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Review

Impact of exercise training on cardiovascular disease and risk☆

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ABSTRACT

Epidemiological studies in large cohorts support the notion that physical fitness is associated with reduced cardiovascular mortality and hospitalization due to cardiovascular disease. During the last 20 years even the concept of resting inactive after a myocardial infarction has dramatically changed and nowadays patients are mobilized and included into exercise training programs very shortly after the insult. Unfortunately, these beneficial effects of exercise training are independent of the genetic background and are only observed in case the training program is not paused for a longer time. Therefore, to take advantage of the effects of exercise training in health care the challenge for the future is to increase exercise compliance by offering interesting and effective exercise training programs. At the physiological and molecular level, exercise training affects several organs like the vascular system and the skeletal muscle. Changes elicited by regular exercise training range in the vascular system from increasing vasodilation due to an elevation of bioavailable nitric oxide to a shift in the catabolic/anabolic balance in the peripheral skeletal muscle. In this review we discuss the healthy benefit of exercise training and the molecular changes triggered by exercise training in the setting of secondary prevention.

Already Hippocrates stated that “Walking is man's best medicine”. Nowadays a plethora of epidemiological evidence obtained from large studies support an inverse and independent association between volume of physical activity and cardiovascular and overall mortality in apparently healthy individuals [1–9].One of the first study documenting that higher physical activity is associated with lower risk for cardiovascular disease (CVD) was Morris and colleagues [10]. In their study they analyzed the incidence of CVD in London bus drives and the conductors and reported that the incidence was much higher in the less active drivers when compared to the more active conductors. Subsequently, three landmark studies performed by Paffenbarger and colleagues based on over 16,000 college alumni provided the first solid evidence in a large cohort that physical activity influences risk of mortality substantially [11–13]. These studies also reported an exercise threshold beyond which health benefits are realized. At least an intensity of about 5–6 METs with an exercise volume of 1000–2000 kcals/week are recommended [8]. Another important outcome of these studies was that exercise-related health benefits are only evident if physical activity was maintained throughout life. It is even calculated that a reduction of inactivity by 10% or 25% would result in a reduction of ~500,000 or 1.3 million deaths worldwide, respectively [14].

What is the impact of genetic factors on this association between exercise and health benefit? Based on the results from the Finnish twin cohort study, where the active twin exhibited a ~40% lower risk of mortality when compared to the sedentary twin, we can conclude that physical activity is associated with lower mortality independent of genetic factors [15]. Nevertheless, according to the work by Claude Bouchard and colleagues the genetic influence to reach a higher fitness level is around 50% (reviewed in [16]). Unfortunately we have not clearly identified a set of genes responsible for achieving a high fitness level, and therefore new methodologies involving next generation sequencing, epigenetic mapping and the analysis of non-coding RNA may help to understand this complex regulation.

1. Impact of exercise training on mortality

To date physical exercise is the only intervention consistently demonstrating an attenuation of age-related declines in physical function. Nevertheless, a direct proof that exercise training also impacts mortality in diseased patients (for example heart failure patients) is still missing. One of the biggest trails attempting to analysis the impact of exercise training on mortality in heart failure patients was the HF-action trail

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[17]. In this multicenter, randomized controlled trial 2331 medically stable outpatients with heart failure and reduced ejection fraction were randomized either to exercise training (36 supervised sessions followed by home-based training) or usual care with a mean follow-up time of 30 month. In the protocol-specified primary analysis, exercise training resulted in nonsignificant reductions in all-cause mortality or hospitalization. A key factor responsible for this negative result was the low adherence to the training intervention. Dividing the exercise training patients into those performing more than 4 MET-hr. per week or those performing less than 4 MET-hr. per week, a significant difference with respect to mortality rate was observed [18] and it could be calculated for a 6% increase in VO_{2max} after 3 month of exercise training, a 5% lower risk of all-cause mortality or all-cause hospitalization was evident [19]. Based on these results the training compliance seems to be one critical point for achieving the exercise-mediated mortality reduction. This statement is further by an elegant study from Belardinelli and colleagues [20] showing that moderate supervised ET performed twice weekly for 10 years maintains functional capacity of more than 60% of VO_{2max} and confers a sustained improvement in quality of life. These improvements were associated with a reduction in major cardiovascular events, including hospitalizations for CHF and cardiac mortality.

