Effects of Acute and Chronic Exercise in Patients With Essential Hypertension: Benefits and Risks

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The importance of regular physical activity in essential hypertension has been extensively investigated over the last decades and has emerged as a major modifiable factor contributing to optimal blood pressure control. Aerobic exercise exerts its beneficial effects on the cardiovascular system by promoting traditional cardiovascular risk factor regulation, as well as by favorably regulating sympathetic nervous system (SNS) activity, molecular effects, cardiac, and vascular function. Benefits of resistance exercise need further validation. On the other hand, acute exercise is now an established trigger of acute cardiac events. A number of possible pathophysiological links have been proposed, including SNS, vascular function, coagulation, fibrinolysis, and platelet function.

In order to fully interpret this knowledge into clinical practice, we need to better understand the role of exercise intensity and duration in this pathophysiological cascade and in special populations. Further studies in hypertensive patients are also warranted in order to clarify the possibly favorable effect of antihypertensive treatment on exercise-induced effects.

Keywords: activity; acute; blood pressure; chronic; exercise; essential hypertension; hypertension; physical.

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Essential hypertension represents a major public health problem leading to over 7.5 million deaths annually,¹ as blood pressure (BP) levels are directly associated with vascular and overall mortality.² Accumulating data point towards a beneficial role of lifestyle modifications and in particular increased physical activity, in promoting cardiovascular risk factor control. The importance of regular physical activity in essential hypertension has been extensively investigated over the last decades and has emerged as a major modifiable factor which can contribute to optimal BP control. However, acute exercise has been related to acute cardiovascular events, suggesting that potentially harmful mechanisms are triggered in response to exercise.

In this narrative review, we sought to summarize current knowledge on effects of acute and chronic exercise and their pathophysiological background in patients with essential hypertension. To that reason, we performed a PubMed search using the following terms: exercise or physical activity; essential hypertension. We focused on data provided by high-quality randomized controlled trials (RCTs), meta-analyses, and systematic reviews. Observational and research studies were included when necessary.

BENEFICIAL EFFECTS OF REGULAR PHYSICAL ACTIVITY ON CARDIOVASCULAR RISK REDUCTION

In 1953, Morris et al. provided the first piece of evidence suggesting an association between fitness status and morbidity/mortality with their study on drivers and conductors of London's double-decker buses.³ Drivers showed a significantly higher incidence of coronary heart disease compared to conductors, whose fitness status was unquestionably higher. Since then, well-designed epidemiological studies have confirmed the beneficial effects of adequate exercise on cardiovascular and all-cause mortality in healthy middle-aged and older men and women. In above-mentioned studies, fitness status has been evaluated by a variety of available means, i.e., in terms of physical activity as assessed by questionnaires, exercise capacity in METs (metabolic equivalents) as assessed by an exercise test, as well as cardiorespiratory fitness measured by maximal oxygen uptake during exercise. Furthermore, recent studies in large cohorts of prehypertensive and hypertensive individuals have shown a reverse and graded association of exercise capacity and all-cause mortality independently of additional cardiovascular risk factors. In addition, exercise capacity has been reported to be a strong and independent predictor of the progression rate from prehypertension to hypertension.⁴

Of note, the beneficial effects of exercise on cardiovascular health depend upon exercise type (strength or resistance vs. endurance exercise), frequency, duration, and intensity. Generally, light-intensity activity is defined as 1.1–2.9 METs, moderate-intensity activity as 3.0–5.9 METs, and vigorous activity as ≥6 METs.⁵

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REGULAR PHYSICAL ACTIVITY AND ESSENTIAL HYPERTENSION

A plethora of epidemiological and interventional studies have explored the association between elevated BP and lifestyle characteristics, including physical activity. In 2002, Whelton et al. meta-analyzed 54 studies in 2,419 normotensive and hypertensive individuals aged 21–79 years, concluding that aerobic exercise resulted in significant reductions of systolic and diastolic BP of 3.84 and 2.58 mm Hg, respectively. BP reduction was independent of hypertensive status, baseline body mass index (BMI), exercise frequency, or intensity. A second systematic review of 21 RCTs in 1,346 patients confirmed these results, showing a significant BP reduction of 4.6/2.3 mm Hg in the aerobic exercise intervention group. It should be noted that these results referred to a relatively young cohort (mean age of 48 years) with mild arterial hypertension (mean BP 141/90 mm Hg). Nevertheless, smaller studies and meta-analysis in older individuals have shown similar results. Lastly, a recent meta-analysis of RCTs with long-term increased physical activity interventions marked the heterogeneity of studies in the field and calculated BP reduction at 5–10/1–6 mm Hg.

