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REVIEW

Novel therapeutic concepts

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

Gerhard Schuler[1]*, Volker Adams[1], and Yoichi Goto[2]

[1]University Leipzig – Heart Center Leipzig, Strümpellstrasse 39, 4289 Leipzig, Germany; and [2]Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan

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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.*[2]). 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

* Corresponding author. Tel: +49 341 865 252000, Fax: +49 341 865 1461, Email: gerhard.schuler@med.uni-leipzig.de

result in gains in life expectancy of 2.0 and 1.4 years, respectively.[7] Numerous studies documented an inverse relationship between self-reported physical activity or objectively measured physical fitness and CVD mortality and all-cause mortality.[9–11] For example, Myers *et al.*[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.*[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.[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,[14,15] CVD mortality,[15,16] and risk of CAD.[17,18] Notably, Wen *et al.*[15] and Sattelmair *et al.*[17] have reported that even 15 min of daily exercise (about half of the minimal level of guideline recommendation[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.[13] This is also evident in the study by Myers, where moving from the worst to the second worst quintile provided the largest benefit.[11]

Prevention of cardiovascular disease in diabetes and obese population

Most deaths due to diabetes are attributable to CVD, especially CAD.[19] Previous data strongly support the role of lifestyle intervention involving physical activity to improve glucose and insulin homeostasis and CVD risk factors.[20,21] The Diabetes Prevention Program Research Group[22] demonstrated that a lifestyle modification program with goals of $\geq$7% weight loss and $\geq$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. Tanasescu *et al.*[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.[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[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[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.[26–30] Witt *et al.*[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.[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.*[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.*[30] performed extensive analyses to control for potential confounding between CR users and non-users among 600 000 Medicare CAD patients (age $\geq$65 years), and found that 5-year mortality rates were 21–34% lower in the CR users than non-users. Unfortunately, in this multidisciplinary 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.*[31] indicated no significant difference in the effect size of CR before and after 1995. However, very recent prospective randomized trials[32,33] have all failed to demonstrate positive results for the primary endpoint (all-cause mortality, MI, and re-admission), although some secondary endpoint such as decreases in the length of hospital stay[32] or non-fatal MI[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.*[34] 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 prevention[5,12] 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 VO_2 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 multicentre trails 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] 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.[57] 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 production[58] (*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.[60–62] 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 being the major source.[64] However, extended periods of ET result in a reduced expression of NAD(P)H oxidase[65] and a stimulation of radical scavenging systems that include copper–zinc containing superoxide dismutase (SOD),[66] extracellular SOD,[67] glutathione peroxidase,[68] and GSH levels.[69]

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

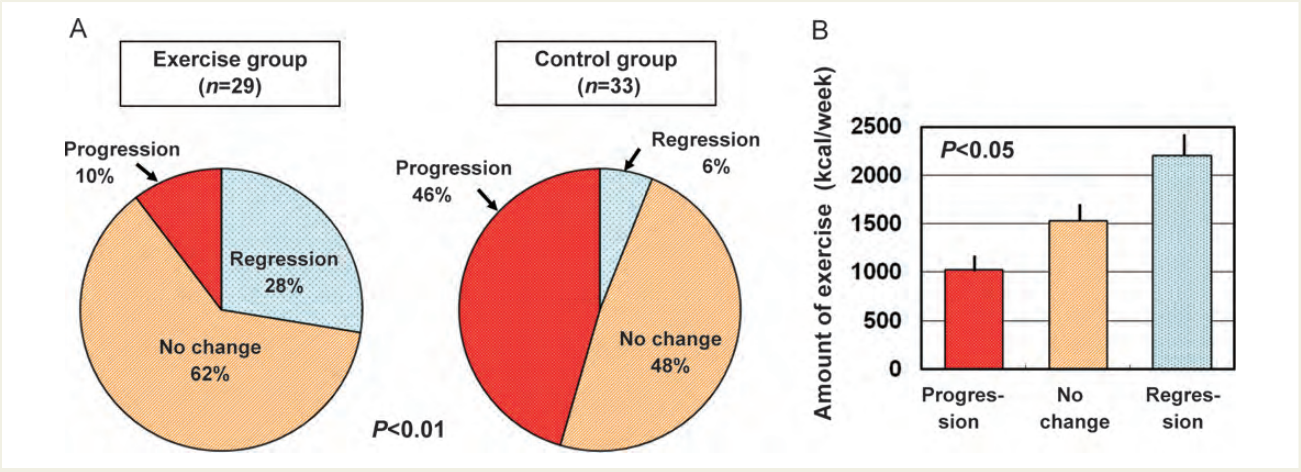

Figure 1 (*A*) Attenuation of progression of coronary atherosclerotic lesions by 12-month exercise training/physical activity in patients with coronary artery disease. (*B*) The relation between amount of exercise (expressed by energy expenditure) and changes in coronary lesions. Higher levels of exercise training/physical activity were associated with a halt of progression, or even regression, of coronary lesions. (Constructed according to data in Suaya *et al.*[30])

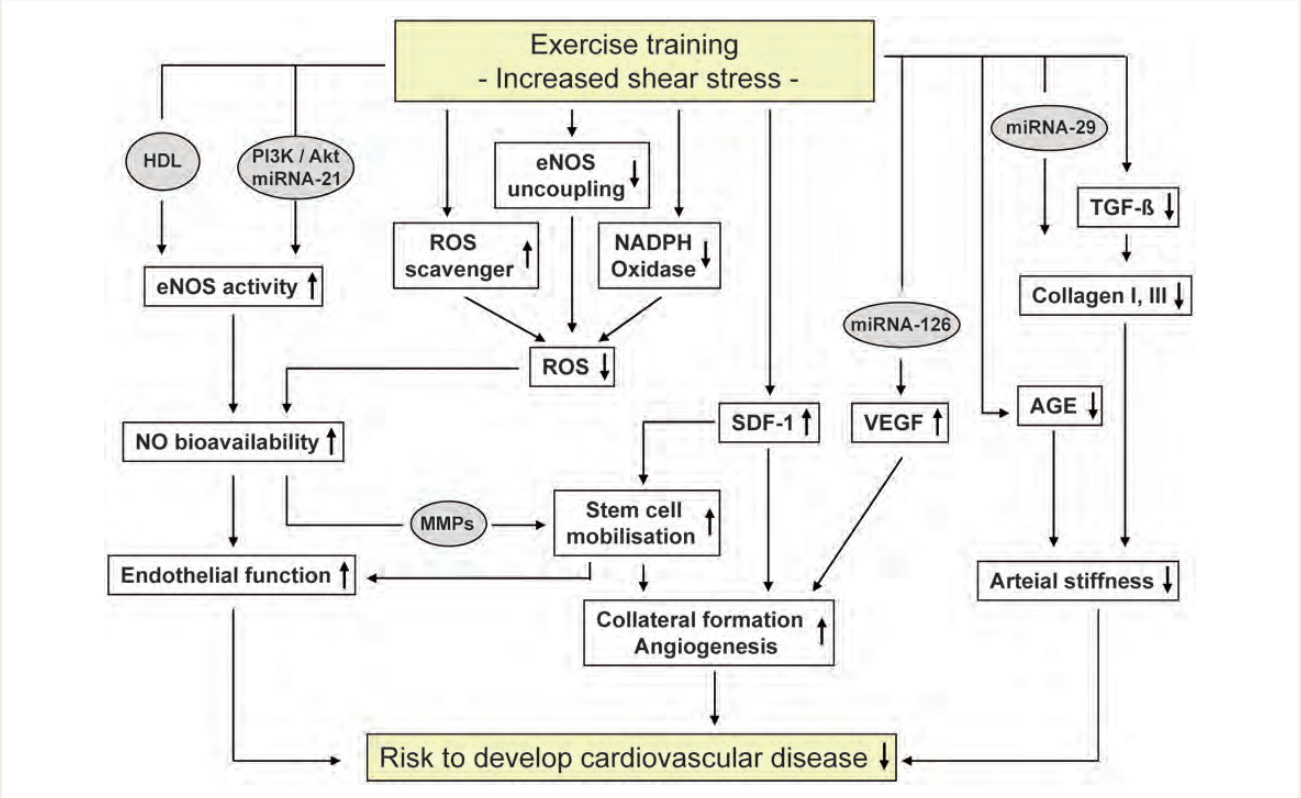

Figure 2 Possible signalling pathways how the beneficial effects of exercise training are translated into a reduced risk of developing cardiovascular disease.

