Mini-Review

Vascular dysfunction in obesity: Beneficial effects of aerobic exercise training in animal models

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Abstract — Cardiovascular disease (CVD) is the leading cause of mortality in the world and several risk factors for developing CVD have been pointed out, including obesity and physical inactivity. Endothelial dysfunction as a consequence of metabolic and inflammatory disorders plays an important role in the onset of vascular complications in obesity. In addition, it is well established that aerobic exercises promote beneficial effects on CVD by increasing nitric oxide (NO) production or its bioavailability in human and experimental models. The interest in exercise studies increased significantly, with promising results. Considering the importance of this field, the purpose of this mini-review is to summarize the animal studies that investigated the physiological mechanisms of vascular dysfunction in obesity and how aerobic exercise training influenced these alterations.

Keywords: aerobic exercise training; vascular dysfunction; obesity.

Introduction

Obesity is a chronic disease with rapid progression and deleterious effects of associated diseases, thus it is undoubtedly one of the major public health challenges in the world. In addition, obesity contributes to the origin of secondary pathologies as well as: type 2 diabetes, hypertension, cardiovascular disease, cancer and neurodegenerative diseases[1]. In the world, nearly 2 billion adults are overweight and, of these, more than half a billion are obese[2].

It is believed that the fundamental cause of weight gain and obesity is the imbalance between calories consumed and expended. Globally, there has been an increase in energy food (especially high fat) intake and an increase in physical inactivity due to the increasingly sedentary nature of many forms of work[2]. Obesity is generally defined as an excess of body fat with the most commonly used anthropometric index being the body mass index (BMI) expressed in kilograms per square meter (kg/m^2). There are other additional anthropometric measurements to establish the diagnosis of obesity such as waist/hip and skin folds[1].

Evidence shows that the sedentary lifestyle is the fourth largest risk factor for global deaths by secondary disease, being the biggest risk factor for the development of obesity[2]. In fact, several studies have shown that regular physical exercise promotes cardiovascular benefits and physically active patients have increased longevity associated with reductions in morbidity and mortality[2].

Animal models are considered an important tool in basic science to study the vascular complications associated with obesity. The studies involving induction of obesity in animal models are useful for research due to their great similarity with the genesis and metabolic responses derived from weight gain/obesity in humans[3].

Considering the practice of exercises has been widely discussed by various groups of researchers, it is necessary to properly describe the protocols of aerobic physical training with animals. In animal models, studies also observed reduced body weight, visceral obesity, and plasma glucose, as well as beneficial effects in cardiovascular parameters in obese rats and mice subjected to aerobic exercise training[4]. The aim of this mini-review is to summarize and integrate animal studies on the physiological mechanisms of vascular dysfunction in obesity and how they are influenced by chronic aerobic exercise training (Figure 1). Special attention will be taken to describe the protocols of physical exercise on the treadmill, including fitness training and strength analysis of the effectiveness of physical training in rodent models of obesity.

Vascular Dysfunction in Obesity

Normal blood vessels have a structure consisting of three layers: tunica intima (endothelial cells), tunica media (smooth muscle cells) and tunica adventitia (extracellular matrix). Endothelial cells are responsible for the synthesis, metabolism and release of a large variety of mediators that regulate platelet and leukocyte activity, vascular tone, vascular permeability and the metabolism of endogenous and exogenous substances. The integrity of the endothelial cells is of fundamental importance in the maintenance and control of the cardiovascular system.

The influence of the endothelium in vascular tone is modulated by the synthesis and release of vasoconstriction (endothelin-1, prostaglandins, tromboxane A_2 – TXA_2, angiotensin II and the reactive oxygen species – ROS) and vasodilator substances (nitric oxide – NO, prostacyclin – PGI2 and endothelium-derived hyperpolarizing factors – EDHF). NO requires special attention, because of its important role in regulatory functions. In the regulation of vascular tone, NO has a significant vasodilator function, being able to spread easily between biological membranes[5].

