Review

Hypertension and physical exercise: The role of oxidative stress

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ARTICLE INFO

Article history:
Received 29 November 2015
Received in revised form
15 January 2016
Accepted 17 January 2016
Available online 29 January 2016

Keywords:
Oxidative stress
Hypertension
Exercise
Redox state
Nitric oxide

ABSTRACT

Oxidative stress is associated with the pathogenesis of hypertension. Decreased bioavailability of nitric oxide (NO) is one of the mechanisms involved in the pathogenesis. It has been suggested that physical exercise could be a potential non-pharmacological strategy in treatment of hypertension because of its beneficial effects on oxidative stress and endothelial function. The aim of this review is to investigate the effect of oxidative stress in relation to hypertension and physical exercise, including the role of NO in the pathogenesis of hypertension. Endothelial dysfunction and decreased NO levels have been found to have the adverse effects in the correlation between oxidative stress and hypertension. Most of the previous studies found that aerobic exercise significantly decreased blood pressure and oxidative stress in hypertensive subjects, but the intense aerobic exercise can also injure endothelial cells. Isometric exercise decreases normally only systolic blood pressure. An alternative exercise, Tai chi significantly decreases blood pressure and oxidative stress in normotensive elderly, but the effect in hypertensive subjects has not yet been studied. Physical exercise and especially aerobic training can be suggested as an effective intervention in the prevention and treatment of hypertension and cardiovascular disease via reduction in oxidative stress.

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1. Introduction

Hypertension is a major risk factor in the development of cardiovascular diseases, including stroke and coronary artery disease. Hypertension is defined as a chronic elevation of systolic blood pressure greater than 140 mm Hg and/or diastolic blood pressure greater than 90 mm Hg, and is classified as either essential (primary) or secondary hypertension [1]. Approximately 95% of all cases are categorized as essential
hypertension which is characterized by a lack of identifiable trigger for blood pressure raise. The remaining 5% of the cases are categorized as secondary hypertension which is caused by various medical conditions, e.g. kidney disease and tumors [2]. It is predicted that the prevalence of hypertension will increase by more than 50% during the next 30 years resulting in an enormous disease burden for society [3]. In line with this ongoing development, the effective treatment of hypertension is becoming increasingly urgent. It is no longer sufficient to depend on pharmacological therapies, when a modest change in lifestyle can be demonstrated to have a beneficial effect.

Previous studies suggested that redox imbalance might be associated with pathogenesis of hypertension although it may not be the only cause of blood pressure elevation [4–7]. This occurs due to imbalance between elevated reactive oxygen species (ROS) (e.g. superoxide, hydrogen peroxide and hydroxyl radical) production and/or reduced antioxidant capacity at the systemic level as well as the localized changes in the circulatory regions [8]. ROS are known to play both physiological and pathophysiological roles in the body [5]. At the appropriate concentrations and sub-cellular localization ROS participate in cellular signaling and phenotype regulation. Moreover, ROS are known to modulate numerous pathways important for control of systemic vascular resistance and blood pressure, including decreased bioavailability of nitric oxide (NO), inflammation, imbalance in salt and water homeostasis, hyperactivity of the sympathetic nervous system (SNS) and disturbances of the renin–angiotensin–aldosterone-system (RAAS) [6,9]. Interestingly, physical exercise has been suggested to be beneficial in hypertension by improving the redox state, particularly, in the vascular wall [10,11]. Physical exercise may therefore be of potential importance for prevention or treatment of hypertension or hypertension-associated pathologies besides conventional pharmacological treatment.

This focused review provides an overview for the role of redox imbalance in hypertension and its therapeutic modulation by physical exercise. The focus is especially made on the ROS-dependent reduction of NO bioavailability in hypertensive subjects and the effects of exercise on this endothelium-dependent pathway.

2. Redox state and NO bioavailability

Redox imbalance has been measured in hypertensive subjects as an elevated level of oxidative stress [12–16]. In this context redox imbalance can be seen as outbalanced production/accumulation of ROS [5]. Along with other pathways, ROS decrease the bioavailability of NO [1]. Hypertension is known to be associated with endothelial dysfunction [17,18] and it might, therefore, be suggested that impairment in hypertension endothelium-dependent vasodilation is the result of oxidative stress [6]. Alternatively, this redox imbalance can be the result of a reduction in antioxidant potential of NO, which occurs secondary to the reduced production of NO. In any of these scenarios, oxidative stress seems to play an important role in hypertension [7,8,19].

