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Physical Activity in the Prevention and Treatment of Coronary Artery Disease

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In primary prevention, regular physical activity decreases the incidence of cardiovascular disease. At the endothelial level, this decreased incidence was attributed to higher expression and phosphorylation of the endothelial isoform of NO synthase, which results in a more effective radical scavenger system, a rejuvenation of the endothelium by circulating progenitor cells (CPCs), and growth of preexisting coronary vessels by angiogenesis.[1,2]

Endothelial dysfunction, which precedes coronary sclerosis by many years, is the first step of a vicious cycle culminating in overt atherosclerosis, significant coronary artery disease (CAD), plaque rupture, and, finally, myocardial infarction.[1,3] In addition to classic risk factors, such as hypertension, smoking, diabetes mellitus, and hypercholesterolemia, physical inactivity has been identified as an independent predictor for the development of CAD.[4,5] In contrast, regular physical activity seems to be effective in the primary prevention of CAD via the modulation of classic risk factors and maintenance of endothelial function.

Once symptomatic CAD has developed, regular exercise training is a potent strategy to increase the threshold of angina-free activity levels in stable disease conditions. Furthermore, exercise training seems to attenuate disease progression and improve event-free survival in the secondary prevention of CAD.[6,7] Mechanistically, numerous studies suggest that regular physical activity partially reverses endothelial alterations: it enhances the vascular production of NO, decreases the generation of reactive oxygen species (ROS; which would otherwise rapidly inactivate NO), rejuvenates the endothelium by activating endogenous progenitor cells, induces the CPC-mediated formation of new vessels by vasculogenesis, and promotes myocardial expression of vascular growth factors (which induce the remodeling of preexisting capillaries and arterioles).[1] An exercise training-induced regression of coronary stenosis and collateral growth has been discussed as a potential mechanism that also contributes to enhanced myocardial perfusion; however, a critical review of the literature raises reasonable doubts that the magnitude of these changes is large enough to explain their survival benefit in CAD.[3,8] Nevertheless, a limited number of recent studies indicate that regular physical activity has an inhibitory effect on platelet and leukocyte activation.[9]

This review will discuss the effects of regular physical activity on vasculature in the primary and secondary prevention of CAD in humans, with a special focus on the endothelium.

Physical Inactivity as a Risk Factor for CAD

In developed countries, cardiovascular diseases are the number one cause of death, despite the fact that primary prevention is easily accessible.[5,10–14] Physical inactivity has been identified as an important risk factor in the development of CAD in epidemiological studies, in which physical activity includes any leisure interest that is associated with an increase in energy expenditure.[1] In contrast, exercise training is understood as a planned, structured, repetitive, and goal-oriented activity. Independent of physical activity or training status, individual cardiorespiratory fitness, expressed as metabolic equivalents or peak oxygen uptake, can be measured with a maximum stress test (eg, on a treadmill or bicycle).

Approximately 40 years ago, Morris et al reported that middle-aged men who perform vigorous physical activity in their leisure time on at least 2 d/wk have a one third lower likelihood of developing CAD than their inactive peers.[4] The outstanding scientific work on physical activity and CAD by Morris et al[4] greatly stimulated further research in this field. In

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the Harvard Alumni Health Study, Sesso et al found an inverse linear relationship between activity and incident CAD, with the lowest relative risk in individuals who expended at least 1000 to 2000 kcal/wk during leisure-time activities.[12] These data are in agreement with a study by Haapanen et al,[15] who explored the CAD risk in volunteers with 3 different leisure-time activity levels: 0 to 1100, 1101 to 1900, and >1900 kcal of energy expenditure per week. The group with the lowest energy expenditure had a cardiovascular risk that was twice as high as the group with the highest activity level.[15] Sattelmair et al[5] pooled data from 33 studies investigating physical activity and primary prevention of CAD. They found a clear dose-response relationship between physical activity and the risk of CAD, with a risk reduction of 20% in men and women who expend ≈1100 kcal/wk. However, even people who engage in <550 kcal/wk in leisure-time physical activity still have a significantly reduced risk of CAD.[5] Recently, interesting findings came from the Aerobics Center Longitudinal Study, evaluating the impact of leisure-time running on mortality in a large cohort of 55 000 participants aged 18 to 100 years. Both all-cause and cardiovascular mortality were significantly reduced in runners compared with nonrunners by 30% and 45%, respectively. These benefits could be achieved even at low running distances, frequencies, speeds, and total amounts. The authors concluded that running for even 5 to 10 min/d or 50 min/wk at a low speed of <6 miles/h (<10 km/h) markedly reduces the risk of death.[13] However, in subgroups with the highest running intensity, the impact of running on mortality leveled off, whereas other trials even showed a loss of mortality reduction in healthy subjects and patients with CAD with high exercise intensities.[10,16–18] O′Keefe et al reviewed the pathophysiologic mechanisms of potential adverse cardiovascular effects from long-term excessive endurance exercise, such as ultramarathons, ironman distance triathlons, or long-distance bicycle races, which might diminish exercise-related mortality benefits.[19] Notwithstanding, the hypothesis of a reverse J-shaped association curve between exercise intensity and mortality is controversial.[14,20] It still needs to be explored if there is an optimum upper limit of exercise intensity for different exercise modalities, such as running, beyond which further exercise produces adverse health effects.

In addition to the intensity of physical activity, the level of cardiorespiratory fitness also appears to be of major importance, as suggested by Myers et al,[21] who evaluated physical fitness in 6000 men referred for treadmill exercise testing for clinical reasons and observed them for 6 years. An inverse linear relationship was elucidated between physical fitness and cardiovascular lethality. Each increase in exercise capacity by 1 metabolic equivalent was linked to a 12% decline in lethality and was identified to be a better predictor of mortality than all "classic" risk factors.[21] In a larger study of men and women, Lee et al confirmed the association between cardiorespiratory fitness and all-cause mortality, which was independent of self-reported physical activity during leisure time.[22]

However, a high level of cardiovascular fitness can be achieved by structured exercise training.[13,23] These data are supported by the population-based Copenhagen City Heart Study. Schnohr et al[24] demonstrated that exercise intensity, not the duration of leisure-time activity, is associated with a reduction of all-cause and coronary heart disease mortality. Cycling is a widespread activity in Copenhagen for recreation and commuting to work, and healthy individuals who reported that they cycled fast had an increase in life expectancy of 4 to 5 years compared with those who cycled slowly. In contrast, the total time spent cycling did not predict mortality at all.[24]

Khera et al[25] evaluated genetic risk by a polygenic risk score of up to 50 single-nucleotide polymorphisms that had achieved genome-wide significance for associations with CAD in 4 studies involving >55 000 participants to determine to what extent increased genetic risk of CAD can be offset by a healthy lifestyle. In addition, adherence to a healthy lifestyle consisting of 4 factors (no current smoking, no obesity, healthy diet, and regular physical activity) was registered. A favorable lifestyle was associated with an ≈50% lower relative risk of CAD in all 3 groups of low, intermediate, and high genetic risk.[25] The impact of physical activity in this context is underscored by the finding that even low-level physical activity, such as low-dose running or commuting to work by bicycle, is associated with a lower incidence of obesity, arterial hypertension, dyslipidemia, and diabetes mellitus[13,26] (Figure 1).