The nitric oxide enzymes (NOS), expressed in various tissues of the body, catalyze the oxidation of L-arginine in the presence of nicotinamide-adenine-dinucleotide phosphate (NADPH)

in NO and L-citruline. In mammals, NO can be generated by three different isoforms of the NO synthase enzyme: neuronal NOS (nNOS or NOS I), inducible NOS (iNOS or NOS II), and endothelial NOS (eNOS or NOS III). All isoforms of NOS use flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), and (6R-) – 5,6,7,8-tetrahydro-L-biopterin (BH4) as cofactors. Endothelial NOS (eNOS) is mostly expressed in endothelial cells, which are very sensitive to the chemical stimulation of agonists such as bradykinin, acetylcholine, histamine, and adenosine triphosphate, among others. However, the best established stimulus is shear stress (mechanical stimulation of blood flow); its activation is mediated by the phosphorylation of the enzyme and it does not produce sustained increases in intracellular Ca^{2+}, but still induces a long-lasting release of NO[5].

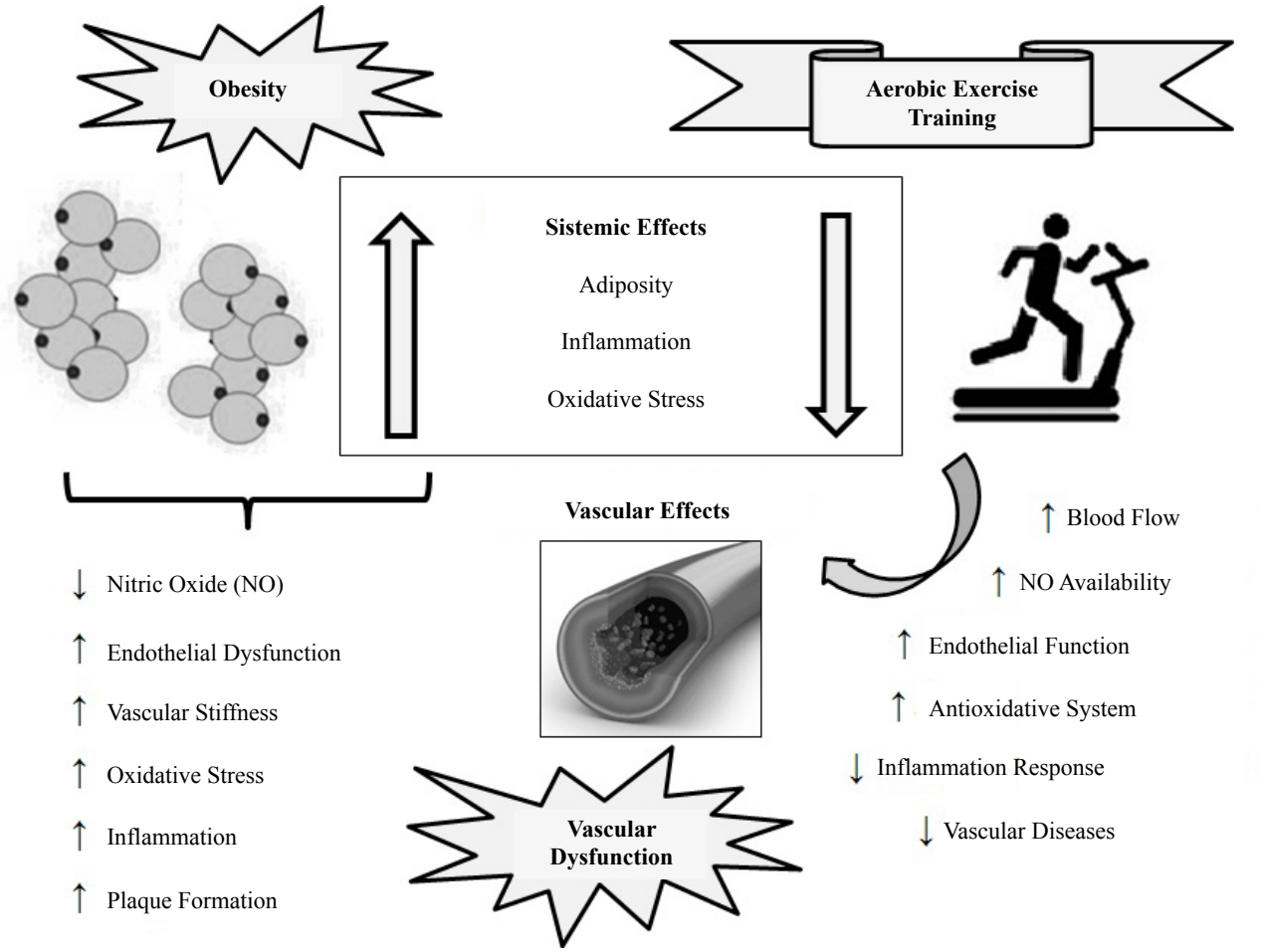

Figure 1. Chronic effects of aerobic exercise training on vascular dysfunction in obese animals.

Endothelial dysfunction (ED) is characterized by an imbalance between endothelium-derived relaxing and contracting factors, and is mostly associated with lower production and/or bioavailability of NO by endothelial cells[3]. ED as a consequence of metabolic and inflammatory disorders plays an important role in the initiation of vascular complications in obesity[6], and it is the hallmark of obesity associated with erectile dysfunction, coronary artery disease and peripheral artery disease[7,8]. Previous studies have demonstrated an impairment of relaxant responses in the aorta, mesenteric[9], femoral, and coronary arteries[10] in experimental models of obesity, that were associated with diminished NO release. The impaired vascular function and an increased vascular oxidative stress observed in obesity were associated with increased levels of inflammatory adipocytokines such as leptin, and tumor necrosis factor alpha – TNF-α, as well as decreased levels of anti-inflammatory adipocytokines such as adiponectin[11].

Considering the interaction between pro-inflammatory mediators and vascular diseases in obesity, many studies demonstrated that increased levels of TNF-α, free fatty acids (FFA), leptin and resistin result in endothelial dysfunction[11]. The physiological levels of leptin boost sympathetic nervous activity with increases in blood pressure and heart rate while its action on vascular tissues promotes NO release causing endothelium-dependent dilatation[12]. However, this vasodilation effect induced by leptin is impaired in obese