Decreased bioavailability of NO is now thought to be one of the critical factors that are common to hypertension [7]. It can involve a number of different mechanisms including a reduction in endothelial NO synthase (eNOS), an uncoupling of eNOS enzymatic activity, scavenging of NO by ROS as well as the oxidation of the NO targets [20]. The calcium-calmodulin controlled eNOS activates by mechanical and chemical stimuli leading to an increase in endothelial cell calcium, e.g. shear stress, acetylcholine, endothelin, bradykinin and other, are known to stimulate NO production. NO then diffuses from endothelial cells into vascular smooth muscle cells where it leads to relaxation and vasodilatation [7]. Through this mechanism NO is able to decrease total peripheral resistance and lower blood pressure.

ROS, the chemically reactive molecules containing oxygen can be generated in different ways. The nicotinamide adenine dinucleotide phosphate oxidases (Nox) are the primary source of ROS in the vascular wall and have been identified to play a key role in the pathogenesis of hypertension [21]. Importantly, Nox-dependent ROS production can be triggered by numerous pro-contractile neurohumoral factors, e.g. angiotensin II, endothelin-1 and norepinephrine [5]. Xanthine oxidase (XO) is another source for ROS in the vascular wall [22]. Furthermore, functional uncoupling of eNOS resulting in the generation of ROS rather than protective NO [23] also occurs and this pathway has been suggested to be important for hypertension [24]. Finally, damage to the mitochondrial respiratory chain leads to dysfunction of the mitochondrial respiration increasing the mitochondrial ROS formation [25].

Oxygen prematurely and incompletely reduced to superoxide radical (O$_2^\cdot$) is not particularly reactive by itself, but can inactivate enzymes by acting primarily on the cysteine containing proteins or can initiate lipid peroxidation into hydroperoxyl (HO$_2^\cdot$), which under normal physiological pH exists in highly aggressive hydroxyl radical. Normally, the level of superoxide is kept low because it is detoxified by the enzyme superoxide dismutase (SOD) into H$_2$O$_2$ and eventually into water. A number of antioxidants including catalase, peroxides, glutathione and thioredoxin protect cells from the inappropriate elevation of ROS [26].

ROS may exert dual effects on signaling in vascular smooth muscle cells. It may be detrimental as well as acting as endogenous signaling molecules. The interaction between NO/cGMP and inositol trisphosphate (IP$_3$) pathways has been suggested in this regard [27]. Thus, IP$_3$-induced intracellular calcium release from sarcoplasmatic reticulum has been shown to be facilitated by superoxide [28] and this might be mediated via the decreased cross-inhibition of IP$_3$ pathway by cGMP in vascular smooth muscle cells [27]. Under normal physiological conditions this might be used for well-tuned regulation of vascular resistance. However, if the level of superoxide is increased, the interaction with NO/cGMP dependent pathway will be imbalanced and this can be detected through the decreased NO bioavailability leading to pathological vasoconstriction. The consequent reduction of tissue perfusion will result in a further increasing ROS production and thereby coupling the process into a malignant cycle of the disease [29].

