Published in final edited form as:

Arch Phys Med Rehabil. 2010 September ; 91(9): 1402–1409. doi:10.1016/j.apmr.2010.06.003.

Exploratory Study on VO₂ On-kinetics During Treadmill Walking in Women With Systemic Lupus Erythematosus

Randall E. Keyser, PhD, FACSM, Violeta Rus, MD, PhD, Jamal A. Mikdashi, MD, MPH, and Barry S. Handwerger, MD

Center for the Study of Chronic Illness and Disability, George Mason University, Fairfax, VA (Keyser), and the Departments of Physical Therapy and Rehabilitation Science (Keyser), and Medicine (Rus, Mikdashi, Handwerger), University of Maryland School of Medicine, Baltimore, MD

Abstract

Objective—To determine if oxygen consumption (VO₂) on-kinetics differed between groups of women with systemic lupus erythematosus (SLE) and sedentary but otherwise healthy controls.

Design—Exploratory case control study.

Setting—Medical school exercise physiology laboratory.

Participants—Convenience samples of 12 women with SLE and 10 sedentary but otherwise healthy controls.

Intervention—None.

Main Outcome Measurements—VO₂ on-kinetics indices including time to steady state, rate constant, mean response time (MRT), transition constant, and oxygen deficit measured during bouts of treadmill walking at intensities of 3-METS and 5-METS.

Results—Time to steady state and oxygen deficit were increased and rate constant was decreased in the women with SLE compared to controls. At the 5-MET energy demand, the transition constant was lower and MRT was longer in the women with SLE than in the controls. For a comparable, relative energy expenditure that was slightly lower than the anaerobic threshold, the transition constant was higher in the controls than in the women with SLE.

Conclusion—VO₂ on-kinetics was prolonged in the women with SLE. The prolongation was concomitant with an increase in oxygen deficit and may underlie performance fatigability in women with SLE.

Keywords

Exercise; Oxygen consumption; Rehabilitation

Systemic lupus erythematosus is a collagen vascular disease that affects as many as 1.5 million people in the U.S. alone¹. Ninety percent of patients with SLE are women and the disease is

Reprint requests to Randall E. Keyser, PhD, Center for the study of Chronic Illness and Disability, College of Health and Human Services, George Mason University, 4400 University Dr, MS 5B7, Fairfax, VA 22030, rkeyser@gmu.edu.

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

most prevalent in the second to fifth decades of life^{2, 3}. Fatigue is among the top three debilitating symptoms of SLE and persists in nearly all patients who have the disease^{4–8}. In patients who have SLE, the severity of fatigue^{9, 10} and physical disability⁹ have been strongly associated with decreases in aerobic capacity^{9–13}.

Phenotypes of aerobic capacity include peak VO_2 , anaerobic threshold, and VO_2 on-kinetics¹⁴. Each phenotype characterizes a different cardiorespiratory response to physical activity and is regulated by a separate mechanism. For example, peak VO_2 is an index of the maximum rate at which the aerobic system can supply energy^{14, 15}. The rate-limiting factor for peak VO_2 is thought to be attainment of maximum cardiac output (Qt) but other factors can limit peak VO_2 as a result of pathomechanisms^{14, 15}. Severely low peak VO_2 has been reported in patients who had SLE compared to healthy controls^{9, 10, 13} and patients who had anemia or hypertension¹¹. Peak VO_2 has been strongly and indirectly associated with self-reports of fatigue severity^{9, 10} and physical disability⁹ in patients with SLE.

The second phenotype, anaerobic threshold, is the VO_2 corresponding to the onset of anaerobic by-product accumulation during cardiopulmonary exercise testing^{14, 16, 17}. A collage of factors, the confluence of which is not completely understood¹⁵, appears to mediate the anaerobic threshold. When aerobic energy output is insufficient for meeting the total energy expenditure, the deficit must be compensated by increased anaerobic glycolysis. High levels of glycolytic activity result in the accumulation of anaerobic by-products in plasma and muscle cells^{14, 15, 17}, which mechanizes work induced fatigue and physical activity intolerance¹⁸. Severe decreases in anaerobic threshold have been reported in patients with SLE^{9–11, 13}. In one study, women with SLE approached their anaerobic threshold while walking on a treadmill at energy demands of only 3-METS¹⁰. Healthy controls reached their anaerobic threshold at approximately 5-METS. For most healthy adults, energy expenditures of between 3-METS and 5-METS are of moderate intensity^{19, 20} and easily tolerated.

VO_2 on-kinetics reflects the rapidity with which the aerobic system can transition to a state of increased energy output^{14, 21, 22}. From the onset of physical work, total energy output must be sufficient for meeting the energy demand. However, aerobic energy output increases gradually over time (Figure 1), continuing until the energy output of the system reaches a steady state that meets the total demand^{14, 21, 23}. Until the steady state is attained, anaerobic glycolysis compensates for what would otherwise be the energy deficit (oxygen deficit). Because the anaerobic energy contribution is indirectly determined by the rate at which aerobic energy output increases, slowing of VO_2 on-kinetics may impair the ability to sustain physical activity. VO_2 on-kinetics appears to be regulated by microcirculatory dynamics^{24–26}, and mitochondrial function^{27–29}. Pathological adaptations occurring in the muscle capillary bed of patients with SLE could impair microvascular reactivity and oxygen diffusion^{30–34}. However, a report on VO_2 on-kinetics in patients with SLE was not found.

The purpose of this study was to provide an initial characterization of VO_2 on-kinetics during treadmill walking in women with SLE. VO_2 on-kinetics was examined at what are typically moderate intensities for most healthy adults in who cardiorespiratory function is uncompromised. The hypothesis that VO_2 on-kinetics may be diminished in women with SLE was tested. The main analysis compared five indices of VO_2 on-kinetics between a group of women with SLE and a group of sedentary but otherwise healthy controls.

