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Original Article

The Effect of Exercise on Different Body Systems, Especially the Heart and Various Components of Blood

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Abstract:

It is widely accepted that regular physical activity is beneficial for cardiovascular health. Frequent exercise is robustly associated with a decrease in cardiovascular mortality as well as the risk of developing cardiovascular disease. Physically active individuals have lower blood pressure, higher insulin sensitivity, and a more favorable plasma lipoprotein profile. Animal models of exercise show that repeated physical activity suppresses atherogenesis and increases the availability of vasodilatory mediators such as nitric oxide. Exercise has also been found to have beneficial effects on the heart. Acutely, exercise increases cardiac output and blood pressure, but individuals adapted to exercise show lower resting heart rate and cardiac hypertrophy. Both cardiac and vascular changes have been linked to a variety of changes in tissue metabolism and signaling, although our understanding of the contribution of the underlying mechanisms remains incomplete. Even though moderate levels of exercise have been found to be consistently associated with a reduction in cardiovascular disease risk, there is evidence to suggest that continuously high levels of exercise (e.g., marathon running) could have detrimental effects on cardiovascular health. Nevertheless, a specific dose response relationship between the extent and duration of exercise and the reduction in cardiovascular disease risk and mortality remains unclear.

Keywords: Body Systems, Heart, Various Components, Blood

Introduction:

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. In the United States, CVD accounts for ~600,000 deaths (25%) each year (1, 2), and after a continuous decline over the last 5 decades, its incidence is increasing again (3). Among the many risk factors that predispose to CVD development and progression, a sedentary lifestyle, characterized by consistently low levels of physical activity, is now recognized as a leading contributor to poor cardiovascular health. Conversely, regular exercise and physical activity are associated with

remarkable widespread health benefits and a significantly lower CVD risk. Several long-term studies have shown that increased physical activity is associated with a reduction in all-cause mortality and may modestly increase life expectancy, an effect which is strongly linked to a decline in the risk of developing cardiovascular and respiratory diseases (4). Consistent with this notion, death rates among men and women have been found to be inversely related to cardiorespiratory fitness levels, even in the presence of other predictors of cardiovascular mortality such as smoking, hypertension, and hyperlipidemia (5). Moreover, better fitness levels in both men and women can partially reverse the elevated rates of all-cause mortality as well as CVD mortality associated with high body mass index (6, 7). Recent work from cardiovascular cohorts shows that sustained physical activity is associated with a more favorable inflammatory marker profile, decreases heart failure risk, and improves survival at 30 years follow-up in individuals with coronary artery disease (8–10). Despite the robust beneficial effects of physical activity and exercise on cardiovascular health, the processes and mechanisms by which frequent physical activity promotes cardiorespiratory fitness and decreases CVD risk remain unclear. In the past several decades, considerable research effort has aimed to identify the major physiological and biochemical contributors to the cardiovascular benefits of exercise, and as a result, significant advances have been made from observational and interventional studies with human participants. In parallel, valuable mechanistic insights have been garnered from experimental studies in animal models. Thus, in this review, we provide a synopsis of the major known effects of exercise and physical activity on principal factors associated with risk for poor cardiovascular health including blood lipids, hypertension, and arterial stiffness. For the purpose of the review, we follow the definition of exercise as "a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness (11)."

Blood Physiology:

Blood Plasma:

Blood Plasma is a light – yellowish liquid. It acts as the base of the blood. It is composed of 91% of water and 9% solids such as coagulants, plasma proteins, electrolytes and immunoglobulins.[12]

In the embryonic stage blood plasma is formed from the mesenchymal cells. The albumin is formed first, followed by globulin and then other plasma proteins. In an adult, the reticuloendothelial cells in the liver are responsible for plasma production; this process is aided by bone marrow and spleen[13].

