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Mechanisms underlying exercise-induced modulation of hypertension

Adam Lelbach [1,2], Akos Koller [2,3,4] *

[1] Dr. Rose Private Hospital, Budapest, Hungary
[2] Institute for Translational Medicine, Medical School, University of Pecs, Hungary
[3] Institute of Natural Science, Sportgenetics and Sportgerontology Research Group, University of Physical Education, Budapest, Hungary
[4] Department of Pathophysiology, Semmelweis University, Budapest, Hungary

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Abstract

Hypertension is one of the most important risk factors of cardiovascular diseases with a high prevalence in developed countries. Hypertension develops as the results of several and simultaneously acting pathomechanisms. A recently appreciated/recognized condition is obesity, which is frequently associated with hypertension due to activation of the sympathetic nervous system and the renin-angiotensin system, as well as sodium retention, but also increased glucose intolerance (in type 2 diabetes mellitus) are the underlying mechanisms. Another unavoidable and recently increasing risk factor is vascular aging leading to arterial remodeling (stiffening) causing isolated high systolic blood pressure. Aging process also leads to a reduced ability and efficiency of kidneys to excrete salt, resulting to a volume overload of the circulatory system affecting both systolic and diastolic pressures. Many of these alterations can be treated with pharmacological means, but in this review we aimed to summarize the potential beneficial effects of several exercise modalities, as well as the effects of physical activity and training programs on blood pressure both in normotensive and hypertensive individuals. The potential blood pressure lowering mechanisms of different exercise modalities and physical fitness programs are discussed, including neuro-hormonal mechanisms (decreasing serum catecholamine levels connected with the decrease of total peripheral resistance), the effects of exercise on vascular function (vasodilator and vasoconstrictor mechanisms) and structural adaptations, such as arterial remodeling (arterial stiffness, hemodynamic adaptations). Changes in coronary and skeletal muscle microcirculation, in myocardial remodeling and in various gene expressions are also discussed, as well as in addition to hypertension the exercise-induced modulation of several cardiovascular risk factors (obesity, dyslipidemia, metabolic syndrome, type 2 diabetes mellitus, inflammation and oxidative stress) which interact with each other. The Frequency, Intensity, Type, and Time (FITT) principle of exercise prescription as powerful therapeutic approach - which represents a translation of the results of cardiovascular basic science research into hypertension treatment - is also presented.

Keywords: hypertension, obesity, vasomotor function, coronary and skeletal microcirculation, metabolic syndrome, inflammation, oxidative stress, FITT principle of exercise

* Correspondence to: Prof. Akos KOLLER MD, PhD
University of Physical Education
Alkotas Street, 44, 1123 Budapest, Hungary.
e-mail: akos.koller@gmail.com, koller@tf.hu

Introduction

Traditional risks factors for the development of hypertension

Hypertension is an important risk factor of cardiovascular diseases with a high prevalence in developed countries [1]. Hypertension develops as the result of several and simultaneous presence of different pathomechanisms. Among others sodium consumption is well known to be associated with elevated blood pressure [2], as well as genetic-predisposition as genomic variants underline the importance of the genetics origins [3]. Chronic kidney disease is not only a common cause but also a consequence of uncontrolled hypertension [4] but such lifestyle habit like smoking also has a role in the development and presence of elevated blood pressure [5]. For most of these forms of hypertension there are readily available pharmacological treatments, especially the so called combined or "polypill" applications [6].

Two novel risks factors for the development of hypertension

However, in recent decades one of the dominating risk factors for the development of hypertension is obesity which is increasing in an alarming rate in the well developed countries, and even in those migrated (African American) or indigenous (American Indians (pima county, etc.) populations, which have genes associated with low BMI [7]. Among others, in addition to the obvious extra weight related increased cardiac output [8], obesity related hypertension is characterized by the activation of the sympathetic nervous system [9] and the renin-angiotensin system [10], as well as sodium retention, but it is also related to other metabolic abnormalities, such as increased glucose intolerance (in type 2 diabetes mellitus) [10].

Another and unavoidable risk factor for hypertension is aging, which is also become important recently, because the average lifespan greatly increased in the so called Western countries. It is important, however to differentiate and separate normal aging, accelerated aging and aging with diseases [11].