METHODS

Subjects

Twelve sedentary women who had SLE and 10 sedentary but otherwise healthy women participated in this study (Table 1). Ages ranged from 27 to 57 years in the subjects with SLE

and from 30 to 43 years in the controls. Subjects denied participating in any physical activity that caused them to perspire for 10 minutes or longer, once or more per week, in the six months prior to participation. Subjects with SLE met at least four of the 11 American College of Rheumatology 1982 Revised Criteria for the Classification of Systemic Lupus Erythematosus³⁵. The women with SLE had Systemic Lupus Activity Measure scores indicating their disease activity had been negligible to mild with no flares for the previous 30 days. Six of the women with SLE were on maintenance doses of prednisone (mean dose = 9.2 ± 3.8 mg/day, $n=6$); two were on five mg/day, three were on 10 mg/day, and one was on 15 mg/day. None of the women with SLE had comorbidities known to impair treadmill walking. Exclusionary conditions included circulatory, chronic or restrictive pulmonary, renal, neurological, or musculoskeletal diseases, which would adversely affect cardiorespiratory function. Those with severe anemia (plasma [HB] < 12 g/dl), fibromyalgia or chronic fatigue syndrome were also excluded. None of the subjects was taking medications known to limit or enhance exercise tolerance or aerobic capacity.

This protocol was reviewed and approved by the institutional, human subjects review board prior to its beginning. Informed consent was obtained from each subject prior to participation in accordance with institutional policies and the Declaration of Helsinki³⁶.

Apparatus and Formulae

Exercise tests were completed on a Trackmaster motorized treadmill^a and pulmonary gas exchange measurements were made using a Medgraphics Cardio 2, breath-by-breath cardiopulmonary exercise testing system^a. The system was calibrated before each test. Anaerobic threshold was determined by the V-slope method³⁷. Peak heart rate was determined electronically from an electrocardiogram by multiplying the six-second cardiac cycle rate by 10. Peak cardiac output (Qt) was measured by the exponential rise CO₂ rebreathing technique³⁸ applied at peak exercise. Peak arteriovenous oxygen difference (a-vO₂) was calculated by dividing peak VO₂ by peak Qt.

VO₂ on-kinetics was characterized using the monoexponential model developed by Whipp²³. VO₂ was plotted on time during continuous work rate tests (Figure 1). The algorithm, $VO_{2(t)} = (\Delta VO_2 + VO_{2rest})(1 - e^{-kt})$ was then applied. In this model ΔVO_2 is the amplitude of increase in oxygen consumption at the sixth minute of exercise, t is time, and K is the rate constant. Attainment of a steady state was determined by the least squares method and confirmed by absence of a statistically significant increase in VO₂ between the third and sixth minutes of the exercise bout. Pearson product moment correlation coefficients (r) were calculated to quantify goodness of fit of the VO₂ kinetics algorithm. Goodness of fit was determined by the relationship between the iterations of VO₂ plotted on time generated by the algorithm and those actually measured. Significant correlation coefficients indicated high goodness of fit for the VO₂ on-kinetics model (Table 2). Eighty nine percent and 91% of the variances in VO₂ were attributed to the time domain in the women with SLE and controls respectively. Oxygen deficit was calculated as [6 minutes times steady state VO₂] minus the area below the VO₂-time curve (Figure 1). The overall VO₂ on-kinetics rate was quantified by a transition constant, calculated as the quotient of VO₂ and MRT³⁹, where MRT is the mean response time.

Procedure

Subjects first rested quietly in the supine position for at least 10 minutes. Subjects then completed a maximum treadmill test according to the modified Bruce protocol⁴⁰. The targeted stopping point for this test was the subject's indication that she could not continue exercising

^aMedical Graphics Corporation. 350 Oak Grove Parkway, St. Paul, MN 55127.

despite strong encouragement from the testing staff. Pulmonary gas exchange and heart rate were measured throughout the test. Cardiac output was measured at peak exercise.

Forty eight to 164 hours after completing the maximum treadmill tests, subjects completed two randomly ordered, continuous work rate tests. A simple Latin square randomization method ensured equal ordering. These tests consisted of six minutes of sustained treadmill walking at 3-MET and 5-MET energy demands. The intensity of 3-METs corresponded to treadmill walking at a speed of 2.0 mph and an inclination of 1.5% grade^{19, 20}. The intensity of 5-METs corresponded to a speed of 2.0 mph and an inclination of 9.0% grade^{19, 20}. Subjects rested quietly for 10 minutes prior to the first test in the order. A recovery period separated the first test in the order from the second test. During recovery, subjects rested in the supine position for 20 minutes or longer, until heart rate and VO_2 returned to resting levels. VO_2 was measured continuously throughout these work bouts and VO_2 on-kinetics was determined from these measurements.

Statistics

Data were analyzed using the SAS, version 9.1, statistical analysis system^b. One and two-way ANOVA and ANCOVA were used for testing for intergroup, test, and interaction differences. The least squares means procedure was applied following the finding of a significant interaction in the two-way analyses. The general assumptions underlying these procedures are that ratio or interval data is being analyzed and that additional observations beyond our small sample ($N=22$) would trend toward a normal distribution of the mean according to the Central Limit Theorem⁴¹. Dependent variables measured during the maximum treadmill test were secondary outcome measures and included were peak VO_2 , anaerobic threshold, Qt , a-vO_2 , respiratory exchange ratio and heart rate. These data were assessed for significant group differences by one-way statistical analyses. The main outcome variables for this study were the indices of VO_2 on-kinetics including transition constant, time to steady state, rate constant, MRT, and oxygen deficit. These data were acquired during the submaximal, continuous work rate tests and assessed for significant group and test differences by two-way analyses. Statistical significance was set at $p \leq 0.05$. Reported means are adjusted for covariance when appropriate. Otherwise, data are reported as simple means $\pm$ one standard deviation.

