In the natural habitat of our ancestors, physical activity was not a preventive intervention but a matter of survival. In this hostile environment with scarce food and ubiquitous dangers, human genes were selected to optimize aerobic metabolic pathways and conserve energy for potential future famines. \(^1\) Cardiac and vascular functions were continuously challenged by intermittent bouts of high-intensity physical activity and adapted to meet the metabolic demands of the working skeletal muscle under these conditions.

When speaking about molecular cardiovascular effects of exercise, we should keep in mind that most of the changes from baseline are probably a return to normal values. The statistical average of physical activity in Western societies is so much below the levels normal for our genetic background that sedentary lifestyle in combination with excess food intake has surpassed smoking as the No. 1 preventable cause of death in the United States.\(^2\)

Physical activity has been shown to have beneficial effects on glucose metabolism, skeletal muscle function, ventilator muscle strength, bone stability, locomotor coordination, psychological well-being, and other organ functions. However, in the context of this review, we will focus entirely on important molecular effects on the cardiovascular system. The aim of this review is to provide a bird’s-eye view on what is known and unknown about the physiological and biochemical mechanisms involved in mediating exercise-induced cardiovascular effects. The resulting map is surprisingly detailed in some areas (ie, endothelial function), whereas other areas, such as direct cardiac training effects in heart failure, are still incompletely understood.

For practical purposes, we have decided to use primarily an anatomic approach to present key data on exercise effects on cardiac and vascular function. For the cardiac effects, the left ventricle and the cardiac valves will be described separately; for the vascular effects, we will follow the arterial vascular tree, addressing changes in the aorta, the large conduit arteries, the resistance vessels, and the microcirculation before turning our attention toward the venous and the pulmonary circulation (Figure 1).
Heat Shock Proteins. Heat shock proteins (HSP) are highly conserved chaperones that are involved in the folding of newly synthesized or damaged proteins. The overexpression of HSP70 in cardiomyocytes protects against ischemic damage and is associated with increased cell survival.9 Stress-induced synthesis of HSP70 is reduced in the aged cardiovascular system, consistent with a diminished stress resistance.10 HSP70 and HSP27 were also elevated in trained old rats versus sedentary old rats, indicating improved resistance to ischemic insults.7

Cardiomyocyte Apoptosis and Regeneration. Despite the increase in LV mass generally observed with aging, the number of cardiomyocytes declines by ~30%.11 The exponential increase of cardiomyocyte death by apoptosis or necrosis and the loss of cardiac regeneration by stem cells have been discussed as key factors for this decline in cell number.12,13 The increase in apoptosis may be a consequence of decreased mitochondrial membrane stability and permeability transition pore formation, which leads to cytochrome c release into the cytosol, resulting in activation of caspase-3 and -9.12 Exercise training seems to be highly protective against cardiomyocyte apoptosis by modulating proapoptotic and antiapoptotic genes.14

Human Functional Data. On the functional level in humans, cardiac aging is associated with a significant increased wall stress, decreased elasticity, impaired early LV diastolic relaxation, increased end-systolic LV volume, and reduced contractile reserve.15 Arbab-Zadeh et al16 were able to show that lifelong physical activity prevents the development of diastolic LV dysfunction in older age. This finding also indicates that so-called healthy aging is in fact primarily sedentary aging and that the lack of physical activity may be more relevant to the observed pathologies than aging by itself.

Cardiac Adaptation to Strenuous Exercise and Cardiac Fatigue

Athlete’s Heart. In normal individuals, regular high-intensity physical activity for >5 to 6 hours per week may result in cardiac adaptations known as athlete’s heart, resulting in compensatory myocardial hypertrophy, which is more eccentric in endurance training and more concentric in resistance training.17 Endurance-trained athletes show mean LV end-diastolic diameters of 53.7 mm compared with 49.6 mm in normal subjects17; however, 14% of 1309 athletes examined by Pelliccia et al18 showed LV end-diastolic diameters between 66 and 70 mm. The diagnostic strategies to distinguish normal LV hypertrophy from hypertrophic cardiomyopathy are a matter of continuing discussions (reviewed by Fagard19 and Maron20).

LV physiological hypertrophy is caused by a proportional increase in myocardial cell length and width without evidence of myocardial hyperplasia in the majority of cases and is mediated via increased cardiac insulin-like growth factor-1 (IGF-1) expression and activation of phosphoinositide-3 kinase (PI3K) (p110α).21 Transgenic mice with decreased cardiac PI3K activity (dnPI3K mice)22 and mice lacking the p85 subunit of PI3K23 show a reduced basal cardiac size and an attenuation of exercise-induced myocardial hypertrophy.

Studies by Carè et al24 in exercised rats suggest that downregulation of cardiac-specific microRNAs (miRNA, miR-133, and miR-1) is regularly involved in exercise-
induced cardiac hypertrophy. Reduction of miR-133 levels in cardiac myocytes caused marked hypertrophy with increased protein synthesis and fetal gene expression. MiR-1 overexpression, on the other hand, significantly reduced protein synthesis and fetal gene expression. Its hypertrophic effects are probably mediated via RhoA, Cdc42, and Whsc2, whose RNA 3' untranslated regions comprise flanking nucleotides matching miR-133.

