Universiteit Antwerpen

5e Forum Européen Coeur, Exercice et Prévention

"Comprendre et explorer la function endotheliale"

Exercise and endothelial function;

Role of endothelial progenitor cells?

Emeline Van Craenenbroeck, MD, PhD
Department of Cardiology
Antwerp University Hospital

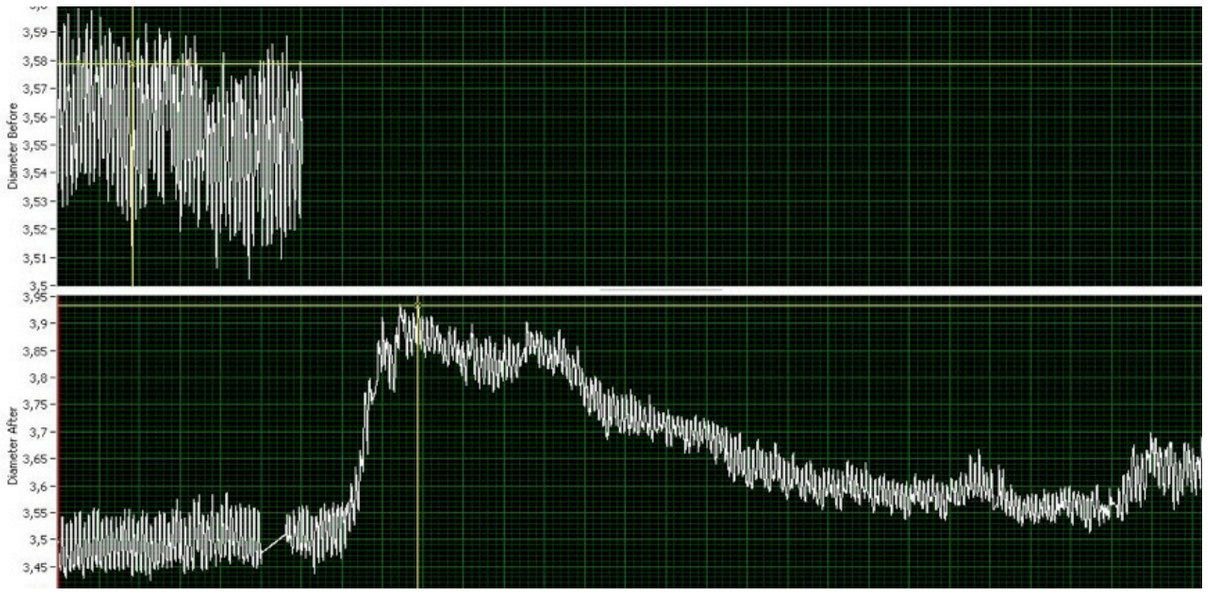
Endothelial dysfunction

Important?

♂ 25 years, no medical history

VO_2peak 45 ml/kg/min

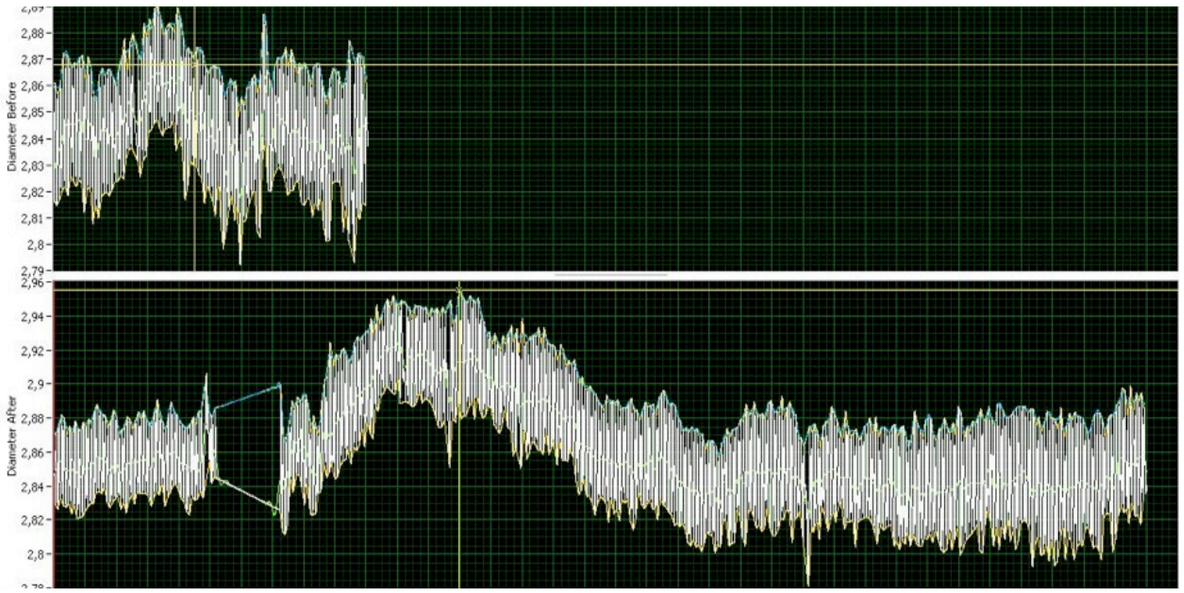
Flow mediated Dilation 9.89%



♂ 65 years, ICMP

VO_2peak 25 ml/kg/min

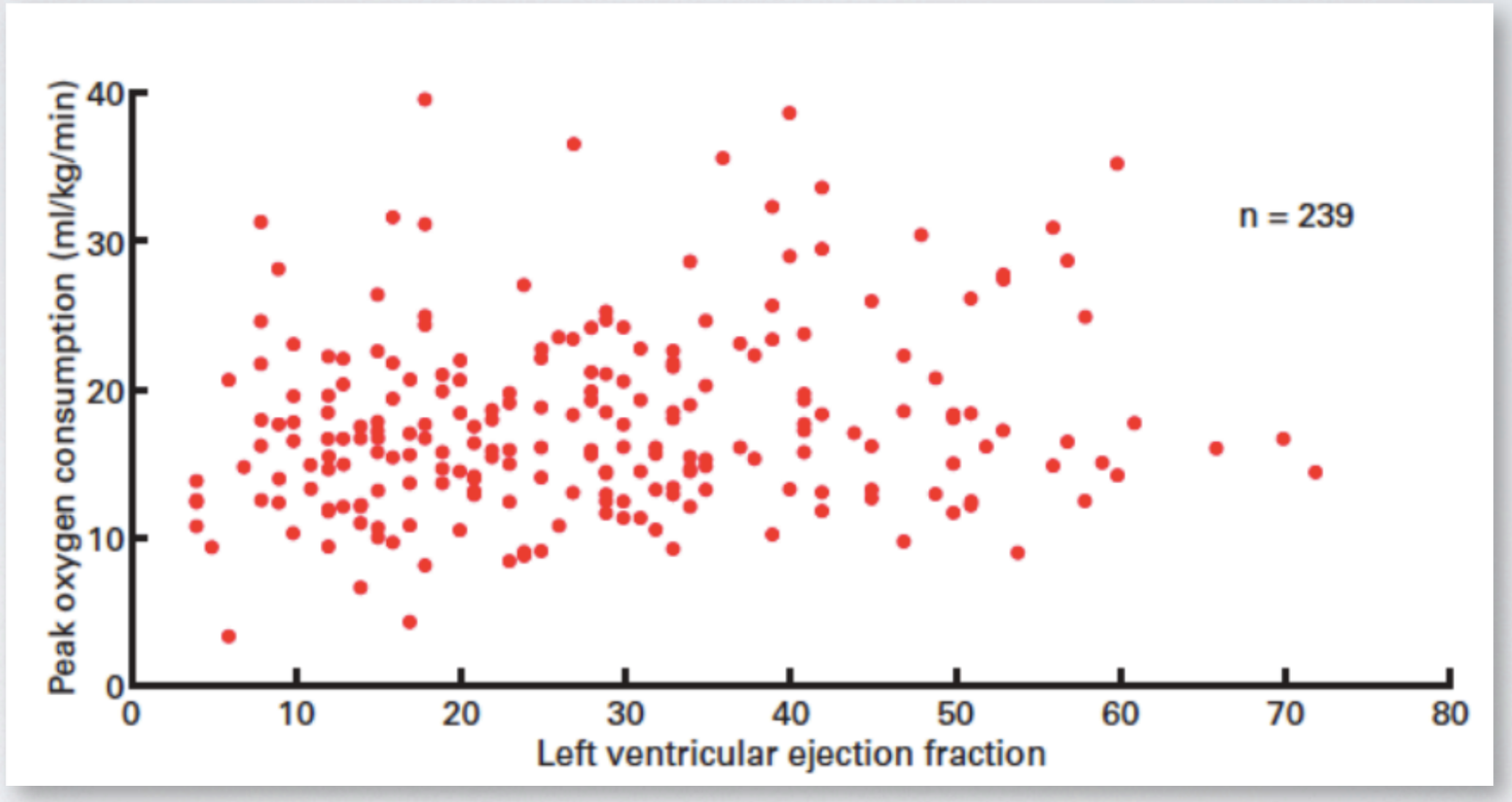
Flow mediated Dilation 3.05%



VO_2 = cardiac output x (arterial-venous)O_2 difference

≈

Exercise = bloodpump x dilation of **bloodvessels** and uptake of O_2 by **skeletal muscle**



Franciosa JA, et al. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol 1981;47:33 - 9.

VO_2 = cardiac output x (arterial-venous)O_2 difference

≈

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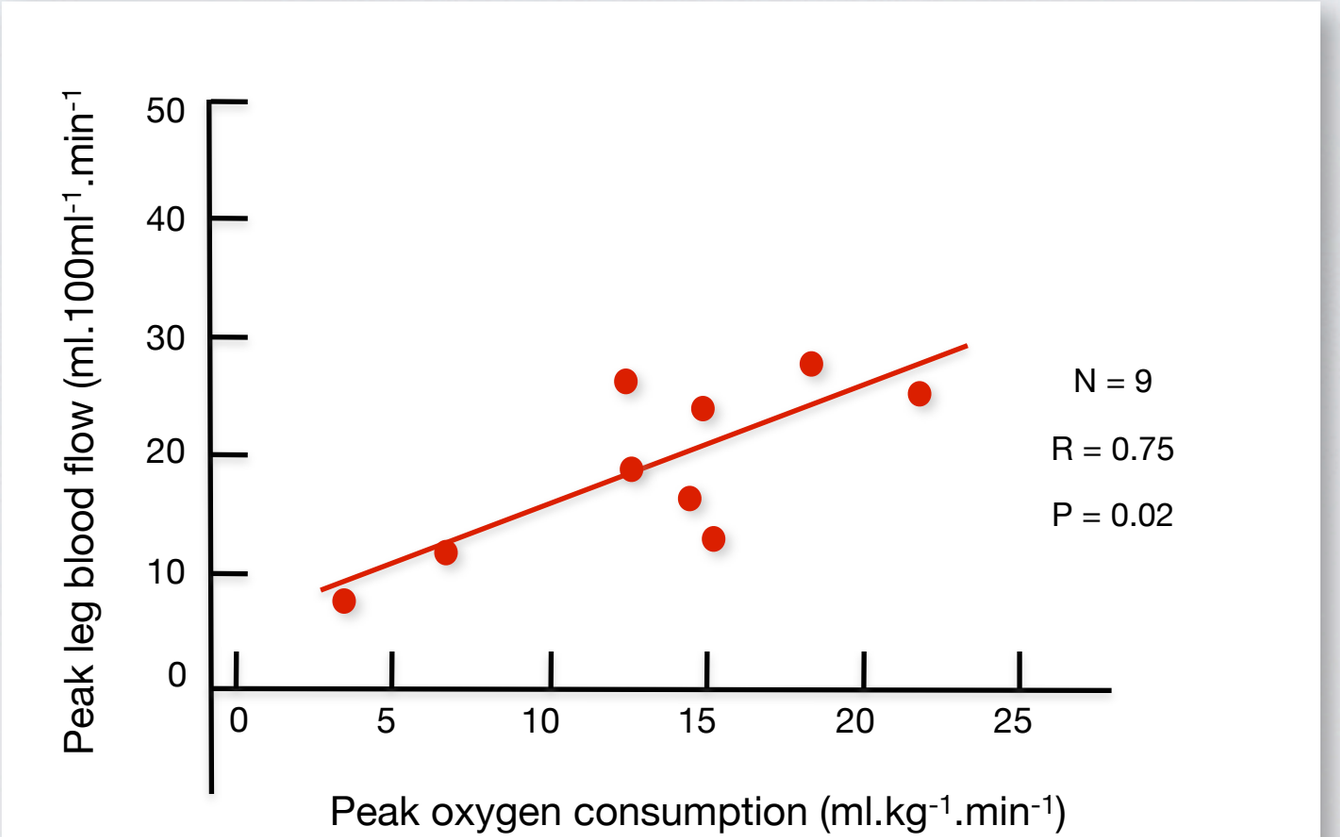
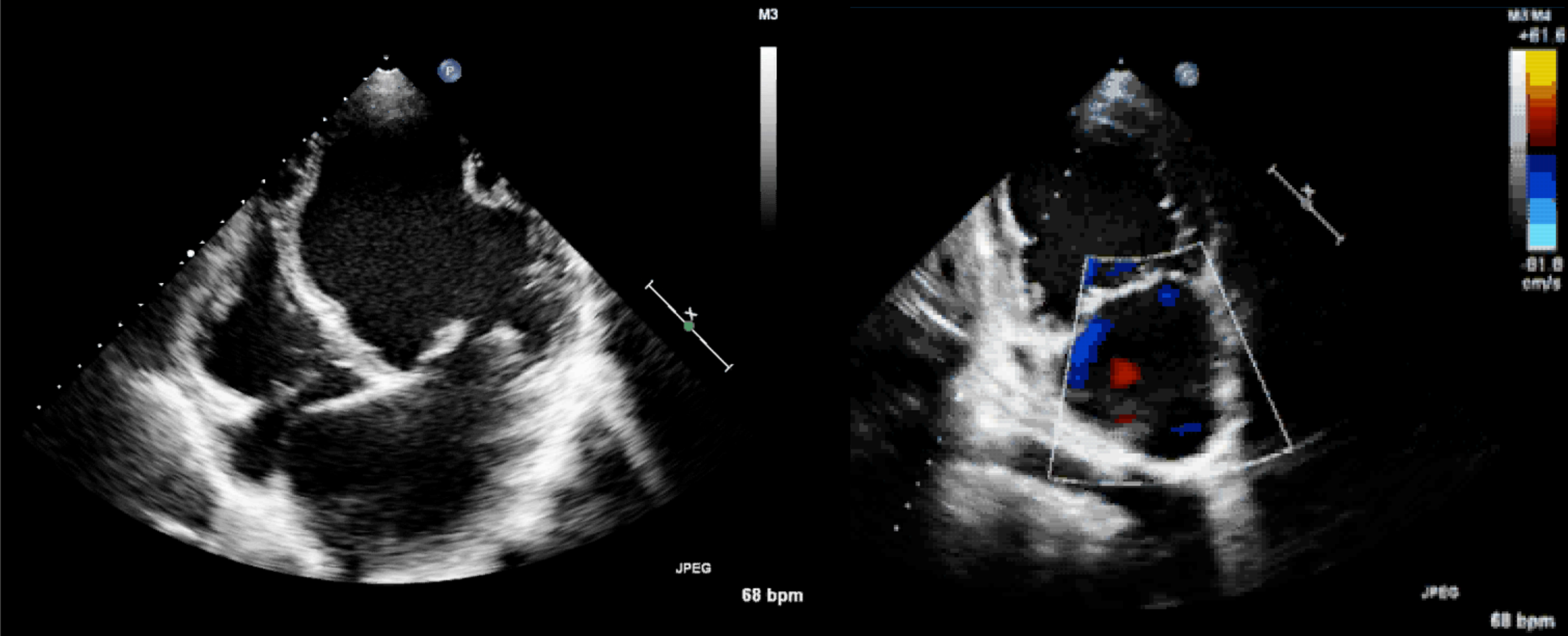


Anker SD, et al. The influence of muscle mass, strength, fatigability and blood flow on exercise capacity in cachectic and non-cachectic patients with chronic heart failure. Eur Heart J 1997;18:259-69.