RESULTS

Despite the difference in the age ranges, mean age and other group demographics were similar for the women with SLE and controls (Table 1). Gas exchange data obtained from the maximum treadmill tests are also provided in Table 1. Both groups attained a peak RER of greater than 1.15 and a peak heart rate of at least 90% of the age predicted peak heart rate, where predicted peak heart rate = $220 \text{ bpm} - 1 \text{ bpm per year of age}$. These criteria are accepted indicators that VO_2 approached a physiologically maximal level at volitional exhaustion^{19, 20, 42} and that tests were not stopped early due to motivational factors.

Age was not a significant covariate in the group comparisons of peak VO_2 , anaerobic threshold, Qt , a-vO_2 , RER, or any of the measures of VO_2 on-kinetics. ANOVA indicated that peak VO_2 and anaerobic threshold were 30.4% and 27.9% lower in the women with SLE than in the controls, respectively (Table 1). Measurements of Qt were available in eight patients with SLE ($14.0 \pm 0.31 \text{ L/min}$) and eight controls ($13.8 \pm 0.28 \text{ L/min}$). Qt was not significantly different between these subgroups. However, peak a-vO_2 was 21% lower ($p < 0.029$ CI: 11.3 to 30%) in the women with SLE ($10.5 \pm 0.24 \text{ vol\%}$) than in the controls ($13.3 \pm 0.21 \text{ vol\%}$).

^bSAS Institute Inc. 100 SAS Campus Drive, Cary, NC 27513-2414

A significant difference in ΔVO_2 was not observed between the women with SLE and the controls (Table 3). ANOVA indicated that ΔVO_2 was significantly higher ($p<0.002$, 95% CI: 180 to 252 ml/min) for the 5-MET energy demand than for the 3-MET energy demand. A significant difference in ΔVO_2 was not observed between the third and sixth minutes of exercise in either group or between the 3-MET or 5-MET tests. ΔVO_2 covaried significantly with rate constant ($p<0.002$), MRT ($p<0.015$) and oxygen deficit ($p<0.001$). ΔVO_2 did not covary with transition constant, or time to steady state.

Time to steady state, rate constant, and oxygen deficit responses are depicted in Figure 2. ANOVA indicated that time to steady state was significantly longer ($p=0.0027$; CI: 0.13 to 2.11 min) for the 5-MET test than for the 3-MET test. ANCOVA and ANOVA main effects indicated that rate constant was lower ($p<0.005$; 95% CI: 0.00 to 0.42 min^{-1}), time to steady state longer ($p<0.016$; 95% CI: -0.08 to 1.86 min), and oxygen deficit higher ($p<0.028$; 95% CI: -32 to 216 ml) in the women with SLE than in the controls.

Figure 3 describes the group and test differences in transition constant and MRT. ANOVA indicated that for the 5-MET test, the transition constant was lower ($p<0.004$; 95% CI: 0.393 to 7.647 ml/min/sec) and the mean response time longer ($p<0.0170$; 95% CI: -2.701 to 34.720 sec) in the women with SLE than in the controls (Figure 3). In the women with SLE, the transition constant did not increase from the 3-MET test to the 5-MET test. However ANCOVA indicated that MRT was significantly ($p<0.0237$; 95% CI: -02 to 32 sec) longer for the 5-MET test than for the 3-MET test in the women with SLE. In controls the transition constant significantly ($p<0.0136$; 95% CI: 0.094 to 6.08 ml/min/sec) increased from the 3-MET test to the 5-MET test, whereas test differences in their MRT were not observed.

In the women with SLE, VO_2 at six minutes of walking at 3-METS was $88.5 \pm 25.9\%$ of the anaerobic threshold value. In the controls, VO_2 at six minutes of walking at 5-METS was $87.3 \pm 23.8\%$ of the anaerobic threshold value. Although these percentages of anaerobic threshold VO_2 were nearly identical between the groups, the transition constant was significantly ($p<0.014$; 95% CI: -0.20 to 7.02 ml/min/sec) higher in the controls than in the women with SLE (Figure 3).

DISCUSSION

In the women with SLE, VO_2 on-kinetics was prolonged in response to what are typically moderate and easily tolerated walking intensities for most healthy individuals. The maximum rate for VO_2 on-kinetics was attained at the 3-MET energy demand in the women with SLE, whereas a significant increase in the rate occurred between the 3-MET and 5-MET energy demands in the controls. Moreover, the VO_2 on-kinetics rate was lower in the women with SLE than in the controls, even at comparable levels of energy expenditure relative to and slightly below the groups' anaerobic thresholds. Results of this study were in agreement with the hypothesis that VO_2 on-kinetics may be reduced in women with SLE, particularly during treadmill walking at work rates that are of moderate intensity for most healthy subjects.

In the control group, peak VO_2 was similar to age predicted, population normative values as determined by the well-established algorithm of Bruce^{43, 44}. Anaerobic threshold occurred on average at approximately 62% of peak VO_2 , a level typical of healthy adults^{45, 46}. In addition, the MRT was similar to previous reports in healthy, sedentary adults^{47–49}. These findings suggest that, in the controls, the aerobic response was indicative of those expected for sedentary but otherwise healthy women in the general population.

