HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

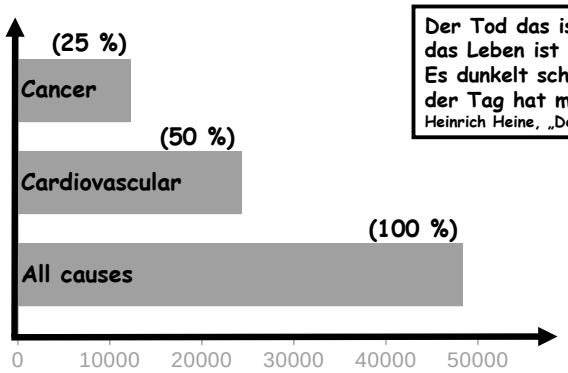
Molecular Mechanisms Of Vascular Adaptations To Exercise. Physical Activity As An Effective Antioxidant Therapy?

Prof. Dr. Georg Kojda
Institut für Pharmakologie und Klinische Pharmakologie,
Universitätsklinikum Düsseldorf,
Düsseldorf, Germany

(No conflict of interest)

Myocardial Infarction and Stroke:

The smirking death silently sneaking around us



Deaths in 2004, State Sachsen, Germany

Der Tod das ist die kühle Nacht,
das Leben ist der schwüle Tag.
Es dunkelt schon, mich schläfert,
der Tag hat mich müd gemacht.
Heinrich Heine, „Der Tod das ist die kühle Nacht"

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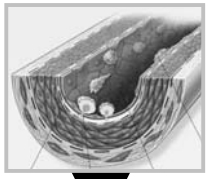
Myocardial Infarction and Stroke come all of a sudden. The Moratlity is high and those who survive leave their best times behind.



50 Years

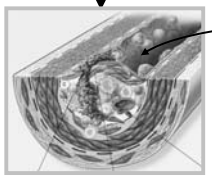


Abb. aus Ross R, NEJM 1998

Acute MI

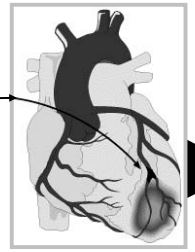


Abb. aus www.heartpoint.com

Infarct Mortality*:
Men: ca. 60 %
Women: ca. 70 %

Abb. aus www.stephentaylor.ca

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* (incl. Reinfarkte) KORA/MONICA-Studie, Löwel et al., 2002

Typical Progression of Coronary Atherosclerosis

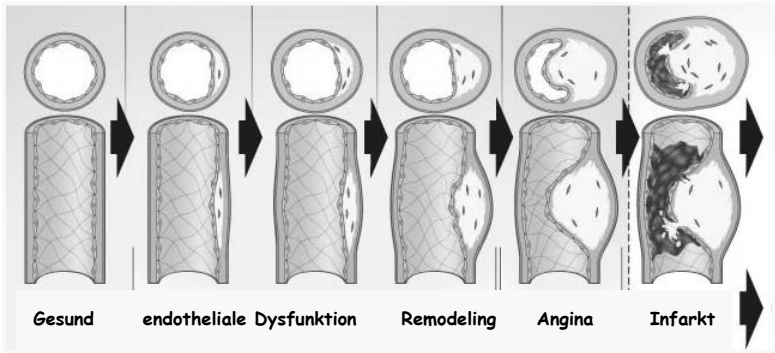

Abb. nach: Abrams J. N Engl J Med 2005;352:2524-2533

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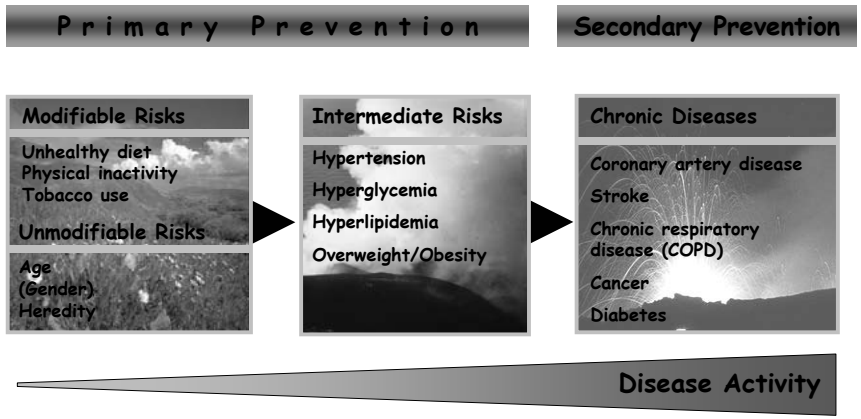
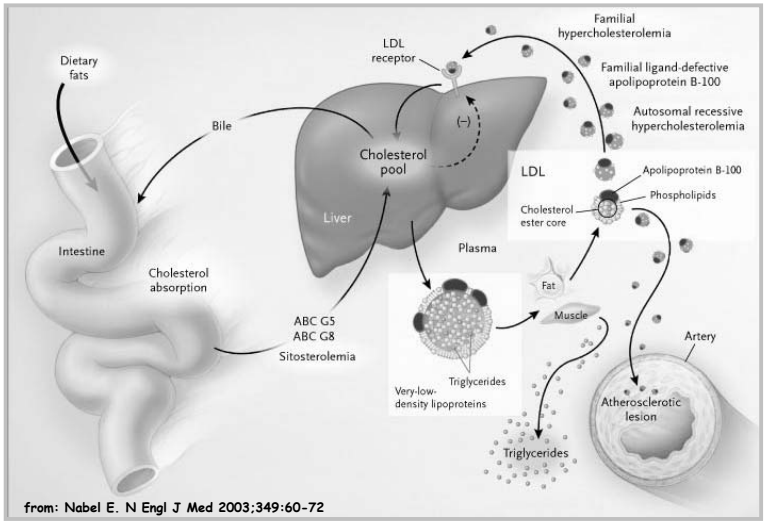


