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Oxygen consumption during exercise: the role of venous occlusion

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OXYGEN CONSUMPTION DURING EXERCISE: THE ROLE OF VENOUS OCCLUSION

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ABSTRACT

Oxygen consumption during exercise is typically used to advance performance, determine fitness level, and make clinical diagnoses. The rate at which VO_2 adjusts to and recovers from (i.e. on- and off- kinetics) a bout of exercise is associated with metabolic processes including restoration of PCr and ATP, replenishment of hemoglobin and myoglobin O_2 stores, and removal metabolic waste. The ability of an individual to utilize these processes can determine the speed at which oxygen consumption rises and falls, and thus is associated with the health of the individual (i.e. faster=fitter; slower=unhealthy). Circulatory occlusion training has become a well-known training technique that allows individuals who cannot exercise at a high intensity to gain physiological adaptations through exercise at a low intensity.

The current study used venous occlusion in an acute bout of exercise to determine whether venous function has an effect on oxygen kinetics. Twelve subjects exercised at ~60% of VO_2 max for 6 minutes on two separate occasions; with lower limb venous occlusion (OCC) and without occlusion (NON). The OCC condition consisted of 40mmHg of pressure applied to the mid-thigh via pressure cuffs. Subjects' VO_2, heart rate, and RER were recorded during exercise and 6 minutes prior and 6 minutes following exercise. All variables were assessed as area under the curve (AUC) 6 minutes prior (pre-exercise rest), during on transition to exercise (on-kinetics), during 6 minutes of exercise (exercise), and 6 minutes after stopping exercise (off-kinetics). No statistically significant differences were observed in AUC between conditions for on- (VO_2;

NON: 6024.97± 1117.56, OCC: 5971.26± 1398.15, HR; NON: 35875± 7713, OCC: 36634± 6379, RER; NON: 246.63± 46.21, OCC: 253.76± 48.78) or off-kinetics (VO_2; NON: 5744.40± 1233.59, OCC: 5913.88± 1498.91, HR; NON: 62672± 22, OCC: 63469± 20, RER; NON: 640.01± 146.53, OCC: 672.01± 156.33). Furthermore, examining truncated time periods showed no significant difference for all variables. In response to venous occlusion, normal healthy individuals showed no alterations in metabolic function suggestive of the potential to buffer accumulated metabolites during acute exercise.

INTRODUCTION

An increasing number of reports can be found in the literature regarding the effects of exercise training with deliberate restriction of venous blood flow on skeletal muscle adaptations. This form of training, known as ‘‘occlusion training’’ or Kaatsu, serves as a powerful stimulant for rapid increases in specific metabolic enzymes, muscle mass, and strength (46). Data suggest that the muscle adaptations seen with KAATSU training protocols can be accomplished with much lower intensities of exercise, which may represent an alternative method of training for individuals intolerant to higher-intensity training protocols. To date, the mechanisms to explain the muscle adaptations seen with KAATSU training are not entirely understood.

Previous work from LSU has revealed some potential negative consequences of occlusion training. Credeur et al. (2010) reported that bilateral handgrip training combined with venous occlusion of the forearm resulted in a significant increase in muscular strength, but a significant decrease in vasodilatory function over a 12 week period. The contrasting change in vascular function after exercise training with venous blood flow restriction in the forearm may in part be the consequence of significant alterations in blood flow patterns during handgrip exercise. It is important that prior to implementation of blood flow restriction training protocols for individuals intolerant to higher-intensity training protocols, greater emphasis should be placed on examining the underlying mechanisms that may contribute to both the potential negative and positive consequences of such training.

One particular area of focus in venous occlusion during exercise appears to be the manner by which blood flow restriction alters skeletal muscle metabolic profiles. It is interesting to note that patients with peripheral arterial disease (PAD), who develop ischemia due to lack of blood flow during exercise, display altered muscle metabolic adaptations in response to exercise training (4). This response is complex and most likely affected by disease severity, duration, and degree of flow restriction during exercise. However, even acute hypoxia has been shown to alter muscle metabolism. For example, Cartee and colleagues (1991) showed that hypoxia stimulates muscle glucose transport by increasing GLUT-4 translocation, with subsequent studies confirming that muscle glucose uptake was enhanced in response to hypoxic conditions. Due to methodological difficulties few studies have examined the acute effects of blood flow restriction on muscle metabolism in humans. An alternative step to examine the effects of blood flow restriction on metabolic responses is to perform whole body gas analyses (whole-body oxygen consumption = VO_2 testing).

Since the early work of AV Hill in the 1920's, VO_2 max testing has been a standard tool in exercise performance (7,18,20,23,54) and clinicians have used peak VO_2 as a criteria to diagnose severity of a disease. For example, peak VO_2 has been used as a prognostic marker for heart failure patients, diseased people have lower average VO_2 max results than do their healthy counterparts, and more recently VE/VCO_2 slope has also been shown to correlate with survival of heart failure patients (1,38). Measuring oxygen utilization has been a valuable tool and, since the discovery of the characteristics of oxygen consumption, much

work has gone in to determining the mechanisms of change before, during, and upon cessation of exercise (VO_2 kinetics).

Recently, VO_2 kinetics, especially during recovery, have also emerged as a powerful diagnostic tool (6,10). The speed at which oxygen consumption changes (kinetics) can shed light into what is happening at the level of muscular metabolism. Many studies have correlated slower oxygen kinetics with untrained subjects, heart patients, PAD patients, and diabetics (1,4,6,38,40,53). A study by Belardinelli et al. (1997) noted slowed VO_2 kinetics, as well as slowed muscle oxygenation, in recovery from exercise in heart failure patients (6). Belardenelli et al. also concluded, that peak VO_2 is inversely correlated with pulmonary VO_2 kinetics and muscle oxygenation mean response times (i.e. the lower the peak VO_2 the higher the mean response times/slower) (6). The conclusion was that people with more severe cardiac dysfunction have slower recovery kinetics with regard to pulmonary VO_2 and muscle oxygenation. The slower kinetics could be attributed to slower resaturation of hemoglobin or the rate of phosphocreatine (PCr) resynthesis (6). Hanada et al. (2000) confirmed the findings from Belardinelli et al. (1997) reporting that heart failure patients have slower rates of PCr resynthesis and hemoglobin resaturation compared to age-matched healthy controls (22). They also noted that the time to re-establish PCr stores was much slower than hemoglobin resaturation in heart failure patients as compared to normal subjects (22). The rates of PCr resynthesis and hemoglobin resaturation were similar in normal subjects, suggesting that the rate of hemoglobin resaturation matches the oxygen utilization to resynthesize PCr (22). Hanada et

al. concluded that the rate of hemoglobin resaturation was not a major determinant of muscle metabolic recovery (evaluated as PCr resynthesis) in heart failure patients (22). Hanada's study suggests that healthy individuals and heart failure patients have different mechanisms controlling oxygen consumption and the rate at which they recover.

The study of oxygen kinetics during submaximal and maximal exercise in diseased individuals led clinicians to use kinetics as a tool to assess functional capacity of unhealthy individuals rather than subjecting them to a maximal exercise test (4). With several studies relating cardiac dysfunction as well as PAD, diabetes, and heart failure with slower kinetics than healthy individuals, it is a wonder why more studies have not examined the mechanisms as to why kinetics are slowed.