The role of miR-1 in physiological hypertrophy was further elucidated by Elia et al., who documented that IGF-1 and IGF-1 receptor are targets of miR-1 and that miR-1 and IGF-1 are inversely correlated in cardiac hypertrophy.25 IGF-1 activation, on the other hand, inhibits the miR-1 transcription factor Foxo3a via an AKT-dependent pathway, further amplifying its hypertrophic effects.

Using a transgenic mouse model with overexpression of a constitutively activated AKT (AKT-E40K), Catalucci et al. confirmed that IGF-1/AKT also improved LV contractility by phosphorylation of phospholamban at threonine. By translocating to the sarcoplasmic reticulum, activated AKT can mediate improved calcium handling by disinhibition of the sarcoplasmic reticulum Ca2+ ATPase pump (SERCA2a) through phospholamban phosphorylation.

Cardiac plasticity in response to exercise training is surprisingly rapid. In a rat model of high-intensity interval treadmill running for 2, 4, 8, and 13 weeks followed by 2 or 4 weeks of detraining, Kemi and colleagues identified cardiomyocyte cell length, diastolic relaxation, and calcium decay as main factors for the training-induced increase in Vo2, max by multiple regression analysis. These training-related cardiac adaptations seem to be dependent on training intensity.

Cardiac Fatigue. Prolonged strenuous activity, as in the Ironman Triathlon, can lead to transient reductions of LV systolic and diastolic function.29 Several mechanisms are involved in cardiac fatigue, including changes in preload conditions, myocardial stunning, β1-receptor desensitization, and altered cardiac autonomic regulation.

Preload conditions were highlighted as a potential mechanism by Dawson et al., who demonstrated the lack of changes in LV function when central venous pressure was well maintained. However, other researchers with different training protocols found depressed LV contractile function unrelated to preload conditions, which confirms the relevance of intrinsic myocardial damage.33 In a dog model, Vatner and Hittinger demonstrated that prolonged strenuous exercise can indeed lead to ischemic myocardial dysfunction and postischemic myocardial stunning in the absence of epicardial coronary stenoses.

Prolonged strenuous exercise results in a 5-fold increase in circulating catecholamines with consecutive desensitization of β1-adrenoreceptors.38 This results in a blunted chronotropic and inotropic response to dobutamine.

Prevention of Functional Decline After Exposure to Ischemia
I/R injury is a classic model of an acute cardiac injury with great clinical relevance in the setting of myocardial infarction with interventional reperfusion therapy. Human epidemiological data indicate that regular endurance exercise reduces the risk of death during clinical I/R injury.

Key Mechanisms for Protection Against I/R Injury. As summarized by Powers et al.,7 the problem of a mechanistic approach to I/R protection to exercise is to differentiate between the mechanisms that are involved in I/R protection and those that are essential. Mechanisms such as collateral formation, elevated HSP, increased myocardial cyclooxygenase-2 expression, and higher levels of endoplasmic reticulum stress proteins have all been shown to be not essential for exercise-mediated I/R protection. Therefore, we will focus on mechanisms found to be a condition sine qua non for I/R protection. Among these are improved antioxidative protection, changes in mitochondrial metabolism and protein expression, increased expression of sarcomemal/mitochondrial K+ ATP channels, and attenuation of I/R-induced calpain activation (Figure 2).

Antioxidative Protection. Production of ROS, accumulation of hydrogen ions, and generation of reactive nitrogen species play a major role in the complex pathophysiology of I/R injury, and the quantity of ROS production critically depends on the duration of anoxia and reoxygenation. The primary source of ROS in I/R situations seem to be the mitochondria. In animal models, exercise training protects cardiac myocytes against I/R-induced oxidative stress and the mitochondria against I/R-associated structural damage.

Several mechanisms for training-induced cardioprotection are under discussion (Figure 2). There is broad consensus that increased antioxidative protection by training-induced upregulation of key antioxidative enzymes such as MnSOD, glutathione peroxidase, and catalase plays an important role; however, myocardial MnSOD is only increased at high training intensities. Recent studies have confirmed that MnSOD is essential for full protection against I/R-induced myocardial infarction (ie, ischemia >20 minutes) and related ventricular arrhythmias; however, protection against myocardial stunning seems to work even in the absence of MnSOD.

Changes in Mitochondrial Metabolism and Protein Expression. Cardiac mitochondria seem to contribute to exercise-induced protection against I/R injury in several ways, as follows: (1) Exercise training results in reduced generation of ROS by cardiac mitochondria; (2) mitochondria isolated from the myocardium of exercised animals are more resistant to calcium-induced opening of the mitochondrial permeability transition pore, a major proapoptotic stimulus; and (3) exercise induces a downregulation of mitochondrial monoamine oxidase-A, which seems to be a major source of oxidative stress by H2O2 generation. Monoamine oxidase-A knockout animals are protected from I/R-induced myocardial damage, highlighting the importance of this pathway for I/R injury.

Role of Sarcomemal/Mitochondrial K+ ATP Channels. Recently, the sarcomemal K+ ATP channel has been described as a potential mechanism for training-induced I/R protection. Opening the sarcomemal K+ ATP channel accelerates myocardocyte repolarization by increasing K+ outflow and shortens the action potential. As a result of the shorter action potential, Ca2+ overloading is prevented by reducing opening rates of the L-type Ca2+ channel.