Functions of Blood Plasma:

Blood Plasma has various vital functions [14],[15]

- Coagulation- Plasma contains fibrinogen and procoagulants such as thrombin and factor x
- Immune Defense- Plasma has Immunoglobulins (antibodies) that play a role in the body's immunological defence process
- Maintenance of osmotic pressure- The presence of plasma proteins such as Albumin which is vital for maintaining a balance of fluid, called oncotic pressure, in the blood (maintained at around 25 mmHg).
- Acid-base balance- Plasma proteins helps in acid-base balance through buffering action.
- Transportation of Nutrients- Nutrients such as glucose, amino acids, liquids and vitamins are transported in the blood plasma from the digestive system to different body parts.
- Transportation of Respiratory Gases. Oxygen is carried to the body from the lungs and carbon dioxide back to the lungs for excretion.
- Transportation of Hormones.
- Excretion- Waste products from cellular metabolism are carried within the plasma and excreted via the kidneys, lungs and skin
- Temperature Regulation
- The erythrocyte sedimentation rate (ESR) is used as a diagnostic tool. As fibrinogen increases in acute inflammatory conditions, the ESR will also increase.

Erythrocytes (RBCs):

Erythrocytes (known as Red Blood Cells (RBCs) are biconcave discoidal cells.[19] RBCs lack a nucleus, contain haemoglobin (the red iron-rich protein that carries O2) and are surrounded by a membrane of lipids and proteins. The normal healthy adult produces 119 million red blood cells per second. It forms 44% of the total blood volume and a single RBC cell is sized 0.000007 m. They are produced by red bone marrow via a process called erythropoiesis.[17]

Functions of Erythrocytes:

- A single Erythrocyte cell lives only for 120 days and in that duration, it performs successive roles[18]
- Oxygen delivery from the lungs to the peripheral tissues.
- Collect CO2 from peripheral cells and return it to the lungs.
- RBCs contain haemoglobin with ferrous heme (Fe) which has an affinity for oxygen. When it arrives at deoxygenated cells the Fe looses its affinity for O2 (due to decreased partial pressure of O2 and low PH).

Leucocytes (WBCs):

Leucocytes are the cellular component of the blood that are also known as white blood cells (WBCs). WBCs have a nucleus and lack hemoglobin. WBCs form 1% of the total blood volume in healthy adults.[20] They are considered to be an important part of the immune system. The leucocytes are produced in the bone marrow in a process called Hematopoiesis[12] and normal WBCs count ranged between 4,000 and 10,000 cells/MCL18.

Types and Function of Leucocytes:

There are several types of WBCs such as Neutrophils, Eosinophils, Basophils, Lymphocytes (B and T) and Monocytes[21].

Neutrophils:

Neutrophils are WBCs that are released from the bone marrow. They represent 50% of total WBCs count. Around 100 billion of the Neutrophils cells are produced every day and they are considered to be the first immune system cells. They are the major pathogen-fighting immune cells that migrate to sites of infection and then identify and kill bacteria and viruses. Neutrophils also send signals to alert other immune system cells.[23]

Monocytes:

Monocytes represent 5 to 12 % of the total WBCs count. They are considered to be the “garbage trucks” of the immune system and play an important function in cleaning dead cells and tissue regeneration.[24]

Eosinophils:

Eosinophils represent less than 5% of the total WBCs. They are found in large amounts in the digestive system. Eosinophils play an important role in dealing with invading bacteria and parasites, such as worms.[25]

Basophils:

Basophils represent 1% of the total WBCs count. These cells play a role in asthma. They stimulate histamine release, leading to the inflammation and bronchoconstriction that occurs in asthma.[26]

Lymphocytes:

Lymphocytes produce antibodies that give immunity to the body if the body is exposed to the same infection again. It consists of two types of cells, T cells which have an invading function and B cells, which in contrast to other WBCs, are responsible for humoral immunity ie immunity associated with circulating antibodies, in contradistinction to cellular immunity[18]. These cells play an important role in developing a lot of the current vaccines.[19]

Pathophysiology of Leucocytes:

Elevated WBCs counts can indicate a variety of conditions. Infection, inflammation, trauma, pregnancy, asthma, allergy, cancers such as leukaemia and even aggressive exercises can result in elevated WBCs.[20]

On the other hand, low WBCs counts can indicate severe infections, bone marrow damage, autoimmune diseases (e.g. Systemic Lupus Erythematosus SLE) and splenic sequestration.[13]

Blood pressure:

