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The Effects Diabetes Has on the Neurovascular System during Exercise

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The Effects Diabetes Has on the Neurovascular System during Exercise

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Report

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Master of Science in Kinesiology

The University of Texas at Austin

May 2016

Abstract

The Effects Diabetes Has on the Neurovascular System during Exercise

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The University of Texas at Austin, 2016

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The autonomic nervous system is responsible for the involuntary control of most visceral organs. This system greatly influences the neurovascular and cardiovascular systems while at rest and during exercise. Central command, the baroreflex, and the exercise pressor reflex are the three systems that are responsible for the distribution of blood during exercise. Specifically, the exercise pressor reflex plays a dominant role during exercise because it is influenced by metabolic and mechanical factors that affect the vasculature health. Diabetes mellitus is a metabolic disease that can alter the way these systems function within the body. The effects of neural damage and exercise-induced hypoglycemia have been thought to be the sources behind the changes seen in the exercise pressor reflex. Currently, not a lot of research has been done on the exact mechanisms behind the changes of the exercise pressor reflex in diabetes; therefore, the explanations to these alterations are unknown. Thus, the purpose of this report is to develop a hypothesis for the effects of diabetes on the autonomic control of exercise, specifically the exercise pressor reflex.

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Chapter 1: Introduction

The sympathetic and parasympathetic divisions of the autonomic nervous system are responsible for involuntary control of most visceral organs, including the heart and vascuature.[130] At rest, these systems work together to maintain homeostasis within our bodies. Specifically, they are in control of aiding in the redistribution of blood flow so that the working muscles as well as the rest of the organs get an adequate supply of blood flow in order to function. During exercise, central command, the baroreflex, and the exercise pressor reflex use these systems to ensure that the neurovascular and cardiovascular systems sufficiently respond to metabolic and functional needs. However, various diseases, such as diabetes, can alter the way the neurovascular system responds.

Diabetes, both I and II, are metabolic diseases characterized by insulin resistance. It is often accompanied by heart disease, blindness, kidney failure, and lower-extremity amputations.[6] Additionally, neural damage, specifically diabetic neuropathy, has been said to be the cause of many of these complications.[136]

The same types of sensory nerves which are affected by diabetic neuropathy are also involved in the exercise pressor reflex. At this time, the effects of diabetes on the exercise pressor reflex are unknown. The purpose of this report is to provide background information on the autonomic control of exercise, specifically the exercise pressor reflex, as well as the effects of diabetes on sensory nerves in order to develop a strong hypothesis for the effects of diabetes on the exercise pressor reflex.

Chapter 2: Type I and Type II Diabetes

Diabetes is a chronic disease in which the body cannot produce insulin or it cannot use the insulin it produces. Insulin is the hormone produced by the beta cells in the pancreas that controls the amount of glucose in the plasma. High blood sugar levels can lead to damaged organs, blood vessels and nerves. It is often a chronic, debilitating disease that can sometimes be fatal.[135]

TYPE I DIABETES

Type I diabetes, also known as early-onset diabetes, juvenile diabetes, and insulin-dependent diabetes, is an autoimmune disease when the body does not produce enough insulin because the beta cells within the pancreas, the cells that produce insulin, are destroyed by the body's immune system.[135] An "environmental trigger," for example, an unidentified virus, has been suspected to trigger this attack on the beta cells in some people that may be genetically predisposed; however, the mechanisms of development for Type I diabetes, as well as Type II, are unknown.[6] In order for those with Type I diabetes to control their blood sugar, they use insulin injections which supplement for the insulin that is not being produced. According to the American Diabetes Association, only 5% of people who have diabetes have Type I diabetes.[33] It is usually diagnosed in young adults and children but can be diagnosed in anyone at any age.

TYPE II DIABETES

Type II diabetes is a major chronic disease where the body does produce insulin but the amount may not be enough or the cells within the body do not react to the insulin that is being produced. This lack of response to insulin is known as insulin resistance or insulin insensitivity.[135] Initially, to compensate for this resistance, the pancreas may produce extra insulin; however, over time, it is unable to keep up with the production,

and the proper amount of insulin is not produced in order to keep the blood glucose levels regular. It is more common in the overweight/obese population because it has been shown that the body releases chemicals that destabilize its cardiovascular and metabolic systems when one has a high percentage of visceral fat.[134] Commonly, type II diabetes is associated with raised blood pressure, a disruption in blood lipid levels, and a propensity to develop thrombosis; also known as metabolic syndrome. Blood glucose lowering therapy tends to be required continuously due to the progressive high glucose levels that tend to worsen throughout the years.[134] Type II diabetes is known to cause an increase in cardiovascular risk such as, coronary artery disease, peripheral artery disease, and carotid artery disease. Additionally, persistent hyperglycemia can lead to permanent microvascular difficulties such as diabetic retinopathy, nephropathy and neuropathy which can result in amputation, painful symptoms, erectile dysfunction, and other issues.[134]

Type II diabetes is the most common form of diabetes; 95% of diabetes cases are classified as being Type II. Currently, 18 million Americans are affected with Type II diabetes. Demographically, there are groups that are at a higher risk for Type II diabetes than others. African Americans, Latinos, Native Americans, and Asian Americans/ Pacific Islanders, in addition to the aged population, are more prone to having diabetes.[33]

Chapter 3: Autonomic Control of Circulation at Rest

THE NEURAL CONTROL IN CIRCULATION

The body's organs and tissues are capable of receiving their functional and metabolic needs from peripheral circulation and its distribution of cardiac output. Blood flow within specific regions can be regulated locally or centrally. Locally, blood vessels have an intrinsic ability to respond to mechanical stimulation, such as shear stress and wall tension, as well as chemical stimuli, such as oxygen and metabolites. Central neural activity coincides with the local regulation by adjusting the cardiovascular function in order to meet the body's needs. The coordination of both systems is important in responding and creating accelerated changes in blood volume distribution, blood pressure changes, and the amount of changes and distribution in the cardiac output; all of which are essential in maintaining perfusion within the heart and brain.[130]

AUTONOMIC NERVES AND CARDIOVASCULAR CONTROL

The autonomic nervous system consists of the sympathetic and parasympathetic branches. It controls all involuntary movements within the viscera including the heart and vasodilators. The motor control within the autonomic system consists of myelinated preganglionic fibers originating in the central nervous system (CNS). The axons of this system synapse on autonomic ganglia located outside of the central nervous system on the cell bodies of the unmyelinated postganglionic fibers. These fibers lead to an innervation on the effector organs. The preganglionic fibers within the parasympathetic and sympathetic systems of both CNS and peripheral nervous system are cholinergic, releasing the neurotransmitter acetylcholine which binds to nicotinic acetylcholine receptors on the postganglionic fibers evoking action potentials.[130] The lengths of the pre- and postganglionic fibers differ between the sympathetic and parasympathetic systems.

The fibers within the parasympathetic division contain long preganglionic fibers that synapse on short postganglionic fibers emerging from ganglia near the effector targets. In contrast, the fibers within the sympathetic division are made up of short preganglionic fibers that synapse on long postganglionic fibers emerging from the paravertebral chain ganglia or collateral ganglia. Due to these differences, the discharge from each system can either cause a regional or localized response; sympathetic causing the more regional effect and parasympathetic causing the more localized effect.[130]

Within the cardiovascular tissues, specifically cardiac and smooth muscle, the axons of the postganglionic neurons branch, coming into close contact with an abundant amount of effector cells. Within these neuronal branches are varicosities that contain synaptic vesicles full of neurotransmitters that are released with every action potential that travels along the axon. Thus, many effector cells can be innervated by a single neuron. Acetylcholine is the primary neurotransmitter released by the postganglionic parasympathetic neurons. This then binds to muscarinic acetylcholine receptors located on target tissues. Norepinephrine is the primary neurotransmitter released by the sympathetic postganglionic fibers, which binds to either the α- or β-adrenergic receptors. Norepinephrine can be repackaged in vesicles and released once more by successive action potentials, allowing it to have greater, prolonged effects than acetylcholine. The neural control of the cardiovascular system is primarily governed by the sympathetic nervous system because it largely contributes directly and indirectly to the control of the cardiac and vascular function; however, the parasympathetic nerves are also important in the effect of cardiovascular functions, despite their innervations being rather limited in comparison to the sympathetic division.[41]