Attenuation of I/R-Induced Calpain Activation. Calpain is a calcium-dependent protease with 2 isoforms (calpain I [milli]
and calpain II (micro), which are activated by prolonged exposure to elevated cytosolic calcium levels and contribute to myocardial I/R injury. French and colleagues showed that calpain inhibition attenuates I/R-induced contractile myocardial dysfunction. Exercise training reduces I/R-associated calpain activation, most likely by improved antioxidative protection and prevention of I/R-induced SERCA2a and phospholamban degradation.

Thresholds and Time Course of I/R Protection

Training Intensity. In a rat model of 40 minutes per day of treadmill exercise at 55% to 60% of VO2max for a total time of 16 weeks, Starnes et al were unable to confirm a significant level of I/R protection. This study therefore provided evidence for a threshold effect (i.e., that a minimum intensity and duration of exercise have to be exceeded to benefit from I/R protection). Lennon et al, on the other hand, compared 2 training protocols at 55% and 75% of VO2max for 60 minutes per day on 3 consecutive days and did not find any difference in training-induced I/R protection between both groups, indicating that there may not be a linear dose-response relation between training intensity and cardioprotection.

Training Duration. Surprisingly, the protective effect is similar after short-term (3 to 5 days) and long-term (weeks to months) exercise training. In a trial specifically designed to assess the loss of cardioprotective effects after training cessation, Lennon et al were able to show a persistence of protection against myocardial stunning for up to 9 days, but cardioprotection was completely lost at 18 days after exercise termination.

Systolic Heart Failure

Reduced exercise capacity and early fatigue in chronic heart failure (CHF) are unrelated to the degree of LV systolic dysfunction but are determined primarily by peripheral alterations with impaired endothelial function, reduced aerobic oxidative metabolism in the skeletal muscle, skeletal muscle atrophy, ventilatory dysfunction, and neurohumoral changes. In the context of this review, we will focus on the cardiac effects of exercise only.

Training Effects on LV Function and Reverse Remodeling

In one of the first small prospective studies of aerobic endurance training in CHF patients (n=12), Sullivan et al confirmed that 4 to 6 months of training did not worsen LV ejection fraction and tended to improve maximal cardiac output. The extent of the cardiac changes did not, however, explain the large 23% improvement in peak oxygen uptake so that peripheral changes in limb perfusion and oxidative metabolism must account for the larger part of the beneficial symptomatic training effects.

The first larger prospective randomized study to actually provide evidence for a training-induced reverse remodeling...
came from Hambrecht et al., who demonstrated that endurance training led to reverse LV remodeling with modest improvements of ejection fraction from 30% to 35% and reductions of LV end-diastolic diameter in a mixed population of subjects with ischemic and dilated cardiomyopathy. These findings were corroborated by the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure study. A recent study in our institution indicates that the reverse LV remodeling occurs as early as 4 weeks after the initiation of endurance training (unpublished data, 2010).

Mechanisms Explaining Reverse Remodeling in CHF
In the absence of myocardial biopsies for molecular analysis of myocardial changes induced by training, most authors interpreted this favorable training effect as secondary to afterload reduction with reduced resting blood pressure due to improved antioxidative protection in the skeletal muscle, increased parasympathetic tone, improved endothelial function as a result of increased NO production and bioavailability, and direct cardiac effects related to improved Ca handling, increased PI3K [p110α] activity, reduction of fibrosis, and cardiomyocyte apoptosis. NE indicates norepinephrine; AT II, angiotensin II; ecSOD, extracellular SOD; GPX, glutathione peroxidase; and ox. Phos, oxidative phosphorylation.

Anabolic/Catabolic Balance in the Myocardium. Animal studies in which an left anterior descending artery ligation model was used demonstrated a significant upregulation of components of the ubiquitin-proteasome system as well as myostatin. Both of these factors were significantly reduced by exercise training over a period of 4 weeks.

Calcium Handling. Alterations in calcium handling are also associated with pathological hypertrophy and transition from hypertrophy to failure: SERCA2a protein levels were reduced in mouse and dog models of heart failure and were normalized by exercise training. In addition, exercise training activates Ca²⁺/calmodulin-dependent protein kinase II, leading to a hyperphosphorylation of phospholamban, which in its phosphorylated form no longer inhibits SERCA2a. In conjunction with an increased expression of Na⁺-Ca²⁺ exchange, activation of PI3K [p110α, caPI3K] improved survival by ~20%. In an aortic banding model of pathological hypertrophy, caPI3K mice showed a blunted increase in heart size compared with wild-type mice. Levels of interstitial fibrosis were reduced in caPI3K mice, highlighting the potential of PI3K as an antifibrotic signal. Another important downstream effect of PI3K is the protection against apoptotic cardiomyocyte death via AKT.
chamber,73 this leads to improved calcium cycling and finally to better cardiomyocyte function. For more detailed information on exercise-induced improvements on the contractile apparatus and calcium cycling, please see a recent review by Kemi and Wisloff.74

Neurohormonal Adaptations. An aerobic training program in patients with CHF regularly reduces the resting heart rate, which indicates a reduction in sympathoadrenergic drive. This has also been confirmed for serum catecholamine levels: Coats et al75 showed a 16% reduction of radiolabeled norepinephrine secretion after 8 weeks of training. This reduction in adrenergic tone was accompanied by an increase in heart rate variability. In addition to the reduction in circulating catecholamines, Braith et al76 described a 25% to 30% reduction of angiotensin II, aldosterone, arginine vasopeptide, and atrial natriuretic peptide after 4 months of walking training in patients with CHF.

