Physical exercise and its effects on coronary artery disease
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The beneficial effects of physical exercise on stable coronary artery disease (CAD) have been shown by an increasing number of studies. Exercise training leads to an improved bioavailability of the endothelial nitric oxide and partially attenuates endothelial dysfunction. Further effects are an economization of ventricular function and a reduction of cardiovascular risk factors. In clinical studies exercise training was associated with a decreased total and cardiovascular mortality and a reduced angina pectoris threshold. Thus exercise training has developed to an evidence-based therapeutic option of stable CAD with a Class 1a recommendation in the guidelines.

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Introduction
In the last decades experimental and clinical study data provided evidence on the favourable effects of exercise training in stable coronary artery disease (CAD).

This article discusses pathophysiological effects of physical exercise and their impact on CAD. Some mechanisms are generally accepted; others, as vasculogenesis and endothelial progenitor cells (EPCs), are still a matter of debate.

Attenuation of endothelial dysfunction
Endothelial function is crucial in the development of atherosclerosis (as formation of fatty streaks or advanced atherosclerotic lesions) and endothelial dysfunction has been increasingly recognized as a conditio sine qua non for atherogenesis. The intact endothelium is important to protect the vessel from injury factors (response to injury hypothesis) and serves as a crucial modulator of vaso-motor tone [1,3,4].

Therefore endothelial function plays a major role in the pathogenesis of exercise-induced angina pectoris.

A key component of endothelial function is synthesis and release of endothelial nitric oxide (NO) [3–7]. In the intact endothelial cell NO is produced by the endothelial NO synthase (eNOS) from L-arginine leaving L-citrulline as a by-product. L-Arginine may be endogenously produced or introduced into the endothelial cell via a transport mechanism. NO diffuses into the extracellular space and may be inactivated by reactive oxygen species (ROS). Remaining NO that reaches the vascular smooth muscle cells stimulates intracellular production of the second messenger cGMP, which induces vasorelaxation by activation of cGMP-dependent protein kinases [2–4].

Exercise training has effects on different steps of endothelial dysfunction and NO bioavailability (Table 1, Figure 1):

eNOS quantity or activity
A central component of endothelial function is eNOS [3–7].

Although eNOS activity is coupled to changes in endothelial cell Ca2+ levels, an increase in Ca2+ alone is not sufficient to affect enzyme activity; protein phosphorylation and dephosphorylation represent crucial Ca2+-independent regulatory pathways. The amino acids serine residue Ser 1177 and threonine residue Thr 495 have been identified to be relevant regulators of these mechanisms [3–6].

Shear stress has been shown to be the most important physiologic activator of eNOS. When cultured endothelial cells were exposed to laminar shear, an upregulation of eNOS mRNA and protein was observed [3–7].

The conversion of physical forces into biochemical signals is mediated by mechanotransducers, expressed by the endothelial cells, the cytoskeleton and cellular adhesion proteins (such as vascular endothelial cadherin). Various signal transduction pathways have been identified involving phosphorylation of kinases such as the phosphatidylinositol-3-kinase and Akt kinase and resulting in phosphorylation and activation of eNOS in response to shear stress [3,5,7] (Figure 2).

In a clinical study 35 patients scheduled for coronary artery bypass surgery were randomized to exercise or
control, left internal mammary artery tissue not needed for bypass grafting was harvested and analyzed with respect to eNOS expression and phosphorylation [5]. Trained patients had 2-fold higher eNOS protein expression and 4-fold higher eNOS Ser 1177 phosphorylation levels. A linear correlation was confirmed between Akt phosphorylation and phospho-eNOS levels and between phospho-eNOS and delta mean blood flow velocity [5].

**Availability of the eNOS substrate and cofactors**

Availability of the eNOS substrate and cofactors is a crucial step for NO synthesis.

It has been shown, that shear stress selectively activates uptake of L-arginine in endothelial cells by improving the endothelial transport system [4].

In addition, physical exercise decreases levels of the L-arginine antagonist ADMA. In a study of patients with CAD or elevated CAD-risk significant reductions of circulation ADMA levels were observed after 12-week exercise training [8].

