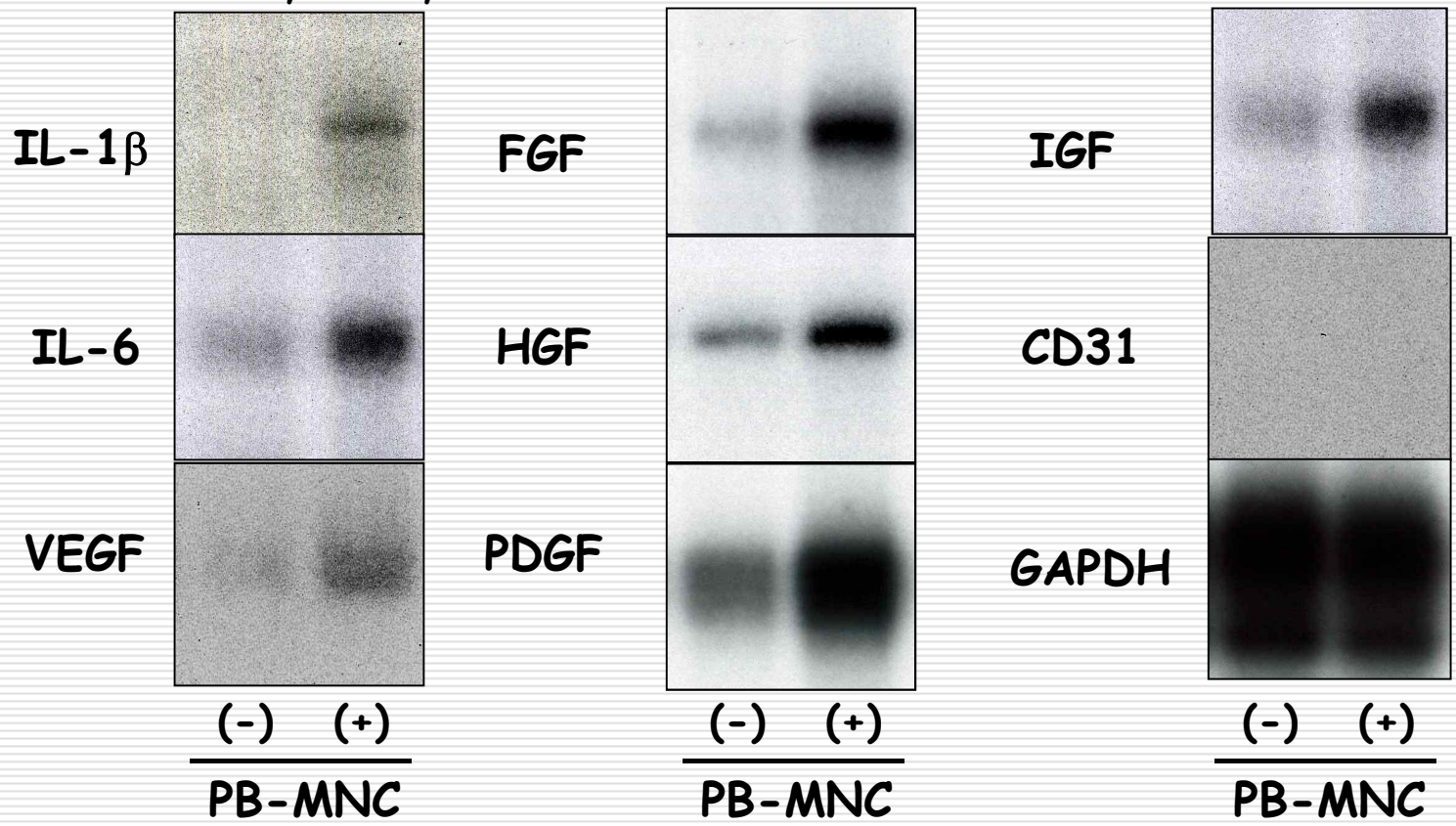
PBS treated



MNC treated

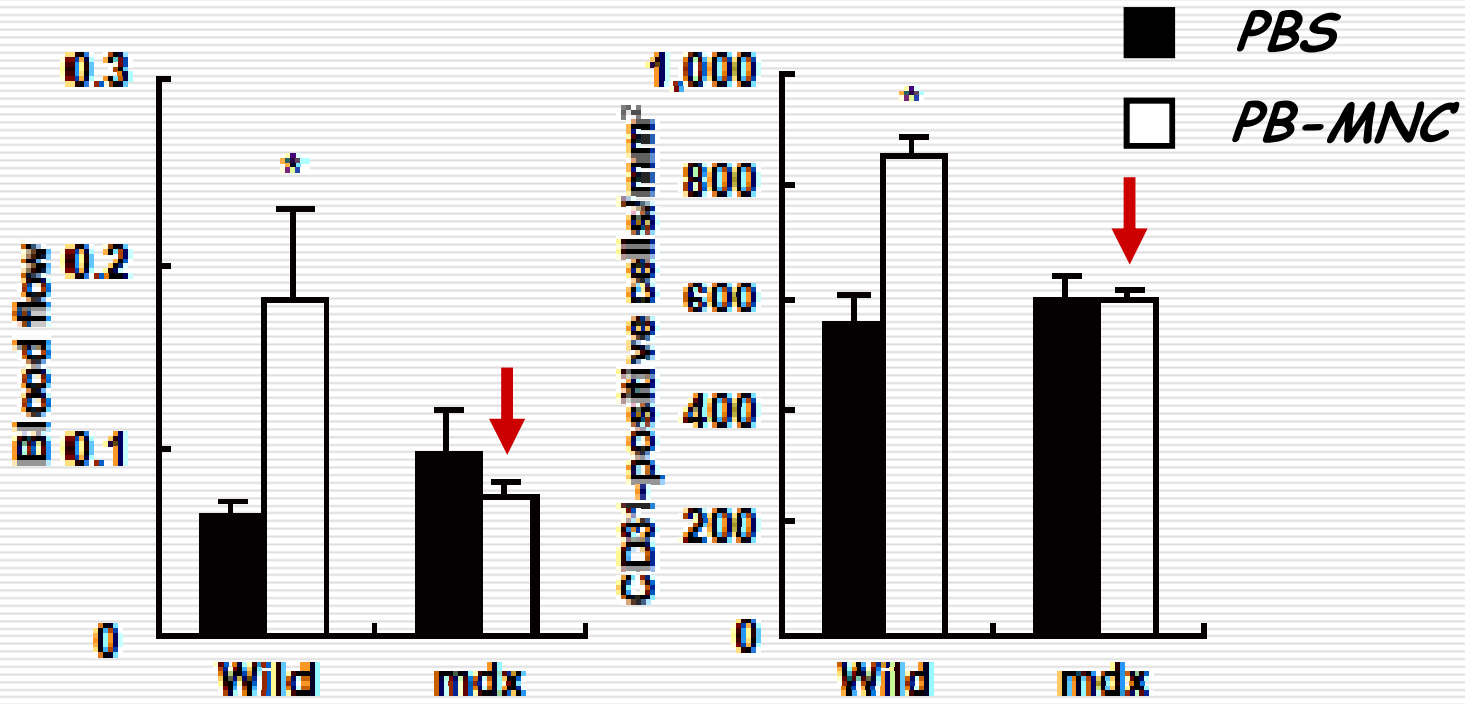
Mononuclear cells stimulate expression of growth factors in skeletal muscle