It has been discussed that the link between physical activity and mortality arises from genetic selection, because the same genes that contribute to an active lifestyle might also increase longevity. However, this hypothesis could be rebutted by a large Swedish twin pair study with 5200 monozygotic twin pairs that documented a 20% reduction in all-cause mortality and a 30% reduction in CAD-related mortality in twins with high physical activity levels compared with their physically inactive genetically identical sibling.[27]

Adaptation of Coronary Circulation to Exercise Training in the Healthy Heart

An increase in cardiac output with physical exercise and increased skeletal muscle perfusion results in augmented myocardial oxygen demand. Because myocardial oxygen extraction from the blood is already ≈70% to 80% at resting conditions, the maintenance of myocardial oxygen and nutrient supply predominantly depends on coronary blood flow.[28] It has been shown that regular exercise training induces functional and morphologic changes of the vascular

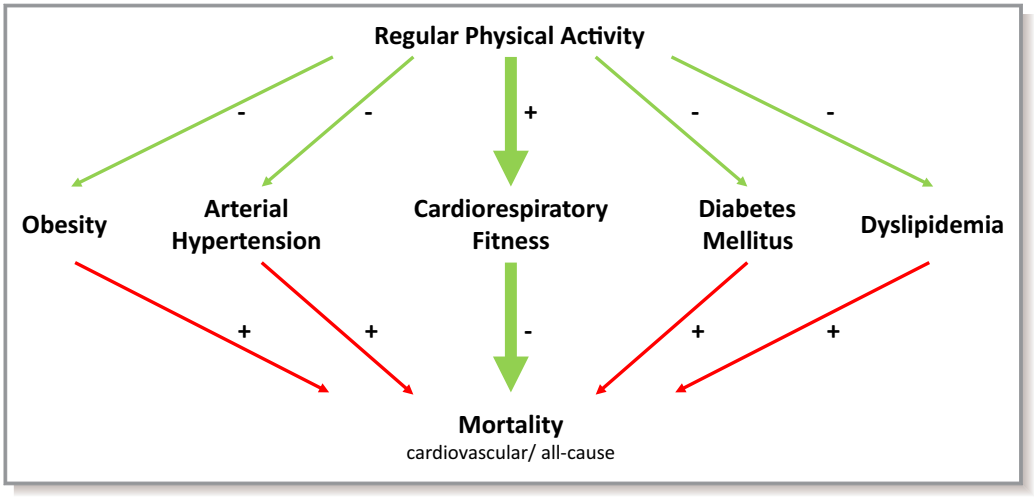

Figure 1. Impact of regular physical activity on mortality in primary prevention. Low cardiorespiratory fitness, obesity, arterial hypertension, diabetes mellitus, and dyslipidemia contribute to increased mortality (+). Regular physical activity improves fitness (+) and counteracts the development of risk factors (−).

tree associated with reduced coronary vascular resistance. These changes allow augmented blood flow during exercise conditions in the presence of normal wall shear stress and blood flow velocity.[28,29]

Numerous studies have shown that NO derived from the endothelial isoform of the NO synthase (eNOS) is a prerequisite of vasomotion in conduit vessels.[30] An increase in shear stress (eg, during physical activity) has been proved to enhance eNOS mRNA and protein expression and promote phosphorylation of the serine 1177 residue of the enzyme, thereby boosting vascular NO production.[31–34] However, animal studies suggest that after a few months of exercise training, eNOS expression levels reduce to the preexercise state.[35] This decline is explained by the fact that the normalization of shear stress at an early adaptive state requires a decline in vascular tone and, hence, vasodilatation; however, this change does not occur at a later stage when the vessels have already grown.[1]

Nevertheless, the bioavailability of NO depends on not only eNOS-derived production but also its inactivation by ROS[1,36–38] (Figure 2). Superoxide dismutase (SOD) is important in this regard, because it scavenges ROS that would otherwise inactivate NO within the endothelium.[39,40] Studies have shown that SOD activity increases in response to shear stress, which was associated with an increase in NO bioavailability and, hence, vasodilatation.[39] In addition, there seems to be a feed-forward mechanism between endothelial extracellular SOD and eNOS, because NO was found to enhance extracellular SOD expression.[39]

In contrast, the sensitivity of vascular smooth muscle for sensing exogenous NO does not seem to be altered by exercise training, suggesting that the early phase of vascular remodeling does not primarily involve vascular smooth muscle.[33] NO also appears to be of minor importance in regard to the vasorelaxation of small arterioles with diameters <100 μm, because these vessels are primarily regulated by myogenic factors.[41,42]

Further remodeling in response to long-term exercise training involves the expression of cytokines and growth factors (eg, vascular endothelial growth factor A, transforming growth factor ß, platelet-derived growth factor, fibroblast growth factors 1 and 2, and insulin-like growth factor), which leads to the proliferation and growth of endothelial cells and smooth muscle cells and ultimately drives the arteriolarization of capillaries[2,43–46] (Figure 2). In the trained heart, the consequence is unaltered capillary density, but there is a larger and more profound arterial supply.[2,47] However, the growth of vessels by angiogenesis is not restricted to capillaries; it is also evident at the level of arterioles (diameter, <30 μm), coronary resistance vessels (diameter, <300 μm), and large proximal conduit vessels.[1,2,48]

In the past, it was thought that growth of the coronary vasculature occurs secondary to the division of preexisting smooth muscle and endothelial cells. The discovery of bone marrow–derived CPC contributing to new vessels in a process known as vasculogenesis made the picture of exercise-induced adaptations even more complex.[49–51] The activation of matrix metalloproteinases 2 and 9 by NO enhances the mobility of CPCs in the bone marrow, resulting in the liberation of these cells into the circulation.[42,52,53] Furthermore, the number and functional capacity of circulating CPCs seem to depend on NO bioavailibility.[53–55] In response to exercise training, CPCs repaired damaged endothelium, enhanced neoangiogenesis, and reduced neointima formation after vascular injury.[1,55] However, their contribution to vascular homeostasis in

