Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/medici

Review

Hypertension and physical exercise: The role of oxidative stress

Monica Korsager Larsen, Vladimir V. Matchkov *

Department of Biomedicine, Faculty of Health, Aarhus University, Aarhus, Denmark

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.

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

* *Corresponding author at*: Department of Biomedicine, Faculty of Health, Aarhus University, Ole Worms Alle bygn. 4, 1160, Aarhus C 8000, Denmark. Tel.: +45 87167723.
E-mail address: vvm@biomed.au.dk (V.V. Matchkov).

Peer review under the responsibility of the Lithuanian University of Health Sciences.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.medici.2016.01.005

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 ($O_2^{-\bullet}$) 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 ($HO_2^{\bullet}$), 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_2O_2 and eventually into water. A number of antioxidants including catalase, peroxidases, 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 sarcoplasmic 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