Scheme adopted from WHO: „Preventing Chronic Diseases: a vital investment", 2004

Non avoidable Risk Factors

Genetic causes of Hypercholesterolemia



from: Nabel E. N Engl J Med 2003;349:60-72

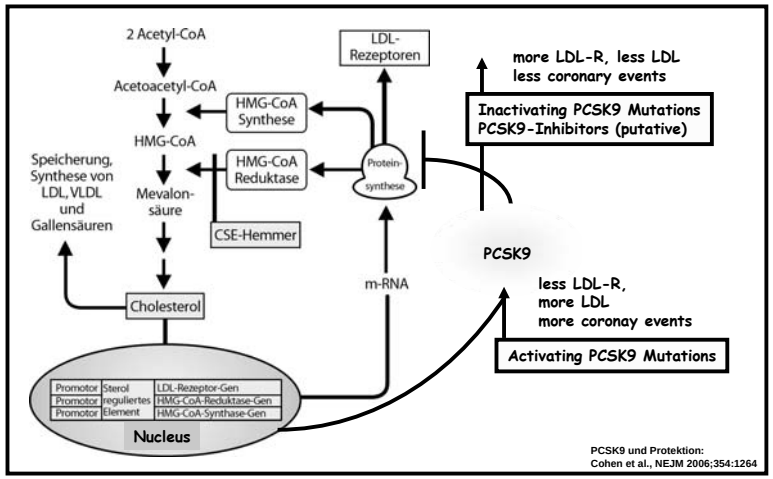
Non avoidable Risk Factors

Genetic causes of Hypercholesterolemia

Erkrankung	Genmutation	Mechanismus	Cholesterol
Familial Hypercholesterolemia heterozygous (1:500) homozygous (1:1.000.000)	LDL-Receptor	LDL-Receptor Deficiency	(mg/dl) 300 650
Familial Ligand-defecive APO B-100 heterozygous (1:1.000) homozygous	APO B-100	no Binding of LDL to LDL-Receptor	 275 325
Autosomal-recessive Hypercholesterolemia (<1:10.000.000)	(ARH) hepatic Adaptorprotein	reduced Activity of LDL-Rezeptor	650
Sitosterolemia (<1:1.000.000)	ABCG5, ABCG8 ATP-Binding Cassette	low biliary and Sterol elimination	150- 650

Non avoidable Protective Factors

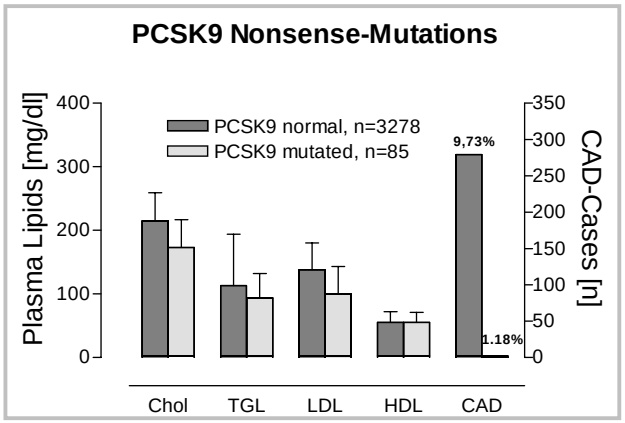
Genetic causes of Low Plasma Cholesterol



Proconvertase Subtilisin/Kexin Typ 9

Abb. nach: Kojda G. Pharmakologie Toxikologie Systematisch, UNI-MED Verlage, Bremen, 2.Auflage 2002

Cardiovascular Protection by Inactivating PCSK9-Mutations



Daten aus:
Cohen et al., NEJM 2006;354:1264

Plasma Lipids (surrogat parameters)

CAD-Incidence (hard endpoint morbidity)

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Physical activity

You'd like to improve your health status?

Try a healthy lifestyle. It's priceless!

Triangle of cardiovascular prevention

Healthy diet

Smoking cessation

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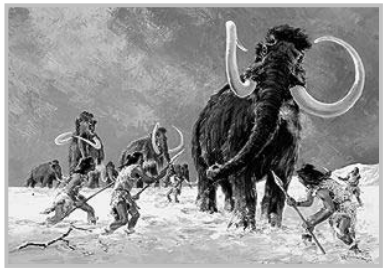
In ancient times survival meant hard work and thus sufficient „exercise" each day.
Eating each day was not normal, though.



www.treffmagazin.de

Der letzte Büffel - Ölgemälde des Deutschen Albert Bierstadt von 1889. Buffalo Bill Historical Center, Cody, Wyoming (USA)

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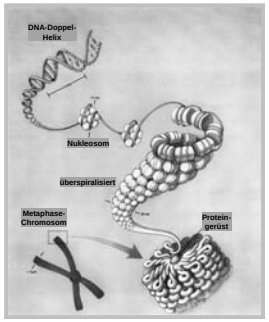
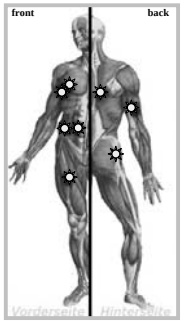
The construction plans of our genetic endowment to convert body cells to an energy storage go well with exercise.
Without exercise, these cells turn from friends to foes.



www.math.ntua.gr/~sofia/

www.fit-company.at



www.ironsport.de

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During our history, daily exercise has always been a constant but this has changed in modern times.

History **Modern Times**


Homo habilis


Homo erectus


Homo sapiens


Homo relaxus

www.treffmagazin.de

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What is the evidence for beneficial effects of regularly physical activity?

Well, just continue, you'll see!

http://www.grinningplanet.com/2004/03-23/funny-news-zombienews-2-joke.htm

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Overt Cardiovascular Disease

Reduction Of Mortality by 30 %
(Metaanalysis, Circulation 1989;80:234-244)

Secondary Prevention

Primary Prevention

Early CAD-Development

20 min/day reduces CAD-Mortality by 29 %
(MRFIT-Study, Int J Sports Med. 1997 Jul;18 Suppl 3:S208-15)

Health status of older men

3.2 km walking/day Reduces Overall Mortality by 50 %
(Hakim et al., N Engl J Med 1998;338:94-9)

Health status of postmenopausal women

2 km walking/day Reduces CAD-Risk by 30 %
(Manson et al., NEJM 2002; 347:716-25)

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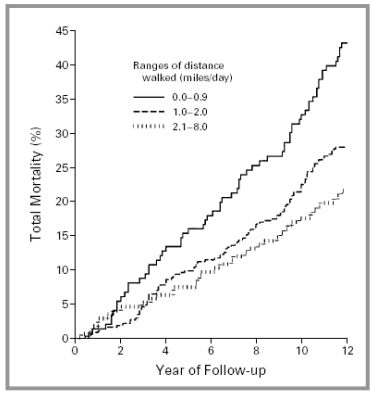
Effect Of Moderate But Regular Exercise On Mortality Of Non-Smoking Retired Men (>65 Years)



Just 1-2 miles of **walking** each days strongly reduces mortality among retired men (23.8 vs. 40.5%, P<0.001).
(N Engl J Med 1998;338:94-9.)