As a whole, the neural control of the circulation is controlled by the parasympathetic innervation to the heart and the sympathetic innervation that can be

classified into three main categories: barosensitive, thermosensitive, and glucosensitive. Arterial barorecepters control the barosensitive sympathetic efferent neurons. Ultimately, the baroreceptors control is determined by central control i.e. the limbic, cortical, and midbrain structures.[48]

AUTONOMIC NEURAL CONTROL OF THE HEART

The autonomic nervous system has an immense impact on the heart because of its capability to control cardiac rate, conduction velocity, contraction, and relaxation. Parasympathetic and sympathetic fibers innervating the sinoatrial (SA) and atrioventricular (AV) nodes influence the cardiac rate and conduction velocity, whereas the contraction and relaxation effects of the heart are primarily facilitated by the innervation of the sympathetic fibers on the atrial and ventricular myocytes. Moreover, the parasympathetic nervous activity negatively regulates the heart rate.[69] Parasympathetic fibers influence the vagus nerve, releasing acetylcholine and activating the M_2 muscarinic acetylcholine receptors which increase the potassium conductance of nodal cells.[69,130] Because of the parasympathetic influence on the membrane polarization, the SA node decreases its firing rate which slows down the conduction in the AV node, resulting in an overall decrease in the intrinsic heart rate.

The release of norepinephrine from the sympathetic fibers binds to the β-adrenergic receptors. Activation of these receptors increases the heart rate by increasing the slope of diastolic depolarization in the SA node, which in turn increases the conduction within the AV node. Within the myocytes there is an increase in the membrane calcium currents and calcium release from the sarcoplasmic reticulum during each action potential, thus increasing force production. Additionally, calcium reuptake in the sarcoplasmic reticulum is improved, which allows for acceleration in the relaxation of

the heart. Jointly, the effects sympathetic stimulation has on the contraction and relaxation of the heart allows for an increased stroke volume.[130]

It is important to note that in conscious humans, the major determinant of baseline heart rate is dependent upon the parasympathetic nerve activity within the heart, whereas the effects of the sympathetic nervous system are trivial.[53,130] According to Smith, endurance exercise-trained humans demonstrated an amplified parasympathetic tone at rest when compared to sedentary individuals, allowing them to have a lower baseline heart rate,[124] thus, confirming that the resting heart rate relies on a greater amount of vagal discharge and a moderate amount of tonic sympathetic discharge.[130]

SYMPATHETIC NEURAL CONTROL OF BLOOD VESSELS

Most arteries, arterioles, and veins in the body are innervated by postganglionic sympathetic neurons; however, venules and capillaries do not have a direct innervation with the sympathetic neurons due to their lack of smooth muscle.[48,130] The norepinephrine released by the sympathetic nerve terminals binds to the α_1- or α_2-adrenergic receptors which are located on the vascular smooth muscle cells. This results in an increase of intracellular calcium. Vessels that have more than a single layer of smooth muscle communicate via gap junctions so that all the inner portions of the medial layer can contract; however, vessels that only contain a single layer of smooth muscle receive the sympathetic innervation on the outermost layer.

In addition to the neurotransmitter norepinephrine, vascular sympathetic nerves may release cotransmitters. Neuropeptide Y (NPY) and ATP can both produce constriction by increasing intracellular calcium. NPY has the ability to also increase the constrictor effects of norepinephrine and ATP. The contribution of NPY and ATP

towards sympathetic vasoconstriction is dependent upon the strength and pattern of sympathetic discharge and various vascular beds.[61]

Similar to the heart, a background level of vasoconstriction is set by sympathetic neuronal innervation. This sympathetic tonic activity is called functional sympatholysis and can either cause more vasoconstriction with greater sympathetic outflow or lesser vasoconstriction with a withdrawal of sympathetic tone. Functional sympatholysis allows for complete control of vascular tone by the sympathetic vasoconstrictor nerves, leaving no need for innervation by the parasympathetic vasodilator nerves.[130]

As stated earlier, the type of vessels involved that are innervated by the sympathetic system are important in the regulation of systemic blood flow. Arterioles in particular have a substantial role when it comes to total peripheral resistance. Blood flow has a direct variance with the fourth power of the vessel radius. Resultantly, even the smallest of changes in the caliber of the vessel can have fairly large effects on vascular resistance and blood flow. Arterioles are the major resistance vessels and are composed of numerous layers of smooth muscle that largely help regulate regional blood flow. Therefore, the regulation of blood flow to individual organs and tissues is a powerful mechanism created by the sympathetic neural control of arteriolar resistance.[130]

Despite the various sympathetic neuronal innervations, all of the vessels do not respond equally. Dependent upon various factors such as local factors, the density of sympathetic innervation, the density and subtype of adrenergic receptors, the concentrations of vasoactive tissue metabolites, the differences in norepinephrine kinetics, and the vessel size and structure, the distribution of blood flow will differ. Responses, such as this, allow for the redistribution of cardiac output towards the parts of the vascular beds that are more essential while maintaining blood flow to the vital organs.[47,50,71]

Veins tend to have a different response when compared to arteries and arterioles. Because they have a lesser amount of smooth muscle and therefore have a lesser amount of sympathetic innervation. This makes them more of capacitance vessels, and when stimulated sympathetically, or in other words constricted, they decrease tissue blood volume.[130]

CENTRAL INTEGRATION OF AUTONOMIC OUTFLOW

The autonomic neurons regulating cardiovascular function are controlled by a system of neurons that are located in the medulla oblongata. This system can receive input from other structures within the brain such as the hypothalamus, cerebral cortex, and medullary chemoreceptors in addition to input from peripheral reflexes emerging from all of the afferent receptors located within the blood vessels, heart, lungs, skeletal muscles, skin, and viscera. The nucleus tractus solitarius (NTS) located in the medulla is where the descending signals from higher brain centers and the afferent sensory signals from the large systemic arteries, cardiopulmonary region, and some of the viscera synapse. The spinal cord sends the other afferent inputs from the skin and skeletal muscles that detect various chemical and physical factors such as muscle stretch to tissue hypoxia and metabolites to the medullary vasomotor centers.[48]

The primary site that regulates sympathetic outflow is the ventrolateral medulla (VLM), and this is where the neural pathways from the NTS project. The excitatory neurons within the rostral VLM synapse on the sympathetic preganglionic neurons within the intermediolateral (IML) gray column of the spinal cord. Inhibitory neurons in the caudal VLM project to the rostral VLM. Vagal outflow controlled by the medulla is also mediated by the NTS neurons that synapse on the preganglionic parasympathetic neurons in the dorsal motor nucleus of the vagus and the nucleus ambiguus.[130] Rapid behavior-

related adjustments to sympathetic tone are controlled by the limbic, cortical, and midbrain structures, but these structures are most likely not involved in the long-term regulation of blood pressure unless in the context of stress-related hypertension.[48]

ARTERIAL BAROREFLEX

The arterial baroreflex is a negative feedback system that regulates the beat-to-beat fluctuations that occur in arterial blood pressure. There is a narrow range of blood pressure within animals that is best for maintaining adequate blood flow to the numerous vascular beds in the body. This set point is primarily determined by the central nervous system. A classic study done by Cowley et. al involved comparing the blood pressure recordings from a dog with an intact baroreceptor and a dog with a chronically denervated baroreceptor. When the arterial baroreceptor afferent nerves were officially severed, the arterial pressure rose substantially. However, after a period of time the mean arterial pressure returned to the levels of predenervation, thus making the levels of the normal dog and the denervated dog similar. Moreover, the baroreceptor-denervated dog had a greater variability around the mean arterial pressure because the beat-to-beat buffering system was no longer functioning.[23]

