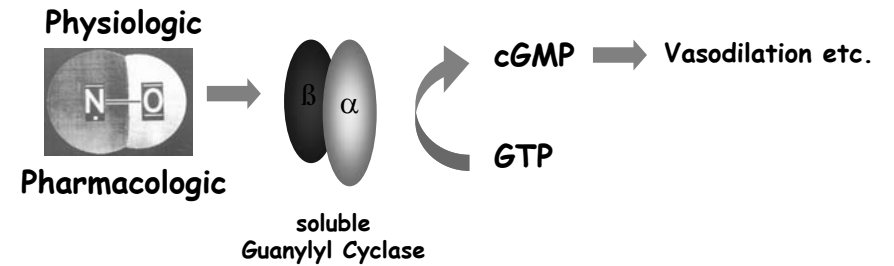


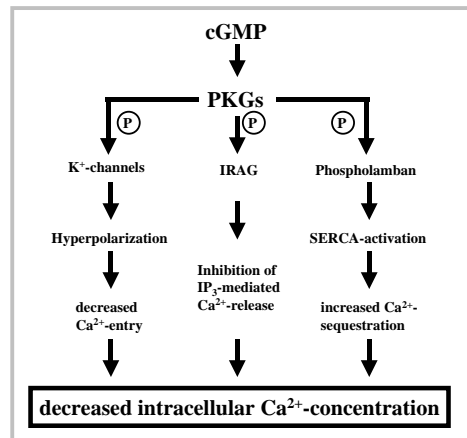
## Vasoprotection By Nitric Oxide. Mechanisms, Physical Activity And Pharmacotherapeutic Potential

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

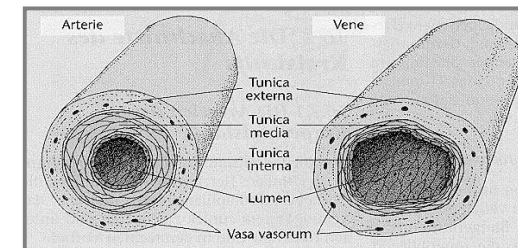
## The NO/cGMP Pathway



## The NO/cGMP Pathway



from Gewaltig & Kojda, Cardiovasc Res 2002;55:250-260



## Effects of NO in the vascular system

- vasodilatory
- antiaggregatory
- antiadhesive
- antioxidative
- antiproliferative
- antiapoptotic

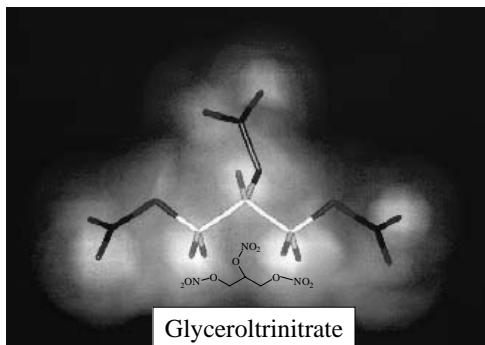
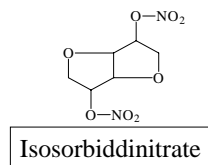
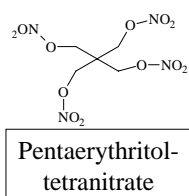
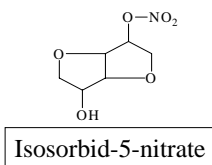
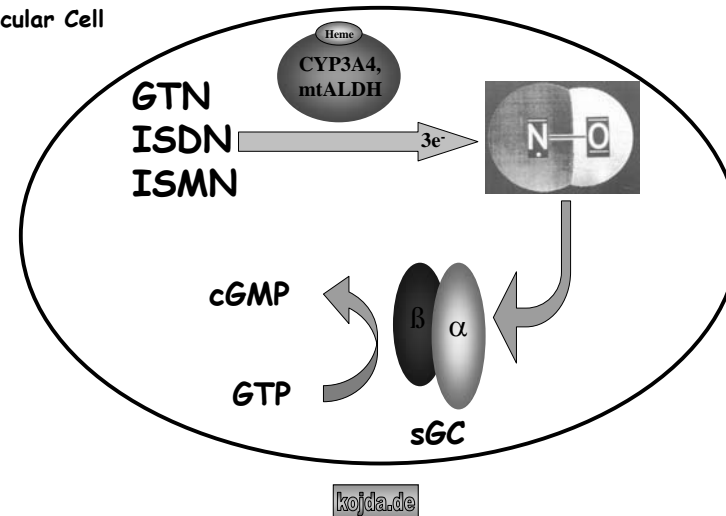


Illustration:  
Prof. Dr. H.-D. Hötje  
Pharmaceutical Chemistry  
University Düsseldorf

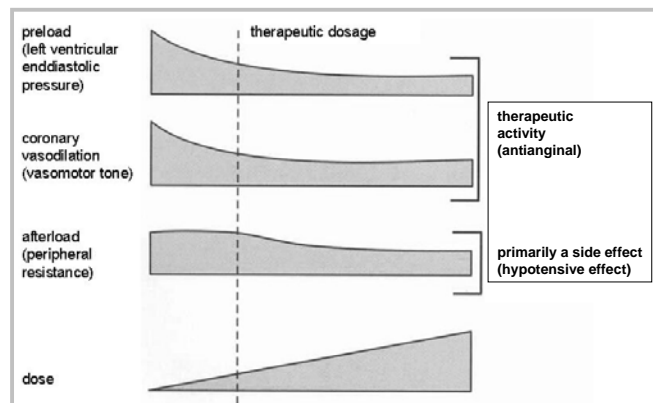


Vascular Bioactivation of Nitrates Determines Venous Pooling, The Positive Steal Effect and Moderate Tolerance