In addition, regular physical activity when combined with other lifestyle modifications, such as diet, salt restriction, and relaxation, had significant and even greater effects on BP reduction. In particular, Dickinson et al. showed that combined interventions resulted in a significant BP reduction of 5.5/4.5 mm Hg. These findings are attributed, at least in part, to the fact that physical activity has proven, although modest, effects on weight reduction or weight gain prevention in different populations and offers additional benefits to dietary restrictions.

Regarding other forms of exercise, existing data are not sufficient to determine the role of resistant exercise in patients with elevated BP. A number of studies emerged supporting dynamic resistance exercise alone or in combination with aerobic exercise in patients with essential hypertension. A most recent meta-analysis by Cornelissen and Smart showed that isometric and dynamic resistance exercise result in significant BP reductions. Dynamic resistance training resulted in higher BP reductions in prehypertensive individuals as compared to hypertensive and normotensive individuals. Isometric resistance exercise proved also efficacious in lowering BP in recent meta-analyses of a small number of RCTs. However, larger, well-designed studies are needed in order to clarify the role of resistance exercise in hypertension.

In accordance with the above-mentioned existing data, the recently published Lifestyle Management Guidelines from the American College of Cardiology and American Heart Association suggested moderate-to-vigorous intensity 40 minute/session aerobic physical activity of at least 12 weeks duration, with 3–4 sessions/week for all individuals, including patients with essential hypertension. According to the same guidelines, data regarding benefits of resistance exercise on BP reduction have been reviewed as insufficient.

Similarly, the recent European Society of Hypertension guidelines suggested at least 30 minutes of moderate-intensity dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5–7 days per week for hypertensive patients. It was also added that the aerobic interval training could be beneficial, mainly due to the findings of recent studies showing an equal or greater improvement of aerobic fitness and cardiometabolic risk reduction in response to interval training compared to continuous exercise. Furthermore, European guidelines have been in favor of resistance exercise for 2–3 days per week, based on an older meta-analysis by Cornelissen et al. and on recommendations by the European Association on Cardiovascular Prevention and Rehabilitation for patients with cardiovascular risk factors. However, based on available evidence until guideline issuance, isometric exercise was not recommended.

UNDERLYING PATHOPHYSIOLOGY OF EXERCISE-INDUCED BENEFICIAL EFFECTS ON THE CARDIOVASCULAR SYSTEM

The beneficial effects of exercise on cardiovascular system are multiple and refer namely to reduction of sympathetic nervous system (SNS) activity, improvement of vascular function, cardiac, and molecular effects. Studies focusing on patients with essential hypertension are limited and are summarized in Table 1.

SNS activity

SNS overactivity, a key characteristic of cardiovascular diseases, such as hypertension and heart failure, has been associated with increased cardiovascular and all-cause mortality in patients with diabetes, end-stage renal failure, and asymptomatic left ventricular (LV) dysfunction. SNS activity reduction is considered a possible pathophysiological mechanism underlying the beneficial effects of exercise on the cardiovascular system. In particular, a large amount of evidence indicates that exercise training increases heart rate variability in healthy individuals and in patients with cardiovascular diseases. Furthermore, regular physical activity attenuates the age-related decline in baroreflex function and improves the impaired cardiovagal baroreflex function observed in sedentary individuals.

Interestingly, the interpretation of exercise effect on SNS depends highly on the method used to assess SNS activation. The most widely used methods are: plasma noradrenaline (NA) levels, muscle sympathetic nerve activity (MSNA), and regional NA spillover. In 1998, a detailed review on the subject concluded that exercise training does not modulate resting MSNA. However, later studies have shown significant reductions in plasma NA levels and in MSNA following exercise training. Significant limitations of plasma NA and MSNA measurements, primarily providing no information regarding regional differentiation of sympathetic activity in internal organs, render regional NA spillover an appealing method of SNS activity measurements. Nevertheless, available data on the effect of exercise on NA kinetics are sparse and limited to acute exercise effects. In general, the...
effects of exercise on SNS activity depends also on a variety of additional individual-related, such as age, obesity, fitness status, and exercise-related factors, such as intensity and duration of exercise programs.

Finally, recent experimental data point toward a beneficial effect of exercise on SNS, by improving also renal, lumbar and cardiac sympathetic nerve activity and by increasing neural plasticity in networks controlling SNS activity.

Effects on the vasculature

Arterial stiffness. Arterial stiffness constitutes a reliable marker of vascular function, namely of the aorta and big arteries, and predicts cardiovascular and all-cause mortality in healthy individuals and patients with essential hypertension. Aortic pulse-wave velocity (PWV) is considered the most accurate and robust non-invasive method to estimate arterial stiffness.