One attempt to increase adherence to exercise training programs was to reduce exercise time by introducing interval training. One of the first introducing the interval training into the treatment of heart failure patients was Ulrik Wisloff and his group from Trondheim in Norway [21–23]. Epidemiological studies investigating the effect of physical activity of different intensities documented that high-intensity exercise may induce larger health benefits. For example, in a study from Taiwan, looking at more than 400,000 individuals, documented that 15 min of vigorous activity per day gave the same health benefit as 60 min moderate training [24]. Nevertheless, the application of high intensity interval training (HIIT) in patients with cardiovascular diseases and the superior effect is still questioned. In the first small study performed by Wisloff and colleagues [23], a superior effect of HIIT was evident when compared to moderate continuous exercise training (MCT) with respect to change in exercise capacity and endothelial function. This superior effect could not be repeated by 2 larger randomized, multi-center trails (SaintEx and SmartEx trail) performed in patients with coronary artery disease heart failure patients. Both studies could document the beneficial effect of exercise training when compared to a non-exercising group, but no difference between HIIT and MCT was evident [25,26].

2. High inborn fitness – is it protective?

Since there is a relation between fitness and mortality the question arises if an inborn fitness may protect from disease development. To test this hypothesis, Koch and Britton started in 1996 to selectively breed rats only differing in intrinsic (inborn) aerobic treadmill running capacity [27]. After 11 generations the rats with low aerobic fitness (LCR rats) developed features of the metabolic syndrome [28] and the cardiomyocytes resembled features observed earlier in heart failure [28,29].In addition life expectancy was higher for the high running capacity animals [30]. Challenging these selected rats with hemorrhagic shock [31], myocardial infarction [32], or chronic heart failure [33] high aerobic capacity did not protect from disease development. It is even suggested that being born with high (rather than low) aerobic fitness to greater skeletal muscle and endothelial impairments developed during chronic heart failure [33].

3. Vascular effects of exercise training in cardiovascular disease

The vascular system is highly impaired in patients with heart failure (HF) [34], and several studies using exercise training (ET) as a therapeutic intervention during the past decades have proven beneficial effects on the vascular system [35,36], like better endothelial function and a better compliance of the vessel (reduced stiffness).

3.1. Nitric oxide system (NO-ROS balance)

One of the most important factors regulating vascular function is nitric oxide (NO) generated by endothelial cells (EC) (reviewed in [37]). In mammals, NO can be generated by three different isoforms of nitric oxide synthase, namely the endothelial nitric oxide synthase (eNOS), the neuronal nitric oxide synthase (nNOS) and the inducible nitric oxide synthase (iNOS) [38,39]. In endothelial cells mainly the eNOS is the most abundant one for generating NO which regulates vasodilation, leading to lower peripheral resistance and increase of perfusion. In animal models of HF the expression of eNOS is significantly reduced when compared to controls [40,41]. Its activity is up-regulated by an increase in flow-mediated shear stress associated with physical exercise by a complex pattern of intracellular signaling like acetylation [42], phosphorylation [43], and translocation to the caveolae [44]. Many studies clearly documented that exercise or increased shear stress up-regulates eNOS activity either in cell culture [45–47], animal [48,49], or human studies [50]. For the shear stress induced eNOS activation, the glycocalyx on the luminar side of the endothelial cells plays an important role [51,52]. The deformation of the glycocalyx activates calcium ion channels, phospholipase activity leading to calcium signaling, PGI2-release, and cAMP-mediated smooth muscle-cell relaxation [51]. Furthermore, vascular endothelial growth factor receptor-2 (VEGFR2) can associate with VE-cadherin, ß-catenin, and phosphatidylinositol 3 kinase to phosphorylate Akt and induce AKT-mediated eNOS phosphorylation, resulting in higher NO production [53]. Another factor known to activate eNOS is high-density lipoprotein (HDL) [54]. Cell culture studies using human umbilical vein endothelial cells (HUVEC) and bovine aortic endothelial cells (BAEC) revealed that HDL and apolipoprotein AI (ApoAI) increase eNOS activity by multisite phosphorylation changes, involving AMPK activation after protein association between ApoAI and eNOS [55]. This HDL-induced activation is impaired in patients with diabetes [56], metabolic syndrome [57], patients with CAD [58], and HF [59] and an ET program of 12 weeks is able to restore this HDL-mediated eNOS activation [59].

The bioavailable concentration of NO does not solely depend on its generation by eNOS, but is also influenced by reactive oxygen species (ROS)-mediated breakdown. Thereby, NO reacts with ROS to form peroxynitrite. Exposing intact vascular segments to laminar flow increases ROS production for a short time period [60], with NAD(P)H being the major source [61]. In contrast extended periods of exercise training leads to reduced expression of hypoxanthin [62], NAD(P)H oxidase [63] and a stimulation of radical scavenging systems that include copper–zinc containing superoxide dismutase (SOD) [64], extracellular SOD [65], glutathione peroxidase [66], and glutathione (GSH) levels [67]. Besides the above mentioned enzymatic sources of ROS, eNOS itself is also able to generate ROS under certain circumstances (eNOS uncoupling). The bioavailability of tetrahydrobiopterin (BH4) seems to be a critical factor and at least cell culture experiments using endothelial cells provide some evidence that elevated blood flow increased BH4 levels significantly [68,69]. Uncoupling of eNOS was detected in several pathologies including atherosclerosis [70], hypertension [71], and HF [72].