Protection assay of myotube RNA



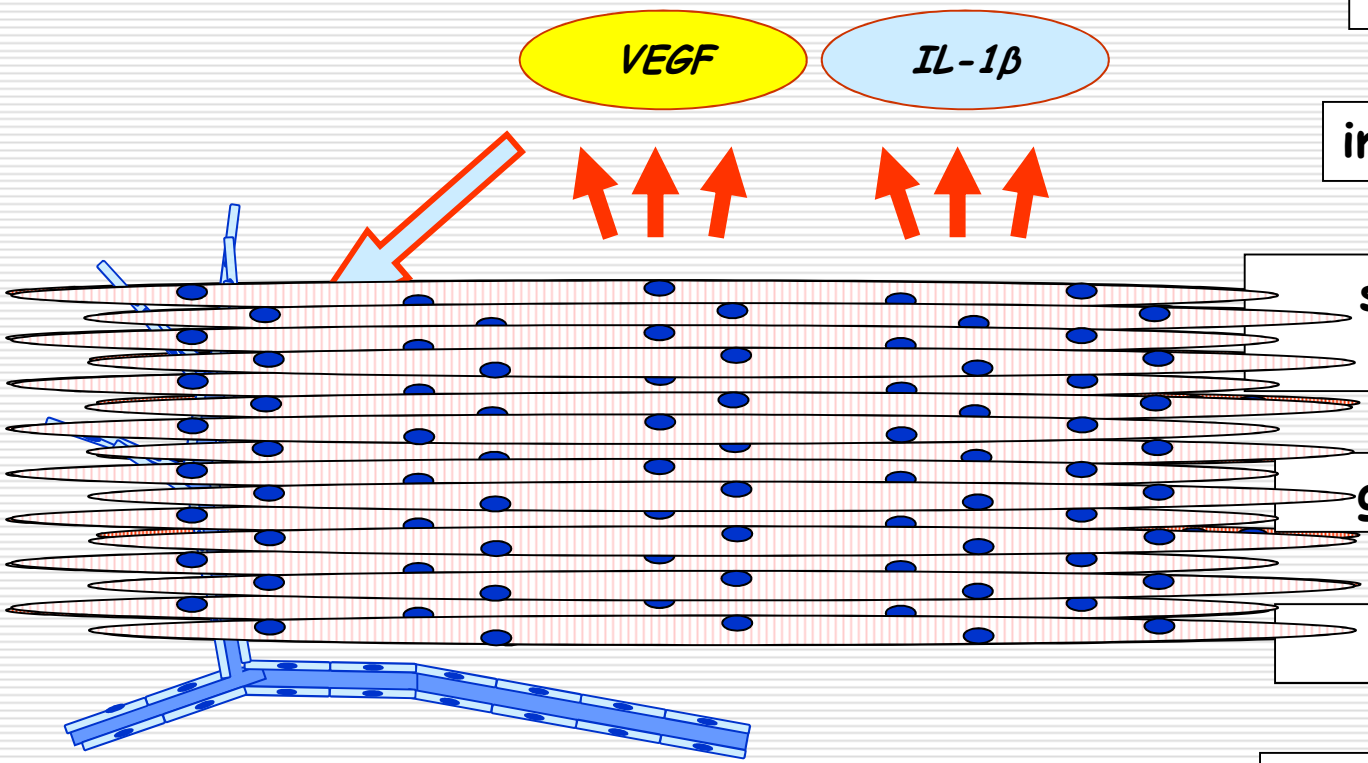
Tateno et al. Circ Res 2004

Skeletal muscle regeneration is necessary for PB-MNC-induced angiogenesis



Tateno et al. Circ Res 2004

Hypothesis 3
Angiogenesis by growth factors from skeletal muscle



ischemia
↓
implantation
↓
skeletal muscle regeneration
↓
growth factors
↓
angiogenesis
↓
improvement

Tateno et al. Circ Res 2004

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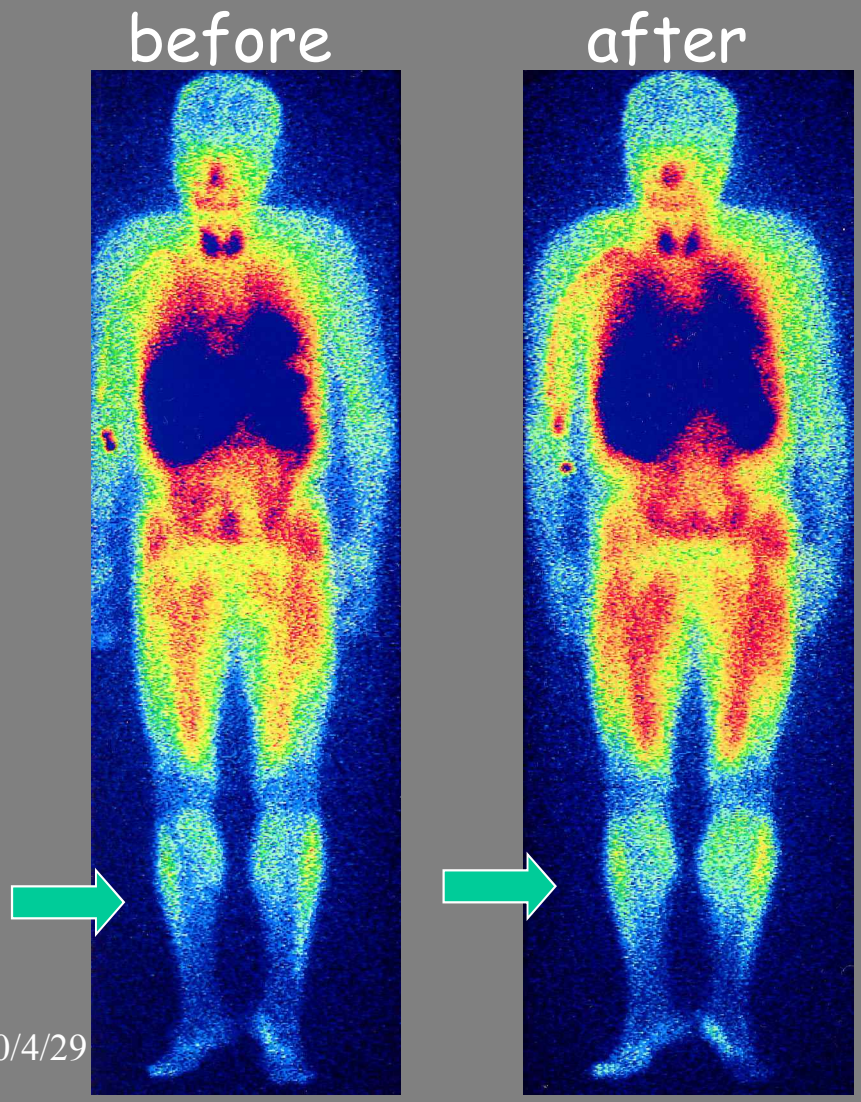
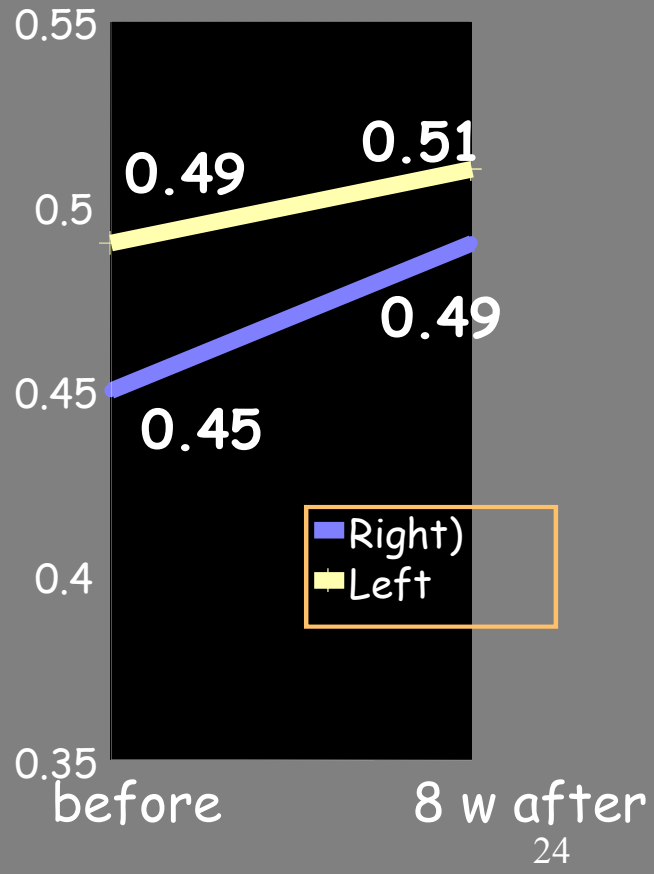
Evaluation of limb ischemia by ^{201}TlCl



