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Benefits of Exercise Training on Coronary Blood Flow in Coronary Artery Disease Patients

*Rebecca S. Bruning, Michael Sturek**

Department of Cellular and Integrative Physiology, Indiana University School of Medicine, Indianapolis, IN 46202–5120

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ABSTRACT

Every 34 seconds an American experiences a myocardial infarction or cardiac death. Approximately 80% of these coronary artery disease (CAD)-related deaths are attributable to modifiable behaviors, such as a lack of physical exercise training (ET). Regular ET decreases CAD morbidity and mortality through systemic and cardiac-specific adaptations. ET increases myocardial oxygen demand acting as a stimulus to increase coronary blood flow and thus myocardial oxygen supply, which reduces myocardial infarction and angina. ET augments coronary blood flow through direct actions on the vasculature that improve endothelial and coronary smooth muscle function, enhancing coronary vasodilation. Additionally, ET promotes collateralization, thereby, increasing blood flow to ischemic myocardium and also treats macrovascular CAD by attenuating the progression of coronary atherosclerosis and restenosis, potentially through stabilization of atherosclerotic lesions. In summary, ET can be used as a relatively safe and inexpensive way to prevent and treat CAD.

The main purpose of this review in the series is to provide an overview of the effects of chronic exercise training (ET) on the adaptations of the coronary circulation, primarily in the setting of coronary artery disease (CAD), and potential cellular and molecular mechanisms for the adaptations.

Globally, more people die from cardiovascular (CV) diseases (CVD) than any other cause,[1] with approximately 40% of these deaths attributable to CAD.[2] One of the main pathological processes leading to CAD-related morbidity is atherosclerosis, whichis a lifelong process, which begins in childhood as fatty lesions and can later progress into flow-limiting stenosis of large epicardial coronary arteries, ultimately manifesting as angina and/or myocardial infarction (MI).[2,3] About 80% of CAD and cerebrovascular disease-related morbidities and mortalities are caused by modifiable behaviors such as physical inactivity, unhealthy diets, tobacco use, and alcohol abuse.[2] The large number of CAD-related morbidities and mortalities caused by modifiable behaviors suggests that the incidence of CAD can be significantly reduced through a number of interventions. In particular, increasing regular physical activity (PA) — which is widely accessible and relatively inexpensive — could significantly reduce the number of deaths related to CVD.

Current CAD therapies and recommended PA guidelines

The current goals of the guideline directed medical therapies for patients with CAD are 1) prevention of premature CVD death and complications from CAD, 2) maintaining or restoring a quality of life (QoL) that is acceptable for the

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* Address reprint requests to Michael Sturek, PhD, Department of Cellular and Integrative Physiology Indiana University School of Medicine, 635 Barnhill Dr., MS Indianapolis, IN 46202–5120.

E-mail address: msturek@iupui.edu (M. Sturek).

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Abbreviation and Acronyms

Ach = Acetylcholine

ADMA = Asymmetrical dimethylarginine

BH_4 = Tetrahydrobiopterin

CAD = Coronary artery disease

CBF = Coronary blood flow

CR = Cardiac rehabilitation

CRF = Cardiorespiratory fitness

CSM = Coronary smooth muscle cells

CV = Cardiovascular

CVD = Cardiovascular disease

EPCs = Endothelial progenitor cells

eNOS = Endothelial nitric oxide synthase

ET = Exercise training

HDL-C = High-density lipoprotein cholesterol

IVUS = Intravascular ultrasound

LDL-C = Low-density lipoprotein cholesterol

MI = Myocardial infarction

NO = Nitric oxide

NOS = Nitric oxide synthase

PCI = Percutaneous coronary intervention

PA = Physical activity

QoL = Quality of life

RF-IVUS = Radiofrequency intravascular ultrasound

ROS = Reactive oxygen species

patient by reducing angina and improving activities of daily living, and 3) minimizing adverse effects of treatments for CAD.[4] In the United States, the current pharmacological therapies for CAD mainly include β-blockers, inhibitors of the renin-angiotensin-aldosterone system lipid-lowering, antiplatelet agents, nitrates, and calcium channel blockers, which treat hypertension, hypercholesterolemia, and angina. ET has similar therapeutic effects, as will be discussed later in this review. Despite recent advances in these pharmacological agents, there still remains a large incidence of CAD in optimally treated patients, especially those with multiple comorbidities. In addition to pharmaco therapy, lifestyle modifications like increasing chronic PA, eating a healthy diet, maintaining a healthy weight, cessation of smoking, and stress management are part of the guideline directed medical therapy for patients with CAD. If the patient is at a high risk for a CAD event, revascularization procedures, such as percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery, are also highly effective.[5]

The current recommendation for PA in stable CAD patients is 30 to 60 minutes of moderate intensity aerobic PA at least 5 days of the week, to elicit a heart rate of 60-85% of maximum.[4] The duration, frequency, and intensity of aerobic ET are the key variables in the "dose" of ET that is optimally therapeutic. Highly controlled modes of PA include brisk walking, running, cycling, or swimming that involves large muscle groups which can increase peak aerobic capacity and are inversely related to all-cause mortality in patients with CAD.[6] The goal of the current review is to discuss how increasing chronic PA improves coronary blood flow (CBF) and, by implication, CAD morbidity and mortality.

Under-prescription of ET

Compliance and access to the necessary resources are often barriers to implementing healthy lifestyle changes in CAD patients. However, it is likely that lifestyle modifications like exercise are "under-prescribed" to CAD patients by physicians.[7,8] It has been estimated that 20-30% of eligible patients receive referrals to cardiac rehabilitation (CR)/ET programs.[7,9–11] Of the referred patients, only approximately 40% actually participate in the programs, with women less likely to be referred or participate in the programs, especially if they are elderly or non-white.[7,11,12] This is alarming because the least fit, inactive individuals comprise the high risk cohort that receives the most benefit from improved cardiorespiratory fitness (CRF).[13–15]

Systemic benefits of ET

Habitual PA (ET) has been shown to reduce the risk of sudden cardiac death and acute MI.[16] Increasing PA is a critically important modifiable behavior that can reduce the relative risk of CAD events because of its systemic benefits (Fig 1), which rival or exceed those achieved with pharmacological interventions and coronary revascularization for secondary treatment of CAD-related events.[7] Other systemic benefits of regular endurance ET—including improving CRF, muscle strength, and mood—could enhance even a healthy individual's QoL. Conversely, being physically inactive is an independent risk factor for CAD,[17,18] and it recently has been reported that sitting for 6–7 hours per day negates the benefits of one hour of moderate-intensity ET per day.[19] Being physically active also propagates other positive lifestyle modifications such as maintaining a healthy weight and stress management.[20] In turn, these positive lifestyle modifications help reduce CAD risk factors such as high blood pressure, high cholesterol, diabetes, and obesity. To date, there has not been any type of pharmacological intervention, i.e. "polypill," that has provided the benefits to as many organ systems as regular PA.

Cardiac-specific benefits of ET

One of the major CV-specific benefits (Fig 1) is reduction of angina through enhanced oxygen delivery to the myocardium. Macroscopic atherosclerosis is an obstructive CAD that attenuates myocardial oxygen delivery despite increased myocardial demand, in times when heart rate and/or systolic blood pressure are elevated, which often occurs during physical work and/or with disease progression. When myocardial oxygen delivery does not meet the needs of myocardial demand cellular anaerobic pathways are activated, evoking symptoms of angina.[7] When CBF to the myocardium is enhanced through ET, the resulting reduction in angina can