L-arginine oxidation, resulting in the production of superoxide rather than NO.[70] A number of mechanisms have been reported to contribute to eNOS uncoupling, and these include tetrahydrobiopterin (BH_4) deficiency, shortage of L-arginine or heat shock protein 90 (Hsp90), eNOS phosphorylation on threonine residue 495, or elevated asymmetric dimethylarginine (ADMA) levels.[70] With respect to BH_4 concentration, cell-culture studies provided the first evidence that elevated shear stress dramatically

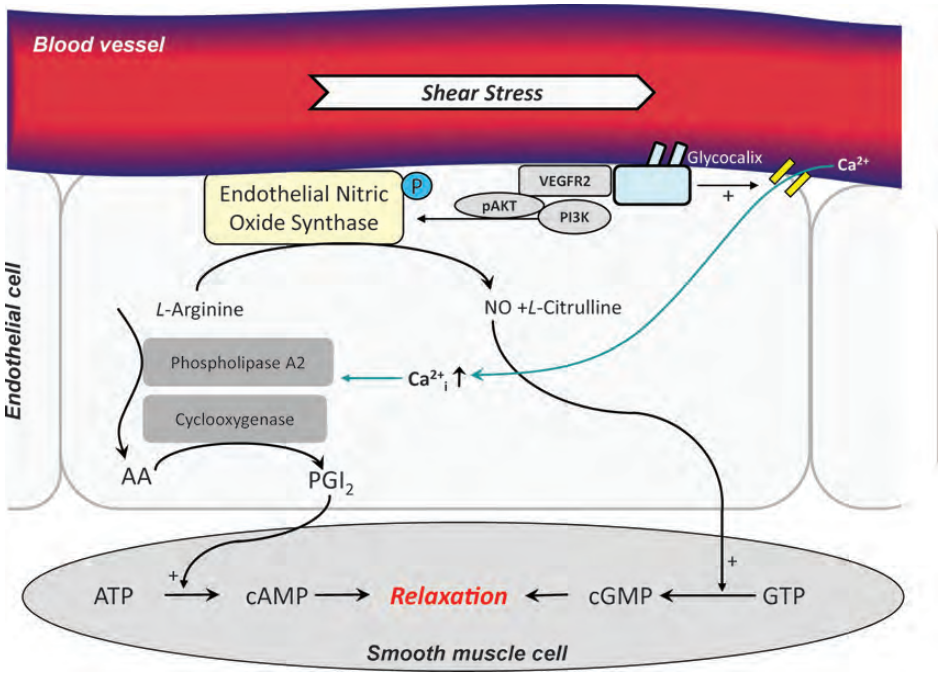

Figure 3 The majority of exercise effects on the vascular endothelium are mediated by intermittent increases of laminar shear stress. On the luminal side of the endothelial cells, direct signalling can occur through deformation of the glycocalyx activating phospholipase activity via an increase in intracellular Ca^{2+}, prostaglandin I2 (PGI2) release, and cAMP-mediated smooth-muscle-cell relaxation. VEGF receptor 2 (VEGFR2) can activate PI3K to phosphorylate Akt and induce AKT-mediated eNOS phosphorylation, leading to higher NO production. Akt indicates protein kinase B; AA, arachidonic acid; VEGF, vascular endothelial growth factor.

increases BH_4 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-9[79] 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 circulation[81] (*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 proliferate[84,85] (*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 vivo*[86] due to an activation of MMP-9 in the BM[87] and that exercise-induced mobilization is abolished in $eNOS^{-/-}$ 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

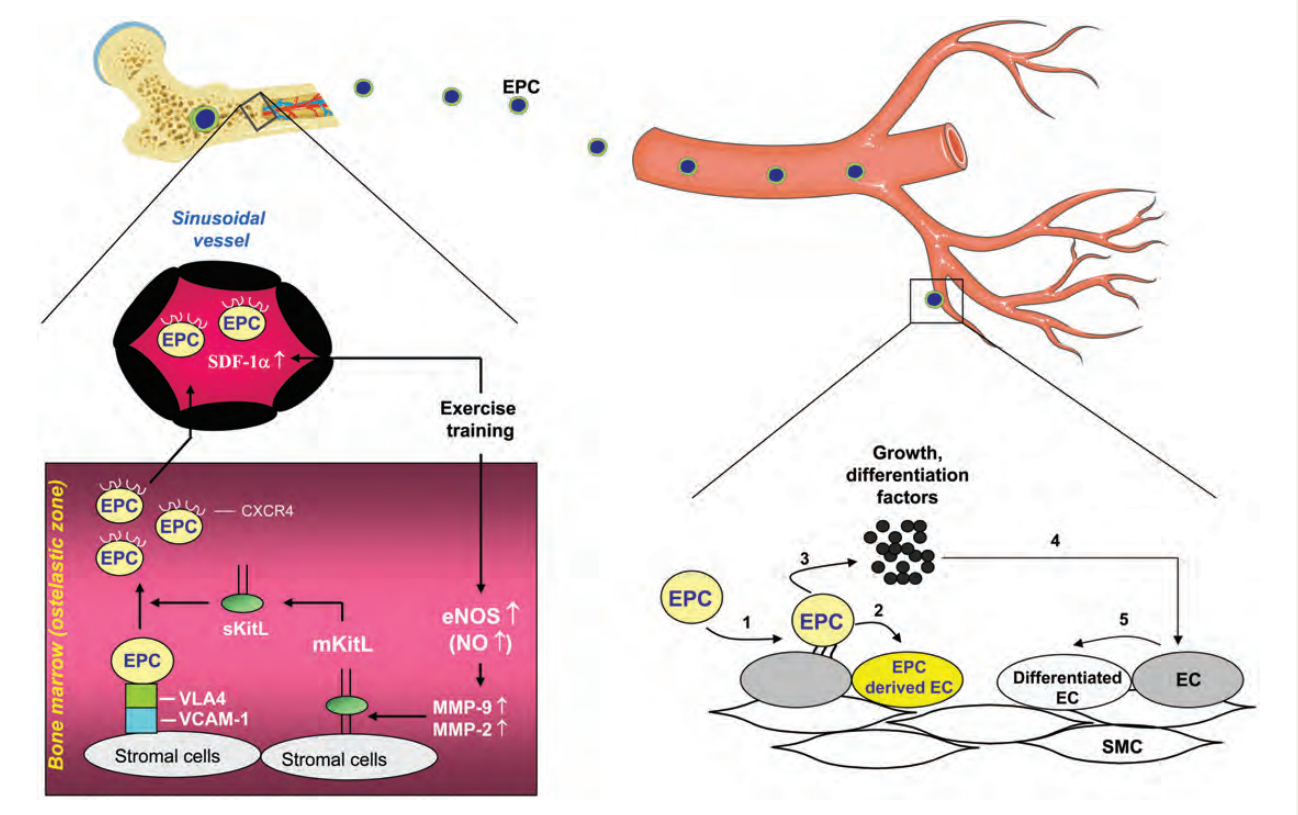

Figure 4 Exercise-induced mobilization of EPCs from the bone marrow leading to arteriogenesis or endothelial cell repair. Exercise-induced activation of eNOS and subsequently of MMP-2/9 results in the release of soluble cKit-ligand (sKitL). SkitL confers signals enhancing mobility of EPCs. Along an SDF-1 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.

