Novel therapeutic concepts

Role of exercise in the prevention of cardiovascular disease: results, mechanisms, and new perspectives

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On an empirical basis, exercise has been regarded as a fundamental pre-requisite for human well-being and physical integrity since classical times. Only in the last decades, however, scientific evidence has accumulated proving its role in the prevention and treatment of multiple chronic diseases beyond any reasonable doubt. Few treatment strategies in medicine have been tested so rigorously in large cohorts of patients as regular physical exercise. With the advent of molecular biology, the underlying mechanisms, such as NO bioavailability and mobilization of progenitor cells, could be identified. This enhances our understanding of this therapeutic tool. Unfortunately, the low compliance rate of the patients is the major drawback of the intervention exercise training (ET). The objective of this manuscript is to summarize the current knowledge with respect to ET on cardiovascular disease (CVD) and the molecular changes elicited by ET. Finally, we will critically assess reasons why ET as therapeutic option is not as effective at the population level in preventing CVD and what we may change in the future to make ET the most effective intervention to fight the development of CVD.

Keywords
Exercise training • Clinical studies • Molecular mechanisms • Limitations

Introduction

The first scientific evidence regarding the beneficial effects of work associated exercise training (ET) was published by Morris in 1953 who examined the incidence of coronary artery disease (CAD) in London bus driver teams.1 He clearly documented that the incidence of CAD was less in the middle-age conductors than in the sedentary drivers of the same age. Subsequently, studies in more than 100,000 individuals clearly documented that the higher the level of physical fitness, the less likely an individual will suffer premature cardiovascular death (reviewed in Lee et al.). Based on these studies, all major cardiovascular societies made physical activity part of their guidelines for prevention of CVD (class I recommendation), recommending at least 30 min of moderate-intensity aerobic activity, 7 days per week with a minimum of 5 days per week.3–5

This review will summarize the current knowledge with respect to ET on CVD and the molecular changes elicited by ET. In the last part of the review, we will critically assess reasons why ET as therapeutic option is not as effective at the population level in preventing CVD and what we may change in the future to make ET the most effective intervention to fight against the development of CVD.

Clinical studies proving the effectiveness of exercise training in cardiovascular disease prevention

Results in primary cardiovascular disease prevention: evidence from observational studies

Several studies have demonstrated positive associations between sedentary behaviours/low cardiorespiratory fitness and health outcomes such as type 2 diabetes, CVD mortality, and all-cause mortality.6–8 Katzmarzyk et al. estimated that reducing excessive sitting to <3 h/day and excessive television viewing to <2 h/day would...
result in gains in life expectancy of 2.0 and 1.4 years, respectively.\textsuperscript{7} Numerous studies documented an inverse relationship between self-reported physical activity or objectively measured physical fitness and CVD mortality and all-cause mortality.\textsuperscript{9–11} For example, Myers et al.\textsuperscript{11} demonstrated a strong inverse relationship between exercise capacity [in metabolic equivalents (METs)] measured by treadmill and 6-year mortality in both 2534 normal subjects and 3679 CVD patients. In a systematic review and meta-analysis of 33 cohort studies consisting of 883 372 participants, Nocon et al.\textsuperscript{9} reported that physical activity was associated with 35% risk reduction for CVD mortality and 33% risk reduction for all-cause mortality. In their analysis, self-reported physical activity was associated with a smaller risk reduction compared with objectively measured physical fitness, probably because participants overestimated their physical activity levels in self-reports. On the basis of these studies, guidelines and performance measures have been published to recommend regular physical activities for primary CVD prevention.\textsuperscript{12,13}