Oxygen kinetics, in relation to blood flow, have been examined in many different ways. Blood flow is a critical component in oxygen delivery so reasonably, many studies have been conducted to examine the effect of limiting or enhancing arterial blood flow on VO_2 kinetics (2,5,10,16,17,47,48,54). Chilibeck et al. (1997), in a study comparing VO_2 kinetics of young and old individuals, determined that young individuals with higher capillarization (more capillaries per muscle fiber) experienced faster recovery kinetics than those with lower capillarization. In this study, the on-kinetics (the time at which oxygen consumption adjusts to a certain workload before reaching steady-state) during 6 minutes of moderate intensity plantar flexion exercise and recovery kinetics were compared for young and old individuals. Also, muscle biopsies were used to

determine capillarization in the gastrocnemius muscle. When the groups were combined, a slight correlation was seen between faster VO_2 kinetics and capillarization. When age groups were broken up into young and old and on- and off- kinetics were separated, the strongest correlation observed was a positive correlation between off- kinetics and capillarization in young individuals. In other words, the more capillaries per muscle fiber, the faster the recovery kinetics in young subjects (10). This correlation was not seen in older adults, suggesting that the two groups have different mechanisms determining speed of off- kinetics (10).

Bauer et al. (2007) reported slower VO_2 kinetics as well as blood flow kinetics in individuals with type 2 diabetes mellitus (T2DM) compared to age-matched healthy controls during moderate exercise. They concluded that slow oxygen uptake at the onset of exercise may be due to impaired control of muscle blood flow, specifically lack of vasodilation due to vascular dysfunction (5). Bauer and colleagues (2004) also conducted a study with PAD patients, which showed that due to their limited arterial flow in the legs, PAD patients had slower oxygen kinetics than did healthy people (4).

Venous occlusion and/or lower body positive pressure (LBPP) have been used experimentally to determine the relationship between pulmonary VO_2 kinetics or muscle VO_2 kinetics (VO_{2musc}) and blood flow. A study by Williamson et al. (1996) examined limited blood flow and on- kinetics of VO_2. Subjects were exercised at moderate and heavy intensities with 45 torr of pressure on the legs for 6 minutes. A custom built LBPP chamber induced pressure during cycle

ergometery so only the subjects legs were pressurized. When VO_2 kinetics at the onset of exercise were examined, no significant change existed between those with limited blood flow and those without at either 60% or 80% VO_2 max (52). Paganelli et al. (1989) used circulatory occlusion and release of the forearm to increase the speed of blood flow and found faster kinetics. Cuffs were used to occlude the forearm for several minutes, when cuffs were released blood flow to the area was increased simultaneously with the onset of exercise. This yielded faster VO_2 on- kinetics (36). Walsch et al. (2002) had similar findings with a nearly identical protocol conducted on the thighs. Occlusion of the thighs for several minutes was used to speed blood flow at the onset of exercise thus increasing the speed of VO_2 on- kinetics (48). Faisal et al. (2010) also used circulatory occlusion in 4 different protocols and examined VO_{2musc} uptake, the uptake of oxygen at the muscular level as determined by ultrasound. Overall, blood flow and VO_{2musc} kinetics were positively correlated. However, when occlusion was done for a longer period of time (15 minutes), forearm blood flow was slowed, which also slowed VO_{2musc} kinetics (16). Studies using LBPP or venous occlusion to assess ventilation, cardiac output, and receptor responses have been conducted; however, taken together, the data are inconclusive. In some cases, VO_2 kinetics and blood flow are positively correlated, suggesting a delivery related controlling mechanism for VO_2. However, in some instances of acute exercise or prolonged occlusion, no relationship is apparent (32, 33, 42, 45). Interestingly, many of these studies looked at on- kinetics. No studies have looked at the off- kinetics when circulatory occlusion was used to manipulate

blood flow. Furthermore, blood flow has been typically characterized as arterial blood flow, and oxygen delivery has been the focus of many of the kinetics studies previously mentioned. The numerous clinical studies that relate slow recovery with unhealthy populations warrant an examination of the mechanisms of recovery and how they may be related to venous outflow.

Aerobically trained people are said to have faster on- and off- kinetics, in the sense that they reach steady state faster and recover faster (40). The mechanism by which trained/healthy people have faster kinetics is attributed to their ability to more quickly replenish depleted systems and remove metabolic wastes post-exercise (6,40). Although little is known about the mechanisms of recovery kinetics, many theories have surfaced since the 1920's. The "oxygen debt" theory was first used by A.V. Hill to describe recovery as a need to repay the "deficit" created at the onset of exercise. The term excess post-exercise oxygen consumption (EPOC) was later coined to define this phenomenon, which extensive research has since explored possible mechanisms. The term EPOC refers to the elevated consumption of oxygen associated with returning the body to homeostasis after exercise. Lactate conversion was thought to solely contribute to the higher VO_2 during recovery; however, there are many other metabolic factors to consider (7). Restoration of phosphocreatine (PCr) stores, oxygen stores, and lactate removal/conversion contribute largely to EPOC, especially during the first/fast phase. Oxygen is still being used in recovery to replenish PCr that was depleted at the onset of exercise, which is a likely reason VO_2 will remain elevated during recovery (7). Also, depleted oxygen stores in

myoglobin and hemoglobin are being reinstated during recovery (7). Mitochondrial respiration, which is upregulated by a number of metabolic processes associated with exercise, may take longer to subside and thus accounting for a prolonged (phase 2) of EPOC. Mitochondrial activity may stay elevated after exercise as a result of increased temperature, accumulated calcium ions, and the reinstatement of elevated hormone levels (7). Thus the faster phase of oxygen recovery may be associated with replenishment and the slower phase may be associated with removal.

Given the present research, the altered VO2 kinetic responses in patients with chronic disease and low fitness are not well understood. Further reseach is necessary to understand the effects of blood flow restriction on VO_2 kinetics in order to determine physiologic limitations potentially present in individuals with chronic disease or low fitness..

Study Purpose

The purpose of the present study was to determine whether manipulating venous blood flow will affect oxygen kinetics in young healthy individuals. Specifically, we will test the effects of reducing venous outflow through partial occlusion on oxygen, heart rate, and RER kinetics.

Hypotheses

Based on the literature which reports that healthier people have faster on- and off- kinetics, and that ill unfit individuals with vascular dysfunction have slower on- and off- kinetics (5,10,40), we hypothesized that manipulating blood flow using partial venous occlusion will slow VO_2 kinetics. Furthermore, we

hypothesized that with venous occlusion, we would see a greater difference in the off- kinetics than the on- kinetics, due to the fact that venous occlusion will limit metabolic clearance rather than oxygen delivery. Along with VO_2, we will analyze heart rate and RER to examine recovery of the cardiovascular system and of respiratory gas exchange.

METHODS

Subjects: Healthy males and females, aged 20-33 years participated in this study. All subjects were recruited from LSU kinesiology classes. Individuals with unstable conditions (cardiovascular, metabolic, orthopedic, etc.) that could affect the results were excluded from this study.