Vascular Cell

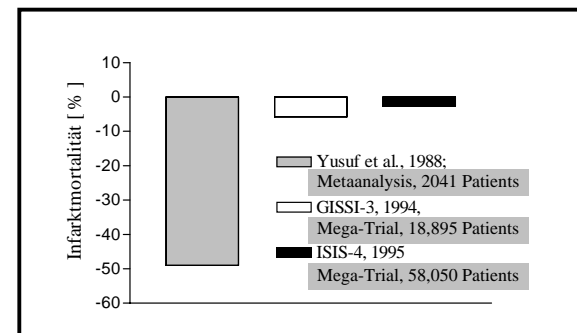


Unique Hemodynamic Profile Improves Quality of Live

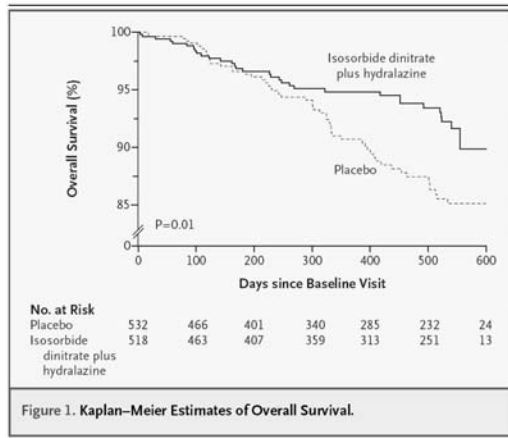


adopted from: Kojda G., Pharmacologie Toxikologie Systematisch, UNI-MED Verlag 2002

In both GISSI-3 and ISIS-4 more than 50 % of the MI-patients in the placebo group received nitrates, most likely because they were considered as indispensable



Improved Survival In Heart Failure



1050 Afroamericans  
NYHA III or IV

Initial:  
37,5 mg Hydralazin plus  
20 mg ISDN, 3x/day

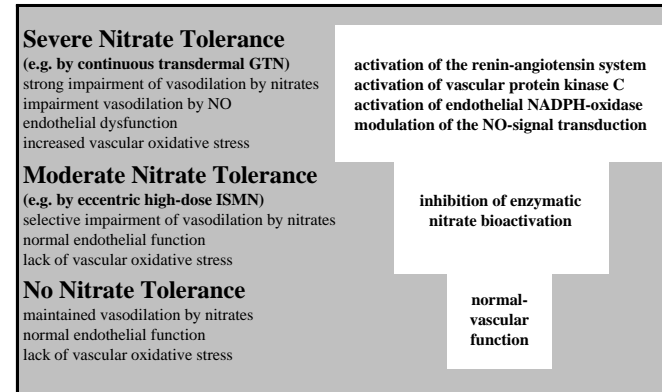
Chronic:  
225 mg Hydralazin plus  
120 mg ISDN/Tag

Figure 1. Kaplan-Meier Estimates of Overall Survival.

N Engl J Med 2004;351:2049-57.

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Intermittent Administration To Avoid Tolerance  
(10 h Nitrate Pause each day is mandatory!)

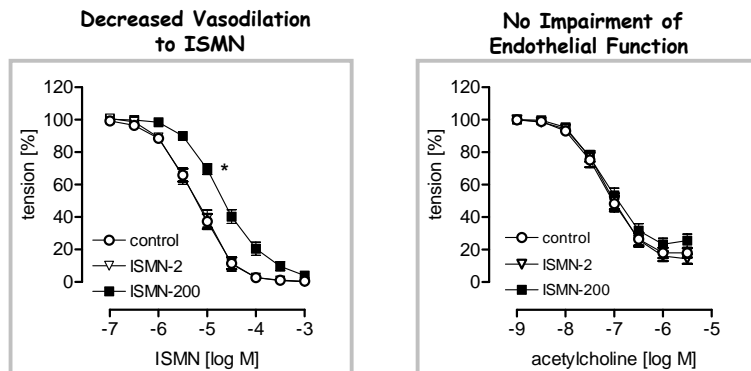


Possibly  
Vasotoxic  
(very rare!)

Decreased  
Vasodilation  
to Nitrates

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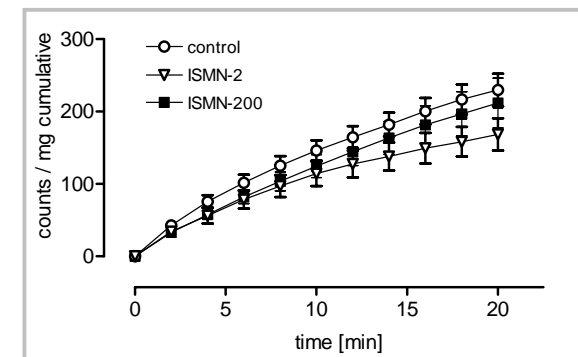
Moderate Nitrate Tolerance After 4 Months of  
High-Dose (200 mg/kg) Oral ISMN



Müller, Laber, Meyer, Kojda, J Am Coll Cardiol 2003, 41:1994-2000

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No Increased Superoxide After 4 Months of  
High-Dose (200 mg/kg) Oral ISMN



Müller, Laber, Meyer, Kojda, J Am Coll Cardiol 2003, 41:1994-2000

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## Pharmacological Activation of the NO/cGMP System is a Useful Approach to Treat CAD and Heart Failure!