During exercise, increases in cardiac stroke volume and heart rate raise cardiac output, which coupled with a transient increase in systemic vascular resistance, elevate mean arterial blood pressure (27). However, long-term exercise can promote a net reduction in blood pressure at rest. A meta-analysis of randomized controlled interventional studies found that regular moderate to intense exercise performed 3–5 times per week lowers blood pressure by an average of 3.4/2.4 mmHg (28). While this change may appear small, recent work shows that even a 1 mmHg reduction in systolic BP is associated with 20.3 fewer (blacks) or 13.3 fewer (whites) heart failure events per 100,000 person-years (29). Thus, reductions in blood pressure observed when exercise is included as a behavioral intervention along with dietary modification and weight loss (30) could have a significant impact on CVD incidence. Lower ambulatory blood pressure, associated with chronic aerobic and resistance exercise, is thought to be driven largely by a chronic reduction in systemic vascular resistance (31). Contributing to this effect, shear forces, as well as released metabolites from active skeletal muscle during exercise, signal the production and release of nitric oxide (NO) and prostacyclin from the vascular endothelium, which promotes enhanced vasodilation via relaxation of vascular smooth muscle cells (32). This effect is especially significant because a reduction in eNOS activity that occurs with aging or due to NOS3 polymorphism, has been reported to contribute to hypertension (33). Long-term exercise training increases eNOS expression as well as NO production in hypertensive individuals, consistent with the blood pressure lowering effect of physical activity (34). An important role of NO in mediating the vascular effects of exercise is further supported by results showing that rats with hypertension induced by chronic NOS inhibition undergoing a swimming exercise regimen for 6 weeks have significantly elevated eNOS protein expression and improved acetylcholine-induced vasodilation (35). Thus, improvements in NO production and bioavailability appear to represent significant factors that contribute to improved endothelium-dependent vasodilation following exercise training, which can reduce resting vascular resistance and lower blood pressure. However, in addition to NO-mediated reductions in resistance vascular tone, adaptive reductions in sympathetic nerve activity, prevention or reversal of arterial stiffening, and suppression of inflammation are also likely contributors to the blood pressure lowering effects of exercise, although the impact of exercise on these outcomes may be population specific (e.g., at-risk versus healthy adults) (36). As with changes in blood lipid profile, it remains unclear to what extent the blood pressure lowering effects of exercise can account for the beneficial effects of exercise on CVD risk and mortality.

Insulin sensitivity:

The association between blood lipids and cardiovascular health is highly influenced by systemic insulin sensitivity, and resistance to insulin signaling is known to promote the development of heart disease, in part by altering the blood lipid profile (37). Resistance of adipocytes to the effects of insulin and resulting reduction in glucose uptake leads to the increased release of free fatty acids and greater production and release of triglycerides, and VLDL by the liver (38). In addition, reduced HDL in the insulin resistant state, resulting in part from increased activity of cholesteryl ester transfer protein (CETP), and transfer of cholesteryl esters from HDL to triglyceride-rich lipoproteins (39), suppresses reverse cholesterol transport from the arterial wall and promotes atherosclerotic plaque formation.

Insulin signaling within the vascular endothelium promotes Akt-dependent phosphorylation and activation of eNOS, which produces the vasodilator - NO. This, however, is antagonized by the activation of the Ras-RAF-MAPK pathway that stimulates cell growth and differentiation and increases the production of the potent vasoconstrictor - endothelin-1 (ET-1) (34, 35). During diabetes, selective inhibition of the PI3K-

Akt-eNOS pathway, together with compensatory hyperinsulinemia leads to unmasking and stimulation of the MAPK-mediated production of endothelin-1 (ET-1) (36, 37), and vascular smooth muscle proliferation, which could contribute to atherosclerotic plaque development and peripheral artery disease (38, 39). Enhanced endothelial production and secretion of ET-1, along with heightened sympathetic activity may represent key contributing factors in enhanced vasoconstriction of small diameter arteries and arterioles in the insulin-resistant state, thereby increasing systemic vascular resistance to blood flow and elevating arterial blood pressure. In addition, as a hallmark of diabetes and insulin-resistance, elevated blood glucose levels also accelerate the formation of advanced glycation end products (AGEs), proteins and lipids that have undergone non-enzymatic glycation and oxidation, leading to cross-linking of collagen and elastin fibers and loss of vascular compliance (i.e., arterial stiffening) (40, 41).