The eNOS function also depends on the essential cofactor (6R)-5,6,7,8-tetrahydro-L-biopterin (BH4) [9]. BH4 levels are elevated by exercise training. Widder et al. showed, that in human endothelial cells laminar shear stress raises BH4 levels [3,10,11]. Diminished BH4 levels promote production of ROS by eNOS. This transformation of eNOS from a protective enzyme to a contributor of oxidative stress is called eNOS uncoupling, as enzymatic reduction of molecular oxygen by eNOS is no longer coupled to L-arginine oxidation, resulting in a production of ROS rather than NO. It has been observed under a number of conditions, including BH4 deficiency, shortage of L-arginine or heat shock protein 90, or elevated ADMA levels [3,9].

**NO breakdown velocity**

The NO breakdown velocity depends on the balance of ROS-generating enzymes as nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase or xanthine oxidase and antioxidative enzymes as superoxide dismutase (SOD) and heme oxygenase-1 (HO-1) [7,12–15].

Several studies showed, that exercise training increases antioxidative enzymes and decreases ROS-generating enzymes [12–15].

Adams et al. demonstrated, that exercise training reduces expression of NAD(P)H oxidase and the regulating angiotensin II type 1 receptor, resulting in decreased ROS formation.
Shear stress-activated signal transduction cascade resulting in NO synthase activation. Laminar shear stress leads to an activation of PI3K, that phosphorylates and activates protein kinase Akt. This results in a phosphorylation and activation of eNOS at site S1177, enhanced by HSP 90. PI3K indicates phosphatidylinositol-3-kinase; PDK, phosphoinositide-dependent kinase Akt (protein kinase B); HSP 90, heat shock protein 90; eNOS, endothelial nitric oxide synthase; S 1177, serin residue 1177.

generation [13]. Elevated HO-1 levels have been found in association to moderate exercise training [14]. HO-1 was identified to be crucial for attenuating ROS-levels and preventing cell damage in numerous pathologic cardiovascular conditions [15].

**Further vasoregulative factors influenced by exercise training**

Distinct from the NO pathway further vasoregulative factors have been recently investigated in experimental studies [16–19]. It has been shown, that exercise training attenuates endothelin-mediated coronary vasoconstriction through reduced endothelin production [16]. In a study of skeletal muscle biopsies in patients with hypertension exercise training altered the balance between vasodilating and vasoconstricting compounds as proved by a decrease in the level of thromboxane, reduction in the exercise-induced increase in ATP and a greater exercise-induced increase in prostacyclin [17]. Thus, it is becoming increasingly obvious, that a variety of mechanisms is involved in the vasoregulating effects of exercise training, thus altering the balance between vasoconstrictors and vasodilators in favour of vasodilatation.

**Clinical studies on exercise and endothelial function**

In a prospective randomized study the clinical effects of exercise on coronary endothelial function were first analyzed in humans by Hambrecht et al. [20]. Endurance training reduced the paradoxical vasoconstriction in epicardial conduit vessels by $-54\%$ and increased average peak flow velocity by $+78\%$ in response to intracoronary acetylcholine. In addition a significantly increased coronary blood flow reserve after adenosine was observed in the training group [20].

Further studies confirmed the beneficial effects of exercise on vascular vasomotor function. Luk et al. described a significantly improved brachial flow-mediated dilatation associated with exercise training. This effect was independent of markers of inflammation and oxidative stress and was inter-related with improved exercise capacity [21]. Beck et al. measured endothelial dysfunction in patients with and without exercise training and analyzed the correlation to circulating growth factors. The training group showed a significantly improved endothelium-dependent vasodilation in close correlation to serum concentrations of vascular endothelial growth factor (VEGF) and erythropoietin [22*].

**Ventricular function in CAD-patients**

Exercise training has beneficial effects on different aspects of ventricular function of CAD-patients (Table 2, Figure 3).

Exercise training reduces blood pressure and total peripheral resistance at least partially by enhanced endothelial function of peripheral vessels. This results in a decreased cardiac afterload at rest and during submaximal exercise [23,24].