### Nitrates in clinical practice

display a rapid onset of action, even with slow-release formulations

### Nitrates in combination therapy

predominantly reduce preload,  
complement the hemodynamics of other CAD drugs

### Nitrates in cardiovascular emergencies

are almost indispensable in CAD (MI) and heart failure

### Nitrates Safety

are devoid of rare but life-threatening side effects such as angioedema (ACE-inhibitors, AT-1-blockers, calcium antagonists), do not change blood levels of lipids and glucose and do not interfere with the hepatic drug metabolism (statins)

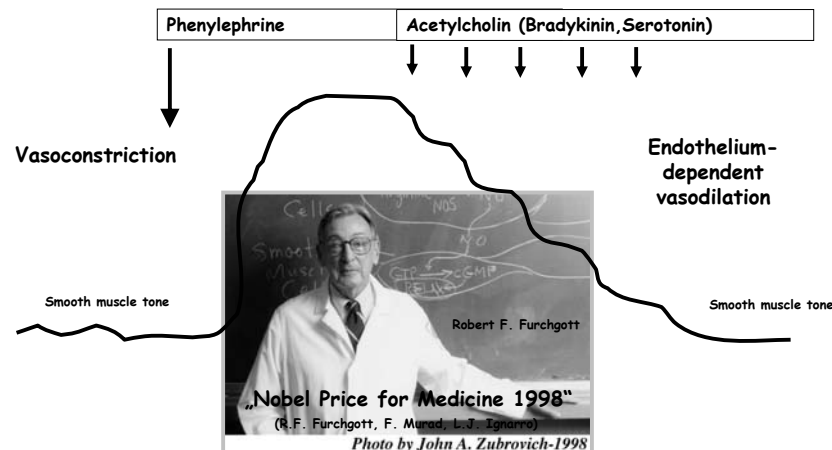
ACE-Inhibitor-Induced Angioedema, which is mediated by bradykinin, can be viewed as a local endothelial overstimulation leading to vasodilation and capillary hyperpermeability to which endogenous NO contributes



Incidence: 0.4 - 0.7 %,  
appr. 1 % lethal

Bas M, Hoffmann TK, Bier H, Kojda G (2005). *Br J Clin Pharmacol* 59(2):233-8

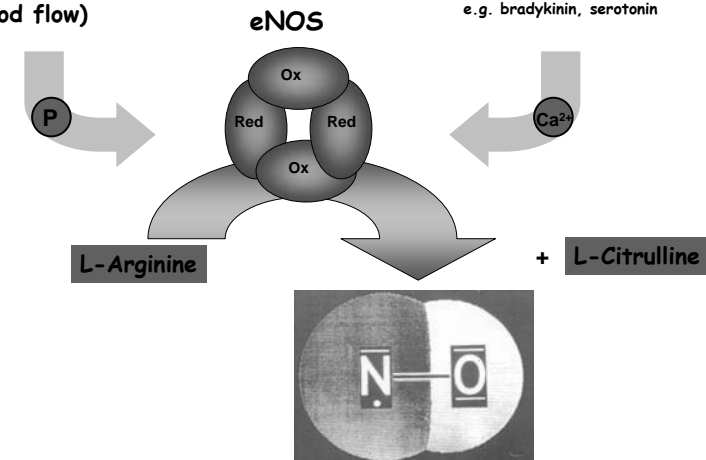
„The discovery of endothelium-dependent vasodilation uncovered an entirely new principle for signalling in the human organism“



## Can We Actively Use Endogenous NO As A Remedy?

Shear stress  
(blood flow)

Mediators  
e.g. bradykinin, serotonin



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

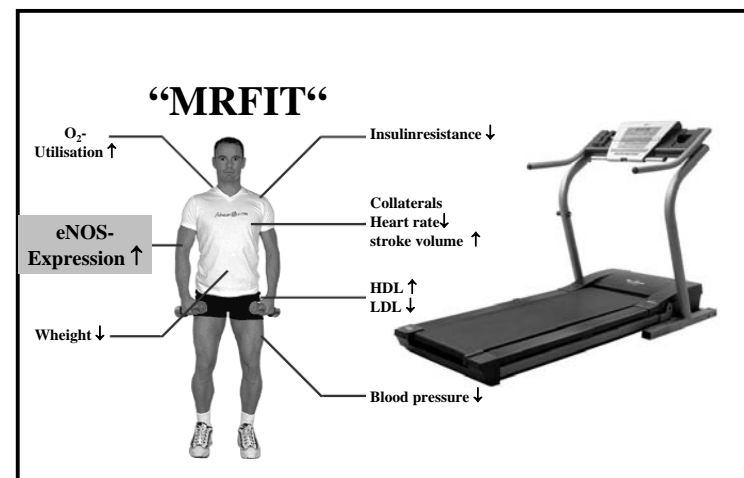
3.2 km walking/day Reduces Overall Mortality by 50 %  
(Hakim et al., N Engl J Med 1998;338:94-9)

