Exercise and endothelial function; 
*Role of endothelial progenitor cells?*

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Endothelial dysfunction

*Important?*

σ↑ 25 years, no medical history

VO$_2$peak 45 ml/kg/min

Flow mediated Dilation 9.89%

σ↑ 65 years, ICMP

VO$_2$peak 25 ml/kg/min

Flow mediated Dilation 3.05%
$\text{VO}_2 = \text{cardiac output} \times (\text{arterial-venous})\text{O}_2 \text{ difference}$

$\approx$

**Exercise** = bloodpump $\times$ dilation of **bloodvessels** and uptake of $\text{O}_2$ by **skeletal muscle**

\[ \text{VO}_2 = \text{cardiac output} \times (\text{arterial-venous}) \text{O}_2 \text{ difference} \]

\[ \approx \]

**Exercise** = blood pump \times \text{dilation of blood vessels} and uptake of \text{O}_2 \text{ by skeletal muscle}

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♂, 30yrs

LVEF 22%

CPET 21/6/2010: VO$_2$peak 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 vascularity in patients with CHF. The correction of endothelial dysfunction is associated with a significant increase in exercise capacity. (Circulation. 1998;98:2709-2715.)
Exercise-induced improvement endothelial function

Mechanisms?

endothelial progenitor cells

endothelial function

exercise training

exercise capacity
Endothelial progenitor cells

What are they?

Origin of EPC

Timmermans F et al. Endothelial progenitor cells: identity defined?
Endothelial progenitor cells

Mediators of vascular repair?

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

Asahara T et al. Science 1997; 275, 964

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

Werner N et al. Circ. Res. 2003;93;e17-e24
Methods to isolate EPC

**EPC culture assay**
- Adherence on Fibronectin/Gelatin
- „Early EPC“ Day 4-10
- „Late EPC“ Outgrowing EPC Day >14
- Ac-LDL, Lectin, KDR^{low}, CD144^{low} vWF, eNOS, CD45, CD14
- Methylcellulose

** „Early“ EPC**
- Prognosis of CVD
- Matrigel (in combination with EC)
- Functional improvement (HFI & AMI)
- Incorporation in capillaries (preferentially perivascular)
- Cytokine release

** „Late“ EPC**
- Matrigel (without addition of EC)
- Functional improvement in HLI
- Incorporation in capillaries (more endothelial?)
- Lower cytokine release

**CFU-EC colony assay**
- 48 hrs: Culture of Non-adherent cells
- Colonies Day 5
- Ac-LDL, Lectin, CD31, CD105, CD144, CD146, KDR, vWF, CD45

**CFU-EC**
- Correlation with EC function
- No vessel growth in Matrigel in vivo
- Therapeutic benefits not well explored

**Endothelial colony forming cells (ECFC assay)**
- Adherence on Collagen I
- Remove non-adherent cells
- Colonies Day 14-21
- Ac-LDL, Lectin, CD31, CD105, CD144, CD146, KDR, vWF, Negative for: CD14, CD45

**ECFC**
- High proliferation capacity
- Vessel growth in Matrigel in vivo
- Therapeutic benefits and impact on prognosis of CAD not tested

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Methods to quantify EPC

Flow Cytometry

CD34+KDR+CD45-
EPC mirror the natural history of atherosclerosis

**Diagram Description:***
- **Normal artery**, **Intima-media thickening**, **Plaque development**, **Plaque progression**, and **Complication** sections are illustrated.
- **EPC decrease** and **Mobilization** are shown along the timeline.
- **EPC level** over time with **High risk** and **Low risk** indicated.

**Citation:**
Endothelial Progenitor Cells

- Reduced circulating numbers
- Impaired angiogenic capacity

Cardiovascular risk factors
Advanced age, hypertension, obesity, diabetes, smoking, hyperlipidemia, sedentarity

Physical activity
Healthy diet
Smoking cessation
Weight reduction
Stress reduction

Endothelial progenitor cells

*Therapeutic use?*

Emerging and future clinical applications of adult vascular progenitor therapy

- Endothelialized grafts
- Tissue engineered heart valves
- Plaque stabilization
- EPC coated stents
- EPC coated LVAD
endothelial progenitor cells

endothelial function

exercise training

exercise capacity
Primary prevention?
Percentage sedentarism across countries

Low income
- Sedentary: 69%
- Mild exercise: 7%
- Moderate to strenuous exercise: 24%

Middle income
- Sedentary: 57%
- Mild exercise: 16%
- Moderate to strenuous exercise: 27%

High income
- Sedentary: 37%
- Mild exercise: 38%
- Moderate to strenuous exercise: 25%

Survival of the fittest

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


![Graph showing the effects of exercise on FBF compared to sedentary and endurance trained groups.](image_url)
Regular Aerobic Exercise Prevents and Restores Age-Related Declines in Endothelium-Dependent Vasodilation in Healthy Men

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

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

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

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

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

Exercise training improves function of circulating angiogenic cells in patients with 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

Mechanisms?

Exercise

Hypoxia/Ischemia

Shear stress

Vessel

Bone marrow

NO ↑

MMP-9 ↑

mKitL

sKitL

cKit

EPC

VEGFR2

CXCR4

SDF-1α ↑

VEGF ↑

Exercise

Shear stress

Hypoxia/Ischemia

Vessel

Bone marrow

NO ↑

MMP-9 ↑

mKitL

sKitL

cKit

EPC

VEGFR2

CXCR4

SDF-1α ↑

VEGF ↑
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

One maximal exercise bout increases the number of circulating EPC.

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

![Image](image_url)

**B**

$r = -0.636$

$p = 0.035$

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

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 Aerobic Interval Exercise 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
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**”

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D. Van Bockstaele

Vercors, France, 2009
Anti-oxidative enzymes ↑
eNOS activity ↑
EPC numbers and CAC function ↑

acute exercise

exercise training

UNTRAINED
Oxidative stress ↑ ↑ ↑ ↑
Endothelial repair ↑ ↑ ↑

TRAINED
Oxidative stress ↑
Endothelial repair ~