**Results in primary cardiovascular disease prevention: dose–response**

Whereas many older studies dichotomized participants into physically active vs. inactive groups, more recent studies have grouped the participants into multiple quantitatively designated categories of physical activity (such as quartiles of leisure-time physical activity), making it possible to assess a dose–response relation between physical activity and mortality. As a result, inverse dose–response relations have been found between volume of physical activity behaviour and all-cause mortality.\textsuperscript{14,15} CVD mortality,\textsuperscript{15,16} and risk of CAD.\textsuperscript{17,18} Notably, Wen et al.\textsuperscript{15} and Sattelmair et al.\textsuperscript{17} have reported that even 15 min of daily exercise (about half of the minimal level of guideline recommendation\textsuperscript{13}) is associated with a significant reduction of all-cause mortality or CAD risk. This finding may support the guideline’s assertion that some physical activity is better than none.\textsuperscript{13} This is also evident in the study by Myers, where moving from the worst to the second worst quintile provided the largest benefit.\textsuperscript{11}

**Prevention of cardiovascular disease in diabetes and obese population**

Most deaths due to diabetes are attributable to CVD, especially CAD.\textsuperscript{19} Previous data strongly support the role of lifestyle intervention involving physical activity to improve glucose and insulin homeostasis and CVD risk factors.\textsuperscript{20,21} The Diabetes Prevention Program Research Group\textsuperscript{22} demonstrated that a lifestyle modification program with goals of ≥7% weight loss and ≥150 min/week of physical activity in overweight patients with impaired fasting glucose resulted in a 58% reduction in the incidence of diabetes mellitus, whereas there was a 31% reduction with metformin (850 mg twice daily) compared with placebo. Tanasecu et al.\textsuperscript{23} reported in their 14-year follow-up study that the total amount of physical activity was inversely related with all-cause mortality in diabetic men. Intriguingly, in their study, walking pace was inversely associated with CVD, fatal CVD, and all-cause mortality, independent of walking hours. On the basis of these findings, the 2009 AHA Scientific Statement on ET in type 2 diabetes mellitus recommends 150 min/week of moderate-intensity exercise combined with resistance training.\textsuperscript{19}

Although weight loss is important in obese patients, current exercise protocols in cardiac rehabilitation (CR) result in little weight loss, in part because of the low energy expenditure of 700–800 kcal/week. In a randomized controlled clinical trial\textsuperscript{24} comparing the effect of high-calorie-expenditure exercise (3000–3500 kcal/week exercise-related energy expenditure) with standard exercise (700–800 kcal/week) on weight loss and risk factors, 5 months, high-calorie-expenditure exercise resulted in greater weight loss (–8.2 vs. –3.7 kg, \(P < 0.001\)) and more favourable CVD risk profiles than standard exercise. In addition, Blair and colleagues\textsuperscript{25} reported that in men with documented or suspected coronary heart disease, cardiorespiratory fitness greatly modifies the relation of adiposity and mortality.

**Results in secondary cardiovascular disease prevention: observational studies**

Several observational studies have been published regarding the relation between participation in a CR program and the CV prognosis in post-myocardial infarction, post-coronary intervention, and elderly CAD patients.\textsuperscript{26–30} Witt et al.\textsuperscript{26} reported that participation in CR was independently associated with decreased mortality and recurrent MI, and that its protective effect was stronger in more recent years. In another study, the relation between the number of CR sessions attended and mortality/MI risk at 4 years in elderly CAD patients was analysed.\textsuperscript{27} An inverse dose–response relation between session attendance and mortality/MI risk was observed at 4 years. Likewise, in a prospective cohort study in Canada, Martin et al.\textsuperscript{28} reported that, compared with non-completers (\(n = 554\)), CR completers (\(n = 2900\)) had a lower risk of death (adjusted hazard ratio 0.59), all-cause hospitalization (adjusted hazard ratio, 0.77), and cardiac hospitalization (adjusted hazard ratio 0.68). Suaya et al.\textsuperscript{30} performed extensive analyses to control for potential confounding between CR users and non-users among 600 000 Medicare CAD patients (age ≥65 years), and found that 5-year mortality rates were 21–34% lower in the CR users than non-users. Unfortunately, in this multi-disciplinary rehabilitation program, the impact of ET on the observed reduction of mortality remains unclear.