In a rat model of ischemic CHF, the beneficial training effects on local neurohumoral balance were analyzed in the noninfarcted LV myocardium. Xu and colleagues77 found a significant reduction of myocardial angiotensin-converting enzyme mRNA expression and AT1-receptor expression after 8 weeks of treadmill training. This finding is of special importance given the fact that >90% of angiotensin II is produced locally in the myocardium and implies that local angiotensin II levels are significantly reduced by training. This reduction also translates into reduced fibrogenesis, as indicated by reduced tissue inhibitor of metalloproteinase-1 expression with unchanged matrix metalloproteinase (MMP)-1 expression and reduced collagen volume fraction in the exercised animals.77

Diastolic Heart Failure
Heart failure with normal ejection fraction is a comparatively new disease category that includes patients who display the typical clinical, physiological, and neurohormonal heart failure phenotype in the absence of reduced LV ejection fraction.78 Thus far, no specific pharmaceutical therapy for heart failure with normal ejection fraction has been found. However, a number of clinical and experimental studies indicate a protective and curative role of exercise training for this disease entity.

Protective Effects
It is well established in sports physiology that endurance training improves LV diastolic filling at rest and during exercise.79 Endurance exercise interventions improve early diastolic relaxation at all ages in healthy individuals, but in the presence of an elevated atrial filling rate in elderly patients, this could be normalized.80 A landmark study for the preventive effects of lifelong physical activity against age-related diastolic dysfunction was published by Arbab-Zadeh et al in 2004.16 They were able to show with invasive measurement of LV pressure-volume relations that senior athletes did not exhibit any degree of diastolic dysfunction compared with young healthy sedentary controls.

Curative Effects
Patients after myocardial infarction and with preexistent abnormal relaxation patterns benefit from endurance training, as shown by Yu et al.81 Although data on training effects in patients with diabetes mellitus derived from small studies are still controversial,82,83 data on patients with established heart failure with normal ejection fraction are convincingly positive.84

CHF with systolic dysfunction is associated primarily with significant diastolic dysfunction. Prospective randomized training studies confirmed that as early as after 4 weeks of endurance training, diastolic dysfunction is significantly improved with reduced E/E′ ratio (unpublished data, 2010).

Molecular Mechanisms
In diastolic heart failure, calcium homeostasis is affected by a reduced expression of SERCA2a,85 which is the key player for calcium reuptake into the sarcoplasmic reticulum and is regulated in its activity by phospholamban and sarcoplasm and increased diastolic calcium leakage via the ryanodine receptors.86,87 Phospholamban affects both the calcium affinity of SERCA and its calcium reuptake rates. Animal studies in healthy rats indicate that endurance training can increase both SERCA and phospholamban expression,77 a finding that was confirmed in a mouse model of sympathetic hyperactivity-induced heart failure (congenic α2a(α2c)-adrenoceptor knockout mice).58 No data are available with regard to training-associated effects on calcium leakage. On the structural level, 12 weeks of treadmill training in old Fischer 344 rats did not affect collagen volume fraction but significantly reduced collagen cross-links by advanced glycation end-products.89

Cardiac Valves
Aortic Valve Sclerosis/Stenosis
Currently, no effective therapy to prevent calcified aortic valve disease is established. Calcified aortic valve disease confers significant morbidity and mortality as the severity of disease progresses.90

Degenerative calcified aortic valve disease and atherosclerosis share similar mechanisms (ie, clinical risk factors and histopathological features). Pathological examinations of diseased aortic valves showed areas of subendothelial thickening with the disruption of the basement membrane, accumulation of inflammatory infiltrates, and calcium deposits.91,92 It is well accepted that regular physical exercise prevents the progression of atherosclerosis by modulating endothelial function or oxidative stress.93,94 Using low-density lipoprotein receptor knockout mice, we recently demonstrated that regular exercise training as primary prevention prevents the development of aortic valve sclerosis.95 It has been proposed that apoptosis of endothelial cells and myofibroblasts in the valve,96 elastin degradation and collagen synthesis by MMPs and/or cathepsin,97 increased oxidative stress,98 and enhanced osteogenesis99 contribute to aortic valve degeneration. In consequence, procalcific gene expression such as bone morphogenetic protein 2 (BMP2), CBFA1/Runx2 (run-related transcription factor 2), and osteocalcin was amplified.98 The activation of BMP2 and CBFA1/Runx2, particularly in the noncalcified valve tissue, reflects an early stage of transdifferentiation of myofibroblast to a more osteoblast-like phenotype.100
In the low-density lipoprotein receptor knockout mouse model, regular exercise attenuated the deleterious elevation of oxidative stress and reduced expression of BMP2, Runx2, and osteoblast differentiation marker. Additionally, the disruption of the aortic valve endothelium was prevented.95