♂, 30yrs

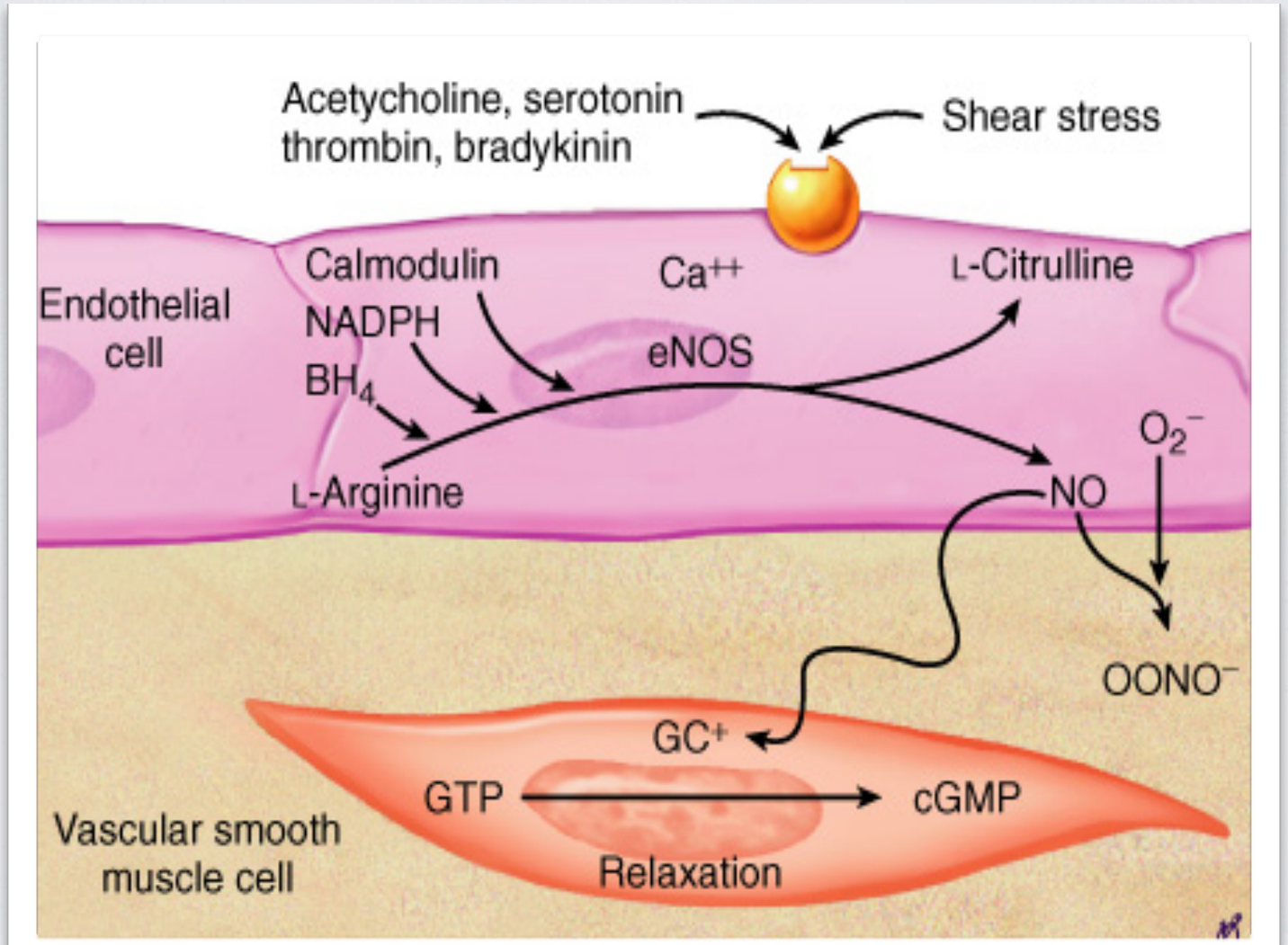
LVEF 22%

CPET 21/6/2010: VO_2peak 49ml/kg/min



Endothelial dysfunction

Reversed by exercise training?



Regular Physical Exercise Corrects Endothelial Dysfunction and Improves Exercise Capacity in Patients With Chronic Heart Failure

Rainer Hambrecht, MD; Eduard Fiehn, MD; Claudia Weigl, MD; Stephan Gielen, MD; Caroline Hamann, BS; Ralf Kaiser, BS; Jiangtao Yu, MD; Volker Adams, PhD; Josef Niebauer, MD; Gerhard Schuler, MD

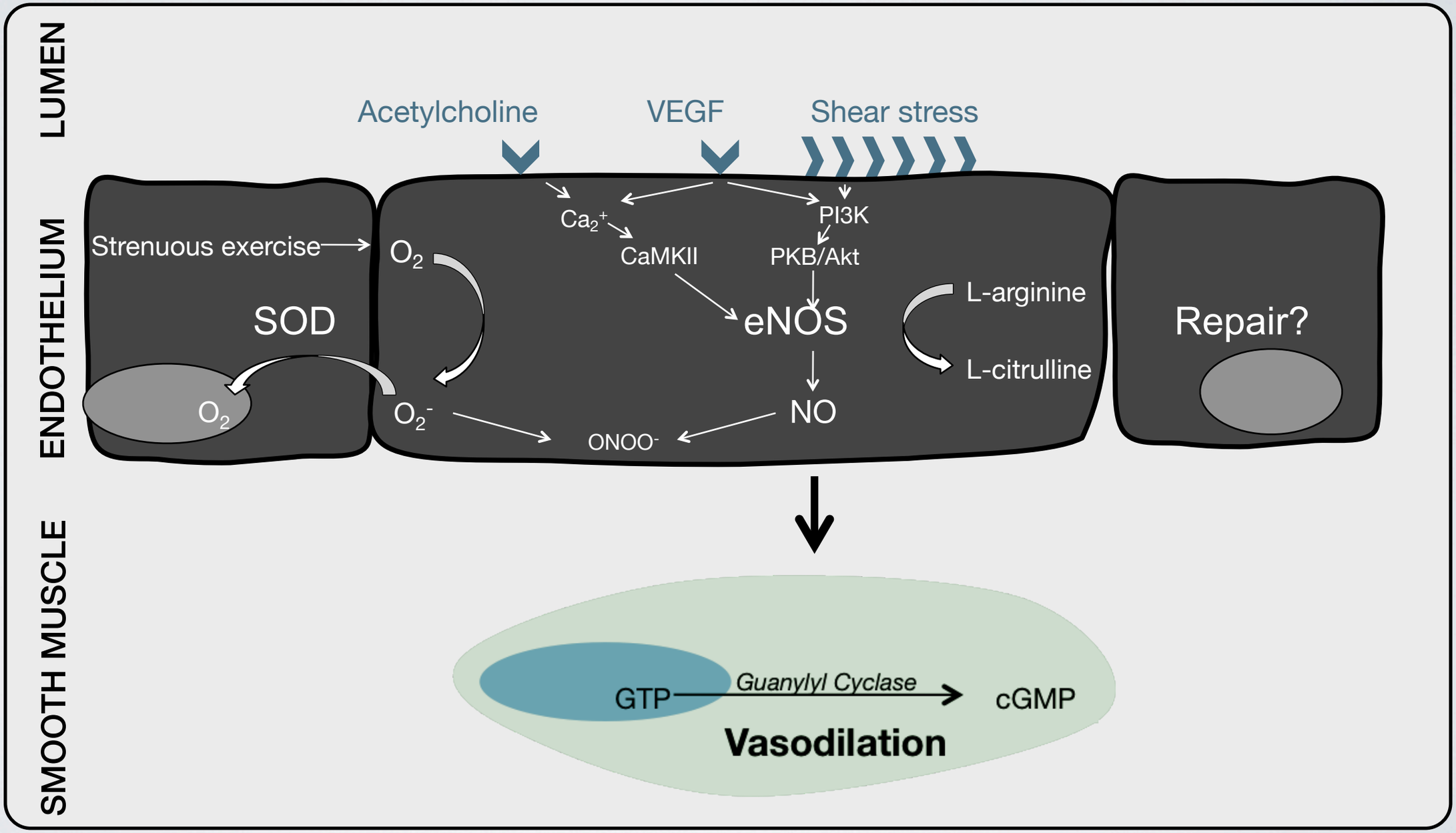
Background—The purpose of this study was to determine the effects of systemic exercise training on endothelium-mediated arteriolar vasodilation of the lower limb and its relation to exercise capacity in chronic heart failure (CHF). Endothelial dysfunction is a key feature of CHF, contributing to increased peripheral vasoconstriction and impaired exercise capacity. Local handgrip exercise has previously been shown to enhance endothelium-dependent vasodilation in conduit and resistance vessels in CHF.

Methods and Results—Twenty patients were prospectively randomized to a training group (n=10, left ventricular ejection fraction [LVEF] 24±4%) or a control group (n=10, LVEF 23±3%). At baseline and after 6 months, peak flow velocity was measured in the left femoral artery using a Doppler wire; vessel diameter was determined by quantitative angiography. Peripheral blood flow was calculated from average peak velocity (APV) and arterial cross-sectional area. After exercise training, nitroglycerin-induced endothelium-independent vasodilation remained unaltered (271% versus 281%, P=NS). Peripheral blood flow improved significantly in response to 90 μg/min acetylcholine by 203% (from 152±79 to 461±104 mL/min, $P<0.05$ versus control group) and the inhibiting effect of L-NMMA increased by 174% (from −46±25 to −126±19 mL/min, $P<0.05$ versus control group). Peak oxygen uptake increased by 26% ($P<0.01$ versus control group). The increase in peak oxygen uptake was correlated with the endothelium-dependent change in peripheral blood flow (r=0.64, $P<0.005$).

Conclusions—Regular physical exercise improves both basal endothelial nitric oxide (NO) formation and agonist-mediated endothelium-dependent vasodilation of the skeletal muscle vasculature in patients with CHF. The correction of endothelium dysfunction is associated with a significant increase in exercise capacity. (***Circulation*. 1998;98:2709-2715.**)

Exercise-induced improvement endothelial function

Mechanisms?



Van Craenenbroeck E et al. Endothelial progenitor cells in vascular health: Focus on lifestyle. Microvasc Res 2010;79:184-192.

endothelial progenitor cells

endothelial function

exercise capacity

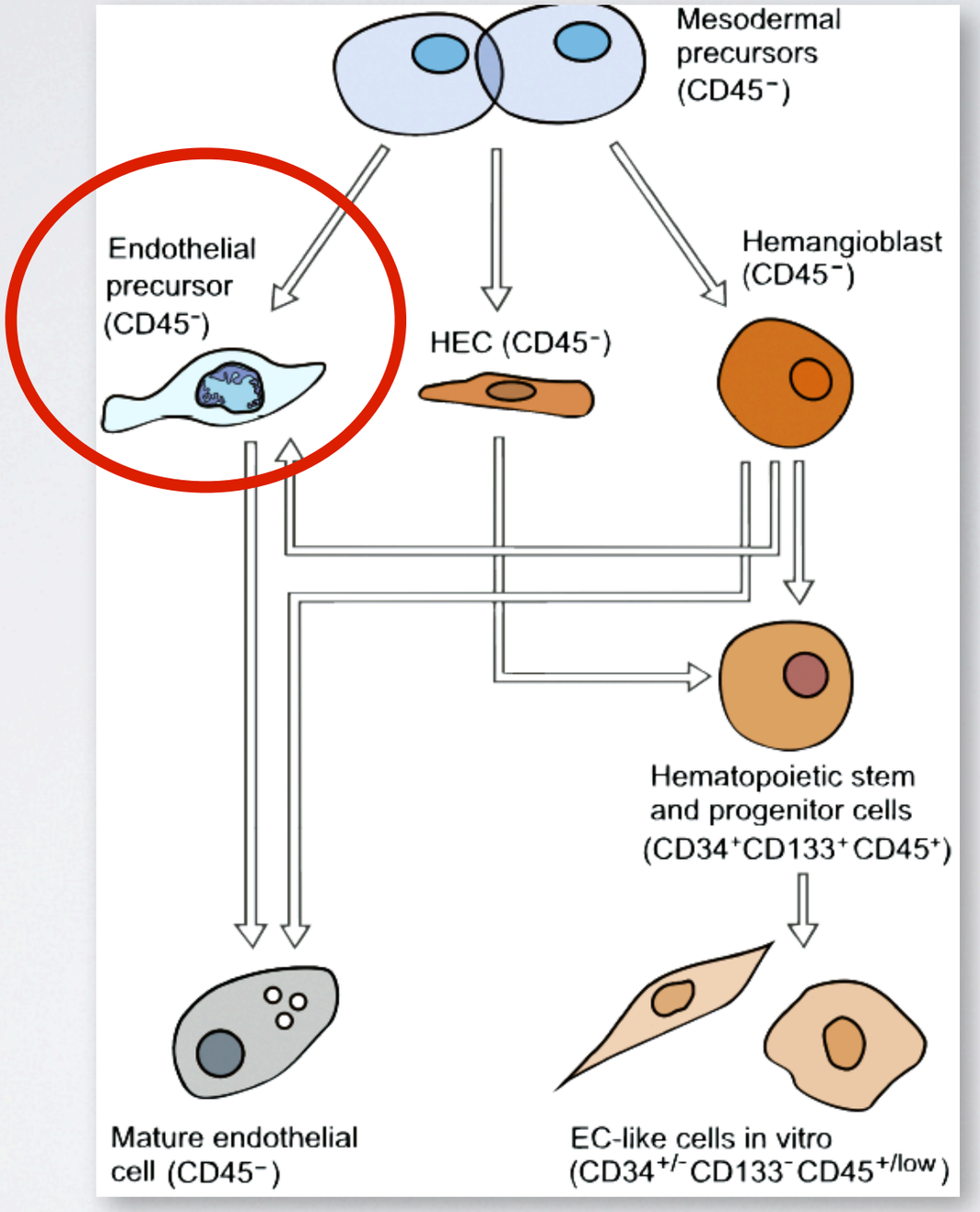
exercise training

Endothelial progenitor cells

What are they?

Asahara T et al. Isolation of Putative Progenitor Endothelial Cells for Angiogenesis. Science 1997; 275, 964

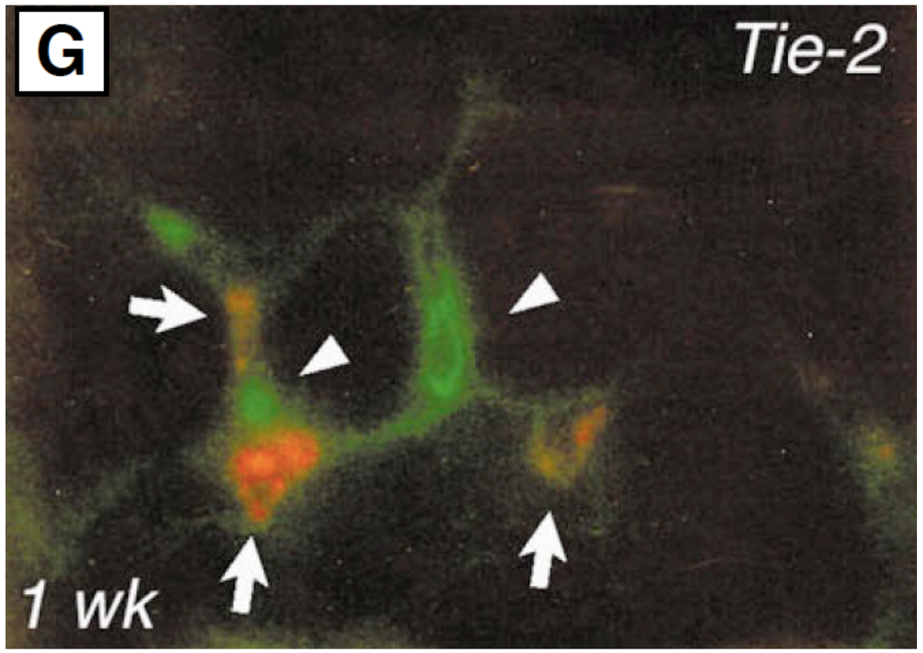
Origin of EPC



Timmermans F et al. Endothelial progenitor cells: identity defined? J. Cell. Mol. Med.2009; 13: 87-102.