The beneficial effects of regular physical activity on indices of arterial stiffness have been well-documented by cross-sectional studies in healthy young, middle-aged, and older men, as well as pre- and post-menopausal women. In addition, endurance training has been shown to statistically reduce systemic vascular resistance in a meta-analysis of interventional studies in normotensive and hypertensive individuals. However, the optimal duration, intensity and type of exercise interventions needed to improve arterial stiffness have not been yet clarified. Interestingly, a recent study reported that vigorous but not light-to-moderate physical activity of young adults was associated with improved arterial stiffness later in life. In particular, a 3-month moderate-intensity aerobic exercise intervention restored arterial stiffness in previously sedentary healthy postmenopausal women and middle-aged and older men. Regarding older adults (aged 71.4 ± 0.7 years) with increased cardiovascular risk (hypertension, type 2 diabetes and dyslipidemia), a 3-month vigorous aerobic exercise program resulted in a statistically significant reduction of aortic PWV by 13.9%, compared to the nonaerobic group which showed an increase of aortic PWV by 4.4%. In a study comparing moderate and high-intensity aerobic exercise interventions in postmenopausal women, both interventions resulted in improved arterial stiffness. Nevertheless, two studies in patients with stage I isolated systolic hypertension (mean age: 64 ± 7 years and 62 ± 9 years, respectively) failed to show an improvement of aortic PWV after moderate-intensity aerobic interventions. Similarly, higher cardiorespiratory fitness was not associated with lower aortic PWV in hypertensive patients, aged 58 ± 14 years. It is possible that the longstanding deleterious effects of high BP on the arterial wall cannot be counterbalanced by the effects of exercise in middle-aged hypertensive patients.

Regarding resistance exercise, its effects on arterial stiffness remain controversial. Furthermore, it is of interest that marathon runners and aerobically trained adults have shown increased aortic stiffness, as reported by two recent studies. In addition, swimmers and runners have improved central BP and arterial stiffness than sedentary controls, whereas runners also have improved endothelial

<table>
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<td>Cornelissen et al.</td>
<td>45</td>
<td>Systemic vascular resistance</td>
<td>N/EH</td>
<td>EH/Dyslipid</td>
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<td>Madden et al.</td>
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Abbreviations: BP, blood pressure; DM, diabetes mellitus; Dyslip, dyslipidemia; EH, essential hypertension; ISH, isolated systolic hypertension; ET-1, endothelin-1; FBF, forearm blood flow; I SH, isolated systolic hypertension.
function (flow-mediated dilation, FMD) than swimmers and sedentary control. Endothelial dysfunction. Endothelial dysfunction represents a common characteristic of cardiovascular diseases, such as essential hypertension, which precedes the atherosclerotic alterations in the vascular bed. FMD is considered the gold standard non-invasive imaging method to estimate endothelial function. An alternative method, widely used in earlier studies, is the invasive method of forearm blood flow (FBF). Moreover, biochemical markers of endothelial dysfunction include asymmetric dimethylarginine (ADMA) and endothelial progenitor cells (EPCs).

A large amount of evidence has pointed towards the beneficial role of chronic exercise on endothelial function both in healthy individuals and in patients with increased cardiovascular disease. Regarding essential hypertension, animal studies in spontaneous hypertensive rats have shown that exercise training restores the EPCs number and function. Further human studies demonstrated that a 3-month aerobic exercise intervention augments FBF in both normoten- tresses and hypertensives. Aerobic exercise training was also associated with improved FMD in postmenopausal women with elevated BP. Postmenopausal women have also exhibited decreased ADMA levels after aerobic exercise training. Referring to resistance exercise, existing data remain controversial even when healthy individuals are studied.

Cardiac effects

Left-ventricular hypertrophy represents significant target-organ damage in hypertensive patients. LV mass and function are influenced by physical activity. In animal studies, chronic exercise improves the electrophysiological parameters of cardiac myocytes in spontaneous hypertensive rats. Myocardial adaptation to regular exercise has been recently shown to be more prominent in young (<35 years) rather than senior (>50 years) adults. Even in healthy sedentary older subjects (>65 years), 1-year endurance training induced physiological LV remodeling, although it had little effect on cardiac compliance. Regarding patients with chronic heart failure, randomized trials have proven a reverse LV remodeling following long-term exercise training. Except for LV remodeling, high levels of physical activity have been also independently associated with higher right ventricular (RV) mass and volumes, both in elite athletes and in individuals without overt cardiovascular disease (mean age 61.8 years).