**Results in secondary cardiovascular disease prevention: prospective randomized studies**

Before the wide spread use of coronary reperfusion therapy, many small-sized randomized trials were conducted in AMI patients, demonstrating a significant reduction of mortality. Although one can infer that the magnitude of risk reduction by CR program may be smaller after the reperfusion era, the meta-analysis by Taylor et al.\textsuperscript{31} indicated no significant difference in the effect size of CR before and after 1995. However, very recent prospective randomized trials\textsuperscript{32,33} have all failed to demonstrate positive results for the primary endpoint (all-cause mortality, MI, and readmission), although some secondary endpoint such as decreases in the length of hospital stay\textsuperscript{32} or non-fatal MI\textsuperscript{33} were achieved. The reasons for this failure of reduction of mortality/CAD risk...
by CR may be attributable to the widespread use of secondary prevention strategy (optimal medical therapy) in the control group, the diversity of CR contents and patient profiles in the European countries, or the insufficient amount of ET in these studies.

There have been prospective randomized trials of ET in other aspects of CVD prevention. Hambrecht et al.36 as well as Niebauer et al.35 have demonstrated that long-term ET can halt the progression and, in some cases, actually promote regression of coronary atherosclerotic lesions (Figure 1). Additionally, in the ETICA trial,36 the ET group showed a significantly better cardiac event-free survival than the non-exercise group in patients after PCI with balloon angioplasty or bare-metal stents at 33-month follow-up. Furthermore, Hambrecht et al.37 compared ET vs. PCI with bare-metal stents in patients with stable angina pectoris, and found that ET improved event-free survival at 12-month follow-up.

Results in secondary cardiovascular disease prevention: meta-analysis and guidelines

Since modern comprehensive CR programs contain not only ET but also patient education and counselling, it is difficult to see how much effect is attributable to exercise per se. In the meta-analysis of 2004, Taylor et al.31 reported that the effect size of total mortality reduction was not significantly different between exercise-only CR and comprehensive CR (~24 vs. ~16%, NS). In a subsequent meta-analysis,38 they estimated that approximately half of the 28% reduction in cardiac mortality achieved with exercise-based CR was attributable to reductions in major risk factors, and hence, the remaining half attributable to exercise per se. Taken together, it is clear that ET/physical activity reduces CVD/CAD risk in addition to dietary and/or pharmacological interventions in primary and secondary prevention. In relation to this, both European and American guidelines for CVD prevention51,52 describe recommendations for physical activity and CR participation in independent sections.

High-intensity interval vs. moderate continuous training

The current guidelines on CR/ET recommend endurance exercise with moderate intensity at 50–85% (mostly 70–85%) of peak heart rate (HRpeak) for CVD and CHF patients.39,40 However, Wisloff et al.41 employed high-intensity aerobic interval training with four cycles of 4-min uphill walking at high intensity (90–95% of HRpeak). After 3 months of ET, peak VO2 increased more with high-intensity interval training than moderate continuous training (~46 vs. +14%). This study has caused a lot of discussion regarding the optimal intensity and mode of exercise in both the research and practice of ET for CHF. In addition to CHF, aerobic interval training has a proven benefit in obese adolescent,42 in patients with CVD,43 severe COPD,44 or metabolic syndrome.45 At least for heart failure patients, the recommended training should still follow the guidelines, since the validity of high-intensity interval training needs to be confirmed in larger multi-centre trials like SMART-Ex.46

Molecular mechanisms

As outlined earlier, ET has proved its efficiency in a multitude of observations and studies. However, molecular biology has helped to identify and describe the underlying mechanisms related to the benefits of exercise, which include alterations in the myocardium,47 skeletal muscle,48 and vascular system.49,50 In the following part, we will focus on the molecular changes that occur in the vascular system in response to ET (Figure 2).