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.[96] Yet in contrast, the use of swim training[97] or treadmill ET[98] 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[99] and CAD.[100]

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.[101–104] With respect to ET in humans, a significant inverse relationship between AGE content in the skin and muscle strength was observed.[105] 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.[106,107]

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.[108,109] In an elegant study, Thum *et al.*[110] 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.[111–114] 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.[115] 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.[113] With respect to the regulation of eNOS activity by increased shear stress, evidence from cell-culture experiments documented an involvement of miRNA-21,[116] 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.[117,118] With exception to these positive animal findings, results from human studies are conflicting (reviewed in Heaps and Parker[119]). Using angiographic methods, Niebauer *et al.*[120] 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.*[121] 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.[122] Mechanistically, the activation of the SDF-1/CXCR4 axis, which of note is also activated by ET,[91] 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,[123] with the most important suggested to be VEGF.[124] 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.[125]

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.[35] 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[126] 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.[127]

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.[128] In order to improve physical activity on a large scale, a task force was convened which recommended six interventions[129]:

(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'.[130]

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.[131] 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.[132] 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.[133,134] 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.[135,136] 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.[137] 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[138] and healthy children.[139]

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

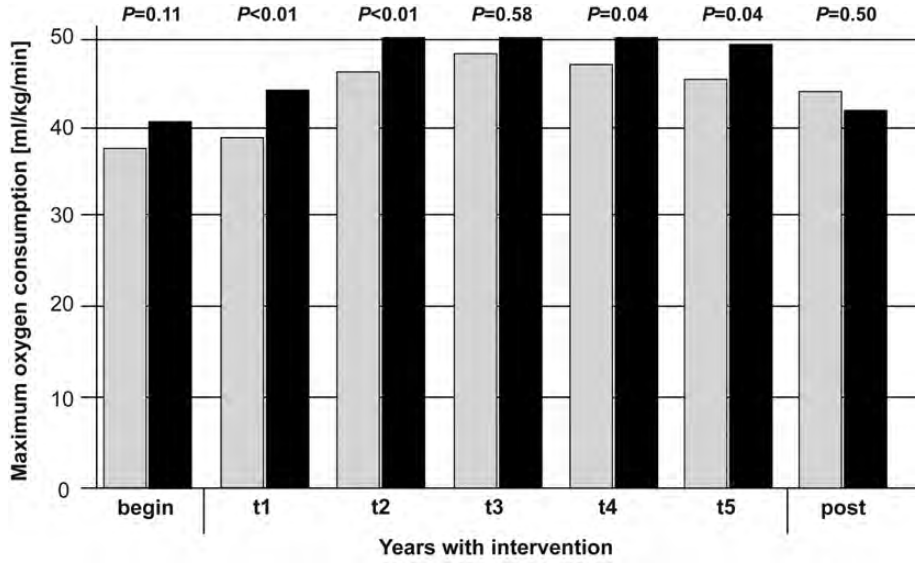

Figure 5 Impact of 5 years training intervention in school children on maximal oxygen consumption. Children were randomized either to a control (grey bars) or a training group (black bars). Maximal oxygen consumption was measured every year during the 5 years intervention (t1–t5) and 1 year after follow-up (post). Significance values between the control and intervention groups are shown on top of the graph for every year.

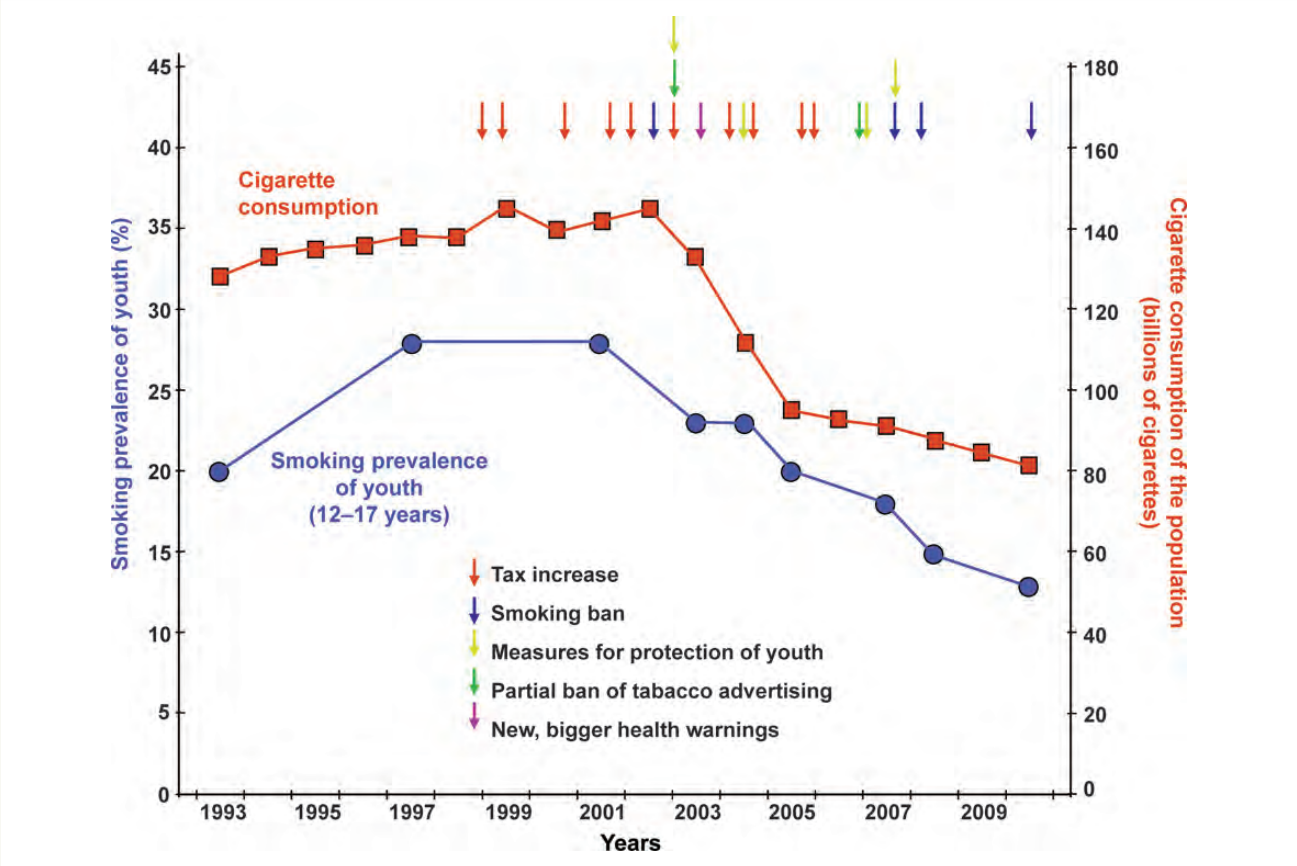

Figure 6 Impact of legal measures on cigarette consumption and of the population and the smoking prevalence of the youth in Germany between 1993 and 2010. *Source*: German Cancer Research Center, Unit Cancer Prevention/WHO Collaborating Centre for Tobacco Control, 2012.