Molecular effects

Although molecular mechanisms by which exercise exerts its beneficial effects on the cardiovascular system are not fully understood, they primarily involve:

![Table 2. Studies assessing the effects of acute exercise on several pathophysiological mechanisms in patients with essential hypertension](image-url)
1. Reduction of oxidative stress, namely by enhancement of superoxide dismutase (SOD) enzymes activity, and HSP70 and HSP27 expression. 

2. Alterations in vasoactive compounds. Most importantly these include increased endothelial nitric-oxide synthase (NOS3) expression and NO-mediated signaling. 

3. Anti-inflammatory effects in terms of increased levels of Interleukin-6, Interleukin-1ra, and Interleukin-10 and decreased levels of tumor-necrosis factor-alpha have been reported.

4. Antiapoptotic effects, such as decreased mitochondrial apoptotic signaling and endothelial cell apoptotic capacity.

**ACUTE EXERCISE AND ACUTE CARDIAC EVENTS**

Despite the beneficial effects of regular physical activity on the cardiovascular system, acute physical activity has been implicated in triggering of acute cardiovascular events. Early studies have indicated an association of physical exercise with the incidence of myocardial infarction (MI), especially in sedentary adults. Later studies have confirmed the association of acute and dynamic exercise with MI and sudden cardiac death (SCD) both in men and women. Similarly, sexual activity has also been associated with MI and sudden cardiac death (SCD) in normotensive postmenopausal women.

In accordance with the aforementioned results, a meta-analysis of 14 studies showed a significant association of episodic physical and sexual activity with acute cardiac events (MI, SCD, and acute coronary syndrome). This association was observed even in individuals with high levels of regular physical activity. However, it should be also noted that the absolute risk increase was relatively small. In particular, according to Dahabreh et al., the absolute risk increase after an hour of additional physical or sexual activity per week was 2-3 per 10,000 person-years for MI and 1 per 10,000 person-years for SCD. By contrast the relative risk for MI and SCD reduced by 45% and 30%, respectively, for each additional exercise session per week.

**PATHOPHYSIOLOGICAL BACKGROUND OF ACUTE EXERCISE EFFECTS**

Acute cardiac events are characterized by a circadian occurrence with a morning excess. According to a meta-analysis of epidemiological studies, 1 of every 11 MIs and 1 of every 15 SCDS can be attributed to this morning peak.

Possible pathophysiological mechanisms implicated in this phenomenon are the following (Table 2):

**SNS activation**

SNS plays a central role in short- and long-term regulation of BP levels. In particular, the 24-hour pattern of plasma NA and adrenaline levels is strongly associated with the circadian variation of BP levels. Furthermore, exaggerated morning BP surge has been linked with vascular damage and atherosclerotic plaque instability. Thus, it has been suggested that the morning BP surge together with the increased catecholamine levels contribute to atherosclerotic plaque rupture, possibly triggering acute cardiac events. Similarly, acute and dynamic exercise stimulates SNS activation and causes an acute increase of BP and catecholamine levels, possibly leading to myocardial ischemia.

**Effects on the vasculature**

**Arterial stiffness.** Arterial stiffness is nowadays considered established subclinical target-organ damage in hypertensive patients; however, data regarding acute exercise effects on arterial stiffness are limited. Interestingly, studies in healthy individuals have shown controversial results that point towards the lack of a significant effect of acute exercise on arterial stiffness indices in young healthy individuals. Similarly, an older study in a small group of previously treated hypertensives has reported no impact of maximal acute exercise on arterial distensibility and β stiffness index. Nevertheless, a more recent study has documented an exaggerated and prolonged PWV increase after acute high-intensity exercise in untreated patients with essential hypertension, as compared with age- and sex-matched normotensive individuals. PWV values were significantly reduced after a 3-month treatment with an angiotensin-receptor blocker (ARB) and this reduction persisted after acute high-intensity exercise.

**Endothelial dysfunction.** Changes of endothelial function after acute exercise remain under investigation and seem to be largely dependent on exercise intensity. More specifically, moderate-intensity exercise improved endothelium-dependent vasodilation in young healthy men, in contrast to the effects of high-intensity exercise. FMD improvement after moderate intensity exercise has been also documented in normotensive postmenopausal women. In a similar manner, FMD showed a trend for improvement at moderate intensity exercise, but was significantly impaired at high intensity exercise in patients with stable coronary artery disease. Interestingly however, healthy smoking men exhibited impaired FMD and decreased femoral vasodilation after moderate intensity exercise, as compared to non-smokers. In addition, it should be noted that there is no study focusing on hypertensive patients in this field.