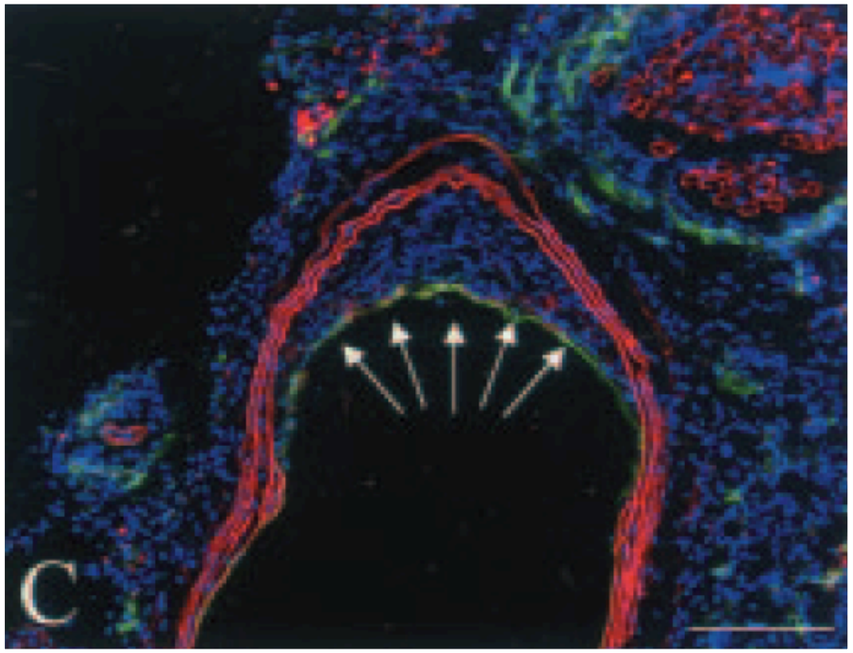
Endothelial progenitor cells

Mediators of vascular repair?



Asahara T et al. Science 1997; 275, 964

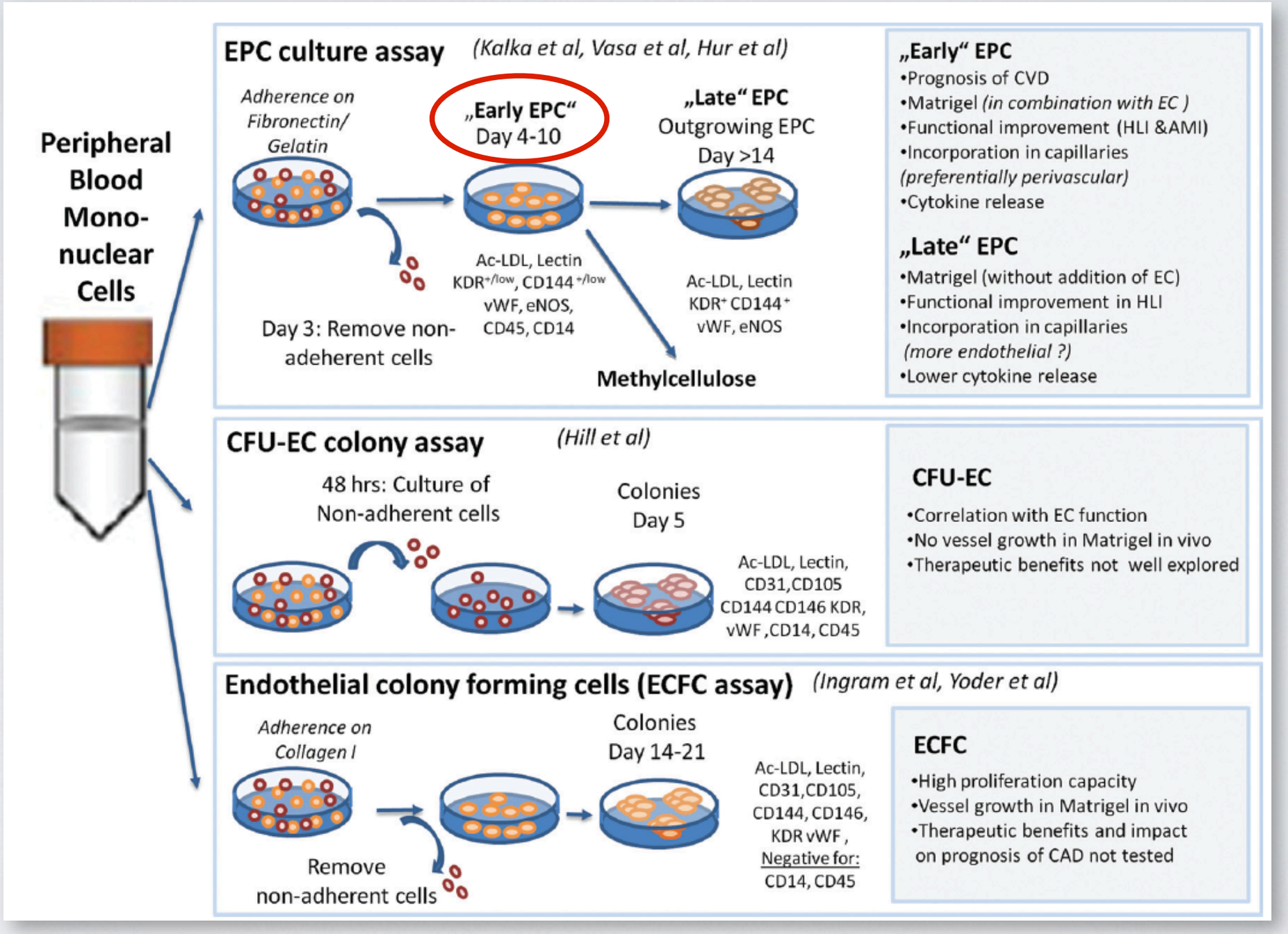
1 week after CD34 injection showing capillaries comprising DiI-labeled CD34-derived cells expressing Tie-2 receptor



Werner N et al. Circ. Res. 2003;93;e17-e24

In animal models of denudation of the carotid artery, transfusion of early EPC at the site of injury leads to re-endothelialisation

Methods to isolate EPC

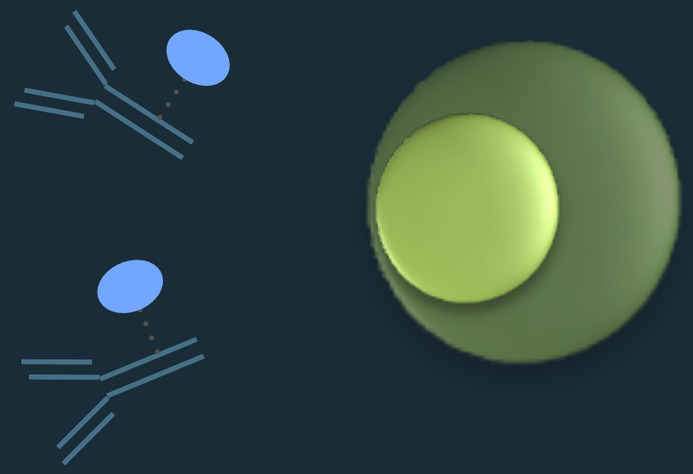


Fadini GP et al. Critical Reevaluation of Endothelial Progenitor Cell Phenotypes for Therapeutic and Diagnostic Use. Circ Res. 2012;110:624-637.

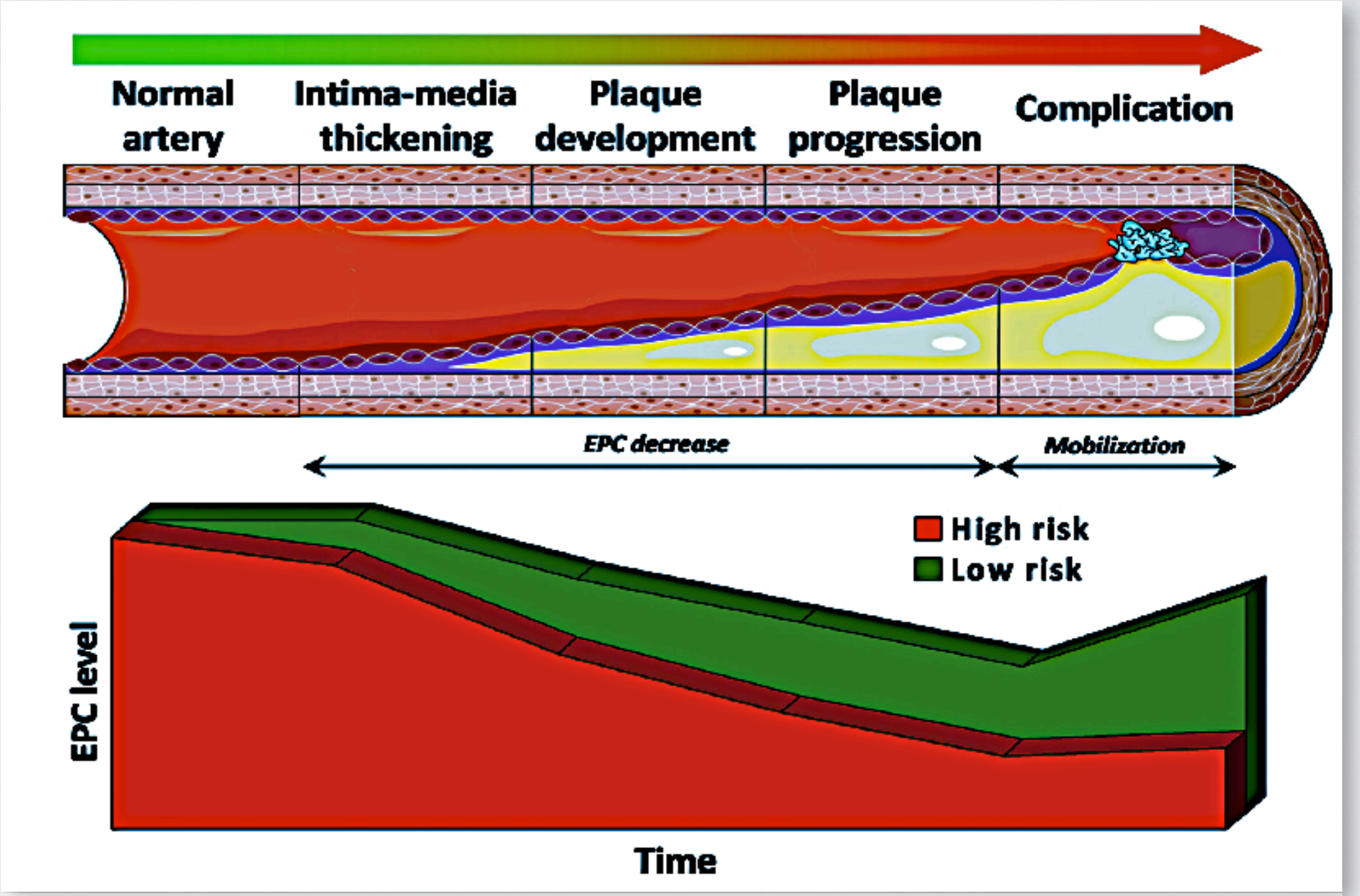
Methods to quantify EPC

Flow Cytometry

CD34+KDR+CD45-



EPC mirror the natural history of atherosclerosis



Fadini GP et al. Critical Reevaluation of Endothelial Progenitor Cell Phenotypes for Therapeutic and Diagnostic Use. Circ Res. 2012;110:624-637.

Cardiovascular risk factors

Advanced age, hypertension, obesity, diabetes, smoking, hyperlipidemia, sedentarity

Endothelial dysfunction

Endothelial Progenitor Cells

- *Reduced circulating numbers*
- *Impaired angiogenic capacity*

⊕

Physical activity

Healthy diet

Smoking cessation

Weight reduction

Stress reduction

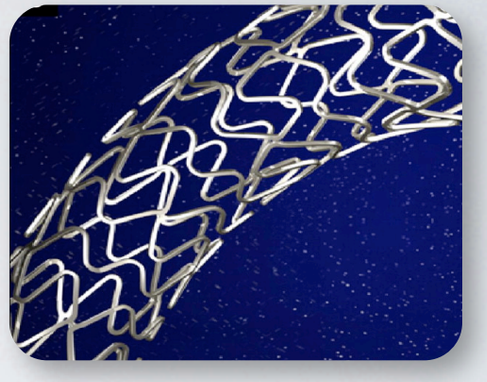
Van Craenenbroeck E et al. Endothelial progenitor cells in vascular health: Focus on lifestyle. Microvasc Res 2010;79:184-192.

Endothelial progenitor cells

Therapeutic use?

Endothelialized grafts

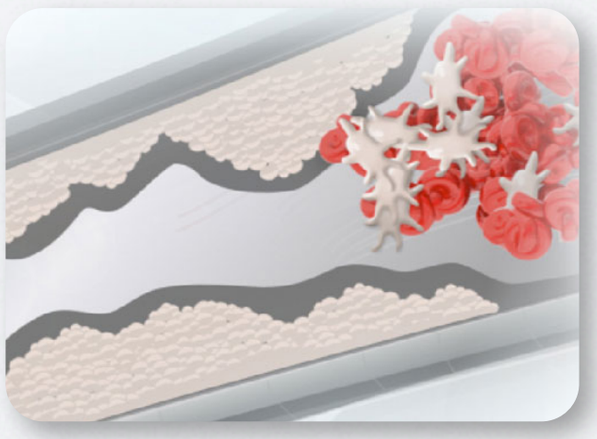
Emerging and future clinical applications of adult vascular progenitor therapy