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/TfLSillyMaps/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.[11] 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

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. In addition, as recently stated by Joyner[140] in an editorial comment, deconditioning should become a recognized syndrome or diagnosis. This would definitively facilitate the education of the general population as well as the medical community about the beneficial effects of ET as treatment options for several diseases.

In conclusion, physical activity is one of the most fundamental factors necessary for maintaining health and warding-off risk factors; long-term compliance, however, is poor in the vast majority of patients. Until today, all strategies to improve adherence significantly have failed and long-term trends seem to point the wrong direction. New concepts need to be contemplated, borrowing from successful fights against other risk factors.

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References

1. Morris J, Heady JA, Raffle PAB, Roberts CG, Parks JW. Coronary artery disease and physical activity of work. *Lancet* 1953;**265**:1053–1057.
2. Lee DC, Artero EG, Xuemei S, Blair SN. Review: mortality trends in the general population: the importance of cardiorespiratory fitness. *J Psychopharmacol* 2010; **24**:27–35.
3. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation* 2007;**116**:1081–1093.
4. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Scholte op Reimer WJ, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, Dudina A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Funck-Brentano C, Filippatos G, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Hellemans I, Altiner A, Bonora E, Durrington PN, Fagard R, Giampaoli S, Hemingway H, Hakansson J, Kjeldsen SE, Larsen ML, Mancia G, Manolis AJ, Orth-Gomer K, Pedersen T, Rayner M, Ryden L, Sammut M, Schneiderman N, Stalenhoef AF, Tokg+ Âzoglu L, Wiklund O, Zampelas A. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. *Eur Heart J* 2007; **28**:2375–2414.
5. Smith SC, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW, Lloyd-Jones DM, Minissian M, Mosca L, Peterson ED, Sacco RL, Spertus J, Stein JH, Taubert KA. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update. *Circulation* 2011;**124**:2458–2473.
6. Proper KI, Singh AS, van Mechelen W, Chinapaw MJM. Sedentary behaviors and health outcomes among adults: a systematic review of prospective studies. *Am J Prev Med* 2011;**40**:174–182.
7. Katzmarzyk PT, Lee IM. Sedentary behaviour and life expectancy in the USA: a cause-deleted life table analysis. *BMJ Open* 2012;**2**:e000828.
8. Wei M, Kampert JB, Barlow CE, Nichaman MZ, Gibbons LW, Paffenbarger RS, Blair SN. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *JAMA* 1999;**282**:1547–1553.
9. Nocon M, Hiemann T, Müller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil* 2008;**15**:239–246.
10. Kodama S. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 2009;**301**:2024–2035.
11. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; **346**:793–801.
12. Task FM, Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvänne M, Scholte op Reimer WJM, Vrints C, Wood D, Zamorano JL, Zannad F, Other experts who contributed to parts of the guidelines, Cooney MT, ESC Committee for Practice Guidelines (CPG), Bax J, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Document Review, Funck-Brentano C, Sirnes PA, Aboyans V, Ezquerra EA, Baigent C, Brotons C, Burell G, Ceriello A, De Sutter J, Deckers J, Del Prato S, Diener HC, Fitzsimons D, Fras Z, Hambrecht R, Jankowski P, Keil U, Kirby M, Larsen ML, Mancia G, Manolis AJ, McMurray J, Pajak A, Parkhomenko A, Rallidis L, Rigo F, Rocha E, Ruilope LM, van der Velde E, Vanuzzo D, Viigimaa M, Volpe M, Wiklund O, Wolpert C. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). *Eur Heart J* 2012;**33**:1635–1701.
13. Redberg RF, Benjamin EJ, Bittner V, Braun LT, Goff DC Jr, Havas S, Labarthe DR, Limacher MC, Lloyd-Jones DM, Mora S, Pearson TA, Radford MJ, Smetana GW, Spertus JA, Swegler EW. ACCF/AHA 2009 Performance measures for primary prevention of cardiovascular disease in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on performance measures (Writing Committee to Develop Performance Measures for Primary Prevention of Cardiovascular Disease) Developed in collaboration with the American Academy of Family Physicians; American Association of Cardiovascular and Pulmonary Rehabilitation; and Preventive Cardiovascular Nurses Association Endorsed by the American College of Preventive Medicine, American College of Sports Medicine, and Society for Women's Health Research. *J Am Coll Cardiol* 2009;**54**:1364–1405.
14. Lee IM, Skerrett PJ. Physical activity and all-cause mortality: what is the dose-response relation? *Med Sci Sports Exerc* 2001;**33**:S459–S471.
15. Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC, Chan HT, Tsao CK, Tsai SP, Wu X. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet* 2011;**378**: 1244–1253.
16. Shiroma EJ, Lee IM. Physical activity and cardiovascular health. *Circulation* 2010; **122**:743–752.
17. Sattelmair J, Pertman J, Ding EL, Kohl HW, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease / clinical perspective. *Circulation* 2011;**124**:789–795.
18. Wagner A, Simon C, Evans A, Ferrieres J, Montaye M, Ducimetiere P, Arveiler D on behalf of the PRIME Study Group. Physical activity and coronary event incidence in Northern Ireland and France. *Circulation* 2002;**105**:2247–2252.
19. Marwick TH, Hordern MD, Miller T, Chyun DA, Bertoni AG, Blumenthal RS, Philippides G, Rocchini A, on behalf of the American Heart Association Exercise CRaPCotCoCC, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, Council on Nutrition P. Exercise training for type 2 diabetes mellitus. *Circulation* 2009;**119**:3244–3262.
20. Sieverdes JC, Sui X, Lee DC, Church TS, McClain A, Hand GA, Blair SN. Physical activity, cardiorespiratory fitness and the incidence of type 2 diabetes in a prospective study of men. *Br J Sports Med* 2010;**44**:238–244.
21. Wing RR, Jakicic J, Nieberg R, Lang W, Blair SN, Cooper L, Hill JO, Johnson KC, Lewis CE. Fitness, fatness, and cardiovascular risk factors in type 2 diabetes: look ahead study. *Med Sci Sports Exerc* 2007;**39**:2107–2116.
22. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, Diabetes Prevention Programm Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;**346**:393–403.
23. Tanasescu M, Leitzmann MF, Rimm EB, Hu FB. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. *Circulation* 2003;**107**:2435–2439.
24. Ades PA, Savage PD, Toth MJ, Harvey-Berino J, Schneider DJ, Bunn JY, Audelin MC, Ludlow M. High-calorie-expenditure exercise. *Circulation* 2009; **119**:2671–2678.
25. McAuley PA, Artero EG, Sui X, Lee DC, Church TS, Lavie CJ, Myers JN, Espana-Romero V, Blair SN. The obesity paradox, cardiorespiratory fitness, and coronary heart disease. *Mayo Clin Proc* 2012;**87**:443–451.
26. Witt BJ, Jacobsen SJ, Weston SA, Killian JM, Meverden RA, Allison TG, Reeder GS, Roger V. Cardiac rehabilitation after myocardial infarction in the community. *J Am Coll Cardiol* 2004;**44**:988–996.
27. Hammill BG, Curtis LH, Schulman KA, Whellan DJ. Relationship between cardiac rehabilitation and long-term risks of death and myocardial infarction among elderly medicare beneficiaries. *Circulation* 2010;**121**:63–70.
28. Martin BJ, Hauer T, Arena R, Austford LD, Galbraith PD, Lewin AM, Knudtson ML, Ghali WA, Stone JA, Aggarwal SG. Cardiac rehabilitation attendance and outcomes in coronary artery disease patients/clinical perspective. *Circulation* 2012;**126**:677–687.