The magnitude of the observed decreases in peak VO_2 , anaerobic threshold, and VO_2 on-kinetics in the women with SLE in this study were similar to those previously reported in patients with chronic illnesses such as congestive heart failure^{50, 51}, chronic obstructive

pulmonary disease⁵² and highly active antiretroviral therapy for HIV infection^{39, 53, 54}. Peak VO_2 in the women with SLE was also far below values reported after 10 days of bed rest in healthy women of similar ages⁵⁵. In the women with SLE, peak VO_2 was $32.0 \pm 13.3\%$ lower than levels expected for healthy, sedentary women of similar ages, as determined by the well established algorithm of Bruce^{43, 44}. The decreases in peak VO_2 ^{9, 11, 13, 56}, and anaerobic threshold^{11, 13, 53, 56} in the women with SLE in this study were also similar to previous reports on patients with SLE. All combined, the number of observations in these reports was substantial. No previous reports were found in which peak VO_2 or anaerobic threshold in patients with SLE were similar to or higher than healthy controls'. In concert, the totality of observations suggest that the trends observed in this and the previous studies may reflect activity-induced, metabolic responses that are characteristic of the population of patients with SLE in general. However, previous information is lacking regarding VO_2 on-kinetics in patients with SLE.

The initial component of VO_2 on-kinetics is a fast response in which VO_2 increases rapidly towards the steady state. Proposed regulators⁵⁷ of the fast component include central circulatory oxygen delivery^{58–60}, capillary blood flow dynamics^{24–26}, and dynamics of muscle fiber recruitment^{24, 61}. Mitochondrial inertia and respiratory chain inhibition have also been suggested as fast component regulators^{27–29, 27, 28, 62}. Group similarity in peak $\dot{V}_{\text{O}_2}$ suggested that central circulatory oxygen delivery was not impaired in these women with SLE. Conversely, the large reduction in peak a-VO_2 suggested that aerobic metabolism could have been limited by restricted muscle oxygen extraction. Microvascular adaptations have been observed in skeletal muscle samples obtained from individuals who had SLE^{30–34}. These adaptations could impair muscle oxygen extraction and slow the fast component by diminishing the microvascular reserve and impeding oxygen influx diffusion.

A plateau in the VO_2 -time plot follows the fast component, indicating that an aerobic steady state has been achieved with the total energy demand^{14, 21, 23}. However, the plateau is often replaced by a slower rise of VO_2 that delays the onset of the steady state when the work being performed is of severe intensity⁶³. This slow component may be less likely to occur during treadmill exercise than during cycling⁶⁴. Some^{29, 65–67} but not all⁶⁸ studies have suggested that progressive recruitment of Type-II muscle fibers may mediate the slow component. Predominance of Type-I muscle fibers and selective Type-II muscle fiber atrophy have been observed in muscle samples obtained from individuals with SLE⁶⁹. This adaptation is not completely understood but could possibly attenuate a slow component transition.

VO_2 on-kinetics is slower in untrained individuals than in those who are more physically fit^{70, 71}. Aerobic exercise training may improve VO_2 on-kinetics^{72–74}. While aerobic exercise training has been reported to increase peak VO_2 and anaerobic threshold in patients with SLE^{12, 75}, further research is needed to determine whether exercise training can improve VO_2 on-kinetics in patients with SLE.

Study Limitations

Half of the women with SLE in the current study were maintained on non-fluorinated, orally administered prednisone with doses well below 40 mg/day. Drug induced myopathy is one possible side effect of this medication, particularly when the agent is fluorinated or dosages exceed 40 mg/day⁷⁶. Orally administered prednisone dosages, similar to those used by patients in the current study, have been shown to neither decrease mitochondrial enzyme concentrations⁷⁷ nor reduce peak VO_2 ⁷⁸. However, the effect of prednisone on VO_2 on-kinetics is yet unknown.

Physically inactive lifestyle was an inclusion criterion of this study. However, routine physical inactivity was determined subjectively and by a single question. Because patients with SLE

may be more fatigable, physical activity levels could have been slightly lower in the women with SLE than in the controls. Bostrom and associates reported that peak VO_2 was not related to daily physical activity levels in women with SLE⁵⁶. However, it remains unknown as to whether VO_2 on-kinetics is associated with daily physical activity in this patient population.

The rate of VO_2 on-kinetics may be increased by prior, strenuous exercise^{79–81}. Equal randomization of test order and a return of VO_2 to baseline levels between the tests were used in an attempt to minimize this effect. An equal number of subjects completed each of the testing orders in both of the groups. However, the 5-MET energy demand was above the anaerobic threshold only in the women with SLE so it may have been more strenuous for them than for controls. Bias in the distribution of this effect may have been introduced despite equality in the test order. If so, the rate of rise in VO_2 during the 3-MET exercise bout could have been slightly increased and the time taken to achieve the steady state slightly decreased, by prior exercise, in the women with SLE who completed the 5-MET test before completing the 3-MET test.

Menstrual cycle phase and use of oral contraceptives were not controlled in this study. Dean and associates reported that in healthy women, menstrual phase had no effect on peak VO_2 or lactate threshold⁸². Lebrun et al⁸³ reported a small decrease in peak VO_2 of 4.7% from the follicular to the mid-luteal phase in a group of healthy women using oral contraceptives. However, a slight increase of 1.4% occurred across these phases in a placebo control group. Similar effects would account for a variance of no greater than -20% to +06% of one standard deviation from the mean peak VO_2 in the women with SLE (-0.95 to +0.28 ml/kg/min) and -27% to +08% in the controls (-1.36 to +0.40 ml/kg/min). Thus the potential bias introduced by variance in the menstrual phase and uncontrolled use of oral contraceptives appears to be minimal.

For this study, a convenience sample of patients with SLE was recruited in which volunteers were identified and selected from patient records. Due to the non-randomized selection of the small sample of subjects, selection bias could have affected the interpretation of the results. Therefore, even though there were response similarities among these subjects with SLE and numerous other reports, generalizations to the overall population of subjects with SLE must be made with due caution.

CONCLUSIONS

VO_2 on-kinetics during treadmill walking was slower in the women with SLE than in sedentary but otherwise healthy controls. Oxygen deficit was higher in the women with SLE than the controls. It is possible that impaired VO_2 on-kinetics may contribute to performance fatigability in patients with SLE.

