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Sex Differences in the Oxygen Uptake Kinetic Response to Moderate Intensity Exercise in Obese Adolescents

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SEX DIFFERENCES IN THE OXYGEN UPTAKE KINETIC RESPONSE TO

MODERATE INTENSITY EXERCISE IN OBESE ADOLESCENTS

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Health and Movement Sciences at Virginia Commonwealth University.

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Table of Contents

List of Tables

List of Figures

Abstract

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The oxygen uptake (VO_2) kinetic response to exercise provides insight into aerobic

performance and the efficiency of the body to maintain oxygen demand during the initiation

of exercise. Previous research in normal weight children reports insignificant differences in

gender VO_2 on-kinetic responses to moderate exercise. No study has evaluated the impact

obesity may have on gender VO_2 on-kinetics. **PURPOSE:** To determine if sex differences

exist in the VO_2 kinetic response to moderate exercise in obese adolescents. **METHODS:**

Male (n=16) and female (n=39) adolescents completed a graded exercise test to exhaustion on

a treadmill. Data from initial 4-min treadmill walking was used to determine a time constant.

RESULTS: The time constant was significantly different (P=0.009) between obese male and

female adolescents (15.42±7.31 s vs. 22.03±8.56 s, respectively). **CONCLUSION**: Sex

differences exist in VO_2 on-kinetics during moderate exercise in obese adolescents indicating

an enhanced potential for males to deliver and/or utilize oxygen.

Review of Related Literature

Oxygen Consumption

Consumption of oxygen (VO_2) provides the energetic basis of physiology. At rest, almost all oxidative phosphorylation, or aerobic metabolism, meets energy demand to maintain homeostasis of the human body. As activity level increases, the working muscles will increase the energy production in proportion to the demand of the activity. An individual's ability to produce energy is dependent upon oxygen consumption. Oxygen consumption is determined by the rate at which oxygen is delivered to the tissue, the oxygen carrying capacity of blood, and the amount of oxygen extracted from the blood. The consumption of oxygen within any tissue can be illustrated by the Fick equation: $VO_2 = Q_T \times (CaO_2 - CvO_2)$

Q_T represents tissue blood flow (L/m), while CaO_2 and CvO_2 represent arterial and venous oxygen content. The difference in CaO_2 and CvO_2, termed arteriovenous oxygen difference (a-VO_2 diff), represents the amount of oxygen extracted from arterial blood by the tissue to support oxidative phosphorylation within the cell's mitochondria. A-VO_2 diff depends on the rate of diffusion of oxygen from blood into the cell and the mitochondria's capacity to utilize oxygen. Hence, the rate of oxygen diffusion is directly affected by the oxygen carrying capacity of blood, in turn determined by hemoglobin (Hb) concentration and the degree of Hb saturation (Guyton & Hall, 2006; Brooks, Fahey, & Baldwin, 2005). Tissue blood flow is regulated by cardiac output

(stroke volume X heart rate) and the amount of vasodilation (total peripheral resistance; TPR) within the vascular beds of active tissue, along with pressure changes across the tissue.

Heart rate and stroke volume are important factors that contribute to the increase seen in cardiac output during exercise. During a constant workload of submaximal exercise, heart rate increases and levels off as oxygen requirement of the activity is satisfied. Additionally, according to the Frank-Starling law of the heart, myocardial stretch will increase (determined by the amount of venous return), raising ventricular pressure thus result in a greater stroke volume. In summary, localized oxygen consumption depends upon oxygen delivery mechanisms (central factors), as well as the extraction and utilization of oxygen in the tissue (peripheral factors) (Guyton & Hall, 2006; Brooks et al., 2005).

Oxygen consumption and cardiac output increase in parallel to each other with increasing levels of work rate. Cardiac output is specifically regulated by the pumping ability of the heart and factors affecting blood flow from peripheral veins back into the heart. Under normal conditions, long term cardiac output level varies reciprocally with changes in TPR. When TPR increases, cardiac output will fall; conversely as TPR drops, cardiac output will increase. An individual with heart failure would exhibit a reduced cardiac output therefore limiting arterial oxygen transport during exercise, ultimately leading to a mismatch between oxygen supply and oxygen demand of skeletal muscle.

Exercise training has been shown to induce beneficial effects on exercise tolerance and peripheral vascular abnormalities in heart failure patients (Roditis et al., 2007; Gerovasili et al., 2009). Gerovasili and colleagues (2009) examined chronic heart failure patients following 3 months of rehabilitation to assess the effect of physical activity on the regulation of blood flow, tissue perfusion, oxygen delivery, and endothelial function. Patients who participated in the

study were randomly assigned to complete 36 sessions (over 12 weeks) of either aerobic training

at 50% of the baseline ramp test alternating 30 seconds of exercise with 60 seconds rest for 40-

mins, or a combination of 20-mins of aerobic training at the same intensity and 20-mins of

strength training.

Investigators continuously measured tissue oxygen saturation using Near-Infrared

Spectrometry (NIRS) during three minute of vascular occlusion before and after the intervention.

NIRS is a noninvasive technique that rapidly determines changes of local oxygen consumption

and blood flow in human skeletal muscle (Kawaguchi, Tabusadani, Sekikawa, Hayashi, & Onari,

2001*)*. Additionally, endothelial function was assessed by examining the resultant increase of

vessel diameter from induced reactive hyperemia via vascular occlusion. Following

rehabilitation, the reperfusion rate post venous occlusion increased significantly, thus researchers

suggest enhanced microcirculation is due to improvements in both oxygen reperfusion rate and

reactive hyperemia. The more rapid oxygen perfusion rate and improved vascular reactivity

could be attributed to decreases seen in peripheral vascular resistance (Gerovasili et al., 2009). A

drop in total peripheral resistance will quantitatively enhance cardiac output; therefore the 3-

month rehabilitation program successfully improved skeletal muscle oxygen consumption in

chronic heart failure patients.

Maximal Oxygen Consumption

Maximal oxygen consumption(VO_{2max}) is largely recognized as both a representation of

the functional limitations of the cardiovascular system as well as a measure of the integrated

capacity of the pulmonary, cardiovascular and neuromuscular systems to perform work in both

healthy and diseased populations (Hughson, Tschakovosky, & Houston, 2001). VO_{2max}, typically

expressed in terms of milliliters of O2 consumer per kilogram of bodyweight per minute (ml•kg $^-$

$^{1}\bullet$min $^{-1}$), determines an individual's physical work capacity and is defined as the highest rate at which oxygen is taken up and utilized by the body during maximal exercise (Bassett & Howley, 2000).

VO$_{2max}$ measurements are used for multiple purposes including the determination of aerobic power in athletes, to quantify the degree of impairment of cardiorespiratory fitness in clinical populations, and to asses change in response to exercise interventions. Measuring the rate of maximal oxygen consumption is commonly performed using a continuous or incrementally graded exercise test protocol in which work rate increases until the subject reaches volitional exhaustion. Achieving VO$_2$max implies a plateau in oxygen uptake regardless of additional increases in work rate. However, in clinical populations the highest VO$_2$ achieved by the subject can be reported as their peak VO$_2$ (VO$_2$peak) if no plateau is detected.

It is understood the mode of exercise, environment, individual characteristics, training, and disease status will reflect the achieved VO$_{2max}$ (Jones & Poole, 2005; Matsumoto et al., 1999) while improvements in VO$_{2max}$ are directly related to intensity, duration, and frequency of training (Pollock, 1977).

Helgerud and colleagues (2007) examined the effects of four 8 week training protocols on changes observed in VO$_{2max}$ values in healthy, moderately trained males. Subjects were randomly assigned to one of four groups: continuous run at 70% max heart rate (MHR) for 45 minutes (long slow distance; LSD); continuous run at lactate threshold (85% MHR) for 24.25 minutes (LT); 47 repetitions of 15 second intervals at 90-95% MHR with 15 seconds of active recovery at 70% MHR between each interval (15/15); or 4 x 4 minute interval training at 90-95% MHR with 3 minute of active recovery of 70% MHR between each interval (4 x 4) (Helgerud et al., 2007). The high aerobic intensity training of 15/15 and 4 x 4 min both revealed higher

absolute VO_{2max} responses of 5.5 and 7.3% respectively, (reflecting increases in VO_{2max} from 60.5 to 64.4 ml•kg^{-1}•min^{-1} and 55.5 to 60.4 ml•kg^{-1}•min^{-1}) over the LSD and LT training groups. Thus, high aerobic intensity training is significantly more effective than moderate and low and intensity training in improving VO_{2max} during an 8 week training period (Helgerud et al., 2007).

In addition to examining VO_{2max} pre- and post training, researchers measured cardiac output and stroke volume using the single breath acetylene uptake method (SB). It is estimated up to 85% of the limitation in VO_{2max} is due to maximal cardiac output (determined by stroke volume and MHR). Because less variation exists in MHR values of sedentary and trained individuals, the changes seen in cardiac output can be determined by changes in stroke volume (Bassett & Howley, 2000; Hill & Lupton, 1923). The SB procedure, performed during a workload close to their pre-determined VO_{2max}, is a breathing cycle initiated by complete emptying of the lungs, then maximal inspiration of a gaseous mixture, directly followed by a continuous expiration (Helgerud et al., 2007). The results of the SB assessment display a significant change in stroke volume from pre- to post training for the 15/15 and 4 x 4 min group, with the highest average stroke volume being 0.16 L·beat^{-1}, comparable to highly trained endurance athletes (Zhou et al., 2001). This experiment shows that improvements in VO_{2max} are followed by similar improvements in stroke volume indicating dependence between the two.

Similar improvements of VO_{2max} were seen in patients with coronary artery disease (CAD) who participated in a 10 week intervention of either LSD or 4 x 4 minute interval training (Rognmo, Hetland, Helegerud, Hoff, & Slordahl, 2004). Patients assigned to the LSD group displayed a 7% increase in VO_{2max}, whereas the 4 x 4 min interval training group exhibited a 17.9% increase in VO_{2max} following training (Rognmo et al., 2004). From the outcomes of these

studies, it can be suggested improvements in VO_{2max} are dependent upon baseline fitness level as shown with the significantly large training enhancements in the CAD patients compared to the healthy men from Helgerud's study (Helgerud et al., 2007; Pollock, 1977).

Energy Sources

Adenosine Triphosphate (ATP) is a chemical intermediate used to initiate and maintain homeostasis of muscle contractions. Energy derived from the oxidation of carbohydrates, fats, and proteins is used to convert adenosine diphosphate (ADP) to ATP which is then consumed by reactions necessary for muscle contraction. During the cyclic process of muscle contraction and recovery, ATP is hydrolyzed to ADP and inorganic phosphate (P_i), and ADP is phosphorylated back to ATP, respectively.

Glucose molecules are a final product of carbohydrate digestion and enter the muscle cell by way of protein carriers. After absorption into the cell, glucose can be used immediately for energy release (ATP formation), or stored in the form of glycogen within the muscle which can later be broken down to provide energy for the muscle cell. Limited ATP is present in the cytoplasm of all cells and is further created as glucose molecules oxidize. The released energy is then used to form new ATP. Formation of additional ATP becomes important during muscular contraction, as cells attempt to maintain a constant ATP concentration with varying rates of muscular activity.

At rest and in steady state exercise, oxidative phosphorylation meets 100% of the energy demands, signifying the precise control of ATP hydrolysis and synthesis during steady state exercise (Brooks, 1986) Cytosolic concentrations of ADP and P_i are important for the feedback mechanism between oxidative phosphorylation and ATPase activity, the enzyme responsible for ATP hyrdolysis. Therefore any variation of cytosolic ADP and P_i concentrations, due to

14

increasing work rates, will conversely control the rate of oxidative metabolism in the mitochondria resulting in the maintenance of cellular ATP concentrations (Balaban, 1990).

Skeletal muscle has three energy systems, used in power (or speed) and endurance activities. Oxygen consumption does not increase instantaneously to a steady state value at the start of exercise, thus anaerobic energy sources will be the first contributor for ATP production (Brooks, 1986). Immediate energy stores are used for power movements lasting only a few seconds. Exercise duration up to one minute will require muscles to rely mainly on glycolytic sources as well as immediate sources while oxidative mechanisms become increasingly important for activities lasting longer than two minutes (Balaban, 1990). It is important to keep in mind that these energy systems are not individually turned on and off as needed but operate by a mixture of metabolic systems with considerable overlap to develop the energy required for exercise.

During the transition from rest to exercise, the first source of energy used to reconstitute ATP is phosphocreatine (PCr). The enzyme, creatine kinase, is responsible for the rephosphorylation of ADP to ATP. However, the total amount of phosphocreatine in skeletal muscle cell is very little. Therefore when combined with stored ATP, only 5 to 9 seconds of maximal muscle contraction is generated (Novak, 2003). As exercise intensity increases, the sum of these high energy phosphates (ATP and PCr) progressively decrease and energy generation is dependent on glycolytic and oxidative pathways that match the rate of ATP hydrolysis and ATP synthesis (i.e. achievement of steady state) (Guyton and Hall, 2006).