Endothelial function and nitric oxide bioavailability

One of the most important molecular consequences of regular physical exercise is the absolute increase of vascular nitric oxide (NO) concentration. NO is responsible for vasodilation, which results in the lowering of peripheral resistance and increase of perfusion. Endothelial nitric oxide synthase (eNOS), the main source of NO, is up-regulated by an increase in flow-mediated shear stress associated with physical exercise due to a complex pattern of intracellular regulation like acetylation,51 phosphorylation,52 and translocation to the caveolae.53 Numerous investigations have now clearly documented that exercise or increased shear stress up-regulates eNOS activity either in cell culture,54 animal,55 or human studies.56,57 Nevertheless, it remains unclear how an elevated shear stress is translated into increased eNOS activity. On the luminal side of the endothelial cells, direct signalling can occur through deformation of the glycocalyx which results in the activation of calcium ion channels, phospholipase activity leading to calcium signalling, PGI2-release, and cAMP-mediated smooth-muscle-cell relaxation.58 In addition, VEGFR2 is located at the luminal surface and can associate with VE-cadherin, β-catenin, and phosphatidylinositol 3 kinase to phosphorylate Akt and induce AKT-mediated eNOS phosphorylation, leading to higher NO production58 (Figure 3).

High-density lipoprotein (HDL) is another factor known to modulate eNOS activity, due to eNOS phosphorylation.59 Recent studies documented that HDL-mediated eNOS activation is significantly impaired in CVD patients.50–52 Mechanistically, it is proposed that malondialdehyde-modified HDL triggers the activation of PKC-βII, thereby reducing eNOS-dependent NO production.61 With respect to ET preliminary and unpublished data from our laboratory revealed that ET was able to restore HDL-mediated eNOS phosphorylation and NO production via modulating the amount of malondialdehyde bound to HDL.

In addition to the activation of eNOS and the concomitant increase in NO production, ET also has an impact on the generation of reactive oxygen species (ROS), scavenging NO. The application of laminar flow to intact vascular segments has been shown to increase ROS production for a short time period,63 with NAD(P)H oxidase,64 and a stimulation of radical scavenging systems that include copper–zinc containing superoxide dismutase (SOD),65 extracellular SOD,66 glutathione peroxidase,67 and GSH levels.68

Another enzyme generating ROS in the vascular system is eNOS itself. Under a number of pathological conditions, the enzymatic reduction of molecular oxygen by eNOS is no longer coupled to
L-arginine oxidation, resulting in the production of superoxide rather than NO. A number of mechanisms have been reported to contribute to eNOS uncoupling, and these include tetrahydrobiopterin (BH₄) deficiency, shortage of L-arginine or heat shock protein 90 (Hsp90), eNOS phosphorylation on threonine residue 495, or elevated asymmetric dimethylarginine (ADMA) levels. With respect to BH₄ concentration, cell-culture studies provided the first evidence that elevated shear stress dramatically

**Figure 1** (A) Attenuation of progression of coronary atherosclerotic lesions by 12-month exercise training/physical activity in patients with coronary artery disease. (B) The relation between amount of exercise (expressed by energy expenditure) and changes in coronary lesions. Higher levels of exercise training/physical activity were associated with a halt of progression, or even regression, of coronary lesions. (Constructed according to data in Suaya et al.)

**Figure 2** Possible signalling pathways how the beneficial effects of exercise training are translated into a reduced risk of developing cardiovascular disease.
increases BH4 levels.71 In addition, a beneficial effect of ET has also been documented for the circulating levels of ADMA.72