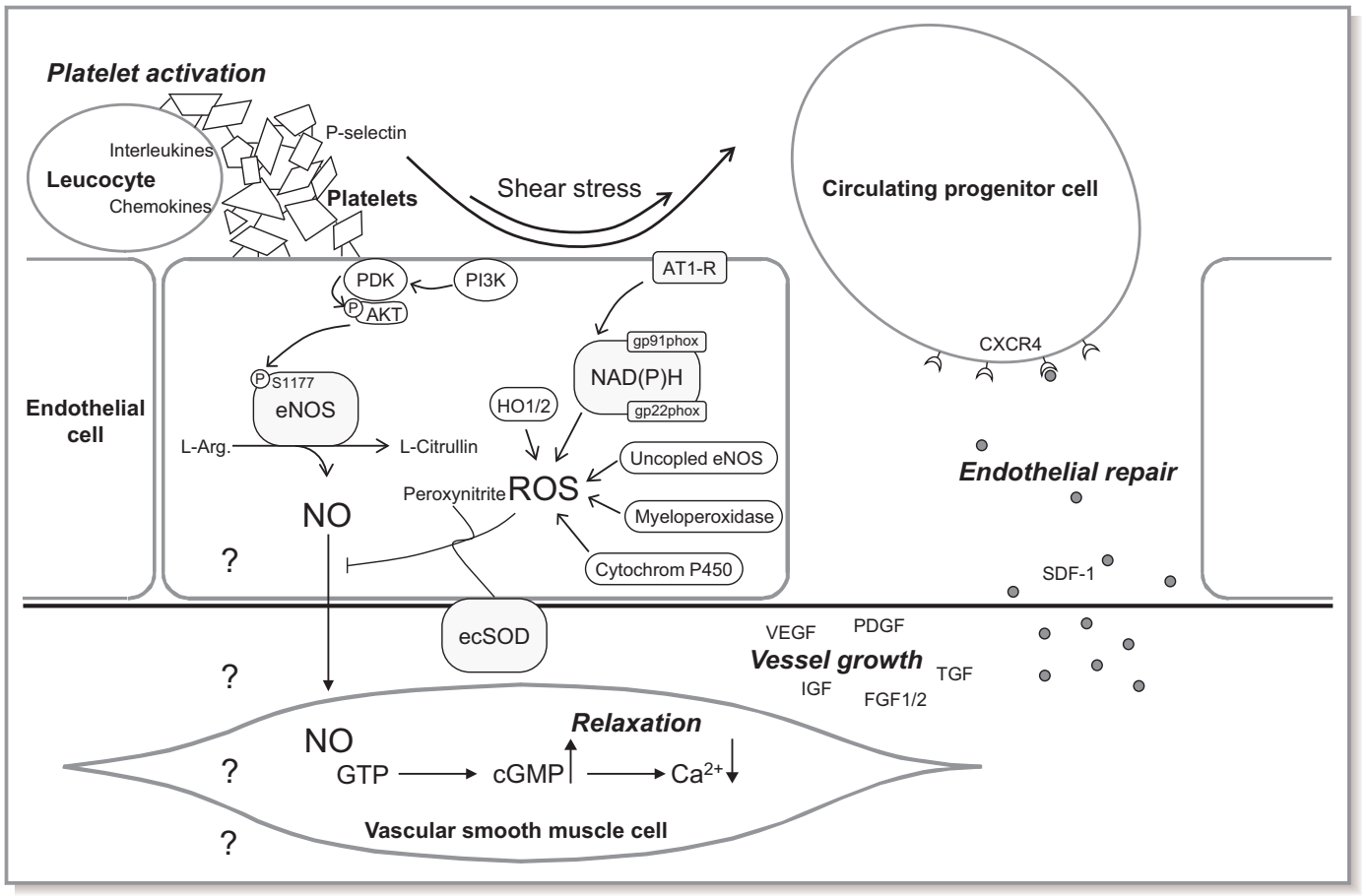

Figure 2. Endothelial function and repair. Endothelial NO synthase (eNOS) produces NO via conversion of L-arginine (L-Arg.) to L-citrulline in the presence of tetrahydrobiopterin (BH4) and calcium-calmodulin. Shear stress activates eNOS activity by phosphorylation at serine 1177 (S1177). This process is mediated by phosphatidylinositol 3-kinase (PI3K), phosphoinositide-dependent kinase (PDK), and protein kinase B (AKT). NO easily diffuses through plasma membranes. In smooth muscle cells, NO activates guanylate cyclase, which, in turn, converts GTP to cGMP. A reduction of the intracellular calcium concentration (Ca^{2+}) leads to hyperpolarization of the cell membrane and, consequently, smooth muscle relaxation. NO is broken down in the presence of reactive oxygen species (ROS), mainly superoxide, generating peroxynitrite. Peroxynitrite, in turn, oxidates BH4 and promotes eNOS uncoupling, resulting in eNOS-derived superoxide production. Additional sources of superoxide are heme oxygenase (HO1/2), myeloperoxidase, cytochrome P450, the mitochondrial electron transport chain, and nicotinamide-adenine dinucleotide [phosphate], reduced form (NAD[P]H) oxidase, which is activated by tumor necrosis factor α and angiotensin II via the angiotensin II receptor type 1 (AT1-R). Extracellular superoxide dismutase (ecSOD) scavenges superoxide. Vessel growth and arteriolarization of capillaries are mediated by vascular endothelial growth factor (VEGF), transforming growth factor ß (TGF), platelet-derived growth factor (PDGF), fibroblast growth factors 1 and 2 (FGFs 1/2), and insulin-like growth factor (IGF). Circulating progenitor cells (CPCs), mobilized from the bone marrow, contribute to repair of the damaged endothelium and the formation of new vascular structures. Homing of CPCs is mediated by the binding of CXC-chemokine receptor type 4 (CXCR4) to stromal cell–derived factor-1 (SDF-1), which is secreted at the site of injury. The adhesion molecule P-selectin mediates the rolling of blood cells on the surface of the endothelium and initiates the activation of platelets and adhesion of leukocytes at the site of injury, allowing them to transmigrate the endothelial layer and perpetuate an inflammatory atherosclerotic process via the secretion of interleukins and chemokines. Question marks indicate that there are several other endothelial-derived relaxing and constricting factors that affect different ion channels, transporters, and second messengers. Further alterations within the vascular smooth muscle cell and perivascular adipose tissue are involved in the regulation of the vascular tone, but they are not in the focus herein.

healthy humans is poorly understood and requires further studies.[56]

Vascular Alterations in CAD

In CAD, the balance between NO production and NO inactivation is disrupted, thereby causing endothelial dysfunction.[36,57] In addition to reduced bioavailability of the NO precursor tetrahydrobiopterin, blunted eNOS expression and phosphorylation at the serine 1177 residue and eNOS inhibition by asymmetric dimethylarginine have been elucidated as the reasons for blunted coronary NO production in CAD.[58] Moreover, NO is rapidly inactivated by ROS produced by a variety of enzymes (eg, uncoupled eNOS, nicotinamide-adenine dinucleotide [phosphate], reduced form, oxidase, cytochrome P450, myeloperoxidase, heme oxygenase,

glucose oxidase, cyclooxygenase, lipoxygenase, and enzymes of the respiratory chain).[3,37]

An elevated apoptotic rate of mature vascular endothelial cells in conjunction with an impaired regenerative capacity of CPC might further aggravate vascular alterations.[55,59,60] Current knowledge of endothelial dysfunction in vascular disease is discussed in detail by Vanhoutte et al.[61]