Blood and vasculature:

The oxygen carrying capacity of blood, determined by the number of circulating erythrocytes and their associated intracellular hemoglobin concentration, is an important determinant of exercise performance and resistance to fatigue (41). High endurance athletes commonly have “athlete's anemia,” possibly due to loss of erythrocytes, or low hematocrit secondary to an expansion of plasma volume (42). Yet, overall total erythrocyte mass is increased in athletes, especially those who train at high altitude (43). This is in part due to a dose-dependent effect of O2 on hypoxia-inducible factor (HIF)-mediated erythropoietin production as well as upregulation of erythropoietin receptors, iron transporters, and transferrins (44). Multiple studies have shown that hematopoiesis is enhanced immediately following exercise (45). Intense exercise is associated with the release of a variety of stress and inflammatory factors that are active on the bone marrow such as cortisol, IL-6, TNF-α, PMN elastase, and granulocyte colony stimulating factor (46). Although HPCs appear to modestly decline in the period immediately following an exercise session in conditioned runners, one study found that circulating CD34+ hematopoietic progenitor cell counts were 3- to 4-fold higher in runners vs. non-runners at baseline (47), which may represent an adaptive response that facilitates tissue repair. A subsequent study found that a bout of intense exercise was associated with a release of CD34+/KDR+ endothelial progenitor cells from the bone marrow and that this effect was enhanced in individuals with elevated LDL/HDL and LDL/TC profiles (48). Likewise, a significant increase in the number of circulating EPCs, associated with increased levels of VEGF, HIF-1α, and EPO was found within hours after varying intensities of resistance training in women (49). Nonetheless, the physiological significance of these responses remains unclear, as the effects of exercise on angiogenesis and the wound healing response have not been systematically studied.

The resistance arterial vascular network also undergoes functional and structural adaptation to exercise (50). During acute exercise, small arteries and pre-capillary arterioles that supply blood to the skeletal muscles must dilate to increase blood flow through the release of vasodilatory signals (e.g., adenosine, lactate, K+, H+, CO2) from active surrounding muscle (51). Repeated exercise leads to an adaptive response in skeletal muscle arterioles that includes increased vascular density coupled with greater vasodilatory capacity, such that enhanced perfusion can occur after conditioning (52). This may be partly due to adaptation of the endothelium to the complex interplay of recurrent variations in hemodynamic stresses and vasodilatory stimuli of exercise. Endothelial synthesis of NO is greatly increased at rest and during exercise in conditioned individuals/animals (53). A similar adaptive response to exercise has also been noted in the coronary vasculature, which must dilate to meet the increased metabolic demands of the myocardium (54). Exercise-trained humans and animals demonstrate reduced myocardial blood flow at rest, which may reflect a reduction in cardiac oxygen consumption primarily as a result of lower resting heart rate (55). However, a large

body of evidence suggests that multiple mechanisms converge to enhance the ability of the coronary circulation to deliver a greater supply of oxygen to the conditioned myocardium during exercise. This includes structural adaptations consisting of an expansion in the density of intramyocardial arterioles and capillaries as well as enhanced microvascular collateral formation (56). Additionally, like skeletal muscle arterioles, coronary arterial network enhances its responsiveness to vasoactive stimuli via a number of distinct mechanisms including, but not limited to, augmentation of endothelial NO production, altered responsiveness to adrenergic stimuli, or changes in the metabolic regulation of vascular tone (57). In addition, some studies implicate hydrogen peroxide (H2O2)-mediated vasodilation in opposing exertion-induced arterial dysfunction in overweight obese adults after a period of exercise training (58), suggesting enhanced contribution of NO-independent mechanisms to improved microvascular endothelial function with exercise. Collectively, these adaptations may act to support enhanced myocardial function and increased cardiac output during repeated exercise, and increased total body oxygen demand following exercise conditioning. Further advancement of our understanding of how blood flow is improved in response to exercise could lead to novel therapeutic strategies to prevent or reverse organ failure in patients resulting from inadequate blood flow.

Physiology of the Heart:

The conduction system includes several components. The first part of the conduction system is the sinoatrial node. Without any neural stimulation, the sinoatrial node rhythmically initiates impulses 70 to 80 times per minute. Because it establishes the basic rhythm of the heartbeat, it is called the pacemaker of the heart. Other parts of the conduction system include the atrioventricular node, atrioventricular bundle, bundle branches, and conduction myofibers. All of these components coordinate the contraction and relaxation of the heart chambers.(59) .

