Abstract
Numerous epidemiological studies show that physical activity improves health and decreases cardiovascular mortality by approximately 30% across age, gender, and race/ethnicity. Regular physical activity using large muscle groups, such as walking, running, or swimming, produces cardiovascular adaptations that increase exercise capacity, endurance, and skeletal muscle strength. Habitual physical activity also prevents the development of coronary artery disease and reduces symptoms and progression in patients with established cardiovascular disease. Exercise capacity has shown to be a more powerful predictor of mortality among men than other established risk factors for cardiovascular disease. Positive and protective effects of physical activity for the cardiovascular system are mediated through the endothelium, the autonomous nervous system, the clotting/coagulation system, and in particular through anti-inflammatory effects. This article summarizes the evidence for the benefits of physical activity and exercise in the prevention and treatment of cardiovascular disease.

State-of-the-Art Article

Exercise is medicine
Prof. Dr. med. Hugo Saner, MD
Preventive Cardiology and Sports Medicine, University Hospitals, Inselspital Bern, CH-3010 Bern, Switzerland

Key Words
• Physical activity
• Exercise
• Fitness
• Cardiovascular risk factors
• Cardiovascular system
• Cardiovascular mortality

Introduction
Over the past 50 years since the pioneering work of Prof. JN Morris, numerous prospective epidemiological studies have consistently shown an inverse association between physical activity and coronary heart disease (CHD). The evidence for the role of physical activity and exercise in preventing CHD is compelling. Leisure time physical activity is associated with a 30–50% reduction in risk of CHD and there is a dose–response relation between physical activity and risk of CHD. Randomized trials have shown physical activity to reduce atherosclerotic risk factors such as obesity, insulin resistance, and blood pressure, and to improve physical fitness.
resistance, blood pressure, and blood lipids. A sedentary lifestyle is now considered to be one of the major risk factors for CHD. With increasing obesity and sedentary lifestyle in most countries, the importance of promoting physical activity has been on the agenda in most government health initiatives for many years. In this article, we describe the cardiovascular effects of physical activity and exercise and their impact on cardiovascular health and mortality.

**Physical activity, exercise capacity, and mortality**

Over the past several decades, numerous large cohort studies have attempted to quantify the protective effect of physical activity on cardiovascular and all-cause mortality. These large cohort studies assessed self-reported physical activity, objective measures of physical fitness, activities of daily living, and systematic exercise training to determine the risk associated with a sedentary lifestyle in men and women. The first scientific evidence regarding the beneficial effects of work associated with exercise training was published by Morris in 1953, who examined the incidence of coronary artery disease (CAD) in London bus drivers' teams. He clearly documented that the incidence of CAD was less in the middle-age conductors than in the sedentary drivers of the same age. In 1975, Paffenbarger and Hale found a similar relationship between work activity and CAD mortality in dockers vs. office workers. A significant correlation between leisure time physical activity and mortality has been shown in the Finnish Twin Cohort Study. They investigated leisure time physical activity and mortality with respect to familial aggregation of health habits during childhood and factors that may enable some individuals to achieve higher levels of fitness. The hazard ratio for death adjusted for age and sex was 0.71 (95% CI 0.6–0.81) in occasional exercisers and 0.57 (95% CI 0.45–0.74) in conditioning exercisers (Figure 1). Absolute peak exercise capacity was a stronger predictor of the risk of death than the percentage of the age-predicted value achieved, and there was no interaction between the use or non-use of beta-blockade and the predictive power of exercise capacity. Each 1 MET increase in exercise capacity conferred a 12% improvement in survival.

In conclusion, exercise capacity has shown to be a more powerful predictor of mortality among men than other established risk factors for cardiovascular disease. One of the largest and most important meta-analyses of studies on physical activity and cardiovascular health concluded that the protective effect of physical activity for cardiovascular health is maintained across a large age group, gender, and race/ethnicity and that the mean reduction of mortality by physical activity is around 30%. Based on these studies, all major cardiovascular societies around the world made physical activity part of their guidelines for prevention of CVD with a Class I recommendation, recommending at least 30 minutes of moderate-intensity aerobic activity, 7 days per week with a minimum of 5 days per week.