animals when hyperleptinemia is observed[13]. Also in the vascular tissue, either eNOS protein expression or NO bioavailability is reduced in the presence of TNF-α [14]. On the other hand, adiponectin exerts vasculoprotective effects through a number of ways which includes increased NO production and/or its bioavailability due to enhanced eNOS activity or suppression of superoxide generation[15]. Moreover, the involvement of adiponectin in the regulation of TNF-α, affecting the coronary

and aortic endothelium function, has been demonstrated[16]. It has been shown that there is an imbalance between the release of inflammatory and anti-inflammatory adipocytokines in obesity, and that it contributes for vascular oxidative stress[17]. This alteration is involved in the increased production of ROS such as superoxide anions (O_2^-), and its reaction with endothelial-derived NO reduces its bioavailability and leads to a highly unstable molecule, peroxynitrite (ONOO-). The damage in cells and tissues by ROS has been associated with the development of endothelial dysfunction, and consequently with cardiovascular diseases[18]. There are many studies that associate obesity and its oxidative and inflammatory disorders with vascular dysfunction, however the mechanisms involved are complex and not fully understood[19]. Therefore, studies involving obese animal models are important to elucidate and develop new approaches in this field, specially the involvement of obesity with cardiovascular diseases.

Physical Exercise and Aerobic Protocols in Animal Models

According to the Centers for Disease Control and Prevention (CDC), physical activity is defined as any bodily movement produced by the contraction of skeletal muscles that increases energy expenditure above the basal level. It generally refers to the subset of physical activities that enhance health. In turn, physical exercises are defined as a subcategory of physical activity that is planned, structured, repetitive, and purposive in the sense that it has the improvement or maintenance of one or more components of physical fitness as objective[20]. On the other hand, physical inactivity is defined as physical activity levels lower than those required for optimal health and prevention of premature death, and functional capacity is the ability of a cell, organ, system, or body to maintain homeostasis within their narrow limits of survival in response to a specified stress[21]. It is well established that regular exercise not only enhances functional capacity but also brings about beneficial health outcomes[22]. Physical exercise leads to a variety of morphological and functional adaptations, which are known as the chronic effects of exercise[23].