Vascular Effects of Exercise

“It has been said that one is as old as one’s arteries. In view of the supreme importance of endothelium in arterial function, I should like to modify this statement by saying that one is as old as one’s endothelium.”101 Perhaps Rudolf Altschul himself would be surprised to see to what extent his prophetic words have become scientific consensus half a century later. There are several reasons why endothelial research became so significant for today’s mechanistic concepts of exercise-mediated cardiovascular effects: (1) Endothelial dysfunction has been found to be a condition sine qua non for atherogenesis (ie, an obligatory initial step in early atherosclerosis).102 Thus, prevention of endothelial dysfunction will necessarily prevent atherosclerosis development. (2) The presence of endothelial dysfunction predicts future cardiovascular events.103,104 Hence, endothelial function measurements were proposed as a surrogate end point in clinical research.105 (3) Endothelial function can be assessed by a large variety of methods in both animal and human studies. Surgical/invasive methods include organ bath measurements of arterial rings harvested in animals or during aortocoronary bypass surgery in humans and catheter-based assessment of acetylcholine-induced vasodilation with angiography of the target vessel. Noninvasive methods such as brachial/radial ultrasound, magnetic resonance imaging, and venous occlusion plethysmography permit serial studies comparing endothelial function before and after an exercise intervention. These classic methodologies are increasingly supplemented by commercial semiautomatic devices using, for example, digital pulse amplitude tonometry to measure microvascular function.106

It is beyond the scope of this article to provide in-depth review of endothelial function in health and disease. We will focus on 2 important aspects of vascular research in exercise physiology: (1) the heterogeneity of molecular mechanisms involved in vasomotor function along the vascular bed and (2) the molecular mechanisms for exercise-mediated improvements of vascular endothelial function with special emphasis on clinical studies in overt heart disease (coronary artery disease and heart failure).

Differential Effects on Different Parts of the Vascular Bed

The vasomotor responsiveness is not uniformly distributed along the arterial tree. Four basic mechanisms have been identified to regulate vascular tone in response to local metabolic demand in the downstream vascular territory: (1) endothelium-mediated flow-induced vasodilation, (2) myogenic control, (3) metabolic vasodilatation, and (4) sympathetic control.107,108 The relative contribution of these mechanisms to vasodilation is different in different microdomains of the coronary vascular tree. Endothelium-dependent vasodilatation is most relevant in small conduit and resistance arteries down to 150 μm of diameter108; metabolic control is dominant in small resistance arteries, in which the myogenic response to increased perfusion pressure is also most pronounced. Although the effects of exercise on the microcirculation and the capillary bed have been studied extensively, little is known about the training-induced mechanism of vascular changes in the venous circulation.

Aorta

Although the aorta is a standard vessel to quantify changes in endothelial function in animal experiments involving small rodents, it is rarely a target vessel in human vascular research. The composition of the extracellular matrix has changed through the evolution of species and is influenced by pulse pressure amplitude and wall tension. In fact, there seems to be a universal elastic modulus that determines the relative proportion of elastic lamellae, collagen fibers, and smooth muscle cells in the aortic wall.109 Aging, coronary artery disease, and myocardial infarction are often accompanied by increased aortic stiffness and reduced compliance.110,111

Among healthy individuals, high-intensity exercise led to vascular remodeling with up to 51% enlarged brachial conduit artery area and reduced distal aortic cross-sectional areas (up to −8%), whereas aortic distensibility remained unchanged.112 However, endurance and strength training have opposite effects on aortic compliance and vascular stiffness; in an elegant study, Otsuki et al113 measured plasma endothelin-1, nitric oxide (NO), and arterial stiffness in young, healthy endurance-trained versus strength-trained men. They demonstrated that aortic pulse-wave velocity as an established index of vascular stiffness was significantly increased in strength athletes and reduced in endurance athletes versus healthy controls.113 Strength athletes displayed elevated endothelin-1 levels that correlated with aortic pulse-wave velocity. Reductions of aortic stiffness after endurance training were confirmed in patients with hypertension114 and coronary artery disease.115

Large Arterial Conduit Vessels

Conduit vessels 2 to 4 mm in diameter are the preferred target vessels in clinical research because they may be assessed readily by either noninvasive of invasive methods. After the first description of coronary endothelial dysfunction,116 it was quickly recognized that coronary endothelial function could serve as a stress index integrating the cardiovascular effects of risk factors and may provide pivotal diagnostic and prognostic information in patients with coronary heart disease.103

Exercise and Conduit Vessel Vasomotor Function in Coronary Artery Disease

The clinical effects of endurance exercise training on coronary endothelial function were first studied in humans by Hambrecht et al117: A 4-week endurance training program was effective in attenuating the paradoxical arterial vasoconstriction in epicardial conduit vessels by −54% and increased average peak flow velocity by +78% in response to intracoronary acetylcholine infusion. The improvements in coronary endothelial function were partially lost during a consecutive 5-month home-based endurance training program at
lower intensity, and changes were related to daily training durations. In a subsequent study examining training effects on the peripheral conduit artery function, Gokce et al. measured brachial and femoral artery endothelial function in patients with coronary artery disease before and after a 10-week leg exercise program. They documented significant improvement in endothelium-dependent, flow-mediated dilation in conduit arteries of the leg but not the arm and hypothesized that training effects could be limited to the trained limb. This may, however, also depend on the distribution of endothelial dysfunction and the intensity of the training program because Linke et al. were able to confirm improved radial artery endothelial function after pure bicycle ergometer training in patients with CHF.

Mechanosensors in the Vascular Wall
Arteries are exposed to 2 main forces: radial strain as a result of the blood pressure wave that is propagated along the arterial tree and laminar shear stress as a result of the frictional forces caused by antegrade blood flow. Whereas increased radial strain (eg, as a result of arterial hypertension) increases the atherogenic risk, laminar shear stress as a result of pulsatile continuous blood flow is a potent survival signal for endothelial cells.