At rest, a lot of continuous information is being received from afferent baroreceptor projections. Simultaneously, the heart is receiving information from both branches of the autonomic system, and the balance between both systems determines the baseline heart rate. The sympathetic nervous system is also maintaining vascular tone. Therefore, under normal resting conditions arterial baroreceptors serve as a constraint, keeping the heart rate and arterial pressure lower than what they would be in the absence of baroreceptor input.[53]

In the heart, the acute changes in arterial blood pressure stimulated by the sympathoinhibitory reflex are due to stretch receptors, or baroreceptors, in the vessel wall of the carotid sinus and aortic arch. Typically, the discharge from the baroreceptors increases quickly during early systole and decreases during late systole and early diastole. The afferent baroreceptor discharge is relayed via the buffer nerves, to the NTS, which induces changes in the sympathetic and parasympathetic outflow to the heart and vasculature that are responsible for adjusting cardiac output and vascular resistance in order to return blood pressure back to baseline levels.[130] Therefore, arterial baroreceptor discharge will decrease when arterial pressure is decreased; however, if arterial pressure increases, arterial baroreceptor discharge will increase inducing reflex inhibition of efferent sympathetic outflow to the blood vessels and heart and eventually causing an activation of parasympathetic outflow to the heart.[53,130] Either an increase or decrease in arterial baroreceptor discharge results in changes in vascular resistance, stroke volume, and heart rate in order to get arterial pressure back to baseline.[130] Stroke volume is largely influenced by venous return and cardiac contractility which both rely on the effects of the sympathetic nervous system; therefore, changes in the sympathetic nerve activity to the arteries and ventricles will affect stroke volume.[53]

If arterial pressure is changed for a period of time, it is possible for the arterial baroreceptors to reset and operate around a new baseline blood pressure. This process is capable of starting within minutes and eventually be completed within a few days to weeks.[73,74,76] There is a sigmoidal relationship that exists between mean arterial pressure and afferent baroreceptor discharge.[130] The exposure to an elevated arterial pressure will cause a rightward shift in the baroreceptor curve towards higher blood pressures, whereas a leftward shift in the baroreceptor curve towards lower blood pressures will occur in the presence of decreased blood pressures.[53] This acute resetting of the baroreceptors and

baroreflex can be viewed as being advantageous because it allows for a wider range of pressures the baroreceptors can remain sensitive to that way they can immediately respond in pressure fluctuations.[53]

The arterial baroreflex resetting can either be acute or chronic. A good example of acute resetting is during exercise. The efferent baroreflex function curve shifts to the right and upward without a reduction in sensitivity. This allows for the blood pressure, efferent sympathetic nerve activity, and heart rate to stay at greater levels throughout exercise and decrease back to baseline once the exercise ceases.[130] A chronic example of baroreflex resetting is the development of hypertension. Over time as the arterial pressure remains elevated, the sensitivity to the baroreflex can be reduced making it more difficult to buffer acute pressure fluctuations.[130]

ARTERIAL CHEMOREFLEX

Arterial chemoreceptors are a collection of chemosensitive cells that are located in the carotid and aortic bodies within the aortic arch and respond to changes in arterial P_{O2}, $P_{CO2,}$ and pH.[53,130] They are primarily responsible for controlling respiration and serve to buffer changes in arterial blood gases. When arterial P_{O2} or pH decreases or arterial P_{CO2} increases, the afferent chemoreceptor nerves increase their discharge, which stimulates the respiratory center to reflexively increase ventilation, and volume as well as stimulates the vasomotor center to reflexively increase sympathetic outflow, which increases arterial blood pressure. Despite arterial chemoreflexes not being a major mechanism for blood pressure regulation, a lower than normal arterial pressure range activates arterial chemoreceptors. This reflex causes the chemoreceptors to have an effect on arterial blood pressure.[53,130]

Chapter 4: Autonomic Control of Circulation during Exercise

During exercise, many mechanisms control the cardiovascular system in order to maintain adequate oxygen flow to the demanding muscles that are being exercised in order to provide sufficient nutrients and metabolites as well as washout the metabolic end-products. Such mechanisms provide a way to regulate arterial blood pressure so that the vital organs can maintain adequate perfusion without excessive pressure variations.[62] Systemic demands such as these provide a challenge to the cardiovascular system because active muscles during exercise induce metabolic vasodilation.[97] Within skeletal muscle nearly a linear increase in blood flow is provided by vascular control mechanisms, which increases the oxygen consumption of the muscle due to changing oxygen extraction. The central control processes allow for a near-linear increase in cardiac output and heart rate that also are in line with the oxygen consumption of the muscle tissue. This increase in cardiac output is directly related to the vasodilation within the resistance vessels that is caused by the increased oxygen demand of the exercising skeletal and cardiac muscles.[144]

Various exercises have different effects on the mean arterial pressure. Dynamic exercise tends to slightly increase the mean arterial pressure whereas static and isomeric exercise progressively increases mean arterial pressure. During physical activity that requires large muscle mass, the vasodilation that occurs in the active muscles results in a reduction in systemic vascular resistance; however, due to various control mechanisms, what would be a drop in blood pressure is augmented and cardiac output is maintained. Various vasodilators are released by active skeletal muscle such as potassium, adenosine hydrogen ions, carbon dioxide and phosphate. Nitric oxide is also produced thereby creating vasodilating effects. The cardiac output is increased by an increase in heart rate

and stroke volume, which act against the reduction in systemic vascular resistance via a flow-increment mechanism.[28,54,81,93]

Cardiovascular responses are controlled by mechanical mechanisms, such as the skeletal-muscle and respiratory pumps, which force blood towards the heart and by nervous mechanisms which help meet the metabolic demand from the exercising muscles by regulating vagal tone and flow.[97] In regards to mechanical pumps, the skeletal-muscle pump has the most important role because the rhythmic pumping caused by muscle contractions during dynamic exercise creates intramuscular oscillations which facilitate blood flow to the heart and enhance cardiac preload. This then increases stroke volume because the Frank-Starling mechanism is recruited.[24,25,27,54,77,83,107] In regards to regulation by the nervous mechanisms, exercise induces sympathetic activation and parasympathetic withdrawal, which are dependent upon the muscle mass recruited and exercise intensity.[119,121] This autonomic regulation is determined by central command. This basic pattern of autonomic regulation is controlled by the mechanoreceptors and metaboreceptors within the muscle, which dictate sympathetic tone based off of the mechanical and metabolic conditions of the working muscle. This is called the exercise pressor reflex, which will be discussed more in depth later.[26,64,102,106,126] Because of the exercise pressor reflex and sympathetic activation heart rate, myocardial contractility, and venous return increase which simultaneously raise cardiac output. As previously discussed, the arterial baroreflex determines sympathetic activation and can be reset during exercise.[97]

In summary, blood flow is controlled by the nervous system during exercise through neural integration within the brain and through the periphery. Within healthy individuals, the parasympathetic tone in the cardiovascular system, which tends to decline during exercise, is overshadowed by sympathetic activity. The resulting

imbalance increases heart rate and myocardial activity while the vascular beds of the organs and tissues not involved in exercise undergo arterial constriction. Moreover, cardiac preload is increased because of muscle pump activation and sympathetic-induced venoconstriction, which contribute to the increase in stroke volume that is common during dynamic exercise.[97]

CENTRAL COMMAND

The term "central command" became a common use name used to describe the central neural mechanism due to the 1972 study done by Goodwin et al. at Oxford University. In this study, a vibration at the distal biceps tendon was applied during static contractions with the biceps or the triceps. The vibration was intended to activate muscle spindle afferents, which provided medullary excitation when the agonist muscle was stimulated, thereby reducing the central motor activation needed to reach a given tension. On the opposing hand, a vibration provided reflex medullary inhibition when it was applied to the antagonist muscle, causing a rise in central motor activation achieving a given tension. What the researchers observed was that there was a decrease in heart rate, blood pressure, and pulmonary ventilation when central motor activation was reduced, and the opposite effect when central motor activation was increased.[45]