Recent research identified high-density lipoprotein (HDL) as an important player in the homeostasis of endothelial function because of reverse cholesterol transport on one hand and anti-inflammatory and antioxidative effects, including eNOS activation and NO production, on the other hand. As reviewed extensively by März et al, HDL confers protection from damage, necrosis, and the apoptosis of endothelial cells.[62] However, HDL from patients with CAD, hypertension, diabetes mellitus, chronic kidney dysfunction, and obesity (independent of its concentration) turns dysfunctional and shows diminished cholesterol efflux capacity and blunted capability of eNOS activation.[62,63]

Additional vascular alterations with an impact on vascular tone and function occur within coronary vascular smooth muscle cells (eg, intracellular calcium handling) and within perivascular adipose tissue. These topics are reviewed elsewhere.[64,65]

Physical Activity as a Key Element of Secondary Prevention in CAD

Historically, numerous patients were immobilized after acute myocardial infarction for weeks, despite compelling evidence of the protective effects of regular physical activity in the primary prevention of cardiovascular disease.[3] This recommendation was based on the assumption that short-term exercise-induced increases in blood pressure, and consequently wall stress, might carry the risk of rupture in the infarcted wall or induce cardiac decompensation or life-threatening arrhythmias. However, this suggested immobilization was associated with further reductions in both quality of life and exercise capacity.

Percutaneous coronary intervention (PCI) is still considered the treatment of choice in clinical practice in patients with stable CAD, despite the fact that clear data showing a survival benefit in those treated with PCI are missing.[66] Thus, current guidelines do not recommend PCI in patients with CAD without proof of myocardial ischemia (>10% of the myocardium) or proof of hemodynamic relevance of the stenosis detected by fractional flow reserve.[67] In contrast, physical activity performed on a regular basis has been proved to blunt symptoms, improve myocardial perfusion, and, most important, reduce mortality in patients with CAD/myocardial infarction. A meta-analysis in 8940 patients, who had either experienced myocardial infarction, undergone coronary revascularization, complained about angina pectoris, or had CAD documented by angiography, from 48 studies revealed a decline in total and cardiovascular mortality by 20% and 26%, respectively, as a result of exercise training intervention.[6] On the basis of these findings, Hambrecht et al[68] conducted a trial comparing PCI, including stent implantation with regular physical exercise training, in patients with CAD who were already receiving optimal medical therapy. Patients with significant stenosis of the left main or proximal left anterior descending artery were excluded.[68] The aim of the study was to determine the effects of these interventions on symptoms, angina-free exercise capacity, myocardial perfusion, cost, and the occurrence of a combined clinical end point of death from any cause, stroke, coronary artery bypass grafting, angioplasty, acute myocardial infarction, or worsening of angina leading to hospitalization. A total of 102 patients underwent randomization to PCI or exercise training (at least 20 minutes daily) for 12 months. Patients in the exercise training group had an 18% higher event-free survival rate at 12 months' follow-up than those with PCI, which was driven by a reduction in repeated revascularizations, and these patients were characterized by an increase in peak oxygen uptake of 16%. In contrast, the PCI group did not experience enhanced exercise capacity despite the fact that symptom relief occurred much earlier than in the exercise training group, suggesting that relief of symptoms was not associated with increased physical activity in these patients.[68] Even if PCI is the first line of therapy, patients still benefit from an exercise training program after the coronary intervention. The ETICA (Exercise Training Intervention After Coronary Angioplasty) trial clearly revealed an increase in peak oxygen uptake of 26%, an improvement in quality of life of 27%, and a reduction in cardiac events of 20%, including a reduction in myocardial infarctions and a lower number of hospital admissions, in patients who underwent a physical exercise training program after successful PCI compared with those who remained sedentary.[69] However, the previously mentioned meta-analysis did not find a reduced incidence of nonfatal myocardial infarctions with exercise training.[6]

But, which mechanisms might account for the beneficial effects of exercise training on angina symptoms, quality of life, and mortality at the vascular level?

Adaptation of the Heart and the Vasculature in Response to Exercise Training in Patients With CAD

Resting heart rate and the heart rate at each level of physical activity are reduced in healthy athletes and in patients with

hypertension in response to exercise training compared with untrained controls.[2,70] This effect could also be seen in some (but not all) studies evaluating the effects of exercise training in patients with CAD.[68,69,71,72] Modulation of the autonomic nervous system with diminished sympathetic tone, increased vagal activity, and augmented baroreflex sensitivity in response to exercise training was identified as an underlying mechanism in animals and patients.[73,74] Restoration of autonomic balance in combination with improved peripheral endothelial function and decreased blood pressure reduces cardiac afterload and improves left ventricular diastolic function.[42,75,76] Exercise training was shown to induce reverse cardiac remodeling in patients with heart failure with reduced left ventricular ejection fraction.[75,77] The impact of exercise training on intracellular calcium handling and myocardial contractility was extensively studied by Kemi and Wisloff and has been reviewed elsewhere.[78] Nonetheless, a significant increase in cardiac output as a result of eccentric myocardial hypertrophy and increased myocardial contractility, which is seen in healthy athletes, could not be detected in patients with CAD in the absence of heart failure.[2,69,76,79] Moreover, bradycardia is associated with reduced myocardial oxygen demand and also enables enhanced diastolic coronary blood flow because the time of systolic compression of intramural coronary arteries is shortened. Therefore, a given level of workload might produce less ischemia in patients with CAD in response to exercise training.[47] However, an improvement in myocardial perfusion is not restricted to a reduction in heart rate.[69] The following mechanisms have been proposed to contribute to enhanced myocardial perfusion in response to exercise training: (1) partial correction of endothelial dysfunction, (2) collateral formation, (3) regression of coronary stenosis, (4) vasculogenesis, and (5) blunted platelet activation.

Mechanism 1: Partial Correction of Endothelial Dysfunction

The impact of exercise training on coronary endothelial functions of conduit and resistance vessels in patients with CAD was thoroughly investigated by Hambrecht and coworkers some years ago.[57] Those patients were randomly assigned to 4 weeks of in-hospital bicycle ergometer training or a control group that continued a sedentary lifestyle. At baseline and after 4 weeks, endothelium-dependent vasomotion of conduit vessels in response to acetylcholine was assessed, and the function of resistance vessels in the microcirculation was evaluated in response to adenosine. Pathologic vasoconstriction of epicardial vessels in response to 7.2 μg of acetylcholine was reduced by 54% after 4 weeks of exercise training. This result was associated with an augmentation in coronary blood flow from 78% at baseline to 142% at 4 weeks, whereas no changes were observed in the control group during the study period. In addition, coronary flow reserve improved from 2.8 at baseline to 3.6 at 4 weeks in the training group, which is indicative of enhanced sensitivity of the microcirculation in response to adenosine and an increase in the total cross-sectional area of the microvasculature, through either vascular growth or the formation of new blood vessels.[57]