EPC coated stents

Tissue engineered heart valves

Plaque stabilization



EPC coated LVAD

endothelial progenitor cells

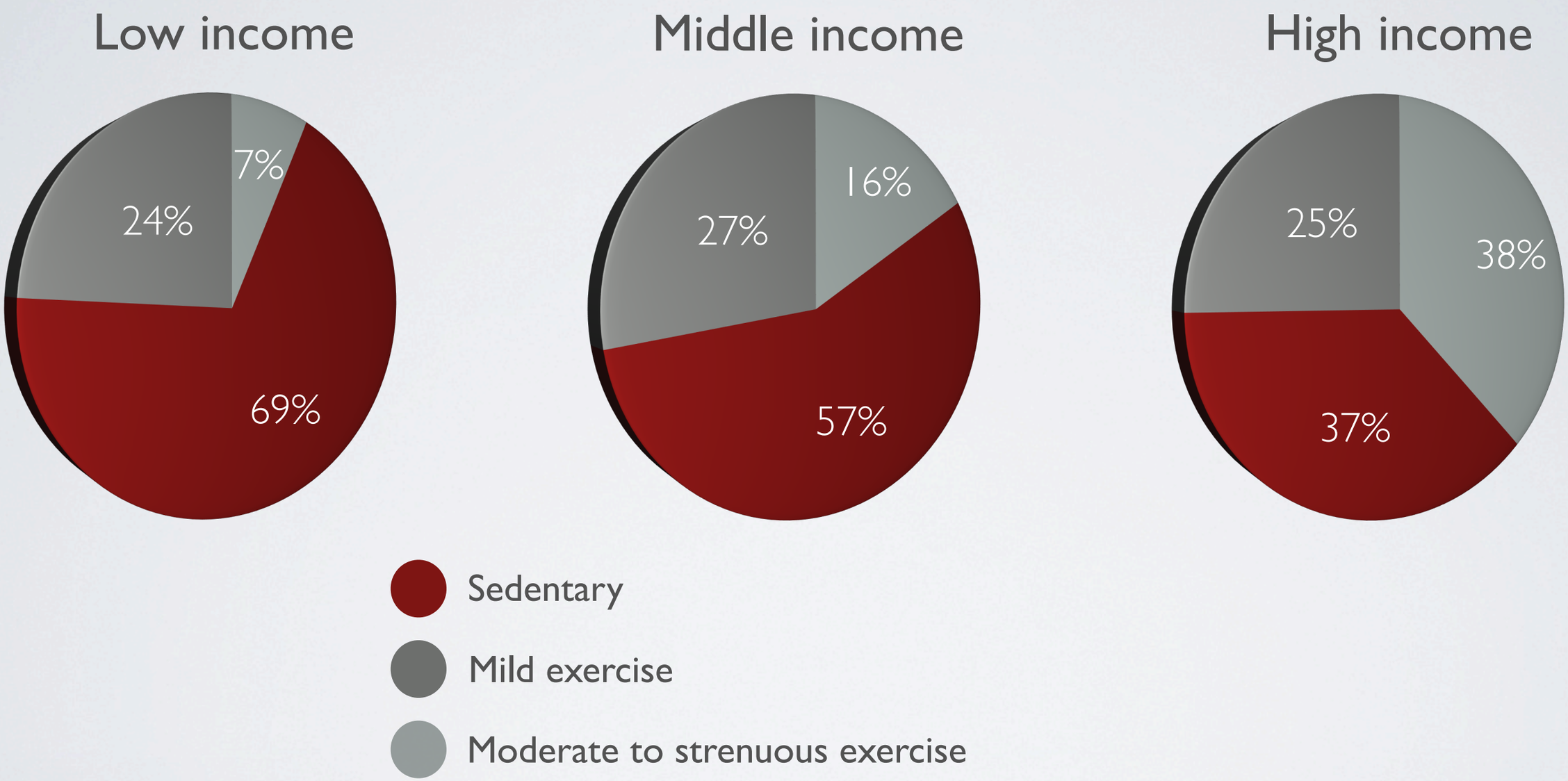
endothelial function

exercise capacity

exercise training

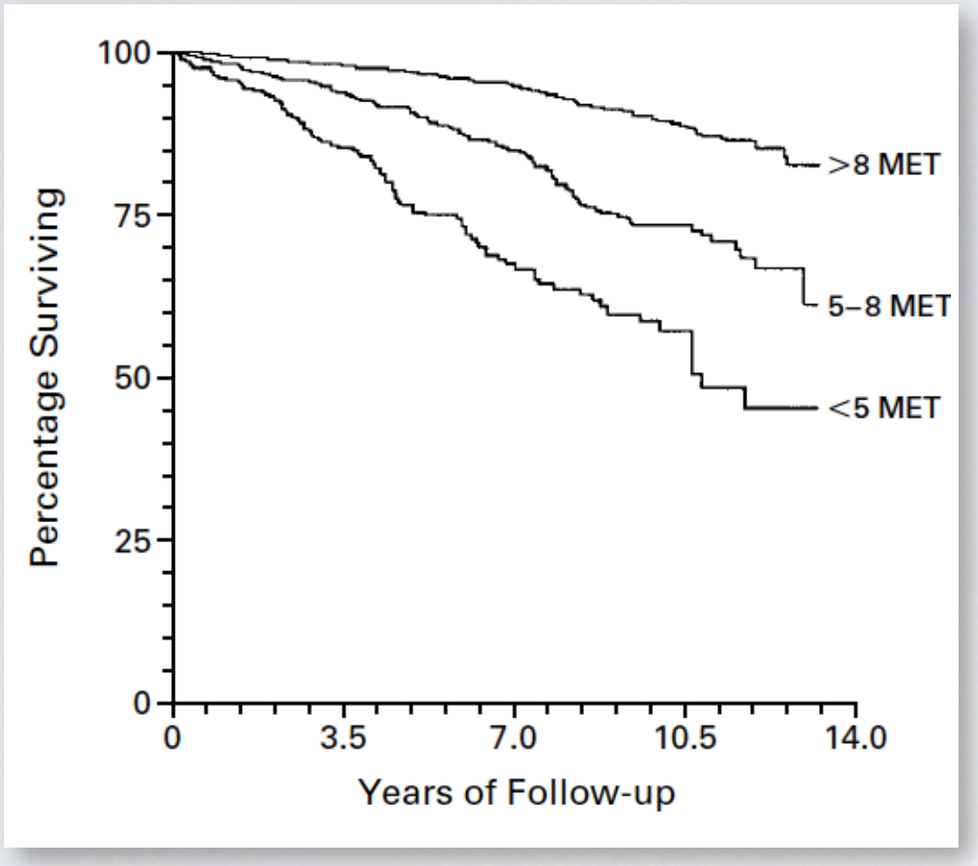
Primairy prevention ?

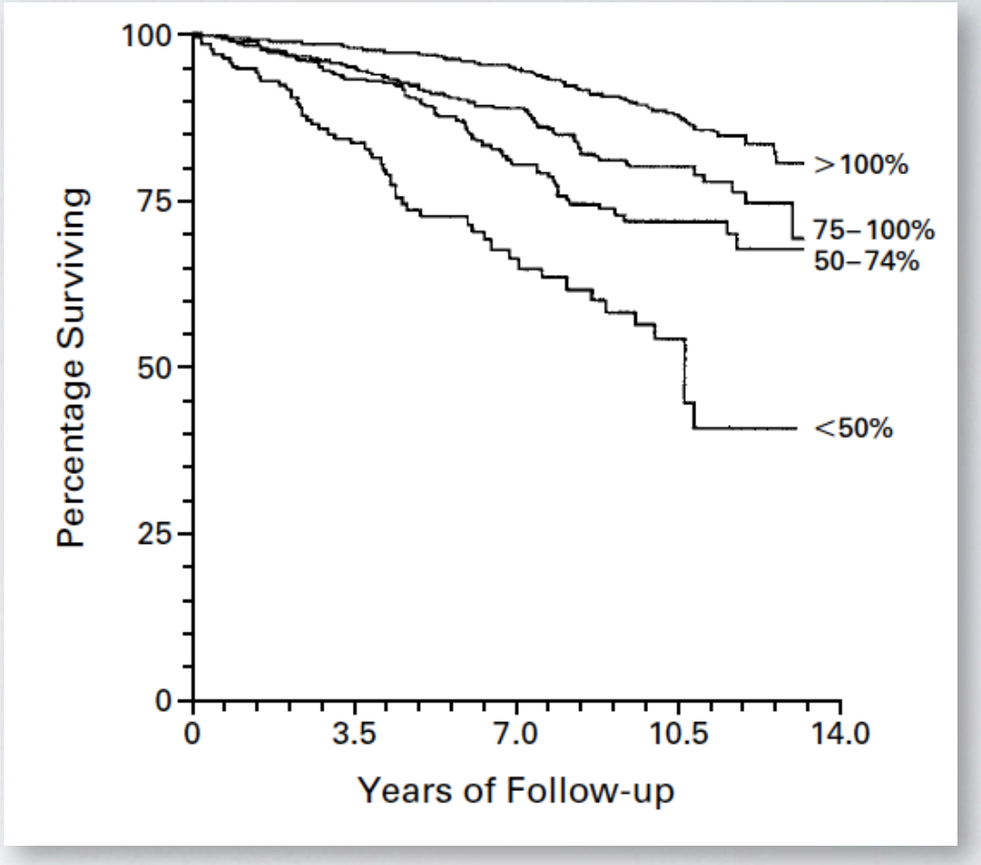
Percentage sedentarism across countries



Held C et al. Physical activity levels, ownership of goods promoting sedentary behaviour and risk of myocardial infarction: results of the INTERHEART study. Eur Heart J. 2012 Feb;33:452-66.

Survival of the fittest



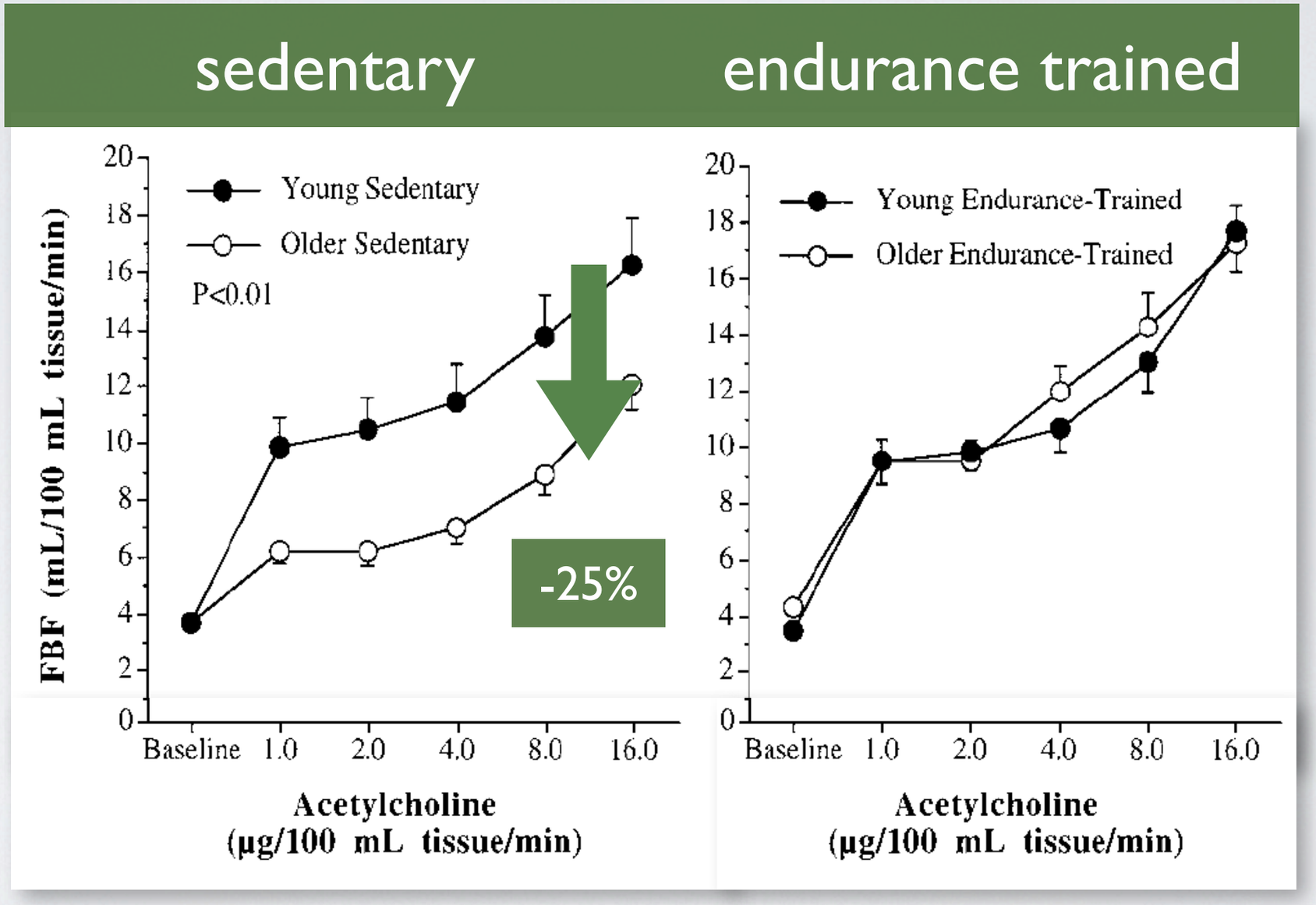


Myers J, et al. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346(11):793-801.

Regular Aerobic Exercise Prevents and Restores Age-Related Declines in Endothelium-Dependent Vasodilation in Healthy Men

DeSouza C et al. Circulation. 2000;102:1351-1357.

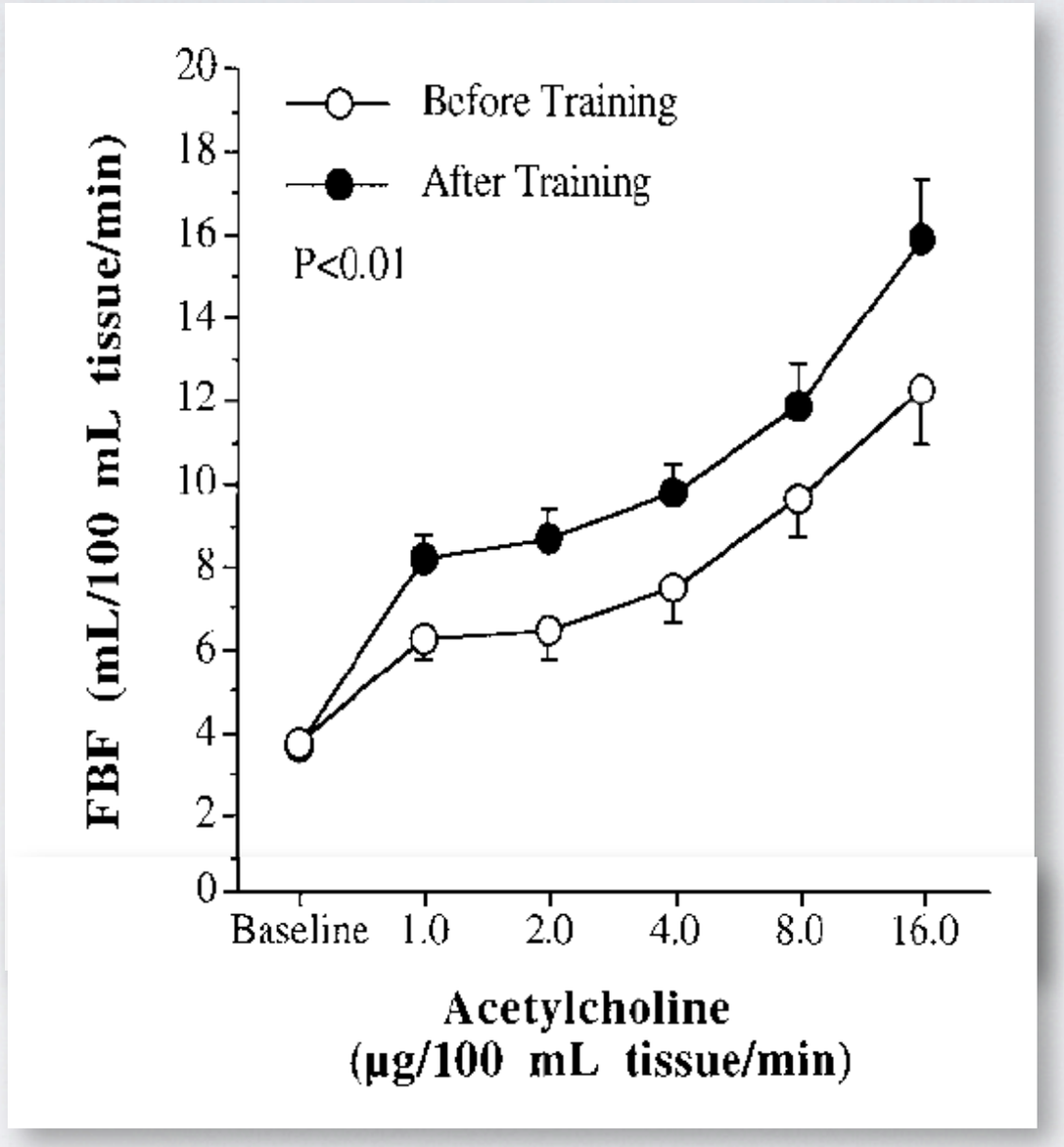
n=68



Regular Aerobic Exercise Prevents and Restores Age-Related Declines in Endothelium-Dependent Vasodilation in Healthy Men

DeSouza C et al. Circulation. 2000;102:1351-1357.