The glycolytic pathway is able to continue by energy release from the glucose molecule. The breakdown of glucose, or glycolysis, occurs rapidly in the cytosol of muscle tissue where glycolytic enzymes are abundant. As glycolysis proceeds, hydrogen molecules released along

15

with an electron, are shuttled into the mitochondria by the carrier molecules, nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD). NADH (the reduced form of NAD) "shuttles" hydrogen and an electron to the mitochondria. Pyruvate is either consumed by the mitochondria, or if there is in sufficient mitochondrial activity to accept the glycolytic flux, then NADH is oxidized and pyruvate is reduced to form lactate in the cytoplasm. The net formation of lactate or pyruvate, then, depends on glycolytic and mitochondrial activities, and not the presence of oxygen (Hoppeler & Fluck, 2003). Muscle and blood lactate accumulation during exercise is a product of glycolytic flux in excess of mitochondrial demand. As cytosolic lactate concentration rises, the intracellular lactate shuttle will carry the monocarboxylate molecule into the mitochondria where it is oxidized by lactate dehydrogenase (LDH) to pyruvate (Hoppeler & Fluck, 2003; Brooks, 1986).

Once in the mitochondria, degradation of the pyruvate molecule continues through the Krebs cycle. Pyruvate dehydrogenase (PDH) assists in the breakdown of pyruvate to acetyl-CoA, the small 2 carbon molecule which enters into the Krebs cycle. Not a great amount of direct energy is released during the Krebs cycle itself, thus the primary function of the Krebs cycle is to complete the oxidation of acetyl-CoA formed during the breakdown of carbohydrates, fats, or proteins (Hoppeler & Fluck, 2003).

Reducing equivalents containing a hydrogen and electron pair will allow entry to the electron transport chain (ETC) located on the mitochondrial inner membrane. Along the ETC, the electron is removed from the hydrogen to continue down the chain and the resulting H^+ is pumped outside the mitochondria (Mitchell, 1965). As NADH and FADH enter the mitochondria, the efflux of protons creates a region of decreased pH and positive charge developing an electrochemical gradient that will ultimately supply the energy to phosphorylate

ADP. More specifically, the electrochemical gradient is used by ATP synthase which acts as an ion channel to allow H^+ back into the mitochondrial membrane. At the same time, electrons are removed from four molecules of cytochrome C oxidase and transferred to molecular oxygen, producing two molecules of water (Novak, 2003; Mitchell, 1965). Oxygen is considered the "final electron acceptor" because the formation of water in the mitochondrion is what drives phosphorylation of ADP (Ritov et al., 2010; Hoppeler & Fluck, 2003).

Feedback control for Oxygen Delivery

Delivery of adequate oxygen supply to muscle requires blood circulation, with the appropriate oxygen transport properties, maintained at a sufficient cardiac output. Additionally, vascular adaptations are required to selectively redistribute blood to active muscular beds dependent upon oxygen needs (Jensen, 2009; Balaban 1990). Aerobic metabolism, which is dependent upon oxygen delivery, causes an increase in local blood flow through both the vasodilation of vessels and greater recruitment of vessels and capillaries with the opening of capillary sphincters (Jensen, 2009; Wagner, 1995).

Metabolic feedback mechanisms are important for signaling a redistribution of blood flow away from non exercising muscles to exercising muscles. Specifically, the oxygen carrying capacity of Hb is an integral part in determining adequate oxygen supply. The degree of arterial vasodilation depends on the concentration of deoxygenated Hb in the veins. As the venous oxygen concentration declines, due to an increase demand in working muscles, the increased level of deoxyghemoglobin will trigger a release of vasodilatory compounds such as ATP and nitric oxide (NO), stimulating an upstream conduction response for arteriolar vasodilation. Additionally, as ATP is hydrolyzed, adenosine levels increase, thus further mediating arterial vasodilation (Novak, 2003).

Oxygen Uptake Kinetics

During the transition from rest to exercise, the pulmonary, cardiovascular, and muscular systems work synergistically to increase the oxygen supply to muscle mitochondria, as a result, increasing oxidative metabolism. Oxidative metabolism is the principle means for an individual to generate energy to perform work; therefore the study of the physiological mechanisms responsible for the oxygen uptake response to exercise is vital in understanding aerobic performance and metabolic activity of the muscle (Poole, Barstow, McDonough, & Jones, 2008; Jones & Poole, 2005, Whipp & Ward, 1990). Determination of muscle oxygen uptake kinetics (mVO_2 on-kinetics) directly at the site of capillary - myocyte oxygen exchange would be a 'true' representation of oxidative capacity of the working muscle. However, in the absence of direct measurements, mVO_2 on-kinetics should be inferred using mathematical models based on pulmonary oxygen uptake kinetics (pVO_2 on-kinetics) (Behnke, Barstow, &Poole, 2005; Koga, Tomoyuki, & Narihiko, 2005). VO_2 is measured most conveniently at the mouth allowing for analysis of pVO_2 on-kinetics at the onset of exercise (Whipp & Ward, 1990).

Pulmonary VO_2 on-kinetics is known to be faster in trained individuals and children when compared to non-trained adults (Fawkner, Armstrong, Potter, & Welsman, 2002), and slower in patients with respiratory or cardiac diseases, as well as individuals with type 2 diabetes (Nadeau et al., 2009; Unnithan et al., 2007; Bradenburg et al., 1999). The assessment of pVO_2 on-kinetics offers the advantage of not requiring maximal efforts that may contraindicate diseased patients or elderly subjects participating in cardiorespiratory testing (Poole and Jones, 2005; Grassi et al., 1996). Pulmonary VO_2 on-kinetics provides a valuable tool for evaluating the aerobic conditioning and individual's tolerance to physical activity.

It is well documented that the nature of VO_2 on-kinetic response to exercise is a function of exercise intensity divided into 4 domains; moderate, heavy, very heavy, and severe exercise (Armstrong & Baker, 2009; Ozyener, Rossiter, Ward, & Whipp, 2001; Gaesser & Poole, 1996; Whipp, 1994). The first domain, moderate exercise, elicits work rate intensity below the lactate threshold (LT) in order to prevent a significant increase in blood lactate. During moderate exercise, healthy adults will display an exponential rise in VO_2 toward a steady state level within three minutes (Xu & Rhodes, 1999).

Exercise intensities above the LT, but below VO_2peak, consist of work rate domains which are classified upon whether the increase in blood lactate stabilizes or inevitably rises with time. During heavy exercise, identified as the second domain, blood lactate levels progressively increase and will stabilize if the intensity is below the maximal lactate steady state (MLSS). MLSS is defined as the highest blood lactate concentration and work load that can maintain equilibrium of lactate production and lactate clearance (Billat, Pascal, Guillaume, Koralsztein, & Mercier, 2003). MLSS differs from LT in that LT is simply the exercise intensity in which the blood lactate concentration begins to increase.

Within the "heavy" domain, pVO_2 kinetics rises exponentially, but is associated with a delayed and elevated increase in pVO_2. This additional cost of pVO_2, or "gain", represents a non-linear increase in the work rate - pVO_2 relationship found during moderate intensity exercise (Armstrong & Baker, 2009). The upper level of the heavy domain is distinguished by the MLSS. Typically during "very heavy" exercise, corresponding to an exercise intensity between the MLSS and VO_2peak, the pVO_2 slow component will rise rapidly and eventually attain VO_2peak. Thus, as exercise intensities increase above MLSS, the magnitude of the slow component will lower (Armstrong & Baker, 2009).

Finally, the fourth domain is severe intensity; a work rate that requires a projected pVO_2 at or above VO_2peak (Armstrong & Baker, 2009). When exercise intensity is above an individual's LT, as shown in the heavy, very heavy, and severe domains, pVO_2 on-kinetics become more complex. Therefore the moderate intensity domain is ideal for analyzing pulmonary on-kinetics (Jones & Poole, 2005; Xu & Rhodes, 1999).

The pulmonary VO_2 response following the onset of exercise has additionally been characterized into three phases. Phase I, or the "cardiodynamic phase" represents the oxygen uptake associated with the rapid increase in cardiac output and return of blood to the lungs by way of the muscle pump. Often, this rapid delivery of blood flow to muscle will exceed the immediate demand in the first 15 seconds of exercise. Phase I does not reflect an increase in metabolism as suggested by a lack of oxygen extraction and is often removed from kinetic analysis (Delorey, Kowalchunk, & Paterson, 2003; Whipp, Ward, Lamarra, Davis, & Wasserman, 1982). After the initial 15-20 seconds of Phase I, a more rapid increase in pVO_2 is referred to as Phase II, or the 'fundamental component' of pVO_2 on kinetics. The pVO_2 on-kinetics in Phase II reflects the arrival of venous blood at the lungs and corresponds to the increase in VO_2 of the exercising muscle.

Although a lag exists between events at the muscle and those recorded in the lung, the pulmonary Phase II time constant ($\tau2$) is a marker of the ability to deliver and utilize oxygen at the level of exercising muscle (Jones & Poole, 2005; Grassi et al., 1996). The $\tau2$ is shown to be invariant with work rate (Zoladz, Korzeniewki, & Grassi, 2006), accelerated by training (Marwood, Roche, Rowland, Garrard, & Unnithan, 2010), and slowed by aging, inactivity, and specific disease states (Murias Kowalchuk, & Paterson, 2010), therefore is a popular choice of measure in researching pVO_2 kinetics (Jones & Poole, 2005). The final phase, Phase III,

represents the steady state value during moderate intensity work rates. During high intensity

exercise Phase III may be delayed or unseen, and often the magnitude of the slow component is

examined (Koga et al., 2005; Barstow, 1994).

Pulmonary VO_2 on-kinetics is determined as the time required to achieve 63% of the

overall VO_2 response. To identify this kinetic parameter, computers can fit the response data of

VO_2 to mono exponential functions that includes a single amplitude and time constant (τ) (Koga

et al., 2005). Analysis of the $\tau2$ for VO_2 on-kinetics entails averaging oxygen uptake from the

initiation of exercise to completion over 10-second intervals. Oxygen uptake at time zero is

calculated as an averaged 2 minute resting value. The initial 20 seconds of exercise is then

removed from kinetic analysis to account for the cardiodynamic effects of Phase I. The

remaining data set is then fitted to a mono exponential curve with a delay relative to the onset of

exercise of the form:

$$VO_{2\,(t)} = VO_{2\,(resting)} + VO_{2\,(steady\text{-}state)}\,[1 - e^{-(t/\,\tau VO2)}]$$

where $VO_{2\,(t)}$ is oxygen uptake at any time t, $VO_{2\,(resting)}$ is the mean VO_2 measured during rest,

$VO_{2\,(steady\text{-}state)}$ is the increase in oxygen uptake above rest (average of the last two minutes of

exercise), e is the base of the natural logarithm, and τVO_2 is the time constant for the

fundamental component of the response (Arena & Peberdy, 2006, Poole & Jones 2005, Whipp &

Ward, 1990).

The $\tau2$ measurement is influenced by exercise intensity, mode of exercise, and prior

exercise to testing (Poole et al., 2008; Arena & Peberdy, 2006; Ozyener et al., 2001). Previous

studies had suggested that attainment of a reliable measure of VO_2 on-kinetics should include

data from multiple transitions of exercise to interpolate to a single $\tau2$ (Ozyener et al, 2001).

However, Arena and Peberdy suggested that a single bout of submaximal exercise on a treadmill

possesses a high degree of reliability in measures of resting VO_2, steady state VO_2, and pVO_2 on-kinetics (Arena & Peberdy, 2006). Twenty-eight apparently healthy adults completed a single 6-min constant work rate exercise session, walking at 2.2 mph and 6% grade without a warm up on 3 consecutive days. The intraclass correlation coefficient (ICC) revealed a high level of reliability for the $\tau2$, resting VO_2, and steady state VO_2 ($P< 0.001$; 0.84, 0.93, 0.98, respectively) over the 3 sessions (Arena & Peberdy, 2006). The findings of Arena and Peberdy give confidence in demonstrating reliability of VO_2 on-kinetics during a single exercise session.

Additionally, research has shown a faster $\tau2$ during the second bout of submaximal exercise, suggesting a "speeding effect" from a priming exercise independent of baseline VO_2 (Buchheit, Laursen, & Ahmaidi, 2009; Gurd, Scheuremen, Paterson, & Kowalchuk, 2009). Therefore, when assessing multiple submaximal constant load exercise bouts on the same day, this priming effect must be considered and removed from $\tau2$ averages.