3.2. Regulation by microRNA

The coordinated regulation of angiogenesis and maintenance of the endothelial cell layer is essential for proper vascular function and prevention of endothelial dysfunction. In recent years microRNAs (miRNAs) were identified as critical regulator of gene expression, due to its ability to suppress protein synthesis by inhibiting the translation of protein from mRNA or by promoting mRNA degradation [73,74]. Looking at the impact of ET on miRNA expression several different miRNAs were described in the recent literature; miRNA-19a, miRNA-21, miRNA-92a, miRNA-126.

MiRNA-92a was identified as an endogenous repressor of the angiogenic program in endothelial cells [75] and the down-regulation of miR-92a by shear stress enhances the expression of the endothelial nitric oxide synthase, whereas the up-regulation of miR-19a contributes to the shear stress-induced inhibition of cell proliferation [76]. Mechanistically, the downregulation of miRNA-92a increased the expression of Krüppel-like factor 2 (KLF-2) resulting in a reduced expression of eNOS [77]. In addition, it is suggested that the inhibition of miRNA-92a by antagomir may be a new atheroprotective therapeutic strategy [77]. Another miRNA upregulated by elevated shear stress is miRNA-21 [78]. Cell culture studies provided evidence that an elevation of miRNA-21 resulted in an enhanced NO production via Akt and eNOS phosphorylation [78].

4. Muscular effects of exercise

The main symptom impairing quality of life of HF patients is exercise intolerance, consequent not only to dyspnoe, but also to severe skeletal muscle weakness observed in the limb and respiratory muscle, the diaphragm. Interestingly alterations in the peripheral skeletal muscle are a main predictor for exercise intolerance, and these alterations can be influenced by ET [79–81]. During the last years several molecular alterations could be identified responsible for the development of muscle atrophy and dysfunction. Subsequently, some of these factors will be shortly discussed.

4.1. Inflammation

During the development of HF inflammatory factors are significantly upregulated when compared to healthy controls (reviewed in [82,83]). The prototype of inflammatory cytokines elevated in HF is tumor necrosis factor alpha (TNF-α) [84,85]. Besides TNF-α also other inflammatory cytokines like interleukin-6 (IL-6) and interleukin-1ß (IL-1ß) are significantly increased in HF patients with reduced or preserved ejection fraction [86–88]. Where do the cytokines come from? At least 3 different possibilities are discussed; (1) production and secretion by circulating mononuclear cells like macrophages [89]; (2) secretion by injured cardiomyocytes or by cells from peripheral tissue, mainly skeletal muscle [90,91]; (3) increased edema of the bowel wall and thereby an induction of TNF-α by lipopolysaccharides (LPS) [92,93]. With respect to ET several authors reported that, depending on the severity of CHF, no change (12956) or a reduced level in serum [94,95] or the skeletal muscle [96,97] was detected.

4.2. Catabolic/anabolic balance

Skeletal muscle atrophy is a hallmark of patients with end stage chronic heart failure. In the literature several pathways responsible for degradation of muscle mass are reported (the calpain pathway, the caspase pathway, and autophagy-lysosomal pathway) with the activation of the ubiquitin proteasome system (UPS) being the best characterized one (for review see [98,99]). The E3-ubiquitin ligases MuRF-1 and MAFbx (or atrogin-1) represent two main ligases in skeletal muscle that attach ubiquitin molecules to proteins identified for removal via the UPS [100]. The expression of MuRF-1 and MAFbx is significantly upregulated in models of muscle atrophy like denervation, aging or heart failure [100–104]. The central role of these two E3 ligases is further supported by the observation that mice deficient in one of these ligases are resistant to muscle atrophy [100] and that the inhibition of MuRF-1 by a small molecule attenuates the development of muscle atrophy and dysfunction [105]. With respect to exercise training and the modulation of MuRF-1 and MAFbx expression there is clear evidence in animal [106,107] and human [102] studies that the expression of both E3 ligases is reduced upon exercise training.

Myostatin is produced and secreted by myocytes and negatively influences muscle mass by modulating muscle growth and differentiation [108]. The role in modulating muscle mass is further supported by observations that animals lacking the myostatin gene [109–111] or humans having mutations in both copies of the gene [112] exhibit greater muscle mass and muscle force. So far only one study examined the impact of exercise training on myostatin expression in HF patients. Lenk and colleagues [113] documented that exercise training resulted in a 36% reduction of myostatin mRNA expression and a 23% decrease in protein expression when compared to prior exercise training.