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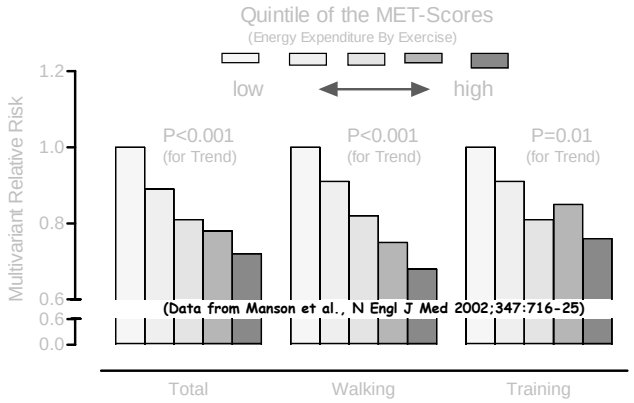
Effect Of Moderate But Regular Exercise On Cardiovascular Risk Among 73.743 Women (>65 Years)



(Abb. aus Kojda G, „Keep Walking - Der kostenlose Infarktschutz", **Apothekenmagazin** 2002;20(11):4-5)

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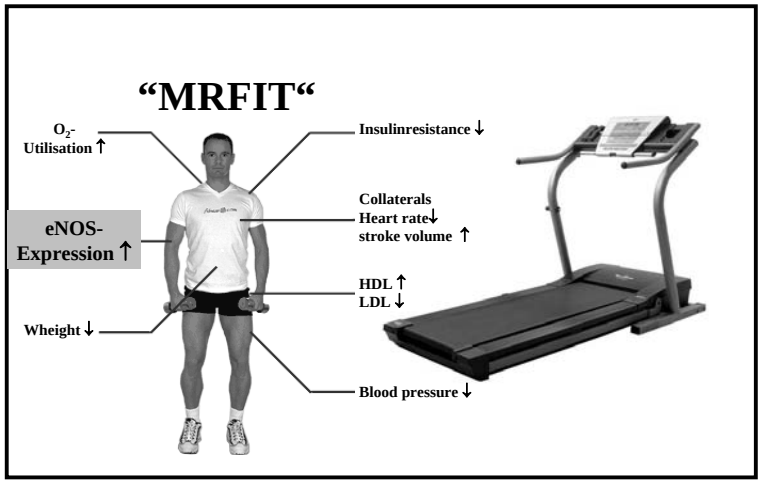
Why is Exercise Beneficial?



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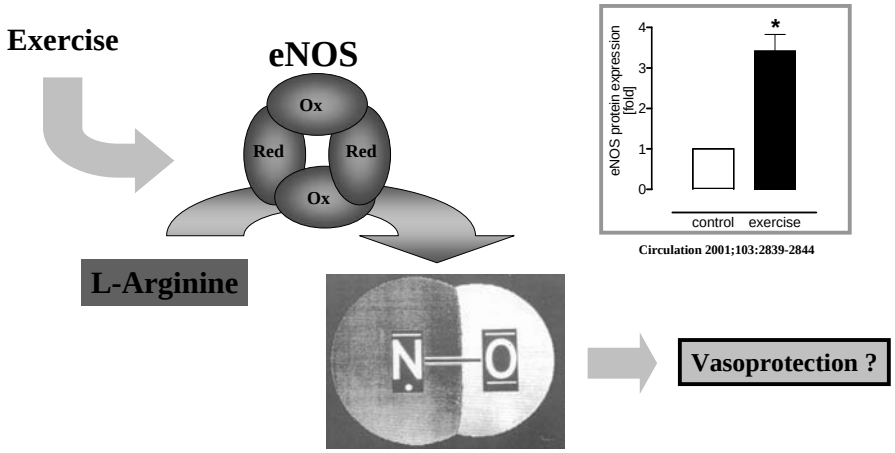
What Can Mouse Models Tell Us?



Circulation 2001;103:2839-2844

Vasoprotection ?

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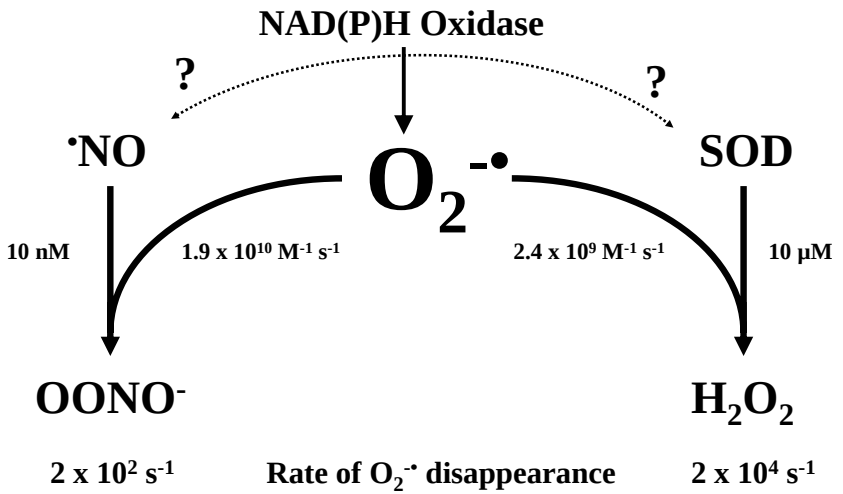

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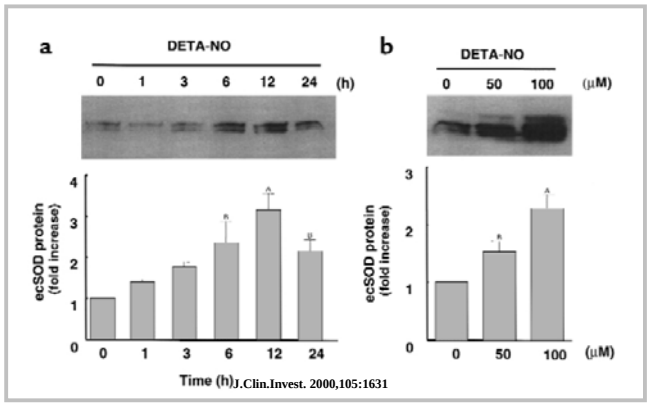
Effect Of The NO-Donor DETA/NO On ecSOD Protein Expression



J.Clin.Invest. 2000,105:1631

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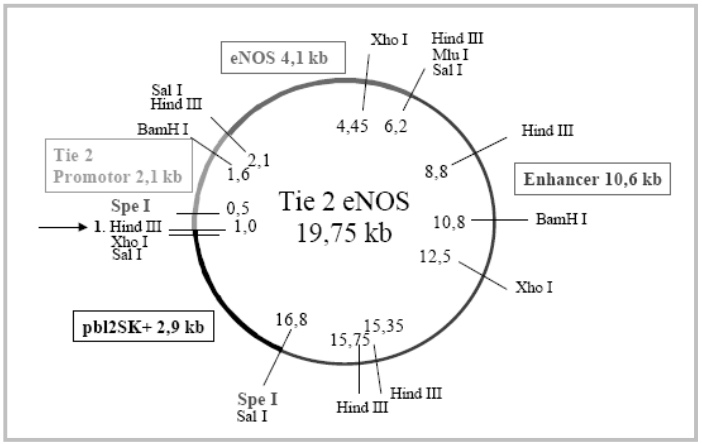
Structure of the Plasmid Constructed For Vascular-Specific Overexpression of eNOS