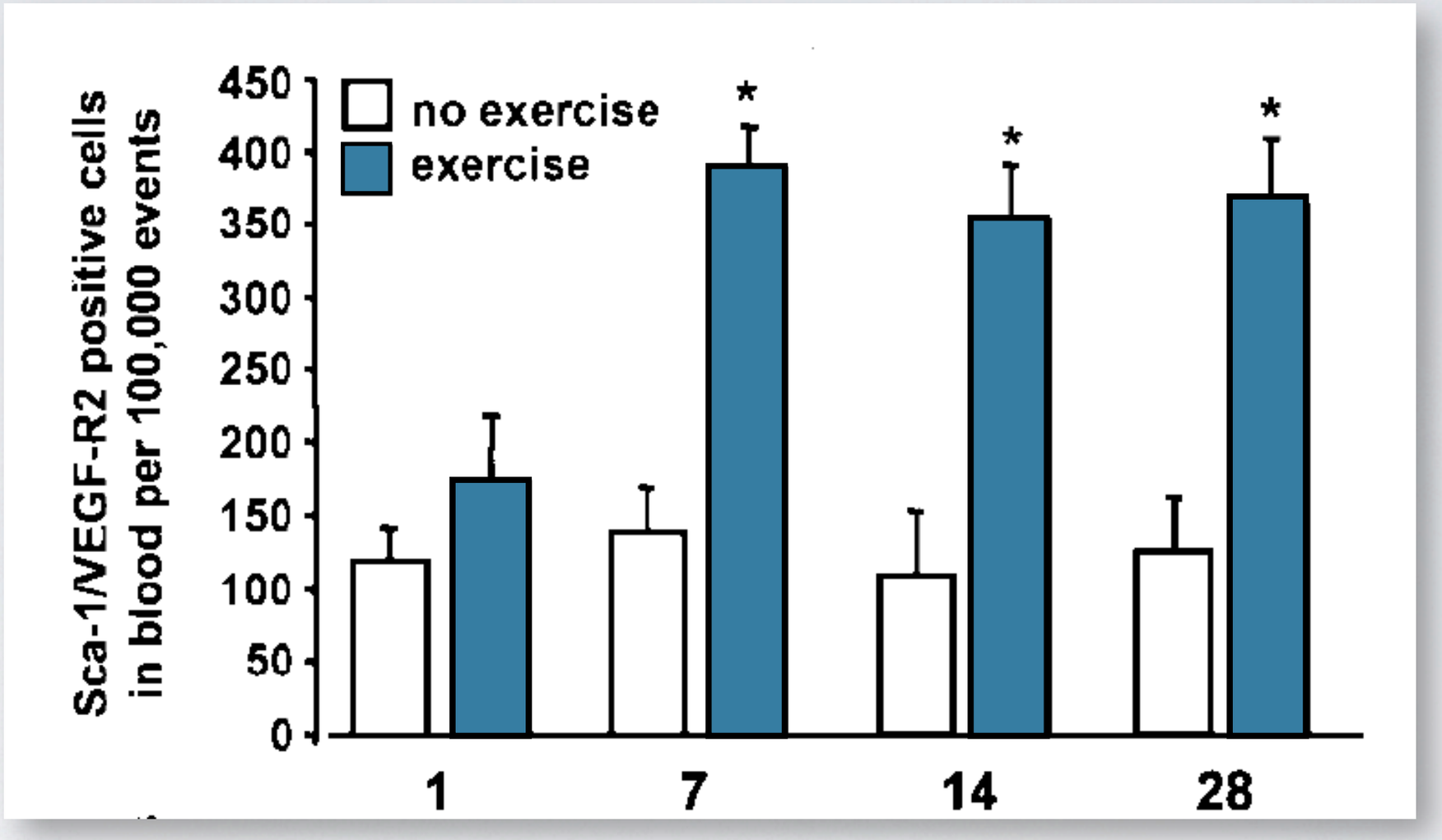
n=13



+30%

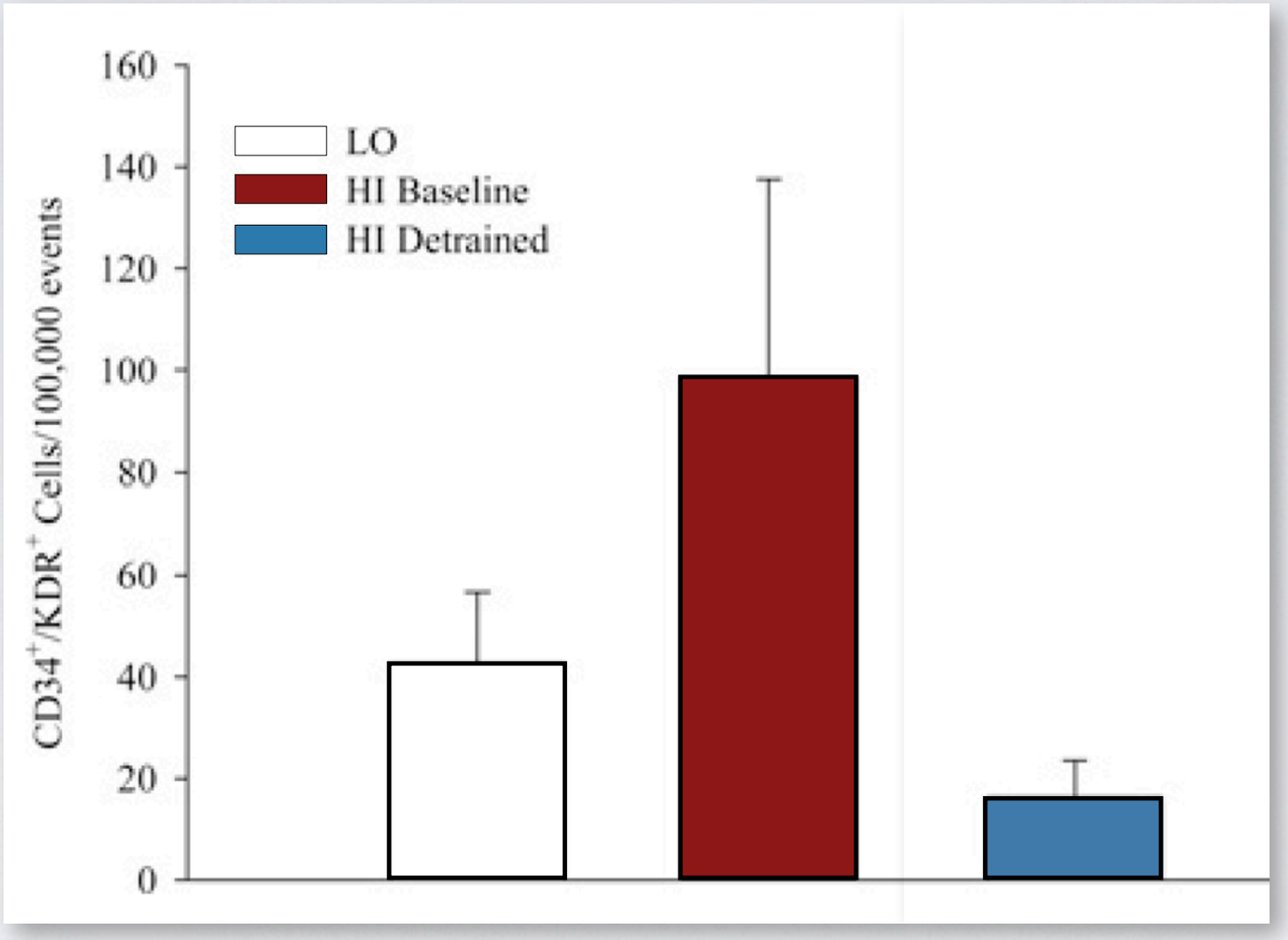
Physical Training Increases Endothelial Progenitor Cells, Inhibits Neointima Formation, and Enhances Angiogenesis.

Laufs U et al. Circulation 2004;109:220-226.



Relationship between circulating progenitor cells, vascular function and oxidative stress with long-term training and short-term detraining in older men

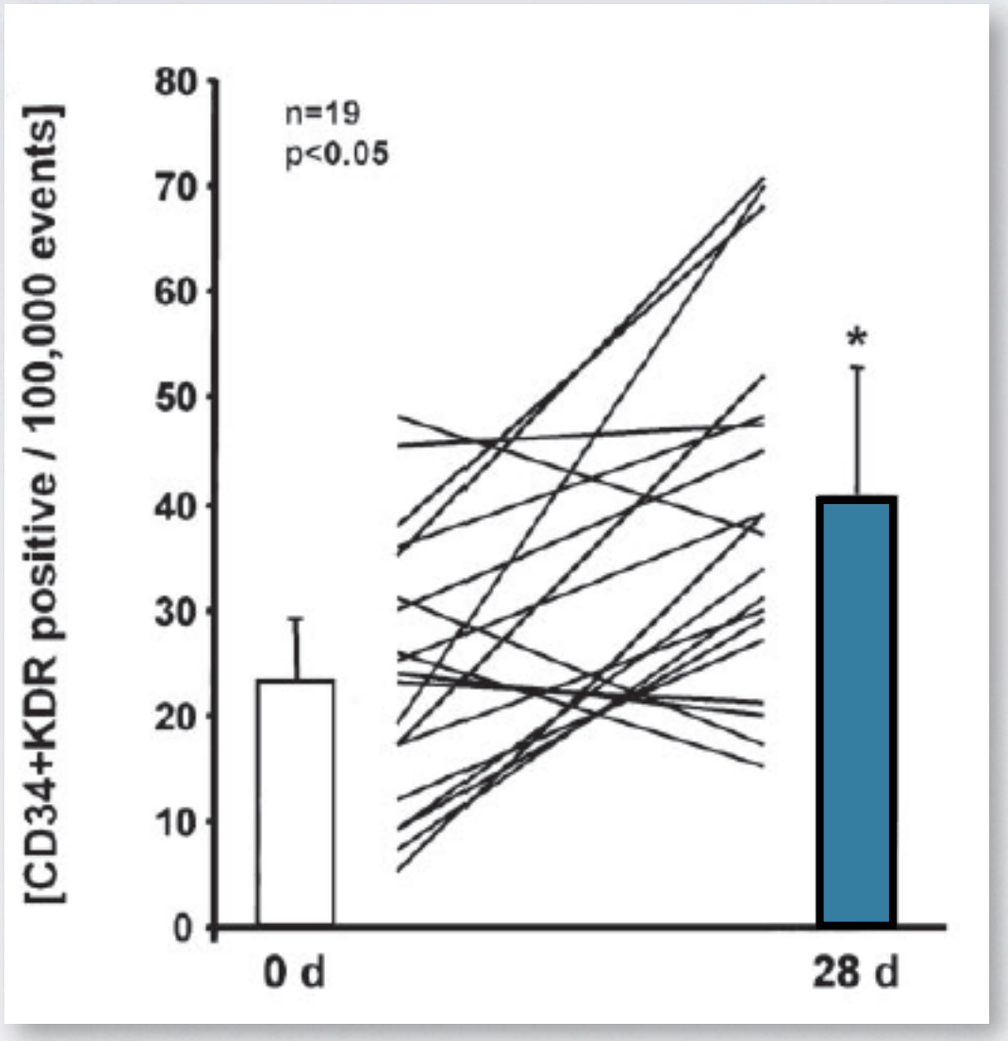
Witkowski S et al. Clin Sci 2010;118:303-11.



Secondary prevention ?

Physical Training Increases Endothelial Progenitor Cells, Inhibits Neointima Formation, and Enhances Angiogenesis.

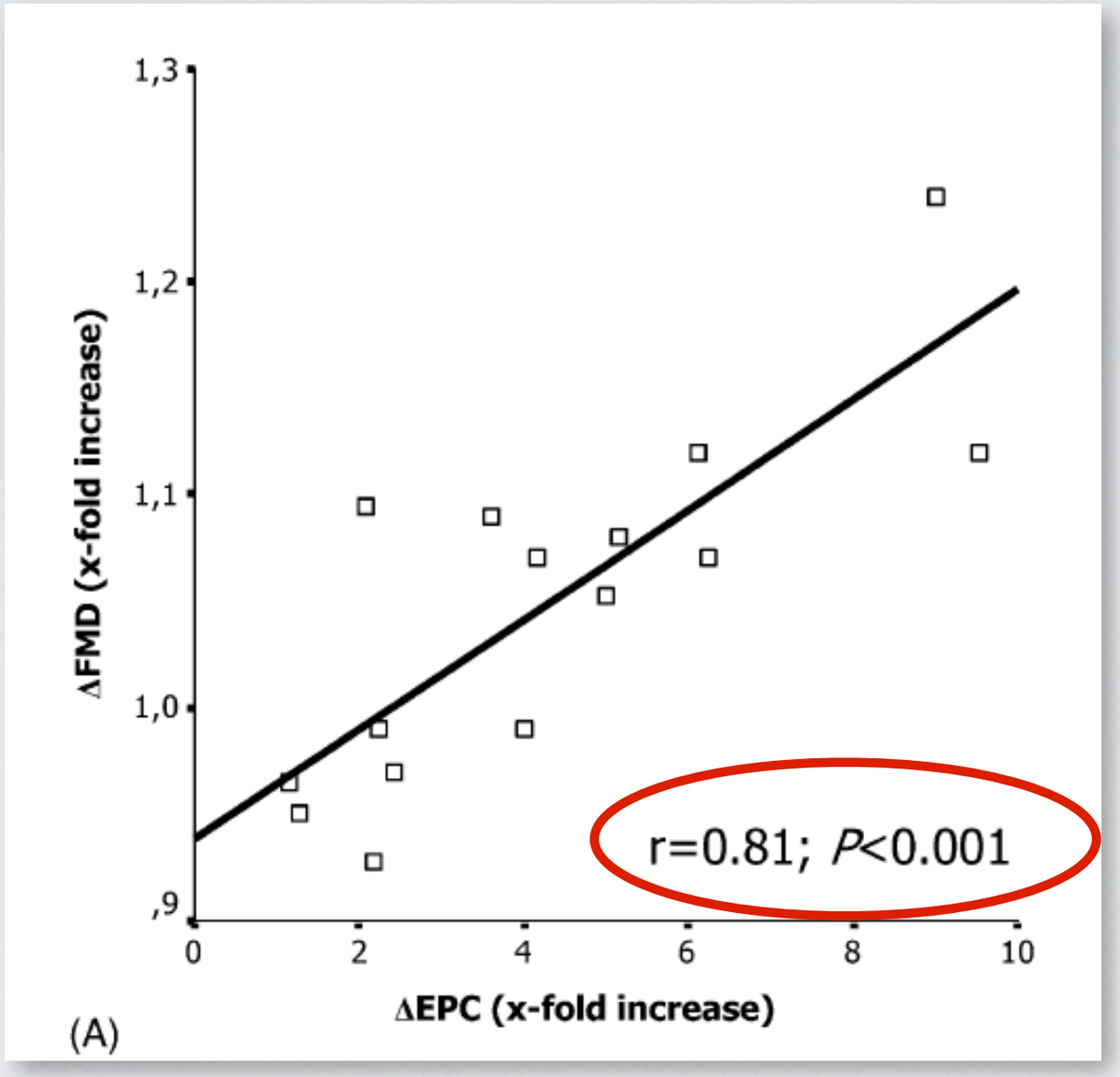
Laufs U et al. Circulation 2004;109:220-226.