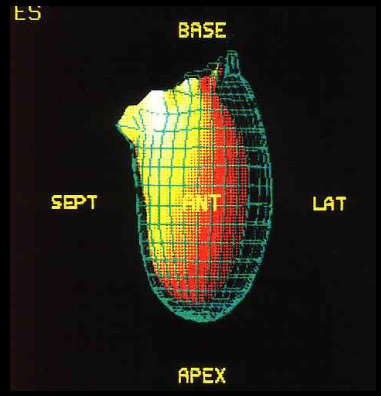


Moriya et al. Circulation 2010

Cardiac ischemia is improved by implantation of PB-MNCs into ischemic limbs

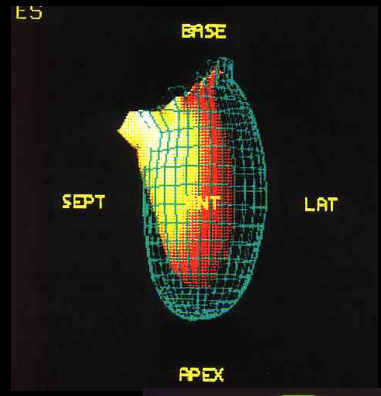
81 yo F
ASO and IHD

before



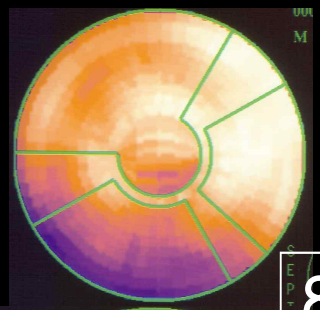
EDV 92
ESV 49
EF 47

8 w after

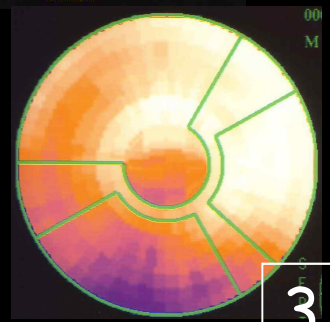


EDV 73
ESV 34
EF 53

STRESS

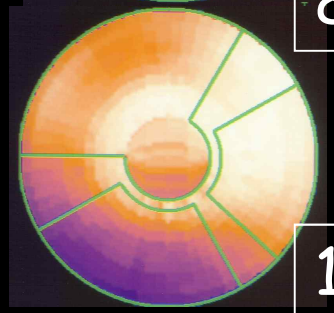


8.1%

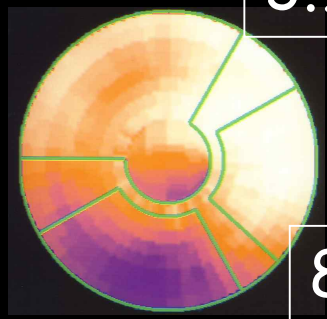


3.9%

REST