Cardiac Cycle:

The cardiac cycle refers to the alternating contraction and relaxation of the myocardium in the walls of the heart chambers, coordinated by the conduction system, during one heartbeat. Systole is the contraction phase of the cardiac cycle, and diastole is the relaxation phase. At a normal heart rate, one cardiac cycle lasts for 0.8 second.

Heart Sounds:

The sounds associated with the heartbeat are due to vibrations in the tissues and blood caused by closure of the valves. Abnormal heart sounds are called murmurs.(60)

Heart Rate:

The sinoatrial node, acting alone, produces a constant rhythmic heart rate. Regulating factors are reliant on the atrioventricular node to increase or decrease the heart rate to adjust cardiac output to meet the changing needs of the body. Most changes in the heart rate are mediated through the cardiac center in the medulla oblongata of the brain. The center has both sympathetic and parasympathetic components that adjust the heart rate to meet the changing needs of the body(61).

Peripheral factors such as emotions, ion concentrations, and body temperature may affect heart rate. These are usually mediated through the cardiac center(62).

Cardiac adaptations:

During exercise, the heart is subjected to intermittent hemodynamic stresses of pressure overload, volume overload, or both. To normalize such stress and to meet the systemic demand for an increased blood supply, the heart undergoes morphological adaptation to recurrent exercise by increasing its mass, primarily through an increase in ventricular chamber wall thickness. This augmentation of heart size is primarily the result of an increase in the size of individual terminally differentiated cardiac myocytes (61). Adaptive remodeling of the heart in response to exercise typically occurs with preservation or enhancement of contractile function. This contrasts with pathologic remodeling due to chronic sustained

pressure overload (e.g., during hypertension or aortic stenosis), which can proceed to a loss of contractile function and heart failure (62). Recent work in experimental animal exercise models has identified several cellular and molecular alterations involved in the physiologic growth program of the heart that accompanies exercise conditioning. Whereas pathologic remodeling of the heart is associated with a reduction in oxidative energy production via fatty acid oxidation and more reliance on glucose utilization, mitochondrial biogenesis and capacity for fatty acid oxidation are enhanced following exercise (63). A recent study suggests that changes in myocardial glycolytic activity during acute exercise and the subsequent recovery period can also play an important role in regulating the expression of metabolic genes and cardiac remodeling (64). Possibly upstream of these metabolic changes, studies have also revealed a dominant role for IGF-1 and insulin receptor signaling, via the PI3K/Akt1 pathway leading to the activation of transcriptional pathways associated with protein synthesis and hypertrophy (65). Untargeted approaches have identified other major determinants of transcriptional programs that drive the exercise-induced hypertrophic response. For instance, it has been reported that exercise-induced reduction in the expression of CCAAT-enhancer binding protein β (C/EBPβ) relieves its negative regulation by CBP/p300-interactive transactivator with ED-rich carboxy-terminal domain-4 (Cited4) (66). Activation of Cited4 has been found to be necessary for exercise-induced cardiac hypertrophy, and cardiac-specific overexpression of the gene is sufficient to increase heart mass and protect against ischemia/reperfusion injury (67). Other transcriptional pathways known to be activated by pathologic stimuli and cardiac hypertrophy, such as NFATc2, are decreased in exercise models (68), suggesting that some signaling pathways activated during exercise-induced growth program may directly antagonize specific factors that promote pathological remodeling. In addition to metabolic and molecular remodeling, exercise can also promote functional adaptation of the heart, which may ultimately increase cardiac output and reduce the risk of arrhythmia. Clinical studies have shown that exercise-trained individuals have improved systolic and diastolic function (69), while results of studies using animal models of exercise show that endurance exercise promotes enhanced cardiomyocyte contraction-relaxation velocities and force generation (70). This effect of exercise on cardiomyocyte contractile function may be related to alterations in the rise and decay rates of intracellular Ca2+ transients, possibly due to enhanced coupling efficiency between L-type Ca2+ channel-mediated Ca2+ entry and activation of subsarcolemmal ryanodine receptors (RyR; i.e., calcium-induced calcium release), and increased expression and activity of the sarcoendoplasmic reticulum Ca2+ ATPase (SERCA2a) and sodium-calcium exchanger (NCX) (71). In addition, the sensitivity of the cardiomyocyte producing a greater force of contraction at a given [Ca2+]i, following exercise, (72). These changes may at least partially depend on upregulation of the Na+/H+ antiporter and altered regulation of intracellular pH.

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