Endothelial repair by stem cells
Endothelial progenitor cells (EPCs)73 and mesenchymal stem cells (MSCs) possess the potential for vascular regeneration and endothelial repair.74 Numerous studies have provided strong evidence that ET mobilizes EPCs and MSCs from the bone marrow (BM) while improving the functional capacity of the cells (reviewed in Lenk et al.75). The principal mechanism of EPC mobilization from the BM seems to depend on the activation of eNOS in the presence of several mobilizing factors such as vascular endothelial growth factor (VEGF),76 or placental growth factor.77 Gene targeting studies using either matrix metalloproteinase-2 (MMP-2)78 or MMP-979 knockout mice demonstrated that the presence of MMPs are crucial in ischaemia-induced mobilization of EPCs, and hence neovascularization and/or endothelial repair. At the molecular/cellular level, the following scenario for the mobilization is proposed. Under steady-state conditions, progenitor cells reside in a niche of the BM, bound to stroma cells via adhesion molecules such as VCAM/VLA4.80 Signal-induced up-regulation of MMP-9 results in a release of sKitL, conferring signals that enhances mobility of progenitor cells into a vascular-enriched niche favouring liberalization of the cells into the circulation81 (Figure 4). Once mobilized from the BM, EPCs are attracted to the damaged endothelium by specific cell-surface receptors, like CXCR-4 (receptor for SDF-1α) or VLA-4 (very late antigen-4). Following attachment to neighbouring cells, EPCs then fill the gap either by differentiating to a mature endothelial cell,82,83 or by secretion of differentiation factors stimulating mature endothelial cells to proliferate84,85 (Figure 4).

Therefore, how can we explain the exercise-induced mobilization of EPC? It is known that BM stromal-cell-derived eNOS/NO is substantial for the mobilization of stem and progenitor cells in vivo86 due to an activation of MMP-9 in the BM87 and that exercise-induced mobilization is abolished in eNOS2/2 mice.88 Immediately after mobilization, the most important factors for tissue engraftment of the mobilized cells are the local concentration of stromal-derived factor-1α (SDF-1α) and its cell receptor CXCR-4.89 The expression of CXCR-4 can be up-regulated either by ET,90 or by adiponectin,91 both known to have an impact on EPC migration.92

Arterial stiffness
Increased arterial stiffness is associated with several pathologies, including systolic hypertension, left-ventricular hypertrophy, and CHF.93 Clinical investigations documented that arterial stiffness is lower in those who performed aerobic exercise on a regular basis compared with sedentary peers.94,95 Despite the clear benefit of aerobic ET, the molecular mechanisms are not completely understood. It is thought that structural changes, in particular collagen and elastin, play a central role in the development of
arterial stiffness. However, studies investigating the impact of ET on these structural components are conflicting. A study in old mice clearly documented that 10–14 week of voluntary wheel running resulted in a reduction of collagen I and III content and a decreased TGF-ß expression. Yet in contrast, the use of swim training or treadmill ET failed to find any changes in collagen or elastin expression by direct measurements or microarray analysis, respectively. In human studies, a reduction of aortic stiffness after endurance training was confirmed in patients with hypertension and CAD.

Advanced glycation end-products (AGE) accumulate with age, leading to the cross-linking of collagen and subsequently to arterial stiffness. Additionally, AGEs also stimulate pro-inflammatory mechanisms, increase production of superoxide anions, affect endothelial-mediated smooth-muscle function, and increase oxidative stress. With respect to ET in humans, a significant inverse relationship between AGE content in the skin and muscle strength was observed. In addition, rodents long-term ET decreased plasma levels of carboxymethyl-lysine as well as inhibiting age-related cross-linking of collagen in the heart muscle.

**Figure 4** Exercise-induced mobilization of EPCs from the bone marrow leading to arteriogenesis or endothelial cell repair. Exercise-induced activation of eNOS and subsequently of MMP-2/9 results in the release of soluble cKit-ligand. SkitL confers signals enhancing mobility of EPCs. Along an SDF-1 gradient, the EPCs are mobilized into the peripheral circulation. Once mobilized, the EPCs follow a gradient of SDF-1 or other factor to the site needed, where they bind to mature endothelial cells (EC) via specific cell-surface marker (1). After binding to EC, the EPC may have to find possible pathways to repair the damage in the endothelial cell layer. First, it fills in the gap and differentiates into a mature endothelial cell (2) or secondly it secretes growth differentiation factors (3) which in turn stimulate mature endothelial cells (4) to proliferate and thereby closing the gap in the endothelial cell layer (5). EPC, endothelial progenitor cells.