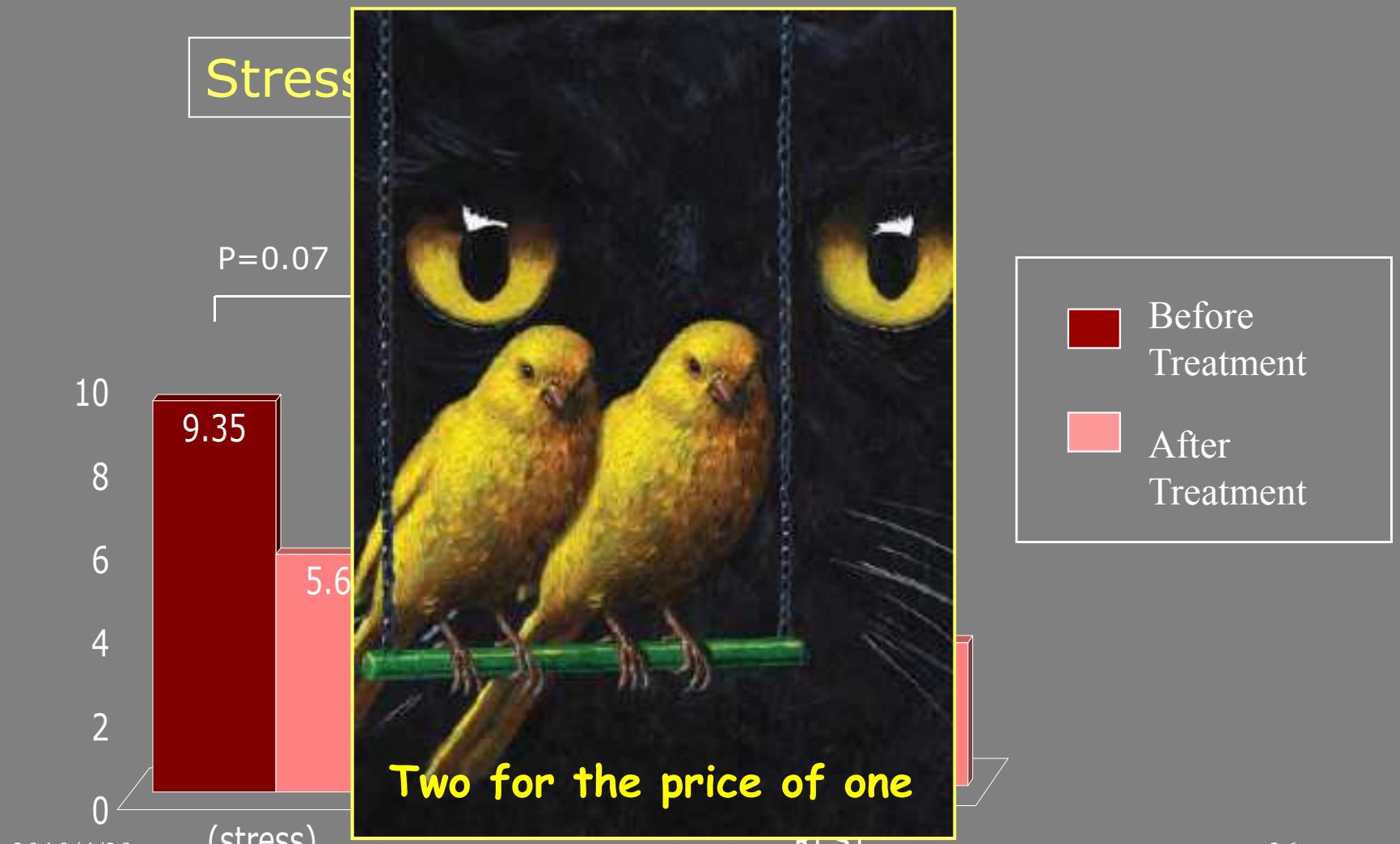
16.5%



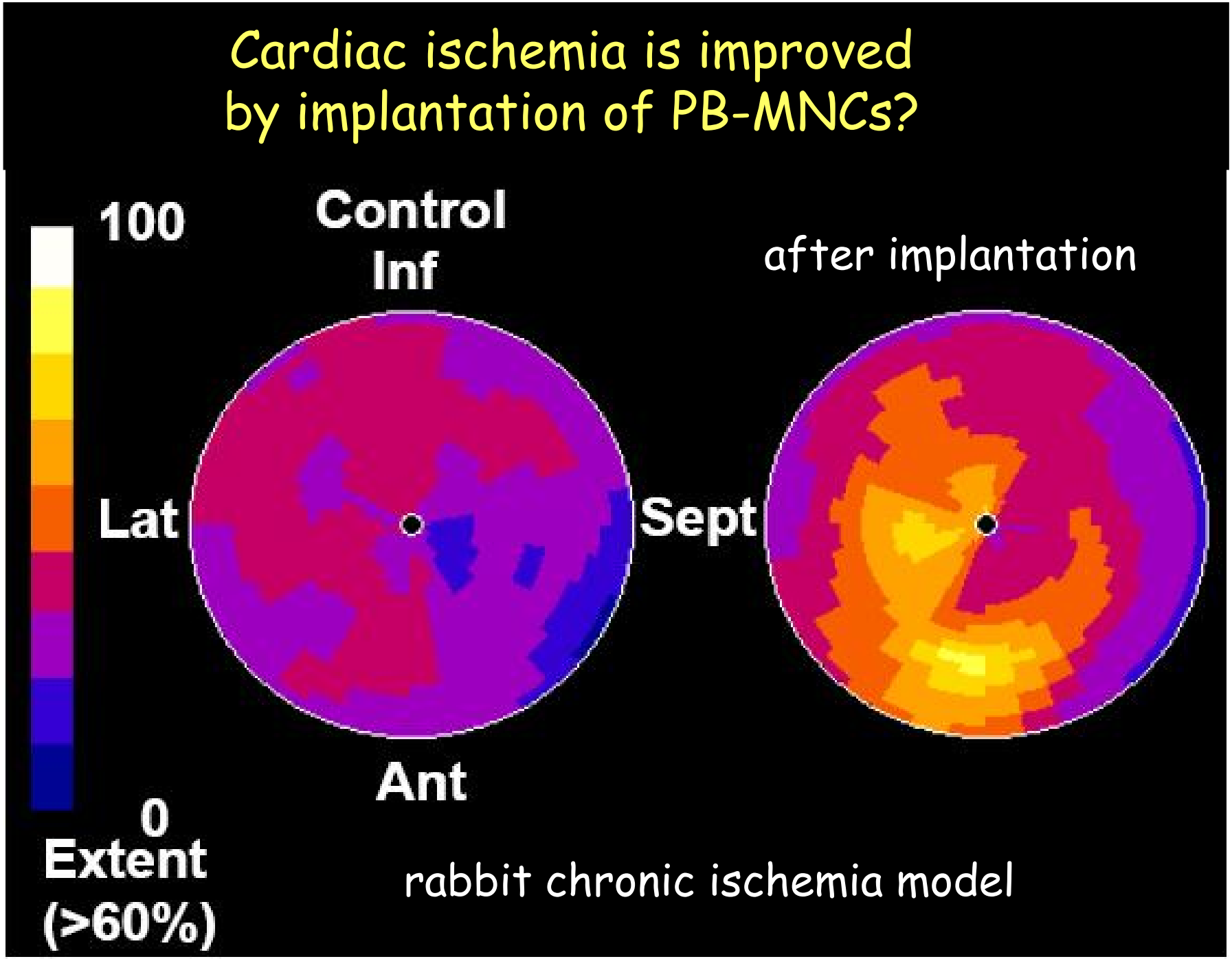
8.5%

Moriya et al. Circulation 2010

Cardiac ischemia is improved by implantation of PB-MNCs into ischemic limbs

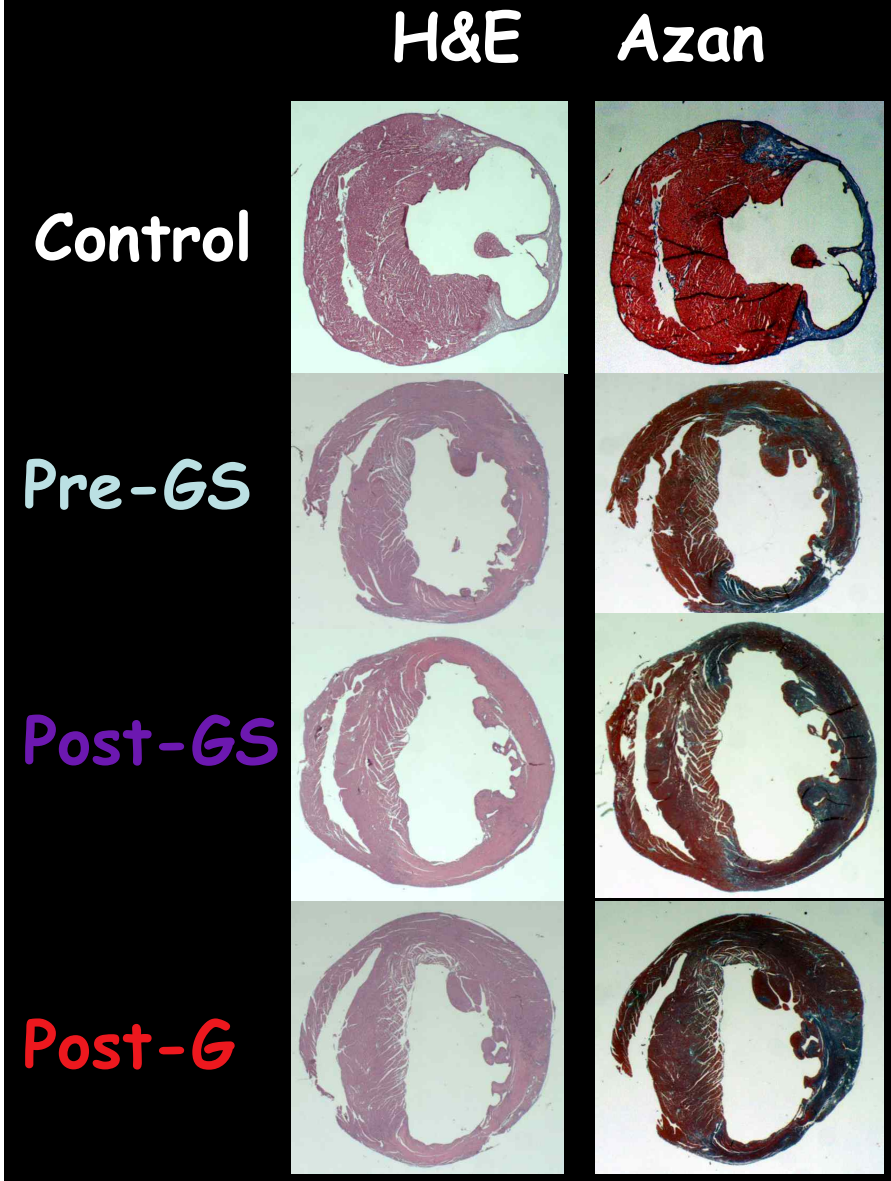


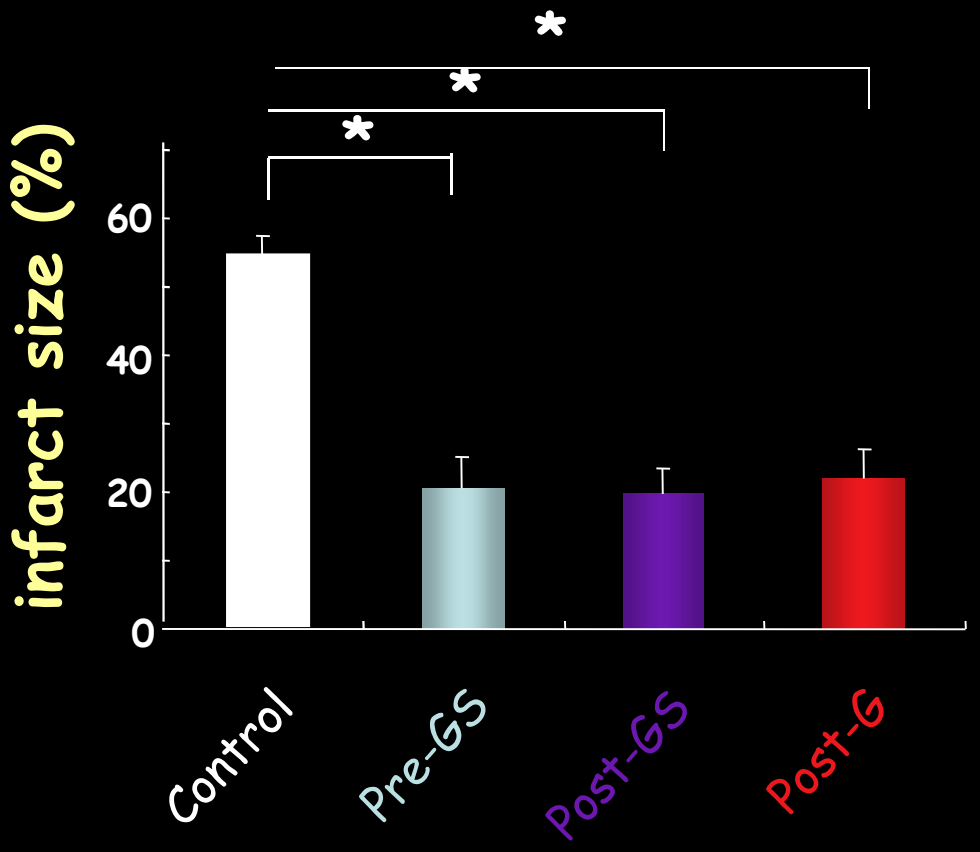
Moriya et al. Circulation 2010


Cardiac ischemia is improved
by implantation of PB-MNCs?
100
Control
Inf
after implantation
Lat
Sept
Ant
0
Extent
(>60%)
rabbit chronic ischemia model