Exercise Testing: All subjects participated in a maximal cycling test to determine cardiorespiratory capacity (VO_2 max), and two submaximal tests on 3 separate visits scheduled at the approximately same time of day (see Table Ia-b). Subjects were advised not to eat 2 hours before the tests. All tests were performed using a Monark cycle ergometer. Peak oxygen uptake was measured using a Parvo True One metabolic cart (Parvo Medics, Sandy, UT). Heart rate was recorded every minute using a Polar monitor and blood pressure was taken manually every 2 minutes.

Maximal test (VO_2 max): A graded exercise test to exhaustion was used to determine VO_2 max. Following a 2 minute warm-up at 0.5 kp (35 watts), the workload was increased by 0.5 kp (35 watts) every 2 minutes. Subjects were required to maintain a cadence of 70 RPM throughout the test. The test was terminated if the subject requested to stop, exhibited symptoms, or could not maintain the speed of 70 RPM. VO_2 max (average of the final 30 seconds of the last stage) was determined if the subject met 3 of the criteria for a true max test: RER > 1.1; RPE > 18; Peak HR (within 10 beats of age-predicted maximum heart rate); VO_2 plateau. Subjects were given 6 minutes of passive recovery at or

below 35 watts before dismounting the bike. Blood pressure and heart rate were monitored during recovery.

Submaximal tests: The two submaximal tests were performed at 60% of peak VO_2 achieved during the max test. Prior to the start of exercise, subjects were seated on the bike for 6 minutes. They commenced exercise at a cadence of 70 RPM, at a workload consistent with 60% of VO_2 max for 6 minutes. After exercise, the subjects remained on the bike for an additional 6 minutes. Subjects were asked to limit movement during the recovery period. Throughout the 18 minutes, expiratory gasses were analyzed using the Parvo True One, heart rate recorded every minute, using the Polar HR monitor, and blood pressure taken every 2 minutes. In addition, rating of perceived exertion (RPE) was recorded at the end of each minute of exercise.

Experimental Conditions:

To examine whether blood flow restriction alters oxygen kinetics the experimental design involved two conditions. Condition one involved inflation of leg cuffs to 40mmHg during the submaximal exercise, as previously described (9,52). The purpose of the pressure was to significantly alter venous outflow, yet allow for normal arterial inflow.

During condition two the same cuffs were placed on the legs but remained deflated, ensuring normal flow. The conditions were randomized to avoid any potential bias or condition effect.

Table Ia: Description of tests during visit 1

Visit 1- Max Test	
Introduction	1. Forms- Consent form, 24-hour history, PAR-Q 2. Explanation of graded exercise test 3. Resting measurements- blood pressure, heart rate, height, weight
Graded Maximal Exercise Test	1. Mode- cycle ergometer (Monarch) 2. Speed- 70 RPM 3. Workload- 35 watts incrementally every 2 minutes 4. Measures- VO_2 peak, HR peak, peak workload

Table Ib: Description of tests during visit 2 and 3

Visits 2 and 3 (Occluded vs. Non-Occluded)			
	Mode	Prescription	Measures
Occluded (OCC)	Monarch cycle ergometer	60% VO_2 max converted to workload in kpm/min 40mmHg pressure on legs	VO_2 HR RER AUC for specific periods
Non-occluded (NON)	Monarch cycle ergometer	60% VO_2 max converted to workload in kpm/min no pressure on legs	VO_2 HR RER AUC for specific periods

Data Analysis:

VO_2, Heart Rate, and Respiratory Exchange Ratio Kinetics- The VO_2, heart rate and RER kinetics for the submaximal tests were assessed using the area under the curve (AUC) method, as previously described (Pruessner, JC, 2003). AUCs were estimated as follows: (1) Pre exercise AUC = first 6 minutes of the data collection period; (2) On- kinetics AUC = from 6 to 9 minutes (i.e. first 3 minutes of exercise); Exercise kinetics = from 6 to 11:59min (all 6 minutes of

exercise); Off- kinetics (2) = from 12:01 to 18:00min (represents all 6 minutes of recovery); Off-kinetics (1) = first 3 minutes of recovery (data was examined rudimentarily and is not reported due to no significance) Total kinetics = from 0 to 18 minutes (all data combined for the entire period). Illustrations of the AUC's examined are presented in figures 1-3.

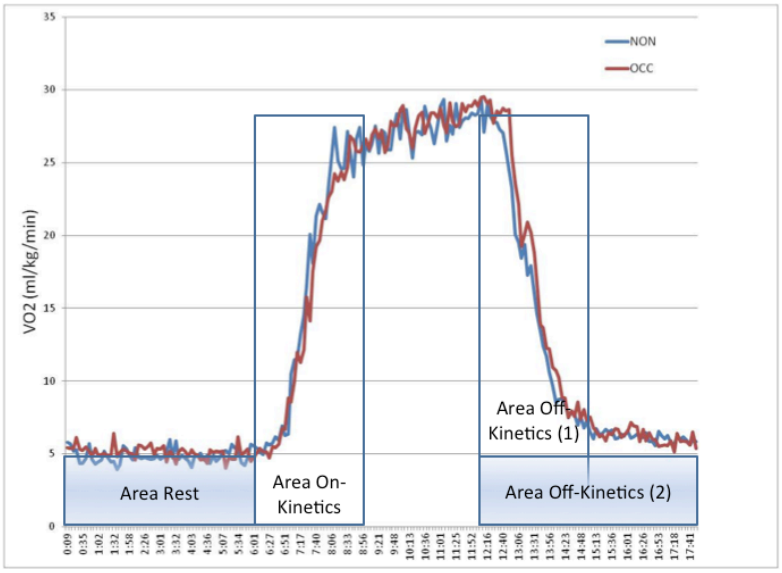

Figure 1

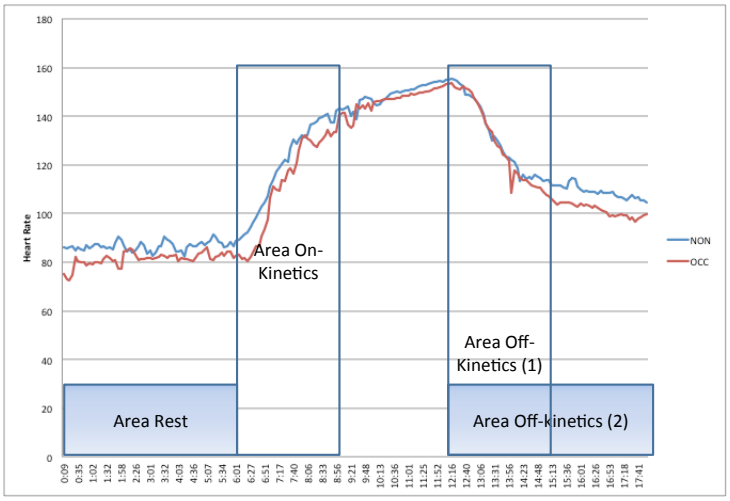

Figure 2

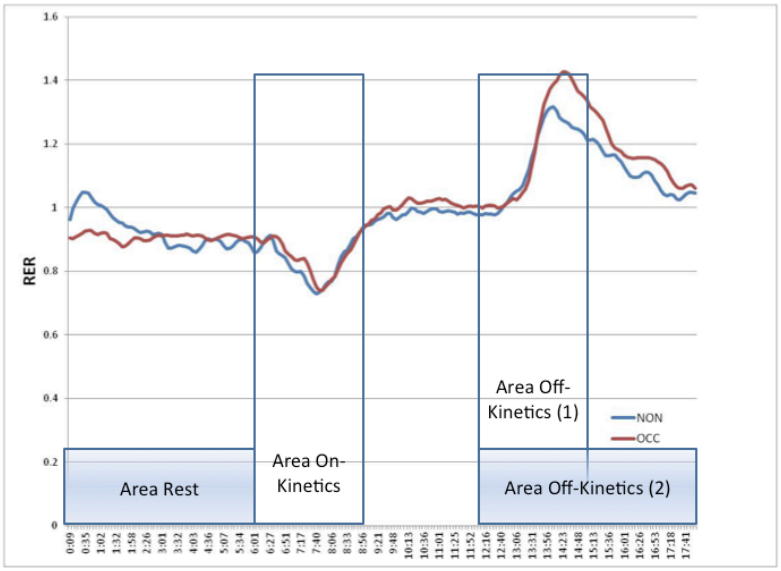

Figure 3

Statistical Analysis:

All statistical analyses were performed using IBM SPSS statistic (version 22.0). Data are presented as mean ± standard deviation. To compare the kinetics for the defined time periods, a multivariate ANOVA was used. Due to technical issues with the Polar monitor, 4 subjects were excluded when analyzing AUC for heart rate (see Table IV and VII). To examine relationships between dependent measures correlational (Pearson Product Moment) analyses were used. An alpha level of $p<0.05$ is required for statistical significance.

RESULTS

Participant Characteristics

Twelve adults (5 male, 7 female) between the ages of 20 and 33 years participated in this study. Baseline measurements of age, height, weight, peak VO_2, BMI, and resting heart rate are listed in Table II.

Table II: Participant Characteristics

Sex	age	height (in)	weight (kg)	VO_2 peak (ml/kg/min)	BMI	Resting HR
F	21	66	60	41.4	21.34	89
F	22	62	52.5	39.4	21.16	95
F	21	63	53.8	38.6	21.01	75
F	20	67	56.4	36.9	19.47	85
M	33	65	86.8	45.7	31.84	58
M	22	67	68.9	48	23.79	76
F	22	61	56.4	37.1	23.49	70
F	22	62	56.6	36.7	22.82	86
M	23	71	83.9	44.8	25.79	93
M	21	71	56.6	49.67	17.40	85
F	22	62	48.8	29.11	19.67	95
M	22	71	77.3	42.67	23.76	84
Average	22.58	65.67	63.17	40.84	22.63	82.58

Pre-Exercise Kinetics for VO_2, Heart Rate, and RER

The average pre-exercise VO_2 was similar between conditions. The data were stable across the 6 minute pre-exercise period, averaging 5.00±0.46 ml/kg/min, for both conditions. No differences were noted for pre-exercise heart rates between conditions either (NON: 87±2; OCC: 82±2. beats/min). The data were not as stable within the 6 minute pre exercise period or between conditions in at least one of the cases due to malfunction of the Polar monitor, resulting in removal of those cases for final analyses. Finally, the average RER during the

pre-exercise period was also similar between the conditions (NON: 0.93±0.06; OCC: 0.91± 0.01).

VO_2, Heart Rate, and RER On-Kinetics

The average on- kinetic responses for VO_2, HR, and RER, are presented in Tables III-V, and Figures 4-6 respectively. No differences were noted for each of the variables, across the first 3 minutes of exercise, between conditions (VO_2: NON: 20.14±2.67; OCC: 20.42±2.45 ml/kg/min; HR: NON: 118±14; OCC: 111±17 bts/min; RER: NON: 0.83±0.08; OCC: 0.84±0.05).

Data for AUC for VO_2, HR, and RER during the first 3 minutes of exercise are presented in Tables VI-VIII. No significant differences were observed for VO_2, HR, and RER kinetics, between conditions. Shortening of the time period from the initial 3 minutes to the first minute of exercise (data not shown) did not reveal any condition differences for the three main variables.

Exercise Kinetics

The average exercise-kinetics (6:01-11:59 min) for VO_2, HR, and RER, are presented in Tables III-V, and Figures 4-6. No differences were noted for each of the variables, across the 6 minutes of exercise, between conditions (VO_2: NON: 21.70±3.00; OCC: 21.40±2.50; HR: NON: 133±14; OCC:128±12; RER: NON: 0.90±0.06; OCC: 0.92±0.04).

Data for the AUC for VO_2, HR, and RER during the 6 minutes of exercise are presented in Tables VI-VIII. No significant differences were observed for VO_2, HR, and RER kinetics, between conditions.

Table III: Average VO_2 (ml/kg/min) response for each time period

Variable/condition		Mean	SD	N
Average Pre-Exercise VO_2	NON	4.8728	0.69084	12
	OCC	5.1164	0.58752	12
	Average	4.9946	0.63939	24
Average VO_2 during first 3 min of exercise	NON	20.1462	2.67397	12
	OCC	20.4250	2.45176	12
	Average	20.2856	2.51293	24
Average VO_2 during 6 min of exercise	NON	21.7095	3.03827	12
	OCC	21.4731	2.70415	12
	Average	21.5913	2.81544	24
Average VO_2 during recovery from exercise	NON	11.5816	2.07551	12
	OCC	12.2606	1.83523	12
	Average	11.9211	1.94713	24
Average VO_2 across the 18 min	NON	13.1830	1.65018	12
	OCC	13.4108	1.45329	12
	Average	13.2969	1.52512	24

Table IV: Average HR (bts/min) response for each time period

Variable/condition		Mean	SD	N
Average Pre-Exercise HR	NON	86.5868	13.04658	12
	OCC	81.3146	14.94910	12
	Average	83.9507	13.98346	24
Average HR during first 3 min of exercise	NON	118.9329	14.25456	12
	OCC	111.0625	16.75446	12
	Average	114.9977	15.73504	24
Average HR during 6 min of exercise	NON	133.6076	14.47576	12
	OCC	128.6024	12.03170	12
	Average	131.1050	13.26604	24
Average HR during recovery from exercise	NON	121.4757	20.16843	12
	OCC	116.9485	18.12620	12
	Average	119.2121	18.89507	24
Average HR across the 18 min	NON	115.4961	15.03970	12
	OCC	110.5811	13.50958	12
	Average	113.0386	14.20450	24

Table V: Average RER response for each time period

Variable/condition		Mean	SD	N
Average Pre-Exercise RER	NON	0.9283	0.22307	12
	OCC	0.9078	0.21886	12
	Average	0.9180	0.21637	24
Average RER during first 3 min of exercise	NON	0.8304	0.08203	12
	OCC	0.8459	0.05217	12
	Average	0.8382	0.06770	24
Average RER during 6 min of exercise	NON	0.9049	0.06596	12
	OCC	0.9251	0.04732	12
	Average	0.9150	0.05708	24
Average RER during recovery from exercise	NON	1.1229	0.11031	12
	OCC	1.1734	0.10830	12
	Average	1.1482	0.10998	24
Average RER across the 18 min	NON	0.9887	0.10043	12
	OCC	1.0077	0.10246	12
	Average	0.9982	0.09969	24