Subjects were classified into two groups: 3,679 had an abnormal exercise test result or a history of cardiovascular disease, or both, and 2,534 had a normal exercise test result and no history of cardiovascular disease. Overall mortality was the end point. After adjustment for age, peak exercise capacity measure in metabolic equivalents (METs) was the strongest predictor of the risk of death among both normal subjects and those with cardiovascular disease (Figure 1). Absolute peak exercise capacity was a stronger predictor of the risk of death than the percentage of the age-predicted value achieved, and there was no interaction between the use or non-use of beta-blockade and the predictive power of exercise capacity. Each 1 MET increase in exercise capacity conferred a 12% improvement in survival.

**Exercise and the cardiovascular system**

Scientific evidence clearly indicates that physical activity has profound positive effects not only on exercise capacity, behavioral characteristics, and quality of life, but also on metabolism and body composition, collateral vessel growth, and mobilization of endothelial progenitor cells (Figure 2). The positive and protective effects of exercise for the cardiovascular system are mainly mediated through the endothelium, the autonomous nervous system, the clotting/coagulation system, and through anti-inflammatory effects (Figure 3).

Many of the main effects of exercise on the cardiovascular system are thought to be mediated by its effect on the carefully orchestrated interplay between the sympathetic and parasympathetic nervous systems. Specifically, exercise training has been shown to increase resting parasympathetic tone and to decrease sympathetic tone in both humans and animals. An abnormal heart rate recovery reflects abnormal vagal tone and has been shown to have prognostic value in multiple patient populations. It has also been shown to give additional prognostic information independently of functional capacity, ischemia, and the results of coronary angiography. Beneficial autonomic responses have been found in healthy adults, in patients with heart failure, and in patients with acute myocardial infarction (MI).

Relationship between exercise and various measures of clotting/coagulation have been reported for more than 80 years. As hemostatic mechanisms have been implicated in disease and have been manipulated in therapy, the relationship between exercise and hemostasis merits attention. Physical activity increases plasma tissue plasminogen activator (tPA) activity and by this fibrinolysis, decreases PAI-1 activity, fibrinogen activity, coagulation factors VII and IX, von Willebrand factor, and D-dimer levels. Even a single bout of walking exercise has shown to enhance endogenous fibrinolysis by increasing plasma tPA activity and decreasing PAI-1 activity.

There is a strong association between cardiorespiratory fitness and C-reactive protein (CRP) in men. Increased cardiorespiratory fitness is correlated with lower levels of CRP in men. This is true in cross-sectional studies of healthy men. Positive effects of exercise training and fitness have also been shown for other inflammatory markers such as interleukin-6, tumor necrosis factor-α, myeloperoxidase, lipoprotein-associated phospholipase A2, matrix metalloproteinase-9, and others. Secondary prevention through exercise-based cardiac rehabilitation (CR) has also shown to reduce inflammation demonstrated by a significant reduction in CRP independent of body weight and cholesterol levels.