On a molecular level, animal studies have shown that in the early stages of CAD, endothelial-dependent vasodilatation of coronary arterioles is at least partially diminished as a consequence of reduced eNOS protein levels. Both eNOS protein levels and endothelial function could be restored with exercise training.[80] However, in humans, molecular adaptations of the coronary circulation in CAD are poorly understood because of difficulties in tissue harvesting before and after exercise training. Some details have been provided by a study from Hambrecht et al that assessed the molecular adaptation of the left internal mammary artery (LIMA) in response to exercise training in patients with severe CAD undergoing elective coronary artery bypass grafting.[32] Again, these patients were randomized to 4 weeks of in-hospital rowing machine and bicycle ergometer training or a physically inactive control group. At baseline and after 4 weeks, LIMA endothelial function in response to acetylcholine and adenosine was assessed invasively. A piece of the LIMA, not required for coronary revascularization, was obtained during coronary artery bypass grafting for further molecular analysis. Exercise training enhanced the average peak flow velocity of the LIMA by 57% compared with the control group. This result was accompanied by 2-fold higher eNOS phosphorylation at the serine 1177 residue and a 4-fold higher eNOS expression in the LIMA of patients in the training group. In contrast, the expression of angiotensin II type 1 receptor, which drives ROS production, and consequently NO degradation, through activation of the nicotinamide-adenine dinucleotide [phosphate], reduced form, oxidase, was significantly reduced in the vasculature of patients who underwent 4 weeks of exercise training. This result was paralleled by lower expression of the nicotinamide-adenine dinucleotide [phosphate], reduced form, subunits pg91phox and p22phox, lower nicotinamide-adenine dinucleotide [phosphate], reduced form, oxidase activity, and hence reduced vascular ROS production. The fact that chest wall muscles were not directly trained in this study suggests that exercise training exerts circulation-wide effects rather than only local adaptations in the blood vessels supplying trained muscles. Hambrecht's milestone studies on human endothelial function combining exercise training intervention, in vivo measurements, and molecular analysis stimulated a vast amount of work on the mechanism of improved endothelial function.[32,36,57] The

impact of exercise training on the multistep activation of eNOS on the one hand and reduced ROS production on the other hand was recently reviewed by Adams et al.[81]

Dysfunctional HDL cholesterol in patients with CAD contributes to impaired NO production and endothelial dysfunction. Two studies in obese adolescents and patients with heart failure clearly demonstrated that regular physical exercise training restores reverse cholesterol transport, HDL-mediated eNOS phosphorylation, and NO production in endothelial cells, which correlated to improved endothelial function.[82,83] However, the composition and function of HDL particles in health and disease are complex and need to be further evaluated.[62]

The importance of NO for vascular remodeling has been shown in eNOS knockout animals and long-term NOS inhibition with N-methylarginine.[84,85] In addition, the beneficial effects of exercise training on remodeling, reendothelialization, and neointimal hyperplasia in response to endothelial injury have been shown to be mainly dependent on NO availability in a rat model of long-term eNOS inhibition. As previously mentioned, the liberation of CPCs from bone marrow in response to exercise was shown to be inhibited in eNOS knockout mice and by N-methylarginine infusion in humans.[53,55,86] The CPC number correlated with endothelial function in these subjects. Nevertheless, the causal role of NO in exercise-related correction of coronary endothelial function is still unproved and should be addressed in animal studies.

Although NO is by far the best-characterized endothelium-derived relaxing factor, others, such as prostacyclin and hydrogen peroxide, and endothelium-derived constricting factors (eg, prostanoids and endothelin-1) contribute to endothelial-dependent vasomotion.[61] Unfortunately, their impact on endothelial function, the development of CAD, and especially the role of exercise training on their regulation is less studied and needs further investigation.

In summary, these data are consistent with the hypothesis that exercise training restores the balance between NO production and inactivation. This balance results in enhanced NO bioavailability, which is associated with a partial restoration of endothelial function[36] (Figure 2).

Mechanism 2: Formation of Collaterals

Although Eckstein, a cutting-edge scientist, could clearly document the formation of coronary collaterals in response to exercise training in animal experiments in 1957, clear data in humans are missing to date.[87,88] Belardinelli and coworkers were able to angiographically show enhanced collateral formation in a subset of patients with ischemic cardiomyopathy after 8 weeks of exercise training.[89] However, despite reduced myocardial ischemia in thallium scintigraphy, the Heidelberg Regression Study failed to document any collateral growth using angiography in patients with stenotic CAD even after 1 year of intense exercise training.[90] An increase in collateral formation could be shown in only patients in whom the progression of atherosclerotic lesions was detected, generating the hypothesis that myocardial ischemia is a necessary force driving collateral formation. Angiography may be too insensitive to visualize the collaterals, or the collaterals may only be recruited at peak exercise (causing myocardial hypoxia); it is also possible that differences in the patient populations in the previously mentioned studies may account for these disparate effects.

Seiler and coworkers developed the measurement of functional collateral circulation by coronary catheterization with a pressure wire during interruption of antegrade flow of the target vessel by balloon occlusion to overcome the low sensitivity of angiography.[91] The mean coronary pressure (measured beyond the occlusion and corrected for central venous pressure) represents the perfusion pressure related to collateral back flow and is expressed as the collateral flow index (CFI) as a ratio to aortic pressure. The same study group detected an increase in collateral flow in patients with CAD after 3 months of exercise training in a small nonrandomized trial. Interestingly, an increase in the CFI was found in coronaries that were treated with PCI and in coronaries without flow-limiting stenosis at baseline, challenging the hypothesis that hypoxia is a prerequisite of collateral flow, which, in turn, severely decreases with reconstitution of antegrade flow.[92] Recently, Mobius-Winkler et al[93] demonstrated in a randomized proof-of-concept study that 4 weeks of moderate- and high-intensity exercise training in patients with significant coronary stenosis (fractional flow reserve, $\leq$0.75) increased CFI by 39% and 41% compared with controls. This result was accompanied by a clinically relevant increase in exercise capacity and angina threshold in both intervention groups. However, coronary collateralization could not be visualized on the angiogram.[93] Although a weak correlation between the change in CFI and angina threshold was evident, a causal relationship must be challenged. The absolute increase in coronary occlusion pressure as a measure of collateral flow was as low as 2 to 5 mm Hg, on average, after exercise training. In addition, antegrade coronary flow, despite documented high-grade stenosis, generated a poststenotic pressure of at least 86 mm Hg during adenosine hyperemia at baseline measurement. This result was much higher than the previously documented upper threshold of 30 to 35 mm Hg coronary perfusion pressure that was associated with myocardial ischemia and sufficient stimulation of collateral growth. Therefore, it seems unlikely that the small change in collateral flow with exercise training is responsible for clinical improvement.[8] Taken together,

these minor changes in CFI with exercise training do not support the idea of exercise-induced growth of epicardial collateral conductance vessels, which redirect blood flow to ischemic myocardium. Moreover, improved endothelial function and, hence, reduced resistance of collateral supply arteries might cause exercise-related perfusion of preexisting collateral channels and changes in CFI (Figure 3). This concept is supported by the finding of an increase in CFI in a completely healthy volunteer before, during, and after training for an alpine ultramarathon race; myocardial ischemia can be ruled out as a driving force for collateralization in this volunteer.[94] In this case, training-related arteriogenesis in combination with high functional capacity of resistance vessels might explain the increase in retrograde capillary flow.