Oxygen Delivery vs. Oxygen Utilization

Currently, two theories are often debated in determining the regulating factor of oxygen consumption during the transition from rest to exercise. The role of oxygen delivery versus oxygen utilization mechanisms in establishing the dynamics of oxygen uptake remain controversial (Murias et al., 2010; Hughson, Tschakovosky, & Houston, 2001; Grassi et al, 2000). Investigators have developed two opposing models in regards to specific mechanisms that limit VO_2 on-kinetics. Some consider VO_2 on-kinetics to be determined by the rate of oxygen delivery to the exercising muscles, which is in direct contrast to the concept that inertia of muscle oxidative metabolism establishes the limit for VO_2 on-kinetics (Grassi et al, 1996). The oxygen delivery hypothesis suggests that oxygen, and the substrates for oxidative phoshorylation, will adapt to the required level at the onset of exercise to meet energy demands,

therefore the actual inability to supply oxygen becomes the limiting factor. Whereas the oxygen

utilization hypothesis proposes a limitation in the availability of substrates and the inability for

metabolic pathways to adapt in determining the rate in which oxidative metabolism increases to

satisfy energy demands (Grassi et al, 2000; Poole et al., 2008).

Researchers have attempted to distinguish the oxygen delivery versus oxygen utilization

dispute by developing studies that instigate a rapid VO_2 on-kinetics through an increase in

oxygen delivery to the muscle. Animal models are often used in a more aggressive approach to

directly measure oxygen delivery and oxygen uptake across the contracting muscle (Hernandez

et al., 2010). Grassi et al. (1998a) isolated the canine gastrocnemius muscle to determine whether

a faster adjustment of oxygen delivery would affect VO_2 on-kinetics. Muscle VO_2 on-kinetics

were compared primarily during two conditions: periods of spontaneous adjustment of oxygen

delivery (Control) and periods in which any delay in the adjustment of oxygen delivery was

eliminated by having the muscle pump perfused at a constant blood flow from rest to throughout

the contraction period (Fast O_2 Delivery) (Grassi et al., 1998a). Each protocol consisted of three

contraction periods lasting 3 minutes, separated by 45 minutes of rest. Blood flow of the

gastrocnemius muscle was continuously measured in the popliteal vein. Samples of arterial blood

entering the muscle and venous blood from the popliteal vein were drawn every 5 to 7 seconds

during the first 75 seconds of contraction, followed by a sample every 30-45 seconds thereafter

until the end of contraction (Grassi et al., 1998a). VO_2 was calculated from the Fick equation at

discrete time intervals corresponding to the timing of blood samples. Investigators compared

VO_2 on-kinetics in the two conditions by mathematically evaluating the time necessary for VO_2

to reach 50% and 63% ($\tau_{50\%}$ and $\tau_{63\%}$) of steady state values obtained during contractions.

As hypothesized, blood flow and oxygen delivery was significantly higher in the Fast O_2 Delivery condition as compared with the Control condition during rest. Despite the absence of a delay in the adjustment of oxygen delivery during the rest-contraction transition, VO_2 on-kinetics during the Fast O_2 Delivery condition displayed no statistical change from the Control condition at both 50 and 63% steady state. This observation provided evidence that the VO_2 on-kinetics was not limited by blood flow and oxygen delivery to the muscle but was presumably determined by an intrinsic inertia of muscle oxidative metabolism (Grassi et al., 1998a).

Peripheral diffusion of oxygen (delivery of O_2 to mitochondria) has been shown to contribute to the limitation of VO_{2max} and may also be a determining factor in VO_2 on-kinetics (Wagner et al., 1995). Grassi and colleagues tested this hypothesis by enhancing the rate of peripheral oxygen diffusion through an increase in the driving pressure of oxygen from the capillaries to the mitochondria. Using the previously described canine gastrocnemius experimental model (Grassi et al., 1998b), investigators evaluated three different conditions in which blood flow perfusion remained constant through a controlled muscle pump: 1) canines breathed ambient air, 2) canines breathed 100% oxygen (hyperoxia), or 3) canines breathed 100% oxygen and were injected with an allosteric inhibitor of oxyhemoglobin binding. It was hypothesized that if peripheral oxygen diffusion was limiting VO_2 on-kinetics, then the increase in the driving pressure of oxygen from capillaries to the mitochondria would speed VO_2 on-kinetics (Grassi et al., 1998b). Despite enhancements in the driving pressures for peripheral oxygen diffusion, no significant effects were seen in skeletal muscle VO_2 on-kinetics when comparing the three groups. These findings further support the principle that muscle VO_2 on-kinetics is not influenced by the delivery of oxygen, rather set by the inertia of muscle oxidative metabolism (Grassi et al., 1998b).

Metabolic Syndrome

Despite major efforts to promote weight reduction, the prevalence of obesity is increasing worldwide in epidemic proportions. The metabolic syndrome (MetS) is a collection of interrelated metabolic factors that concomitantly raise an individual's risk for developing coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM) (Grundy et al., 2005; Wildman et al., 2010). According to the National Cholesterol Education Program's (NCEP) Adult Treatment Panel III (ATP III), MetS is identified when an individual expresses at least three of the following criteria: (1) Abdominal obesity defined by a waist circumference exceeding 102 or 88 cm for men and women, respectively, (2) Triglyceride levels greater than or equal to 150 mg/dL, (3) HDL cholesterol less than 40 or 50 mg/dL for men and women, respectively, (4) Blood pressure values greater than or equal to 130 mmHg systolic or 85 mmHg diastolic, and (5) Fasting plasma glucose levels greater than or equal to 110 mg/dL. Among this diagnostic criterion for the metabolic syndrome, abdominal obesity, hypertension, and hyperglycemia are found to be most prevalent (Ervin, 2009). Additionally, current prevalence rates from the NCEP/ATP III and NHANES III suggest that one-third of US adults have the metabolic syndrome (Ervin 2009; Grundy 2005).

Obesity and type 2 diabetes mellitus (T2D) often occur simultaneously, both characterized by insulin resistance. Therefore, it is often suggested that these conditions may share a common pathological mechanism. Awareness of a pre-diabetic state, or suppressed insulin sensitivity, is important because of the cardiovascular damage that occurs prior to the diagnosis of T2D. According to a 20 year follow up study of more than 117,000 females, the risk for cardiovascular disease (non fatal myocardial infarction and non fatal stroke) were significantly increased previous to their diagnosis of T2D (Hu, Stampfer, Haffner, Solomon,

Willett, 2002). Moreover, changes in fasting glucose levels as well as insulin sensitivity have been shown to occur 3 to 6 years before the diagnosis of T2D (Tabak et al., 2009). Prevention and treatment of diabetes and subsequent deterioration of the cardiovascular system is vital for the proper assessment of known risk factors, allowing health care professionals to properly determine an individual's need for screening.

Type 2 Diabetes (T2D)

The pathogenesis of T2D has been studied extensively and it is well established that in addition to predisposing genetic factors, poor nutrition and sedentary lifestyle instigate manifestation of the disease. Insulin deficiency and ineffective insulin production initiate abnormalities of carbohydrate, fat, and protein metabolism. Consequently, this pathogenic process will cause destruction of pancreatic beta cells ultimately leading to the development of diabetes (Albert & Zimmet, 2009; Tripathy & Chavez, 2010)**.**

Following a meal or glucose ingestion, blood glucose levels increase promoting insulin release from beta (β) cells, in turn stimulating glucose uptake by the liver and muscle tissue. Insulin resistance (IR) is a condition in which insulin becomes less effective in lowering blood sugar. As individuals progress from normal glucose tolerance to impaired glucose tolerance, the level of insulin sensitivity will decrease. β cells are able to compensate by increasing the amount of insulin secreted which will temporarily offset IR in the muscle and liver in order to maintain a normal range of plasma glucose (Defronzo et al., 2009). In healthy individuals, blood glucose levels are maintained within a narrow range, thus failure to suppress glucose release into the blood can cause adverse health effects. The inability of β-cells to produce sufficient insulin during hyperglycemia is what characterizes the transition from insulin resistance to T2D (Tripathy & Chavez, 2010).

Additionally, skeletal muscles play a key role in whole body lipid metabolism and the pathogenesis of IR conditions. It has been reported that individuals diagnosed with T2D exhibit increased glycolytic enzymes and decreased oxidative enzyme activity (citrate synthase and NADH oxidase, key enzymes of the Krebs cycle and ETC, respectively) compared to their lean and obese nondiabetic counterparts (Simoneau & Kelley, 1997). Insufficient NADH oxidation will consequently cause excess muscle lactate and interfere with fatty acid oxidation, leading to the buildup of lipid byproducts. This accumulation of intramyocellular lipids (IMCL), associated with obesity and IR, will inhibit muscle insulin signaling and impair mitochondrial function (Nadeau et al., 2009; Van der Heijden et al., 2009). Furthermore, the misbalance between ETC and Krebs cycle is a defect of mitochondrial respiration that will predispose skeletal muscle to the development of IR, ultimately hindering exercise capacity (Toledo et al., 2007; Toledo et al., 2008; Ritov et al., 2010).

Toledo and colleagues (2008) investigated whether mitochondrial capacity increased because of weight loss, improvements in IR, or exercise training by comparing the effects of a diet versus diet/exercise weight loss intervention (Toledo et al., 2008). Sixteen sedentary overweight/obese adults (age 46.1 ± 2 years, and BMI 34.8 ± 1.1 kg/m^2) were randomized into one of the two interventions for 16 weeks. The diet/exercise group exercised 3-5 days/week at a moderate intensity of 70% MHR. A research dietician met weekly with all participants to give instruction on how to reduce portion sizes, lower fat consumption, keep dietary logs, and reduce caloric intake by 25%. In addition to physical fitness evaluations and insulin sensitivity measures, muscle biopsies were obtained before and after the intervention to estimate mitochondrial content and size, ETC activity, and IMCL content (determined by histology). The intent of this study design was to achieve similar weight loss in the two interventions for

comparative examination of changes in insulin sensitivity and skeletal muscle mitochondria (Toledo et al., 2008).

Both interventions resulted in significant weight loss (mean individual weight loss: -10.8 ± 1.6%, Diet; -9.2 ± 1.2%, Diet/Exercise), decreased fasting insulin concentrations, and increase insulin stimulated glucoses disposal, indicating improved insulin sensitivity in the muscle tissue (Toledo et al., 2008). The diet/exercise intervention significantly improved VO_{2max} values (10.7 ± 3.7%) from baseline. Despite the gain in aerobic fitness, participation in moderate intensity exercise did not further improve IR values compared to those of diet only. Additionally, the exercise/diet group experienced a significant increase in mitochondrial density (reflecting greater mitochondrial capacity) and ETC activity while no changes were seen in IMCL content when compared within group baseline values (Toledo et al., 2008). In contrast, the diet only group significantly decreased IMCL content and lacked enhancements of mitochondrial density and ETC activity when compared within group baseline values (Toledo et al., 2008).

The diet/exercise intervention resulted in a clear increase in mitochondrial content and oxidative capacity indicating that exercise is a large factor in controlling mitochondrial capacity among IR individuals (Toledo et al, 2008, Ritov et al, 2010). However, reduced mitochondrial content and functional capacity in obesity are not solely consequences of IR, but may be related to lack of habitual physical activity. Furthermore, reduced mitochondrial capacity associated with obesity and IR is not a fixed defect and can be reversed when stimulated by an intervention combining moderate weight loss with moderate physical activity (Toledo et al., 2007; Toledo et al., 2008). In response to weight loss and regular exercise, improvements in adiposity, aerobic capacity, hyperglycemia, and insulin sensitivity creates an ideal scenario of metabolic changes to examine the resiliency of skeletal muscle mitochondria. Often following diagnosis of T2D, a

change in diet may be the only attempt individuals make to gain control of resting blood glucose values. However, because physical activity plays a large role in controlling mitochondrial capacity and enhancing oxidative capacity, attempts should be made to reduce sedentary lifestyles in those who are IR or T2D.

Adults with T2D have a reduced VO_{2max} even in the absence of cardiovascular complications, compared with non-diabetic subjects (Regenesteiner, Sippel, McFarling, Wolfel, & Hiatt, 1995). Regensteiner and colleagues (1998) aimed to further identify any cardiovascular limitation by evaluating the hypothesis that changes in VO_2 on-kinetics are delayed in individuals diagnosed with T2D. Ten sedentary women with uncomplicated T2D, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women performed a maximal graded cycle exercise test to determine VO_{2max} and LT. The following two days consisted of constant load submaximal exercise tests; 3 bouts at 20W, 3 bouts at 30W, and 2 bouts at 80W. Each constant load submaximal exercise bout lasted 7 minutes and was separated by a 15 minute rest period. To reduce the variability of results, VO_2 on-kinetic data was averaged within the predetermined workloads of 20W, 30W, 80W over the 2 day period (Regenesteiner et al., 1998).