Table VI: AUC for VO_2 responses for each time period

Variable/condition		Mean (AU)	SD	N
AUC Pre-Exercise VO_2	NON	2501.3613	482.05064	12
	OCC	2619.7725	374.47442	12
	Average	2560.5669	426.44997	24
AUC for VO_2 during first 3 min of exercise	NON	6024.9771	1117.55556	12
	OCC	5971.2653	1398.14657	12
	Average	5998.1212	1238.13493	24
AUC for VO_2 during 6 min of exercise	NON	13056.7957	2445.19615	12
	OCC	13210.4112	2596.83060	12
	Average	13133.6035	2467.96196	24
AUC for VO_2 during recovery from exercise	NON	5744.4009	1233.58582	12
	OCC	5913.8800	1498.90844	12
	Average	5829.1404	1345.28815	24
AUC for VO_2 across the 18 min	NON	21349.3803	3942.57285	12
	OCC	21810.6856	4038.03234	12
	Average	21580.0329	3909.97753	24

Table VII: AUC for HR responses for each time period

Variable/condition		Mean (AU)	SD	N
AUC Pre-Exercise HR	NON	40836	9651	7
	OCC	42486	10096	8
	Average	41716	9571	15
AUC for HR during first 3 min of exercise	NON	35875	7713	7
	OCC	36634	6379	8
	Average	36280	6782	15
AUC for HR during 6 min of exercise	NON	70794	16722	7
	OCC	72138	14434	8
	Average	71511	14983	15
AUC for HR during recovery from exercise	NON	62672	22033	7
	OCC	63469	20362	8
	Average	63097	20385	15
AUC for HR across the 18 min	NON	175691	47732	7
	OCC	179239	43643	8
	Average	177583	43956	15

Table VIII: AUC for RER responses for each time period

Variable/condition		Mean (AU)	SD	N
AUC Pre-Exercise RER	NON	450.6920	102.00004	11
	OCC	440.7273	95.36897	11
	Average	445.7097	96.49540	22
AUC for RER during first 3 min of exercise	NON	246.6317	46.20825	11
	OCC	253.7635	48.77620	11
	Average	250.1976	46.50804	22
AUC for RER during 6 min of exercise	NON	499.2970	101.88315	11
	OCC	511.8983	106.06771	11
	Average	505.5977	101.69486	22
AUC for RER during recovery from exercise	NON	640.0976	146.52571	11
	OCC	672.0076	156.32637	11
	Average	656.0526	148.75316	22
AUC for RER across the 18 min	NON	1598.8329	316.86115	11
	OCC	1635.3258	336.67698	11
	Average	1617.0793	319.58666	22

VO_2, Heart Rate, and RER Off- Kinetics

The average off- kinetics for VO_2, HR, and RER, are presented in Tables III-V, and Figures 4-6. No differences were noted for each of the variables, during the 6 minutes of recovery, between conditions (VO_2: NON: 11.59 ±2.07; OCC: 12.26±1.83; HR: NON: 121.47±20; OCC: 116.95±18.12; RER: NON: 1.12±0.11; OCC: 1.17±0.11).

Data for the AUC for VO_2, HR, and RER during the 6 minutes of recovery are presented in Tables VI-VIII. No significant differences were observed for VO_2, HR, and RER kinetics, between conditions.