Because of a lack of tissue specimens, the role of exercise training on morphological formation of collaterals beyond functional coronary/collateral responsiveness has not been fully resolved. Sixty years after Eckstein's important work in dogs, future large-animal studies combining detailed hemodynamic assessment of coronary flow in vivo with in-depth tissue analysis are essential to resolving the issue of exercise-induced collateralization.

Mechanism 3: Regression of Coronary Stenosis

Thus far, 3 randomized clinical trials have assessed the impact of exercise training on the regression of coronary stenosis angiographically.

In the Lifestyle Heart Trial, a multifactorial intervention lasting 1 year that included 3 hours of exercise training per week induced a 3.1% regression in coronary stenosis that was associated with a decline in cardiovascular event rates. In contrast, the physically inactive control group was characterized by an 11.8% progression of coronary stenosis. Although 195 coronary artery lesions were analyzed in this trial by quantitative coronary angiography, this study was limited in terms of the few patients evaluated (intervention group: n=22; control group: n=19); one patient died during the study period, and several angiograms were lost.[95] However, the Stanford Coronary Risk Intervention Project, a multifactorial approach of low-fat diet, smoking cessation, stress management training, and moderate exercise training, reduced cardiovascular event rates in 145 patients of the intervention group by 49% within 4 years of follow-up. It also led to a slowed progression of atherosclerotic coronary narrowing, with a reduction in coronary lumen diameter by 0.024 mm/y in the target area, whereas a decline of 0.045 mm was evident in the control group (n=155).[96] In the Heidelberg Regression Study, a regression of coronary lesions after 1 year was only evident in patients expending >9228 kJ/wk during exercise. Finally, a halting of CAD progression was evident in 90% of patients in the training group, with a mean increase in the minimal stenosis diameter of 0.02 mm in the training group compared with −0.15-mm diameter in the target lesion in the control group.[72]

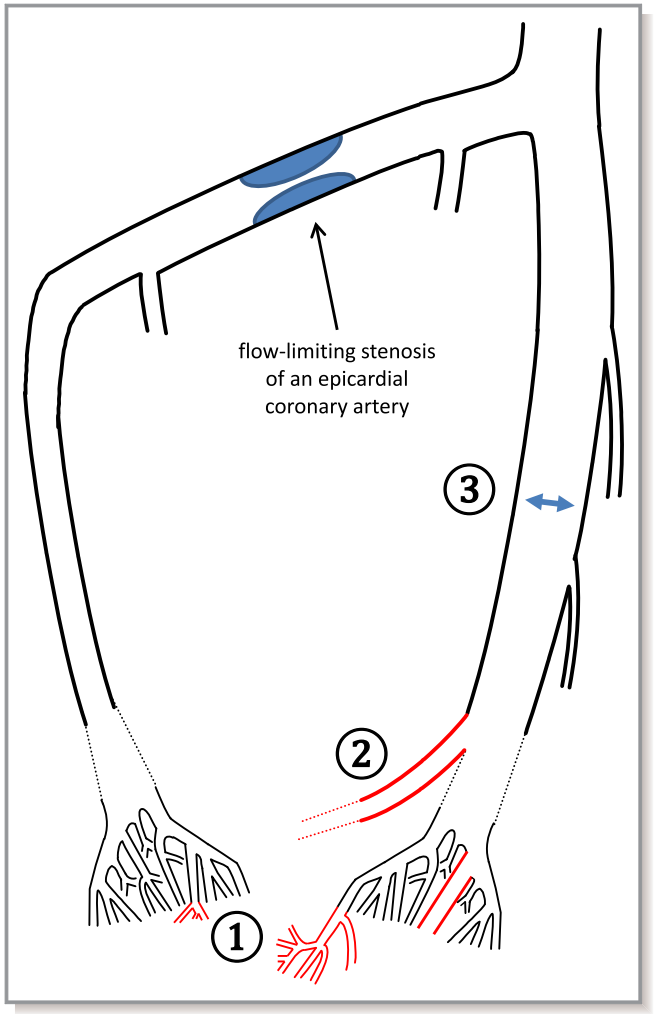

Figure 3. Mechanisms of improved collateral blood flow. Improvement of collateral blood flow in occlusive coronary artery disease in response to exercise training might be a consequence of the following: (1) angiogenesis, which is the sprouting of endothelial cells from preexisting capillaries and the formation of a capillary network; (2) the arteriolarization of capillaries and microvessels; or (3) improved vasomotor function of conduit arteries and resistance vessels of the collateral supply arteries.

In recent years, the more accurate technique of intravascular ultrasound has been used to test the hypothesis of exercise-related coronary plaque regression. However, several limitations hamper the significance of these studies.

Sixt et al[97] invasively evaluated the impact of exercise training with the combination of a hypocaloric diet and optimized medical treatment on coronary endothelial function and intramural plaque burden of nonsignificant atherosclerotic lesions in patients with CAD with type 2 diabetes

mellitus. Glucose metabolism and coronary endothelial function improved after 6 months of intervention, whereas plaque burden remained unchanged.[97] However, the sample size (11 versus 12 patients) was small. Atherosclerotic plaque burden was only evaluated within the target vessel for endothelial function testing with insignificant stenosis (<25% lumen narrowing), although all patients had significant CAD with at least 1 coronary stenosis of ≥50% in a different coronary artery. Additional evaluation of these significant lesions would have strengthened this trial. Tani et al[98] reported as much as a 12.9% decrease in coronary plaque volume in a nonrandomized group of 84 Japanese patients with CAD at 6 months after a combination of statin therapy and lifestyle modification that consisted of a 1-hour lecture at study enrollment on dietary counseling, smoking cessation, weight management, and physical activity. Lifestyle modification was assessed by a questionnaire with special focus on daily exercise, weight management, and smoking status. Multivariate regression analysis revealed that lifestyle modification independently predicted plaque regression, leading the authors to conclude that increased physical activity may play an important role.[98] However, the change in physical activity over time was not reported and not correlated with plaque regression, independent of other lifestyle factors. Furthermore, cardiopulmonary exercise testing to document an exercise-related change in fitness over time was not performed. Therefore, this study is at most hypothesis generating. A small randomized trial from Norway tested the hypothesis that aerobic high-intensity interval training (HIT) more effectively induced a regression of intravascular ultrasound–determined plaque burden compared with moderate continuous training (MCT). The induction of higher endothelial shear stress during repeated training intervals at submaximal intensity might substantiate the advantage of this training mode. After 12 weeks of exercise training, the change in plaque burden did not differ between groups. A regression of stenosis could not be shown in any group. Even if all patients were analyzed irrespective of group assignment, the 10.7% decline in plaque burden over time was not statistically significant (P=0.06).[99] Because of a missing control group, this trend might have been confounded by observational bias or a change in medical therapy, especially in statin treatment. Given that morphologic alterations in CAD are more difficult to change than functional alterations (eg, of the endothelium), 12 weeks of exercise training might be too short to expect any impact on the structure of the vessel wall. In a longer-term study by Nytroen and coworkers,[100] HIT was also used to evaluate the impact of 1 year of exercise training on atheroma volume in a cohort of heart transplant recipients. Intravascular ultrasound analysis revealed a significantly smaller mean increase in atheroma volume of 0.9% with HIT compared with 2.5% in the control group.[100] Although circulating inflammatory markers (C-reactive protein and interleukins 6, 8, and 10) did not change with HIT, immunologic mechanisms of slowed atherosclerotic disease progression in this patient group cannot be ruled out.