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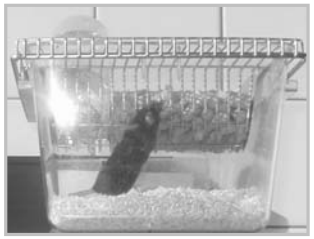
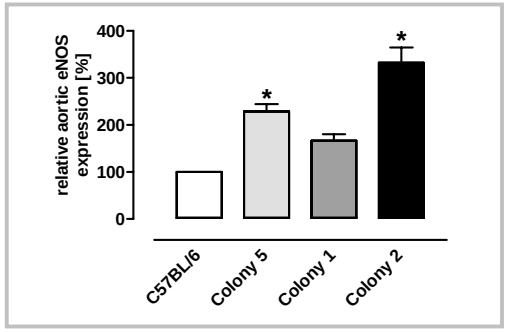
Overexpression of eNOS in different Colonies





Suvorava, Oppermann, Kojda, unpublished

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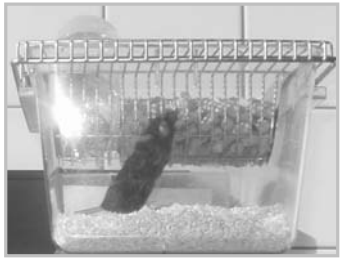
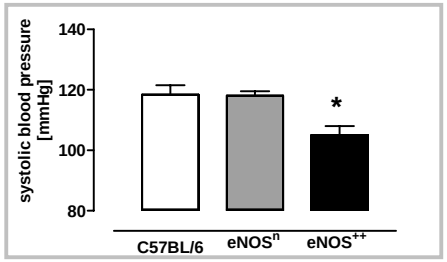
Reduction of Blood Pressure in eNOS^{++} Mice.





Suvorava, Oppermann, Kojda, unpublished

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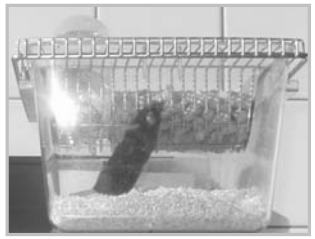
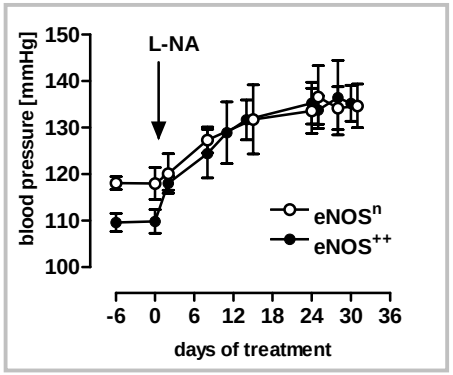
Reduction of Blood Pressure in eNOS^{++} is inhibited by the NOS-Inhibtor L-Nitroarginine (L-NA)





Suvorava, Oppermann, Kojda, unpublished

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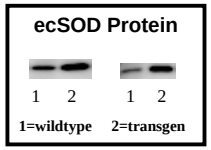
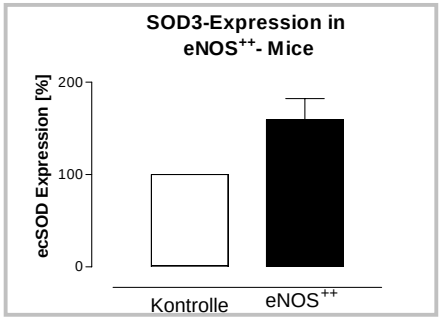
Overexpression Of eNOS In eNOS^{++} Drives Overexpression Of ecSOD





Suvorava, Oppermann, Kojda, unpublished

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Exercise Increases Vascular eNOS Expression. Does Exercise Increase ecSOD-Expression As Well?

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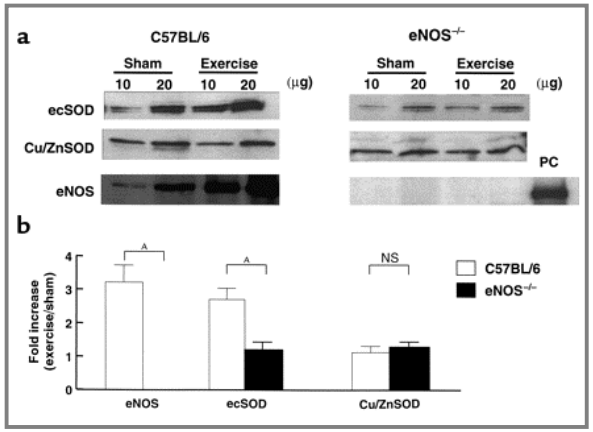
Exercise Increases ecSOD Expression NO-Dependently



J.Clin.Invest. 2000,105:1631

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Vascular Adaptations To Exercise

"Based on these observations it appears resonable to assume that exercise training can be viewed as an effective antioxidant and antiatherogenic therapy."

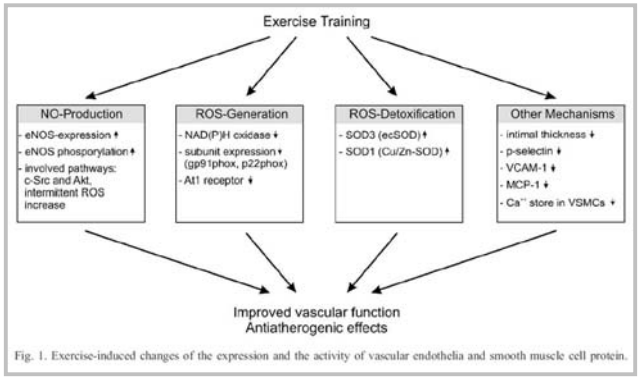

Fig. 1. Exercise-induced changes of the expression and the activity of vascular endothelia and smooth muscle cell protein.