**Changes in coagulation and fibrinolysis**

Another pathophysiological link between dynamic exercise and acute cardiac events are changes in coagulation and fibrinolysis. Earlier studies have reported a circadian variation of human blood viscosity and fibrinolytic activity, with excessive blood viscosity and low fibrinolytic activity in the
early morning hours. Although further studies were conducted to explore the activity of coagulation and fibrinolysis during exercise, data in patients with essential hypertension are scant. In general, the hypercoagulant response to acute exercise is evident in all studies; whereas the fibrinolytic response is less clear and largely dependent on the type and degree of exercise.141–144

In particular, submaximal exercise resulted in a 28% increase of plasmin–a2 antiplasmin complex (PAP), a marker of fibrinolysis activation, and 11% increase of thrombin–antithrombin III complex (TAT), a marker of coagulation activation in patients with essential hypertension. One hour postexercise, TAT levels decreased back to baseline levels, whereas PAP levels showed a 43% increase compared to baseline.142 Recently, we have shown that acute high-intensity exercise induces an increased thrombotic and impaired fibrinolytic in untreated hypertensive patients, which were ameliorated post a 3-month treatment period with an ARB.143 However, long-term treatment with an angiotensin-converting enzyme (ACE) inhibitor resulted in an attenuated activation of coagulation and fibrinolysis following sub-maximal acute exercise.144 Therefore, further studies are essential in order to clarify whether coagulation exceeds fibrinolysis or vice versa, after acute exercise in untreated and treated hypertensive individuals.

Platelet activation

In accordance with the circadian rhythm of acute cardiac events, platelet aggregation rises in the morning shortly after awakening.145 Moreover, a large amount of studies in healthy individuals and in patients with cardiovascular disease indicate that acute and dynamic exercise induces platelet activation, as shown by increased mean platelet volume (MPV),148 β-thromboglobulin and thromboxane B2 levels,149,150 platelet aggregation,151,152 expression of platelet P-selectin,153,154 platelet–leukocyte,155,156 and platelet–platelet aggregates157 levels. The most robust marker of platelet activation, monocyte–platelet aggregates (MPA),158,159 has been recently studied by our group following a treadmill test.160 Never treated patients with essential hypertension exhibited an exaggerated and prolonged increase of platelet activation as compared to normotensive individuals.

From the therapeutic point of view, exercise-induced platelet activation was found significantly decreased following a 3-month treatment with an ARB in the same study.160 Similarly, Galea et al. have found no change in soluble P-selectin levels post peak exercise in hypertensive patients after one year treatment with an ACE inhibitor.146 Previous studies have reported that exercise-induced platelet activation could be abolished neither by aspirin161 and clopidogrel162 nor by argatroban and enoxaparin (thrombin inhibitors).155

Underlying pathophysiology of RAS inhibitors’ favorable effects on exercise-induced platelet activation may involve not only BP reduction but also NA release reduction. Our group has shown that catecholamines are significantly increased at exercise peak.126 Post-treatment changes of plasma catecholamine levels during exercise followed the same pattern, but were significantly decreased compared to pretreatment values.126 Taking into consideration that NA at a concentration similar to that of exercise peak has been shown to in vitro and in vivo enhance platelet activation,163,164 it can be concluded that increased levels of catecholamines contribute, at least partly, to platelet activation after exercise. Interestingly though, a most recent study in a small heterogeneous group of previously treated hypertensives failed to show a significant reduction of exercise-induced platelet activity (measured only by platelet P-selectin and platelet–platelet aggregates levels) following a 2-month treatment with RAS inhibitors.157

CONCLUSIONS AND FUTURE PERSPECTIVES

In conclusion, aerobic exercise exerts its beneficial effects on the cardiovascular system by promoting traditional cardiovascular risk factors’ regulation, as well as by favorably regulating SNS activity, inflammatory response, cardiac, and vascular function. Benefits of resistance exercise need further validation. On the other hand, episodic physical activity is considered an increased relative risk of acute cardiac events, although absolute risk is much lower especially in individuals with high fitness status. A number of possible pathophysiological links have been proposed, including SNS, vascular function, coagulation, fibrinolysis, and platelet function.

In order to fully interpret this knowledge into clinical practice, we need to better understand the role of exercise intensity and duration on triggering or inhibiting this harmful pathophysiological cascade. Furthermore, of great importance is to elucidate optimal exercise training type, duration, and intensity in special populations, such as patients with essential hypertension. Risks and benefits should be carefully assessed in specific subgroups, such as untreated or uncontrolled hypertension. Further studies in hypertensive patients are warranted in order to clarify the possibly favorable effect of antihypertensive treatment on exercise-induced effects.

DISCLOSURE

The authors declared no conflict of interest.

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