Specifically, cardiorespiratory endurance or aerobic endurance is the ability of the whole body to sustain prolonged and rhythmic exercise[24]. This type of adaptation involves an increase in the capacity of the muscles for aerobic metabolism with an increase in endurance and is found in its most highly developed form in the muscles of competitive athletes, such as long-distance runners, long-distance cross-country skiers, bicyclists, and swimmers. It is well established that endurance exercises involving large muscle groups are recommended for the maintenance or improvement of cardiovascular fitness[25]. Considering the cardiovascular benefits of exercise have been attributed to aerobic exercise training, in this review we will focus on this type of exercise training.

The intensity of exercise could determine the degree of benefit to the cardiovascular system. Two tests of cardiorespiratory endurance – submaximal and maximal – appear in the literature. The test of submaximal (cardiorespiratory) endurance capacity is more closely related to actual competitive endurance performance and is likely determined by both the individual's maximum oxygen consumption (VO_2max) and his or her lactate threshold. Maximal cardiorespiratory endurance capacity (aerobic power – VO_2peak) is defined as the highest rate of oxygen consumption attainable during maximal or exhaustive exercise[24]. Well-controlled training studies in animal models are important, as they form the basis for translational research.

In rats and mice, accurate training intensity may be obtained by directly measuring the maximum oxygen consumption (VO_2max). For animal studies to mimic human standards for maximal cardiovascular endurance tests a determination of the VO_2max or VO_2peak may be obtained, as previously described[26]. This approach, however, is time consuming and expensive, especially in comprehensive and long-lasting studies. Therefore, several other methods have been proposed to estimate exercise intensity without directly measuring the VO_2max. Heart rate increases linearly with power output and VO_2 both in humans[6] and rats[7]. In humans, this method is easy to use through a number of commercial systems. In rats and mice, control by heart rate is more challenging, as monitoring requires implantation of transducers that impose a significant extra weight, especially in mice. Controlling training intensity by critical velocity[8], and lactate threshold has also been proposed[27]. The lactate threshold normally changes during a period of regular training, and frequent assessments are necessary for it to be used as a means of controlling the training stimulus[6]. In addition, frequent blood sampling is likely to affect the performance because of increased stress levels and reduced hemoglobin. Moreover, a correlation between the VO_2max and maximal running speed in rats and mice has been established. A previous study demonstrated that maximal running speed may be used both as a tool to adjust training intensity and to estimate the VO_2max at low and moderate intensity exercise training[26]. Thus, this method may be a great way to control the intensity of physical exercise training in animal models.

Also, voluntary wheel running is used to assess physical performance and endurance (as an endurance and fitness test, which generally lasts less than 7 days) and to model exercise training as a way to enhance health in rodents, especially mice. Wheel running is a voluntary activity in contrast to other experimental exercise models, which rely on aversive stimuli to force active movement. This protocol consists of allowing mice to run freely on the wheel placed inside a standard cage. Each wheel is connected to a computerized activity monitoring system that provides a detailed analysis of voluntary wheel running for individual mice. Thus, rotations, frequency and rate of running can be captured via a software program for data storage and analysis for various time periods. Factors such as mouse strain, gender, age, and individual motivation, which affect running activity, must be considered in the design of experiments using voluntary wheel running[28]. The advantage of voluntary running models is that animals are allowed to exercise at their own initiative, in terms of frequency, length and intensity of training. Voluntary exercise avoids some of the stressful factors related to forced training[29]. Self-administered exercise may also be convenient for researchers, because it requires less supervision time[26]. A disadvantage is the variability in the amount and intensity of the running performed by the mice on the wheels[30]. The ability to control the dose of physical activity

in terms of duration, frequency and intensity is therefore lost. Therefore, the question is whether the intensity of voluntary wheel running would provide the same protective benefits as 1 hour/day of controlled/forced exercise training. Mice run most intensely during the first several hours of the beginning of the active dark cycle, and it has been shown that voluntary wheel running for one hour a day five days a week generates physiological responses in mice in the long term[31]. However, more studies are needed to assess the health benefits of voluntary wheel running in mice, particularly in chronic disease models.