In agreement with previous and current research, investigators found T2D individuals exhibit impaired maximal and submaximal cardiopulmonary responses to exercise, despite an absence of clinical cardiovascular disease or diabetic complications (Segerstrom et al., 2008; Bradenburg et al., 1999; Regenesteiner et al., 1996). Furthermore, significantly reduced VO_2 kinetics was evident in T2D women as compared to control lean and obese women during all workloads (20Wτ, 42.6±23.8 vs. 18.4±9.9 vs. 21.4±8.9 s; 30Wτ, 36.8±6.2 vs. 27.8±8.9 vs. 28.8±5.3 s; 80Wτ, 55.7±20.6 vs. 41.2±8.2 vs. 42.8±7.5 s; T2D vs. obese vs. lean respectively) when compared to obese and lean groups. Steady state VO_2 did not differ between groups at any

workload. Additionally, VO_2 as a percentage of VO_{2max} was significantly higher for the group

with T2D at all workloads (Regensteiner et al., 1998). The difference in percentage of VO_{2max}

obtained was strictly due to a reduced VO_{2max} in T2D individuals. Relative VO_2 during each

submaximal workload was not significantly different between the three groups. VO_2 percentage

obtained in accordance with significantly elevated lactate concentrations at 20W in the T2D

group (1.09 ± 0.68 mmol versus obese, 0.69 ± 0.45 mmol, and lean, 0.49 ± 0.19) implies a greater

effort was required for T2D women during each workload compared to lean and overweight

controls.

VO2 On-Kinetics – Children and Adolescents

Maturation and Gender

Previous research suggests the VO_2 on-kinetic response to the onset of moderate intensity

exercise may mature from childhood (Hughson et al., 2001). By examining fiber type profiles

and muscle enzymes, Eriksson and Saltin suggested that children, as compared to adults, may

rely more heavily upon aerobic muscle metabolism (1974). After hypothesizing that the VO_2

dynamic response would actually be independent of age, sex, and VO_2peak, Fawkner and

colleagues (2002) analyzed pVO_2 on-kinetics during moderate intensity exercise in 23 children

(n= 11 male, 12 female) and 25 adults (n= 12 male, 13 female). Each subject completed a

maximal exercise bout to exhaustion on a cycle ergometer for the determination of VO_{2peak} and

ventilatory threshold. On subsequent visits, subjects completed a step change exercise test that

began with unloaded pedaling and instantaneously rose to an individual work rate designed to

elicit 80% of the ventilatory threshold. Subjects completed no less than four, 6-min transitions,

and no more than two transitions were completed in one session. The τ2 was estimated using

similar exponential equations as previously discussed in this review (Poole et al., 2008; Arena & Peberdy, 2006; Ozyener et al., 2001).

The $\tau2$ pVO_2 on-kinetic response to moderate intensity exercise was indeed more rapid in children than in adults confirming previous suggestions of a maturation effect (Fawkner et al, 2002). The children's more rapid rise in VO_2 to steady state and less anaerobic ATP contribution during the non steady state may be due to greater relative capacity for oxygen utilization, more efficient oxygen transport, or both. Additionally, when examining the influence of gender, investigators reported no significant differences in the mean $\tau2$ between males and females in both adults and children during moderate intensity exercise. Previous research supports this finding among adults by reporting similar time constants between 9 men and 7 women (Chilibeck et al. 1996).

Though the pVO_2 kinetic response to moderate intensity exercise is thought to be independent of sex in children and adults, the response to heavy intensity exercise (above the anaerobic threshold) is suggested to vary between genders. Specifically, Fawkner and Armstrong continued examining sex differences among prepubertal boys and girls, albeit during high intensity exercise (corresponding to 40% of the difference between VO_2 at the anaerobic threshold and VO_{2peak}). The results displayed a significant difference ($P < 0.05$) in the phase II time constants between the boys and girls (17.6s vs. 21.9s, respectively). Furthermore, the boys additional oxygen cost, attributed to the slow component, was significantly ($P < 0.05$) less than the girls (1.2 vs. 1.6 ml min^{-1} W^{-1}), suggesting a greater percentage of Type 1 muscle fibers in boys compared to girls. However, the authors were unable to provide a general consensus within the literature regarding sex difference in fiber type distribution (Fawkner & Armstrong, 2004).

At intensities above the ventilatory threshold, oxygen delivery may play a more prominent role in limiting VO_2 on-kinetics than at moderate intensity which typically emphasizes oxygen utilization as the limiting factor. Fawkner and Armstrong suggest the possibility of a more rapid cardiac output response in the boys, better enabling perfusion of blood to the working muscles, therefore matching oxygen delivery to oxygen demand (2004). Since phase 1 is considered to be related to the immediate cardiodynamic response, the significantly shorter phase I as seen in boys compared to the girls (P< 0.05, 17.0s vs. 19.3s, respectively) may be indicative of a more rapid rise in cardiac output.

In summary, sex-related differences have been identified during heavy, but not moderate exercise with prepubertal boys, displaying a faster phase II pVO_2 kinetic response and smaller pVO_2 slow component compared with prepubertal girls (Fawkner & Armstrong, 2004; Fawkner et al, 2002; Chilibeck et al. 1996). There is evidence in support of the τ2 becoming progressively longer (i.e., slower kinetics) and the magnitude of the slow component becoming greater during the transition from childhood to adulthood. The mechanisms underlying these differences of metabolic control are not well understood, but may reside in the influence of age, sex, and maturation.

Training Status

Marwood and colleagues (2009) examined pVO_2 in-kinetics in sixteen trained (7.4 ± 2.2 yrs of soccer training at a premier athletic club, 15 ± 0.8 yrs old) and nine untrained (report little or no physical activity, 15 ± 0.6 yrs old) male adolescents. During the first laboratory visit, VO_{2max} was determined by an incremental exercise test to volitional exhaustion on a cycle ergometer and further analyzed to determine LT by the v-slope method. The v-slope method is a visual determination of the point at which carbon dioxide output and oxygen uptake are no longer linear during incremental exercise (Schneider, Phillips, & Stoffolano, 1993; Beaver,

32

Wasserman, & Whipp, 1986; Wasserman, Whipp, Koyl, & Beaver, 1973). At the second visit, subjects completed two, 6-minute square wave exercise transitions from rest to a workload eliciting 80% of LT. Each bout was separated by a one hour rest period. Throughout each exercise bout, continuous noninvasive muscle deoxygenation measurements were collected via Near Infrared Spectroscopy (NIRS). Pulmonary $VO_{2\ data}$ was fitted to a monoexponential curve with a delay relative to the onset of exercise: $VO_{2\ (t)} = VO_{2\ (resting)} + A_{VO2}\ [1 - e^{-(\tau - TDVO2)/\tau VO2}]$ (Marwood et al., 2009). NIRS kinetic analysis was modeled similarly to pVO_2 on-kinetic analysis to determine the Hb response to exercise. Additionally, capillary blood flow kinetics was estimated by rearrangement of the Fick equation with muscle VO_2 on-kinetics and Hb kinetics for oxygen extraction, $(a - v)O_2$ (Marwood et al., 2009). The data was also fitted to a monoexponential curve with a delay relative to the onset of exercise: $Hb_{(t)} = Hb_{(resting)} + A_{Hb}$ (1- $e^{(t-TDHb/\tau hb)}$ (Marwood et al., 2009).

It was found that trained subjects displayed a 25% faster τ during the fundamental phase of oxygen uptake kinetics (22.3 ± 7.2 s) compared to untrained subjects (29.8 ± 8.4 s). In contrast, no significant differences in τ of Hb kinetics were seen between the groups despite a higher baseline oxyhemoglobin saturation of trained subjects. When assessing capillary blood flow kinetics, the time delay of capillary blow flow (i.e. Phase 1) did not significantly differ between groups, however trained adolescents displayed a faster τ (19 ± 10 s) compared to untrained counterparts (30 ± 13 s).

These results suggest that enhancements in oxygen utilization and oxygen supply associated with training status were essential in determining speed of the VO_2 on-kinetic response to exercise. As previously noted, precise mechanisms that pose limitations on oxygen uptake kinetics remain in debate. Therefore, although it is not fully understood why untrained

male adolescents may be limited in their functional aerobic capacity, potential enhancements in central and peripheral mechanisms have been shown to speed VO_2 on-kinetics (Marwood et al., 2009). Additionally, these findings are similar to those seen in adult populations (Berger, Tolfrey, Williams, & Jones, 2008; Babcock, Paterson, & Cunningham, 1994; Powers, Dodd, & Beadle, 1985).

Obesity

Recently, it has been suggested that overweight children have an impaired exercise capacity when compared to non-overweight counterparts (Unnithan et al., 2007). Unnithan and colleagues (2007) aimed to evaluate oxygen uptake kinetics and diastolic function in 14 overweight (29.6 $\pm$ 11.9 kg/m^2; 11.7 $\pm$ 1.9 yrs) and 10 non-overweight children (17.9 $\pm$ 2.5 kg/m^2; 12.5 $\pm$ 2.1 yrs). Participants underwent two submaximal constant work rate exercises; 3 minutes of unloaded pedaling at 50 revolutions per minute (rpm), followed with 5 minutes of pedaling at 50 watts at 50 rpm. Following the 5 minute submaximal exercise bout, workload was increased every two minutes until volitional exhaustion was achieved to determine VO_2max. The mean response time (MRT) for VO_2 was calculated with the following monoexponential equation: $\Delta VO_{2\,(t)} = \Delta VO_{2\,(steady\,state)}$ x $(1\text{-}e^{-t/\tau})$. Left ventricular dimensions were assessed during a resting ECG to determine cardiac output and stroke volume.

Results from this study found an insignificant difference in pVO_2 on-kinetics between overweight (52.6 $\pm$ 11.6 s) and non-overweight (45.6 $\pm$ 7.4 s) groups. However, relative VO_{2peak} was significantly lower in overweight (29.7 $\pm$ 5.4 ml•kg^{-1}•min^{-1}) children compared to non-overweight children (34.8 $\pm$ 3.2 mL/kg/min) (Unnithan et al., 2007). These findings are in agreement with a previous study that found no difference in pVO_2 on-kinetics between obese and non-obese adolescents of similar age, but did observe significantly lower VO_{2peak} values between

the two groups (Nadeua et al., 2009). The lack of differences among groups for MRT of VO_2 suggests overweight status is not indicative of poor submaximal VO_2 kinetics in children.

However, the same study interestingly reported that resting cardiac output was 23% greater in the overweight group compared with the non-overweight group, reflecting a significantly larger stroke volume. This in conjunction with no connected bradycardiac responses could indicate enhanced ventricular pre-load, potentially providing benefits for the overweight group during submaximal exercise (Unnithan et al., 2009). An increased cardiac output and stroke volume in overweight children may propose a possible adaptation of the cardiovascular system to the additional weight. With this possible compensation in cardiac output (and thus oxygen delivery), a delay in pVO_2 on kinetics would not likely be seen in a young population.

This significant finding provides the possibility that the effects of excess adiposity have not yet reduced the functional capacity of children or adolescents. Therefore, the question is raised as to how long an obese child has before experiencing the deleterious effects of the cardiovascular system that will in turn decrease oxidative capacity. Overweight and obese adolescents should be encouraged to engage in exercise before excessive adiposity reduces their functional capacity. In addition, overweight/obese adolescents who engage in physical activity can reverse the unfavorable effects that may be concomitant with obesity, such as insulin resistance.

Insulin Resistance and T2D

Nadeau et al. (2009) compared VO_{2peak} and pVO_2 on-kinetics of obese T2D adolescents to sedentary lean and obese adolescents without diabetes (15 ± 2 yrs). VO_{2peak} and lactate threshold (determined by v-slope method) were assessed using a graded cycle ergometer to volitional exhaustion. Subjects returned to the lab and completed 3 identical bouts of submaximal constant work-load exercise equal to 85% of LT to determine the phase 2 time

constant (τ2). Each bout, separated by ten minutes of rest, consisted of 2 minutes of rest for measurement of baseline gas exchange, followed by 6 minutes of exercise maintaining 65 rpm. Glucose disposal rates during a 3-hour hyperinsulinemic-euglycemic clamp estimated IR (Nadeau et al., 2009). As expected, the T2D group displayed significantly lower glucose disposal rates than obese subjects (8.1 ± 2.7 ml$\bullet$kg$^{-1}\bullet$min^{-1}, 4.1 ± 2.3 ml$\bullet$kg$^{-1}\bullet$min^{-1}, respectively).

T2D adolescents displayed a significantly lower VO$_{2peak}$ (21.8 ± 4.2 ml$\bullet$kg$^{-1}\bullet$min^{-1}) and τ2 (40.2 ± 9.7 s) versus the control (40.4 ± 9.9 ml$\bullet$kg$^{-1}\bullet$min^{-1}; 28.6 ± 10 s) and obese group (27.2 ± 5.3 ml$\bullet$kg$^{-1}\bullet$min^{-1}; 34.9 ± 10.5 s). The τ2 values were consistent with observations in adults with more advanced T2D who exhibited a τ2 of 42.6s (Regensteiner et al., 1998). Results from the study suggested that the presence of T2D in children and adolescents presented a reduction in exercise capacity beyond what is typically observed during obesity alone (Nadeau et a.l, 2009; Unnithan et al., 2009). Furthermore, when compared to the nondiabetic control groups, T2D adolescents were the only group that displayed a significant correlation between VO$_{2peak}$ and IR, suggesting a significant impairment in exercise capacity (Nadeau et al., 2009).