Health status of postmenopausal women

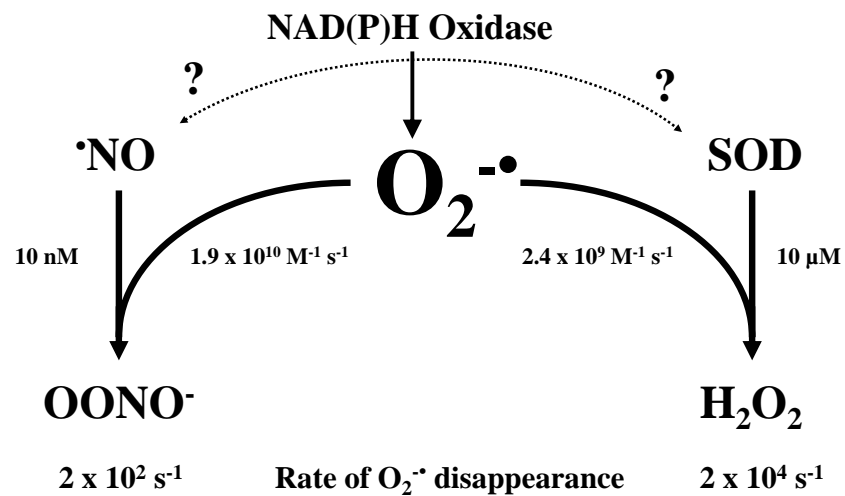
2 km walking/day Reduces CAD-Risk by 30 %  
(Manson et al., NEJM 2002; 347:716-25)

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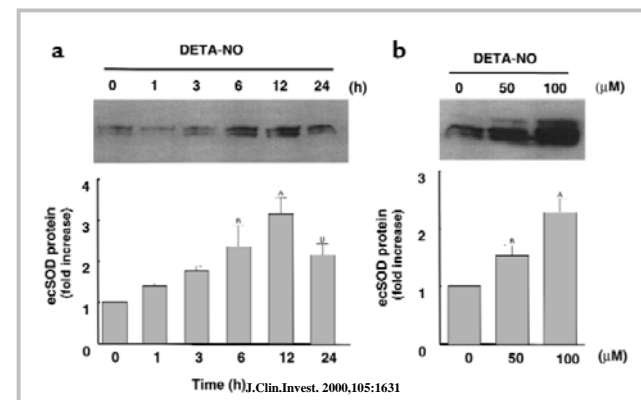
Why is Exercise Beneficial?



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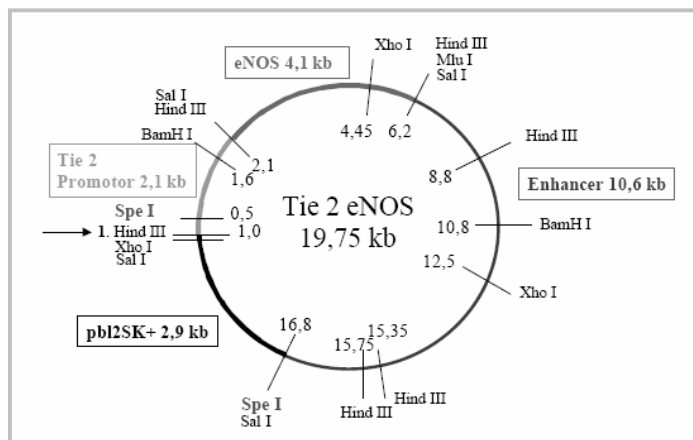


**Effect Of The NO-Donor DETA/NO On ecSOD Protein Expression**

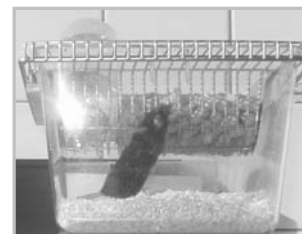


J.Clin.Invest. 2000;105:1631

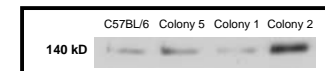
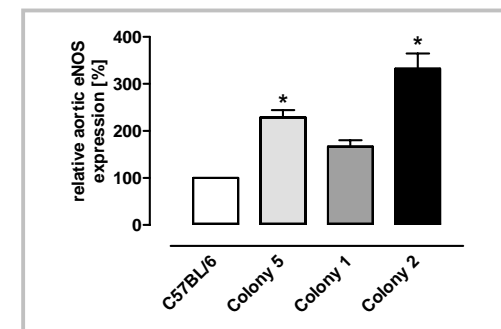
**Structure of the Plasmid Constructed For Vascular-Specific Overexpression of eNOS**

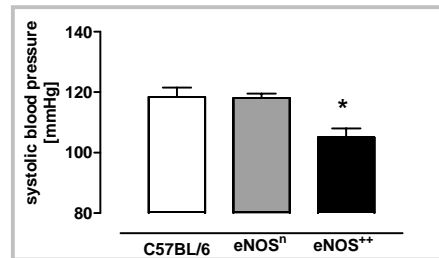
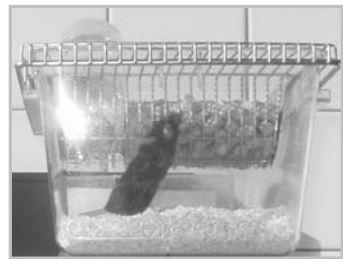


**Overexpression of eNOS in different Colonies**



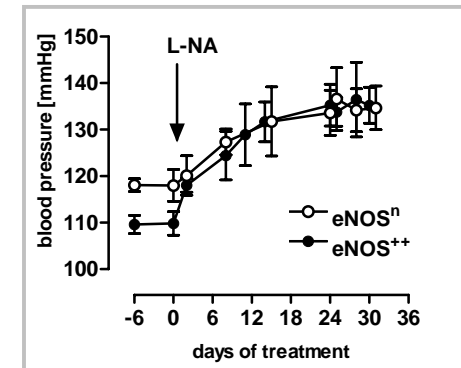
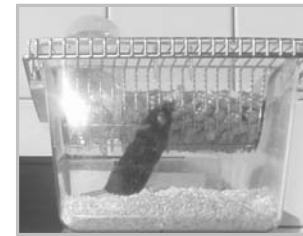
Suvorava, Oppermann, Kojda, unpublished



Reduction of Blood Pressure in eNOS<sup>++</sup> Mice.