Kojda G, Hambrecht R, Cardiovasc Res 2005,67:187-197

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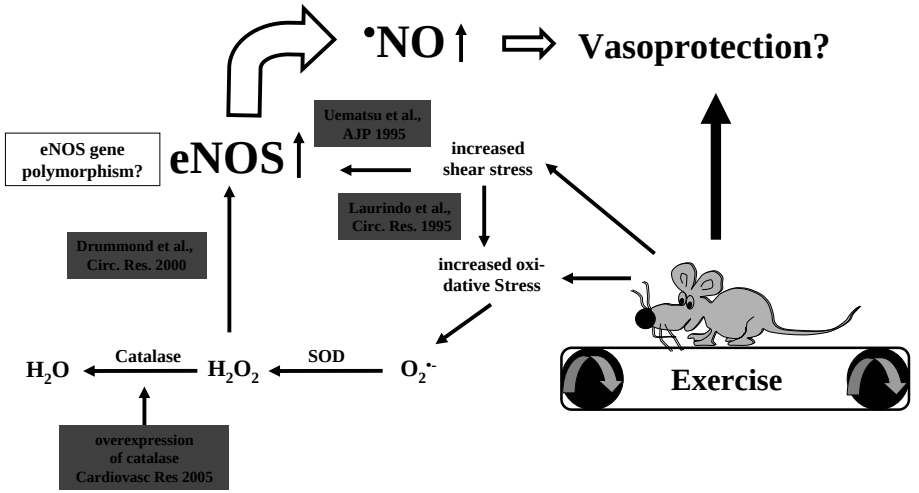
Mechanisms of Vascular Adaptations To Exercise



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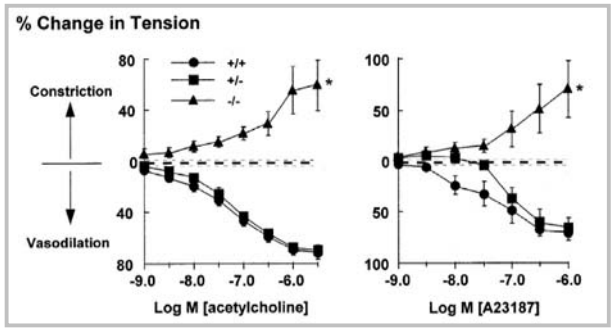
Mechanisms of Vascular Adaptations To Exercise

Does permanent malfunction of one eNOS gene inhibit exercise-induced expression of vascular eNOS?



Endothelium-dependent vasodilation unchanged

Cardiovasc Res 1999;42:205-213

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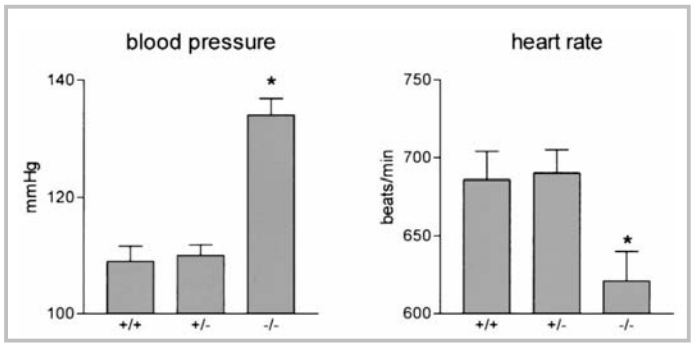
Mechanisms of Vascular Adaptations To Exercise

Does permanent malfunction of one eNOS gene inhibit exercise-induced expression of vascular eNOS?



Blood pressure and heart rate are unchanged

Cardiovasc Res 1999;42:205-213

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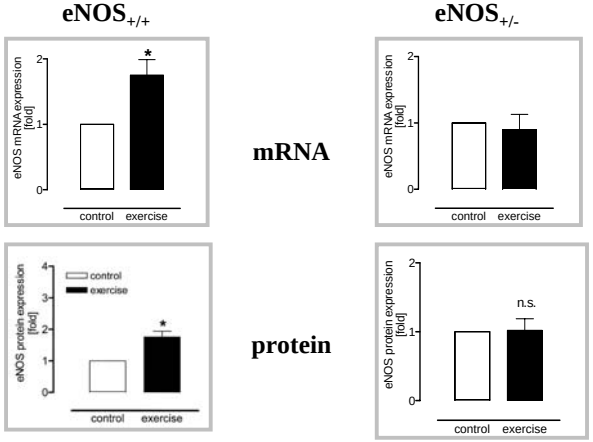
Mechanisms of Vascular Adaptations To Exercise

The loss of one eNOS Gene impairs the upregulation of eNOS expression induced by exercise



Circulation 2001;103:2839-2844

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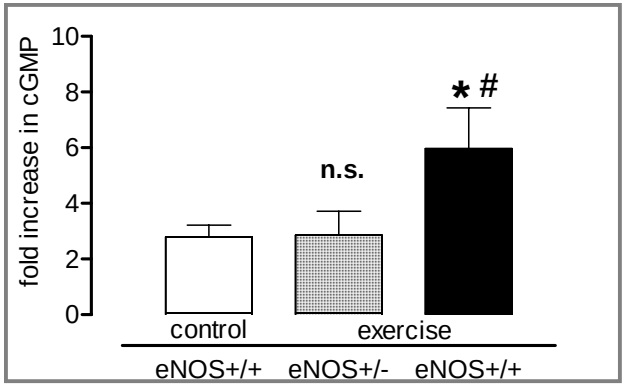
Mechanisms of Vascular Adaptations To Exercise

The loss of one eNOS Gene impairs the upregulation of eNOS function induced by exercise



Circulation 2001;103:2839-2844

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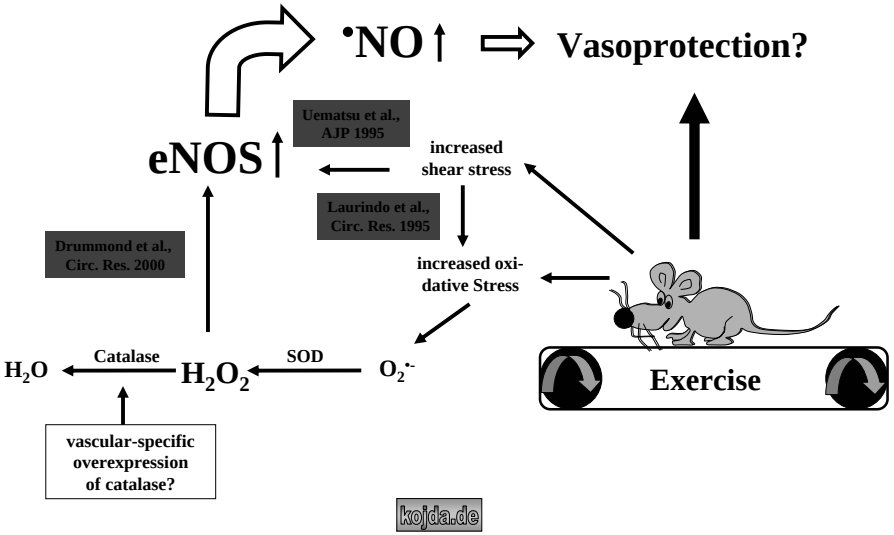
Mechanisms of Vascular Adaptations To Exercise