29. Goel K, Lennon RJ, Tilbury RT, Squires RW, Thomas RJ. Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community/clinical perspective. *Circulation* 2011;**123**: 2344–2352.
30. Suaya JA, Stason WB, Ades PA, Normand SL, Shepard DS. Cardiac rehabilitation and survival in older coronary patients. *J Am Coll Cardiol* 2009;**54**:25–33.
31. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, Skidmore B, Stone JA, Thompson DR, Oldridge N. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med* 2004;**116**:682–692.
32. Zwisler ADO, Soja AMB, Rasmussen S, Frederiksen M, Abadini S, Appel J, Rasmussen H, Gluud C, Iversen L, Sigurd B, Madsen M, Fischer-Hansen J. Hospital-based comprehensive cardiac rehabilitation versus usual care among patients with congestive heart failure, ischemic heart disease, or high risk of ischemic heart disease: 12-month results of a randomized clinical trial. *Am Heart J* 2008;**155**:1106–1113.
33. Giannuzzi P, Temporelli PL, Marchioli R, Maggioni AP, Balestroni G, Ceci V, Chieffo C, Gattone M, Griffo R, Schweiger C, Tavazzi L, Urbinati S, Valagussa F, Vanuzzo D. Global secondary prevention strategies to limit event recurrence after myocardial infarction: results of the gospel study, a multicenter, randomized controlled trial from the Italian cardiac rehabilitation network. *Arch intern med* 2008;**168**:2194–2204.
34. Hambrecht R, Niebauer J, Marburger CH, Grunze M, Kälberer B, Hauer K, Schlierf G, Kübler W, Schuler G. Various intensities of leisure time physical activity in patients with coronary artery disease: effects on cardiorespiratory fitness and progression of coronary atherosclerotic lesions. *J Am Coll Cardiol* 1993;**22**:468–477.
35. Niebauer J, Hambrecht R, Velich T, Hauer K, Marburger C, Kälberer B, Weiss C, von Hodenberg E, Schlierf G, Schuler G, Zimmermann R, Kübler W. Attenuated progression of coronary artery disease after 6 years of multifactorial risk intervention: role of physical exercise. *Circulation* 1997;**96**:2534–2541.
36. Belardinelli R, Paolini I, Cianci G, Piva R, Georgiou D, Purcaro A. Exercise training intervention after coronary angioplasty: the ETICA trial. *J Am Coll Cardiol* 2001;**37**:1891–1900.
37. Hambrecht R, Walther C, Möbius-Winkler S, Gielen S, Linke A, Conradi K, Erbs S, Kluge R, Kendziorra K, Sabri O, Sick P, Schuler G. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease - a randomized trail. *Circulation* 2004;**109**:1371–1378.
38. Taylor RS, Unal B, Critchley JA, Capewell S. Mortality reductions in patients receiving exercise-based cardiac rehabilitation: how much can be attributed to cardiovascular risk factor improvements? *Eur J Cardiovasc Prev Rehabil* 2006;**13**: 369–374.
39. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JM, Franklin B, Sanderson B, Southard D. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update. *Circulation* 2007;**115**:2675–2682.
40. EACPR Committee for Science Guidelines, Corrá U, Piepoli MF, Carree F, Heuschmann P, Hoffmann U, Verschuren M, Halcox J, Document Review, Giannuzzi P, Saner H, Wood D, Piepoli MF, Corra U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, McGee H, Mendes M, Niebauer J, Zwisler ADO, Schmid JP. Secondary prevention through cardiac rehabilitation: physical activity counselling and exercise training. *Eur Heart J* 2010;**31**: 1967–1974.
41. Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, Tjönna AE, Helgerud J, Slordahl SA, Lee SJ, Videm V, Bye A, Smith GL, Najjar SM, Ellingsen O, Skjaerpe T. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients. *Circulation* 2007;**115**:3086–3094.
42. Tjonna AE, Stolen TO, Bye A, Volden M, Slordahl SA, Odegard R, Skogvoll E, Wisloff U. Aerobic interval training reduces cardiovascular risk factors more than a multitreatment approach in overweight adolescents. *Clin Sci* 2009;**116**: 317–326.
43. Warburton DER, McKenzie DC, Haykowsky MJ, Taylor A, Shoemaker P, Ignaszewski AP, Chan SY. Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *Am J Cardiol* 2005; **95**:1080–1084.
44. Coppoolse R, Schols AM, Baarends EM, Mostert R, Akkermans MA, Janssen PP, Wouters EF. Interval versus continuous training in patients with severe COPD: a randomized clinical trial. *Eur Respir J* 1999;**14**:258–263.
45. Tjonna AE, Lee SJ, Rognmo O, Stolen TO, Bye A, Haram PM, Loennechen JP, Al-Share QY, Skogvoll E, Slordahl SA, Kemi OJ, Najjar SM, Wisloff U. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation* 2008;**118**:346–354.
46. Stoylen A, Conraads V, Halle M, Linke A, Prescott E, Ellingsen O. Controlled study of myocardial recovery after interval training in heart failure: SMARTEX-HF—rationale and design. *Eur J Prev Cardiol* 2012;**19**:813–821.
47. Kemi OJ, Wisloff U. Mechanisms of exercise-induced improvements in the contractile apparatus of the mammalian myocardium. *Acta Physiol* 2010;**199**: 425–439.
48. Adams V, Döring C, Schuler G. Impact of physical exercise on alterations in the skeletal muscle in patients with chronic heart failure. *Front Biosci* 2008;**13**: 302–311.
49. Kojda G, Hambrecht R. Molecular mechanisms of vascular adaptations to exercise. Physical activity as an effective antioxidant therapy? *Cardiovasc Res* 2005;**67**: 187–197.
50. Haram PM, Kemi OJ, Wisloff U. Adaptation of endothelium to exercise training: insights from experimental studies. *Front Biosci* 2008;**13**:336–346.
51. Busconi L, Michel T. Endothelial nitric oxide synthase; N-terminal myristoylation determines subcellular localization. *J Biol Chem* 1993;**268**:8410–8413.
52. Kolluru GK, Siamwala JH, Chatterjee S. eNOS phosphorylation in health and disease. *Biochimie* 2010;**92**:1186–1198.
53. Ortiz PA, Garvin JL. Trafficking and activation of eNOS in epithelial cells. *Acta Physiol Scand* 2003;**179**:107–114.
54. Boo YC, Sorescu G, Boyd N, Shiojima I, Walsh K, Du J, Jo H. Shear stress stimulates phosphorylation of endothelial nitric-oxide synthase at Ser1179 by Akt-independent mechanisms: role of protein kinase A. *J Biol Chem* 2002;**277**: 3388–3396.
55. Woodman CR, Muller JM, Laughlin MH, Price EM. Induction of nitric oxide synthase mRNA in coronary resistance arteries isolated from exercise-trained pigs. *Am J Physiol* 1997;**273**:H2575–H2579.
56. Hambrecht R, Adams V, Erbs S, Linke A, Kränkel N, Shu Y, Baither Y, Gielen S, Gummert JF, Mohr FW, Schuler G. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. *Circulation* 2003;**107**:3152–3158.
57. Pahakis MY, Kosky JR, Dull RO, Tarbell JM. The role of endothelial glycocalyx components in mechanotransduction of fluid shear stress. *Biochem Biophys Res Commun* 2007;**355**:228–233.
58. Jin ZG, Wong C, Wu J, Berk BC. Flow shear stress stimulates Gab1 tyrosine phosphorylation to mediate protein kinase B and Endothelial nitric-oxide synthase activation in endothelial cells. *J Biol Chem* 2005;**280**:12305–12309.
59. Yuhanna IS, Zhu Y, Cox BE, Hahner LD, Osborne-Lawrence S, Lu P, Marcel YL, Anderson RG, Mendelsohn ME, Hobbs HH, Shaul PW. High-density lipoprotein binding to scavenger receptor-BI activates endothelial nitric oxide synthase. *Nat Med* 2001;**7**:853–857.
60. Sorrentino SA, Besler C, Rohrer L, Meyer M, Heinrich K, Bahlmann FH, Mueller M, Horvath T, Doerries C, Heinemann M, Flemmer S, Markowski A, Manes C, Bahr MJ, Haller H, von Eckardstein A, Drexler H, Landmesser U. Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release Niacin therapy. *Circulation* 2010;**121**:110–122.
61. Besler C, Heinrich K, Rohrer L, Doerries C, Riwanto M, Shih DM, Chroni A, Yonekawa K, Stein S, Schaefer N, Mueller M, Akhmedov A, Daniil G, Manes C, Templin C, Wyss C, Maier W, Tanner FC, Matter CM, Corti R, Furlong C, Lusis AJ, von Eckardstein A, Fogelman AM, Lüscher TF, Landmesser U. Mechanisms underlying adverse effects of HDL on eNOS-activating pathways in patients with coronary artery disease. *J Clin Invest* 2011;**121**:2693–2708.
62. Charakida M, Besler C, Batuca JR, Sangle S, Marques S, Sousa M, Wang G, Tousoulis D, Delgado Alves J, Loukogeorgakis SP, Mackworth-Young C, ÓCruz D, Luscher T, Landmesser U, Deanfield JE. Vascular abnormalities, paraoxonase activity, and dysfunctional HDL in primary antiphospholipid syndrome. *JAMA* 2009;**302**:1210–1217.
63. Laurindo FR, Pedro Mde A, Barbeiro HV, Pileggi F, Carvalho MH, Augusto O, da Luz PL. Vascular free radical release. Ex vivo and in vivo evidence for a flow-dependent endothelial mechanism. *Circ Res* 1994;**74**:700–709.
64. De Keulenaer GW, Chappell DC, Ishizaka N, Nerem RM, Alexander RW, Griendling KK. Oscillatory and steady laminar shear stress differentially affect human endothelial redox state. Role of a superoxide-producing NADH-Oxidase. *Circ Res* 1998;**82**:1094–1101.
65. Adams V, Linke A, Kränkel N, Erbs S, Gielen S, Möbius-Winkler S, Gummert JF, Mohr FW, Schuler G, Hambrecht R. Impact of regular physical activity on the NAD(P)H oxidase and angiotensin receptor system in patients with coronary artery disease. *Circulation* 2005;**111**:555–562.
66. Inoue N, Ramasamy S, Fukai T, Nerem RM, Harrison DG. Shear stress modulates expression of Cu/Zn superoxide dismutase in human aortic endothelial cells. *Circ Res* 1996;**79**:32–37.
67. Fukai T, Siegfried MR, Ushio-Fukai M, Cheng Y, Kojda G, Harrison DG. Regulation of the vascular extracellular superoxide dismutase by nitric oxide and exercise training. *J Clin Invest* 2000;**105**:1631–1639.