Exercise training has beneficial effects on the autonomic nervous system leading to a reduced sympathetic tone activity and a reduced heart rate [23].
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Table 2

<table>
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<tr>
<th>Key effects of exercise on ventricular function in CAD</th>
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<td>Decreased cardiac afterload (at least partially by enhanced endothelial function);</td>
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<tr>
<td>Decreased sympathetic tone activity;</td>
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<tr>
<td>Improved calcium handling and myocardial contractility;</td>
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<td>Improved diastolic function.</td>
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These effects lead to an economization of ventricular function due to endurance training and can result in a decreased myocardial oxygen demand and angina pectoris threshold [25].

Myocardial contractility can be improved by exercise training [3,26–28]. An important molecular role plays homeostasis and handling of calcium and the regulating sarcoplasmic reticulum Ca\(^{2+}\) ATPase pump (SERCA2a). SERCA2a protein levels are reduced in mouse and dog models of heart failure and are normalized by exercise training [3,26,27].

Recent studies also observed an improvement of diastolic function by training interventions [3,29]. Sandri et al. found significantly improved echocardiographic parameters of diastolic function and decreased N-terminal pro brain natriuretic peptide serum levels in patients with endurance training compared to controls [29].

It has been further shown, that the functional cardiac decline after exposure to ischemia (ischemia-reperfusion tolerance) can be prevented by exercise training [3]. Different mechanisms have been identified for this prevention: improved antioxidative protection, changes in mitochondrial metabolism and protein expression, increased expression of sarcolemmal/mitochondrial K\(_{\text{ATP}}^{+}\) channels and attenuation of calpain activation [3].

Reduction of CAD risk factors

Exercise training has beneficial effects on different risk factors of CAD and reduces the overall cardiovascular risk of individuals [30–34] (Figure 3).

Lifestyle modification with physical activity is the first step in antihypertensive treatment due to the inhibitory effects of exercise training on blood pressure by attenuation vasoconstrictors and increasing vasodilator activity [17,31] and by inhibiting sympathetic activation [23]. Regular physical activity is also an important therapeutic component in the treatment and prevention of obesity and obesity-associated diseases such as diabetes and hypertension [31–33]. A number of studies have shown that regular physical exercise leads to an improvement of insulin sensitivity/glucose utilization in diabetics and a favourable impact on dyslipidemia with raising levels of HDL cholesterol and lowering triglyceride levels [32–34] (Figure 3).

Attenuation of coronary atherosclerosis progression

Several randomized intervention studies like the Lifestyle Heart Trial assessed the influence of exercise training in combination with lifestyle changes on the progression of CAD [4,35]. An attenuation of the progression of coronary atherosclerosis could be shown; however, the comparatively small changes observed in coronary diameter make this mechanism unlikely to explain the significant clinical effects of exercise training on CAD.

Formation of collaterals

Animal studies suggested that physical exercise leads to an improvement of coronary collateralization. Data from angiographic studies in humans were controversial [4]. However, it has to be considered, that angiography can only detect collaterals >200 μm and the method may be not sensitive enough to detect formation of small intramyocardial collateral vessels that will be recruited only during exercise.

Vasculogenesis and endothelial progenitor cells

The role of EPCs derived from the bone marrow to support vascular endothelium integrity and induce postnatal vasculogenesis in ischemic tissue is a matter of ongoing debate [3,36\(^{*,37–44}\)].

It was recently shown, that an impairment of mobilization and functional activity of EPCs is associated with severe CAD [36\(^*\)].

Physical exercise improves the function and number of circulating EPCs. Steiner et al. measured a significant increase of the number of circulating EPCs after 3 months.

Synopsis of clinical effects of exercise training on CAD. Exercise training has different beneficial impacts on the endothelium/peripheral vessels, ventricular function and cardiovascular risk factors.
of exercise training, this was positively correlated with an improved endothelial function and an increased NO synthesis [37]. Cesari et al. described an increased numbers of circulating EPCs in association with physical activity and weight loss in overweight and obese patients [38].