Although conflicting data exist, the degree of coronary stenosis regression seems to be almost negligible and most likely does not explain the massive improvement in myocardial perfusion in response to exercise training in patients with CAD.

Mechanism 4: Vasculogenesis

In rodents and pigs, the transplantation of CPC after experimental myocardial infarction was associated with increased capillarization of the infarct and border zone and improved myocardial perfusion and function.[101,102] In humans, Sandri and coworkers[103] were able to show that exercise training for 4 weeks improves the expression of homing factor CXCR4 on the surface of CPCs, which mediates the incorporation of CPCs into vascular structures. Furthermore, exercise training enhances functional CPC capacity in patients with CAD, which is essential for the formation of new vascular structures through vasculogenesis.[103] However, the authors failed to determine any effect of the exercise training intervention on the gross number of CPCs in this study cohort. In contrast, Laufs and coworkers elucidated an exercise training–induced increase in CPC number in humans with CAD and in mice.[55] These findings are consistent with the hypothesis that exercise training might rejuvenate the damaged vascular tree through CPC mobilization and activation, thereby leading to an enhancement of myocardial perfusion. Exercise training in patients with advanced heart failure was shown to increase the number and functional capacity of CPCs, which was associated with improved endothelial function and skeletal muscle capillary density.[104] However, to date, clinical studies assessing the impact of exercise training on CPC-mediated alterations in myocardial vasculogenesis and perfusion are lacking because of ethical concerns about myocardial tissue harvesting. Nevertheless, further studies are necessary to address this issue in detail.

Mechanism 5: Platelet Activation

Vascular inflammation involving the activation of platelets, leukocytes, and endothelial cells is an early feature of the atherosclerotic disease process. High levels of shear stress promote the tightening of initially loose contacts between platelets and the endothelium by the adhesion molecule P-selectin, culminating in platelet activation. The platelets release inflammatory and mitogenic molecules (eg, interleukins and chemokines) that facilitate the adhesion of leukocytes and monocytes to the endothelium. After

transmigration of the endothelial layer, these cells differentiate into foam cells and perpetuate the inflammatory process within atherosclerotic plaques.[105] A short-term bout of intense physical activity in untrained healthy subjects is known to increase platelet activity and reactivity and number of platelet-leukocyte aggregates.[106] In patients with CAD, even low levels of physical exercise have been shown to transiently increase platelet aggregability, which might result in coronary occlusion in case of plaque rupture.[107] Scalone et al demonstrated that a short episode of myocardial ischemia in symptomatic patients with CAD (induced by an exercise bout at low work load and stopped at 1-mm ST-segment depression) protected these patients from an increase in platelet reactivity in a subsequent maximum exercise stress test.[108] Remote upper arm ischemic conditioning resulted in comparable protective effects on platelet reactivity.[109] In contrast to short-term exercise bouts, regular physical activity reduces platelet reactivity and the number of platelet-leukocyte conjugates in healthy subjects and in those with CAD, which is consistent with the vasoprotective and antiatherosclerotic effect of exercise training interventions.[110–112] However, additional randomized controlled trials are warranted to determine the clinical impact of these findings.

Exercise Prescription

International guidelines, such as the European guidelines on cardiovascular disease prevention in clinical practice (published in 2016), clearly recommend regular exercise training as a cornerstone of CAD prevention and treatment.[113] In general, >150 minutes of endurance exercise training per week at moderate to vigorous intensity, with a total energy expenditure of 1000 to 2000 kcal or >75 minutes at vigorous intensity, ideally spread over 3 to 5 days, is recommended. Exercise training should be started at a low(er) intensity and gradually increased over time. Endurance exercise should be complemented by resistance exercise training 2 times per week at moderate intensity.[113] With evidence in mind that cardiorespiratory fitness is a better predictor of mortality than physical activity, it was thought that a certain amount of exercise is necessary to increase fitness and thereby achieve any beneficial health effect, with exercise intensity having higher importance than duration.[23,24] However, the recommended thresholds of minimum physical activity cannot be reached by many subjects with mobility limitations. Frith and Loprinzi demonstrated that the duration of light-intensity physical activity in these patients is still inversely associated with all-cause mortality, with a reduction of 14% for every 60 minutes of activity per day.[114] Warburton and Bredin[14] recently demonstrated, in an outstanding review of 16 systematic reviews and/or meta-analyses, that the relationship between physical activity and health benefits is curvilinear, with the greatest benefits at minor volumes of physical activity and attenuation at high volumes of physical activity. They did not find evidence for a certain threshold of physical activity for the occurrence of any health benefit. The authors noted that the threshold-based messaging that is used in many guidelines, with a recommendation of >150 minutes of physical activity, is not based on evidence and might even represent a barrier to healthy living for people who do not attempt to reach this threshold. However, these people are the ones who particularly stand to benefit greatly from routine physical activity when moving from an inactive to a more active state. Notwithstanding, this review again supports the finding of greater health benefits with higher physical activity volume and fitness level.

Although bouts of (sub)maximal training intensity are regularly used in healthy athletes to optimize training results, high training intensity was avoided in patients for several years because of safety concerns (eg, orthopedic or cardiovascular complications), such as rhythm disturbances, myocardial infarction, and acute heart failure. Nevertheless, Moholdt et al found minor positive impact of higher exercise intensity beyond exercise volume on mortality in epidemiologic data from patients with CAD.[115] In recent years, the treatment effects of HIT, which is composed of low-level exercise with short bouts of high-intensity exercise at 90% to 95% of peak heart rate, were tested prospectively in different patient populations. Contrary to the promising results of smaller trials, the SAINTEX-CAD (Study on Aerobic Interval Exercise Training in CAD Patients) failed to show an additional improvement in peak oxygen uptake and endothelial function with HIT compared with MCT in patients with CAD.[116] In patients with heart failure, HIT was not associated with additional reverse left ventricular remodeling or peak oxygen uptake compared with MCT in the SMARTEX-HF (Study of Myocardial Recovery After Exercise Training in Heart Failure) trial.[77] Both multicenter trials demonstrated that HIT is hardly feasible because many patients did not reach target heart rates during high-intensity intervals despite high adherence to supervised training. A recent meta-analysis of studies comparing HIT and MCT in patients with CAD confirmed the equality of these exercise modalities in achieving peak oxygen uptake, at least when exercise training was isocaloric between groups. The authors, therefore, speculated that the total energy spent on exercise training is more important to increasing peak oxygen uptake than exercise intensity.[117] The number of serious adverse events with HIT was low and did not differ from MCT in patients with CAD.[116,118] In patients with heart failure, serious adverse events were numerically higher with HIT than with MCT. This finding and the association of myocardial infarction, need for coronary intervention, and mortality in patients with CAD with exercise session duration or intensity, even though these findings are

controversial, should receive attention in future trials.[17,18,77,119]