**Reduction of atherosclerotic risk factors**

Physical inactivity increases oxidative stress, endothelial dysfunction, and atherosclerosis, whereas physical...
An inflammatory mean (±SD) of 6.2 ± 3.7 years of follow-up. Subjects had cardiovascular death (reviewed in Lee et al.). Myers et al. found familial factors are taken into account. The effect of physical activity remained after controlling for sex was 0.71 (95% CI: 0.6–0.81) in occasional exercisers compared with those who were sedentary. The beneficial reduction of mortality by physical activity is around 30%. Based on these studies, all major cardiovascular disease (CAD) in London bus drivers’ teams. He clearly documented that the incidence of CAD was less in the middle-age conductors than in the sedentary drivers of the same age. In 1975, Paffenbarger and Hale found a similar relationship between work activity and CAD mortality in dockers vs. office workers. A significant correlation between leisure time physical activity and mortality has been shown in the Finnish Twin Cohort Study. They investigated leisure time physical activity and mortality with respect to familiy aggregation of health habits during childhood and factors that may enable some individuals to achieve higher levels of fitness. The hazard ratio for death adjusted for age and sex was 0.71 (95% CI: 0.6–0.81) in occasional exercisers and 0.57 (95% CI: 0.45–0.74) in conditioning exercisers compared with those who were sedentary. The beneficial effect of physical activity remained after controlling for other predictors of mortality. The main finding of this study is that leisure-time physical activity is associated with reduced mortality, even after genetic and other familial factors are taken into account. Subsequently, studies in more than 1,000 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.). Myers et al. found a total of 2,013 consecutive men referred for treadmill exercise testing for clinical reasons during a mean (±SD) of 6.2 ± 3.7 years of follow-up. Subjects were classified into two groups: 3,679 had an abnormal exercise test result or a history of cardiovascular disease, or both, and 2,534 had a normal exercise test result and no history of cardiovascular disease. Overall mortality was the end point. After adjustment for age, peak exercise capacity measure in metabolic equivalents (METs) was the strongest predictor of the risk of death among both normal subjects and those with cardiovascular disease (Figure 1). Absolute peak exercise capacity was a stronger predictor of the risk of death than the percentage of the age-predicted value achieved, and there was no interaction between the use or non-use of beta-blockade and the predictive power of exercise capacity. Each 1 MET increase in exercise capacity conferred a 12% improvement in survival.

Over the past several decades, numerous large cohort studies have attempted to quantify the protective effect of physical activity on cardiovascular and all-cause mortality. These large cohort studies assessed self-reported physical activity, objective measures of physical fitness, activities of daily living, and systematic exercise training to determine the risk associated with a sedentary lifestyle in men and women. The first scientific evidence regarding the beneficial effects of work associated with exercise training was published by Morris in 1953, who examined the incidence of coronary artery disease (CAD) in London bus drivers’ teams. He clearly documented that the incidence of CAD was less in the middle-age conductors than in the sedentary drivers of the same age. In 1975, Paffenbarger and Hale found a similar relationship between work activity and CAD mortality in dockers vs. office workers. A significant correlation between leisure time physical activity and mortality has been shown in the Finnish Twin Cohort Study. They investigated leisure time physical activity and mortality with respect to familial aggregation of health habits during childhood and factors that may enable some individuals to achieve higher levels of fitness. The hazard ratio for death adjusted for age and sex was 0.71 (95% CI: 0.6–0.81) in occasional exercisers and 0.57 (95% CI: 0.45–0.74) in conditioning exercisers compared with those who were sedentary. The beneficial effect of physical activity remained after controlling for other predictors of mortality. The main finding of this study is that leisure-time physical activity is associated with reduced mortality, even after genetic and other familial factors are taken into account. Subsequently, studies in more than 1,000 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.). Myers et al. found a total of 2,013 consecutive men referred for treadmill exercise testing for clinical reasons during a mean (±SD) of 6.2 ± 3.7 years of follow-up. Subjects were classified into two groups: 3,679 had an abnormal exercise test result or a history of cardiovascular disease, or both, and 2,534 had a normal exercise test result and no history of cardiovascular disease. Overall mortality was the end point. After adjustment for age, peak exercise capacity measure in metabolic equivalents (METs) was the strongest predictor of the risk of death among both normal subjects and those with cardiovascular disease (Figure 1). Absolute peak exercise capacity was a stronger predictor of the risk of death than the percentage of the age-predicted value achieved, and there was no interaction between the use or non-use of beta-blockade and the predictive power of exercise capacity. Each 1 MET increase in exercise capacity conferred a 12% improvement in survival.