Despite the relatively short duration of the disease, early cardiovascular abnormalities may negatively impact exercise function in T2D adolescents. The inability to accommodate and perform simple physical tasks could provide a practical implication of low-level exercise impairment in T2D adolescents, ultimately decreasing the likelihood that adolescents engage in physical activity (Nadeau et al., 2009).

Ruth L. Kirschstein Proposal

At the onset of exercise, pulmonary oxygen consumption (pVO_2) increases exponentially following a short time delay and eventually leading to the attainment of steady state. Calculating the dynamic response of pVO_2 provides researchers with an estimation of oxygen consumption at the site of capillary - myocyte oxygen exchange (Jones & Poole, 2005; Grassi et al., 1996). The assessment of pulmonary oxygen uptake kinetics (pVO_2 on-kinetics), specifically the primary component, termed Phase II, presents a valuable tool in evaluating aerobic conditioning and an individual's tolerance to physical activity. The phase II time constant ($\tau 2$) is shown to be invariant with work rate (Zoladz et al., 2006), accelerated by training (Marwood et al., 2010), and slowed by aging, inactivity, and specific disease states (Murias et al., 2010), therefore the $\tau 2$ is a popular and reliable choice of measure in researching pVO_2 kinetics (Jones & Poole, 2005).

It is generally understood, yet often remains in debate, that the primary rise of pVO_2 on-kinetics upon exercise initiation is dependent on the rate of adaption of the metabolic pathways in the muscle and not oxygen delivery to the muscle (Murias et al., 2010; Hughson et al., 2001; Grassi et al., 1998b). By examining fiber type profiles and muscle enzymes, Eriksson and Saltin (*1974*) found that compared to adults, children may rely more heavily upon aerobic muscle metabolism. Furthermore, current data shows the pVO_2 on-kinetic response to moderate intensity exercise is indeed more rapid in children than adults confirming previous suggestions of a maturation effect (Willcocks et al., 2009; Fawkner et al., 2002; Chilibeck et al. 1996).

Fawkner and Armstrong expanded previous research to examine sex differences among prepubertal boys and girls during high intensity exercise. The results displayed a significant difference (P < 0.05) in the τ2 between the boys and girls (17.6s vs. 21.9s, respectively). Furthermore, the boys additional oxygen cost above the anaerobic threshold, which is attributed to the slow component, was significantly (p<0.05) less than the girls (1.2 vs. 1.6 ml min^{-1} W^{-1}). This suggests that boys may have a greater percentage of Type 1 muscle fibers compared to the girls (Fawkner & Armstrong, 2004). In contrast, when examining sex differences in prepubertal children at moderate intensity exercise, there have been no significant differences in the mean τ2, despite a higher peak VO$_2$ in males (Fakwner et al., 2002). Calculated moderate effect sizes are often observed for studies investigating sex differences in pVO$_2$ on-kinetic response for both adolescents and adults. Those studies reporting no differences have an observed small sample size and may lack appropriate power to detect significant differences.

During weight-bearing activities the cardiorespiratory responses to exercise in obese individuals is often characterized by an elevated ventilatory response to exercise with excess levels of oxygen uptake beyond what is typically seen in normal weight controls (Armstrong & Barker, 2009; Reybrouck et al. 1987). However, when examining the pVO$_2$ on-kinetic response, non-significant differences are reported between overweight (52.6 ± 11.6 s) and non-overweight (45.6 ± 7.4 s) groups despite relative VO$_{2peak}$ appearing significantly lower in overweight children compared to non-overweight children (34.8 ± 3.2, 29.7 ± 5.4 ml•kg^{-1}•min^{-1} respectively) (Unnithan et al., 2007). These findings are in agreement with a previous study that found no difference in pVO$_2$ on-kinetics between obese and non-obese children, but did observe significantly lower VO$_{2peak}$ values between the two groups (Nadeua et al., 2009). The lack of

differences among groups suggests overweight status may not be indicative of poor submaximal capacity in children or adolescents.

Interestingly, the same study reported resting cardiac output to be 23% greater in the overweight group compared with the non-overweight group, reflecting a significantly larger stroke volume. This, in conjunction with no connected bradycardiac responses, could indicate enhanced ventricular pre-load, which may potentially provide benefits for an overweight group during submaximal exercise (Unnithan et al., 2009). An increased cardiac output and stroke volume in overweight children may propose a possible adaptation of the cardiovascular system to the additional weight. With this possible compensation in cardiac output (and thus oxygen delivery), a delay in pVO_2 on-kinetics is not likely to be observed in a young overweight population. Compared to adults, the children's more rapid rise in VO_2 to steady state and less anaerobic ATP contribution during the non steady state may be due to greater relative capacity for oxygen utilization, more efficient oxygen transport, or both (Fawkner et al., 2002; Chilibeck et al. 1996). This finding further adds debate in determining the limiting factor of pVO_2 on-kinetics among overweight adolescents and children.

Though the current literature supports the notion that overweight and obese adolescents do not display significantly impaired VO_2 on-kinetics compared to their normal weight counterparts, they are presumably at risk for developing such limitations later in life (Hu et al., 2002; Brandenburg et al., 1999; Regensteiner et al., 1998). Significantly delayed pVO_2 on-kinetics may provide enough of a disincentive to participate in exercise, furthering limiting one's ability to make healthy lifestyle modifications. Research is warranted to further understand metabolic activity of the muscle in obese adolescents before the onset of cardiovascular and/or metabolic disease. Furthermore, the potential to recruit a large sample through the T.E.E.N.S.

weight management program will provide this study with greater power than often observed in the literature. Therefore, the purpose of this study is to identify differences in the VO_2 on-kinetic response to moderate intensity exercise between obese male and female adolescents.

Specific Aims

1) The proposed study aims to identify differences in the VO_2 on-kinetic response to moderate intensity exercise between obese male and female adolescents. Previous results have indicated that sex differences exist in pVO_2 on-kinetics among apparently healthy adolescents during high intensity exercise. However, no significant differences in pVO_2 on-kinetics have been observed during moderate intensity exercise. Although previous research has suggested that obesity does not impair pVO_2 on-kinetics in adolescents, no study has examined if sex differences exist in VO_2 on-kinetic response to moderate intensity exercise among obese adolescents. Furthermore, medium effect sizes were calculated from earlier results in adolescents during moderate and heavy intensity exercise. This suggests that the sole study investigating pVO_2 on-kinetics in adolescents during moderate intensity exercise may have lacked an appropriate sample size (total n = 23) to detect significant differences. The potential in recruiting a large sample through the T.E.E.N.S. program will provide this study with greater power than used in previous research studies.

2) A secondary aim of the present student is to examine the dynamic response to oxygen uptake in obese adolescents during a single bout of submaximal treadmill walking exercise. Although never shown in obese adolescents, previous findings have suggested strong reliability of a single exercise transition, therefore providing more clinical

40

significance compared to repeated transitions performed over consecutive days. While

this study will lack a control group, we expect to produce a mean time constant

comparable to reported studies with similar populations.

Methods

Participants

Overweight male and female adolescents between 11 and 16 years of age (BMI ≥ 85th percentile

for age and sex according to the 2000 CDC Growth Charts) will be recruited from the Teaching,

Encouragement, Exercise, Nutrition, and Support Program (T.E.E.N.S.). The T.E.E.N.S.

program is a comprehensive weight management intervention at Virginia Commonwealth

University. The program is designed to address physical activity participation, healthy nutritional

practices, and psychosocial aspects of a healthy lifestyle. Informed consent and assent documents

are obtained from parent and participant, respectively. This study is approved by the VCU

Institutional Review Board.

Anthropometric/Body Composition Measures

Upon enrollment into the T.E.E.N.S. program, each adolescent will undergo a comprehensive

anthropometric and metabolic assessment. All anthropometric measurements and metabolic

testing will be conducted in the Clinical Research Center (CRC) at Virginia Commonwealth

University Health System (VCUHS) following an overnight fast. Measurements will include

blood pressure measure, temperature, resting heart rate, height (to the nearest 0.5 cm), weight (to

the nearest 0.25 kg), and waist - hip circumference measurements (to the nearest 0.5 cm).

Additionally, blood samples will be collected to complete a fasting comprehensive metabolic

panel, lipid panel, and glucose/insulin levels during a standard 2-hour oral glucose tolerance test

(OGTT). As previously discussed in the review, it is found that adolescents diagnosed with T2D

exhibit delayed pVO_2 on-kinetics (Nadeau et al., 2009). Therefore, any participants who present glucose intolerance as determined by the OGTT will be excluded from the study. Lastly, whole body dual energy X-ray absorptiometry (DXA) scanning will be performed on the adolescent to assess lean and fat mass (using the Hologic 4500a/Discovery scanner). *Exercise Protocol*

Maximal oxygen uptake (VO_{2max}) and pulmonary oxygen uptake kinetics (pVO_2 on-kinetics) will be determined using a maximal graded exercise test to exhaustion on a treadmill (Trackmaster TMX425C, Full Vision, Inc., Newton KS). During exercise, breath by breath gas exchange variables will be measured using the VMAX Sepctra Sensormedics gas analyzer (Sensormedics Corp., Yorba Linda, CA). The ventilatory expired gas analysis system will be calibrated prior to each exercise session according to manufacturer specifications. Additionally, heart rate responses we be recorded at each minute during the test via heart rate monitor (Polar Electro) and ratings of perceived exertion (6-20 Borg Scale) will be documented near the end of each stage.

Following a 3-min period of resting gas exchange, subjects will begin the progressive protocol consisting of a 4 minute warm-up at 2.5 mph and 0% grade, followed by a 2 minute stage at 3 mph at 0% grade. Subsequent 2 minute stages will be held constant at 3.0 mph while grade is increased to 2.0, 5.0, 8.0, 11.0, 14.0, and 17.0%. Subjects will be verbally encouraged to give maximal effort during the test until volitional exhaustion is achieved, at which time the test is terminated. VO_2max will be taken at the highest recorded 10s average during the maximal exercise test.

Oxygen Uptake Kinetics

Following the VO_2max assessment, ventilatory threshold (VT) will be determined non-invasively using the V-slope method. VT will be defined as the inflection point in which CO_2

production begins to rise at a more rapid rate than VO_2 (Beaver et al, 1986). Data from the initial 4-min stage will be used for the exercise transition to assess pVO_2 on-kinetics. As discussed earlier in the review, a single bout of submaximal exercise on a treadmill provides a high degree of reliability in measures of pVO_2 on-kinetics (Arena & Peberdy, 2006). In determining the VT, we are able to confirm whether or not subjects reached 75-95% of their VT within the initial 4-min stage. If a subject exceeds the estimated VT during this initial stage, there is risk of a secondary rise in oxygen uptake that may alter the reliability of the $\tau 2$. Therefore any individual who exceeds 95% of their VT during the initial stage will be removed from further kinetic analysis.

Breath-by-breath data will be averaged into 10 seconds to reduce noise and enhance the underlying physiological response characteristics. Baseline VO_2 is defined as the average VO_2 measured during rest, 2-min prior to the start of the first 4-min stage. The initial 20 seconds of exercise are then removed from kinetic analysis to account for the cardiodynamic effects of Phase 1. The remaining data set will be fitted to a mono exponential curve with a delay relative to the onset of exercise of the form:

$$VO_{2\ (t)} = VO_{2\ (resting)} + VO_{2\ (steady\text{-}state)}\ [1 - e^{-(t/\ \tau VO2)}]$$

where $VO_{2\ (t)}$ is oxygen uptake at any time t, $VO_{2\ (resting)}$ is the mean VO_2 measured during rest, $VO_{2\ (steady\text{-}state)}$ is the increase in oxygen uptake above rest (average of the last two minutes of exercise), e is the base of the natural logarithm, and τVO_2 is the phase II time constant ($\tau 2$) or the fundamental component of the increase in VO_2 above baseline reported in seconds (Arena & Peberdy, 2006; Poole & Jones 2005; Whipp & Ward, 1990).

Statistical Analyses

        An independent samples t-test will be used to investigate differences in anthropometric and exercise responses between the adolescent male and females. Additionally, correlation coefficients will be used to investigate possible relationships between pVO_2 on-kinetics and VO_2max between the adolescent male and females.