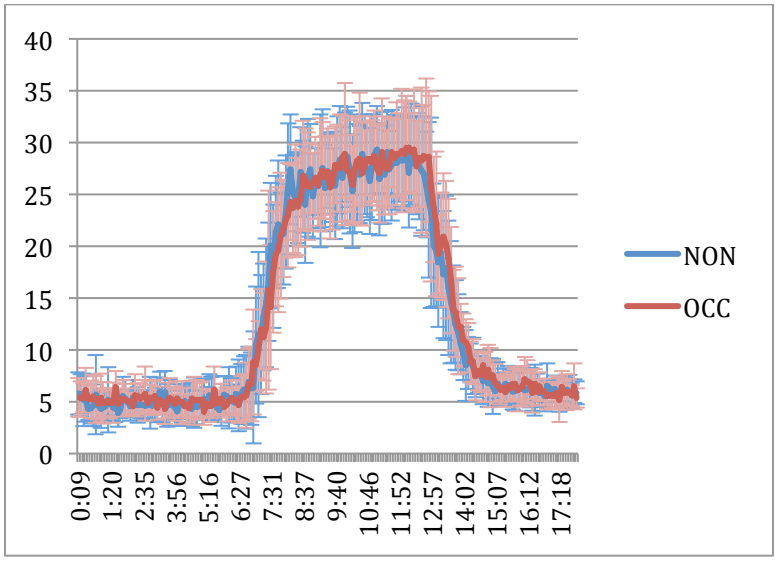

Figure 4: VO_2 Responses (mean±SD) across the 18 minutes

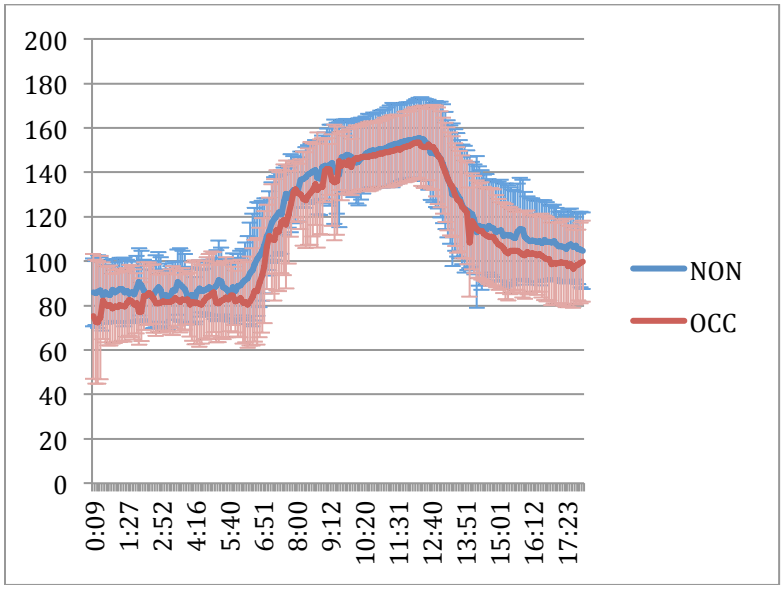

Figure 5: HR Responses (mean±SD) across the 18 minutes

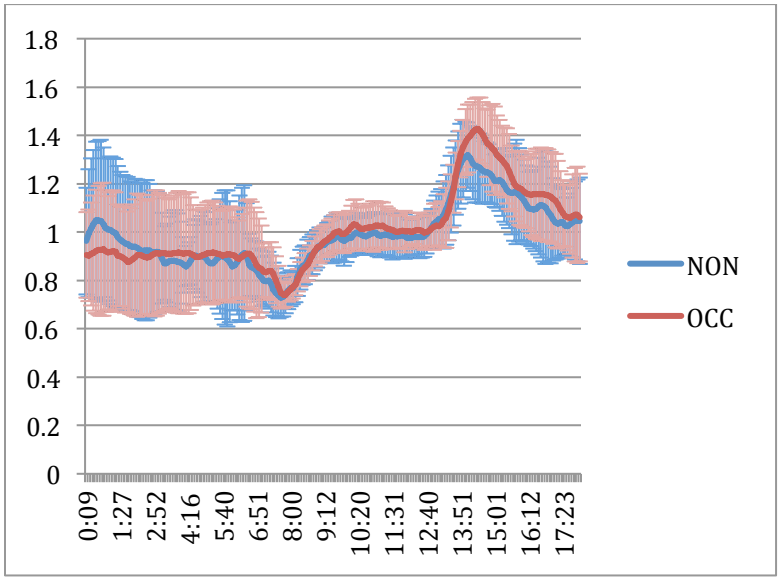

Figure 6: RER Responses (mean±SD) across the 18 minutes

Table IX: Associations between variables of interest

Table IX: Correlation Analyses for Variables of Interest

		VO_2peak (ml/kg/min)	VO_2 On Kinetics (AUC)	VO_2 Off Kinetics (AUC)	VO_2 Exercise Kinetics (AUC)	HR Exercise Kinetics (AUC)	HR Pre Exercise (AUC)	RER Exercise Kinetics (AUC)	RER Off Kinetics (AUC)
VO_2peak (ml/kg/min)	Pearson Correlation	1.00							
	Sig. (2-tailed)								
	N	12							
VO_2 On Kinetics (AUC)	Pearson Correlation	0.41	1.00						
	Sig. (2-tailed)	0.18							
	N	12	24						
VO_2 Off Kinetics (AUC)	Pearson Correlation	-0.05	0.448*	1.00					
	Sig. (2-tailed)	0.87	0.03						
	N	12	24	24					
VO_2 Exercise Kinetics (AUC)	Pearson Correlation	0.24	0.825**	0.763**	1.00				
	Sig. (2-tailed)	0.46	0.00	0.00					
	N	12	24	24	24				
HR Exercise Kinetics (AUC)	Pearson Correlation	-0.54	0.31	0.723**	0.496*	1.00			
	Sig. (2-tailed)	0.07	0.14	0.00	0.01				
	N	12	24	24	24	24			
HR Pre Exercise (AUC)	Pearson Correlation	-0.592*	0.19	0.593**	0.28	0.878**	1.00		
	Sig. (2-tailed)	0.04	0.39	0.00	0.18	0.00			
	N	12	24	24	24	24	24		
RER Exercise Kinetics (AUC)	Pearson Correlation	-0.46	0.451*	0.799**	0.649**	0.917**	0.728**	1.00	
	Sig. (2-tailed)	0.14	0.03	0.00	0.00	0.00	0.00		
	N	12	24	24	24	24	24	24.00	
RER Off Kinetics (AUC)	Pearson Correlation	-0.23	0.441*	0.755**	0.680**	0.761**	0.662**	0.790**	1.00
	Sig. (2-tailed)	0.47	0.03	0.00	0.00	0.00	0.00	0.00	
	N	12	24	24	24	24	24	24	24

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Results for the correlation analysis are presented in Table IX. The data reveal an inverse association between pre exercise heart rates and VO_2peak ($r = -0.592$, $p = 0.04$).

DISCUSSION

The purpose of the present study was to examine whether venous blood flow restriction would affect oxygen consumption (VO_2) kinetics, before, during, and immediately after exercise. Based on the literature, which reports that healthier people have faster recovery kinetics and better vascular function and blood flow (5,10,40), we hypothesized that blood flow manipulation, using partial venous occlusion, would slow oxygen kinetics. The present findings lead us to reject the stated hypothesis. The findings do not reveal a change in VO_2 kinetics, prior to, during the first phase of exercise, throughout exercise, or during the recovery phase from an acute bout of exercise. Moreover, the data did not show significant changes in heart rate and/or the respiratory exchange kinetics, for the same time periods examined. The data suggest healthy, young individuals are capable of normal hemodynamic and metabolic responses during an acute bout of exercise, despite a restriction of venous outflow. The findings also suggest a sufficient buffering capacity, or redundant systems to handle acute venous outflow restriction.

Participant Characteristics

All participants denied having any significant health issues. The age range and VO_2 peak average for all participants in this study are similar to other studies, which focused on the examination of VO_2 kinetics at the onset and in recovery from exercise (6,10,40,52). Based on the findings the present participants can be classified as “healthy” individuals, with below average cardiorespiratory exercise capacity. The present population (average age of 22

years with a VO_2 peak average of 40 ml/kg/min) is very similar to the control group used by Short et al. (1997) who examined postexercise oxygen consumption and recovery in trained and untrained subjects. Their control group averaged 23 years, with an average VO_2 peak of 37 ml/kg/min (40).

Pre-Exercise Kinetics for VO_2, Heart Rate, and RER

The average pre-exercise VO_2, HR, and RER were similar between conditions. The data were quite stable across the 6 minute pre-exercise period for all variables, except in one case where pre-exercise heart rates appeared unreliable secondary to technical issues with the Polar monitoring system. The data do reveal a slight anticipatory effect prior to exercise given the slightly elevated levels for VO_2 and HR. In addition, the RER during pre-exercise period of ~0.91 indicates a tendency for preferential utilization of glucose/carbohydrates. This is not surprising given these measurements were obtained in a seated position on the cycle ergometer.

On- Kinetics

Based on previous studies involving patients with cardiovascular disease, and studies that report acute hypoxia has been shown to alter muscle metabolism, we hypothesized that on-kinetics (specifically O_2 kinetics) would be slower, during an acute bout of exercise with venous occlusion. In contrast, in the present study no significant differences in the on-kinetics were observed for VO_2, Heart Rate, and RER kinetics, between conditions. Further analyses by shortening the time period from the initial 3 minutes of exercise, to the first minute of exercise (data not shown) also did not reveal any condition differences

(VO_2; NON: 6024.97, OCC: 5971.26, HR; NON: 35875, OCC: 36634, RER; NON: 246.63, OCC: 253.76).

Importantly, we recognize that the pressure used to “restrict” blood flow more than likely had its greatest impact on the venous, and not the arterial side of circulation. The purpose of occlusion, in this study, was to limit metabolite clearance rather than induce hypoxia. Thus, it could be argued that oxygen and nutrient delivery was not significantly affected, and subsequently the on-kinetics would remain the same, despite the venous occlusion pressure.

The present findings are in agreement with a previous report by Williamson et al. (1996). Williamson et al. (1996) used LBPP in a similar protocol (6 minute bout of acute exercise) and compared moderate to heavy exercise (below and above lactate threshold, respectively) with 45 torr (similar to the pressure used in the current study) of LBPP (52). No changes in the VO_2 on-kinetics were observed at either intensity, which is consistent with the current findings, suggesting that LBPP and/or increased venous pressure do not discernibly influence the non-steady-state response of oxygen uptake at the onset of a single bout of exercise, in healthy individuals. Conversely, we can argue that the balance between oxygen transport and utilization at the onset of exercise are not that tightly regulated, as previously suggested by Williamson et al. (52). Although relatable, we must note that LBPP and occlusion with the use of cuffs are not entirely the same. LBPP induces a pressure throughout the entire lower body, while occlusion is a localized pressure (i.e. the upper thigh in this case). However, the effects of both are considered to be similar.