**Impact of exercise training on microRNA**

MicroRNAs (miRNAs), first recognized as regulators in the development of worms and fruit flies, have emerged as pivotal modulators of mammalian cardiovascular development and disease. Individual miRNAs modulate the expression of collections of messenger RNA targets that often have related functions, thereby governing complex biological processes. Heart failure and several CVDs are associated with a specific signature pattern of miRNAs. In an elegant study, Thum et al. clearly documented that in heart failure, miR-21 is significantly up-regulated and that this elevation of miR-21 stimulated fibroblasts to generate more collagen leading to an increase in fibrosis. There are only four recent studies that report the involvement of miRNAs in cardiovascular adaptive response to ET. In one study, swim training in rats increased cardiac expression of miR-126 expression, which is regarded as an endothelial specific miRNA supporting angiogenesis by directly repressing two negative regulators of VEGF. Another study reported that miR-29 is involved in the improvement of ventricular compliance and this is promoted by aerobic ET due to a modulation of decreased collagen synthesis.
in cardiac fibroblasts. With respect to the regulation of eNOS activity by increased shear stress, evidence from cell-culture experiments documented an involvement of miRNA-21, where overexpression of the former resulted in an activation of eNOS and a 3.7-fold increased NO production, yet inhibition of miRNA-21 abolished the shear-induced activation of eNOS.

Collateral growth

There has been strong evidence from animal studies that chronic intensive physical exercise leads to an increase collateral growth (arteriogenesis) in the myocardium. With exception to these positive animal findings, results from human studies are conflicting (reviewed in Heaps and Parker). Using angiographic methods, Nibelauer et al. did not find any evidence that physical exercise >3 h per week resulted in an increased collateral formation. Assessing collateral flow as a marker for collateral growth, Zbinden et al. recently documented that 3 months of endurance training lead to a significant increase in collateral formation. With respect to the molecular determinants responsible for the exercise-induced collateral growth, a number of different mechanisms have been discussed. Similar to other regenerative processes like angiogenesis, part of the arteriogenic growth has been attributed to circulating stem cells and their paracrine function as recently detailed by Heil and Schaper. Mechanistically, the activation of the SDF-1/CXCR4 axis, which of note is also activated by ET, results in the recruitment of progenitor cells followed by an enhanced collateral artery growth. In addition to stem cells, the release of specific growth factors promoting collateral growth is discussed, with the most important suggested to be VEGF. The importance of VEGF for the exercise-induced collateral growth is further supported by a recent study demonstrating a close correlation between myocardial blood flow and expression levels of VEGF and its receptor Flk-1.

Limitations and new strategies

The presently available knowledge regarding exercise as a therapeutic intervention is by no means complete, but evidence suggests it is effective in treating a wide range of patients as outlined earlier. However, we are lacking the algorithm on how to make it work in the general population. Generation of new guidelines defining unrealistic aims regarding the amount and intensity of ET is a futile attempt if they are not backed up by strategies to improve compliance rates.

Limitation: exercise compliance

In most exercise studies, no detailed record was kept on patient compliance with respect to participation in group-exercise sessions or home training. It was assumed that the majority of patients would adhere to the exercise prescription defined by the study protocol. But not surprisingly, the recently published HF-ACTION trail documented that during the initial period of supervised training sessions only 84% of the patients were compliant decreasing even to 62% at 1 year, and to 40% at 3 years during individual home-based ET. There is considerable evidence indicating that this finding is not unique but rather the norm in most exercise studies; particularly, in home-based exercise programs where supervision is less intensive and compliance rates are much lower. In a recent position statement of the study group on ET in heart failure of the Heart Failure Association of the European Society of Cardiology, the authors clearly stated that low adherence of patients to the prescribed ET program is the ‘Achilles heel’ of the treatment and that solutions are warranted to overcome the barriers.