Exercise and the cardiovascular system
Scientific evidence clearly indicates that physical activity has profound positive effects not only on exercise capacity, behavioral characteristics, and quality of life, but also on metabolism and body composition, collateral vessel growth, and mobilization of endothelial progenitor cells (Figure 2). The positive and protective effects of exercise for the cardiovascular system are mainly mediated through the endothelium, the autonomous nervous system, the clotting/coagulation system, and through anti-inflammatory effects (Figure 3).
Increased mitochondrial activity prevents these negative developments. Physical activity also helps to treat many established atherosclerotic risk factors, including elevated blood pressure, insulin resistance and glucose intolerance, elevated triglyceride concentration, low high-density lipoprotein (HDL) cholesterol concentrations, and obesity. Exercise in combination with weight reduction can decrease low-density lipoprotein (LDL) cholesterol concentrations and limit the reduction in HDL-cholesterol that often occurs with a reduction in dietary saturated fat (Figure 4). In obese persons, increased delivery of fatty acids to myocytes leads to a defect in insulin signaling. The resistance to insulin action in muscle leads to more generalized insulin resistance and increased release of fatty acids from adipose tissue. The liver synthesizes and secretes increased amounts of triglycerides and apolipoprotein B in the form of very-low-density lipoprotein (VLDL). Increased levels of triglycerides in VLDLs are exchanged for cholesterol esters in low-density lipoprotein and high-density lipoprotein. Subsequent lipolysis of HDL and LDL triglycerides results in decreased size of particles. Exercise may reverse these abnormalities in part by diverting fatty acids in muscle toward mitochondrial oxidation. Other mechanisms for changes in LDL and HDL include increases in lipoprotein lipase activity and decreases in hepatic lipase and cholesteryl ester transfer protein CETP. The average reduction in systolic and diastolic blood pressure was 3.4 and 2.4 mmHg, respectively. Baseline blood pressure is an important determinant of the exercise effect. Average systolic and diastolic blood pressures decreased to 2.6 and 1.8 mmHg in normotensive subjects and to 7.4 and 5.8 mmHg in hypertensive subjects, suggesting that exercise may serve as the only therapy required in some mildly hypertensive subjects. There was no relationship between the weekly training frequency, time per session, or intensity of exercise training and the magnitude of the blood pressure reduction, which suggests that the dose response curve for exercise and blood pressure is flat. Several studies have examined the adjunctive effect of exercise on smoking cessation. Continuous smoking cessation may be achieved in about 20% of patients compared with 10% in controls for at least 2 months and 12% in exercisers compared to 5% in controls at 12 months follow-up. Results are preliminary, but they suggest that physical activity facilitates long-term smoking cessation by increasing the initial quit rate.

Endothelial repair by stem cells

Endothelial progenitor cells (EPCs) and mesenchymal stem cells possess the potential for vascular regeneration. The current guidelines on CR-exercise training recommends moderate intensity exercise training with a dose–response between physical activity and risk of CHD. The most recent and comprehensive meta-analysis done by the Cochrane Collaboration identified randomized controlled trials of exercise-based CR. Studies included men and women of all ages who had had MI, coronary artery bypass graft (CABG), or percutaneous transluminal coronary angioplasty (PTCA) or who have angina pectoris or CAD defined by angiography. This systematic review has allowed analyses of 47 studies randomizing 10,794 patients to exercise-based CR or usual care. In medium to long-term trials (i.e., 12 or more months follow-up), exercise-based CR reduced overall and cardiovascular mortality [RR: 0.87 (95% CI: 0.75–0.99) and 0.74 (95% CI: 0.63–0.87), respectively], and hospital admission [RR: 0.69 (95% CI: 0.51–0.93) in the shorter term (<12 months follow up) with no evidence of heterogeneity of effect across trial. CR did not reduce the risk of total MI, CABG, or PTCA.