The rate of the increase in VO_2 during the rest-to-work transition has been described as a mono-exponential process (24,30,49), and more complex models of description of the VO_2 on-kinetics (3, 39). Currently, during the exercise of low and moderate intensity (*i.e.* below LT), two phases in the VO_2 on-kinetics are recognized and characterized: the cardiodynamic phase, also called phase I; and the primary component, also called phase II (55). The mechanism underlying the VO_2 on-kinetics continues to be a contentious issue that has intrigued physiologists and exercise scientists. The oxygen kinetics at the onset of exercise has been examined thoroughly, but the explanation for the phenomena remains controversial. Currently, two distinct hypothetical explanations exist: 1) the concept of an O_2 limitation to VO_2 kinetics (25); and 2) Evidence for intracellular control of VO_2 kinetics (37).

Data from the current study would support those critical of Hughson's (25,37) concept and confirm several studies that report no changes in O_2 on-kinetics under conditions of blood flow restriction. Compensatory adjustments can apparently be made to maintain adequate muscle O_2 supply. Evidence that the present study resulted in a reduced O_2 supply (secondary to reduced arterial inflow) does not exist. However, data from Sundberg & Kaijser, 1992 suggests a LBPP of 50 Torr, results in a mean leg flow reduction of 16% (range, 13-20%) and a decrease in venous oxygen saturation of 12%, which assuming cardiac output (Q) does not change, would cause a decrease in VO_2 (VO_2= Q* A-VO_{2diff}) (46). The pressure used in the current study was similar (40 Torr) suggesting a similar flow reduction, however VO_2 remained consistent between conditions.

The present data also suggest that flow restriction did not alter those factors involved in intracellular control of VO_2 kinetics. This is in contrast to the stated hypothesis, which was in part based on the premise that the inability to remove metabolites from the working muscle would slow VO_2 on-kinetics. Thus, there appears to be sufficient buffering capacity (i.e. O_2 availability) during the onset of an acute, short bout of exercise with blood flow restriction in “healthy” subjects.

The contrasting hypotheses to explain VO_2 kinetics are always more complex than originally thought. Recent work by Barstow et al. and McDonough et al. suggests the dynamics of capillary muscle blood flow and O_2 kinetics are more closely coupled in comparison to overall muscle blood flow (3). If so, working muscles may operate much closer to a “tipping” point, where significant changes in VO_2 kinetics may arise from only minor impediment to the normal hyperemic control processes. In addition, evidence exists that recruitment of different fiber types may also modify the O_2 supply-to-VO_2 relationships. Whether the imposed condition in this experiment could have had a significant effect on micro-circulatory blood flow, or fiber type recruitment is unknown.

The various phases of the on-kinetics have been linked to different physiological factors. For example, the first phase of the on- kinetics is typically associated with the activation of metabolic pathways and enzymes needed for the initial increase in performance. Components of the metabolic pathways which are in high concentrations at rest (i.e. ATP, PCr) rapidly decline at the on-set of exercise the time course of which is inversely correlated with phase 1 kinetics of

oxygen consumption (23, 52, 53). When oxygen extraction at the muscular level increases during this first phase, the aerobic pathways begin to regulate the production of ATP and PCr levels begin to stabilize, identifying the second phase of the on- kinetics (23, 53). During moderate exercise this happens rapidly, and the individual is able to attain steady state quickly. Factors such as fitness level, fiber type, metabolic activity, and health status of the individual all play a role in determining the speed at which this happens (23). A rudimentary examination of the phase 1 kinetics in the present study also did not reveal significant differences, which was not surprising as we expected metabolite accumulation after steady state to influence kinetics.

In summary, the present data did not reveal significant changes in the on-kinetics, for O_2, HR, and RER, at the onset of a short bout of moderately intense exercise with blood flow restriction. This suggests that compensatory adjustments can apparently be made to maintain adequate muscle O_2 supply and/or that flow restriction (both arterial and venous), did not alter those factors involved in intracellular control of VO_2 kinetics.

Exercise Response

No significant differences were observed for VO_2, Heart Rate, and RER kinetics, between conditions during exercise. During the 6 minutes of exercise, averages for all variables were similar (tables III-V) between occluded and non-occluded conditions. During the 6 minutes of submaximal work, subjects in our study maintained an ability to exercise with a steady state VO_2, heart rate, and RER response even during the occluded condition (see figure 4). A slightly

elevated RER value during exercise (NON: 0.90; OCC: 0.93) suggests a tendency for the body to shift towards an increased carbohydrate (CHO) oxidation during occlusion (see figure 6). Nishiyasu et al. (1998) observed an increase in RER during recovery when they examined the effect of LBPP on cycling positions. Using different pressures (25, 50, and 75 mmHg) and different cycling positions (supine and upright) Nishiyasu's main finding was that with LBPP in the upright position, which is most similar to our study, heart rate and oxygen consumption were unchanged (32). Stickland et al. (2006) used a much more aggressive protocol. Subjects cycled incrementally up to 90% VO_2 max with 52 torr of LBPP. Although oxygen consumption was not Stickland's primary variable, still no change was seen in oxygen uptake during exercise (44). Smith et al. (1999) used a combination of LBPP and cuffs to observe ventilatory responses. Four conditions; control, cuff (90mmHg), LBPP (45 torr), and cuff+LBPP were done at two workloads (60% and 80%). Ventilation was only increased with LBPP and cuff+LBPP at the 60% workload (42). The cumulative take away from these studies is inconclusive; however, the only change in any variable associated with ventilation during exercise was seen with extremely high levels of occlusion (90+45mmHg). This response would likely be more related to a limitation in delivery of blood to the working muscles. Further explanation of these complex results may be attributed to factors related to sympathetic drive, however in relation to the current study there seems to be no conclusive answer in terms of how occlusion affects oxygen consumption.

Off- Kinetics

No significant differences were observed for VO_2, Heart Rate, and RER kinetics, between conditions (tables VI-VIII) during the 6 minutes post-exercise. Shortening of the time period from the end of exercise to the first minute of recovery (data not shown) also did not reveal any conditional differences. A graphic representation of RER kinetics shows an elevated RER value around 2 minutes into recovery (see figure 6). As stated before, a few studies (Williamson; 1996, Nishiyasu; 1998) have also demonstrated elevated RER values during exercise and in recovery. Although the change that we saw was statistically insignificant, we find it interesting because it may indicate a shift toward increased CHO oxidation during occlusion.

The off- kinetics at submaximal workloads can also be described as having 2 phases. The first, fast phase falling quickly for about 40 seconds, then leveling off but still dropping slowly for about 8 minutes (18, 21). However, oxygen consumption in recovery can stay elevated for over an hour (18). Similar to on- kinetics, which is suggestive of using and depleting substrates, the first phase of the off- kinetic response can be associated with the replenishment of substrates (7). During the first 30-40 seconds of recovery, PCr, ATP, hemoglobin and myoglobin stores are being reinstated. The second phase of recovery is thought to be attributed to the upregulation of mitochondrial activity due to accumulated by-products of exercise (7). Factors such as pH change, temperature change, and accumulated calcium and potassium ions can cause mitochondrial activity to stay elevated long after exercise has ceased.

All of the clinical studies, whether CHF, diabetes, PAD, or LVD, patients had slower on- and off- kinetics when compared to healthy controls (1,4,6,38,40,53). The slower kinetics in clinical populations is typically attributed to factors such as compromised aerobic metabolism of muscle, impaired oxygen transport and/or delivery, and an inability to resynthesize PCr (1,4,6,38,40,53). Interestingly, one can argue that the vasculature, and perhaps more directly blood flow, is an important controller of the on- kinetics. The majority of populations that have been found to have slow on- kinetics have compromised heart and/or vascular function. The link between poor vascular function and slow kinetics is what led to the study hypothesis, which was that reducing blood flow using partial venous occlusion would slow oxygen kinetics.