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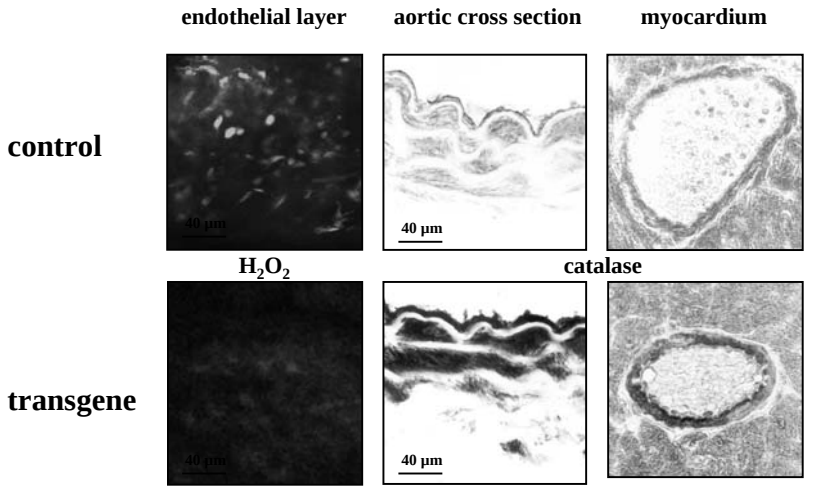
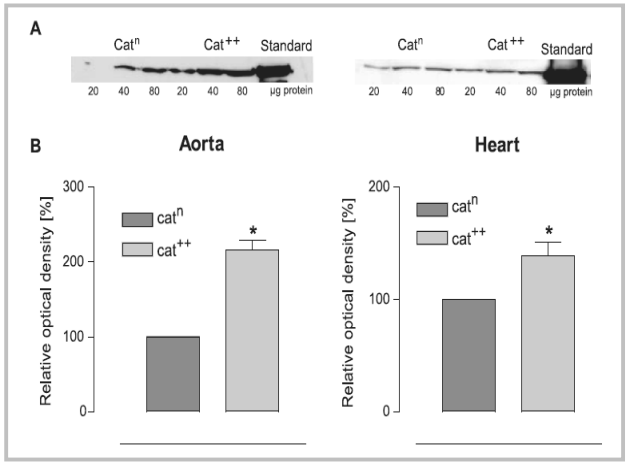
Mechanisms of Vascular Adaptations To Exercise



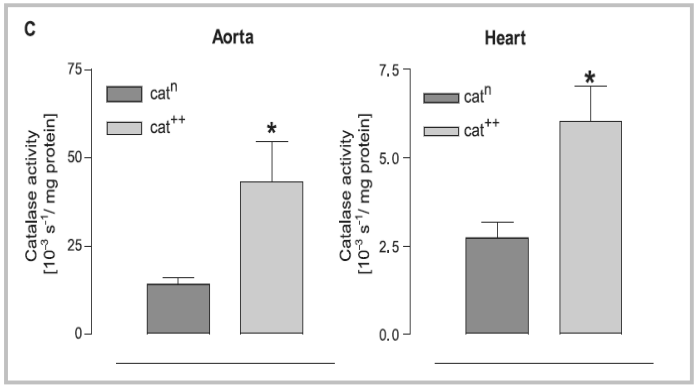
Permanent Vascular Overexpression of Catalase



Cardiovasc Res 2005; 65(1):254-62

Mechanisms of Vascular Adaptations To Exercise

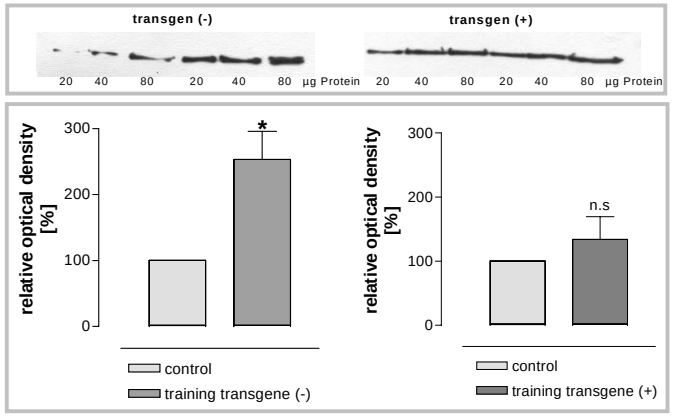
Permanent Vascular Overexpression of Catalase



Cardiovasc Res 2005; 65(1):254-62

Mechanisms of Vascular Adaptations To Exercise

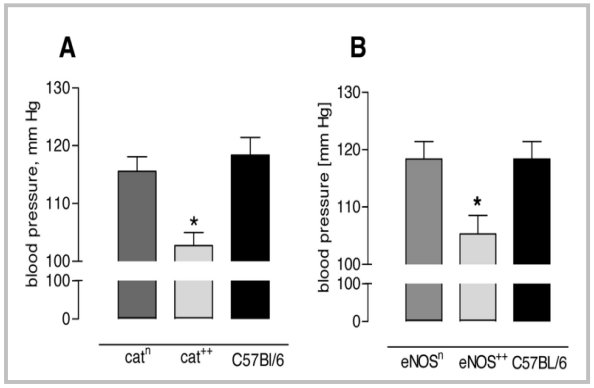
Permanent reduction of Hydrogen Peroxide Inhibits Exercise-Induced Expression of Vascular eNOS



Cardiovasc Res 2005; 65(1):254-62

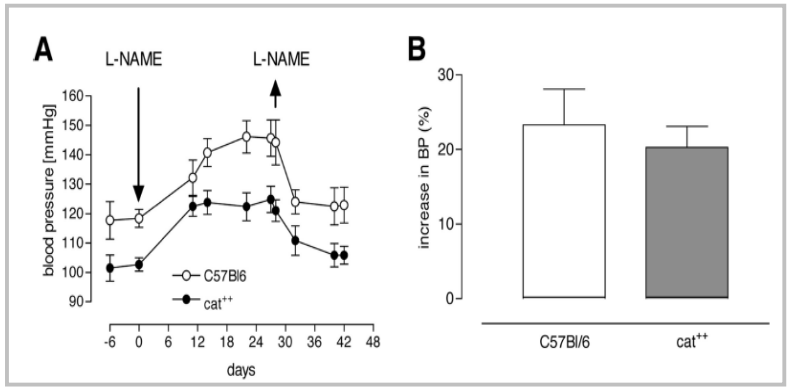
Mechanisms of Vascular Adaptations To Exercise

Permanent Reduction of Vascular Hydrogen Peroxide Reduces Blood Pressure



Circulation. 2005;112:2487-2495.

Permanent Reduction of Vascular Hydrogen Peroxide Reduces Blood Pressure Independent of eNOS.



Circulation. 2005;112:2487-2495.