Coronary artery disease

Endurance training increases the number of endothelial progenitor cells in patients with cardiovascular risk and coronary artery disease

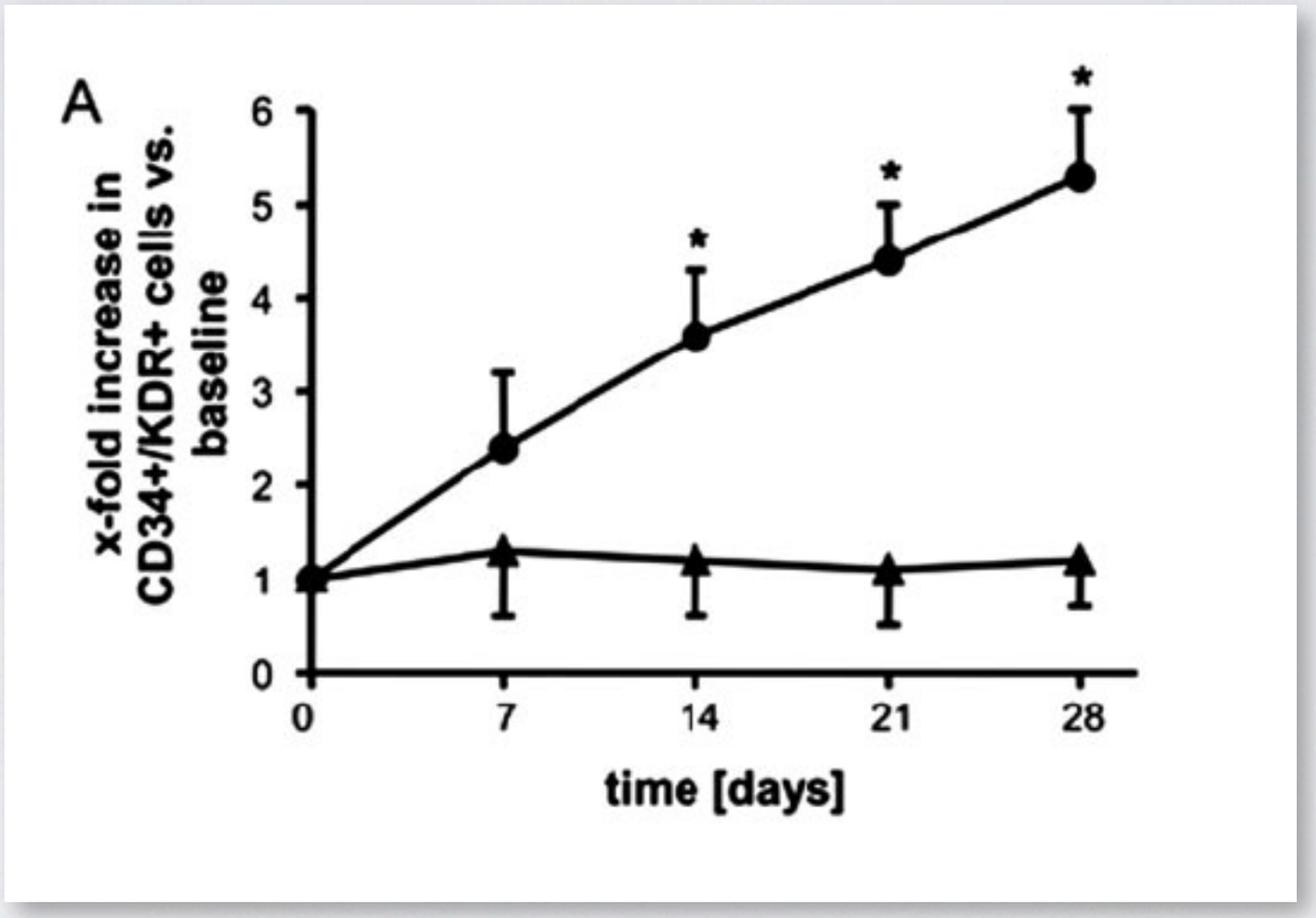
Steiner S et al. Atherosclerosis 2005; 181: 305–310.



Coronary artery disease

Effects of exercise and ischemia on mobilization and functional activation of blood-derived progenitor cells in patients with ischemic syndromes

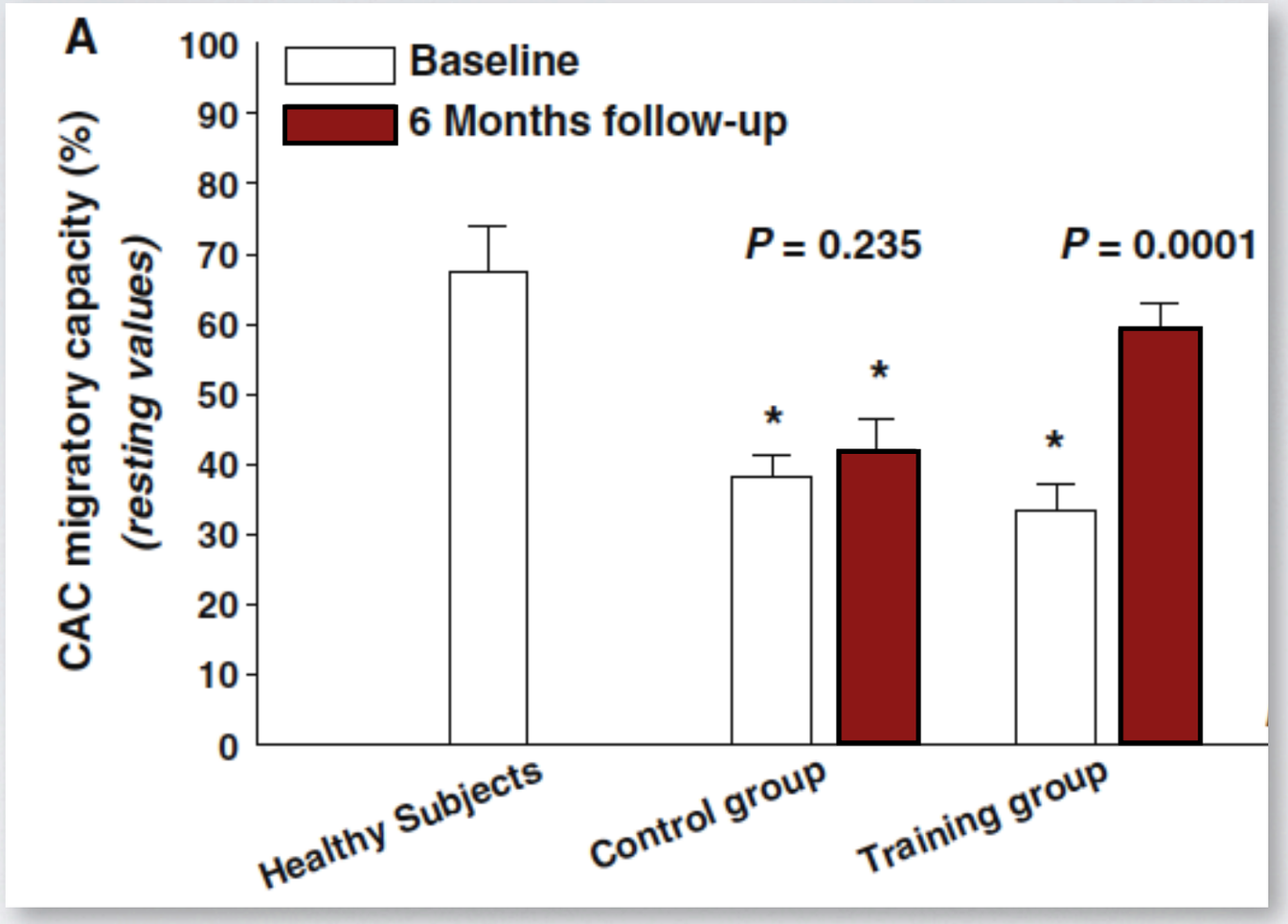
Sandri M et al. 2005;111:3391-9.



Peripheral occlusive arterial disease

Exercise training improves function of circulating angiogenic cells in patients with chronic heart failure

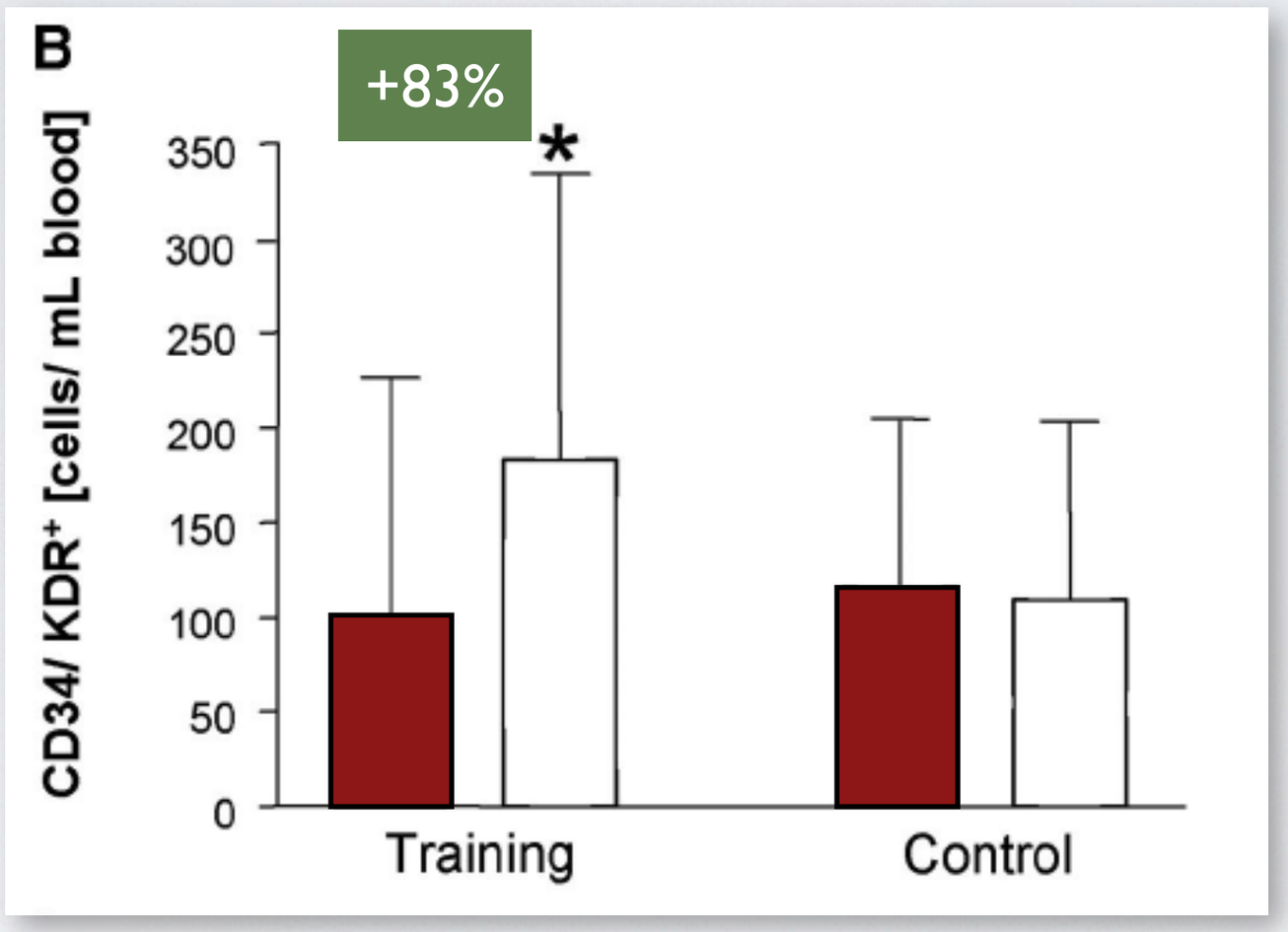
Van Craenenbroeck E et al. Basic Res Cardiol 2010;105:665–673.



Chronic Heart Failure

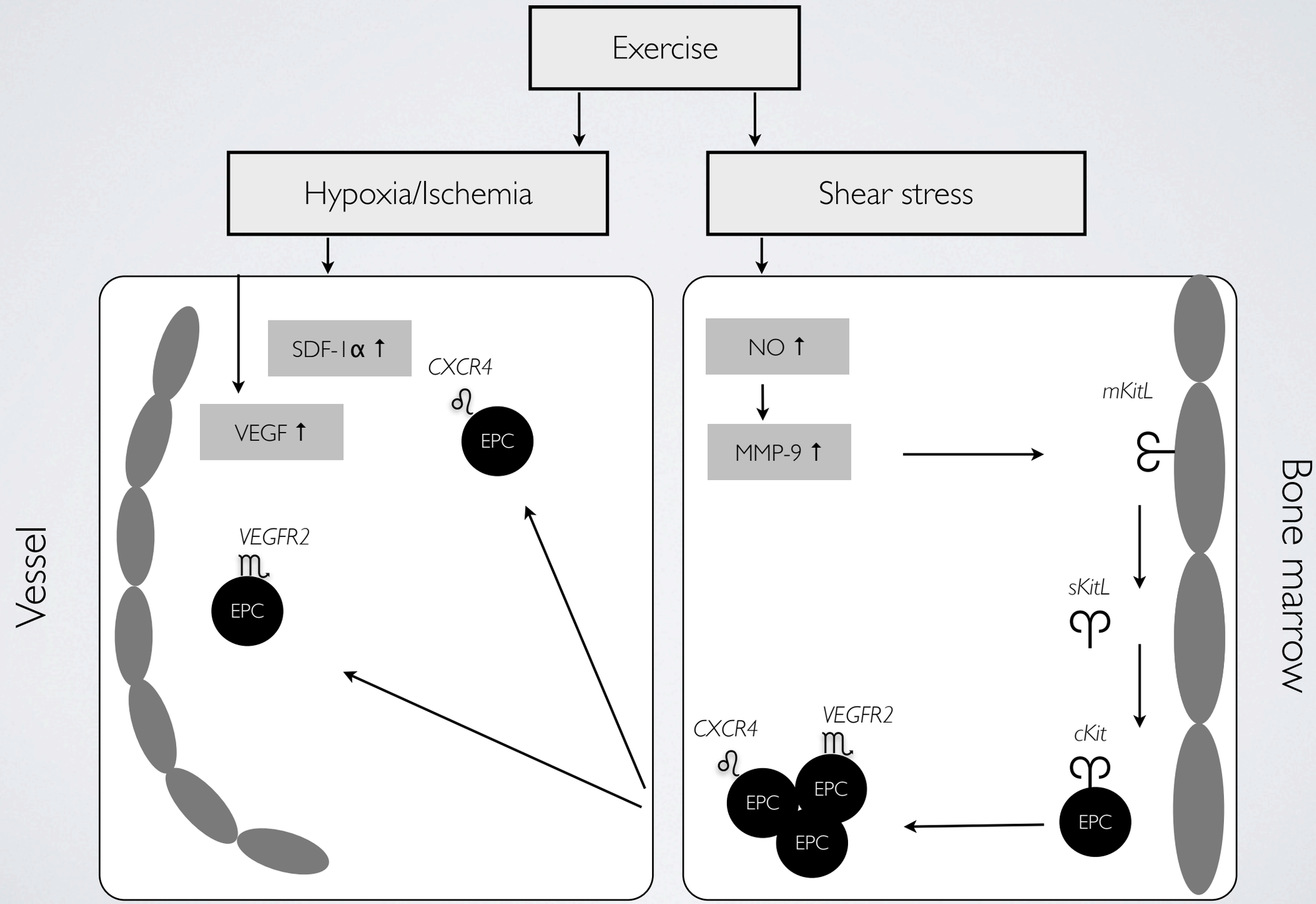
Exercise Training in Patients With Advanced Chronic Heart Failure (NYHA IIIb) Promotes Restoration of Peripheral Vasomotor Function, Induction of Endogenous Regeneration, and Improvement of Left Ventricular Function

Erbs S et al. Circ Heart Fail. 2010;3:486-494.