68. Takeshita S, Inoue N, Ueyama T, Kawashima S, Yokoyama M. Shear stress enhances glutathione peroxidase expression in endothelial cells. *Biochem Biophys Res Commun* 2000;**273**:66–71.
69. Mueller CF, Widder JD, McNally JS, McCann L, Jones DP, Harrison DG. The role of the multidrug resistance preotein-1 in modulation of endothelial cell oxidative stress. *Circ Res* 2005;**97**:637–644.
70. Förstermann U, Münzel T. Endothelial nitric oxide synthase in vascular disease. *Circulation* 2006;**113**:1708–1714.
71. Widder JD, Chen W, Li L, Dikalov S, Thony B, Hatakeyama K, Harrison DG. Regulation of tetrahydrobiopterin biosynthesis by shear stress. *Circ Res* 2007; **101**:830–838.
72. Richter B, Niessner A, Penka M, Grdic M, Steiner S, Strasser B, Ziegler S, Zorn G, Maurer G, Simeon-Rudolf V, Wojta J, Huber K. Endurance training reduces circulating asymetric dimethylarginine and myeloperoxidase levels in persons at risk of coronary events. *Thromb Haemost* 2005;**94**:1306–1311.
73. Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, Witzenbichler B, Schatteman G, Isner JM. Isolation of putative progenitor endothelial cells for angioneogenesis. *Science* 1997;**275**:964–967.
74. Huang NF, Li S. Mesenchymal stem cells for vascular regeneration. *Regen Med* 2008;**3**:877–892.
75. Lenk K, Uhlemann M, Schuler G, Adams V. Role of endothelial progenitor cells in the beneficial effects of physical exercise on atherosclerosis and coronary artery disease. *J Appl Physiol* 2011;**111**:321–328.
76. Asahara T, Takahashi T, Masuda H. VEGF contributes to postnatal neovascularization by mobilizing bone-marrow endothelial progenitor cells. *EMBO J* 1999; **18**:3964–3972.
77. Li B, Sharpe EE, Maupin AB, Teleron AA, Pyle AL, Carmeliet P, Young PP. VEGF and PlGF promote adult vasculogenesis by enhancing EPC recruitment and vessel formation at the site of tumor neovascularization. *FASEB J* 2006;**20**: 1495–1497.
78. Cheng XW, Kuzuya M, Nakamura K, Maeda K, Tsuzuki M, Kim W, Sasaki T, Liu Z, Inoue N, Kondo T, Jin H, Numaguchi Y, Okumura K, Yokota M, Iguchi A, Murohara T. Mechanisms underlying the impairment of ischemia-induced neovascularization in matrix metalloproteinase 2-deficient mice. *Circ Res* 2007;**100**:904–913.
79. Huang PH, Chen YH, Wang CH, Chen JS, Tsai HY, Lin FY, Lo WY, Wu TC, Sata M, Chen JW, Lin SJ. Matrix metalloproteinase-9 is essential for ischemia-induced neovascularization by modulating bone marrow-derived endothelial progenitor cells. *Arterioscler Thromb Vasc Biol* 2009;**29**:1179–1184.
80. Lapidot T, Petit I. Current understanding of stem cell mobilization: The roles of chemokines, proteolytic enzymes, adhesion molecules, cytokines, and stromal cells. *Exp Hematol* 2002;**30**:973–981.
81. Heissig B, Hattori K, Dias S, Friedrich M, Ferris B, Hackett NR, Crystal RG, Besmer P, Lyden D, Moore MA, Werb Z, Rafii S. Recruitment of stem and progenitor cells from the bone marrow nighe requires MMP-9 mediated release of kit-ligand. *Cell* 2002;**109**:625–637.
82. Kalka C, Masuda H, Takahashi T, Kalka-Moll WM, Silver M, Kearney M, Li T, Isner J, Asahara T. Transplantation of ex vivo expanded endothelial progenitor cells for therapeutic neovascularization. *Proc Natl Acad Sci USA* 2000;**97**: 3422–3427.
83. Sata M. Circulating vascular progenitor cells contribute to vascular repair, remodeling, and lesion formation. *Trends Cardiovasc Med* 2003;**13**:249–253.
84. Sieveking DP, Buckle A, Celermajer DS, Ng MKC. Strikingly different angiogenic properties of endothelial progenitor cell subpopulations: insights from a novel human angiogenesis assay. *J Am Coll Cardiol* 2008;**51**:660–668.
85. Urbich C, Aicher A, Heeschen C, Dernbach E, Hofmann WK, Zeiher AM, Dimmeler S. Soluble factors released by endothelial progenitor cells promote migration of endothelial cells and cardiac resident progenitor cells. *J Mol Cell Cardiol* 2005;**39**:733–742.
86. Aicher A, Heeschen C, Mildner-Rihm C, Urbich C, Ihling C, Technau-Ihling K, Zeiher A, Dimmeler S. Essential role of endothelial nitric oxide synthase for mobilization of stem and progenitor cells. *Nat Med* 2003;**9**:1370–1376.
87. Iwakura A, Shastry S, Luedemann C, Hamada H, Kawamoto A, Kishore R, Zhu Y, Qin G, Silver M, Thorne T, Eaton L, Masuda H, Asahara T, Losordo DW. Estradiol enhances recovery after myocardial infarction by augmenting incorporation of bone marrow-derived endothelial progenitor cells into sites of ischemia-induced neovascularization via endothelial nitric oxide synthase-mediated activation of matrix metalloproteinase-9. *Circulation* 2006;**113**: 1605–1614.
88. Laufs U, Werner N, Link A, Endres M, Wassmann S, Jürgens K, Miche E, Böhm M, Nickenig G. Physical training increases endothelial progenitor cells, inhibition of neointima formation, and enhances angiogenesis. *Circulation* 2004;**109**: 220–226.
89. Askari AT, Unzek S, Popovic ZB, Goldman CK, Forudi F, Kiedrowski M, Rovner A, Ellis SG, Thomas JD, DiCorleto PE, Topol EJ, Penn MS. Effect of stromal-cell-derived factor 1 on stem-cell homing and tissue regeneration in ischaemic cardiomyopathy. *Lancet* 2003;**362**:697–703.