In both obesity- and aging-induced hypertension cardiac remodeling occurs resulting the increase of wall tension and thickness - primarily - in the left ventricle. On the other hand there is also a remodelling in the vascular wall, eliciting loss of the elasticity of the conduit arteries leading to the alteration of the structure and function of arterial wall, leading to stiffening. Obviously stiffening of aorta and large arteries reduces their "windkessel" function, which then results in isolated high systolic blood pressure, "systolic hypertension", when usually the systolic pressure values increases above 150 mmHg whereas the diastolic pressure values remain below 95 mmHg [12, 13].

At the level of smaller arteries and arterioles there is an increased basal tone and reduced dilator capacity - eventually - contributing to the development of increased peripheral resistance, and thus increased diastolic pressure, as well. These process take years to develop thus it is important to measure blood pressure periodically and once it reaches levels that are above 140/90 mmHg, medical attention is needed [14].

Interestingly both cardiac and vascular remodeling can be influenced and modulated beneficially by well designated physical exercise and training programs reducing thereby the impetus of these risks factors [15]. Regular exercise can especially be effective in the early phase of the development of hypertension, preventing and/or delaying the need for pharmacological interventions [16].

Aging of course affects numerous other tissues and organs, such as the ability and efficiency of kidneys to excrete salt leading to a volume overload of the circulatory system affecting both systolic and diastolic pressures [17, 13], as well as age related molecular biological changes of such interacting mechanisms like chronic inflammation and oxidative stress modifying numerous immunological actions (e.g. through continuous pro-inflammatory cytokine production) and endocrine effects (e.g. influencing the IGF system). These changes however also can be delayed by improving the cardiovascular system thereby the oxygen and nutritional supply of these organs, reducing their negative feedback impact on the cardiovascular system [18-20].

Below we are describing and discussing various exercise modalities, which could be used to delay or prevent the development of hypertension, by affecting - among others - the structure and function of the cardiovascular system.

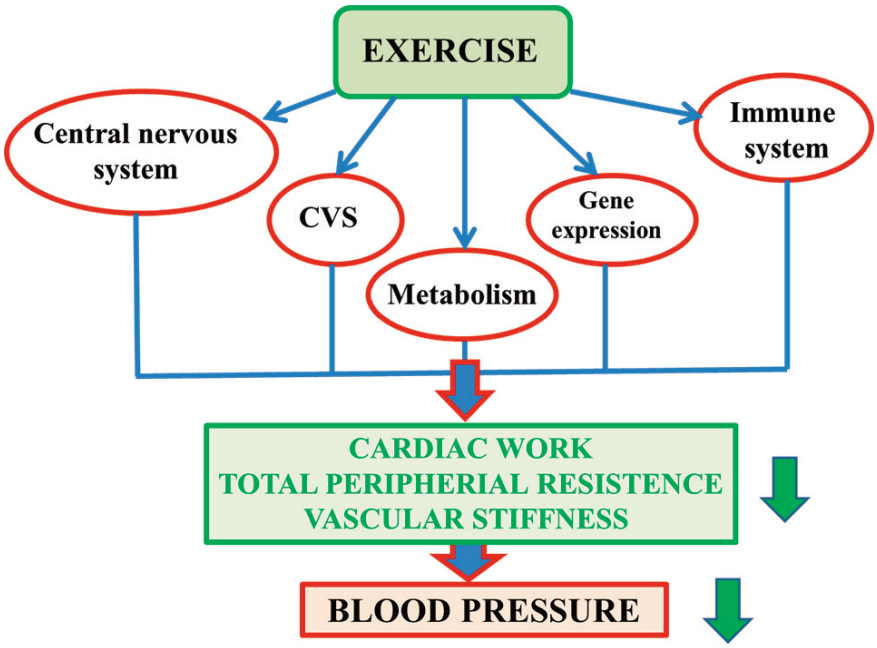

Fig. 1. Effects of exercise on hypertension.

Effect of acute and chronic exercise programs on the cardiovascular system - general considerations

Acute and chronic exercise programs have well-known beneficial influence in cardiac-, vascular- and blood-tissues.

Hemodynamic and molecular effects of exercise on the heart

In general, from a physiological point of view physical training consumes a high level of energy, which is predominantly derived from oxidizing glucose [21]. Both glucose and oxygen delivered to the tissues by the blood through the circulation. This means that the heart has to work in a more intense levels than at rest to supply more blood to the organs thus to beat faster to perform a sufficient capacity (blood flow = heart rate x stroke volume) [22] (Figure 1).