Further studies have been done after the Goodwin et al. study within animal models and humans using neuroimaging, deep brain electrical recordings, or deep brain stimulation and have validated and accepted that the central command is a feed forward process.[45] This means that feedback information from skeletal muscles, blood, lungs, heart, etc. is not necessary in order to function. Conversely, other quantities of data have stated that the central and peripheral inputs can control the central command, yet this type

of parallel motor activation is not necessary for the control of cardiovascular responses by central command.[97]

A study done by Morgan et al.[95] demonstrated this. Subjects had to exercise at a constant workload and were hypnotized being told that the load was light, moderate, or heavy. The cardiorespiratory responses and effort sense were higher during hypnotic suggestion but were not different between light and moderate hypnotic suggestions.[95] A similar study was done by Williamson et al.[145] using single-photon-emission measuring regional cerebral blood flow during exercise under hypnosis. Their findings supported the Morgan et. al findings since the sense of increased effort due to hypnosis during constant-load exercise heightened cardiovascular responses, which is associated with the activation of the insular cortex, anterior cingulate cortex, and the thalamus. On the other hand, a reduction in effort sense that was induced by hypnosis did not decrease cardiovascular responses below the level needed to sustain the metabolic needs of exercise, despite there being a decrease in brain activation.[145] The evidence from both studies suggests that the central command is autonomous in the presence of motor activation, and that the magnitude of cardiovascular response necessary for sustaining a given metabolic demand when effort sense is lower than a critical level is determined by the afferent input from the exercising muscle.[97]

Generally, numerous studies have found that central command does not operate well without adequate feedback from peripheral muscles. There are some limitations to this; however, the activation of central command leads to vagal withdrawal and sympathoexcitation.[98,104,146]

BAROREFLEX

There has been controversy on whether the strength or gain of the arterial baroreflex is reduced during exercise while both heart rate and arterial pressure rise. Some of the initial studies concluded that the arterial baroreflex does steadily decline while exercise workload increases[13,29]; however, following studies found sustainability in the reflex gain during exercise.[91] Despite this dispute, the major mechanism used by the arterial baroreflex to control arterial pressure at rest and during exercise is the regulation of peripheral vasoconstriction.[19,105] Temporary changes may occur in the cardiac output due to the initial carotid sinus perturbations, but these changes are not constant and in steady state, most of the reflex changes in pressure are because of the vascular responses.[105] A larger fraction of cardiac output and total vascular conductance begins to incorporate the blood flow to the active skeletal muscle as workload increases. At greater workloads, the control of vascular conductance in the active skeletal muscle is the only way there can be effective regulation of arterial pressure.[103]

There is a resulting triphasic change during exercise in the vascular intraluminal pressure which is referred to as the myogenic response. Initially, there is a passive dilation in the arterioles that increase in pressure. As soon as the pressure is within the desired range, a myogenic constriction is elicited. Anything beyond the desired pressure range promotes an increase in dilation.[144] There can also be a similar result in the relaxation of the vascular smooth muscle which is thought to be stimulated by acetylcholine.[34,146]

As stated earlier, the baroreflex is capable of resetting due to the stimulation of skeletal muscle afferents and the activation of the central command.[90,108] Constant input to the central brainstem neural networks controlling baroreflex resetting is provided by the skeletal muscle afferents and central command activation as the workload increases.

The resetting occurs either through the ascending feedback input from the skeletal muscle mechanosensitive and metabosensitive group III and IV afferents or through the descending feed-forward input from central command.[97]

EXERCISE PRESSOR REFLEX

The exercise pressor reflex can be termed as a "feedback" mechanism that originates in contracting skeletal muscle that functions to increase cardiovascular, ventilator, and locomotor function.[39,40,75] It is likely that the cardiovascular and respiratory responses work together as part of the same reflex, and these together may be properly called the exercise reflex.[20] The two reflexes termed the metaboreflex and the mechanoreflex are responsible for generating the exercise pressor reflex. The metaboreflex is defined as being the metabolic reflex devising from skeletal muscle that mediates the cardiovascular adjustments to exercise. The mechanoreflex can be defined as being the mechanical changes within muscles and tendons that create cardiovascular responses.[66,67] Central command is also responsible for cardiovascular and ventilation increases; however, central command does not require muscle afferent input.[51]

There are four groups (I, II, III,and IV) of afferent fibers from skeletal muscle that are classically subdivided by their anatomically and electrophysiological characteristics.[85] It was McCloskey and Mitchell that showed the involvement of the group III and IV afferents in this reflex. They found that the cardiovascular and ventilator increases induced by static contraction were caused by the stimulation of group III and IV muscle afferents during the reflex.[87] Efforts have been made for categorizing some of the group III and IV afferents into two groups.[65] Nocioceptors are those of group III and IV afferents that a stimulated by algesic chemicals and vigorous pinching of the muscle, so they transduce muscle pain sensation.[70] The fibers that cause the exercise pressor reflex

are called ergoreceptors and are thereby stimulated by skeletal muscular contraction.[65] The slow conducting afferent nerve fibers of groups III and IV have been thought to be excitable by mechanical and chemical stimulation.[68,79] Specifically, group III thinly myelinated fibers probably serve as mechanoreceptors because they can be rapidly excited by mechanical distortion of their receptive field.[86] The unmyelinated fiber group IV afferents are more often stimulated by mechanical stimuli. There is onset latency in which the metabolic products of contraction accumulate in the muscle undergoing constant contraction. The firing rate of these fibers increased throughout contraction because of the metabolite buildup.[1,52] These mechanical conditions, such as muscle length and strain, tissue compression, and deformation due to contractions, and the metabolic conditions, such as the amount of metabolic accumulation, within the exercising muscles send information to the receptors within the muscles. In turn, the given information is provided for the cardiovascular controlling areas, which control the hemodynamic adjustments for the regulation of blood flow within the contracting muscle.[97]

There are different viewpoints that express the relationship between the metaboreflex and cardiovascular control. The first viewpoint is that the metaboreflex is activated whenever blood flow to the contracting muscles is unable to efficiently produce both oxygen delivery and metabolite washout.[21,106,115] It is said that the metaboreflex acts as a way to correct any disconnect between muscle blood flow and metabolism by overlaying the activity of central command.[97] The second viewpoint is that the metaboreflex is responsible for a tonically, active feedback to the cardiovascular control area that is activated once muscle contraction occurs.[2,3]

The hemodynamic response to the metaboreflex is an increase in arterial blood pressure.[26,106,115] The increase in systemic vascular resistance is thought to create this

cardiovascular adjustment because the periphery is undergoing sympathetic vasoconstriction.[106,115] Heart rate is also affected by this reflex; in fact, it strongly depends on the setting of metabolic activation.[97] Despite the fact that it is understood that the exercise pressor reflex is induced by contraction-induced metabolites, the exact nature of it is not known and is thought to be multifactorial. Specifically, bradykinins, cyclooxygenase products of arachidonic acid, lactic acid, purines, ATP, and adenosine all stimulate the exercise pressor reflex.[51]

The mechanoreflex has also been shown to produce a cardiovascular reflex. Within humans, the exercise pressor reflex can be evoked by the mechanical distortion of receptive fields of sensory nerve endings in the contracting muscle.[42,59] It appears that the main effect of mechanoreflex activation is inhibiting cardiac vagal tone which produces a rapid and sustained increase in heart rate at the onset of exercise.[67,100] This is either done by directly creating mechanical stimuli or by modifying the mechanical response by a chemical mediator.[20] However, mechanoreflex has been hard to distinguish from metaboreflex activation. Evidence suggests that mechanoreceptors are sensitive to metabolite accumulation, thus enhancing the sympathetic response that arises from their activation; therefore, this makes it difficult to distinguish true mechanostimulation from metabostimulation.[96] The damage of one or more of the cardiovascular parameters controlled during the metaboreflex can lead to an altered hemodynamic response, which can be seen in various cardiovascular and metabolic diseases such as hypertension, metabolic syndrome, obesity, and type I and 2 diabetes mellitis.[97]