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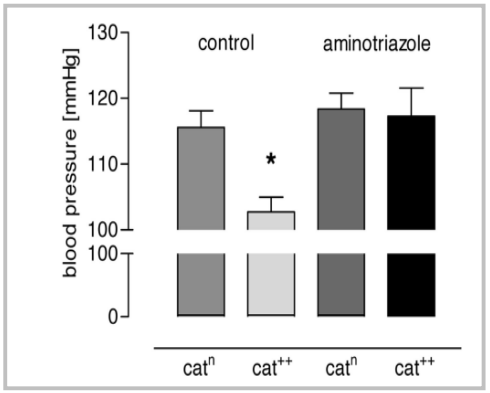
Permanent Reduction of Vascular Hydrogen Peroxide Reduces Blood Pressure: Inhibition by Aminotriazole.



Circulation. 2005;112:2487-2495.

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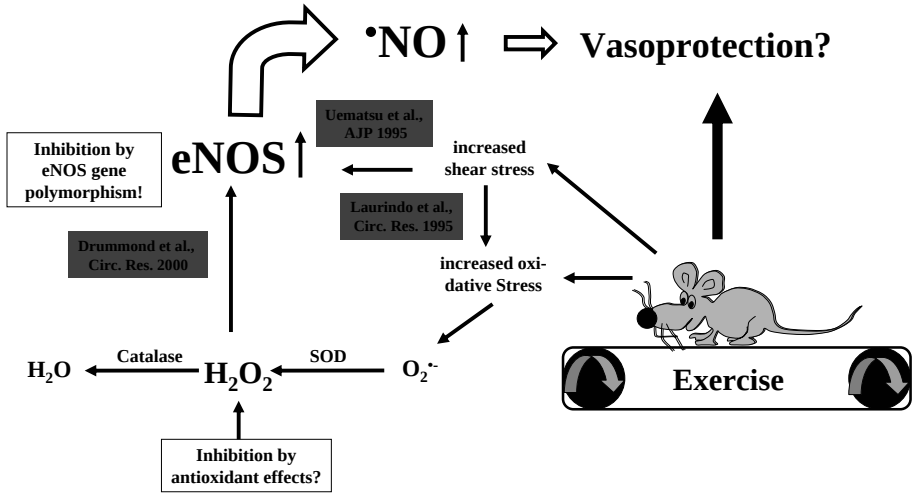

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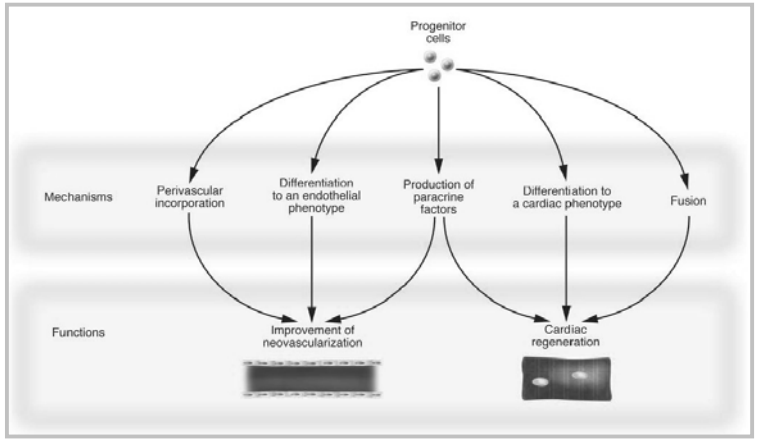

Dimmeler et al., J Clin Invest 2005;115:572-583

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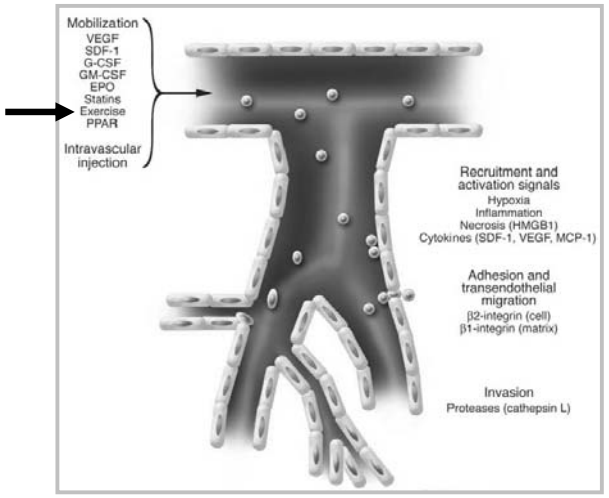
Mechanisms of Vascular Adaptations To Exercise



Dimmeler et al., J Clin Invest 2005;115:572-583

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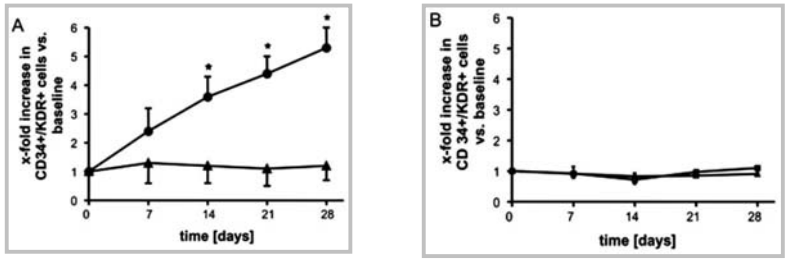
Mechanisms of Vascular Adaptations To Exercise

Symptomatic tissue ischemia in training programs seems to be a prerequisite for the mobilization of circulating progenitor cells.

Ischemia **No Ischemia**



Sandri et al., Circulation 2005;111:3391-3399

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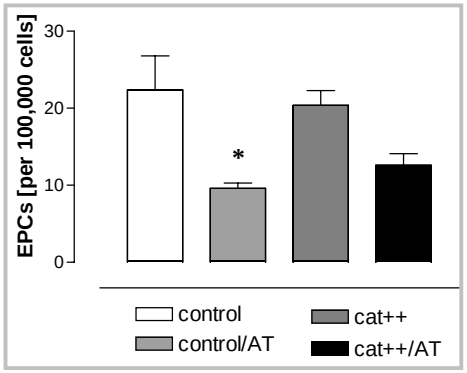
Mechanisms of Vascular Adaptations To Exercise

Effect of aminotriazole treatment on CD34/FLK-1 positive cells in resting mice as measured by FACS analysis



(P=0.026, One Way ANOVA, *, P<0.05 vs. control)

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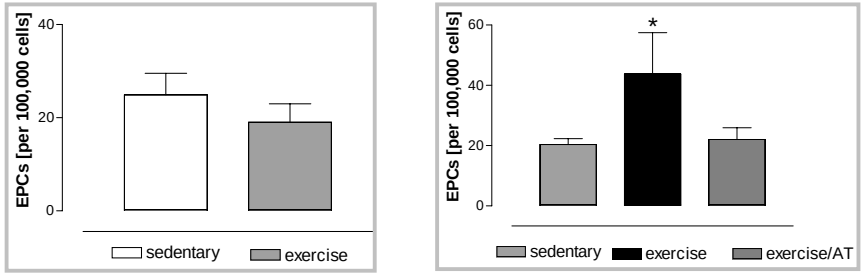
Mechanisms of Vascular Adaptations To Exercise

Effect of exercise training on CD34/FLK-1 positive cells in cat^{n} and cat^{++} mice.