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On the molecular level, laminar shear stress affects multiple signaling pathways, which include the PI3K, extracellular signal-regulated kinase 5 (also known as mitogen-activated protein kinase 7), and NO pathways. Endothelial cells must therefore express specific mechanotransducers that convert physical stress into biochemical signals. The cytoskeleton plays an important part in the sensing of shear stress, and high strain is observed at the luminal and basal membrane. In addition, cellular adhesion proteins such as platelet endothelial cell adhesion molecule-1, vascular endothelial cadherin, and the transmembrane tyrosine kinase vascular endothelial growth factor receptor-2 (KDR) were found to mediate biochemical responses to flow. Vascular endothelial growth factor receptor-2 activates...
PI3K, which is essential for AKT-mediated phosphorylation and activation of endothelial NO synthase (eNOS). In contrast to laminar shear stress, the atherogenic flow patterns include turbulent or disturbed flow, low flow, gradients, and flow reversal. These conditions are associated with high rates of endothelial cell proliferation and apoptosis, increased production of ROS, and increased expression of inflammatory markers inducing a preatherosclerotic vascular phenotype. In the presence of additional atherogenic risk factors, such as hypertension, dyslipidemia, and diabetes mellitus, atherogenesis is significantly accelerated.

**NO Generation in the Endothelium**

A key component of intact endothelial function is a functional eNOS. Located in the luminal endothelial cell membrane, it produces NO from L-arginine. By diffusion, the short-lived NO reaches the vascular smooth muscle cells in the media and causes relaxation via cyclic guanosine monophosphate-NO generation in the endothelium. Under a number of pathological conditions, such as hypertension, dyslipidemia, and diabetes mellitus, NO bioavailability is also influenced by ROS-mediated injury programs resulted in an increased vascular expression of antioxidative enzymes, such as SOD, catalase, and glutathione peroxidase and a reduced expression of ROS-generating enzymes such as nicotinamide adenine dinucleotide phosphate (NAD[P]H) oxidase and xanthine oxidase. Nicotinamide adenine dinucleotide phosphate (NAD[P]H) oxidase expression and activity are regulated mainly by the dominant influence of angiotensin II type 1 receptor activation by inducing a rapid rac1 translocation to the cell membrane. In addition, a 4-week exercise training program in patients with coronary artery disease resulted in a significantly lower expression of angiotensin II type 1 receptor compared with a sedentary control group.

**Exercise and EPCs.**

The first description of postnatal vasculo genesis and the characterization of EPCs derived from adult bone marrow changed our concept of vascular plasticity in health and disease. In addition to EPCs, mesenchymal stem cells also possess the potential for vascular regeneration. Both mesenchymal stem cells and EPCs are mobilized from the bone marrow in response to ischemia, exercise, and neurohormonal factors (e.g., vascular endothelial growth factor [VEGF], placental growth factor) and critically contribute to maintaining the integrity of the endothelial cell layer. EPC number and function correlate with the number of cardiovascular risk factors and disease severity and predict cardiovascular events and death from cardiovascular causes.

It is a matter of continuing debate whether training-induced flow changes or ischemia induction is required to stimulate EPC release. In 2 clinical studies, we demonstrated that an increase in circulating EPCs was only achieved in response to exercise-induced ischemia, whereas matrigel assays indicated improved EPC function in nonischemic training. Both mesenchymal stem cells and EPCs are mobilized from the bone marrow in response to ischemia, exercise, and neurohormonal factors (e.g., vascular endothelial growth factor [VEGF], placental growth factor) and critically contribute to maintaining the integrity of the endothelial cell layer. EPC number and function correlate with the number of cardiovascular risk factors and disease severity and predict cardiovascular events and death from cardiovascular causes.

The principal mechanism of EPC mobilization from the bone marrow seems to depend on the activation of eNOS in the presence of several mobilizing factors such as VEGF or placental growth factor. Gene-targeting studies using either MMP-2 or MMP-9 knockout mice demonstrated that the presence of MMPs is crucial in ischemia-induced mobilization of EPCs and hence neovascularization. At the molecular/cellular level, the following scenario for the mobilization is proposed (Figure 5): Under steady state conditions, progenitor cells reside in a niche of the bone marrow, bound to stroma cells via adhesion molecules such as vascular cell adhesion molecule/very late antigen-4. Signal-induced up-regulation of MMP-9 results in a release of sKitL, conferring signals that enhance mobility of progenitor cells into a vascular-enriched niche favoring liberalization of the cells into the circulation. How can we explain the exercise-induced mobilization of EPCs? In several studies, it was demonstrated that exercise increases the concentration of NO, which in turn can activate MMP-9 in bone marrow.
leading to enhanced mobilization of progenitor cells, as depicted above. As soon as the EPCs are circulating, the most important factors for tissue engraftment of the mobilized cells are the local concentration of stromal-derived factor-1 and its cell receptor CXCR4. This notion is further supported by the observation that mice lacking CXCR4 die in utero because of defects in vascular development. Although the animal data make shear stress–induced NO generation a likely mechanism for NO-mediated EPC mobilization, animal experiments with ischemic exercise are still lacking. Therefore, the aforementioned controversy still awaits experimental resolution.