Chronic Heart Failure

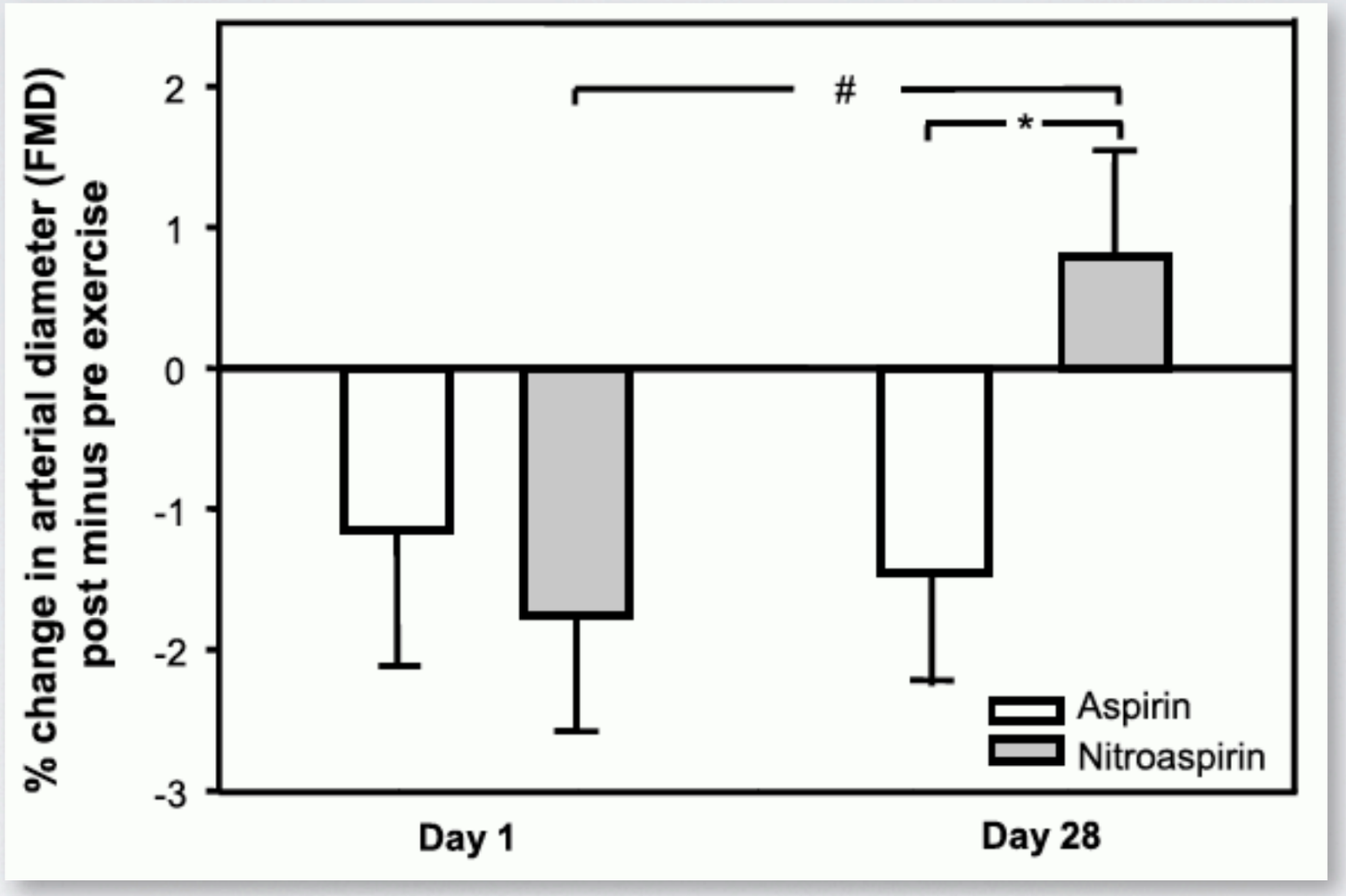
Mechanisms?


Exercise
Hypoxia/Ischemia
Shear stress
SDF-1α ↑
CXCR4
VEGF ↑
EPC
VEGFR2
EPC
Vessel
NO ↑
MMP-9 ↑
mKitL
sKitL
cKit
CXCR4
VEGFR2
EPC
EPC
EPC
EPC
Bone marrow

Single exercise bout ?

Prevention by NCX 4016, a nitric oxide-donating aspirin, but not by aspirin, of the acute endothelial dysfunction induced by exercise in patients with intermittent claudication

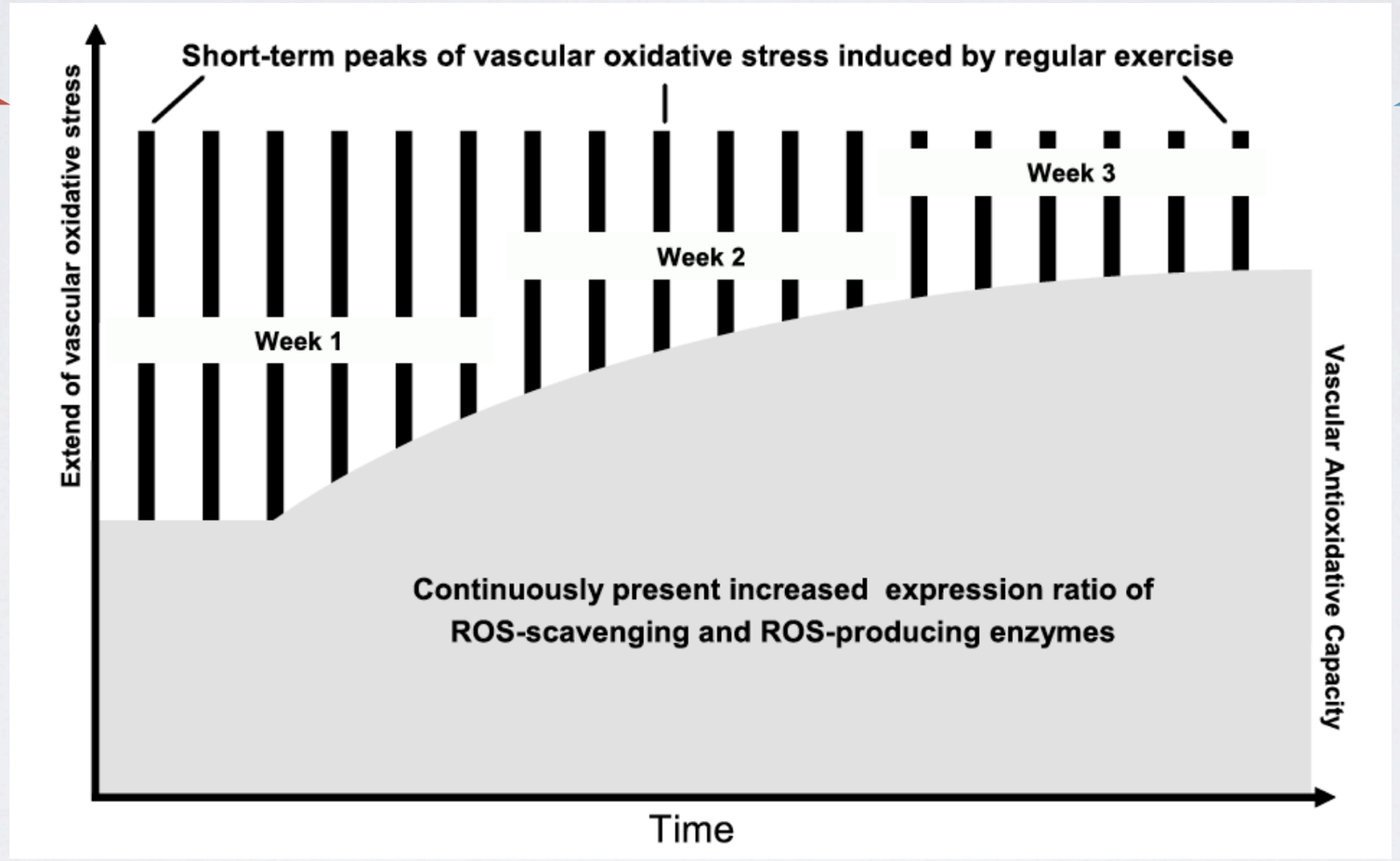
Gresele P et al. Thromb Haemost 2007; 97: 444–450.



Acute exercise

Exercise training

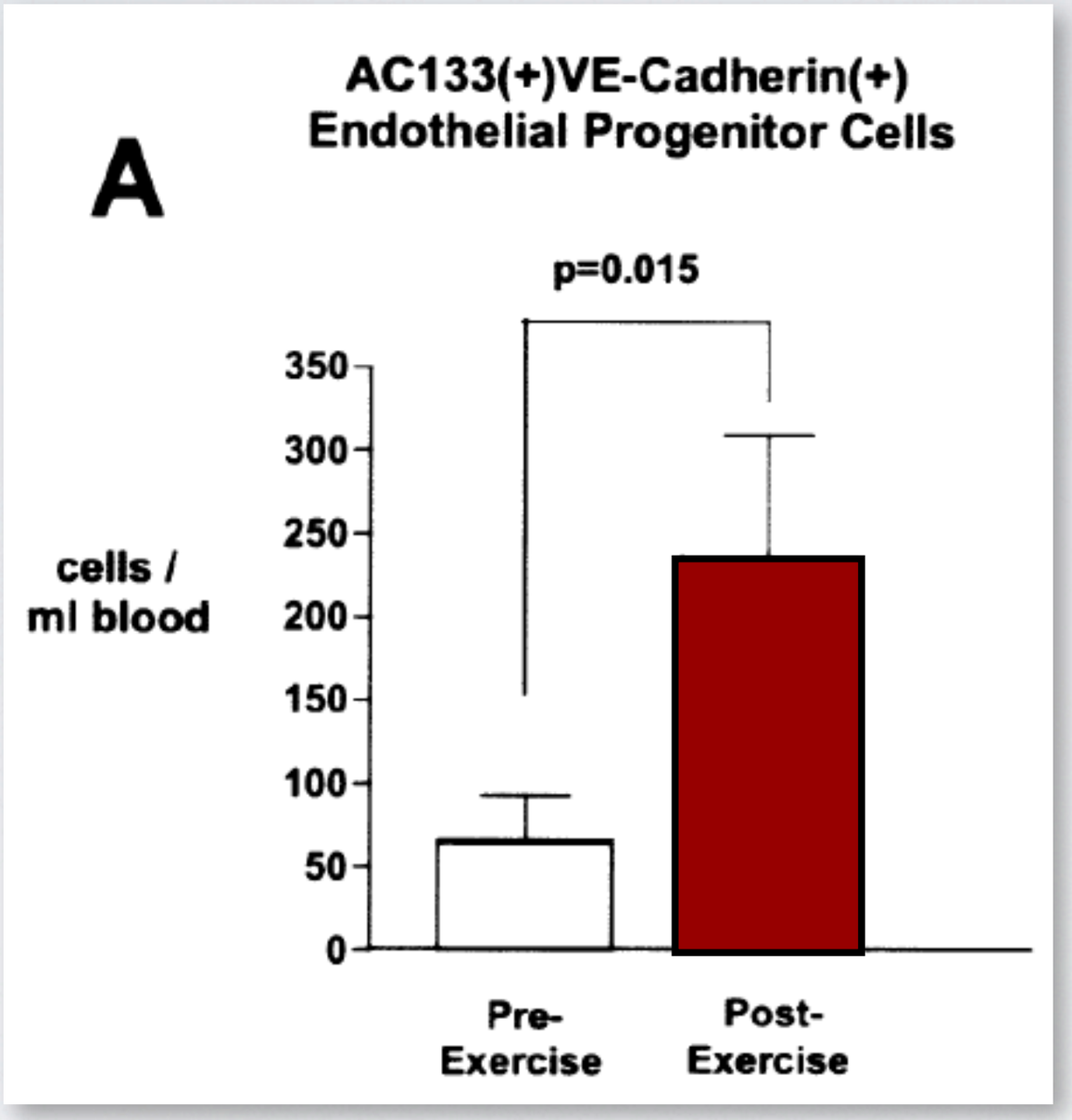
Oxidative stress



Anti-oxid capacity

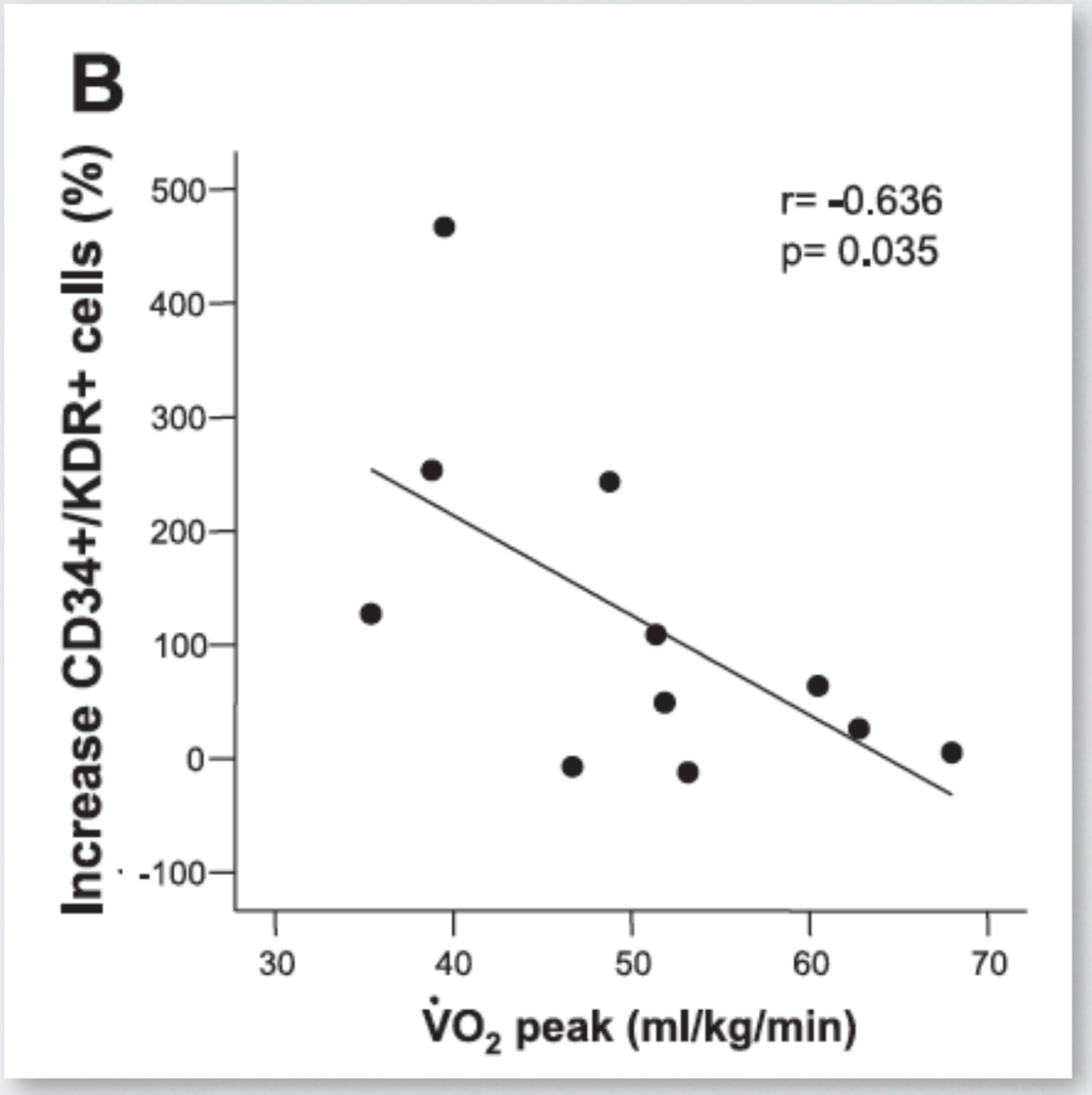
Suvorava T et al. Prevention of transient endothelial dysfunction in acute exercise: A friendly fire? Thromb Haemost 2007; 97: 331–333

One maximal exercise bout increases the number of circulating EPC.....