90. Sandri M, Adams V, Gielen S, Linke A, Lenk K, Krankel N, Lenz D, Erbs S, Scheinert D, Mohr FW, Schuler G, Hambrecht R. Effects of exercise and ischemia on mobilization and functional activation of blood-derived progenitor cells in patients with ischemic syndromes: results of 3 randomized studies. *Circulation* 2005;**111**:3391–3399.
91. Adams V, Heiker JT, Höllriegel R, Beck EB, Woitek FJ, Erbs S, Blüher M, Stumvoll M, Beck-Sickinger AG, Schuler G, Linke A. Adiponectin promotes the migration of circulating angiogenic cells through p38-mediated induction of the CXCR4 receptor. *Int J Cardiol* 2012. Advance Access published June 6, 2012, doi:10.1016/j.ijcard.2012.05.056.
92. Shibata R, Skurk C, Ouchi N, Galasso G, Kondo K, Ohashi T, Shimano M, Kihara S, Murohara T, Walsh K. Adiponectin promotes endothelial progenitor cell number and function. *FEBS Lett* 2008;**582**:1607–1612.
93. Arnett DK, Evans GW, Riley WA. Arterial stiffness: a new cardiovascular risk factor? *Am J Epidemiol* 1994;**140**:669–682.
94. Tanaka H, DeSouza CA, Seals DR. Absence of age-related increase in central arterial stiffness in physically active women. *Arterioscler Thromb Vasc Biol* 1998; **18**:127–132.
95. Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. *Circulation* 2000;**102**: 1270–1275.
96. Fleenor BS, Marshall KD, Durrant JR, Lesniewski LA, Seals DR. Arterial stiffening with ageing is associated with transforming growth factor-ß1-related changes in adventitial collagen: reversal by aerobic exercise. *J Physiol* 2010;**588**:3971–3982.
97. Nosaka T, Tanaka H, Watanabe I, Sato M, Matsuda M. Influence of regular exercise on age-related changes in arterial elasticity: mechanistic insights from wall compositions in rat aorta. *Can J Appl Physiol* 2003;**28**:201–212.
98. Maeda S, Iemitsu M, Miyauchi T, Kuno S, Matsuda M, Tanaka H. Aortic stiffness and aerobic exercise: mechanistic insight from microarray analyses. *Med Sci Sports Exerc* 2005;**37**:1710–1716.
99. Collier SR, Kanaley JA, Carhart R Jr, Frechette V, Tobin MM, Hall AK, Luckenbaugh AN, Fernhall B. Effect of 4 weeks of aerobic or resistance exercise training on arterial stiffness, blood flow and blood pressure in pre- and stage-1 hypertensives. *J Hum Hypertens* 2008;**22**:678–686.
100. Edwards DG, Schofield RS, Magyari PM, Nichols WW, Braith RW. Effect of exercise training on central aortic pressure wave reflection in coronary artery disease. *Am J Hypertens* 2004;**17**:540–543.
101. Basta G, Lazzerini G, Massaro M, Simoncini T, Tanganelli P, Fu C, Kislinger T, Stern DM, Schmidt AM, De Caterina R. Advanced glycation end products activate endothelium through signal-transduction receptor RAGE. *Circulation* 2002; **105**:816–822.
102. Wautier MP, Chappey O, Corda S, Stern DM, Schmidt AM, Wautier JL. Activation of NADPH oxidase by AGE links oxidant stress to altered gene expression via RAGE. *Am J Physiol Endocrinol Metab* 2001;**280**:E685–E694.
103. Hogan M, Cerami A, Bucala R. Advanced glycosylation endproducts block the antiproliferative effect of nitric oxide. Role in the vascular and renal complications of diabetes mellitus. *J Clin Invest* 1992;**90**:1110–1115.
104. Chen J, Brodsky SV, Goligorsky DM, Hampel DJ, Li H, Gross SS, Goligorsky MS. Glycated collagen I induces premature senescence-like phenotypic changes in endothelial cells. *Circ Res* 2002;**90**:1290–1298.
105. Momma H, Niu K, Kobayashi Y, Guan L, Sato M, Guo H, Chujo M, Otomo A, Yufei C, Tadaura H, Saito T, Mori T, Miyata T, Nagatomi R. Skin advanced glycation end product accumulation and muscle strength among adult men. *Eur J Appl Physiol* 2011;**111**:1545–1552.
106. Boor P, Celec P, Behuliak M, Grancicì P, Kebis A, Kukan M, Pronayova N, Liptaj T, Ostendorf T, Sebekova K. Regular moderate exercise reduces advanced glycation and ameliorates early diabetic nephropathy in obese Zucker rats. *Metabolism* 2009;**58**:1669–1677.
107. Choi SY, Chang HJ, Choi SI, Kim KI, Cho YS, Youn TJ, Chung WY, Chae IH, Choi DJ, Kim HS, Kim CH, Oh BH, Kim MH. Long-term exercise training attenuates age-related diastolic dysfunction: association of myocardial collagen cross-linking. *J Korean Med Sci* 2009;**24**:32–39.
108. van Rooij E, Sutherland LB, Liu N, Williams AH, McAnally J, Gerard RD, Richardson JA, Olson EN. A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart failure. *Proc Natl Acad Sci USA* 2006;**103**:18255–18260.
109. Thum T, Galuppo P, Wolf C, Fiedler J, Kneitz S, van Laake LW, Doevendans PA, Mummery CL, Borlak J, Haverich A, Gross C, Engelhardt S, Ertl G, Bauersachs J. MicroRNAs in the Human Heart. *Circulation* 2007;**116**:258–267.
110. Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, Galuppo P, Just S, Rottbauer W, Frantz S, Castoldi M, Soutschek J, Koteliansky V, Rosenwald A, Basson MA, Licht JD, Pena JTR, Rouhanifard SH, Muckenthaler MU, Tuschl T, Martin GR, Bauersachs J, Engelhardt S. MicroRNA-21 contributes to myocardial