Chronic Effects of Aerobic Exercise Training on Vascular Dysfunction in Obesity

The association between obesity and physical inactivity is the most important risk factor for the development of cardiovascular diseases (CVD). Actually, physical inactivity is now regarded as one of the most prevalent cardiovascular risk factors[2]. Numerous studies, confirmed by meta-analyses, indicate that exercise training reduces cardiovascular mortality and cardiovascular events[32], particularly stroke, coronary heart disease, heart failure, and atherosclerosis[33]. Moreover, exercise training is an effective therapeutic strategy for patients with peripheral arterial diseases, coronary heart disease, heart failure, atherosclerosis, and hypertension[32]. Specifically for the endothelial function, the time course of endothelial adaptation following acute and regular exercise in rats was demonstrated. They found that a single bout of exercise improves endothelium-dependent dilation for about 2 days, with peak effect after 12-24 h, and regular exercise further improves adaptation and promotes an approximately fourfold increase in the sensitivity to acetylcholine, which slowly returns to sedentary levels within a week of detraining[34].

The cardiovascular benefits of exercise have been frequently attributed to the reduction of many classical cardiovascular risk factors including blood lipids, high blood pressure, obesity, glucose, and type 2 diabetes as well as novel risk factors such as inflammation, and oxidative stress[32,35]. In the endothelial cells one of the most important molecular consequences of exercise training is the increase of vascular NO concentration. NO is responsible for vasodilation, which results in the lowering of peripheral resistance. The eNOS is up-regulated by an increase in flow-mediated shear stress associated with physical exercise due to a complex pattern of intracellular regulation like acetylation[36] phosphorylation[37] and translocation to the caveolae[38]. It is now clearly documented that exercise or increased shear stress up-regulates eNOS activity in animal models[39]. Besides the cardiovascular benefits of exercise training associated with a variety of cellular and molecular alterations including up-regulation of eNOS, an increase in the expression and/or activity of antioxidant enzymes, as well as a decrease in pro-oxidant enzyme systems have been demonstrated in animal models[40]. The antioxidant defense systems consist of enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase. These enzymes are scavengers of ROS resulting in an increase of NO bioavailability to the vascular smooth muscle and enhancement of endothelium-dependent vasodilatation[9]. However, it should be noted that exercise intensity seems to be a crucial variable in this response. A recent study evaluated the impact of exercise training on vascular gene expression profiles, using a transcriptome-wide RNA-Seq analysis in obese rats[41]. In particular, the analysis was performed on the soleus and gastrocnemius muscle feed arteries (SFA and GFA, respectively) and aortic endothelial cell-enriched samples from obese Otsuka Long-Evans Tokushima Fatty (OLETF) rats that underwent an endurance exercise training program (EndEx) or interval sprint training program (IST). They found that the number of genes which had their expression altered in response to both EndEx and IST was greater in the SFA compared with the GFA. Considering the fact that exercise produces greater relative increases in blood flow in the gastrocnemius muscle compared with the soleus muscle, these data suggest an interesting disassociation between the magnitude of exercise-induced vascular transcriptional changes and the magnitude of exercise-induced blood flow stimulus to which the arteries are exposed. They suggested that the signals produced by bouts of exercise that result in altered gene expression are not totally driven by hemodynamic forces associated with increased blood flow, suggesting that other signals produced by exercise may also be involved[41]. Thus, it is still unclear which mechanisms explain the beneficial effects of exercise in vascular cells.

Therefore, well-controlled training studies in animal models are important, as they form the basis for translational research. Considering the increased number of studies which investigate the effects of exercise training in pathological conditions, such as cardiovascular diseases and obesity, in recent years, it is important to know which methodologies are employed to study exercise or exercise training, and also if the exercise protocols were properly described by the authors. In this review we focused on animal models of obesity studies that investigated the effects of aerobic exercise training on the cardiovascular system, which were summarized in Table 1.