4.3. Energy metabolism

Heart failure is associated with an augmented energy demand and a diminished energy metabolism, resulting in an energetic imbalance [114,115]. Especially the phosphocreatine (PCr) shuttle and the recovery of the (PCr) following exercise is impaired [116,117]. Analyzing skeletal muscle tissue obtained either from animal models of HF [114] or human HF patients [117–119] revealed an altered expression of the cytosolic and mitochondrial creatine kinase. Nevertheless, when measuring ADP-stimulated respiratory features in skeletal muscle, similar respiration rates were detected in CHF and sedentary controls [119]. Performing exercise training, skeletal muscle metabolism adapts by quantitative and qualitative changes in mitochondria and the capillary supply [120,121]. PGC-1α [122] and other signaling molecules like MAPKs, CaMKs and AMPK are central player in triggering the exercise induced changes observed in the skeletal muscle energy metabolism (for review see [123,124]).

4.4. Fiber type composition

A shift in fiber type composition is often observed in skeletal muscle biopsies obtained from HF patients when compared to healthy controls. A relative increase in less aerobic type II and a relative decrease in aerobic type I fibers is documented [125,126]. Recently, also in patients with heart failure and preserved ejection fraction (HFpEF), the percentage of type I fibers, the type I-to-type II fiber ratio, and capillary-to-fiber ratio were reduced, whereas the percentage of type II fibers was greater [127]. Performing regular exercise training resulted in a reversal of the changes observed in fiber type composition and the reduced capillary-to-fiber ratio in HF [126,128].

5. Myocardial effects of exercise

For a long time, exercise training was strictly forbidden for patients with CHF due to the fear that the increased load during exercise would harm the myocardium resulting even in sudden cardia death. This dogma had to be revised after several studies proofed the opposite effect – a benefit for myocardial function as documented by an increase in left ventricular ejection fraction (LVEF) and a reduction in left ventricular end-diastolic diameter [129–131]. What is the molecular mechanism mediating these beneficial effects on the myocardium? Due to the absence of myocardial biopsies taken before and after performing an exercise training program one may speculate that the myocardial changes are secondary to an after load reduction and an improvement in blood pressure [132,133] due to a better endothelial function [35,50]. Nevertheless, animal studies using ET to treat CHF and ischemia-reperfusion induced myocardial changes revealed, that molecular changes occur finally leading to myocardial remodeling and physiological hypertrophy [134–136]. Molecular alterations described included (1) modulation of the anabolic/catabolic balance [137,138], (2) modulation of calcium handling [29,139–142], (3) modulation of stem cell proliferation [143,144], and an increase in capillary density [143].

6. Future directions

To transmit the benefits of ET to the patients enrolled in exercise programs, one of the biggest challenges in future is to increase adheres to ET recommendations. As we learned from the HF-Action trail adherence is one of the most important factor for increasing exercise capacity and reducing mortality [18,19]. Often there is also a big discrepancy between subjective physical activity levels reported by patients and the objectively measured levels [145]. Known barriers to physical activity include impaired physical health, symptoms of CHF and low energy [146–148]. Psychosocial factors, such as patient knowledge and understanding of self-care requirements, social support and mental health, are also predictors of exercise behavior [146,147,149]. According to the current literature the patient's own confidence to engage in exercise, otherwise known as self-efficacy, is one important key component for exercise adherence (for review see [150]). Therefore to increase adherence better and self-motivating exercise training programs have to be offered to the patients.

With respect to the molecular mechanisms responsible for the beneficial effect of exercise training in CHF, and especially in HFpEF, more studies are warranted. These investigations are limited at the moment since the ideal animal model, resembling the human disease, is not defined yet. Furthermore, more research should focus on the interaction/communication between different organ systems – how is the heart influencing the skeletal muscle and vice versa and what are the signaling molecules.

7. Conclusions

Based on epidemiological observations it is fair to conclude that an active life style is associated with a reduced risk to develop cardiovascular disease. These exercise-related health benefits are only evident if physical activity is maintained throughout life. These beneficial effects of exercise training are also reported in secondary prevention in patients with cardiovascular diseases, independent of age and disease severity. Unfortunately, the genetic impact on exercise-induced health benefits is low, and therefore only the active form of exercise elicits the beneficial effects. Therefore, the challenge for the future is to increase exercise training compliance by offering better training programs to maintain physical fitness. At the molecular level several organs ranging from the vascular system to the skeletal muscle are modulated by active exercise training.

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None declared.

Transparency document

The Transparency document associated with this article can be found, in online version.

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