G-CSF Therapy for Myocardial Infarction

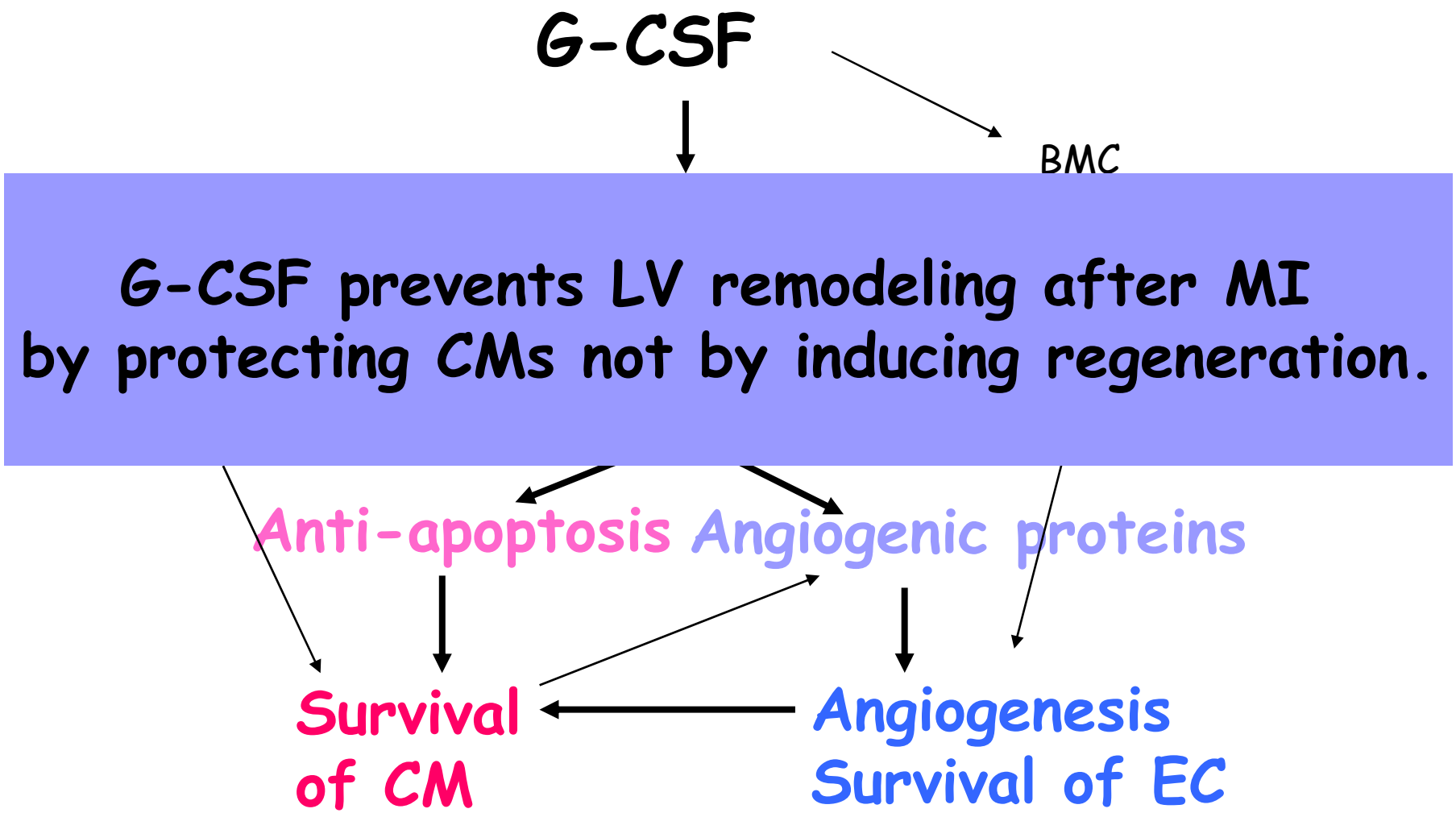
G-CSF prevents remodeling after MI





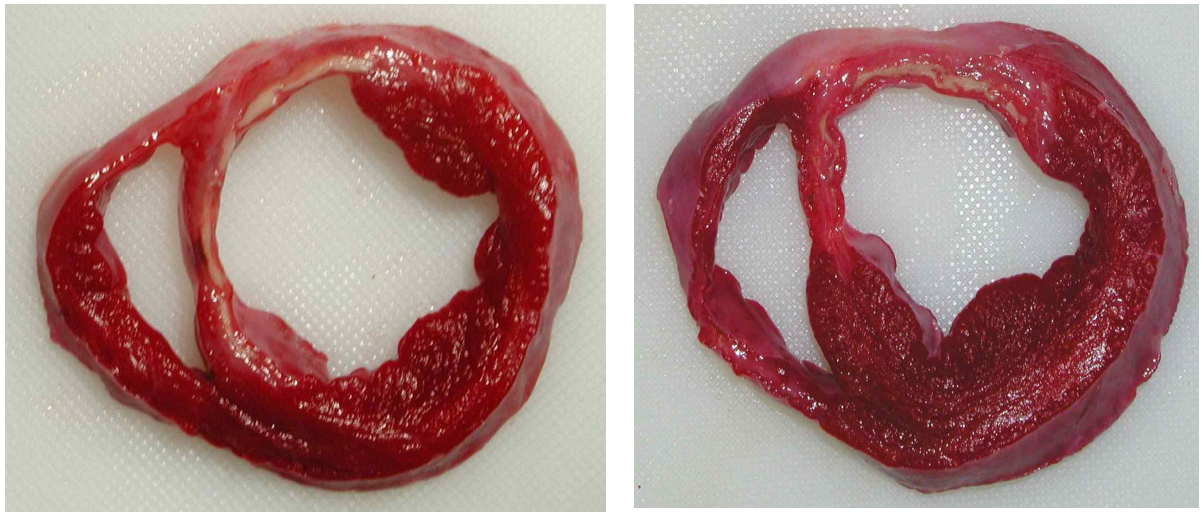
Ohtsuka et al. FASEB J, 2004

Mechanisms of G-CSF-induced prevention of LV remodeling after MI

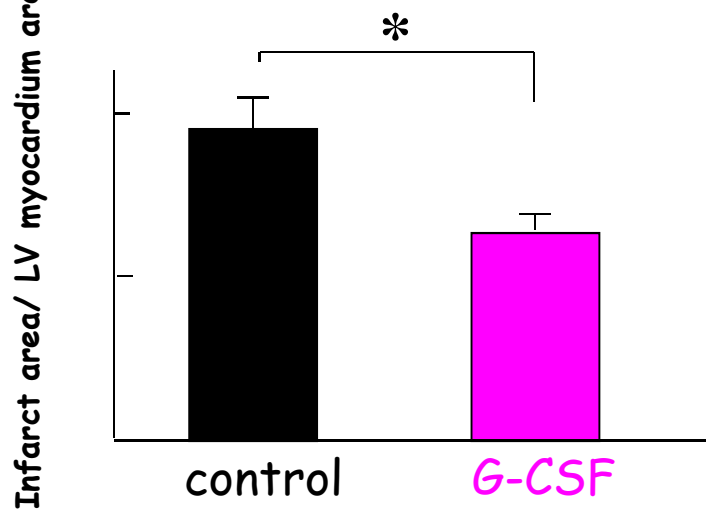