Rehman J et al. Exercise acutely increases circulating endothelial progenitor cells and monocyte-/ macrophage-derived angiogenic cells. J Am Coll Cardiol. 2004 Jun 16;43(12):2314-8.

..... and this acute exercise-induced response is higher in subjects with low physical fitness



Van Craenenbroeck E, et al. A maximal exercise bout increases the number of circulating CD34+/KDR+ endothelial progenitor cells in healthy subjects. Relation with lipid profile. J Appl Physiol. 2008 Apr;104(4):1006-13.

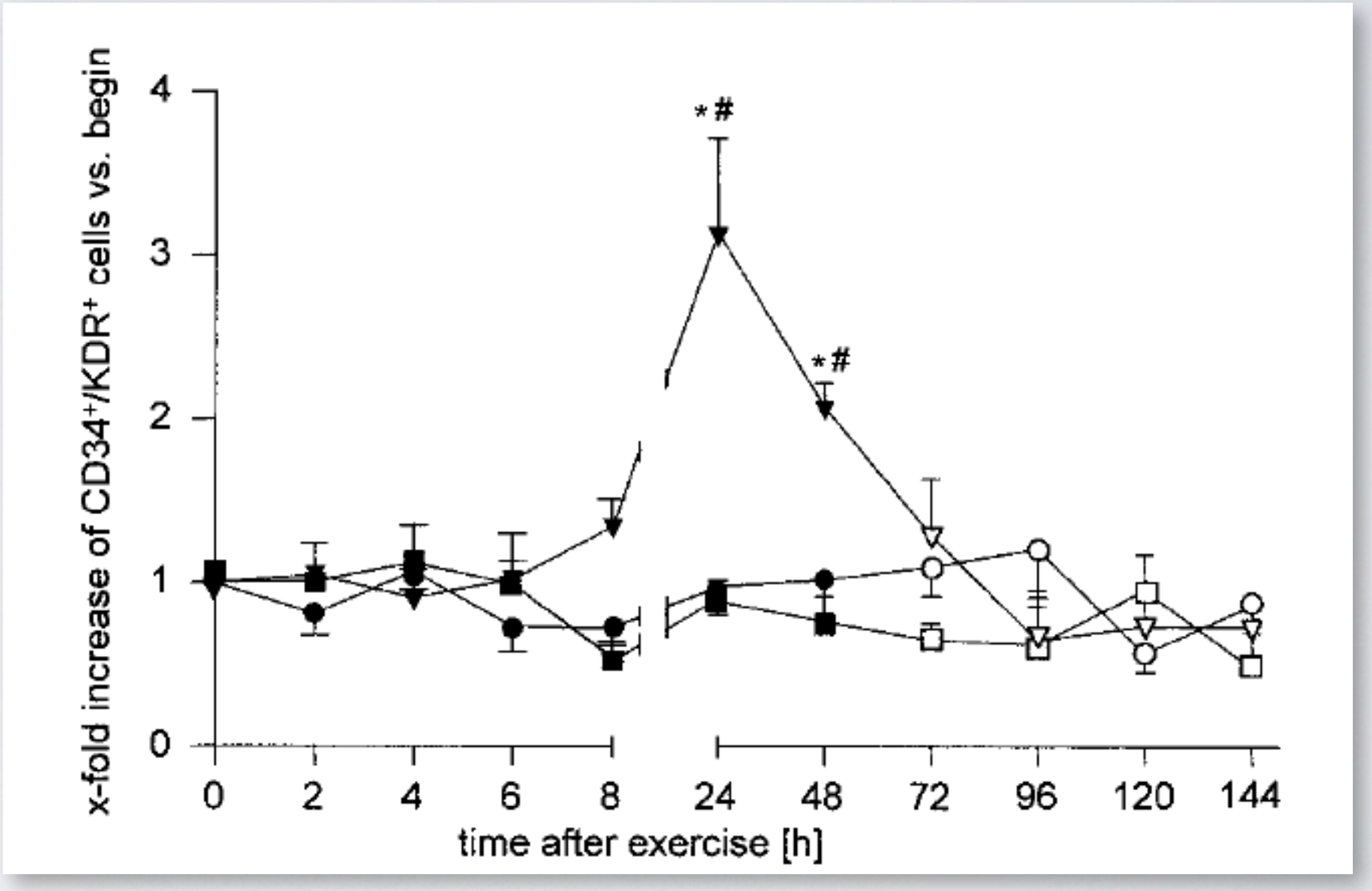
Increase of Circulating Endothelial Progenitor Cells in Patients with Coronary Artery Disease After Exercise-Induced Ischemia

Adams V et al. Arterioscler Thromb Vasc Biol 2004;24;684-690;

▼ Ischemic CAD

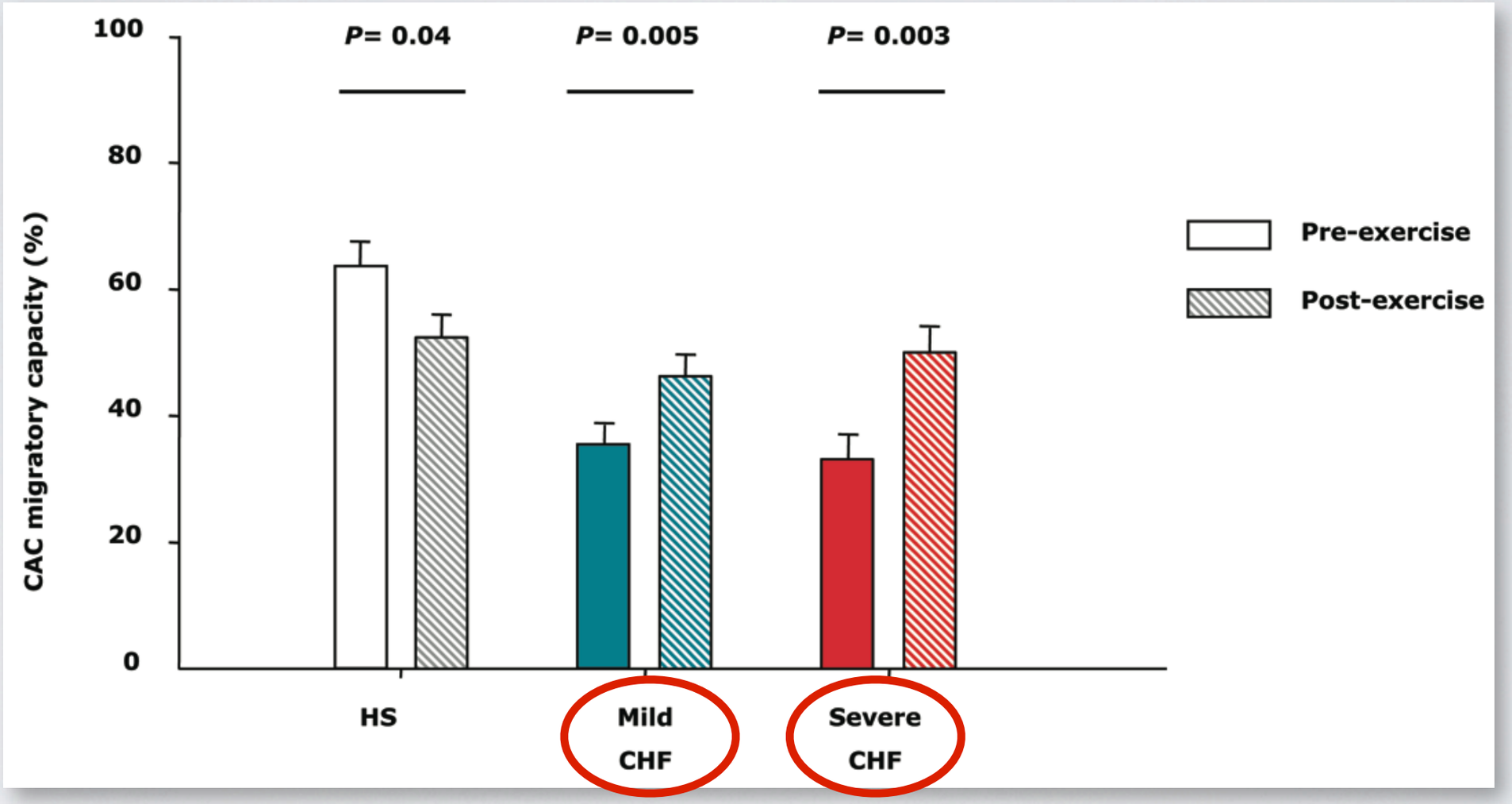
● Revascularized CAD

■ Healthy



Exercise acutely reverses dysfunction of circulating angiogenic cells in chronic heart failure

Van Craenenbroeck EM et al. Eur Heart J 2010;31:1924-34



New training modalities ?

SAINTEX-CAD

Study on **A**erobic **Int**erval **Ex**ercise Training in **CAD**

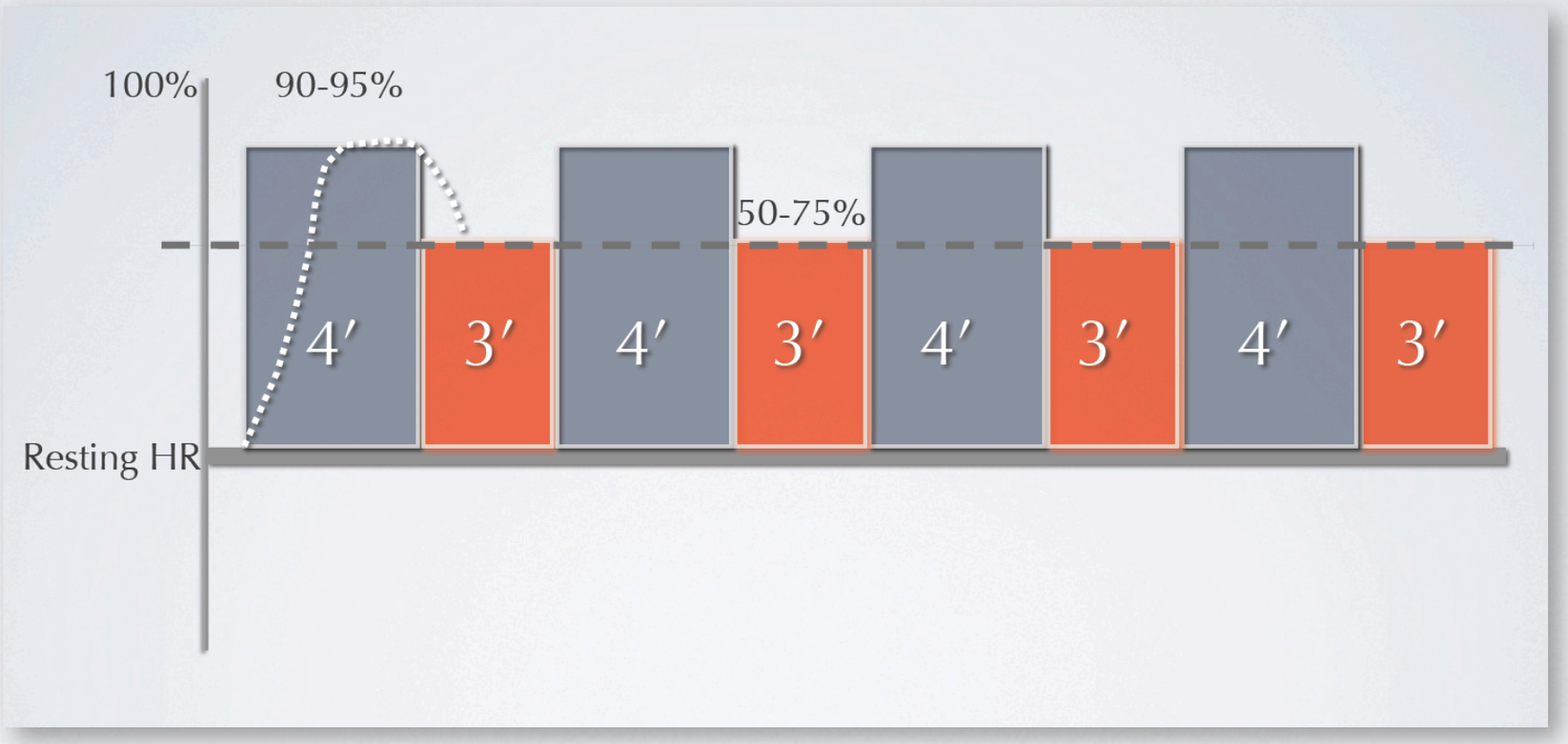
randomized controlled trial

High intensity interval versus moderate continuous training (n=200)

UZA-KUL

http://www.saintexcad.be/

High intensity interval training



AEROBIC INTERVAL TR

CAD Patients with LVEF > 40%

Exclusion:
Not eligible, Refuse participation

CPET
Echocardiography

Exclusion:
Not eligible

Cluster randomisation
N=200 CAD pts

AIT-group	MCT-group
clinical evaluation, peripheral endothelial function, contrast echocardiography, IMT, laboratory tests, questionnaires	*clinical evaluation, peripheral endothelial function, contrast echocardiography, IMT, laboratory tests, questionnaires*
WEEK 0	**WEEK 0**
START SUPERVISED TRAINING	**START SUPERVISED TRAINING**
12 weeks of AIT at 85-90% of VO_2peak 3x/week	12 weeks of MCT at 70-75% VO_2peak 3x/week
IPAQ, QoL and AE every 4 weeks	*IPAQ, QoL and AE every 4 weeks*
WEEK 6	**WEEK 6**
clinical evaluation, CPET, peripheral endothelial function	*clinical evaluation, CPET, peripheral endothelial function*
WEEK 12	**WEEK 12**
STOP SUPERVISED TRAINING	**STOP SUPERVISED TRAINING**
clinical evaluation, CPET, echocardiography, QoL, peripheral endothelial function, contrast echocardiography, IMT, laboratory tests	*clinical evaluation, CPET, echocardiography, QoL, peripheral endothelial function, contrast echocardiography, IMT, laboratory tests*
START HOME-BASED TRAINING	**START HOME-BASED TRAINING**
IPAQ, QoL and AE every 4 weeks	*IPAQ, QoL and AE every 4 weeks*
MONTH 12	**MONTH 12**
clinical evaluation, CPET, echocardiography, QoL, peripheral endothelial function, contrast echocardiography, IMT, laboratory tests	*clinical evaluation, CPET, echocardiography, QoL, peripheral endothelial function, contrast echocardiography, IMT, laboratory tests*

MODERATE CONTINUOUS TR

ENDPOINTS

1. peakVO2
2. Endothelial function
3. Safety
4. CV risk factors
5. ~~Quality of Life~~
6. EPC/EMP/CAC

"Coronary interventions treat a **very short segment** of the diseased coronary tree, whereas exercise exerts beneficial effects on endothelial function and disease progression in the **entire arterial bed**"

Green D et al. Point: exercise training does induce vascular adaptations beyond the active muscle beds. J Appl Physiol 2008; 105:766-768.

Vercors, France, 2009

Antwerp University Hospital

Cardiac Rehabilitation Unit
V. Conraads
C. De Maeyer
P. Beckers
N. Possemiers
K. Wuyts

Cardiology department
C. Vrints
I. Goovaerts
G. Ennekens

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Laboratory for Cellular and Molecular Cardiology
G. Frederix
S. van Ierssel
A. Van Craenenbroeck
L. Bruyndonckx
V. Hoymans

Laboratory for Experimental Hematology
N. Cools
V. Van Tendeloo
D. Van Bockstaele

acute exercise

acute exercise

acute exercise

UNTRAINED

Oxidative stress ↑ ↑ ↑

Endothelial repair ↑ ↑ ↑

Anti-oxidative enzymes ↑
eNOS activity ↑
EPC numbers and CAC function ↑

exercise training

TRAINED

Oxidative stress ↑

Endothelial repair ~