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SEX DIFFERENCES IN THE OXYGEN UPTAKE KINETIC RESPONSE TO MODERATE INTENSITY EXERCISE IN OBESE ADOLESCENTS

ABSTRACT

The pulmonary oxygen uptake (VO_2) kinetic response to exercise provides insight into aerobic performance and the integrated efficiency of the cardiovascular, pulmonary, and muscular systems to maintain oxygen demand during the initiation of exercise. Previously, investigators have reported no significant differences in the VO_2 kinetic response to moderate intensity exercise in normal weight male and female children. However, the small sample size in conjunction with a large effect size may have confounded the interpretation of the time constant. Additionally, evidence is stronger in female adolescents than in males that obesity leads to an earlier onset of puberty. To date, no study evaluating adolescent on-kinetics has considered the impact of maturational status nor evaluated the effect that excess adiposity may have on gender pVO_2 on-kinetics differences. **PURPOSE:** To determine if sex differences exist in the VO_2 kinetic response to moderate intensity exercise in obese male and female adolescents. **METHODS:** 55 obese subjects volunteered to participate. Male (n=16, 12.97±1.16 yrs, 34.59±5.64 kg/m^2) and female (n=39, 14.07±1.82 yrs, 36.36±4.63 kg/m^2) adolescents completed a graded exercise test to exhaustion on a treadmill. Breath by breath data from the first 4-min of

treadmill walking (2.5 mph, 0% grade) at moderate intensity (75-95% of ventilatory threshold) was averaged into 10s intervals and fit with a monoexponential equation to determine the phase II time constant. **RESULTS:** The phase II time constant was significantly different (P=0.009) between obese male and female adolescents (15.42 ± 7.31 s vs. 22.03 ± 8.56 s, respectively). Additionally, VO_{2peak} was significantly greater ($P<0.012$) in males compared to females (2.7 ± 0.38 vs. 2.41 ± 0.37; LO_2/min). The initial 4-min walking stage during the graded exercise test elicited a similar relative exercise intensity between the two groups (male, $87.39\pm3.52\%$ vs. female, $87.05\pm5.27\%$ of VO_{2peak}; P=0.816). **CONCLUSION**: The sex differences that exist in the VO_2 kinetic response to moderate intensity exercise in obese adolescents, may indicate an enhanced potential for males to deliver and/or utilize oxygen. A longer time constant may reflect the dependency upon anaerobic energy sources, therefore functional exercise may be perceived as more difficult by obese female adolescents.

INTRODUCTION

the transition from rest to aerobic exercise, the pulmonary, cardiovascular, and muscular systems work synergistically to increase the oxygen supply to muscle mitochondria resulting in an increase in oxidative metabolism. Upon the start of exercise, there is an immediate demand in energy production, however the energy supplied from oxidative phosphorylation as a proportion of the total energy required, elevates at a much slower rate creating an oxygen deficit. During this period of oxygen deficit, ATP production is reliant on anaerobic sources including stored ATP, phosphocreatine hydrolysis, and cytosolic glycolysis. Within 2-3 minutes, steady state is achieved and ATP production becomes predominantly dependent on oxidative metabolism (Whipp et al., 1982). The study of the physiological mechanisms responsible for the oxygen uptake response to exercise is vital in understanding aerobic performance and metabolic activity of the muscle (Poole, Barstow, McDonough, & Jones, 2008; Jones & Poole, 2005, Whipp & Ward, 1990). The oxidative capacity of working muscle is often indirectly calculated from pulmonary oxygen uptake kinetics (pVO_2 on-kinetics) (Behnke, Barstow & Poole, 2005; Koga, Tomoyuki, & Narihiko, 2005). This noninvasive measured response, reported as a time constant or time taken to reach 63% of steady state oxygen consumption, has been a valuable tool in providing information related to an individual's ability to tolerate physical activity.

Furthermore, kinetics of phosphocreatine breakdown at the start of exercise may play a role in the control of mitochondrial respiration (Chilibeck et al., 1996; McCreary et al., 1996). Prior research suggests relatively small changes in phosphocreatine is associated with relatively fast VO_2 on-kinetics thus the breakdown of PCr is indicative of muscle VO_2 kinetics during moderate intensity exercise (Zoladaz et al., 2004; McCreary et al., 1996). Much of the research assessing pVO_2 on-kinetics to this point has focused on the slowed pulmonary response

attributed to physical inactivity, specific disease states, and aging (Chilibeck, Paterson, Smith, & Cunningham, 1996; Marwood, Roche, Rowland, Garrard, & Unnithan, 2010; Matsumoto et al., 1999) and has been found to improve following exercise training in both old and young adults (Murias, Kowalchuk, & Paterson, 2010; Brandenburg et al., 1999).

Previous research displays the t2 to become progressively longer during the transition from adolescence into adulthood (Fawkner, Armstrong, Potter, & Welsman, 2002; Herbstreit et al., 1998). The dynamic response to moderate intensity exercise is generally accepted as being regulated by oxygen delivery capacity and relative oxygen utilization (Marwood et al., 2010; Hughson, Tschakovosky, & Houston, 2001). Although there is no support for greater oxygen delivery capacity in adolescents compared to adults, there is support for enhanced oxidative enzymatic activity (Leclair et al., 2012; Haralambie, 1982) in adolescents when compared to adults. Nevertheless, when evaluating the comparison between adolescents and adults, it has been suggested that a maturation effect significantly decreases the moderate-intensity kinetic VO_2 response in adults (Fawkner, Armstrong, Potter, & Welsman, 2002; Chilibeck et al., 1996; Delorey et al., 2004).

Interestingly, studies evaluating the pVO_2 on-kinetics during moderate intensity exercise in adolescents have reported equivocal results between genders. Cooper et al. (1985) reported a significantly slower time constant in adolescent females when compared to males. The investigators attributed this to possible social and cultural factors that may have led to decreased cardiorespiratory fitness levels, as a significant inverse relationship has been observed with the pVO_2 on-kinetics time constant and maximal VO_2 (Salvadego et al., 2010; Regenesteiner et al., 1998; Cooper et al., 1985). More recently, researchers contradicted these earlier findings and suggested that no significant differences existed in the pVO_2 on-kinetics time constant between

male and female children (Fawkner et al., 2002 & 2004). Fawkner et al. (2002) further

suggested that maximal VO_2 was not a determinate of the pVO_2 on-kinetics time constant, as a

poor relationship existed between these submaximal and maximal exercise variables. However,

depending on the similarity in the intensity of exercise, a relationship may exist between pVO_2

on-kinetics and oxygen consumption. Investigating the relationship between submaximal oxygen

consumption and the pVO_2 on-kinetic response to submaximal exercise may allow for a better

understanding of metabolic control during the exercise transition.

According to the National Health and Nutrition Examination Survey (NHANES) the

prevalence of sexual maturation (i.e. menarche) in female adolescents is significantly elevated in

those with BMI levels near the 85th and 95th percentiles (Ogden & Carroll, 2010). Furthermore,

evidence is stronger in female adolescents than in males, suggesting that obesity leads to an

earlier onset of puberty (Wagner et al., 2012). In the United States, the prevalence of excess body

weight in adolescents (i.e. classified as overweight/obese) has tripled from 1980 to 2000 placing

overweight and obese adolescents at a significantly elevated risk for becoming an obese adult

(Ogden, et al., 2002). Overweight and obese adolescents exhibit daily functional limitations in

physical activity leading to a generalized perception of fatigue and ultimately a poor quality of

life (Salvadego, et al., 2010).

Recently, it has been suggested that overweight children have an impaired exercise

capacity when compared to their normal weight counterparts (Unnithan et al., 2007). Studies

evaluating the pVO_2 on-kinetics time constant in obese and non-obese adolescents of similar age

do not report significant differences (Nadeau, et al., 2009; Unnithan et al., 2007), suggesting that

increased adiposity is not indicative of poor submaximal pVO_2 on-kinetics in adolescents.

However, Salvadego and colleagues (2010) found that compared to lean male adolescents, obese

males display a markedly slower t2 during both moderate and high intensity exercise. Interestingly, these studies that attempt to provide an explanation of the metabolic differences between adults and adolescents primarily utilize the male gender. To date, no study evaluating children and adolescent pVO_2 on-kinetics has considered the impact of maturational status nor evaluated the impact that excess adiposity may have on gender pVO_2 on-kinetics time constant differences. Therefore, the aim of this study is to investigate pVO_2 on-kinetic time constant responses to moderate intensity exercise in obese male and female adolescents. Additionally, we aim to examine if a relationship exists in the dynamic response of oxygen uptake and oxygen consumption to moderate intensity exercise between obese male and female adolescents.

HYPOTHESIS

The first null hypothesis (H_{01}) of the present study was that no significant differences will exist in the phase II time constant between obese male and female adolescents. The second null hypothesis (H_{02}) is that no significant relationships would be observed between the dynamic response of oxygen uptake and oxygen consumption.

METHODS

Subjects

Obese male and female adolescents between 11 and 16 years of age [Body Mass Index (BMI) $\geq$ 85th percentile for age and sex according to the 2000 CDC Growth Charts] were recruited to participate in this study. Study procedures were explained and written consent/assent was obtained. Upon enrollment in the study, participants received a comprehensive anthropometric and metabolic assessment prior to having a physical evaluation performed by a physician. Included was a tanner assessment of sexual maturation. Each participant had the option to decline the assessment and individuals were cleared for

participation in exercise testing by a physician. All procedures were approved by Virginia

Commonwealth University's (VCU) Institutional Review Board.

Anthropometric and Metabolic Measures

Following an overnight fast, each adolescent underwent a comprehensive anthropometric

and metabolic assessment that was conducted in the Clinical Research Center at VCU Health

System. Measurements included height (to the nearest 0.5 cm), weight (to the nearest 0.25 kg),

and whole body dual energy X-ray absorptiometry (DXA, Hologic 4500a/Discovery scanner)

scanning for determination of fat and lean mass. Additionally, blood samples were collected

during a standard 2-hour oral glucose tolerance test (OGTT) for the analysis of glucose levels.

Adolescents diagnosed with type 2 diabetes exhibit delayed pVO_2 on-kinetics (Nadeau et al,

2009). Therefore, any participants who presented with impaired fasting glucose (>110 mg/dL) as

determined by the OGTT were excluded from the study.

Exercise Protocol

Subjects were scheduled within one week for a maximal exercise test and informed to

report to the Human Performance Laboratory at least 4 hours postprandial. Peak oxygen uptake

(VO_{2peak}) and pVO_2 on-kinetics were determined using a maximal graded exercise test to

exhaustion on a treadmill (Trackmaster TMX425C, Full Vision, Inc., Newton KS). During

exercise, breath by breath gas exchange variables were measured using a VMAX Sepctra

Sensormedics gas analyzer (Sensormedics Corp., Yorba Linda, CA). The ventilatory expired gas

analysis system was calibrated prior to each exercise session according to manufacturer

specifications. Additionally, heart rate responses were recorded at each minute during the test via

heart rate monitor (Polar Electro) and ratings of perceived exertion (6-20 Borg Scale) were

documented near the end of each stage.

Following a 3-min period of resting gas exchange, subjects began the progressive protocol consisting of a 4 minute warm-up at 2.5 mph and 0% grade, followed by a 2 minute stage at 3 mph at 0% grade. Subsequent 2 minute stages were held constant at 3.0 mph while grade was increased to 2.0, 5.0, 8.0, 11.0, 14.0, and 17.0%. Subjects were verbally encouraged to give maximal effort during the test until volitional exhaustion was achieved, at which time the test was terminated. VO_{2peak} was taken at the highest recorded 10s average during the maximal exercise test.

Oxygen Uptake Kinetics

Following the VO_{2peak} assessment, ventilatory threshold (VT) was determined non-invasively using the V-slope method. Ventilatory threshold was defined as the inflection point in which CO_2 production begins to rise at a more rapid rate than VO_2 (Beaver et al, 1986). Data from the initial 4-min stage was used for the exercise transition to assess pVO_2 on-kinetics. A single bout of submaximal exercise on a treadmill has provided a high degree of reliability in measures of pVO_2 on-kinetics (Arena and Peberdy, 2006). Additionally, to determine an intensity similar to that used in a previous investigation evaluating pVO_2 on-kinetic gender differences during transition from rest to moderate intensity exercise, only subjects with an initial stage VO_2 ($mLO_2 \bullet kg^{-1} \bullet min^{-1}$) less than 60% of VO_{2peak} were included for data analysis (Fawkner, et al., 2002). Furthermore, in determining the VT, it was confirmed whether or not subjects reached 75-95% of their VT within the initial 4-min stage. If a subject exceeded their VT during the initial exercise stage, there was a risk of a secondary rise in oxygen uptake that may have altered the reliability of the phase II time constant ($\tau2$). Therefore any individual who exceeded 95% of their VT during the initial stage were removed from further kinetic analysis.