3. Redox imbalance in hypertension

The importance of redox imbalance in the development of hypertension is clearly demonstrated in experimental animal
Table 1 – Reviewed studies addressing the role of oxidative stress in exercise-induced changes of blood pressure. Studies focused on association between blood pressure control and redox state. The association was analyzed under control conditions and as a response to different forms of exercise in humans and animal studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design, study population</th>
<th>Aim</th>
<th>Measured parameters</th>
<th>Results</th>
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<td>[6]</td>
<td>Case–control; controls vs. hypertensive patients</td>
<td>Vascular sources of oxidative stress, including COX-1, COX-2, and Nox</td>
<td>Superoxide – fluorescent detection with dihydroethidium; Western blot – COX-1 and COX-2 expression in small arteries</td>
<td>In hypertensive patients: • vascular oxidative stress enhanced; • COX-2 and Nox upregulation in the vascular media • endothelial dysfunction through the reduction of NO availability</td>
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<td>[37]</td>
<td>Double-blind randomized; controls vs. essential hypertensive patients</td>
<td>Could the calcium antagonist (lacidipine) increase antioxidant activity and restore NO bioavailability?</td>
<td>Forearm blood flow; ROS – measured by 2,7-dichloro-fluorescin-diaceate oxidation; NO – vasoconstriction to L-NMMA</td>
<td>Lacidipine: • restores NO bioavailability; • increases endothelium-dependent vasodilation; • decreased markers of oxidative stress</td>
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<td><strong>Aerobic exercise</strong></td>
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<td>[38]</td>
<td>Normotensive vs. mild hypertension patients</td>
<td>Effect of 12 weeks aerobic exercise on endothelial function</td>
<td>Forearm blood flow response to acetylcholine</td>
<td>Long-term exercise improves vasorelaxation through an increase in NO release in normotensive as well as hypertensive patients</td>
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<td>[39]</td>
<td>Case–control; aerobic training (&lt;12 months) vs. sedentary controls</td>
<td>Does the moderate-intensity exercise reduce oxidative stress in type 2 diabetes</td>
<td>Urinary 8-OHdG measurements</td>
<td>Aerobic exercise improved glycemic control and reduced oxidative stress in patients with diabetes</td>
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<td>[40]</td>
<td>Walking exercise (12 weeks of 40–50 min three times/week) of patients with metabolic syndrome</td>
<td>Short-term effects of moderate intensity exercise</td>
<td>Blood pressure and heart rate; O₂ consumption; Inflammatory and metabolic parameters</td>
<td>Systolic and diastolic blood pressures reduced by exercise</td>
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<td>[41]</td>
<td>6 months of aerobic exercise training; pre-hypertensive and hypertensive subjects</td>
<td>To determine whether the p22phox subunit polymorphisms is associated with the oxidative stress</td>
<td>TAC in blood plasma; NOx in urine; 8-iso-GF2α in urine</td>
<td>Aerobic exercise increases antioxidant levels but decrease in NO and increase in oxidative stress</td>
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<td><strong>Isometric exercise</strong></td>
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<td>[42]</td>
<td>Cohort study; bilateral/unilateral IHG training (four 2 min 3 times/week for 8 weeks)</td>
<td>Effect of IHG training on endothelial function and blood pressure</td>
<td>Forearm blood flow/FMD – measured in both arms</td>
<td>IHG training improved FMD only in trained arm; Systolic blood pressure significantly reduced after both bi- and unilateral IHG training; Diastolic blood pressure remained unchanged</td>
</tr>
<tr>
<td>[43]</td>
<td>Controlled prospective cohort study; hypertensive individuals (training 3 times/week for 6 weeks)</td>
<td>Effect of short-term isometric exercise training in hypertensive individuals</td>
<td>Blood pressure measurements; ROS measured by electron spin resonance spectroscopy in plasma</td>
<td>Short-term exercise lowers systolic but not diastolic blood pressure in hypertensive individuals; Decrease in the exercise-induced oxygen centered radicals</td>
</tr>
<tr>
<td><strong>Alternative exercise</strong></td>
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<tr>
<td>[44]</td>
<td>Case–control; non-hypertensive elderly (12 months Tai chi vs. control)</td>
<td>Effect of alternative (Tai chi) exercise in elderly</td>
<td>Antioxidant activity in blood samples: GPx, SOD, CAT, MDA; Nutrient intake: FFQ</td>
<td>Tai Chi exercise stimulates endogenous antioxidant enzymes and reduced oxidative stress markers. Systolic blood pressure lowered in Tai Chi subjects</td>
</tr>
</tbody>
</table>
models [30,31]. However, the results from clinical studies are less clear since many antioxidant trials have failed to show beneficial effects [32]. Nevertheless, it is appreciated that, in patients with essential hypertension, blood pressure positively correlates with biomarkers of oxidative stress and negatively correlates with the level of antioxidants [33–36]. A number of epidemiological studies clearly indicate the relationship between hypertension, oxidative stress and exercise (Table 1). Oxidative stress has been measured experimentally in several ways. It was indirectly evaluated noninvasively as an endothelial function using brachial artery flow-mediated vasodilation [46]. Moreover, many biomarkers listed in Table 2 have been used to determine oxidative stress in various cell types, tissues, urine, blood, etc. [1].