There is a continuing debate what triggers exercise-induced change in EPC release from bone marrow — ischemia induction or flow changes and increased NO production [3,39–43]. Sandri et al. observed in 2005 that an increase in circulating EPCs was only achieved in response to exercise-induced ischemia, in this study matrigel assays showed improved EPC function in non-ischemic training [39]. However, newer studies found an increase of EPCs also in the absence of ischemia, and NO bioavailability was suggested to be the main mechanism of EPC mobilization [3,42,43]. EPC mobilization from the bone marrow seems to depend on eNOS activation in the presence of mobilizing factors as VEGF or placenta growth factor [3]. A model for EPC-mobilization from the bone marrow induced by exercise was demonstrated by Gielen et al. (Figure 4) [3].

After mobilization, tissue engrafting and migration of the circulating EPCs are essential for their function. Several studies investigate the mechanisms, including homing factors as CXCR4, CXCR7 or stromal-cell derived factor 1, that seems to be a principal regulator of EPC function [3,44].

**Prevention of cellular senescence**
The effects of physical exercise on indicators of cellular aging (telomeres) were investigated by Werner et al. [45]. Telomeres and telomere-regulating proteins affect cellular senescence and survival. Telomere biology was compared in endurance athletes and untrained individuals. An increased telomere activity and expression of telomere-stabilizing proteins could be found in the endurance training group, suggesting a cell protective effect by exercise training [45].

**Studies with clinical end points**
The effects of 12 months of exercise training in stable CAD were compared with percutaneous coronary interventions (PCIs) in a randomized clinical trial [25].
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Exercise training was associated with a higher event-free survival (88% versus 70% in the PCI group, \( p = 0.023 \)) and increased maximal oxygen uptake (+16%) [25].

In a recent meta-analysis of 47 studies 10794 CAD-patients, randomized to exercise-based cardiac rehabilitation or usual care, were analyzed [46**]. Exercise-based cardiac rehabilitation was associated with a reduced overall and cardiovascular mortality [RR 0.87 (95%CI 0.75–0.99) and RR 0.74 (95%CI 0.63–0.87), respectively] and a lower rate of hospital admissions [RR 0.69 (95%CI 0.51–0.93)] [46**].

Recommendations for exercise training in coronary artery disease

Exercise training is an important component of the therapeutic management of stable CAD, with a Class Ia recommendation in the international guidelines [32,47,48*].

The prognostic benefits in CAD patients are only documented for endurance training, not for resistance training [48*].

Individual exercise prescription and identification of patients who require more intensive monitoring should depend on an initial risk stratification, based on medical history, physical examination and a symptom-limited exercise test [32,47,48*]. Physical activity should be increased slowly. Exercise intensity depends on individual conditions, however generally 50–80% of peak oxygen consumption or 40–60% of heart rate reserve, respectively 10/20–14/20 of the Borg Rating of Perceived Exertion are recommended [47,48*]. The European guidelines on cardiovascular disease prevention recommend moderate-to-vigorous intensity aerobic exercise training ≥3 times a week and 30 minutes per session [32]. Prophylactic application of short-acting nitrates can improve compliance with the exercise program by elevating the angina pectoris threshold [47]. The individual exercise prescription should be reevaluated regularly [32,47,48*].

Conclusions

Exercise training has different beneficial effects on stable CAD-patients [3–5,7,8,10–14,16–35,37–43,45–47,48*].

Recent studies have confirmed that physical exercise partially attenuates endothelial dysfunction. NO bioavailability is improved due to increased eNOS expression and activity and decreased ROS-related NO breakdown velocity but also inhibition of vasoconstrictors such as angiotensin II and endothelin-1 [13,16,17].

Further important effects of physical exercise are an improvement of venricular function and the cardiovascular risk factor profile, including beneficial effects on HDL cholesterol, blood pressure, and insulin sensitivity [3,23,30–34].

Clinical studies have shown that physical exercise in patients with CAD is associated with reduced clinical symptoms such as angina pectoris and a reduction in mortality [25,46**]. Therefore, exercise training is now an important guideline-recommended therapeutic component of cardiovascular therapy in patients with stable CAD [32,47,48*].

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


Physical exercise and coronary artery disease


23. The effect of exercise training in CAD-patients on invasively measured endothelium-dependant vasodilatation and the involvement of growth factors are analyzed in this study.


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