Table 1: Chronic effects of aerobic exercise training on the cardiovascular system in obese animals: summary of studies.

Reference	Obesity Animal Model	Aerobic Exercise Protocol	Results on the Cardiovascular System
Xiang L, et al. 2005 (42)	Obese Zucker Rats (OZR)	Treadmill (24 m/min) for 4–5 wk, (10-day acclimation period).	**Obese Trained vs Obese Sedentary rats** -No difference in MAP; -Improved functional hyperemia and endothelial-dependent vasodilation in the spinotrapezius muscle.

Reference	Obesity Animal Model	Aerobic Exercise Protocol	Results on the Cardiovascular System
De Moraes C, et al. 2008 (9)	Male *Wistar* rats, high-caloric diet	Treadmill (70-80% VO_{2max}), 1h/day, 5 days/wk for 12 wk.	**Obese Trained vs Obese Sedentary rats** -No difference in NOx – levels; -Improved relaxation responses to acetylcholine in aortic and mesenteric rings; -Increased protein expression of CuZn-SOD in aorta and mesenteric arteries.
Sebai M, et al. 2011 (43)	Obese Zucker Rats (OZR)	Treadmill (24 m/min), 30 min/day, 5 days/wk for 6 wk.	**Obese Trained vs Obese Sedentary rats** -Increased VO_2max and workload; -Improved functional vasodilation in spinotrapezius and cremaster muscles.
Touati S, et al. 2011 (44)	Male Sprague-Dawley rats, high-fat diet for 12 wk.	Treadmill (27 m/min), 60 min/day, 5 days/wk for 12 wk.	**Obese Trained vs Obese Sedentary rats** -Decreased SAP and atherogenic index; -Improved endothelium-dependent relaxation to acetylcholine and insulin in aorta; -Increased contents of aortic p-Akt at $Serin^{473}$ and peNOS at $Serin^{1177}$.
Barbosa VA, et al. 2012 (45)	Male *Wistar* rats, high fat-diet for 8 wk	Treadmill (1.0 km/h), 50 min/day, 5 days/wk for 8 wk.	**Obese Trained vs Obese Sedentary rats** -Decreased TBARS and superoxide in myocardial tissue; -Decreased TBARS, superoxide and carbonyl content in aorta; -Increased CuZn-SOD, CAT and GPx activities in myocardial and aorta.
Barretti DL, et al. 2012 (46)	Obese Zucker Rats (OZR)	Swimming sessions (1h/day, 5 days/wk, for 10 wk), wearing caudal dumbbells weighing 5% of their body weight.	**Obese Trained vs Obese Sedentary rats** -No difference in the systemic ACE activity, resting heart rate and cardiac function; -Prevented increase in cardiac hypertrophy, cardiac ACE activity, Ang II and AT2 receptor; -Increased cardiac protein expression and activity of ACE2.
Mostarda C, et al. 2012 (47)	Male *Wistar* rats, overload of D-fructose (100 g/l) in drinking water for 10 wk	Treadmill (50-70% of the maximum running speed), 1h/day, 5 days/wk for 10 wk.	**Obese Trained vs Obese Sedentary rats** -Improvement in SAP, DAP, MAP, and diastolic function; -No difference in HR, and systolic function.
Moraes-Silva IC, et al. 2013 (48)	Male *Wistar* rats overload of D-fructose (100 g/l) in drinking water for 10 wk	Treadmill (50 –70% maximal running speed, 0.6 –1.3 km/h, 0% inclination), 1h/day, 5 days/wk for 10 wk.	**Obese Trained vs Obese Sedentary rats** -Improvement in SAP, DAP, MAP, HRV, SAPV, RMSSD, TR and BR; -No difference in HR.
Boa BC, et al. 2014 (49)	Male hamsters, high-fat diet starting on the 21st day of birth, for 12 wk.	Treadmill (50–70% of VO_{2max}), 1h/day, 5days/wk for 8 wk.	**Obese Trained vs Obese Sedentary rats** -Decreased MAP and HR; -Improved endothelial-dependent vasodilation in microcirculatory and macromolecular permeability after ischemia/reperfusion in three 2nd to 3rd order arterioles; -Increased eNOS protein expression in thoracic aorta.
Oharomari LK, et al. 2014 (50)	Male *Wistar* rats, highly palatable diet for 11 wk	Treadmill (60% maximal running speed), 1h/day, 5 days/wk for 7 wk.	**Obese Trained vs Obese Sedentary rats** -Improved relaxation response in aorta; -Increased protein expression of Ec-SOD, CuZn-SOD and reduced $gp91^{phox}$ in aorta; -Decreased superoxide formation in aorta.
Pieri BL, et al. 2014 (51)	Diet-induced obesity (DIO) *Wistar* rats	Treadmill 50-min/day, 5 days/wk, velocity of 1.0 km/h for 8 wk.	**Obese Trained vs Obese Sedentary rats** -Increased p-P38MAPK, REDD1, and 14-3-3 protein levels in the myocardium of trained obese rats.