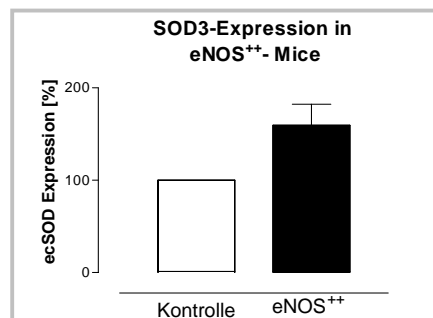
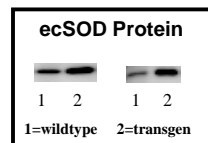
Suvorava, Oppermann, Kojda, unpublished

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Reduction of Blood Pressure in eNOS<sup>++</sup> is inhibited by the NOS-Inhibitor L-Nitroarginine (L-NA)

Suvorava, Oppermann, Kojda, unpublished

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Overexpression Of eNOS In eNOS<sup>++</sup> Drives Overexpression Of ecSOD

Suvorava, Oppermann, Kojda, unpublished

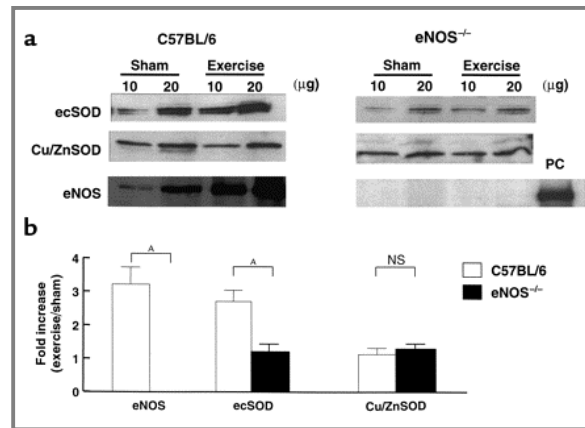
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## Exercise Increases Vascular eNOS Expression. Does Exercise Increase ecSOD-Expression As Well?



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## Exercise Increases ecSOD Expression NO-Independently



J.Clin.Invest. 2000;105:1631

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

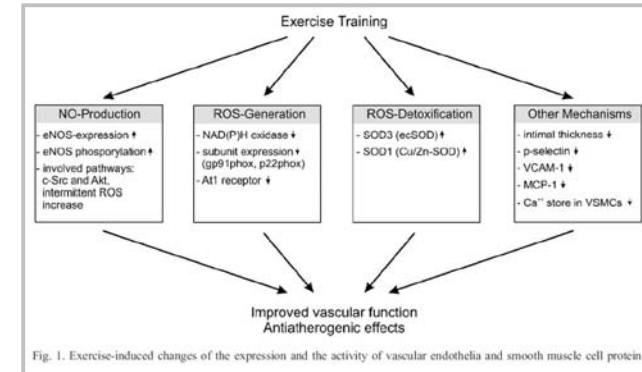
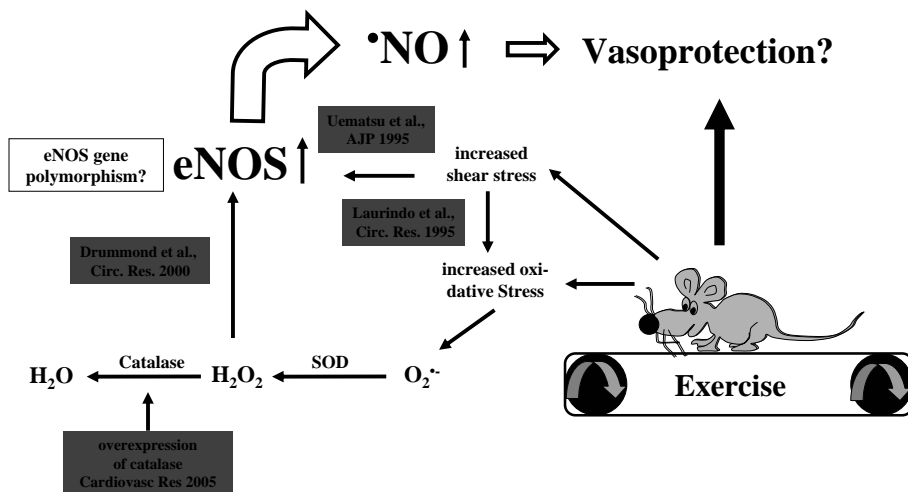


Fig. 1. Exercise-induced changes of the expression and the activity of vascular endothelia and smooth muscle cell protein.