Nevertheless, the most efficient exercise type, frequency, intensity, session duration (these parameters can be summarized as volume [eg, in metabolic equivalent hours per week]), and program duration are still unknown because the exercise prescriptions used in clinical trials were heterogeneous. The vast number of possible combinations makes absolute recommendations difficult to mandate in every situation. Furthermore, different goals, depending on patient needs (primary prevention, treatment of risk factors, such as obesity, hypertension, or diabetes mellitus, or treatment of CAD), may require an individually tailored exercise prescription.[14,120,121] The European Association of Preventive Cardiology recently aimed to improve exercise prescription in patients with overt CAD or CAD risk factors (diabetes mellitus types 1 and 2, obesity, hypertension, and hypercholesterolemia) on the basis of current evidence. Therefore, the Exercise Prescription in Everyday Praxis and Rehabilitative Training tool, an interactive, digital training, and decision support system, was designed to assist healthcare professionals with prescribing effective and safe exercise training programs for patients with CAD (risk).[120] This tool might have a major impact on the implementation of current guidelines on exercise training in CAD, which is insufficient to date, and might lead to the collection of data on exercise training in clinical practice.

Abell et al recently reviewed the contribution of individual exercise training components to clinical outcomes in randomized trials of cardiac rehabilitation and identified adherence to exercise prescription, not exercise intensity, session duration, or frequency, as a predictor of mortality.[119] This result was also found in a long-term analysis of 435 cardiac rehabilitation participants in Leeds, UK.[122] Although this finding might be biased by a "healthy adhere effect," these studies underscore the need to improve patient compliance and long-term adherence to exercise prescriptions.

In conclusion, it seems to be most important to replace sedentary behavior with some physical activity (eg, 5 to 10 minutes of moderate activity per day).[13] Wherever applicable, higher volumes are recommended. Meeting the current guidelines' recommendation of >150 minutes of moderate to vigorous activity per week to achieve close to the optimum risk reduction seen at 3 to 5 times the recommendation can be reached.[14] High exercise intensity training is an option, especially for individuals who are interested in saving time.

Perspectives

In a population-based approach, it is of utmost importance to increase daily physical activity in all age groups to address cardiovascular health and reduce disease burden in most societies. It is a dilemma that the successful activities of the past century to improve access to high-caloric and low-priced food to overcome undernutrition, on the one hand, and offer motorized transport to almost everywhere, including elevators and escalators, to allow all individuals to participate in social life, despite physical limitations or disabilities, on the other hand, promote a sedentary lifestyle and obesity. Thus, it is recommended to start physical activity education early in childhood.[113] A randomized trial of daily exercise lessons at school compared with regular school sports twice weekly was shown to improve cardiovascular fitness and prevent obesity and supports the recommendation of regular classroom physical activity and exercise lessons.[123] Active commuting to school or workplaces should be strongly encouraged, along with taking the stairs instead of elevators or escalators.[24,124] Policy makers, urban planners, architects, and employers are asked to provide easy access to walkways, bicycle lanes, and stairs and to create an environment with high appeal for physical activity.

On the individual level, workplace-related health promotion interventions reach most of the population and can easily identify people with adverse lifestyle factors. The effectiveness of such interventions is widely debated, especially because of low participation rates.[125,126] High-quality trials of workplace-related multimodal lifestyle interventions in employees at risk for cardiovascular disease are currently on the way and will provide further information.[127,128] Individual financial incentives from caregivers or employers for participation in exercise programs or for the achievement of physical activity goals (eg, 10 000 steps/day) seem to be an effective strategy to nudge people towards more activity and need to be further evaluated.[129]

Currently, risk factor control in secondary prevention is largely insufficient.[130] As outlined previously, it is of prognostic relevance to achieve long-term participation in regular exercise and risk factor control.[119,122] The ongoing IPP (Intensive Intervention Program) trial evaluates the impact of a study nurse–coordinated prevention program consisting of structured education sessions in combination with regular telephone calls and telemetric care on risk factor control during 1 year of follow-up in patients after acute myocardial infarction (URL: http://www.clinicaltrials.gov. Unique identifier: NCT01896765). An Internet-based telerehabilitation program, in addition to a center-based rehabilitation program, in cardiovascular patients from Belgium, with telemonitoring of accelerometer data and semiautomatic telecoaching, has already demonstrated greater effects on aerobic capacity and higher durability of the treatment effect after >2 years compared with center-based rehabilitation only.[131] Skobel et al also reported greater training effects with a smartphone-based steering/feedback tool in patients with CAD, but technical problems have to be overcome before routine

clinical use.[132] Another interesting finding came from the RESPONSE-2 (Randomised Evaluation of Secondary Prevention by Outpatient Nurse Specialists 2) study, which studied the impact of a nurse-coordinated referral to community-based lifestyle programs to control smoking, overweight, and physical inactivity. Participation of patient's partners was associated with a significantly greater success rate.[133] Thus, regular face-to-face contacts with specialized nurses and physicians in combination with telemonitoring systems and the inclusion of partners might help translate the proven health benefits of rehabilitation programs into long-standing lifestyle changes and improved prognoses.

Conclusion

As a result of a series of epidemiological studies, it can be concluded that leisure-time physical activity is effective in the primary prevention of cardiovascular disease, with a dose-response relationship that leads to an ≈20% reduction in cardiovascular events and an increase in life expectancy of ≈5 years. In this respect, high cardiovascular fitness as a result of vigorous activity levels seems to be more important than total activity time. Vascular remodeling in the healthy heart in response to exercise training is composed of increases in the size of conduit and resistance arteries and arterioles and more capillaries, which improves the arterial blood supply.

In secondary prevention, exercise training improves endothelial function and halts the progression of coronary stenosis, partially via antiatherosclerotic effects on platelets and leukocytes. Vasculogenesis at the capillary level, which is induced by CPCs, and the formation of collaterals at the small-artery level might further improve myocardial perfusion in response to exercise training. In conjunction with a bradycardia-related reduction in myocardial oxygen demand, improved myocardial perfusion raises the threshold of angina-free activity levels, making exercise training a potent symptomatic therapeutic approach. Moreover, interventional studies have convincingly shown that exercise training reduces cardiovascular event rates in patients with CAD and reduces mortality.

Therefore, current scientific insights on the primary preventive effects of exercise training should have an impact on public and political decisions to create an environment that supports everyday physical activity. On the other hand, additional research is needed to better understand the effects of exercise training in detail to establish optimized training programs as an inherent component of CAD therapy.

Disclosures

None.

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