Harada et al. Nature Med 2005, Takano et al. J Mol Med 2009

Effects of G-CSF on swine hearts after MI

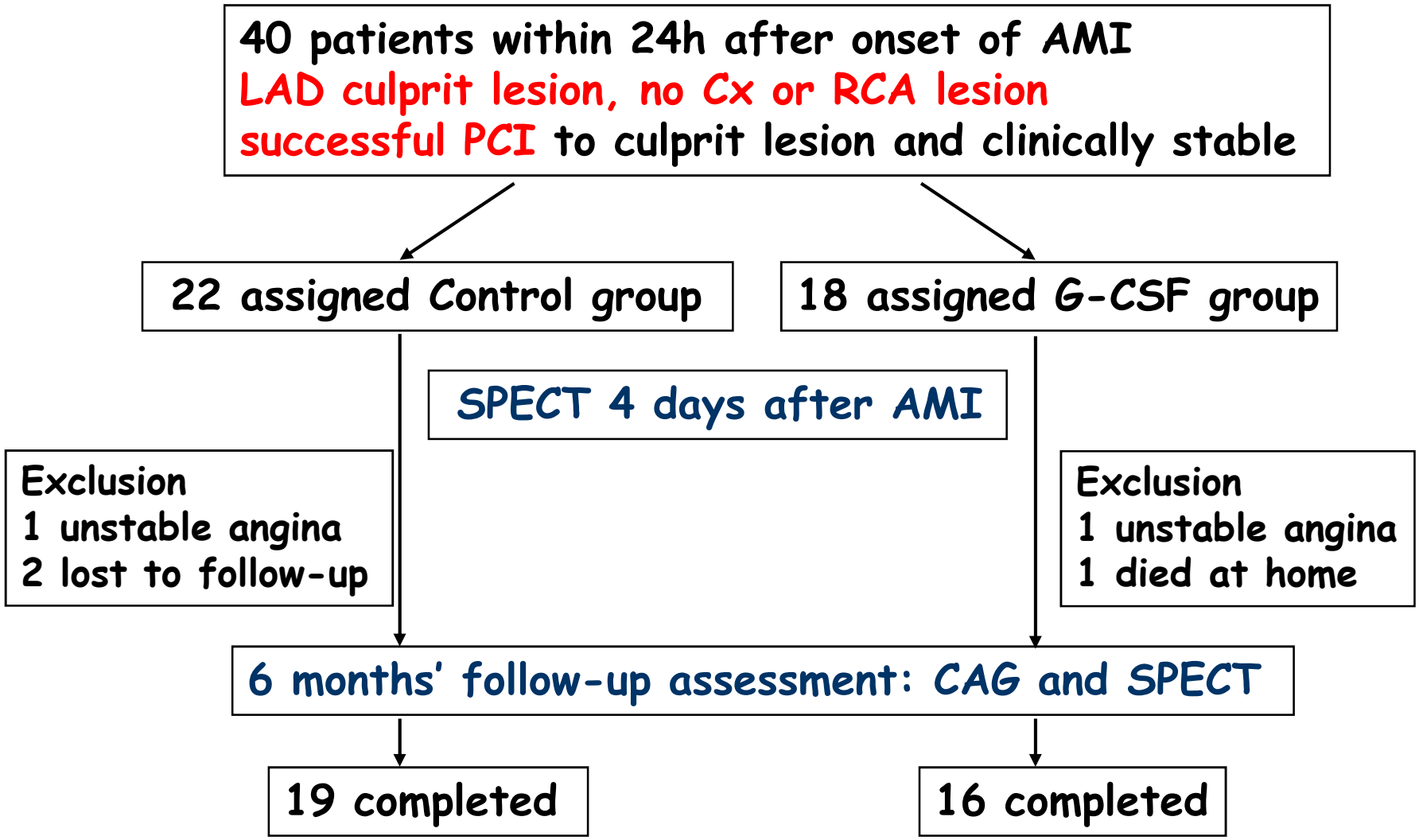


Control G-CSF



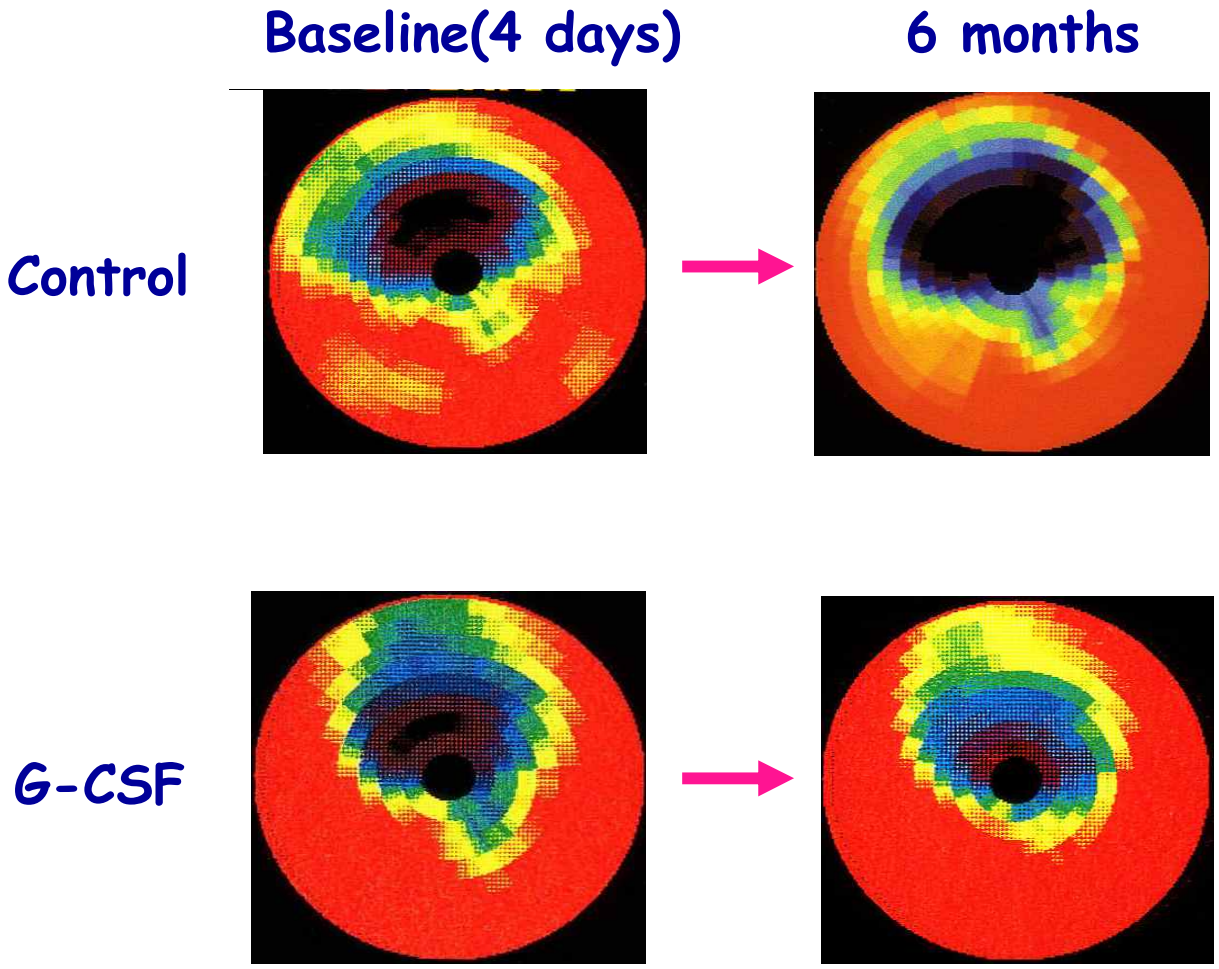
Iwanaga et al. BBRC 2004, Hasegawa et al. JACC 2006

Trial profile