Reference	Obesity Animal Model	Aerobic Exercise Protocol	Results on the Cardiovascular System
Touati S, et al. 2015 (52)	Male Sprague-Dawley rats, high-fat diet for 12 wk.	Treadmill (27 m/min), 60 min/day, 5 days/wk for 12 wk.	**Obese Trained vs Obese Sedentary rats** -Decreased NADPH oxidase activity in aorta; -No difference in Nox1 and Nox2 expression in aorta. -Decreased protein expression of Nox4, $p47^{phox}$ translocation, VCAM-1, pERK 1/2 (Thr^{202}/Tyr^{204}) and pJNK/SAPK (Thr^{183}/Tyr^{185}) in aorta; -Increased CuZn-SOD protein expression in aorta.

MAP: mean arterial pressure; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; HR: heart rate; VO_2max: maximum oxygen consumption; NOx^-: nitrite/nitrate concentrations; CuZn-SOD: CuZn superoxide dismutase; Ec-SOD: extracellular superoxide dismutase; pAkt: phosphor protein kinase B; peNOS: phosphor endothelial nitric oxide synthase; TBARS: thiobarbituric acid-reactive substances; CAT: catalase; GPx: glutathione peroxidase; ACE: angiotensin I-converting enzyme; Ang II: angiotensin II; AT2: angiotensin II receptor; ACE2: angiotensin II-converting enzyme; HRV: heart rate variability; SAPV: systolic arterial pressure variability; RMSSD: root mean square successive difference; TR: tachycardia; BR: bradycardia; $gp91^{phox}$: subunit of NADPH oxidase complex; p-P38MAPK: phosphor P38 mitogen-activated protein kinase; REDD1: regulated in development and DNA damage responses 1; Nox 1: NADPH oxidase subunit enzyme 1; Nox 2: NADPH oxidase subunit enzyme 2; Nox 4: NADPH oxidase subunit enzyme 4; $p47^{phox}$: cytosolic subunit of NADPH oxidase complex; VCAM-1: vascular cell adhesion molecule-1; pERK 1/2: phosphor extracellular signal-regulated kinase; pJNK: phosphor c-Jun N-terminal kinase; SAPK: stress-activated protein kinase.

Conclusion

The association between obesity and physical inactivity is the most important risk factor for the development of cardiovascular diseases. Endothelial dysfunction as a consequence of metabolic and inflammatory disorders plays an important role in the initiation of vascular complications in obesity. On the other hand, many studies have shown the importance and effectiveness of exercise training in the prevention and treatment of cardiovascular disease in obesity. However, it is still unclear which mechanisms explain the beneficial effect of exercise in vascular cells. Therefore, well-controlled training studies in animal models are important, as they form the basis for translational research.

In summary, animal models of aerobic exercise training against obesity show promising benefits to the cardiovascular system. We found that most studies investigating the effects of aerobic exercise training on the cardiovascular system in animal models of obesity were concerned with the exercise training protocol used and also have been reported properly by the authors.

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