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

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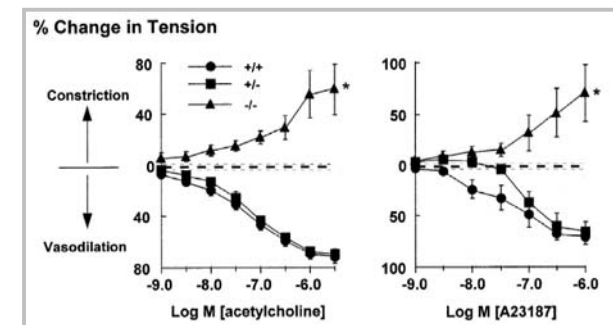
## Mechanisms of Vascular Adaptations To Exercise



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## Mechanisms of Vascular Adaptations To Exercise

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



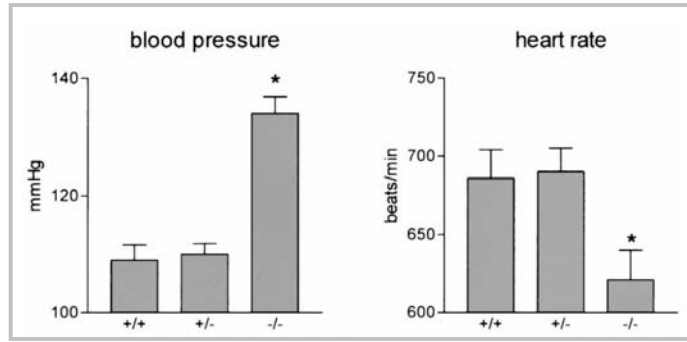
Endothelium-dependent vasodilation unchanged

Cardiovasc Res 1999;42:205-213

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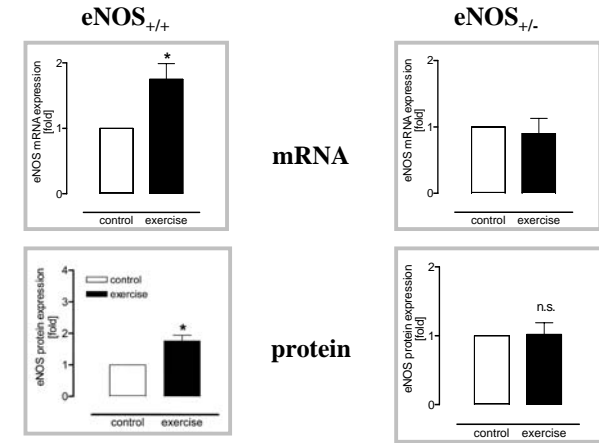
Does permanent malfunction of one eNOS gene inhibit exercise-induced expression of vascular eNOS?



Blood pressure and heart rate are unchanged

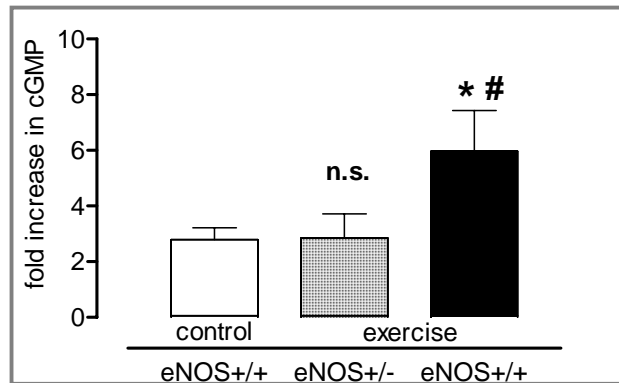
Cardiovasc Res 1999;42:205-213

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

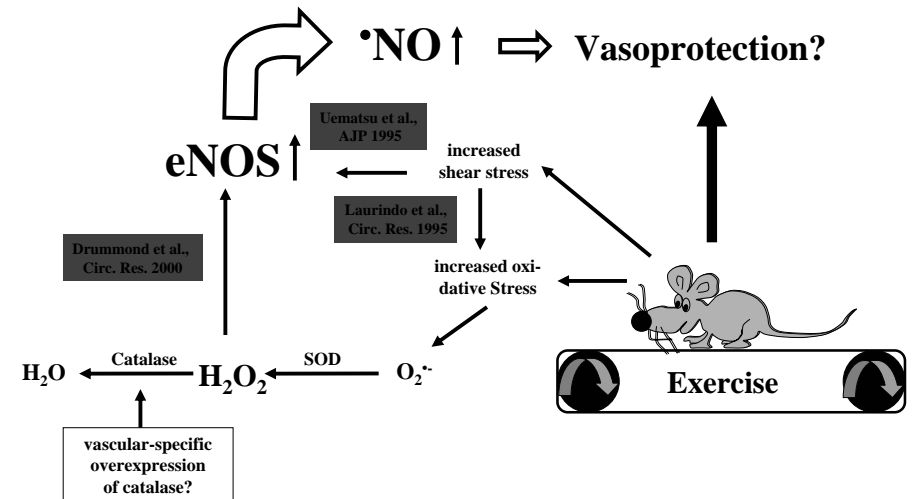


Circulation 2001;103:2839-2844

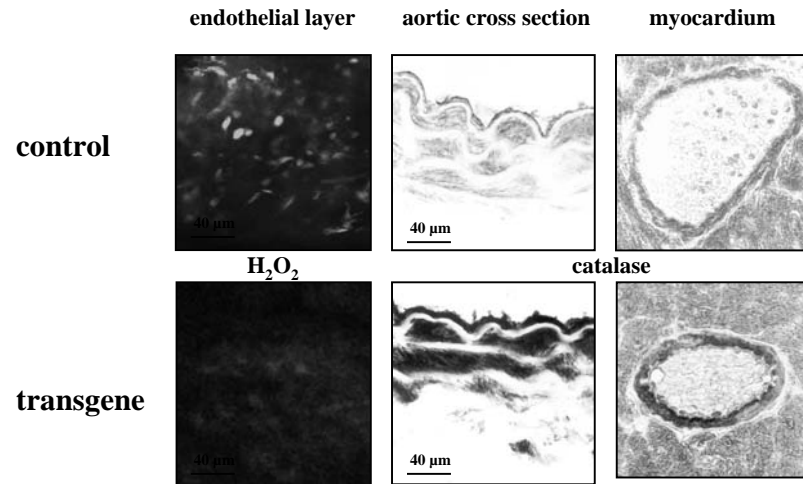
The loss of one eNOS Gene impairs the upregulation of eNOS function induced by exercise