Several observational studies have been published regarding the relation between participation in a CR program and the cardiovascular prognosis in post-MI, post-PTCA, and elderly CHD patients. Several assessments documented that aerobic exercise training is associated with better cardiovascular outcomes, including in patients with diabetes, severe chronic obstructive pulmonary disease, and metabolic syndrome. However, before high-intensity interval training can be recommended in CHF patients, the validity of high-intensity interval training needs to be confirmed in larger multi-center studies. Exercise is medicine.
Increased mitochondrial effect of exercise training on resting blood pressure. (Adapted from Tall AR, N Engl J Med. 2002; 347: 1522) Mechanism of reversal by exercise

Figure 4: Metabolic abnormalities in obese persons and persons with insulin resistance and the potential mechanism of reversal by exercise

(Adapted from Tall AR, N Engl J Med. 2002; 347: 1522–24) At least 44 randomized controlled trials have studied the effect of exercise training on resting blood pressure. The average reduction in systolic and diastolic blood pressure was 3.4 and 2.4 mmHg, respectively. Baseline blood pressure is an important determinant of the exercise effect. Average systolic and diastolic blood pressures decreased to 2.6 and 1.8 mmHg in normotensive subjects and to 7.4 and 5.8 mmHg in hypertensive subjects, suggesting that exercise may serve as the only therapy required in some mildly hypertensive subjects. There was no relationship between the weekly training frequency, time per session, or intensity of exercise training and the magnitude of the blood pressure reduction, which suggests that the dose response curve for exercise and blood pressure is flat.

Several studies have examined the adjunctive effect of exercise on smoking cessation. Continuous smoking cessation may be achieved in about 20% of patients compared with 10% in controls for at least 2 months and 12% in exercisers compared to 5% in controls at 12 months follow-up. Results are preliminary, but they suggest that physical activity facilitates long-term smoking cessation by increasing the initial quit rate.

Endothelial repair by stem cells

Endothelial progenitor cells (EPCs) and mesenchymal stem cells possess the potential for vascular regeneration. Decreased capacity of EPCs are found with increasing age, with increasing numbers of risk factors, and with the presence of ischemic heart disease. EPCs are mobilized by ischemia, exercise, chemokines, and cytokines, and factor vascular endothelial growth factor (VEGF) and hydroxymethylglutaryl-CoA reductase inhibitors. These findings indicate that ischemia-induced gain in VO2 peak should thus make a difference not only in functional capacity but also in survival prospects. Flow-mediated shear stress is the mediator between exercise intensity and a complex pattern of intercellular regulations. Increased exercise intensity leads to increased shear stress and up-regulates eNOS activity either in cell culture, animal, or human studies.

The current guidelines on CR exercise training recommend endurance exercise with moderate intensity at 50–85% (mostly 70–85%) of peak heart rate (HR peak) for CAD and CHF patients. However, some researchers employed high-intensity aerobic interval training with four cycles of 4 minutes at high intensity (90–95% of HR peak). After 3 months of exercise training, peak VO2 increased more with high-intensity interval training than moderate continuous training (146% vs. 114%). This study caused a lot of discussion in regard to optimal training intensity and mode of exercise. In addition to CHF, aerobic interval training has proven beneficial in obese adolescents, in patients with CAD, severe chronic obstructive pulmonary disease, or metabolic syndrome. However, before high-intensity interval training can be recommended in CHF patients, the validity of high-intensity interval training needs to be confirmed in larger multi-center studies.

CR following an acute coronary event or in patients with chronic heart failure reduces subsequent overall and cardiovascular mortality and morbidity, and it has been shown to be a cost-effective intervention to improve exercise tolerance and psychological well-being. Despite the body of professional recommendations on cardiovascular disease prevention, integrative prevention strategies into daily practice is still inadequate. In Europe, only about one-third of CHF patients receive any form of CR, with considerable variation between European regions.