On the molecular biological and cell physiological level among many positive effects increased antioxidant levels [23] have been observed which support the important role of one in the cardiovascular protection offered by exercise. Increased gene-expression of heat shock proteins which are associated with increased cell survival and protection against ischemic damage has also been observed [24]. Mitochondrial adaptations, as well as potassium channels of sarcolemma and mitochondria are notably influenced by exercise contributing to cardioprotection [25, 26].

Hemodynamic and molecular effects of exercise on the vascular system

Blood flow depends consumedly on the width of the blood vessels primarily the arterioles and venules, so that slight change of the diameter has a large impact on the flow of blood [27]. The organs that need less oxygen during physical training have constricted vessels and decreased blood flow but arterioles are distended to the organs which need more [28]. This regulation is essential machinery for supplying oxygen and glucose to the tissues that need it most. Exercise-induced vascular remodeling and improvement of endothelial function also has an important role [26].

In the regulation of vasoconstrictor and vasodilator mechanisms the endothelium plays an essential role regulating arterial dilation and constriction by synthetizing among others mediators like vasodilator nitric oxide (NO), prostacyclin (PGI2) and vasoconstrictor molecules like endothelin-1 (ET-1) and platelet-activation factor (PAF) [29].

It is essential for proper endothelial function the presence of sufficient NO, since in the vasculature NO - as mentioned before - has significant vasodilator effect. NO production is regulated by endothelial nitric oxide synthase (eNOS) [30]. Physical training increases

the gene expression of eNOS, most probable through increases in wall shear stress, which elicits increased synthesis of NO, and release of other dilator factors, such as prostaglandins all of them leading to vasodilation, important anti-inflammatory action and platelet inhibition, as well, other cardioprotective influences, which are in addition to the vascular and metabolic effects [27, 31].

Effects of exercise on the hemorheological characteristics of blood

According to the latest results of scientific research exercise training can improve the hemorheological status in elderly, such as enhanced plasma and blood viscosity, impaired red blood cell deformability and enhanced red blood cell aggregation, thereby causing improved flow properties of blood and consequently tissue perfusion [32]. In terms of hematological benefits, exercise-induced fibrinolytic and rheological changes should be emphasized [26], since many studies have documented elevated plasma fibrinogen levels and pro-inflammatory conditions in aged people [32]. Also ATP and NO released from red blood cells due to altered flow during exercise training doubtlessly have regulatory effects on blood flow dynamics since they are acting in a paracrine manner near to the neighboring cells and vascular wall [33].

Effects of exercise on the skeletal muscle

In regard of physical training at low-to-moderate intensities of physical exercise the main source to skeletal muscle for energy supply is glucose, which originates from hepatic glycogenolysis (or gluconeogenesis) or oral intake and also from free fatty acids (FFAs) through lipolysis in the adipocytes primarily in various adipose tissues [34]. The rate of adenosine triphosphate (ATP) need depends on the absolute power output and energy expenditure, while the relative contributions of carbohydrate and lipid sources, and circulating (extramuscular) and intramuscular energy stores to energy supply depends on the relative exercise intensity [34].

In case of progressive, increasing exercise (and also during isometric-isotonic exercises when "muscle pump" in efficient thus called anaerobic exercise and discussed later) insufficient oxygen supply can develop and anaerobic energy production is accelerated, thus lactate synthesis increases progressively at the beginning and then more rapidly as the exercise becomes more intense [35]. An elevated lactate could be indicative of ischemia or hypoxemia but also as described a physiological response to exertion.

Exercise types: aerobic - anaerobic - flexibility exercises

In the previous paragraph we have described - in general - the cardiovascular and metabolic effects of exercise, however the various types of exercise can invoke different adaptations of the cardiovascular system, which should be considered and to be recommended accordingly in various forms of hypertension.

Several exercise types are known, which can be classified into three main categories:

1) the aerobic exercises (e.g. cycling, walking, running, hiking, playing tennis, etc.), which focus on increasing cardiovascular endurance [36], and in case they work at low-to-moderate intensities - as discussed previously - the main energy sources are glucose and FFAs [34].
2) the anaerobic exercises (e.g. weight training), which increase short-term muscle strength [37] and through which the above mentioned not sufficient oxygen supply can develop with an accelerated anaerobic energy production and increased lactate synthesis [35]. Similar happens in case of progressive, increasing very intense physical training where at the beginning major aerobic mechanisms switch to anaerobic metabolism [35].
3) the stretching/flexibility exercises, which improve the range of motion of muscles and joints mostly at low intensities using aerobic mechanisms for energy supply.