Acknowledgments

Supported by a grant from the National Institutes of Health, (grant no. 1R03HD39775).

List of Abbreviations

ANCOVA	analysis of covariance
ANOVA	analysis of variance
SLE	Systemic lupus erythematosus
METS	metabolic equivalents

MRT	mean response time
RER	respiratory exchange ratio
VO ₂	oxygen consumption

References

1. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008;58:26–35. [PubMed: 18163497]
2. Pisetsky, D.; Buyon, J.; Manzi, S. Systemic lupus erythematosus. In: Klippel, H.; Crofford, L.; Stone, J.; Weyand, C., editors. *Primer on the Rheumatic Diseases*. 12. Atlanta: Arthritis Foundation; 2001.
3. Rus, V.; Hajeer, A.; Hochberg, M. Systemic lupus erythematosus. In: Silman, A.; Hochberg, M., editors. *Epidemiology of the Rheumatic Disease*. 2. New York: Oxford University Press; 2001.
4. Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria for Fatigue AH. Measurement of fatigue in systemic lupus erythematosus: A systematic review. *Arthritis Rheum* 2007;57:1348–57. [PubMed: 18050225]
5. Krupp LB, LaRocca NG, Muir J, Steinberg AD. A study of fatigue in systemic lupus erythematosus. *J Rheumatol* 1990;17:1450–2. [PubMed: 2273484]
6. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46:1121–3. [PubMed: 2803071]
7. Lahita, RG. Systemic lupus erythematosus. 4. San Diego, Calif: Academic Press; 2004.
8. Tench CM, McCurdie I, White PD, D'Cruz DP. The prevalence and associations of fatigue in systemic lupus erythematosus. *Rheumatology (Oxford)* 2000;39:1249–54. [PubMed: 11085805]
9. Tench C, Bentley D, Vleck V, McCurdie I, White P, D'Cruz D. Aerobic fitness, fatigue, and physical disability in systemic lupus erythematosus. *J Rheumatol* 2002;29(3):474–81. [PubMed: 11908559]
10. Keyser RE, Rus V, Cade WT, Kalappa N, Flores RH, Handwerker BS. Evidence for aerobic insufficiency in women with systemic Lupus erythematosus. *Arthritis Rheum* 2003;49:16–22. [PubMed: 12579589]
11. Sakauchi M, Matsumura T, Yamaoka T, Koami T, Shibata M, Nakamura M, et al. Reduced muscle uptake of oxygen during exercise in patients with systemic lupus erythematosus. *J Rheumatol* 1995;22:1483–7. [PubMed: 7473470]
12. Tench CM, McCarthy J, McCurdie I, White PD, D'Cruz DP. Fatigue in systemic lupus erythematosus: a randomized controlled trial of exercise. *Rheumatology (Oxford)* 2003;42:1050–4. [PubMed: 12730519]
13. Forte S, Carlone S, Vaccaro F, Onorati P, Manfredi F, Serra P, et al. Pulmonary gas exchange and exercise capacity in patients with systemic lupus erythematosus. *J Rheumatol* 1999;26:2591–4. [PubMed: 10606367]
14. Wasserman, K.; Hansen, JE.; Sue, DY.; Stringer, WW.; Whipp, BJ. *Principles of Exercise Testing and Interpretation*. 4. Philadelphia: Lipincott, Williams and Wilkins; 2004.
15. Brooks, G.; Fahey, T.; Baldwin, K. *Exercise Physiology: Human Bioenergetics and Its Applications*. boston: Mcgraw Hill; 2005.
16. Wasserman K. Determinants and detection of anaerobic threshold and consequences of exercise above it. *Circulation* 1987;76:VI29–39. [PubMed: 3315297]
17. Wasserman K, Koike A. Is the anaerobic threshold truly anaerobic? *Chest* 1992;101:211S–8S. [PubMed: 1576837]
18. Harris, C.; Adams, KJ.; Keith, N. Exercise Physiology. In: Kaminski, L.; Bonheim, KA.; Garbor, CE.; Glass, SC.; Hamm, LF.; Kohl, HW., et al., editors. *ACSM's Resource Manual for Guidelines For Exercise Testing and Prescription*. 5. Philadelphia: Lipincott, Williams and Wilkins; 2001. p. 45-78.