Contrary to our hypothesis, we observed no significant change in VO_2 on- or off- kinetics in the occluded versus non-occluded conditions (see table VI). Thus the hypothesis is rejected and we interpret that acute blood flow restriction does not affect the on- and/or off- kinetics significantly. Data suggest that the subjects retained the ability to switch on the metabolic pathways, without significant interference. The simple explanation is that the venous restriction did not impair oxygen delivery, and thus did not impose an alteration on the on-kinetics. In contrast, we hypothesized that venous restriction would result in metabolite accumulation during and immediately after exercise thereby slowing the recovery kinetics. Again the hypothesis is rejected. Explanations may include technical limitations and physiological compensation. In terms of technical limitations, whether the set up truly resulted in a significant impedance to outflow

is difficult to discern. Based on other research, we have evidence to support the amount of pressure used in the current study. Literature dictates that occlusion pressure between 20-40mmHg is sufficient to cause impedance to venous flow in the legs (9, 52). It appears that these individuals retained the ability to recover despite the limitation of metabolite removal.

During exercise CO_2 is removed in three ways, dissolving in blood plasma or in hemoglobin, combining with plasma proteins and forming an amino compound that is carried through the plasma, and the bicarbonate buffer system (7). The limitations to venous outflow should cause the first two processes to be restricted; however, the buffer system would have been unaffected. The amount of CO_2 produced from cellular respiration is greater than the amount that can be carried by hemoglobin or plasma proteins under normal conditions; in order to compensate for this, the buffer system converts CO_2 into bicarbonate and a hydrogen ion (7). Perhaps some individuals are able to upregulate the buffering capacity when presented with an excess of CO_2 in the plasma. If the buffering capacity of our subjects was great enough to over come the amount of accumulated CO_2 (and perhaps other by-products) than this could be an explanation as to why no change was seen during recovery across all variables. Perhaps the level and duration of occlusion was not sufficient to overcome the ability of our subjects to neutralize metabolites.

The fact that we saw no change in kinetics in young, healthy individuals with occlusion may be attributable to the fact that young individuals do have dense capillarization (6,10,40). Chilibeck et al. (1997) suggested that young

individuals' off- kinetics are more dependent upon O_2 delivery because of the strong correlation to capillary density. This correlation was not seen in older individuals suggesting that the kinetics of young and old individuals have different controlling mechanisms (10). Perhaps the subjects in our study were able to rely more on their ability to deliver O_2 due to strong capillary density so much so that VO_2 in recovery was not altered with occlusion.

As stated earlier, there was a separation seen in the RER values at about 2 minutes into recovery. Nishiyasu et al. (1998) also observed an increase in R during recovery at pressures of 50 and 75mmHg when he examined the effect of LBPP on cycling positions. However, this change was only seen in the supine position. Although the change we observed was not statistically significant, questions arise as to what pathways are being relied on during occlusion. An increase in RER could mean a shift towards anaerobic pathways rather than relying mostly on aerobic metabolism.

Future Considerations

The subjects in our study were unaffected by venous occlusion; however, we may have seen different results with a group of older individuals who do not necessarily have vascular problems. Apparently healthy older individuals, experience muscle atrophy and have low capillary density (capillaries per fiber area). Perhaps these limitations to flow would produce different results than those we observed in younger adults. Further investigation should be directed toward older individuals, especially since this is the population in which we typically see vascular disease.

The amount of occlusion used in this study was sufficient to limit venous outflow, but not arterial inflow. Furthermore, the level of occlusion will not completely halt removal of metabolites, but merely slow removaland allow for them to accumulate in the tissues. The other studies mentioned above used different amounts of and techniques to induce occlusion. Perhaps the variability in previous studies is a product of the level of occlusion and the way in which it was applied. Lower body positive pressure seems to be a more realistic approach to causing the type of vascular resistance that one might experience with cardiovascular dysfunction. The use of LBPP and repeated bouts of occlusion may produce different results and give a better representation of what is happening in diseased populations.

The primary goal of this study was to determine whether or not a link exists between venous occlusion and VO_2 kinetics. The purpose of this investigation is mainly clinical, due to the issues that patients with cardiovascular disease experience with tolerance to exercise and slower rates of adjustment to and recovery from exercise. Although we were unable to prove a link between acute flow restriction and VO_2 kinetics, an interesting design would be to examine repeated bouts with venous restriction. After all, the patients who experience vascular problems do so chronically, not acutely. A study like this would further advance upon the current discrepancies among kinetic studies using LBPP, and would also provide a link between VO_2 kinetics and the use of flow restricted training (KAATSU). The use of KAATSU has been shown to increase muscle hypertrophy compared to controls (i.e. the same intensity

training with flow restriction). Studies have shown resistance training, as well as walk training at intensities as low as 20% VO_2 max, result in increases of up to 7% muscle mass and 10% isometric strength. These muscle gains are attributed to an increase in serum growth hormone as well as a down regulation of myostatin seen after repeated bouts of KAATSU training. The mechanism by which this happens is still unclear. Considering the large interest in adapting this training method for older, clinical population who are less tolerable to high intensities of exercise, these types of occlusion studies could benefit from simultaneous research lines.

Limitations

Pressure fluctuations in the limb cuffs during exercise represent a relative limitation of the study. As the muscle contracted, the cuffpressure was altered. However, the pressure always stayed above 20mmHg, which is sufficient for venous occlusion. Through observation, the subjects with larger muscle mass in the legs caused a larger fluctuation in cuff pressure. With these observations in mind, the lack of change in VO_2 seen among our subjects could be due to a mechanical advantage and ability to move blood due to the muscle pump.

CONCLUSION

In conclusion, this study has provided additional information about the mechanisms involved with recovery kinetics. The fact that we saw no change in VO_2 kinetics adds to the debate over whether kinetics are dependent or independent of O_2 delivery. The findings of this study support the research demonstrating O_2 kinetics are independent of venous blood flow; however, we cannot be certain that O_2 delivery was unaltered in this study. In addition, this study may also provide insight for further research into KAATSU trainingAt this point, it appears that an acute bout of exercise with venous occlusion is safe. These findings also provide future researchers with a starting point for investigating multiple bouts of occlusion training.

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VITA

Tiffany Saltzman is 26 years old from the small town of Kaplan, Louisiana. She graduated from Kaplan High School in 2006 in the top 8% of her class. She was a track athlete at the University of Louisiana at Lafayette. The choice of kinesiology as a major came easy as she was involved in sports throughout her life, and always took an interest in biology. She graduated from the University of Louisiana at Lafayette with a Bachelor's of Science in Kinesiology with a concentration in Exercise Science with a 3.75 GPA. Tiffany gained her personal trainer certification during college. She has been working as a trainer for 5 years. As a former track athlete and a currently avid runner, her research interests are drawn toward cardiovascular physiology. She began work on her Master's degree in 2011, finishing two and a half years later. Upon completion of her Master's, Tiffany plans to get certified as a clinical exercise physiologist, in hopes of taking her passion for training to the next level.