Combined Effects of Exercise Pressor Reflex

An animal study done on rats by Stone et al. measured the effects of combined receptor blockade that is required to attenuate the exercise pressor reflex. Initially, the

researchers of this study individually blocked purinergic 2X (P2X) receptors, acid-sensing ion channel 3 (ASIC3) channels, and EP4 receptors.[125] Lactic acid, prostaglandin E_2 (PGE_2), and adenosine triphosphate (ATP) are all substances produced during muscular contraction.[4,88,114,127] The muscle interstitium, where many nerve endings of the Group III and IV afferents are located, is where all of these substances accumulate during exercise.[125] The role these substances play in the exercise pressor reflex is controversial. The researchers found that individually blocking each receptor had minimal effects on the exercise pressor reflex. Instead, it was the blockade of all three receptors that attenuated the exercise pressor response. They found that the peak pressor response was reduced by 27% and the overall pressor component of the reflex was reduced by almost half. The blockage of one receptor did not have an effect on the exercise pressor reflex because the remaining input from the other receptors helped compensate and stimulate the reflex at its preblockade magnitude. Contrarily, removing all three receptors caused a reduction in the afferent input to the dorsal horn of the spinal cord that made the reflex insufficient in maintaining the preblockade magnitude.[125]

The cardioaccelerator response to contraction was not affected despite the response of a reduction in blood pressure. The authors of the study interpreted this finding as the receptors not having an effect on the metaboreflex control in rats. On the other hand, the decrease in baroreceptor stimulation observed before combined blockade caused by an attenuated pressor response could be a possible explanation to the researchers' findings of the combined blockade not decreasing the cardioaccelerator response to contraction. As a result, the reduced baroreflex opposed the effect on heart rate of a reduced exercise pressor reflex, thus resulting in an identical cardioaccelerator response to contraction before and after combined blockade.[125]

In summary, the metabolite receptors of the group III and IV afferents work together in order to maintain the exercise pressor reflex. If there is a blockage, the receptors can compensate for that reduction in order to maintain the reflex. Additionally, there is still the stimulation of mechanoreceptors that can be found in the exercise pressor reflex.

Chapter 5: The Effect of Type I and II Diabetes on the Autonomic Control of Circulation

As stated in the previous chapter, the exercise pressor reflex causes an increase in sympathetic activity which in turn increases cardiac output and peripheral vasoconstriction. However, the mechanisms involved in the metaboreflex response are constantly dependent on whether there is a rise in cardiac output, and this can be seen in those with diabetes.[63]

Diabetic patients are prone to cardiovascular diseases such as hypertension, atherosclerosis, congestive heart failure, and cardiac autonomic neuropathy.[134] High morbidity and mortality rates are associated with patients with autonomic neuropathy because it is one of the most common complications of diabetes mellitus.[136,147] Many believe that the increased mortality rate may be related to the disorders within cardiovascular control, which include impairments in autonomic reflex control.[32]

It has frequently been described that individuals who have Type I diabetes have a reduction in catecholamine levels during exercise. A sympathetic deficit is created because adrenaline tends to not respond to hypoglycemia in these individuals.[113] An almost complete loss of response of glucagon is seen within these individuals. Normally, adrenaline is the response for hormonal counterregulation when an individual is glucagon deficient; however, the adrenaline responses are blunted.[11] Several studies support the idea of there being an association with autonomic neuropathy and hypoglycemia in Type I diabetes; however, there are others that disagree.

DIABETIC NEUROPATHY

Diabetic neuropathy incorporates dissimilar disorders that involve proximal, distal, somatic, and autonomic nerves. It is capable of being an acute, self-limiting

condition or a chronic, indolent condition because it can affect distinct regions of the nervous system.[136] The causative factors include persistent hyperglycemia, microvascular insufficiency, oxidative and nitrosative stress, defective neurotrophism, and autoimmune mediated nerve destruction.[136] Diabetic neuropathy is the most common and taxing complication when it comes to diabetes mellitus. The neurological complications associated with diabetic neuropathy equally occur in type I and type II diabetes mellitus as well as in other forms of acquired diabetes.[35] For example, due to the precursor of gangrene and limb loss, foot ulceration is a major morbidity associated with somatic neuropathy. Neuropathy accounts for more hospitalizations than all other shared diabetic complications and is responsible for 50-75% of non-traumatic amputations.[14,60] The quality of life for a patient with diabetic neuropathy is tremendously impacted because weakness, ataxia and incoordination predisposing to falls and fractures are caused.[140] Life for these individuals can become quite bleak and the mortality rate approximates 25-50% within 5-10 years once autonomic neuropathy sets in.[80,110]

Different types of diabetic neuropathy can often coincide in the same patient.[136] Different types of neuropathies progress differently, and this is a way to separate them into separate entities. Sensory and autonomic neuropathies generally progress gradually.[143] The progression is related to the glycemic control of both types of diabetes mellitus.[30,31] Patients presenting with painful neuropathy typically have impaired fasting glucose or impaired glucose tolerance and are typically overweight and have autonomic dysfunction 50% of the time.[122] Soon after the onset of type I diabetes is when the most rapid deterioration of nerve function occurs; then within 2-3 years, the progress slows and the slope to the curve of dysfunction shallows. Conversely, type II diabetes shows a slowing of nerve conduction velocities as being one of the earliest neuropathic abnormalities that is often present after diagnosis.[148] There is a positive correlation to the

duration of diabetes and the level of impairment because after diagnosis, the slowing of nerve conduction velocities generally progresses at a steady rate of approximately 1m/sec/year.[136]

Pain in Diabetic Neuropathy

Pain is a common reason for patient visits in a primary care setting. About 2.7 million patients have painful neuropathy in the US.[136] Chronic pain may be nocioceptive or neuropathic. Nocioceptive pain "occurs as a result of disease or damage to tissue wherein there is no abnormality in the nervous system or there may be no somatic abnormality."[133] Contrarily, neuropathic pain is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."[133] It can come from neuronal dysfunctions along the most peripheral part of the somatosensory system, such as the nocioreceptor terminal membrane, to the cortical neurons within the somatosensory system. Peripheral sensitization may be induced by nerve damage. The release of inflammatory mediators activates intracellular signal transduction pathways in the nocioreceptor terminal and is related to the peripheral sensitization. The activated intracellular signal transduction pathways prompt an increase in the voltage-gated ion channels and the production, transport, and membrane insertion of transducer channels.[5,22] Following nerve damage, various voltage-gated sodium channels are up-regulated at the site of lesion and the dorsal root ganglion membrane. This promotes ectopic spontaneous activity along the primary afferent neuron and determines hyperexcitability that is related to a decreased activation threshold, hyper-reactivity to stimuli, and irregular release of neurotransmitters.[5] Consequently, because of this hyperactivity in the primary afferent nocioceptive neurons, neuron hyperexcitability higher up in the central nervous system and dorsal horn of the spinal cord may occur as

secondary changes.[136] This is known as central sensitization and is a form of use-dependent synaptic plasticity which is considered a major pathophysiological mechanism of neuropathic pain.[22]

It is becoming clearer that the contributing factors causing pain have strong neuro-endocrine, autonomic, pro-inflammatory, and neuro-degenerative influences.[10,94,109,118] Increasing evidence has supported the role of inflammatory cytokines such as IL6, TNFa, chemokines, adhesion molecules and acute phase reactants, and activation of the oxidative/nitrosative stress pathway invoking NFkb, all playing an important role in the complex relationship among the macrophages, adipose tissue, and glial and dendritic cells in the nervous system.[118] A study done by Martinez-Lavin demonstrated that the infusion of norepinephrine heightens the pain experienced.[84] Also, with the increases in the circulation of IL-6, IL-8, and IL 1-ra, there is a significant effect of chronic pain on immune function.[142] IL-8 is a proinflammatory cytokine responsible for mediating sympathetic pain; IL 1-ra contributes to stress; and IL-6 is involved with stress, fatigue, hyperalgesia, and depression and activates sympathetic pain.[142]