19. ACSM. ACSM's Guidelines For Exercise Testing and Prescription. 7. Philadelphia: Lippincott, Williams and Wilkins; 2006.
20. Thompson, W.; Gordon, N.; Pescatello, L., editors. ACSM'S Guidelines or Exercise Testing and Prescription. 8. Philadelphia: Wolters kluwer / Lippincott Williams and Wilkins; 2009.
21. Whipp BJ. Dynamics of pulmonary gas exchange. *Circulation* 1987;76:VI18–28. [PubMed: 3119250]
22. Whipp BJ, Ward SA, Lamarra N, Davis JA, Wasserman K. Parameters of ventilatory and gas exchange dynamics during exercise. *J Appl Physiol* 1982;52:1506–13. [PubMed: 6809716]
23. Whipp B. Rate constant for the kinetics of oxygen uptake during light exercise. *Journal of Applied Physiology* 1971;30:261–3. [PubMed: 5539892]
24. Barstow TJ, Jones AM, Nguyen PH, Casaburi R. Influence of muscle fibre type and fitness on the oxygen uptake/power output slope during incremental exercise in humans. *Exp Physiol* 2000;85:109–16. [PubMed: 10662900]
25. Kemp G. Kinetics of muscle oxygen use, oxygen content, and blood flow during exercise. *J Appl Physiol* 2005;99:2463–8. author reply 8–9. [PubMed: 16288106]
26. Kinker JR, Haffor AS, Stephan M, Clanton TL. Kinetics of CO uptake and diffusing capacity in transition from rest to steady-state exercise. *J Appl Physiol* 1992;72:1764–72. [PubMed: 1601784]
27. Jones AM, Wilkerson DP, Wilmshurst S, Campbell IT. Influence of L-NAME on pulmonary O₂ uptake kinetics during heavy-intensity cycle exercise. *J Appl Physiol* 2004;96:1033–8. [PubMed: 14657038]
28. Kindig CA, McDonough P, Erickson HH, Poole DC. Effect of L-NAME on oxygen uptake kinetics during heavy-intensity exercise in the horse. *J Appl Physiol* 2001;91(2):891–6. [PubMed: 11457807]
29. Wilkerson DP, Campbell IT, Jones AM. Influence of nitric oxide synthase inhibition on pulmonary O₂ uptake kinetics during supra-maximal exercise in humans. *J Physiol* 2004;561:623–35. [PubMed: 15358808]
30. Finol HJ, Montagnani S, Marquez A, Montes de Oca I, Muller B. Ultrastructural pathology of skeletal muscle in systemic lupus erythematosus. *J Rheumatol* 1990;17:210–9. [PubMed: 2319520]
31. Neumark T. Ultrastructural study of neuromuscular and vascular changes in connective-tissue diseases. *Int J Tissue React* 1986;8:111–7. [PubMed: 3700003]
32. Norton WL. Endothelial inclusions in active lesions of systemic lupus erythematosus. *J Lab Clin Med* 1969;74:369–79. [PubMed: 4896818]
33. Norton WL. Comparison of the microangiopathy of systemic lupus erythematosus, dermatomyositis, scleroderma, and diabetes mellitus. *Lab Invest* 1970;22:301–8. [PubMed: 5429531]
34. Norton WL, Hurd ER, Lewis DC, Ziff M. Evidence of microvascular injury in scleroderma and systemic lupus erythematosus: quantitative study of the microvascular bed. *J Lab Clin Med* 1968;71:919–33. [PubMed: 5654777]
35. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–7. [PubMed: 7138600]
36. Gandevia B, Tovell A. Declaration of Helsinki. *Medical Journal of Austria* 1964;2:320–1.
37. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986;60:2020–7. [PubMed: 3087938]
38. Cade WT, Nabar SR, Keyser RE. Reproducibility of the exponential rise technique of CO(2) rebreathing for measuring P(v)CO(2) and C(v)CO(2) to non-invasively estimate cardiac output during incremental, maximal treadmill exercise. *Eur J Appl Physiol* 2004;91:669–76. [PubMed: 14652761]
39. Cade WT, Fantry LE, Nabar SR, Shaw DK, Keyser RE. Impaired oxygen on-kinetics in persons with human immunodeficiency virus are not due to highly active antiretroviral therapy. *Arch Phys Med Rehabil* 2003;84:1831–8. [PubMed: 14669191]
40. Handler CE, Sowton E. A comparison of the Naughton and modified Bruce treadmill exercise protocols in their ability to detect ischaemic abnormalities six weeks after myocardial infarction. *Eur Heart J* 1984;5:752–5. [PubMed: 6499863]
41. KIRKWOOD, B. *Essentials of Medical Statistics*. Oxford: Blackwell Scientific Publications; 1988.

42. Howley ET, Bassett DR Jr, Welch HG. Criteria for maximal oxygen uptake: review and commentary. *Med Sci Sports Exerc* 1995;27:1292–301. [PubMed: 8531628]
43. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 1973;85:546–62. [PubMed: 4632004]
44. Bruce RA, Kusumi F, Niederberger M, Petersen JL. Cardiovascular mechanisms of functional aerobic impairment in patients with coronary heart disease. *Circulation* 1974;49:696–702. [PubMed: 4817710]
45. Farrell PA, Wilmore JH, Coyle EF, Billing JE, Costill DL. Plasma lactate accumulation and distance running performance. *Med Sci Sports* 1979;11:338–44. [PubMed: 530025]
46. Cerretelli P, Ambrosoli G, Fumagalli M. Anaerobic recovery in man. *Eur J Appl Physiol Occup Physiol* 1975;34:141–8. [PubMed: 1181176]
47. Zhang YY, Johnson MC 2nd, Chow N, Wasserman K. The role of fitness on VO₂ and VCO₂ kinetics in response to proportional step increases in work rate. *Eur J Appl Physiol Occup Physiol* 1991;63:94–100. [PubMed: 1748111]
48. Hughson RL, Morrissey M. Delayed kinetics of respiratory gas exchange in the transition from prior exercise. *J Appl Physiol* 1982;52:921–9. [PubMed: 6806226]
49. Hagberg JM, Nagle FJ, Carlson JL. Transient O₂ uptake response at the onset of exercise. *J Appl Physiol* 1978;44:90–2. [PubMed: 627505]
50. Arena R, Humphrey R, Peberdy MA. Measurement of oxygen consumption on-kinetics during exercise: implications for patients with heart failure. *J Card Fail* 2001;7:302–10. [PubMed: 11782852]
51. Arena R, Humphrey R, Peberdy MA, Madigan M. Comparison of oxygen uptake on-kinetic calculations in heart failure. *Med Sci Sports Exerc* 2002;34:1563–9. [PubMed: 12370556]
52. Mathur RS, Revill SM, Vara DD, Walton R, Morgan MD. Comparison of peak oxygen consumption during cycle and treadmill exercise in severe chronic obstructive pulmonary disease. *Thorax* 1995;50:829–33. [PubMed: 7570432]
53. Cade WT, Fantry LE, Nabar SR, Keyser RE. Decreased peak arteriovenous oxygen difference during treadmill exercise testing in individuals infected with the human immunodeficiency virus. *Arch Phys Med Rehabil* 2003;84:1595–603. [PubMed: 14639557]
54. Cade WT, Fantry LE, Nabar SR, Shaw DK, Keyser RE. A comparison of Q_t and a-vO₂ in individuals with HIV taking and not taking HAART. *Med Sci Sports Exerc* 2003;35:1108–17. [PubMed: 12840630]
55. Convertino VA, Goldwater DJ, Sandler H. Bedrest-induced peak VO₂ reduction associated with age, gender, and aerobic capacity. *Aviat Space Environ Med* 1986;57:17–22. [PubMed: 3942565]
56. Bostrom C, Dupre B, Tengvar P, Jansson E, Opava CH, Lundberg IE. Aerobic capacity correlates to self-assessed physical function but not to overall disease activity or organ damage in women with systemic lupus erythematosus with low-to-moderate disease activity and organ damage. *Lupus* 2008;17:100–4. [PubMed: 18250132]
57. Poole DC, Barstow TJ, McDonough P, Jones AM. Control of oxygen uptake during exercise. *Med Sci Sports Exerc* 2008;40:462–74. [PubMed: 18379208]
58. Engelen M, Porszasz J, Riley M, Wasserman K, Maehara K, Barstow TJ. Effects of hypoxic hypoxia on O₂ uptake and heart rate kinetics during heavy exercise. *J Appl Physiol* 1996;81:2500–8. [PubMed: 9018498]
59. Hughson RL, Xing HC, Butler GC, Northey DR. Effect of hypoxia on VO₂ kinetics during pseudorandom binary sequence exercise. *Aviat Space Environ Med* 1990;61:236–9. [PubMed: 2317178]
60. Palange P, Galassetti P, Mannix ET, et al. Oxygen effect on O₂ deficit and VO₂ kinetics during exercise in obstructive pulmonary disease. *Journal of Applied Physiology* 1995;78:2228–34. [PubMed: 7665422]
61. Groebe K. A versatile model of steady state O₂ supply to tissue. Application to skeletal muscle. *Biophysics Journal* 1990;57:485–98.
62. Adams NP, Bestall JC, Jones PW, Lasserson TJ, Griffiths B, Cates C. Inhaled fluticasone at different doses for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2005;CD003534. [PubMed: 16034902]