disease by stimulating MAP kinase signalling in fibroblasts. *Nature* 2008;**456**:980–984.
111. Da Silva ND, Fernandes T, Soci UP, Monteiro AW, Phillips MI, De Oliveira EM. Swimming training in rats increases cardiac microRNA-126 expression and angiogenesis. *Med Sci Sports Exerc* 2012;**44**:1453–1462.
112. Fernandes T, Magalhaes FC, Roque FR, Phillips MI, Oliveira EM. Exercise training prevents the microvascular rarefaction in hypertension balancing angiogenic and apoptotic factors. *Hypertension* 2012;**59**:513–520.
113. Soci UPR, Fernandes T, Hashimoto NY, Mota GF, Amadeu MA, Rosa KT, Irigoyen MC, Phillips MI, Oliveira EM. MicroRNAs 29 are involved in the improvement of ventricular compliance promoted by aerobic exercise training in rats. *Physiol Genomics* 2011;**43**:665–673.
114. Fernandes T, Hashimoto NY, Magalhaes FC, Fernandes FB, Casarini DE, Carmona AK, Krieger JE, Phillips MI, Oliveira EM. Aerobic exercise training–induced left ventricular hypertrophy involves regulatory microRNAs, decreased angiotensin-converting enzyme-angiotensin II, and synergistic regulation of angiotensin-converting enzyme 2-angiotensin (1–7). *Hypertension* 2011;**58**:182–189.
115. Fish JE, Santoro MM, Morton SU, Yu S, Yeh RF, Wythe JD, Ivey KN, Bruneau BG, Stainier DYR, Srivastava D. miR-126 regulates angiogenic signaling and vascular integrity. *Dev Cell* 2008;**15**:272–284.
116. Weber M, Baker MB, Moore JP, Searles CD. MiR-21 is induced in endothelial cells by shear stress and modulates apoptosis and eNOS activity. *Biochem Biophys Res Commun* 2010;**393**:643–648.
117. Stevenson JAF, Feleik V, Rechnitzer P, Beaton JR. Effect of exercise on coronary tree size in the rat. *Circ Res* 1964;**15**:265–269.
118. Roth DM, White FC, Nichols ML, Dobbs SL, Longhurst JC, Bloor CM. Effect of long-term exercise on regional myocardial function and coronary collateral development after gradual coronary artery occlusion in pigs. *Circulation* 1990;**82**:1778–1789.
119. Heaps CL, Parker JL. Effects of exercise training on coronary collateralization and control of collateral resistance. *J Appl Physiol* 2011;**111**:587–598.
120. Niebauer J, Hambrecht R, Marburger C, Hauer K, Velich T, von Hodenberg E, Schlierf G, Kübler W, Schuler G. Impact of intensive physical exercise and low-fat diet on collateral vessel formation in stable angina pectoris and angiographically confirmed coronary artery disease. *Am J Cardiol* 1996;**76**:771–775.
121. Zbinden R, Zbinden S, Meier P, Hutter D, Billinger M, Wahl A, Schmid JP, Windecker S, Meier B, Seiler C. Coronary collateral flow in response to endurance exercise training. *Eur J Cardiovasc Prev Rehabil* 2007;**14**:250–257.
122. Heil M, Schaper W. Influence of mechanical, cellular, and molecular factors on collateral artery growth (arteriogenesis). *Circ Res* 2004;**95**:449–458.
123. Kersten JR, Pagel PS, Chilian WM, Warltier DC. Multifactorial basis for coronary collateralization: a complex adaptive response to ischemia. *Cardiovasc Res* 1999;**43**:44–57.
124. Thomas KA. Vascular endothelial growth factor, a potent and selective angiogenic agent. *J Biol Chem* 1996;**271**:603–606.
125. Lu X, Wu T, Huang P, Lin S, Qiu F, Meng XB, Gao J, Li JA. Effect and mechanism of intermittent myocardial ischemia induced by exercise on coronary collateral formation. *Am J Phys Med Rehabil* 2008;**87**:803–814.
126. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Pina IL. Efficacy and safety of exercise training in patients with chronic heart failure: Hf-action randomized controlled trial. *JAMA* 2009;**301**:1439–1450.
127. Conraads VM, Deaton C, Piotrowicz E, Santaularia N, Tierney S, Piepoli MF, Pieske B, Schmid JP, Dickstein K, Ponikowski PP, Jaarsma T. Adherence of heart failure patients to exercise: barriers and possible solutions. *Eur J Heart Fail* 2012;**14**:451–458.
128. Jiles R, Hughes E, Murphy W, Flowers N, McCracken M, Roberts H, Ochner M, Balluz L, Mokdad A, Elam-Evans L, Giles W. Surveillance for certain health behaviors among states and selected local areas–Behavioral Risk Factor Surveillance System, United States, 2003. *MMWR Surveill Summ* 2005;**54**:1–116.
129. Increasing physical activity. A report on recommendations of the Task Force on Community Preventive Services. *MMWR Recomm Rep* 2001;**50**:1–14.
130. Huffman MD, Capewell S, Ning H, Shay CM, Ford ES, Lloyd-Jones DM. Cardiovascular health behavior and health factor changes (1988–2008) and projections to 2020 / clinical perspective. *Circulation* 2012;**125**:2595–2602.
131. Leijon ME, Faskunger J, Bendtsen P, Festin K, Nilsen P. Who is not adhering to physical activity referrals, and why? *Scand J Prim Health Care* 2011;**29**:234–240.
132. Strong WB, Malina RM, Blimkie CJR, Daniels SR, Dishman RK, Gutin B, Hergenroeder AC, Must A, Nixon PA, Pivarnik JM, Rowland T, Trost S, Trudeau F. Evidence based physical activity for school-age youth. *J Pediatr* 2005;**146**:732–737.
133. Cardon GM, De Bourdeaudhuij IM. Are preschool children active enough? Objectively measured physical activity levels. *Res Q Exerc Sport* 2008;**79**:326–332.
134. Reilly JJ. Low levels of objectively measured physical activity in preschoolers in child care. *Med Sci Sports Exerc* 2010;**42**:502–507.
135. Steinbeck KS. The importance of physical activity in the prevention of overweight and obesity in childhood: a review and an opinion. *Obes Rev* 2001;**2**:117–130.
136. Zahner L, Puder J, Roth R, Schmid M, Guldimann R, Puhse U, Knopfli M, Braun-Fahrlander C, Marti B, Kriemler S. A school-based physical activity program to improve health and fitness in children aged 6–13 years ('Kinder-Sportstudie KISS'): study design of a randomized controlled trial [ISRCTN15360785]. *BMC Public Health* 2006;**6**:147.
137. Walther C, Gaede L, Adams V, Gelbrich G, Leichtle A, Erbs S, Sonnabend M, Fikenzer K, Korner A, Kiess W, Bruegel M, Thiery J, Schuler G. Effect of increased exercise in school children on physical fitness and endothelial progenitor cells: a prospective randomized trial. *Circulation* 2009;**120**:2251–2259.
138. Corte de Araujo AC, Roschel H, Picano AR, do Prado DML, Villares SMF, de Sa Pinto ALc, Gualano B. Similar health benefits of endurance and high-intensity interval training in obese children. *PLoS One* 2012;**7**:e42747.
139. Baquet G, Gamelin FX, Mucci P, Thévenet D, Van Praagh E, Berthoin S. Continuous vs. interval aerobic training in 8- to 11-year-old children. *J Strength Cond Res* 2010;**24**:1381–1388.
140. Joyner MJ. Standing up for exercise: should deconditioning be medicalized? *J Physiol* 2012;**590**:3413–3414.