Redox imbalance evaluated as an elevated level of oxidative stress has been measured in both humans and experimental animals. Importantly, experimental animal studies clearly demonstrate a well-documented association between high blood pressure and oxidative stress [1,21,47]. Accordingly, prohypertensive treatment of normotensive rats with angiotensin II is known to stimulate the production of ROS by Nox and raise blood pressure [48]. A pharmacological improvement of mitochondrial respiratory chain dysfunctions has been shown to produce an antihypertensive effect in hypertensive rats [49]. Metabolic syndrome in hypertensive rats [50] is suggested to be one of the reasons for the association between elevated blood pressure and redox imbalance, ROS-mediated inactivation of NO and decreased NO availability. Moreover, blood pressure,
redox state and NO availability have been shown to improve 2 months after switching animals from prodiabetic to normal diet [50]. Several contributory factors can influence oxidative stress in hypertensive subjects. For example, a study of immobilizing stress in rats demonstrated that psychical stress can also lead to redox imbalance [51]. Redox imbalance was also shown in association with chronic mild stress in rats [52]. It has been found that arterial eNOS and NO decreased by psychical stress leading to reduced acetylcholine-induced relaxation [52,53], and that this was associated with an increase in plasma malondialdehyde (MDA) suggesting elevated oxidative stress (Table 2).

Experimental results from animal studies have received substantial support from the clinical studies in hypertensive patients where redox state was evaluated [6,37]. An association between oxidative stress and essential hypertension in humans was identified [5]. The importance of redox imbalance in hypertension has also been demonstrated in many population-based studies where reduced level of antioxidant protection was correlated to high blood pressure [14,54,55]. Direct measurements in vascular smooth muscle cells derived from resistance arteries of hypertensive patients demonstrated the elevated level of ROS at rest and after angiotensin II stimulation in comparison with normotensive controls [56]. In the study by Taddei and coauthors, it is assumed that essential hypertension is associated with impaired endothelium-dependent vasodilation caused by ROS-induced NO breakdown. It was suggested that, since calcium antagonists can improve endothelial function, the potential beneficial effect can relate to restoration of NO availability caused by antioxidant activity [37]. Accordingly, they have found that the calcium channel blocker lacidipine increases endothelium-dependent vasodilation by restoring NO availability possibly via antioxidant activity (Table 1). Thus, the reduction of ROS by lacidipine was suggested to have a beneficial mechanism mainly because it might prevent the formation of the peroxynitrite anion (ONOO−) (Figure). In the follow up study resistance arteries from patient biopsies were studied in vitro for endothelium-dependent (acetylcholine-induced) and endothelium-independent (sodium nitroprusside induced) relaxations after the preconstriction with noradrenaline [6]. It was found that resistance arteries of hypertensive subjects showed a significant impairment of the endothelium-dependent relaxation compared with normotensive subjects due to overexpression of cyclooxygenase-2 (COX-2) and Nox. Since both these enzymes are sources for generating ROS (Figure), an elevation of oxidative stress was suggested to be responsible for the reduced availability of NO [6].

4. Redox state and physical exercise

The hypothesis about the importance of redox imbalance for hypertension pathology suggests that oxidative stress may be a possible target and focus for therapeutic intervention in the treatment of hypertension. A number of different therapeutic strategies including physical exercise have been suggested [4,5]. The beneficial effects of exercise in hypertensive subjects are thought to be mediated by an improvement of the redox state [57]. Since hypertension is known to be associated with endothelial dysfunction – an early feature of vascular diseases in humans – lifestyle modifications, including exercise, are expected to prevent cardiovascular complications and appear to be an effective nonpharmacological therapy for prevention and control of hypertension [11].

It has been shown that exercise improves endothelial function in animal experimental models of hypertension and in patients with essential hypertension (Table 3). In normotensive humans exercise is also shown to have a beneficial effect on cardiovascular control and particularly for endothelial function [38]. Although the mechanisms underlying the antihypertensive effects of exercise have not yet been fully clarified, it has been suggested that the improvement of endothelium-dependent relaxation, endothelial adaptation, is mainly mediated by a significant increase in vascular NO production and/or decrease in NO scavenging by ROS [57,58]. This endothelial adaptation has been suggested to be, at least in part, a product of exercise-induced changes in shear stress [59]. Thus, this increase in NO bioavailability, mainly through the reduction of oxidative stress, is an important contributor to the improvement of endothelial function observed as a result of exercise. Moreover, exercise has also been demonstrated to normalize the levels and/or expression of proinflammatory cytokines that decrease NO bioavailability by stimulation of ROS production [57].