**Exercise and Plaque Regression in CAD**

Although it is high on the agenda in lipid research, plaque regression ceased to be a research focus of exercise research in recent years. Two decades ago, a series of angiographic long-term follow-up studies documented that regular endurance exercise training can retard the progression of coronary atherosclerosis or even reduce stenosis diameter if combined with lipid-management techniques of smoking cessation and other lifestyle interventions. Surprisingly, not a single study has addressed exercise-mediated changes in plaque volume by intravascular ultrasound thus far to control the findings of the early regression studies with a more accurate technique, which also permits insight into changes of plaque composition.

**Arterial Resistance Vessels**

Larger and medium-sized resistance vessels (>150 μm) are exposed to the predominant influence of endothelium-mediated vasodilatation, whereas smaller arterioles are subject to metabolic and myogenic control. The vasomotor state of the distal microvasculature is influenced by the dominant effects of local myocardial metabolic demands.

**Metabolic Control**

In principle, all concepts for metabolic control of resistance vessel diameter are based on the presence of an oxygen/metabolic sensor coupled to vascular smooth muscle cell tension to control vascular tone. Four models are currently under discussion, as follows:

1. An oxygen sensor in the vessel wall leads to production of the vasodilatory prostaglandin G2 in response to decreases in PO₂. There is evidence for prostaglandin-mediated vasodilation via Kst channels.
2. Adenosine serves as a myocardial oxygen sensor because it is generated at an accelerated rate when oxygen supply-to-demand relationship falls.
3. Carbon dioxide production, which in turn leads to tissue acidosis, is known to increase coronary flow. Acido-
sis in turn increases the sensitivity of adenosine A2A receptors.

4. Erythrocyte ATP release may cause vasodilatation, as documented in studies confirming the necessity of erythrocytes to mediate vasodilation under hypoxic conditions.167

All vasodilatory stimuli converge on the activation of the KATP channels, the opening of which leads to vascular smooth muscle cell hyperpolarization and reduced activation of voltage-gated calcium channels (Figure 6).

Exercise training increases resistance vessel sensitivity and maximal responsiveness to adenosine. This has been confirmed in dogs and miniature swine in vivo.168,169 In humans, adenosine-induced microvascular function improved by 29% after exercise training, as assessed by coronary flow reserve ratio in response to intracoronary adenosine infusion. With regard to the different mechanisms described above, no data are currently available to describe exercise-mediated specific changes.

**Myogenic Control**

It is well established in porcine animal models of treadmill training that myogenic vasoconstriction to increases in perfusion pressure (particularly >40 mm Hg) is augmented after exercise.170 Evidence is accumulating that L-type voltage-gated calcium channels and protein kinase C determine myogenic tone under physiological conditions.171 Korzick et al172 demonstrated that increased myogenic tone in trained pigs involves changes in protein kinase C-α expression and phosphorylation, which augment the depolarization-related opening of voltage-gated calcium channels in smooth muscle cells and increase of intracellular calcium.

**Angiogenesis and Microcirculation**

In the cardiac muscle, White et al173 conclusively showed in a porcine model of exercise training that training increases the total vascular bed cross-sectional area by up to 37% after 16 weeks. In humans, changes in cardiac vascularization are difficult to assess.

More data, however, are available for the skeletal muscle. In addition to an effect on metabolic alterations and the
Catabolic/anabolic balance within the skeletal muscle, exercise also affects the vascularization of the skeletal muscle. It has been known for a long time that endurance exercise training induces a significant increase in muscle capillaries in either animals or humans.\textsuperscript{174,175} This process is largely coordinated by soluble factors emanating from tissues in need of vascularization. One of the best factors to study in this scenario is VEGF. It is a powerful activator of endothelial proliferation and is crucial for nearly all forms of neovascularization.\textsuperscript{176} With respect to exercise training, several studies showed that VEGF transcription in skeletal muscle is increased by short-term\textsuperscript{177} as well as endurance training.\textsuperscript{142} It is thought that local skeletal muscle hypoxia stabilizes the transcription factor hypoxia inducible factor-1\textsubscript{α} (HIF-1\textsubscript{α}) because of local hypoxia or a reduction in energy equivalents.\textsuperscript{178} However, if this pathway is only responsible for basal VEGF expression and capillarization and not for exercise-induced angiogenesis is still an ongoing discussion.\textsuperscript{182} In addition to activation of AMPK, the activation of the p38MAPK (Mitogen-activated protein kinase) pathway by exercise training also leads to the activation of PGC-1\textsubscript{α}.\textsuperscript{183} Last but not least, the increased production of ROS by exercise training can also contribute to the induction of PGC-1\textsubscript{α}.\textsuperscript{184} Therefore, one may summarize that endurance exercise by activating PGC-1\textsubscript{α} via AMPK or p38MAPK or ROS leads to an enhanced transcription of VEGF, finally resulting in angiogenesis (Figure 7).

