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Exercise Interventions and Peripheral Arterial Function: Implications for Cardio-Metabolic Disease

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ABSTRACT

Physical inactivity is a major risk factor for the development of obesity and other cardiovascular (CV) disease (CVD). Vascular endothelial dysfunction is a key event in the development of CVD and is associated with a sedentary lifestyle in otherwise healthy adults. In addition, vascular endothelial dysfunction may be exacerbated in sedentary individuals who are obese and insulin resistant, since excess body fat is associated with elevated levels of pro-atherogenic inflammatory adipokines and cytokines that reduce the nitric oxide (NO) and other upstream paracrine signaling substances which reduces vascular health. Since blood flow-related shear stress is a major stimulus to NO release from the endothelium, disturbed flow or low shear stress is the likely mechanism by which vascular endothelial function is altered with inactivity. Evidence shows that regular physical exercise has beneficial effects on CVD and the risk factors that promote peripheral arterial function and health. Both aerobic and resistance exercise training are generally believed to improve endothelial function and are commonly recommended for CV health, including the management of obesity, hypertension, and insulin resistance. However, many factors including age, disease status, and race appear to influence these outcomes. Although evidence supporting the health benefits of exercise is compelling, the optimum prescription (volume and intensity) and the exact mechanism underlying the effects of exercise training on arterial function and cardiometabolic risk has yet to be identified. The focus of this review will be on the evidence supporting exercise interventions for peripheral arterial function.

Introduction

Arterial health is compromised in cardiovascular (CV) disease (CVD) and in the presence of CVD associated risk factors. The process of atherosclerosis involves vascular wall inflammation, monocyte infiltration, smooth muscle cell proliferation, and endothelial dysfunction. It appears that endothelial dysfunction is the earliest precursor to the development of atherosclerosis and the target of potential therapies for the prevention and treatment of CVD. Among non-pharmacological therapies, exercise training (ET) has been shown to improve arterial function and in particular endothelium-dependent vasodilation in conduit arteries and in the microcirculation. The mechanism of this effect on

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Abbreviations and Acronyms

AA = African Americans

ACh = acetylcholine

ACE = angiotensin converting enzyme

BH_4 = tetrahydrobiopterin

BP = blood pressure

cGMP = cyclic guanosin monophosphate

CHD = coronary heart disease

CRP = C-reactive protein

CV = cardiovascular

CVD = cardiovascular disease

eNOS = endothelial nitric oxide synthase

ET = exercise training

ET1 = endothelin-1

FMD = flow-mediated dilation

HTN = hypertension

IGT = impaired gluucose tolerance

IL-6 = interleukin-6

L-NMMA = NG-monomethyl-L-arginine

NO = nitric oxide

PA = physical activity

PWV = pulse wave velocity

ROS = reactive oxygen species

sGC = soluble guanylate cyclase

SOD = superoxide dismutase

TGF-α = transforming growth factor

TNF-α = tumor necrosis factor alpha

T2DM = type 2 diabetes mellitus

endothelial function is complex and involves local and systemic factors.[1] Regardless of the specific mechanism for this benefit, physical ET leads to long-term adaptations in the vasculature that improve systemic arterial vascular function in health, in patients with hypertension (HTN), and in patients with coronary heart disease (CHD). While the common mechanism of improved endothelial function during many CVD states appears to be in improving the balance between anti-atherogenic (nitric oxide) and pro-atherogenic (reactive oxygen species) signaling pathways of vasodilation, in this review we explore some exceptions to this signaling paradigm specifically in the microcirculation where there appears to be greater diversity in vasodilator mechanisms.

A preponderance of evidence shows that the primary mechanism of endothelial dysfunction is a reduction in endothelium-derived nitric oxide (NO) bioavailability.[2] Although the exact mechanism by which this reduction occurs is still under debate, several key mechanisms have been identified that involved alterations in the NO signaling pathway. These include reduced bioavailability of the endothelial nitric oxide synthase (eNOS), reduced substrate L-arginine and/or tetrahydrobiopterin (BH_4); modified expression and functional activity of eNOS; extracellular scavenging of NO by reactive oxygen species (ROS); and increased production of endothelium-derived vasoconstrictors[3] (Fig 1).

The primary mechanism that contributes to reduced NO bioavailability in the peripheral circulation endothelium during CVD involves lower eNOS expression and/or increased quenching of NO by superoxide[4] (Fig 1). Evidence for the importance of this mechanism in patients stems from previous studies showing that the administration of antioxidants reduces superoxide levels and improves endothelium-dependent vasodilator function.[5] In the sections that follow, we will review the mechanisms that mediate endothelium-dependent vasodilation in humans and the current state of the evidence supporting the role of ET paradigms in restoring and/or preventing endothelial dysfunction in CVD and cardiometabolic disease.

Mechanisms mediating endothelium-dependent vasodilation in the peripheral circulation

Vascular endothelial function refers to a variety of physiologic processes related to maintenance of vascular wall homeostasis, namely the functional integrity of the endothelium. The production of NO by the vascular endothelium is particularly important in the regulation of blood flow. Endothelium-derived NO is formed from the guanidine–nitrogen terminal of L-arginine through the action of the enzyme endothelial nitric oxide synthase (eNOS) upon activation by receptor-dependent agonists (i.e. acetylcholine/ACh) or receptor-independent stimuli such as increased flow or shear stress[4] (Fig 1). In the context of blood flow-induced shear stress, elevated cytosolic calcium (Ca^{2+}) triggers activation of eNOS to catalyze the conversion of L-arginine to L-citrulline and NO, with tetrahydrobioterin (BH_4) and nicotinamide adenine dinucleotide phosphate (NADPH) as essential cofactors.[6,7] NO diffuses into adjacent smooth muscle cells to signal the soluble enzyme guanylate cyclase (sGC) to produce cyclic guanosine monophosphate (cGMP).[4] This signaling cascade ultimately causes smooth muscle cells to relax and results in vasodilation (Fig 1). Physiologic impairment of endothelium-dependent vasodilation can lead to deleterious alterations in blood flow during physiologic stress (i.e. exercise, hypoxia, hemorrhage) and contributes to elevations in blood pressure (BP) and CVD.

Reduced responsiveness to endothelium-dependent vasodilator stimuli is indicative of endothelial dysfunction and commonly results from an imbalance between vasodilator and vasoconstrictor substances produced by the endothelium. There is ample evidence demonstrating that the most prominent feature of endothelium dysfunction is a reduction in endothelium-derived NO bioavailability,[5,8] although the exact mechanism by which this reduction occurs may depend on disease phenotype, disease severity and CVD risk factors. Regardless, the likely mechanisms include: disturbances in the NO signaling pathway; reduced bioavailability of L-arginine and/or BH_4; modified expression and functional activity of eNOS; extracellular scavenging of NO by reactive oxygen species (ROS); and increased production of endothelium-derived vasoconstrictors.

The presence of endothelial dysfunction has been demonstrated in a variety of chronic diseases, including HTN, type 2 diabetes mellitus (T2DM), renal disease and obesity.[9–11] Its pathophysiology in these disease states is linked to both oxidative stress and an overexpression of pro-inflammatory mediators (i.e. tumor necrosis factor-alpha and interleukin-6).[12,13] Oxidative