63. Xu F, Rhodes EC. Oxygen uptake kinetics during exercise. *Sports Med* 1999;27(5):313–27. [PubMed: 10368878]
64. Carter H, Jones AM, Barstow TJ, Burnley M, Williams CA, Doust JH. Oxygen uptake kinetics in treadmill running and cycle ergometry: a comparison. *J Appl Physiol* 2000;89:899–907. [PubMed: 10956332]
65. Connes P, Monchanin G, Perrey S, Wouassi D, Atchou G, Forsuh A, et al. Oxygen uptake kinetics during heavy submaximal exercise: Effect of sickle cell trait with or without alpha-thalassemia. *Int J Sports Med* 2006;27:517–25. [PubMed: 16802246]
66. Poole DC, Barstow TJ, Gaesser GA, Willis WT, Whipp BJ. VO₂ slow component: physiological and functional significance. *Med Sci Sports Exerc* 1994;26:1354–8. [PubMed: 7837956]
67. Whipp BJ. The slow component of O₂ uptake kinetics during heavy exercise. *Med Sci Sports Exerc* 1994;26:1319–26. [PubMed: 7741865]
68. Zoladz JA, Gladden LB, Hogan MC, Nieckarz Z, Grassi B. Progressive recruitment of muscle fibers is not necessary for the slow component of VO₂ kinetics. *J Appl Physiol* 2008;105:575–80. [PubMed: 18483168]
69. Oxenhandler R, Hart MN, Bickel J, Searce D, Durham J, Irvin W. Pathologic features of muscle in systemic lupus erythematosus: a biopsy series with comparative clinical and immunopathologic observations. *Hum Pathol* 1982;13:745–57. [PubMed: 7049895]
70. Caputo F, Mello MT, Denadai BS. Oxygen uptake kinetics and time to exhaustion in cycling and running: a comparison between trained and untrained subjects. *Arch Physiol Biochem* 2003;111:461–6. [PubMed: 16026035]
71. Marwood S, Roche D, Rowland T, Garrard M, Unnithan VB. Faster pulmonary oxygen uptake kinetics in trained versus untrained male adolescents. *Med Sci Sports Exerc* 42:127–34. Epub 2009/12/17. [PubMed: 20010121]
72. Barstow TJ, Scremin AM, Mutton DL, Kunkel CF, Cagle TG, Whipp BJ. Changes in gas exchange kinetics with training in patients with spinal cord injury. *Med Sci Sports Exerc* 1996;28:1221–8. [PubMed: 8897377]
73. Brandenburg SL, Reusch JE, Bauer TA, Jeffers BW, Hiatt WR, Regensteiner JG. Effects of exercise training on oxygen uptake kinetic responses in women with type 2 diabetes. *Diabetes Care* 1999;22:1640–6. [PubMed: 10526728]
74. Murias JM, Kowalchuk JM, Paterson DH. Speeding of VO₂ kinetics with endurance training in old and young men is associated with improved matching of local O₂ delivery to muscle O₂ utilization. *J Appl Physiol*. Epub 2010/02/13.
75. Carvalho MR, Sato EI, Tebexreni AS, Heidecker RT, Schenkman S, Neto TL. Effects of supervised cardiovascular training program on exercise tolerance, aerobic capacity, and quality of life in patients with systemic lupus erythematosus. *Arthritis Rheum* 2005;53:838–44. [PubMed: 16342102]
76. Lim, S.; Foye, P. Steroid Myopathy 2008 [cited 2010 May]. Available from: URL: <http://emedicine.medscape.com/article/313842-overview>
77. Short KR, Nygren J, Bigelow ML, Nair KS. Effect of short-term prednisone use on blood flow, muscle protein metabolism, and function. *J Clin Endocrinol Metab* 2004;89:6198–207. [PubMed: 15579778]
78. Kobashigawa JA, Leaf DA, Lee N, Gleeson MP, Liu H, Hamilton MA, et al. A controlled trial of exercise rehabilitation after heart transplantation. *N Engl J Med* 1999;340:272–7. [PubMed: 9920951]
79. DeLorey DS, Kowalchuk JM, Heenan AP, Dumanoir GR, Paterson DH. Prior exercise speeds pulmonary O₂ uptake kinetics by increases in both local muscle O₂ availability and O₂ utilization. *J Appl Physiol* 2007;103:771–8. [PubMed: 17495116]
80. Endo M, Usui S, Fukuoka Y, Miura A, Rossiter HB, Fukuba Y. Effects of priming exercise intensity on the dynamic linearity of the pulmonary VO₂ response during heavy exercise. *Eur J Appl Physiol* 2004;91:545–54. [PubMed: 14648126]
81. Gurd BJ, Peters SJ, Heigenhauser GJ, LeBlanc PJ, Doherty TJ, Paterson DH, et al. Prior heavy exercise elevates pyruvate dehydrogenase activity and speeds O₂ uptake kinetics during subsequent moderate-intensity exercise in healthy young adults. *J Physiol* 2006;577:985–96. [PubMed: 16990406]
82. Dean TM, Perreault L, Mazzeo RS, Horton TJ. No effect of menstrual cycle phase on lactate threshold. *J Appl Physiol* 2003;95:2537–43. [PubMed: 14600163]