According to the American College of Sports Medicine (ACSM) to treat hypertension the most effective and recommended physical activities are the aerobic dynamic exercise trainings (evidence category A) [38].

Blood pressure lowering mechanisms of exercise modalities and fitness programs

There are several physiological processes through which exercise modalities and fitness programs make blood pressure lowering effects happen.

1. Neuro-humoral effects

The most important of them are neuro-hormonal mechanisms as decreasing serum catecholamine levels connected with the decrease of total peripheral resistance [39]. The general response to low-to-moderate circulating concentrations of cathecholamines is an increased cardiac output and a redistribution of the blood flow to the musculature and the liver without significant change in mean arterial pressure [40]. In this case the physiological reason of the almost unchanged (or slightly changed) arterial pressure despite increased cardiac output is the activation of vascular β2-adrenoceptors which cause the decrease of systemic vascular resistance. In case of high plasma concentration of cathecholamines they elevate arterial pressure through binding to α-adrenoceptors on blood vessels, which compensate the β2-adrenoceptor mediated vasodilation [40]. General cathecholamines response is influenced by such parameters as being trained or untrained, as well as age, nutritional and emotional state (e.g. psychically highly stressed managers) [39]. Long term exercise training, especially endurance exercise training (e.g. cycling, running) can improve autonomic nerve function through the decrease of sympathetic activity and increasing parasympathetic (vagal) modulation [41].

2. Vasomotor effects of exercise

Important effects of exercise on vascular function are the modulation of vasodilator and vasoconstrictor mechanisms [42] and that of structural adaptations, such as arterial remodeling (arterial stiffness, hemodynamic adaptations) [43]. In addition, changes in coronary and skeletal muscle microcirculation have also been documented.

As we discussed before in the regulation of vasoconstrictor and vasodilator mechanisms the endothelium of all size and types of vessels (even lymphatic) plays an essential role through the synthesis of vasodilator and vasoconstrictor mediators [29]. One of the main regulators of endothelium smooth muscle is the vasodilator NO, the synthesis of which is regulated by the gene expression of eNOS stimulated by physical training, most probable through shear stress [30], but prostaglandins and antioxidant enzymes, such as superoxide dismutase are also up- regulated.

From the point of view of the heart, exercise-induced cardiac remodeling (EICR) has structural cardiac adaptations, such left ventricular hypertrophy with a sport-specific appearance (eccentric instead of concentric hypertrophy). According to congruent scientific observations the myocardial adaptation is interconnected to the gain of VO2 max [44].

Genetic changes in response to long term exercise programs

Chronic exercise elicits changes in various gene expressions (e.g. ACE (angiotensin I converting enzyme), APOE (Apolipoprotein E), EDN1 (Endothelin 1), LPL (Lipoprotein lipase), NFκβ1 (Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1), NOS3 (nitric oxide synthase 3), PPARA (Peroxisome proliferator-activated receptor alpha)) influencing blood pressure. In addition, daily training affects lipid metabolism, endothelial function, oxidative- and glucose homeostasis, and also important factors of blood pressure lowering mechanisms of exercise modalities and fitness programs [45]. The function of the above mentioned molecules are well known and discussed before, reduced or increased synthesis of them through the regulation of their gene expression can be a consequence of different exercise trainings (some are transient post-exercise changes including activation of immediate early genes). These effects are regulated through the modulation of different signal transduction pathways by such molecular biological changes as the interaction of molecules of chronic inflammation and oxidative stress interfering also with obesity and aging [13, 20].

The effect of various exercise modalities on serum lipid parameters

Various dyslipidemias are important risk factors of cardiovascular diseases. Beyond diet, weight loss and lipid-lowering medications physical activity has an essential role to improve serum lipid parameters. According to several meta-analyses of multicenter randomized controlled trials aerobic training observed having an increasing effect on serum high density lipoprotein cholesterol (HDL-C) [46], while resistance training a rather lowering effect on serum low density lipoprotein cholesterol (LDL-C) levels [47]. Combined resistance and aerobic

Fig. 2. The Frequency, Intensity, Type and Time (FITT) principle.

training (concurrent aerobic and resistance training) showed beneficial effect both increasing serum HDL-C and lowering serum LDL-C at the same time [47].