(P=0.026, One Way ANOVA, *, P<0.05 vs. control)

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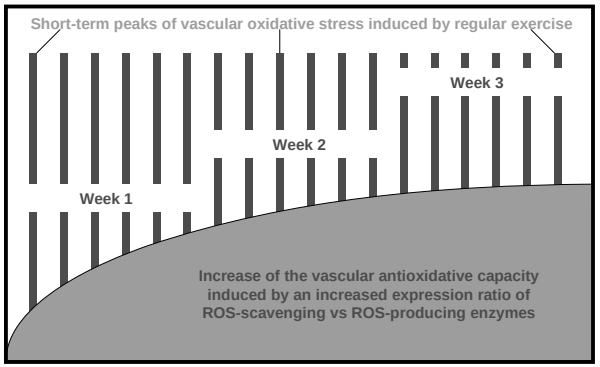
Endogenous generation of reactive oxygen species such as hydrogen peroxide might reduce the number of circulating EPCs and thereby inhibit important stem cell-induced vascular repair mechanisms.

(P=0.026, One Way ANOVA, *, P<0.05 vs. control)

Short Term Peaks of Vascular Oxidative Stress Induced by Exercise Appear to Increase Vascular Antioxidative Defense Mechanisms

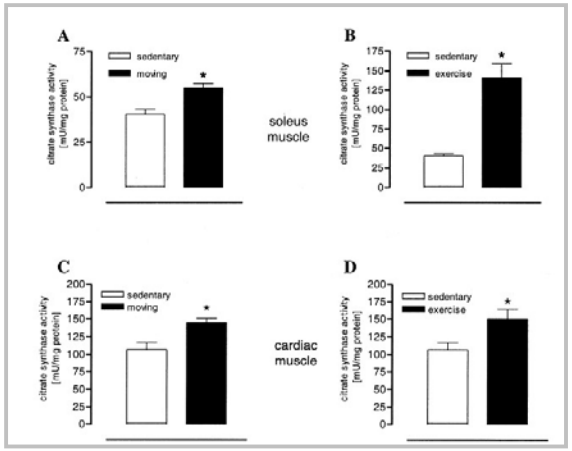


Experimental sedentary lifestyle induced by singularization

Forced physical inactivity

J Am Coll Cardiol 2004; 44:1320-1327.

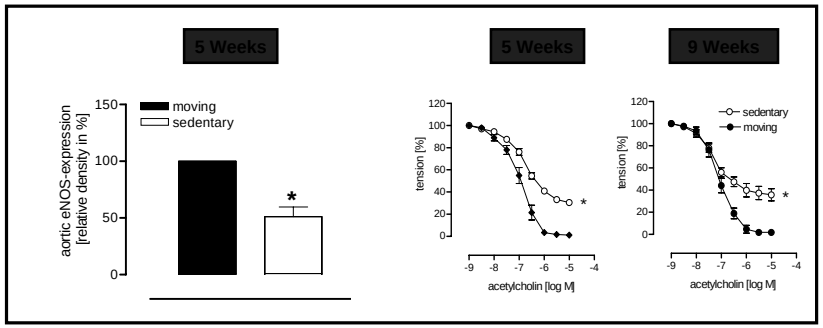
Quantitation of regular physical activity in mice by skeletal muscle citrate synthase activity



J Am Coll Cardiol 2004; 44:1320-1327.

Mechanisms of Vascular Adaptations To Exercise

Physical inactivity, the so-called sedentary lifestyle, may increase cardiovascular risk in young healthy individuals by inducing endothelial dysfunction.



J Am Coll Cardiol 2004; 44:1320-1327.

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Summary

Exercise training increases vascular NO-production and decreases vascular ROS-production.

The effects of exercise training on vascular eNOS expression are dependent on both eNOS genes.

The induction of vascular eNOS expression by exercise training is dependent on endogenous hydrogen peroxide formation.

Physical inactivity - the so-called sedentary lifestyle - rapidly causes reduced eNOS expression and endothelial dysfunction in young healthy individuals.

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Conclusions

Exercise training can be viewed as an effective antioxidant and antiatherogenic therapy.

In cardiovascular disease patients exercise reduces the degree of endothelial dysfunction

In young healthy individuals normal physical activity and/or moderate exercise might delay the development of cardiovascular disorders by maintaining normal endothelial function

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Co-Workers

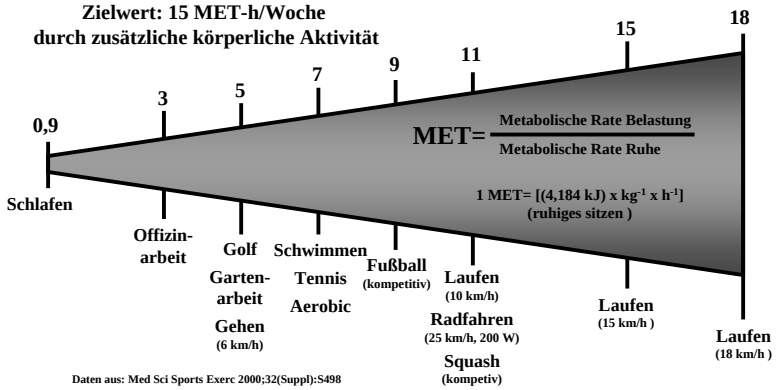
Björn Hüsgen, MD
Andreas Hacker, PharmD
Thorsten Kober, MD
Ute Laber, MD
Nadine Lauer, PharmD
Dorothea Martens, MD
Senta Müller, DMV
Petra Nix, MD
Verena Schmitz, PharmD
Martina Weber, PharmD

Cooperation-Partners

Eberhard Bassenge, MD, Freiburg
Thoru Fukai, MD, Atlanta
Rainer Hambrecht, MD, Leipzig
David Harrison, MD, Atlanta
Henning Morawietz, PhD, Halle
Jost Müllenheim, MD, Düsseldorf
Hans-Michael Piper, MD, Gießen
Benedict Preckel, MD, Düsseldorf
Klaus-Dieter Schlüter, PhD, Gießen
Volker [illegible]er, MD, Düsseldorf
[illegible] Zimmer, MD, Leipzig

Das Kompendium der körperlichen Aktivitäten

(oder welche Aktivität verbrennt wieviel Energie)



Daten aus: Med Sci Sports Exerc 2000;32(Suppl):S498

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