Out of all the complications associated with diabetes, diabetic periphery neuropathy is the most common because it is seen in both type I and type II diabetes with similar frequency. According to the Toronto Diabetic Neuropathy Expert Group, diabetic peripheral neuropathy is defined as being a symmetrical, length dependent sensorimotor polyneuropathy attributable to metabolic and microvascular alterations as a result of chronic hyperglycemia exposure, such as diabetes, and cardiovascular risk covarities.[129] It can be subdivided into focal/multifocal neuropathies, such as diabetic amyotrophy, and symmetric polyneuropathies, including sensorimotor polyneuropathy, which is considered the most common.[136] Loss of thermal and pain perception is a result due to the loss of small fiber-mediated sensation, whereas the loss of touch and vibration perception

results from the large fiber impairment. “Positive” symptoms, such as paresthesias and pain, may also occur due to sensory fiber involvement. Patients may also experience negative symptoms such as numbness in the feet and legs which in time can lead to painless foot ulcers and subsequent amputations if the neuropathy goes unnoticed and treated. Unsteadiness may also be seen frequently due to abnormal proprioception and muscle sensory function.[136]

Diabetic peripheral neuropathy is frequently paired with the autonomic nervous system and classified as diabetic autonomic neuropathy. It rarely causes severe symptoms, but in its cardiovascular form the risk for mortality can increase at least a three-fold.[12,137-139,149]

Autonomic Neuropathy

Blood glucose levels are normally maintained during starvation or increased insulin action by an asymptomatic parasympathetic response with mild hypotension and bradycardia, followed by a sympathetic response with epinephrine and glucagon secretion for short-term glucose counterregulation, and growth hormone and cortisol secretion for long-term regulation.[92] The catecholamine release acts as an alert for patients to take the necessary measures to prevent coma due to low blood glucose. When a patient doesn’t have these warning signs of imminent neuroglycopenia it is called “hypoglycemic unawareness” and is a symptom of autonomic neuropathy.[92] The absence of glucagon and epinephrine responses to hypoglycemia induced by a normal, consistent dose of insulin confirms the failure of glucose counterregulation.[92] Studies have shown that due to the reduction in catecholamines, the maximal tolerable workloads and maximal oxygen consumption are reduced.[111] Those with type I diabetes mellitus and

autonomic neuropathy have an absence of the glucagon and adrenaline response, and this defect is considered to be irreversible.[11,136]

Studies That Do Support Hypoglycemia and Autonomic Neuropathy

Hypoglycemia primarily develops because of therapeutic insulinemia and may develop into a more severe episode because of the impaired responses of the counterregulatory hormones.[11] As stated above, the response during exercise of catecholamines to hypoglycemia is blunted in patients with type I diabetes mellitus; thus, suggesting that there is a loss of sympathetic response to various stimuli. An elevated sympathetic drive is vital to the metaboreflex; therefore, impairment to the sympathetic system can affect the hemodynamic responses to metaboreflex recruitment.[113]

A study done by Roberto suggested that patients with Type I diabetes without autonomic neuropathy were unable to elevate sympathetic tone which blunts the mean blood pressure response to the metaboreflex. Compared to the controls, the catecholamine levels were reported to be lower in the diabetic subjects; type I diabetic patients exhibited a reduced capacity to increase systemic vascular resistance in response to the metaboreflex; stroke volume was higher during the metaboreflex in the type I diabetic patients than in the controls.[113] All of this indicated that the cardiovascular regulation was altered in the patients with type I diabetes. A speculation that has been made for this phenomenon is that autonomic failure may be an outcome because of continuous incidents of overt or subclinical hypoglycemia that may reduce the capability to initiate sympathetic tone.[43,89,113] Despite these results being found in patients without autonomic neuropathy, similar results have been found in patients with the disorder.

For short durations, adrenaline responses tend to be normal or reduced in type I diabetics, but in the long-term, they tend to become blunted. Autonomic neuropathy,

hypoglycemia-associated autonomic failure, and diabetes are all proposed possible causes.[11] Bottini et. al conducted a study measuring the effects diabetic autonomic neuropathy and hypoglycemia in patients with postural hypotension and diabetic neuropathy and in patients without postural hypotension and with diabetic neuropathy. The results found that in type I diabetic patients without clinically overt autonomic neuropathy, the responses of adrenaline to hypoglycemia were blunted in comparison to the nondiabetic subjects.[11] Contrarily, in the presence of autonomic neuropathy, the responses of adrenaline to hypoglycemia in patients with type I diabetes were even further reduced.[11] These results indicate that autonomic neuropathy further impairs the adrenaline response to hypoglycemia. A study done by Dagogo-Jack found similar results.

Both studies demonstrated that autonomic neuropathy in its stage of predominant parasympathetic involvement concerning the cardiovascular reflexes is associated with marked deficiency of adrenaline responses to hypoglycemia. In the Bottini study, this was found in the patients that had diabetic autonomic neuropathy but lacked postural hypotension. This deficiency appears to be as severe as that in patients with more severe autonomic neuropathy i.e. patients with diabetic autonomic neuropathy and postural hypotension in the Bottini study.[11] Lastly, the Bottini study indicates that patients with type I diabetes and without diabetic autonomic neuropathy have a deficient adrenaline response to hypoglycemia, but rather than being absolutely selective it is relatively selective because it is largely preserved in response to a stimulus that is different from hypoglycemia.[11]

Studies That Do Not Support Hypoglycemia and Autonomic Neuropathy

On the contrary, there are studies that disagree with the explanation of diabetic autonomic neuropathy being the suggested etiology for the cause of defective adrenaline secretion in insulin-dependent diabetics. RE Ryder is one of these researchers who felt that the studies that attributed diabetic autonomic neuropathy to the cause of defective adrenaline secretion used limited assessments of autonomic function; therefore, the present study used more extensive investigations to reexamine the relations between autonomic neuropathy, hypoglycemic unawareness, and inadequate hypoglycemic counterregulation.[117]

There were five groups of patients: the controls, patients with adequate counterregulation, patients with inadequate counterregulation, patients with adequate counterregulation but without autonomic neuropathy, and patients with autonomic neuropathy. Out of the seven patients that had autonomic neuropathy, only one had marginal results that were for inadequate hypoglycemic counterregulation and the rest had sufficient counterregulation. Out of the seven patients that had inadequate counterregulation, there was little evidence of autonomic neuropathy. There is evidence suggesting that diabetic autonomic neuropathy is symmetrical polyneuropathy that affects the longest fibers first, similar to diabetic peripheral neuropathy of the sensory type.[131,132] Consequently, sweating abnormalities in the feet may be present in advance of abnormalities that were evident in the cardiovascular autonomic function tests which is one of the tests performed in the study.[117] Moreover, if diabetic autonomic neuropathy affects the longest fibers first and is present anywhere in the body, then it should also be present on the feet. In this study, only one out of seven patients with inadequate hypoglycemic counterregulation had an abnormal sweatspot test result, making autonomic neuropathy as cause for the defect unlikely.

It is true that patients with autonomic denervation have reduced adrenaline responses to hypoglycemia, but they also have increased sensitivity to catecholamines.[57] Ryder accounts the sensitivity to catecholamines to the patients of their study with autonomic neuropathy not having inadequate hypoglycemic counterregulation or unawareness of hypoglecemia.[117] According to the authors, the attribution of the unawareness of hypoglycemia to diabetic autonomic neuropathy is erroneous. The results of this study therefore suggest that there is no relation between autonomic neuropathy and either unawareness of hypoglycemia or the hypoglycemic counterregulatory defect and these problems have an entirely different etiology. Instead, the etiology thought to be the reason behind this phenomenon is that the autonomic activity during hypoglycemia is abnormally diminished rather than the cause being autonomic neuropathy, meaning that the nerves are present but are not being activated.[117]

Another study done by Hoffman assessed whether the pathogenesis of the decreased response of catecholamines in children and adolescents with type I diabetes is due to the relationship to autonomic neuropathy or hyperinsulinism. The authors found that after insulin withdrawal, there is a diminished catecholamine response to hypoglycemia compared to the control subjects and that short-term intensive insulin therapy reduces the response further.[58] Therefore, the suppression of the catecholamine response is due to hyperinsulinism, and there was no evidence for the role of autonomic neuropathy as an explanation for this suppression.[58]

Chapter 6: Conclusion

In conclusion, the effect of diabetes mellitus on the exercise pressor reflex is unknown. The majority of the studies that have been done on this topic are on diabetic individuals that are insulin-dependent, and is likely because hypoglycemia is a common clinical problem found in insulin-dependent diabetics whereas type II diabetics more commonly experience hyperglycemia.[111] It is possible for a type II diabetic to be hyperglycemic, but it is not common.[111] Therefore, I will only focus on individuals with type I diabetes.