Exercise training is the cornerstone of CR and has shown to have direct benefits on the heart and coronary vasculature. However, findings of the original Cochrane review of exercise-based CR for CHD supported the hypothesis that reductions in mortality may also be mediated via the indirect effects of exercise through improvements in the risk factors for atherosclerotic disease. The most recent and comprehensive meta-analysis done by the Cochrane Collaboration identified randomized controlled trials of exercise-based CR. Studies included men and women of all ages who had MI, coronary artery bypass graft (CABG), or percutaneous transluminal coronary angioplasty (PTCA) or who have angina pectoris or CAD defined by angiography. This systematic review has allowed analyses of 47 studies randomizing 10,794 patients to exercise-based CR or usual care. In medium to long-term follow-up, exercise-based CR reduced overall and cardiovascular mortality [RR: 0.87 (95% CI: 0.75–0.99) and 0.74 (95% CI: 0.63–0.87), respectively], and hospital admission [RR: 0.69 (95% CI: 0.51–0.93)] in the shorter term (<12 months follow up) with no evidence of heterogeneity of effect across trial. CR did not reduce the risk of total MI, CABG, or PTCA.

Several observational studies have been published regarding the relation between participation in a CR program and the cardiovascular prognosis in post-MI, post-PTCA, and elderly CHD patients. Several randomized trials demonstrated that intervention controls to potential confounding between CR users and non-users among 600,000 Medicare CHD 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
exercise training on the observed reduction of mortality remains unclear. In another study, the relation between the number of CR sessions attended and mortality/MI risk at 4 years in elderly CHD patients was analyzed. 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. reported that, compared with non-completers (n = 554), CR completers (n = 2,900) 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). A recent study reported that participation in CR was independently associated with decreased mortality after PTCA and another recent study reported that participation in CR after CABG surgery was independently associated with decreased mortality and recurrent MI.

Risks during intense exercise training

Regular exercise training and physical activity provide protection against major cardiovascular events. However, during intense exercise training, the risk of sudden cardiac death (SCD) or MI is transiently increased. In the 1,128 survivors of acute MI, 5% of cases seemed to be triggered by heavy exertion. Therefore, physical activity and exercise training are promoted in most government health initiatives for primary and secondary prevention of cardiovascular disease. Physical activity is a Class IB recommendation for primary prevention and a Class IA recommendation for all eligible patients with acute coronary syndrome, for patients immediately post-CABG or post-percutaneous coronary intervention, for patients with peripheral artery disease and a Class IB recommendation for patients with stable chronic angina in most national and international guidelines.

References

9. Lee DC, Arteo EG, Sui X, et al. Mortality trends in the prevention and treatment of cardiovascular disease beyond any reasonable doubt. Few treatment strategies in medicine have been evaluated so rigorously in large patient groups as regular physical exercise. Exercise training has been shown to have direct benefits on the heart and coronary vasculature, including on endothelial function, autonomic tone, coagulation and clotting factors and inflammatory markers, the development of coronary collateral vessels, and the mobilization of endothelial progenitor cells. Reduction in mortality may also be mediated via the indirect effects of exercise through improvements in risk factors for atherosclerotic disease. Therefore, physical activity and exercise training are promoted in most government health initiatives for primary and secondary prevention of cardiovascular disease. Physical activity is a Class IB recommendation for primary prevention and a Class IA recommendation for all eligible patients with acute coronary syndrome, for patients immediately post-CABG or post-percutaneous coronary intervention, for patients with peripheral artery disease and a Class IB recommendation for patients with stable chronic angina in most national and international guidelines.