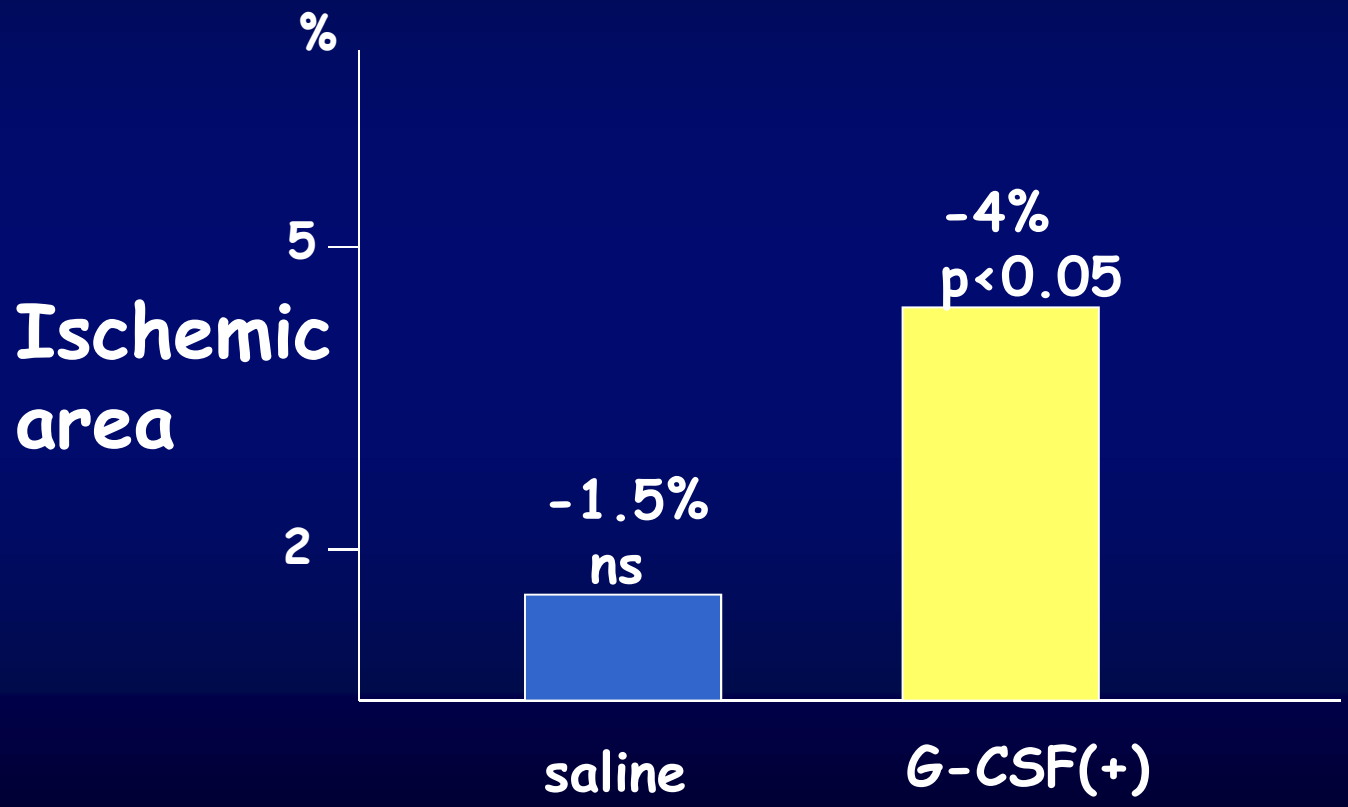
LAD=left anterior descending coronary artery; PCI=percutaneous coronary intervention; SPECT= single-photon emission computed tomography; UAP=unstable angina pectoris; CAG=coronary angiography

Effects of G-CSF on myocardial perfusion after AMI (^{99m}Tc-tetrofosmin SPECT)