In a cross-sectional telephone survey conducted by state health departments in the USA, physical activity was assessed by a structured interview. The percentage of adults who reported sufficient vigorous physical exercise ranged from 35.5% in UT to 15.9% in PR. In order to improve physical activity on a large scale, a task force was convened which recommended six interventions:

1. Community wide campaigns
2. Point-of-decision prompt to encourage using stairs
3. School-based physical education
4. Social support interventions in community settings
5. Individual adapted health behaviour change
6. Creation of enhanced access to places for physical activity combined with informal outreach activities.

The effectiveness of these interventions is difficult to assess, especially as no strong data are available at the present time. The American Heart Association’s 2020 Strategic Impact Goals target a 20% relative improvement in overall cardiovascular health. Physical inactivity prevalence declined non-significantly from 1999 to 2006 in both men (from 37 to 30%, \( P = 0.40 \)) and women (from 42 to 32%, \( P = 0.87 \)). Corresponding increases in the prevalence of intermediate and ideal physical activity levels were also not statistically significant in either sex. The authors concluded that ‘the American Heart Association 2020 target of improving cardiovascular health by 20% by 2020 will not be reached if current trends continue.’

There are many reasons why patients evade exercise; in older patients sickness and pain are the dominant reasons given for non-adherence, whereas younger patients usually blame economic factors and lack of time. Low motivation was a more common reason for non-adherence among those prescribed home-based activities compared with those referred for facility-based activities. Most patients entering secondary prevention programs are beyond the age of 50 years; they have not participated in anything that deserves the term physical exercise for decades since leaving school. To assume that any form of counselling will significantly and permanently change this behaviour is totally unwarranted and without precedence in medicine.

Can we solve the compliance problem by starting with prevention in children?

Changing personality traits in adults is a difficult and unrewarding task; in particular, elderly patients beyond the age of 60 years, having followed a sedentary life style for decades, are hard to motivate to engage in regular physical exercise. Therefore, a legitimate approach to this problem would be an early start in childhood when minds and bodies are still open to change. Based on scientific evidence, a minimum of 60 min/day of exercise is recommended for school children. However, as noted in adults, the activity observed in school children is far lower; only 7% engage in vigorous physical activity for 60 min per day, and only 26% reach the
standard of 120 min/day of total activity. If physical exercise would become an integral part of the school curriculum then compliance rates should reach levels of >90%, a scenario totally unrealistic in adult patients. It could be postulated that early adaptation to an active life style may prevail through adulthood. At present, physical education has been neglected in many school systems throughout the world. In Germany 2 h/week of physical education is deemed sufficient in most high schools for fostering an active life style; not infrequently one or both of these periods have to be cancelled due to teachers being unavailable.

A large number of intervention programs have been initiated in recent years aimed at reducing childhood obesity. Most of these studies were not randomized and an insufficient amount of school-based exercise was observed. In the Leipzig High School Study, a total of 182 students from seven different classes were randomized between an intervention group with daily physical exercise, and compared with a control group with 2 h of physical education per week. Compliance in the intervention group reached nearly perfect levels throughout the study period and weekend activities, which were offered in addition to scheduled training sessions. Following 1 year, significant treatment effects were noticed with regard to the maximal oxygen consumption, and there was a trend for a reduction in overweight and an improvement of motor abilities in favour of the intervention group. Increasing physical activity is apparently a positive way of lifestyle modifications as it does not rely on dietary and other restrictions, which may be perceived as a negative incentive. Following uninterrupted attendance of daily exercise for 5 years, the intervention was stopped and students were encouraged to continue the active lifestyle at their responsibility. After a time interval of 6 months they were asked to return for a follow-up visit. A structured interview was conducted to determine the frequency and duration of leisure-time physical activity and maximal work capacity was measured. As shown in Figure 5, maximal oxygen consumption in the intervention group was significantly higher when compared with the control group throughout the study period. However, after termination of school-based exercise, it decreased rapidly within 6 months and even ranged below the control group (Figure 5). Although many factors are likely to be involved in this development, one has to realize that contrary to our expectations, it is impossible to change personal traits by prolonged training over 5 years even in the young. Once continuous encouragement and supervision is terminated, the original lifestyle re-emerges. One promising strategy to improve results would consist in involving the child’s family from the very beginning. Although this strategy may work for some families, logistic problems are impressive when dealing with a great number of them. Also an argument that different ET forms (continuous moderate-intensity vs. high-intensity interval training) would result in a higher benefit can be neglected, because a recently published report demonstrated no obviously measurable benefit comparing both modalities in obese and healthy children.