Importantly, endothelial adaptations are also reported for vascular beds of skeletal muscles and other organs which are not active or less active during exercise [60,61]. These endothelial adaptations beyond the active muscular beds suggest that other than shear stress factors are involved in linking physical activity and endothelial function. These might include the whole body shear stress profile changes and humoral factors, e.g. insulin [for review see: 59]. Moreover, active muscles suggested releasing several cytokines and other peptides, termed myokines, and exerting anti-inflammatory action [62] which in turn increases NO bioavailability via decrease of ROS production [57]. In general, the phenomenon of endothelial adaptation supports the systemic effect of exercise on redox state of the whole body suggesting it...
Aerobic exercise has shown to be effective in significantly reducing ROS levels and in a decrease of the occurrence of ROS in cells, including endothelial cells [6]. It has been demonstrated that aerobic exercise enhances the adaptive response to oxidative stress and improves endothelial function [6].

According to the study [6], aerobic exercise enhances the adaptive response to oxidative stress and improves endothelial function. This is in line with findings that the urinary marker of oxidative stress, 8-OHdG, decreased in patients of forearm ischemia reperfusion injury. Similarly, an exercise intervention significantly improves the endothelial function in patients with metabolic syndrome [6].

Table 3 - Exercise interventions and the effect on vascular state.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Analyzed Tissue</th>
<th>Benefit</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humans</td>
<td>Brachial artery</td>
<td>Increased antioxidant activity</td>
<td>[41]</td>
</tr>
<tr>
<td>Rats</td>
<td>Aorta</td>
<td>Decreased NO levels</td>
<td>[42]</td>
</tr>
<tr>
<td>Humans</td>
<td>Brachial artery</td>
<td>Increased eNOS expression</td>
<td>[43]</td>
</tr>
<tr>
<td>Humans</td>
<td>Forearm</td>
<td>Increased NO levels</td>
<td>[44]</td>
</tr>
<tr>
<td>Humans</td>
<td>Brachial artery/plasma</td>
<td>Decreased oxidative stress</td>
<td>[45]</td>
</tr>
</tbody>
</table>

These results and their implications suggest that regular aerobic exercise is beneficial for maintenance of the resistance and mechanical functions of coronary arteries, and resistance arteries in hypertensive patients [6]. This benefit appears to be mainly due to the elevated NO bioavailability, increased expression of eNOS, and the reduced levels of superoxide dismutase, which can be attributed to the exercise-induced reduction in ROS levels [6].

The effect of exercise on the maintenance of the resistance and mechanical functions of coronary arteries, and resistance arteries in hypertensive patients [6]. This benefit appears to be mainly due to the elevated NO bioavailability, increased expression of eNOS, and the reduced levels of superoxide dismutase, which can be attributed to the exercise-induced reduction in ROS levels [6].
6. Isometric exercise

An isometric or static contraction is a form of resistance exercise which is defined as a sustained muscle contraction (i.e., increase in tension) with no change in length of the involved muscle group. Resistance exercise has not been evaluated to the same extent as aerobic exercise in relation to redox imbalance. Two studies examining the effect of isometric exercise in hypertension are of interest in this regard [42,43]. The first demonstrated that isometric handgrip training (IHG) improves endothelial-dependent vasodilation [42]. Of interest, the improvement only occurred locally in the trained limbs. The second study examined the effect of isometric exercise in hypertensive patients and showed that systolic but not diastolic blood pressure was significantly lowered by training [43] (Table 3). Importantly, the markers of oxidative stress were affected by isometric exercise and a major decrease in exercise-induced oxygen radicals was reported [43].