Based on the reported studies, I believe that a patient with type I diabetes will still have an exercise pressor reflex; however, the reflex will be weaker and unable to be sustained for a long period of time or at a high workload due to autonomic neuropathy. Not many studies have been done on patients with type II diabetes; however, I believe that they will experience greater sympathetic tone in the exercise pressor reflex compared to the type I diabetics but will have lesser sympathetic tone than a healthy individual.[113] My deduction can be supported by the following studies.

Impairment in Heart Rate and Blood Pressure

The first study found impairment in the increase of heart rate and a lower blood pressure and aerobic capacity in patients with diabetic neuropathy. Circulatory and metabolic adjustments during exercise are generally considered important in the changes within the autonomic nervous system.[116] Hilsted and colleagues did a study determining whether the decreased beat-to-beat variation in heart rate during deep respiration implies that the blood pressure and heart rate responses to exercise capacity are impaired in diabetics.[55] The study revealed dysfunction of the sympathetic and parasympathetic regulation during graded exercise in diabetic autonomic neuropathy. Six similarly aged,

type I diabetics with the mean duration of diabetes for 15 years participated in the study. They had signs of autonomic neuropathy meaning that they had a decreased beat-to-beat variation in heart rate during deep breathing. Seven control patients of similar age and duration of diabetes also participated in the study. The participants had to perform graded exercise on an ergometer cycle until exhaustion.

The resting heart rate was higher and the increase in heart rate at the lowest workload was lessened in the patients with autonomic neuropathy compared to the control group, thus indicating a vagal defect.[55,82] For a given type of exercise in healthy people, the oxygen uptake in percent of the maximal oxygen uptake has a closer relationship to the increased sympathetic outflow to the heart and to peripheral resistance vessels than does the actual work load.[18] This is because the body size and degree of training dictate the amount of stress caused by a certain work load.[55] With that said, in this study, the patients with decreased beat-to-beat variation needed to be more stressed in order to reach a given heart rate when compared to the controls. An interesting finding in this study is that when the autonomic neuropathy diabetic subjects were given atropine, a parasympatholytic drug, and propranolol, a beta blocker, the relationship between heart rate and relative work load corresponded exactly to that seen in the normal subjects.[38,55]

A REDUCTION IN MAXIMAL OXYGEN UPTAKE

Many studies had similar findings that the VO2 max was reduced in subjects with diabetic neuropathy when compared to the subjects with diabetes but without neuropathy[55,72] that the exercise-induced increases in catecholamines, cortisol, and growth hormones are depressed.[56] In the Kremser article, the oxygen uptake kinetics was measured during exercise in patients with diabetic neuropathy. Seven diabetic patients with peripheral sensory and cardiac autonomic neuropathy were measured against eight

diabetics without neuropathy, and eight normal subjects. The maximal oxygen uptake, ventilatory anaerobic threshold, and oxygen uptake kinetics were assessed. In the patients with diabetic neuropathy, the VO2 max was reduced compared to the diabetic and normal participants.[72] However, the ventilatory anaerobic threshold showed no difference between the groups. Importantly, during the constant-load exercise at 40% VO2 max, the estimated cardiac output and the time constant were similar in all groups. Kremser and colleagues believe that the instantaneous increase in the maximal oxygen uptake and cardiac output at exercise onset in diabetes with weakened neurogenic reflexes is primarily caused by metabolic and mechanical events in the exercising muscle that cause venous compression and vasodilation.[72]

One of the possibilities attributed to the reduction in VO2 max by Kremser and colleagues was insulin deficiency. The depletion of muscle glycogen stores can deprive the muscle of the substrate needed for performance of heavy exercise. However, the researchers found similar levels of glycosylated hemoglobin during the time of exercise, which indicated similar degrees of glucose homeostasis for months prior to the study.[72] Additionally, the researchers normalized the blood glucose levels twelve hours before and during exercise; so, insulin deficiency is not an explanation for a reduction in VO2 max in neuropathic diabetics according to Kremser and colleagues.[72]

The sympathetic nervous system during maximal exercise stimulates the heart and peripheral circulation in order to increase heart rate and contractile force, to maintain perfusion pressure throughout the body while redirecting cardiac output toward the exercising muscle, and to maintain a pressure gradient for venous blood pressure as it returns to the heart.[123] In support of Hilsted article, Eckberg et al. demonstrated that patients with peripheral and parasympathetic nervous system abnormalities also exhibit a dysfunctional sympathetic nervous system.[36] The participants of the study exhibited

reduced basal plasma norepinephrine concentrations, blunted heart rate and norepinephrine concentration changes in response to baroreceptor stimulation, and a greater than normal increase in blood pressure in response to phenylephrine infusion, which indicated denervation hypersensitivity.[36] In the Kremser study, the absence of parasympathetic control of the heart rate and extensive peripheral sensory neuropathy among neuropathic diabetics is believed to suggest defects in sympathetic nervous control, which may play an important role in VO2 max reduction seen in these patients.[72]

The blood lactate threshold in the diabetic subjects with neuropathy was normal despite a reduced exercise cardiac output; however, the mechanism that maintains a normal blood lactate is unknown.[72] Additionally, contraction is achieved from high-energy phosphates and muscle stores of oxygen and from the conversion of muscle glycogen stores to lactate during the first few minutes of exercise before VO2 reaches a new steady state.[78] Because a normal time constant for VO2 is preserved, this may suggest that muscle glycogen stores during the transition from rest to exercise are not unduly exerted by diabetic neuropathy. This is important especially during periods of insulin deficiency when there is a depletion of glycogen stores due to a lack of extracellular substrate for glycolysis.[72]

The diabetics with neuropathy in this study exhibited a preservation of a normal phase I VO2 which was similar to normal subjects. This means that during the first 15s of exercise, before venous blood from the legs has reached pulmonary circulation, the arteriovenous difference was essentially unchanged.[37] The increase of VO2 occurring during this period is a result of an increase in cardiac output as well as stroke volume.[72] Because the phase I VO2 was unchanged, this suggests that a substantial portion of the immediate increase in blood flow at the beginning of exercise is comprised of nonneurogenic influences.[72] An animal study done by Guyton et al. demonstrated that

cardiac output increased even when the sympathetic nervous response was blocked by hexamethonium.[49] This increase seen in cardiac output was a result of mechanical compression of skeletal muscle veins.[72] It is likely that the local metabolic factors that induce vasodilation played a role by facilitating cardiac emptying.[123]

HYPOGLYCEMIA AND A REDUCTION IN CATECHOLAMINES AND HORMONES

The plasma concentrations of norepinephrine and epinephrine are exaggerated in exercise-induced increments in poorly controlled insulin-dependent diabetics; as a consequence, there are increases in heart rate and plasma concentrations of free fatty acids and glucose.[16,128] Contrastingly, better-controlled diabetics may develop hypoglycemia during or after exercise. This observation can be explained by serum insulin not being suppressed during exercise. Thus, an adequate increase of hepatic glucose production may not occur.[111,141]

Diabetic patients with autonomic neuropathy tend to have a severely impaired exercise performance. The adrenergic activity is deficient, so the maximal tolerable work load, the maximal heart rate, and the maximal oxygen uptake as well as the plasma catecholamine concentrations during maximal work load are lower than diabetic patients without neuropathy.[56,57] According to Christensen and Galbo, the plasma concentration of norepinephrine has a close relationship to pulmonary arterial oxygen saturation and increases in proportion to the workload.[15] This is in concordance with the Kremser and Eckberg studies presented earlier.