63

Breath-by-breath data was averaged into 10 seconds to reduce noise and enhance the underlying physiological response characteristics. Baseline VO_2 was defined as the average VO_2 measured during rest, 2-min prior to the start of the first 4-min stage. The initial 20 seconds of exercise were then removed from kinetic analysis to account for the cardiodynamic effects of Phase 1. The remaining data set was fitted to a mono exponential curve with a delay relative to the onset of exercise of the form:

$$VO_{2\,(t)} = VO_{2\,(resting)} + VO_{2\,(steady\text{-}state)}\,[1 - e^{-(t/\tau VO2)}]$$

where $VO_{2\,(t)}$ is oxygen uptake at any time t, $VO_{2\,(resting)}$ is the mean VO_2 measured during rest, $VO_{2\,(steady\text{-}state)}$ is the increase in oxygen uptake above rest (average of the last two minutes of exercise), e is the base of the natural logarithm, and τVO_2 is the phase II time constant ($\tau2$) or the fundamental component of the increase in VO_2 above baseline reported in seconds (Arena & Peberdy, 2006, Poole & Jones 2005, Whipp & Ward, 1990).

Statistical Analyses

An independent samples t-test was used to investigate differences in anthropometric and exercise responses between the adolescent male and females. Additionally, correlation coefficients were used to investigate possible relationships between pVO_2 on-kinetics and submaximal and maximal VO_2 variables between the adolescent male and females. Furthermore, all analyses were conducted on an age and tanner stage matched sub-sample of 10 males and females. Statistical significance was set at $P \leq 0.05$ for all analyses.

RESULTS

The participants' physical characteristics and responses to the graded exercise test are presented in **Table 1**. No significant differences were seen in age, BMI, and body composition variables between the two groups. Male adolescents displayed a significantly higher VO_{2peak} and

faster $\tau 2$ than females. End stage VO_2 was approximately 87% of VT among both groups ($P = 0.816$). End stage heart rate, percentage of max heart rate and percentage of VO_{2peak} were found significantly different between genders at the end of the 4-min stage ($p < 0.05$).

Because participants were given the option to decline tanner assessment for determination of sexual maturation, analysis of tanner stage differences included 14 males and 34 females. Female adolescents presented with a significantly higher tanner stage than males ($P < 0.001$). A second analysis was conducted with age and tanner matched male and female subjects. The results of the independent samples t-test are shown in **Table 2.** Males displayed a significantly higher VO_{2peak} and faster $\tau 2$ compared to females. A Pearson product moment correlation was used to asses any potential relationships between the $\tau 2$ and relative VO_{2peak}, VO_{2peak} per lean mass and absolute VO_{2peak}. Additionally, the correlation analysis was used to evaluate relationships between $\tau 2$ and moderate intensity (end stage 1) relative VO_2, VO_2 per lean mass and absolute VO_2. No significant relationships were observed between the $\tau 2$ and all variables among both males and females ($P > 0.241$). A scatter plot with regression lines is provided in **Fig.1** as a graphical display of the insignificant relationship between stage 1 relative VO_2 per lean mass among the male and female groups. Additionally, a typical response for resting VO_2 and the initial 4-mins for a single male (a) and female (b) are shown in **Fig. 2**. The exponential fit for a single male and female subject are shown in **Fig. 3.**

Table 1. Subject Characteristics

Variable	Males (N=16)	Females (N=39)	P value
Age (years)	12.97 ± 1.16	14.07 ± 1.82	0.298
Body mass (kg)	94.40 ± 21.33	96.03 ± 15.56	0.755
BMI (kg/m^2)	34.59 ± 5.64	36.36 ± 4.63	0.234
%Body Fat (DXA)	40.99 ± 4.86	42.39 ± 3.90	0.278
Lean Mass (kg)	37.19 ± 8.47	40.96 ± 8.94	0.165
Body Mass (kg)	51.63 ± 7.21	53.88 ± 7.63	0.330
Tanner stage	2.71 ± 0.99	3.79 ± 0.72	<0.001
VO$_{2peak}$ (L•min^{-1})	2.70 ± 0.38	2.41 ± 0.37	0.012
$\tau 2$ (seconds)	15.42 ± 7.31	22.03 ± 8.56	0.009
Stage 1 VO$_{2ABS}$ (L•min^{-1})	1.27 ± 0.23	1.22 ± 0.18	0.391
Stage 1 VO$_{2LEAN}$ (L• kg of LM•min^{-1})	22.44 ± 6.90	22.86 ± 2.76	0.733
Ventilatory Threshold (L•min^{-1})	1.46 ± 0.27	1.41 ± 0.21	0.451
% Ventilatory Threshold	87.39 ± 3.52	87.05 ± 5.27	0.816
% VO$_{2peak}$	47.43 ± 7.09	51.1 ± 5.01	0.034
% Max Heart Rate	65.56 ± 6.23	70.68 ± 6.59	0.011

Mean ± S.D.; Statistical significance was set at $P \leq 0.05$; BMI, Body Mass Index; DXA, Dual Energy X-ray Absorptiometry; VO$_{2peak}$, peak oxygen consumption; $\tau 2$, Phase II Time Constant

Table 2. Tanner Matched Subject Characteristics

Variable	Males (N=10)	Females (N=10)	P value
Age (years)	13.19 ± 1.29	13.67 ± 1.60	0.470
Body mass (kg)	98.61 ± 23.15	87.45 ± 12.88	0.395
BMI (kg/m^2)	34.61 ± 4.81	35.04 ± 4.69	0.843
%Body Fat (DXA)	39.53 ± 3.47	42.01 ± 3.64	0.149
Fat Mass (kg)	36.23 ± 4.17	36.65 ± 5.35	0.853
Lean Mass (kg)	54.33 ± 7.48	49.27 ± 8.63	0.192
Tanner stage	3.20 ± 0.63	3.20 ± 0.63	1.000
VO$_{2peak}$ (L•min^{-1})	2.75 ± 0.43	2.36 ± 0.39	0.050
$\tau2$ (seconds)	15.22 ± 9.21	22.64 ± 5.14	0.039
Stage 1 VO$_{2ABS}$ (L•min^{-1})	1.30 ± 0.28	1.23 ± 0.23	0.542
Stage 1 VO$_{2LEAN}$ (L• kg of LM•min^{-1})	22.66 ± 1.66	25.03 ± 2.55	0.030
Ventilatory Threshold (L•min^{-1})	1.48 ± 0.32	1.42 ± 0.27	0.611
% Ventilatory Threshold	87.39 ± 3.52	87.05 ± 5.27	0.841
% VO$_{2peak}$	47.43 ± 7.09	51.10 ± 5.01	0.039
% Max Heart Rate	64.8 ± 6.90	71.6 ± 5.55	0.031

Mean $\pm$ S.D.; Statistical significance was set at $P \leq 0.05$; BMI, Body Mass Index; DXA, Dual Energy X-ray Absorptiometry; VO$_{2peak}$, peak oxygen consumption; $\tau2$, Phase II Time Constant

Table 3. Pearson Product Correlation Between VO_2 & $\tau 2$

Variable	Males	P value	Females	P value
Stage 1 Rel. VO$_{2\,LEAN}$ (mL•kg of LM•min)	0.128	0.636	-0.192	0.241
Stage 1 VO$_{2REL}$ (mL•kg•min)	0.137	0.613	-0.120	0.467
Stage 1 VO$_{2ABS}$ (L • min)	-0.153	0.571	0.103	0.533
Rel. VO$_{2peak}$ (mL•kg•min)	0.180	0.504	-0.068	0.680
Rel. VO$_{2\,Peak\,LEAN}$ (mL•kg of LM •min)	0.162	0.565	0.169	0.305
Abs. VO$_{2peak}$ (L • min)	-0.049	0.858	0.138	0.403

Figure 1.
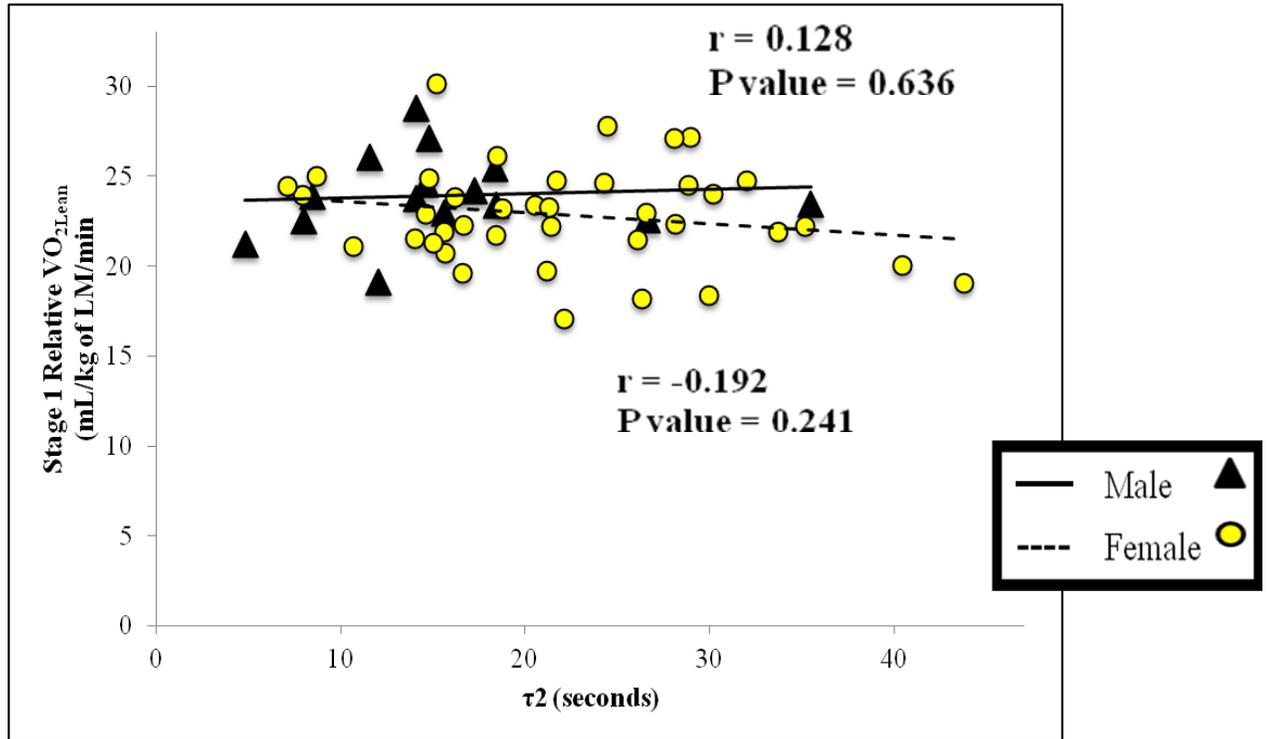
Pearson Product Correlation between Stage 1 VO$_{2LEAN}$ and $\tau2$

Figure 2.
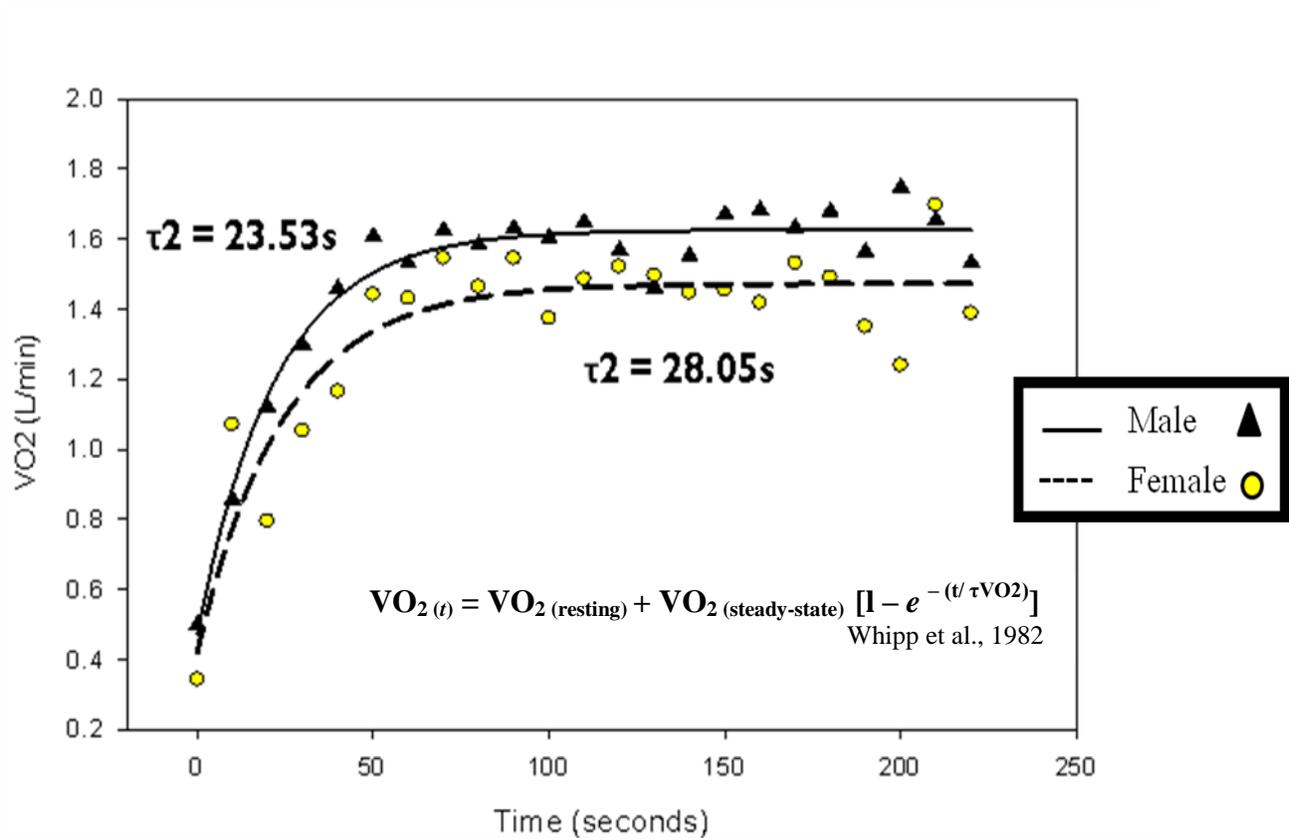
Single Male and Female subject representation of pVO2 on-kinetic response.