Can we learn from tobacco control to fight physical inactivity?

Control of tobacco consumption has been impressively successful despite deep-rooted addiction in many countries. Warning labels, tax increases, and smoke-free places resulted in elimination of tobacco consumption from many areas of public life. Figure 6 shows the change in cigarettes consumption and prevalence of smoking in youths during a period of nearly 20 years in Germany. Although no single intervention was effective by itself, the combination of several tax hikes, smoking ban in public

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**Figure 5** Impact of 5 years training intervention in school children on maximal oxygen consumption. Children were randomized either to a control (grey bars) or a training group (black bars). Maximal oxygen consumption was measured every year during the 5 years intervention (t1–t5) and 1 year after follow-up (post). Significance values between the control and intervention groups are shown on top of the graph for every year.
areas, warning signs, and restriction of tobacco sales to youths caused a highly significant downturn of cigarette consumption by nearly 50% (Figure 6). Can this experience therefore serve as a template for fighting physical inactivity? Probably not but there are some parallels: tobacco consumption and physical inactivity are major risk factors for CAD; both of them are difficult to fight and there is no pill as is the case for the treatment of hypercholesterolaemia or hypertension. But there are also major differences: tobacco consumption is susceptible to powerful negative incentives such as the taxation and a ban in public areas, transportation, and restaurants. To increase physical activity, positive incentives would be required, but presently they are weak or missing altogether. There are numerous aspects how improvements could be implemented without major changes in existing regulations or great investments: membership fees for gyms and sports clubs as well as sports equipment could be made tax deductible. Physical activity could be encouraged by establishing safer cycling routes especially for school children, to promote walking as a means of at least partial daily transportation (e.g. the London Underground station map with walking distances between individual stops: http://www.steveprentice.net/tube/TfL.SillyMaps/milesdistances.gif. or assistance with walking in cities http://www.walking-uk.com/walk-it.htm).

New perspectives
In face of a nearly complete failure to increase the prevalence of physical activity in the general population, new ideas need to be contemplated and tested; some health insurance companies have started to reward patients for participating in coronary exercise groups on a regular basis. These rewards, for instance, could come in form of rebates on their health insurance rates. Presently, these benefits are marginal and therefore unattractive; moreover, the question remains of how ‘adherence to an active lifestyle’ can be measured. However, after clearing legal hurdles, this idea could be expanded into a system of rewards and benefits on the individual state of physical fitness. Assessment of physical fitness is simple, well standardized, and has proved its predictive value in large numbers of patients. Maximal work capacity achieved during a treadmill exercise test is highly reproducible and shows a tight correlation with the patient’s prognosis. In this hypothetical system for instance, an exercise stress test would be performed at certain time intervals on a totally voluntary basis. Individuals

Figure 6 Impact of legal measures on cigarette consumption and of the population and the smoking prevalence of the youth in Germany between 1993 and 2010. Source: German Cancer Research Center, Unit Cancer Prevention/WHO Collaborating Centre for Tobacco Control, 2012.
reaching the age-dependent work capacity would qualify for a substantial rebate on their health insurance rates. Exceptions would have to be made, of course for patients with physical handicaps.

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