**Venous Circulation**

Compared with the arterial bed, the venous circulation has received less attention in vascular research, particularly with regard to training effects. The reasons are diverse, ranging from methodological problems to underestimation of the physiological relevance of venous function.\textsuperscript{185} Key parameters of venous function such as venous capacitance, which reflects the blood volume stored in the venous system, and venous compliance, which represents the change in volume in response to a change in pressure, change with aging, posture, and physical activity. Aging alters the composition of the venous wall, resulting in lower venous compliance in sedentary senior individuals.\textsuperscript{186} In both young and elderly endurance-trained men, however, venous compliance was 70% to 120% higher compared with their sedentary age-matched counterparts. It is currently unclear whether these changes are primarily the result of factors such as increased venous NO availability and decreased venous smooth muscle tone, sympathetic α-adrenergic vasomotor control, or structural effects on elastin-to-collagen ratio.
Immobilization, as tested in bed rest studies, demonstrated a significant decline in venous capacitance after 52 days, which was not affected by resistive vibration exercise.\(^{187}\) Venous compliance remained unaffected.

In patients with heart failure, exercise forearm venous capacitance and venous outflow, as measured by strain-gauge plethysmography, are significantly reduced and seem to be related to maximal walking distance.\(^{188}\) Although the methodology of strain-gauge plethysmography was used in a number of studies to examine training effects on vascular function,\(^{189,190}\) changes of venous capacitance induced by training have not been reported thus far. From animal experiments, we know that the capillary domain area values for venular capillaries were significantly decreased after 4 weeks of training.\(^{191}\)

**Pulmonary Circulation**

Pulmonary hypertension is a frequent accompanying problem in heart failure or valvular heart disease. Similar to heart failure, exercise has long been regarded as detrimental and was discouraged in pulmonary hypertension because of the fear of fatal cardiovascular compromise.

**Human Data**

The first reports on training effects on pulmonary pressure came from aerobic training studies in patients with stable CHF. Lee et al\(^{192}\) were the first to demonstrate the lack of any exercise-induced rise in resting pulmonary artery pressure in patients with CHF, a finding confirmed by Dubach et al\(^{193}\) 18 years later. In a large prospective randomized study involving 73 patients with CHF, Hambrecht et al\(^{65}\) were finally able to demonstrate that pulmonary vascular resistance at rest and at peak exercise was decreased after 6 months of endurance training.

Just recently, the first clinical study in patients with stable precapillary pulmonary hypertension confirmed that 15 weeks of endurance exercise are effective in significantly improving 6-minute walking distance on top of optimal medical therapy.\(^{194}\)

**Animal Experiments**

The first rat model of pulmonary hypertension to be used with exercise training was hypobaric hypoxia. Rats were trained for 4 and 6 weeks under hypobaric hypoxia (equivalent to altitudes of 2500 and 5500 m). Kashimura et al\(^{196}\) found that the increase in resting mean pulmonary arterial pressure with increasing equivalent altitude was lower in the 2 trained groups than in the control group and greater after 6 than after 4 weeks of exercise.\(^{195}\) In a follow-up study, they showed that 6 weeks of training can attenuate the hypoxia-induced and angiotensin II–induced PH. These findings were extended by Favret et al,\(^{197}\) who demonstrated that exercise training improved lung gas exchange and attenuated acute hypoxic pulmonary hypertension but did not prevent pulmonary hypertension of prolonged hypoxia.

In rabbits, it was soon documented that treadmill exercise improved acetylcholine-induced endothelium-dependent vasodilatation not only in aortic rings but also in precontracted pulmonary artery rings,\(^{198}\) a finding that could not be reproduced in Sprague-Dawley rats, however.\(^{199}\) A possible explanation for the discrepant results can be derived from 2 studies by Johnson et al.\(^{200,201}\) Whereas long-term training enhanced endothelium-dependent vasorelaxation in pulmonary arteries by mechanisms of increased reliance on NO and reduced production of a prostanoid constrictor in miniature swine with surgically induced chronic coronary artery occlusion, it did not alter pulmonary vasorelaxation in normal pigs.\(^{200}\) However, short-term 1-week training was effective in improving bradykinin-induced vasorelaxation and in increasing pulmonary artery eNOS protein expression. SOD remained unchanged.\(^{201}\) In essence, training-induced changes in pulmonary vasomotion are modified by preexistent endothelial dysfunction and by training duration.

In a rat model, Handoko et al\(^{202}\) induced compensated and progressive pulmonary hypertension using different doses of monocrotaline. Only the compensated pulmonary hypertension animals benefited from exercise training with increased exercise tolerance and right ventricular capillarization, whereas animals with progressive right ventricular failure had reduced cardiac output and died prematurely from right ventricular failure.

**Conclusion**

To summarize, cardiac effects of exercise include an improved protection against I/R injury primarily as a result of higher antioxidative protection and improved LV diastolic and systolic function in chronic heart failure due to favorable changes in neurohormonal state, activation of PI3K (p110\(\alpha\)) attenuating pathological hypertrophy, normalization of cardiomyocyte calcium handling, and inhibition of the catabolic ubiquitin-proteasome system.

Vascular effects are based on improved endothelium-mediated flow-induced vasodilatation in conduit arteries and larger resistance arteries, higher myogenic control, and increased metabolic vasodilatation in small resistance arteries. Vascular regeneration by mobilization of endothelial progenitor cells is augmented by exercise. Recently, improved endothelial vasodilatation has also been confirmed in the pulmonary artery.

Extending our concept of molecular mechanisms of exercise is essential to further optimize training interventions with regard to their clinical efficacy and to identify novel targets for pharmaceutical intervention. However, certain areas (ie, microcirculation and the venous system) are still incompletely understood and merit further molecular studies. Residual incomplete molecular understanding should not prevent the clinical use of training interventions with established clinical benefit.

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**Disclosures**

None.

**References**


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