83. Lebrun CM, Petit MA, McKenzie DC, Taunton JE, Prior JC. Decreased maximal aerobic capacity with use of a triphasic oral contraceptive in highly active women: a randomised controlled trial. *Br J Sports Med* 2003;37:315–20. [PubMed: 12893716]

Figure 1.

Oxygen consumption during continuous exercise. t_0 is the onset of exercise and t_1 is the time taken to reach a steady state or an asymptote and (t_6) is 6-minute test endpoint. Area between Line A and the X-axis the resting VO_2 and Line B represents the energy demand of the activity being performed. The area above the trajectory line and under Line B is the oxygen deficit. VO_2 is the amplitude of change in oxygen consumption at the 6-minute test endpoint.

Figure 2.

Time to steady state, rate constant, and oxygen deficit in women with SLE and controls. Error bars equal one standard deviation unit. * Significantly different main effects for women with SLE than for controls ($p < 0.005$ rate constant, $p < 0.016$ time to steady state, $p < 0.028$ oxygen deficit)

Figure 3.

Transition constant and mean response time in women with SLE. Error bars are one standard deviation unit. * significantly higher than 3-METS ($p < 0.004$), + significantly higher than 3-METS in the women with SLE, **significantly higher than 3 METS ($p < 0.017$).

Table 1**Demographic Characteristics and Maximum Treadmill Exercise Test Responses**

	SLE	Control
Age (years)	38.3 ± 09.4	39.1 ± 04.0
Height (cm)	160.80 ± 06.5	165.60 ± 08.0
Weight (kg)	70.03 ± 09.51	72.50 ± 15.73
Body Mass Index (kg/meter ²)	27.42 ± 05.65	26.48 ± 05.44
Peak Respiratory Exchange Ratio	1.19 ± 0.07	1.29 ± 0.07
Attained Peak Heart Rate (beats/min)	163 ± 17	168 ± 29
Predicted Peak Heart Rate (beats/min)	182 ± 10	181 ± 04
% Predicted Max Heart Rate	90.2 ± 0.09	91.0 ± 0.17
Peak VO ₂ (ml/kg/min)	20.1 ± 04.7*	28.9 ± 05.1
Anaerobic Threshold (ml/kg/min)	12.9 ± 02.9**	17.9 ± 03.1

Data are means ± one standard deviation unit. BMI = body mass index, RER = respiratory exchange ratio,

* Significantly different from controls; p=0.0001; 95% CI: 03.7 to 15.3 ml/kg/min,

** Significantly different from controls; p=0.0001; 95% CI: 01.5 to 09.3 ml/kg/min

Table 2

Goodness of FIT for the VO₂ Kinetics Model

	<u>Median</u>	<u>Mode</u>	<u>Mean</u>	<u>SD</u>	<u>Min</u>	<u>Max</u>
Lupus	0.966	0.970	0.945	0.063	0.688	0.991
Controls	0.960	0.973	0.960	0.031	0.866	0.981

Pearson product moment correlation coefficients for relationships among VO₂-time iterations calculated from the model algorithm and those actually measured during the steady state tests. Data include both 3-MET and 5-MET energy demands for each group. SD is one standard deviation, Min is the lowest r-value, and Max is the highest r-value.

Table 3Changes in ΔVO_2 for the 3-MET and 5-MET Energy Demands

	3-MET		5-MET	
	<u>Lupus</u>	<u>Control</u>	<u>Lupus</u>	<u>Control</u>
ΔVO_2 (ml/min) *	599 $\pm$ 293	540 $\pm$ 144	766 $\pm$ 261	817 $\pm$ 225
$\Delta\text{VO}_{2(6-3)}$ (ml/min)	-06.3 $\pm$ 66.7	-03.8 $\pm$ 56.4	05.8 $\pm$ 80.0	-05.6 $\pm$ 58.2

Data are means $\pm$ one standard deviation. ΔVO_2 is the change in oxygen consumption above rest at minute six of exercise, and $\Delta\text{VO}_{2(6-3)}$ is the difference in VO_2 above rest between the third and sixth minutes of exercise.

* Significantly higher for 5-METS than for 3-METS (statistical main effect, $p=0.0016$, 95% CI: 180 to 252 ml/min)