Conclusions

Over the past decades, scientific evidence has accumulated proving the role of physical activity and exercise in the prevention and treatment of cardiovascular disease. Exercise is medicine.
exercise training on the observed reduction of mortality remains unclear. In another study, the relation between the number of CR sessions attended and mortality/MI risk at 4 years in elderly CHD patients was analyzed. 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. reported that, compared with non-completers (n = 554), CR completers (n = 2,900) 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). A most recent study reported that participation in CR was independently associated with decreased mortality after PTCA.29 And another recent study reported that participation in CR after CABP surgery was independently associated with decreased mortality and recurrent MI.20

Risks during intense exercise training

Regular exercise training and physical activity provide protection against major cardiovascular events. However, during intense exercise training, the risk of sudden cardiac death, MI, or MI is transiently increased.24 Unfortunately, in the lay press, this information often receives much more publicity than do the marked benefits of exercise training and physical activity.24 In the United States, 1,128 survivors of acute MI, 5% of cases seemed to be triggered by heavy exertion.24 However, the annual incidence of exercise-related SCD in previously healthy persons is only 5.4 per 100,000.24 The incidence of SCD is 56 times higher than at rest for previously healthy persons.24 The incidence of sudden cardiac death (SCD) or MI is transiently increased.24 Unfortunately, in the lay press, this information often receives much more publicity than do the marked benefits of exercise training and physical activity.24

References

9. Lee DC, Artero EG, Sui X, et al. Mortality trends in the prevention and treatment of cardiovascular disease beyond any reasonable doubt. Few treatment strategies in medicine have been evaluated so rigorously in large patient groups as regular physical exercise. Exercise training has been shown to have direct benefits on the heart and coronary vasculature, including on endothelial function, autonomic tone, coagulation and clotting factors and inflammatory markers, the development of coronary collateral vessels, and the mobilization of endothelial progenitor cells. Reduction in mortality may also be mediated via the indirect effects of exercise through improvements in risk factors for atherosclerotic disease. Therefore, physical activity and exercise training are promoted in most government health initiatives for primary and secondary prevention of cardiovascular disease. Physical activity is a Class IB recommendation for primary prevention and a Class IA recommendation for all eligible patients with acute coronary syndrome, for patients immediately post-CABP or post-percutaneous coronary intervention, for patients with peripheral artery disease and a Class IB recommendation for patients with stable chronic angina in most national and international guidelines.

J. Preventive Cardiology Vol. 5 No. 3 Feb 2016

Saneer H

Exercise is medicine


J. Preventive Cardiology Vol. 5 No. 3 Feb 2016

853

Saneer H

Exercise is medicine

Abstract
Exercise training has become an established evidence-based therapeutic strategy with prognostic benefits for patients with cardiovascular disease. In stable coronary artery disease, exercise training decelerates disease progression by positively influencing cardiovascular disease risk factors (i.e., hyperlipidemia and hypertension), coronary endothelial function, and endothelial regeneration. In chronic heart failure with reduced ejection fraction, exercise training prevents the progressive loss of exercise capacity by antagonizing skeletal muscle catabolism and left ventricular reverse remodeling with reduction in cardiomegaly and improvement of ejection fraction. New fields for exercise interventions include heart failure with preserved ejection fraction (HFpEF), pulmonary hypertension, and valvular heart disease. In HFpEF, studies indicate a lusitropic effect of training on diastolic function associated with an improvement of exercise capacity. In pulmonary hypertension, reduced pulmonary artery pressure is observed following an exercise training program. Recently, innovative training methods such as high-intensity interval training, resistance training, and others have been established. In this review, we provide an overview of the prognostic and symptomatic benefits of exercise training in the most prevalent cardiac disease entities.

Key Words
• Exercise
• Molecular mechanisms
• Regeneration

Introduction
In the given environment of our human ancestors, physical activity was a simple matter of survival. In a rather hostile habitat with scarce food and permanent dangers, the human genome was selected to conserve energy for future famine periods and optimize aerobic metabolic pathways. Cardiovascular functions have been continuously challenged by frequent and intermittent bouts of high-intensity physical activity and adapted to meet the metabolic needs of skeletal muscle under these conditions. The average of physical activity in modern Western societies is far below these levels normal for the human genetic background that sedentary lifestyle combined...