Circulation 2001;103:2839-2844

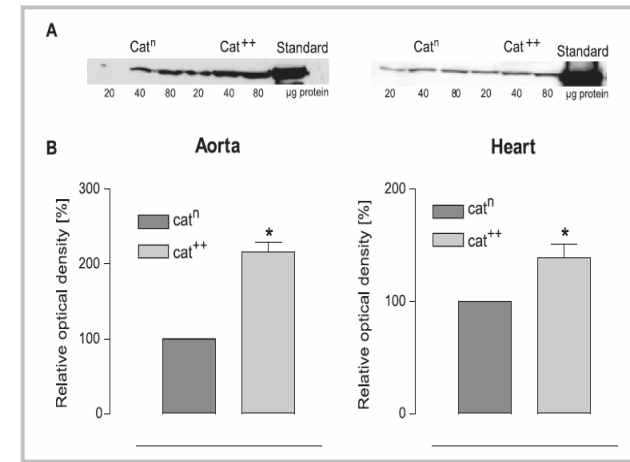


## Mechanisms of Vascular Adaptations To Exercise



## Mechanisms of Vascular Adaptations To Exercise

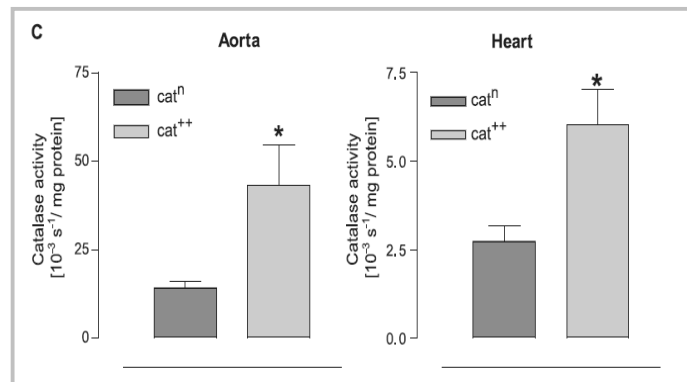
### Permanent Vascular Overexpression of Catalase



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

## Mechanisms of Vascular Adaptations To Exercise

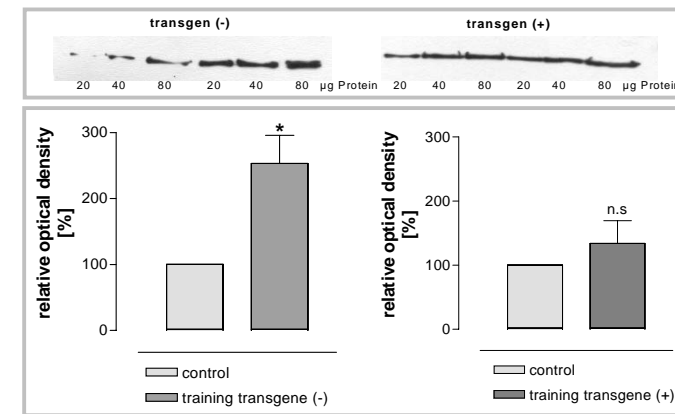
### Permanent Vascular Overexpression of Catalase



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

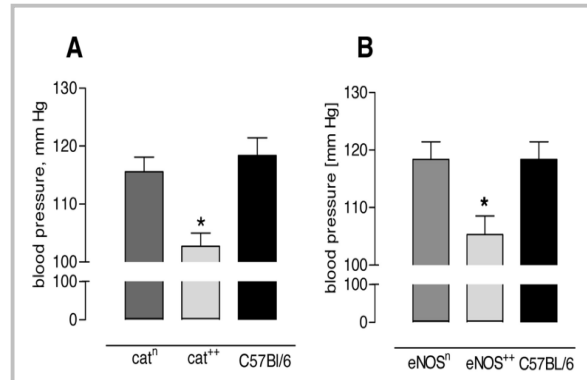
## Mechanisms of Vascular Adaptations To Exercise

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



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

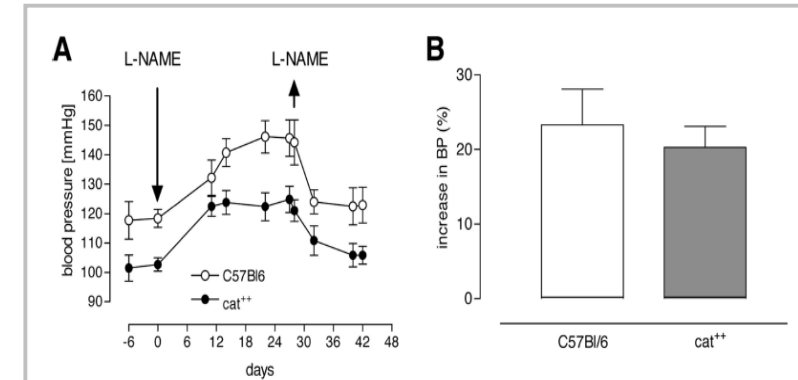
### Permanent Reduction of Vascular Hydrogen Peroxide Reduces Blood Pressure



Circulation. 2005;112:2487-2495.