Ischemic area

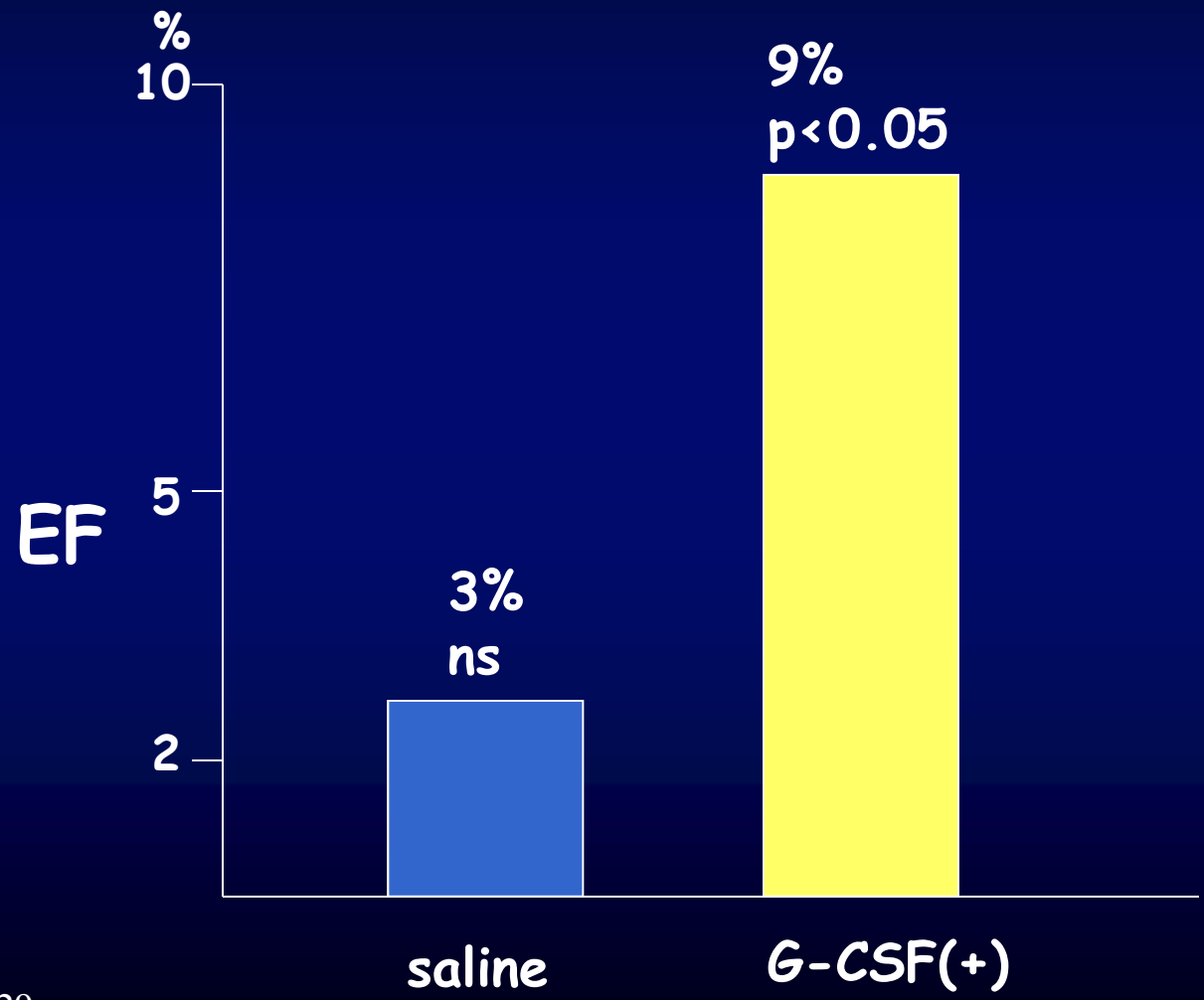
comparison between 4 days and 6 months after MI



Takano et al. Int J Cardiol 2007

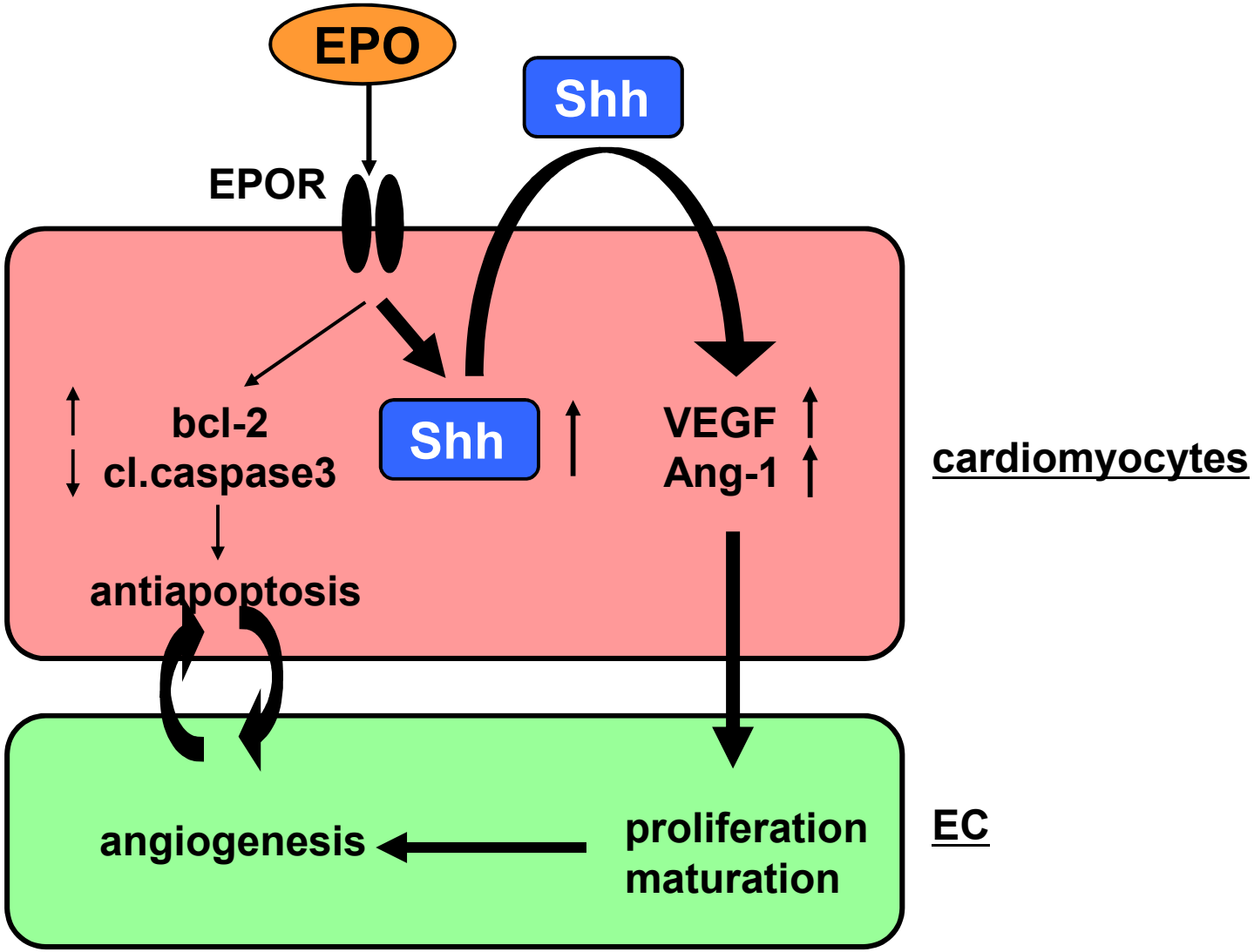
Changes of EF

comparison between 4 days and 6 months after MI



Takano et al. Int J Cardiol 2007

Mechanisms of Epo-induced cardioprotection



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