7. Alternative training

Tai chi is a gentle exercise program that is a part of traditional Chinese medicine. Derived from the martial arts, Tai chi is composed of slow, deliberate movements, meditation, and deep breathing, which should enhance physical health and emotional wellbeing. Accordingly, Tai chi exercise was found associated with similar physiological and biochemical improvements seen with other forms of physical training [44]. Tai chi exercise was found to decrease systolic blood pressure but it had no effect on diastolic blood pressure in middle-aged adults. Similar to the results associated with other forms of physical training [43], an enhanced level of antioxidant protection has been suggested as the mechanism underlying the decrease in ROS which, in turn, lowers blood pressure [44]. This was suggested to be a result of a mild training-associated induction of oxidative stress leading to stimulation of antioxidant defenses.

Importantly, this latter study did not include hypertensive patients [44] and, therefore, may not necessarily be the representative exercise intervention for hypertensive patients. Moreover, the individuals that performed Tai chi were not sedentary and a sedentary lifestyle is known to be a risk factor of hypertension [66]. Furthermore, the lowered blood pressure in the Tai chi training group was only compared to blood pressure in this group before the training program started, and not to the sedentary group. Tai chi is focusing on mind and body which could also be a reason for the beneficial effects of this training linked to the well-known association between stress and hypertension [51,66,68].

8. Conflicting results

Although most of the studies reviewed here (Table 1) found that moderate aerobic exercise and isometric training had beneficial effects, conflicting results have also been shown. The study by Sun and coauthors [45] have demonstrated the beneficial effects of acute and chronic aerobic training. However, the effect of high-volume intense training in this study resulted in mild hypertension with significant impairment in the endothelium-dependent vasodilation. Another study of aerobic exercise with participants in a relatively large population (94 participants) found an increase in oxidative stress marker (8-iso-PGF2α) 6 months after aerobic exercise [41]. This was also associated with a decrease in urinary NO metabolites though antioxidant levels was increased. This result conflicts with the results showing the beneficial effects of aerobic exercise [39].

It has also been shown that IHG training only lowered blood pressure in the trained limb [42] suggesting that the enhanced systemic endothelial-dependent vasodilation is not the mechanism responsible for post-IHG training reduction of blood pressure in hypertensive patients. It should be noted that isometric exercise training involves markedly smaller time commitment (8–10 min/session) compared with the aerobic exercise programs (≥30 min/session). In the study by Higashi and coauthors [38] blood pressure was reduced after aerobic exercise but there was no significant correlation between this exercise-induced reduction in blood pressure and the increase in acetylcholine-induced forearm response to after exercise. This suggests that other than endothelium-dependent mechanisms might be involved including cardiac and neuronal functions. Moreover, the aerobic exercise augmented endothelium-dependent vasodilation but did not alter blood pressure in normotensive subjects. This suggests that the reduction in blood pressure may not be directly associated with the improved response of forearm vasculature to acetylcholine and the increase in NO release [38].

The range of different and sometimes conflicting results could be due to variations in intensity, duration, and the type of exercise. The available data on redox imbalance in humans are still limited with only one marker of oxidative stress often being measured. This is, at least in part, because redox imbalance is primarily confined to the kidney, the heart and the brain, and is therefore difficult to access in living humans [69]. For this reason, most of the clinical results are obtained from urine and blood samples. As such, they are not necessarily reflective of a complete redox state in the body.

In addition, most of the clinical studies are based on small populations and this affects integrity of the results, while some of the samples are not representative since they deal with populations that are restricted territorially, e.g. the study of Japanese people from a particular area [38]. Altogether, this may compromise the validity of clinical experimental results. Animal studies overcome these obstacles, but the clarity of their results cannot always be easy applied to humans. It is therefore clear, that further studies are needed to determine the exact mechanisms involved in the effects of exercise in humans.

9. Concluding remarks

The available experimental results indicate that physical exercise has a beneficial effect on redox state and hypertension. However, it is clinically important to select the appropriate intensity, duration, frequency and type of exercise. This is not simply because inappropriate exercise will be ineffective but also because it can be pathogenic, leading to
endothelial dysfunction and cardiac injury. This point is especially important for extreme sport athletes or elderly patients that are of greater vulnerability to mechanical injury. For elderly patients exercise should be carefully selected and it can be suggested, that Tai chi may be a suitable form of exercise and that it may provide the beneficial effect on blood pressure. Isometric training has shown some effectiveness and is as well time-efficient, but it needs further study. Finally, aerobic exercise of moderate intensity has been shown to have the best results in reducing blood pressure.

Conflict of interest

The authors have no any conflict of interest.

References