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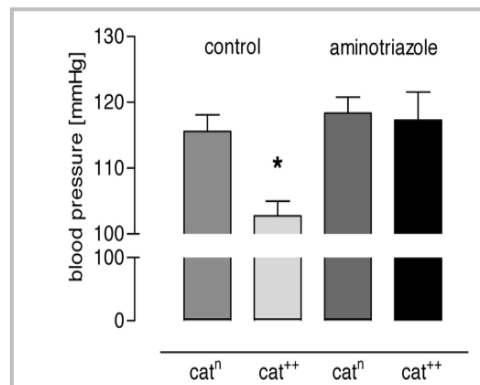
### Permanent Reduction of Vascular Hydrogen Peroxide Reduces Blood Pressure Independent of eNOS.



Circulation. 2005;112:2487-2495.

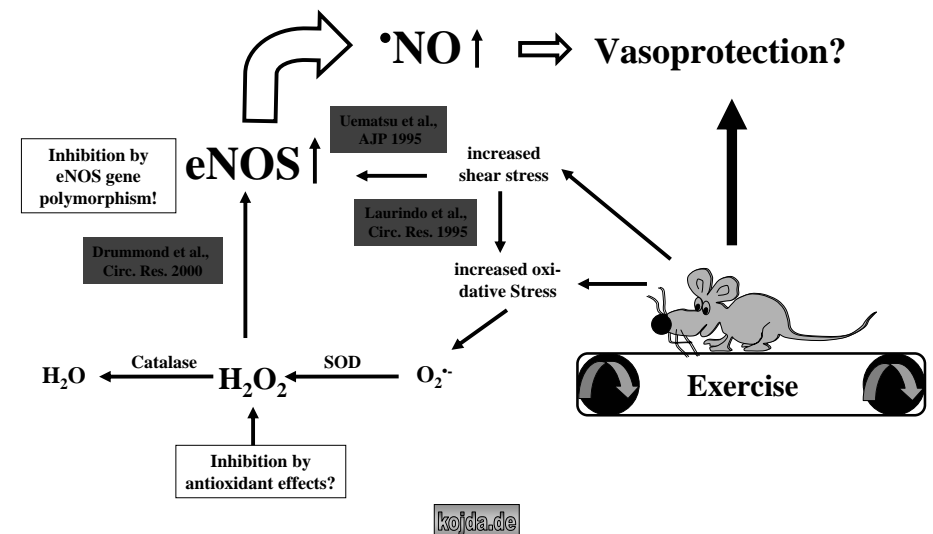
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### Permanent Reduction of Vascular Hydrogen Peroxide Reduces Blood Pressure: Inhibition by Aminotriazole.



Circulation. 2005;112:2487-2495.

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## Experimental sedentary lifestyle induced by singularization

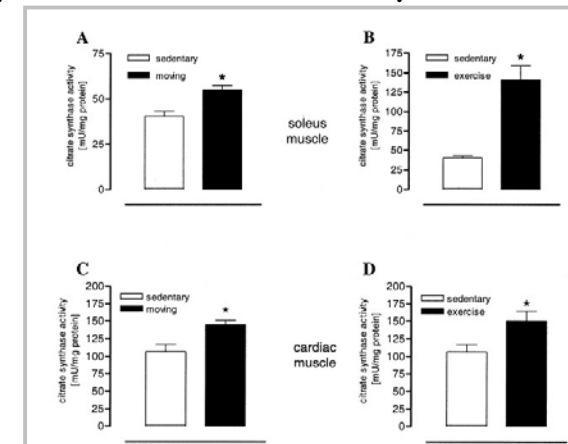
Forced physical inactivity



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

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



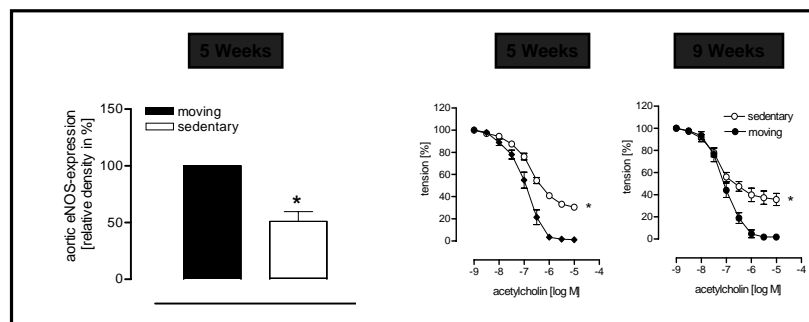
J Am Coll Cardiol 2004; 44:1320-1327.

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

Expression of eNOS

Endothelial Function



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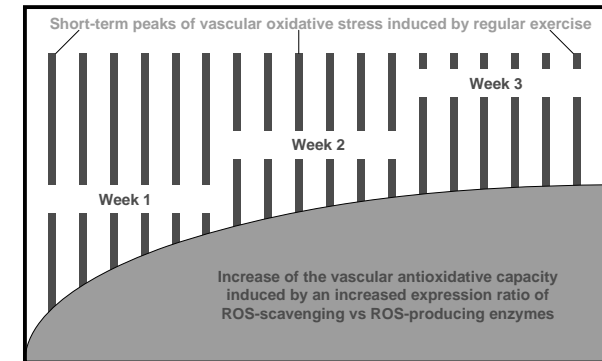
Exercise training can be viewed as an effective antioxidant and antiatherogenic therapy.

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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Short Term Peaks of Vascular Oxidative Stress Induced by Exercise Increase Vascular Antioxidative Defense Mechanisms, because gene expression lasts longer than exercise-induced vascular oxidative stress



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## Co-Workers

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