In a healthy individual, plasma epinephrine is dependent on the general level of sympathetic nervous activity,[17] which is reflected by plasma norepinephrine, as well as on the plasma glucose concentration.[111] When plasma glucose begins decrease, plasma epinephrine tends to increase; however, it is only once norepinephrine has increased that

epinephrine then increases.[44] The increase in plasma epinephrine is most likely a response to maintain normoglycemia during prolonged exercise. As a result, lipolysis is enhanced, there is a stimulation of hepatic glycogen breakdown, and muscular glycogen breakdown is enhanced during prolonged exercise.[15,111]

Many studies have been done on insulin-dependent diabetics and hypoglycemia, which have been discussed more in depth in earlier sections. In summary, there is a diminished catecholamine response that is primarily due to the decrease in plasma epinephrine.[11,57,58,92,113,117,120] In patients with diabetic neuropathy, the defective responses of adrenaline to hypoglycemia were further reduced.[11]

THE EXERCISE PRESSOR REFLEX IN DIABETIC PATIENTS

The Roberto study is probably the first, if not the only, study that focuses on the hemodynamic response to the muscle metaboreflex in type I diabetics. Roberto and colleagues assessed the hemodynamics during the metaboreflex in patients with type I diabetes mellitus.[113] There were 14 type I diabetics and 11 healthy controls in the study. The individuals had to perform at a workload that increased linearly on an ergometer until exhaustion. The results that were observed were a blunted blood pressure response in the patients with diabetes compared to the controls, a reduced capacity to increase systemic vascular resistance in the diabetic subjects, and higher stroke volumes as a consequence of reduced cardiac afterload in the diabetic subjects compared to the control subjects.[113] Ultimately, the cardiovascular regulation was altered, and there was a reduced capacity to increase sympathetic tone in the patients with type I diabetes. The findings of a blunted mean arterial blood pressure are indicative of some form of autonomic failure, even if autonomic neuropathy is not evident.[9,11,120] As seen in previous studies, the catecholamine levels were reported as being lower than the control group.[113] Repeated

episodes of subclinical hypoglycemia have been thought to be an explanation for this.[43,89,113] This is because at an early age, this reduction in sympathetic activity appears to be well tolerated in type I diabetics and the exercise capacity of these individuals was normal.[43] Yet, this condition could decline gradually and lead to symptomatic indicators of sympathetic deficit.[113]

Along with the blunted mean blood pressure response, the ability for the patients with type I diabetes to increase the systemic vascular resistance, i.e. create arteriolar vasoconstriction, was impaired. This observation further supports the indication of there being an autonomic deficit in these subjects. However, the researchers found that these patients compensated for the deficit by increasing their stroke volume with respect to the controls. This occurrence led to a more evident cardiac output response in the group with diabetes compared to the controls during the metabolic reflex. In the researchers' opinion, a reduced cardiac afterload was the consequence of the observed stroke volume in these patients, which probably caused a more proficient cardiac emptying.[113]

The heart rate between groups was very similar, which speaks against the reduced sympathetic tone phenomenon in the diabetic patients. The reduction in the baroreflex stimulation could be an explanation for this occurrence, since the mean blood pressure was blunted compared to the control group. Because the baroreflex acts as a buffer increasing parasympathetic tone at the sinus node during the induced increase of sympathetic tone during the metaboreflex, it is possible that there was a reduction in both parasympathetic and sympathetic tone that took place in the diabetic patients.[113] At the sinus node, the metaboreflex activation led to a similar sympatho-vagal balance in both groups, so the heart rate power spectrum between the groups was not different.

The data presented in the Roberto study support the idea that the metaboreflex-induced increase in blood pressure is the consequence of both systemic vascular

resistance and cardiac output increments.[113] There are studies that found conflicting results[7,99]; however, other studies support the findings in the Roberto study that the metaboreflex-induced increase in blood pressure relies on a flow-mediated mechanism.[101] An animal study done on dogs found that the mechanisms responsible for the muscle metaboreflex response continuously depend on whether a rise in cardiac output occurs. In other words, a rise in cardiac output determines whether vasoconstriction occurs.[63] According to the authors of this study, their findings appear to be in line with the concept that the rise in blood pressure during the metaboreflex was because there was an increase in cardiac output.[113]

DISCUSSION

Again, the Roberto study was not performed on individuals with diabetic neuropathy; however, the study confirms that in a diabetic individual that is insulin-dependent, the exercise pressor reflex will be blunted. I believe that only at high intensities (i.e. at maximal and submaximal exercises) the exercise pressor reflex will truly be affected and not work as efficiently. This is because the exercise pressor reflex is made up of two parts: the metaboreflex and the mechanoreflex. It is also highly dependent on sympathetic activation. Diabetic neuropathy only affects the sympathetic and parasympathetic branches of the nervous system, thus indicating that the production of metabolites is affected i.e. the metaboreflex. According to Hilsted, the increase of catecholamines, cortisol and growth hormones are depressed during exercise.[56] If there is a depression of the hormones that help makeup sympathetic activation, then in regards to the blood vessels, there will be a deficit of sympathetic tone. If sympathetic tone is decreased, the mean arterial pressure will be reduced. Having already been observed in the Roberto study, the blunted mean blood pressure resulted in a decrease in the

baroreflex, which could possibly be explained by a reduction in both sympathetic and parasympathetic tone in diabetic patients.[113] Ultimately, this will lead to a diminished exercise pressor reflex.

To my knowledge, not many studies have been done on the production of the algesic substances during exercise that stimulate the nociceptors in patients with diabetes, specifically with diabetic neuropathy. Because the parasympathetic and sympathetic stimulation is deficient in these individuals, I am making the assumption that the nocioceptors of the Group III and IV afferents will be affected and their activation will be decreased. This is because in order for the metaboreflex to continue firing, there needs to be an accumulation of metabolic products in the contracting muscle,[97] which I believe will not occur as quickly because the parasympathetic and sympathetic stimulation are reduced. The mechanoreflex, which responds to skeletal muscle contractions, can still function only until muscle glycogen stores are depleted, as discussed in the Kremser article. This goes along with the Hilsted findings that the exercise performance and the maximal tolerable workload in a patient with diabetic neuropathy will be severely impaired.[55] Overall, I believe that the ergoreceptors of the group III and IV afferents will be unaffected because their stimulation is skeletal muscle contraction. They will only be affected when the working skeletal muscle is unable to contract due to a shortage of oxygen supply and energy availability at higher intensity levels.

At low to moderate intensities of exercise it is still possible for a patient with moderately well-controlled diabetes to use free fatty acids and ketones as a source of energy[8] despite these circulating levels being lower in diabetics compared to normal individuals.[120] Therefore, I believe that the mechanoreflex still would be able to work, not maximally, but efficiently. The production of free fatty acids could enhance liver gluconeogenesis,[46] thus releasing more glucose into the plasma and providing more

energy for the contracting muscle. Secondly, because the metabolism is not being overly stressed and the oxygen demands of the working muscle are compatible with the metabolism, the metaboreflex should work efficiently as well.[97] I believe that the ergoreceptors and nocioreceptors will still be activated at low to moderate intensities only until the plasma catecholamine levels begin decreasing as the duration of exercise continues.

Schneider et al. investigated the metabolic and hormonal response to exercise in individuals with type I diabetes. The subjects were exercised at 60% to 65% of their VO2 max for 60 minutes. The findings of the study were similar to the numerous studies that measured the levels of catecholamines in the blood. The increments of epinephrine and norepinephrine were lower in individuals with diabetes compared to those without. Hypoglycemia was found during and after exercise in the group with type I diabetes. The authors of this study do not believe that the hypoglycemia and subnormal catecholamine response is due to autonomic neuropathy but instead due to hyperinsulinemia. They found that only after 30 minutes of exercise were there significant differences found in the levels of norepinephrine and epinephrine.[120]

As I stated, I believe the researchers came to this conclusion because the individuals were working at moderate intensity. The previously discussed studies that concluded that hypoglycemia was due to autonomic neuropathy used exercise tests that pushed the participants to exhaustion thereby working at high VO2 levels. I believe that had the researchers of this study used comparable methods seen in the other studies, their findings would have been different if not similar.

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