Although aerobic and anaerobic training should have a beneficial reducing role on serum triglycerides (TG), it cannot be unambiguously characterized and presumably dose and intensity dependent [47]. Even more mysterious the so called obesity paradox (OP) observed recently by meta-analysis of big data bases [48]. OP suggests that although overweight people have an increased risk of cardiovascular disease, their mortality risks are decreased compared to people with normal body weight [49]. Possible explanations could be the better survival rate in case of severe life threatening conditions, such as myocardial infarction or stroke.

The Frequency, Intensity, Type and Time (FITT) principle of exercise prescription

The Frequency, Intensity, Type, and Time (FITT) principle of exercise prescription is a powerful therapeutic approach as a translation of the results of cardiovascular basic science research into hypertension treatment through which an individually designed physical activity program is provided according to the individuals medical needs (Figure 2).

As we discussed previously the three main categories of exercise types are the aerobic exercises (evidence category A to treat hypertension), the anaerobic exercises and the flexibility exercises. Concurrent exercise training refers aerobic and resistance training (anaerobic exercise) workouts during the same training session or within a few hour of one another [50], which is a usual training method and could have a moderating effect on hypertension, as well as several connected cardiovascular risk factors [50, 51].

A way of measuring physical activity intensity level is „The Borg Rating of Perceived Exertion (RPE)" is a perceived exertion scale - how hard you feel like your body is working during physical activity, including increased heart rate-, respiration or breathing rate-, sweating- and muscle fatigue. It ranges from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion" [52].

The Metabolic Equivalent of Task (MET) is expressing the energy cost of physical activities. Originally, 1 MET was accounted the Resting Metabolic Rate (RMR) obtained during quiet sitting. MET values of activities range from 0.9 (sleeping) to 23 (running at 22.5 km/h) [53].

According to the current consensus of the ACSM the aerobic dynamic exercise trainings for hypertensive individuals recommended as follows:

Frequency - mostly daily aerobic exercise with a complementary resistance exercise three times a week [38].

Intensity - moderate intensity aerobic exercise between 40-60% oxygen consumption reserve (VO2 reserve) or HR (heart rate) reserve (R), (HRR= HRmax-HRrest), as well as a 11-13 rate (between the level of exertion of "light (11)" and "somewhat hard (13)", when "somewhat hard" means it is still feels fine to continue) on the Borg scale [38].

Time - it is recommended to perform 45-80 minutes exercise per session in the way of a concurrent exercise, having 30 minutes aerobic training and 15-40 minutes of dynamic resistance exercise [38].

Type - concurrent exercise training including aerobic activities as walking, jogging and cycling and dynamic resistance exercise as free weights, machine weights and circuit resistance training showed proper effect without special order of the modality [54, 55].

FITT exercise prescriptions also mention volume and progression of the training protocols (FITT-VP), where volume refers the metabolic equivalent (MET) value and progression refers the training progression. According to the ACSM in point of the volume 500 - ≥1000-min per week MET exerted the greatest antihypertensive benefits, related to progression exercise is recommended to be gradually increased in intensity and volume [56].

Conclusion

On the basis of literature survey and our previous studies it seems plausible and justified to conclude that various exercise programs can be useful to modulate and/or temper hypertension and its consequences, and that they should be included early on in the treatment modalities. According to the American College of Sports Medicine (ACSM) [38] and The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC8) [57] the most effective and recommended physical activity to treat hypertension are the aerobic dynamic exercise trainings (evidence category A). Although resistance training should be carefully practice in hypertension (e.g. Valsalva maneuver) it has certainly a role in prevention of high blood pressure and connected chronic diseases [37]. Concurrent exercise training (involving both aerobic and resistance exercises during the same training session or within hours of one another) seems to have similar beneficial effects on hypertension as isolated aerobic exercise [50, 51]. After careful consideration of individual needs and conditions hypertension specialists - on the base of FITT guideline - should design exercise programs for their patients, which could be more successful if they involving them in the decision making process. Latest epidemiological studies underline the significance of physical activity in the broadest social groups [58], since worldwide more than hundred millions of people live with disability whose equal access and opportunities for healthy living is not just an essential human right, but also a common economic interest.

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Disclosure Statement

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