DISCUSSION

The primary finding of the present study was a significantly slower pVO_2 on-kinetic response to moderate intensity exercise in obese female adolescents compared to their male counterparts. The markedly slower $\tau 2$ in female subjects reveal a greater oxygen deficit, presumably increasing the need for phosphocreatine breakdown and anaerobic glycolysis during exercise transitions. These metabolic cascades are negatively associated with exercise intolerance and may occur when an obese female adolescent participates in activities that require sudden increases in physical exertion.

Previous studies investigating pVO_2 on-kinetics in lean and obese children and adolescents have presented insignificant differences between populations (Unnithan, et al., 2007; Nadeua et al., 2009). However, relative VO_{2peak} has been significantly lower in the overweight and obese children and adolescents compared to their non-overweight and non-obese counterparts. The lack of differences observed in the pVO_2 on-kinetic response among groups led investigators to suggest that an overweight status did not indicate poor submaximal exercise capacity in children or adolescents (Unnithan, et al., 2007; Nadeua et al., 2009). The findings of the current study pose implications on the previously mentioned research by failing to consider gender differences.

In the current study, we found a weak relationship between VO_{2peak} and the $\tau 2$ among male and female adolescents. This may suggest the kinetic response is primarily influenced by the mitochondrial inertia of the cell (Hughson, Tschakovosky, & Houston, 2001; Grassi et al, 2000) rather than the capacity of oxygen delivery. The primary increase in pVO_2 on-kinetics after the onset of exercise has been shown to closely reflect the kinetics of phosphocreatine hydrolysis and muscle oxygen utilization (Haralambie, 1982; Barstow et al., 1994). This is

further supported in research performed by Grassi and colleagues (1998a & 1998b), who demonstrated that VO_2 on-kinetics during moderate intensity contraction in the isolated canine gastrocnemius was not enhanced during elevated peripheral oxygen diffusion nor oxygen delivery, by means of muscle pump perfusion to levels associated with steady state exercise. In adults, it has been shown that cardiac output and bulk muscle blood flow are faster than the pVO_2 on-kinetic response (Grassi et al, 1996). These studies indicate that oxygen delivery is adequate to support oxygen demand of the muscle during the transition from rest to exercise.

Furthermore, in the current study we did not find a significant relationship $(P > 0.241)$ between submaximal VO_2 variables, in neither relative nor absolute terms, to submaximal phase II on-kinetics in either the male or female groups. This leads us to suggest that regardless of sex, oxygen delivery may not be the limiting factor during the transition from rest to aerobic exercise.

If oxygen delivery is not considered a limiting factor in the on-kinetic response, one explanation for the observed gender differences is that obese males may exhibit greater enzyme activation allowing for more efficient muscle oxidative metabolism thus the faster on-kinetic response (Grassi et al., 1996, 1998a.). Leclair et al. (2012) examined levels of deoxygenated hemoglobin via near-infrared spectroscopy and found that faster oxygen extraction at the onset of exercise occurs in children compared to adults, thus supporting the notion of enhanced muscle oxidative enzyme activity in children (Green et al., 1984; Eriksson et al. 1974). To date, no studies have examined potential gender differences in enzyme profiles in either lean or obese adolescents or children.

Previous studies report the presence of overweight and obesity is found to be higher among early-maturing girls and lower in early-maturing boys (Wagner et al., 2012; Wang, 2002). Despite a large body of evidence associating early maturating females and obesity, it fails to

confirm a direct cause between fatness and maturational events (i.e. menarche) (Wang, 2002). However, Frisch et al. (1996) proposed the hypothesis that subcutaneous fat may double as a secondary hormonal gland, influencing release and synthesis of sex hormones such as estrogen thus promoting menarche. These hormonal changes associated with early sexual maturation in obese females may result in the observed pVO_2 on-kinetic differences within our population of obese male and female adolescents.

During the initial data analysis, the females' mean tanner stage (representing sexual maturation) was found to be significantly higher than the males implying a potential maturation effect on the $\tau2$. Previous investigators suggested a delayed kinetic response in older normal weight adolescents compared to their younger counterparts leading the authors to attribute the differences to varying maturation between the groups (Armstrong, Tomkinson, & Ekelund, 2011). To control for this potential effect, we matched male and female subjects for age and tanner stage. In further support of our initial results, the analyses continued to demonstrate significant differences in the pVO_2 on-kinetic response to moderate intensity exercise between obese male and female adolescents.

The secondary analysis of age and tanner matched subjects continue to support enhanced pVO_2 on-kinetic in obese males compared to females. Early studies demonstrate enhanced muscle enzyme and fiber type profiles among adolescents compared with adults suggesting that adolescents may rely more heavily on aerobic metabolism (Eriksson 1974; Haralambie, 1982). Furthermore, these studies solely focused on normal weight male adolescents. To date, only one other study has evaluated gender differences in pVO_2 on-kinetics in adolescents (Fawkner et al., 2002). Fawkner and colleagues demonstrated insignificant gender differences between lean male and female adolescents. Although the results of the current study are not in agreement with

those of Fawkner et al. (2002), their results display moderate effect sizes (0.49) in evaluating the differences between gender pVO_2 on-kinetics. The larger sample size presented in the current study may have allowed for greater detection of differences between genders.

In summary, despite relatively similar $\tau 2$ to those previously reported in normal weight prepubertal males and females (Fawkner et al., 2002), the current study suggests that the VO_2 kinetic response to moderate intensity exercise presents a sex difference in the obese adolescent population. The males more rapid rise in VO_2 to steady state and lower energy contribution from anaerobic sources during non-steady conditions (as shown by a smaller time constant), may be due to more efficient oxygen transport mechanisms, greater capacity for oxygen utilization, or both. Furthermore, though time constant values are similar to previous reports in lean children, it remains unclear as to when obese children, specifically females, begin experiencing deleterious effects of the cardiovascular system that may decrease oxidative capacity. Future research is warranted that investigates the impact of cardiovascular risks on VO_2 in overweight or obese male and female adolescents.

Clinical application

Despite prior research suggesting no clinically meaningful differences in the time constant values between normal weight and obese children (Armstrong et al., 2005, Nadeau et al., 2009), the findings in the present study suggests gender differences indeed exist and should be taken into consideration when prescribing exercise programs. Overweight adolescents are encouraged to engage in exercise before excessive adiposity reduces their functional capacity, and also to reverse the unfavorable affects that may be concomitant with obesity, such as insulin resistance. Because males exhibit a relatively faster rise to steady state at the onset of exercise compared to females, it should be recommended that females engage in a longer warm up period

prior to initiation of an exercise regimen. In return, the female may perceive the subsequent

exercise to be less difficult therefore preventing an early termination of the exercise session.

Limitations

To our knowledge, this is the first study to utilize a single step transition from rest to

exercise in evaluating pVO_2 on-kinetics on a treadmill in obese adolescents. Previous studies

have utilized multiple rest-to-work transitions on bicycle ergometers to determine the pVO_2 on-

kinetic response. However, we believe a single bout of submaximal exercise on a treadmill

provides a high degree of reliability in measures of pVO_2 on-kinetics as shown by previous

research in adult populations (Arena and Peberdy, 2006). Although mechanical work generated

from treadmill walking generates breath by breath noise that is commonly observed during the

kinetic analysis, treadmill walking requires a subject to move his/her own weight which may

potentially affect the cardiovascular and metabolic responses to exercise and exercise

intolerance. Thus using treadmill data may be more clinically relevant to an obese population.

Lastly, the current study lacks a physiological mechanism that contributes to the observed gender

differences.

Future Research

The findings from the present study add to the current literature associated with

adolescents and oxygen kinetics. It continues to remain unclear in the direct cause of delay in

oxygen kinetics among obese female adolescents compared to obese males. Designing a research

protocol which examines skeletal muscle enzymes and fiber type profiles of obese adolescents

may provide greater insight into the metabolic control of muscle cells. Also, future research is

warranted in understanding the role of pubertal status in females and any hormonal influence that

may impact the dynamic oxygen uptake response to exercise.

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VITA

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ACADEMIC EDUCATION

M. S.   Virginia Commonwealth University, Anticipated graduation May, 2012
School of Education, Department of Health and Human Performance
Major Field of Study: Health and Movement Science, Exercise Science
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PROFESSIONAL EXPERIENCE

2011 – Present   Virginia Commonwealth University (Richmond, VA)
Adjunct Faculty, Department of Health and Human Performance

2011 – Present   Department of Pediatrics (Children's Medical Center)
Exercise Program Coordinator for the Teaching, Encouragement, Exercise, and Nutrition Support program (T.E.E.N.S.).

2010 – 2011   Virginia Commonwealth University (Richmond, VA)
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Annual meeting of the American College of Sports Medicine, San Francisco, CA, June 2012.
Graduate Research Symposium, Virginia Commonwealth University, April 2012

Hall, S.L., **M.K. Bowen**, R.K. Evans, E.P. Wickham, R.L. Franco. Examining Racial Differences in Sympathetic Overactivity Assessed During Recovery from Exercise in Obese Female Adolescents.
Annual meeting of the American College of Sports Medicine, San Francisco, CA, June 2012.

Hall, S.L., R.L. Franco, **M.K. Bowen**, and R.K.Evans. Reductions in Functional Sympathetic Overactivity in Obese Adolescents Following a Weight Management Program.
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Bowen, M.K., S.L. Hall, R.A. Arena, R. K. Evans, E.P. Wickham, R. L. Franco. Sex Differences in the Oxygen Uptake Kinetic Response to Moderate Intensity Exercise in Obese Adolescents. Medicine and Science in Sports and Exercise 2012: 44(5)(Suppl).

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S.L. Hall, R.L. Franco, **M.K. Bowen**, and R.K.Evans. Reductions in Functional Sympathetic Overactivity in Obese Adolescents Following a Weight Management Program. <u>Medicine and Science in Sports and Exercise</u> 2011:43(5)(Suppl):S3112.

Bowen, M.K., Franco, R.L., Wickham, E.P., Evans, R.K. Agreement between BIA and DXA in Estimating Body Composition Changes in Obese Adolescents. <u>Medicine and Science in Sports and Exercise</u> 2010:42(5)(Suppl):S2418

CLINICAL PRACTICE

2010 – 2012   Y.M.C.A. of Greater (Richmond, VA)
                          Personal Trainer and Wellness Coach,

Spring 2009   Medical University of South Carolina (Charleston, SC)
                          Exercise Science Intern

Fall 2008   Virginia Commonwealth University *(*Richmond, VA)
                          Health and Human Performance Lab
                          Exercise Science Intern – T.E.E.N.S.

2008 -2009   Advanced Orthopaedics Center (Richmond, VA)
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COURSES TAUGHT

Virginia Commonwealth University

HPEX 200 Strength, Endurance, & Flexibility Training	Fall 2011, Spring 2012
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COMMUNITY AND VOLUNTEER SERVICES

2011 – Present   Alumni Advisor - Undergraduate Exercise Science Club,
                          Virginia Commonwealth University

          2012   Member of the V.C.U. Student Jeopardy Bowl Team – Placed 2nd at the
                          South East American College of Sports Medicine annual meeting

          2010   Y.M.C.A. of Greater Richmond
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          2009   Cooper River Bridge Run 10k Race committee - Elite Runner Coordinator
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          2008   Undergraduate Student Research, Virginia Commonwealth University
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2007 – 2008	Tutor, Virginia Commonwealth University Campus Learning Center
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PROFESSIONAL CERTIFICATIONS

2009 – Current	Health Fitness Specialist, American College of Sports Medicine
2011 – Current	TRX Suspension Training Class Instructor
2007 – Current	Adult, Child, and Infant CPR/AED and First Aid; American Red Cross

HONORS AND AWARDS

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RELATED COURSEWORK

Human Anatomy and Physiology
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