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Impaired Aerobic Capacity in Systemic Lupus Erythematosus Patients: What are the Physiological Mechanisms?

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown origin affecting virtually all organ systems. In addition, SLE patients can present limitations in exercise capacity and reduced quality of life due to various clinical conditions such as fatigue, cardiorespiratory disease and muscle involvement. For instance, impaired tissue O_2 transport due to altered convective O_2 transport (product of arterial O_2 content and blood flow) to the working locomotor muscles or O_2 diffusive transport from muscle capillaries to mitochondria is the major determinant of reduced aerobic capacity in patients with SLE. In this respect, scientific evidences suggest that during exercise SLE patients show an attenuated increase in heart rate and systolic volume, reduced ventilatory efficiency and oxidative metabolism impairment.

Importantly, recent investigations suggest that aerobic exercise training has direct effects on improving both aerobic capacity and exercise tolerance in SLE patients. Within this context, previous studies suggest that either central or peripheral components are involved in improved aerobic capacity after exercise training program.

In this light, the present review sought to clarify the physiological mechanisms associated with reduced aerobic capacity in SLE patients. Secondly, special focus was given to the role of physical training in improving aerobic capacity in these patients as well as to the underlying mechanisms.

Keywords: Systemic lupus erythematosus; Aerobic capacity; Exercise tolerance; Exercise training

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease of unknown origin affecting virtually every organ in the human body [1]. Although its pathogenesis is believed to lie in the dysregulation of the immune system, the involvement of various organ systems often leads to secondary comorbidities resulting from renal failure, hypertension, and central nervous system disorders [2]. Furthermore, SLE patients can present limitations in exercise capacity and reduced quality of life due to various clinical conditions such as fatigue, cardiorespiratory disease and muscle involvement [3-6]. In this sense, the ability to sustain daily physical activities is inextricably linked to the integrity of the oxygen (O_2) transport pathway, which in turn depends on several multi-organ interactions involving the heart and vessels, lungs, respiratory/peripheral muscles and autonomic nervous systems [7]. In fact, impaired tissue O_2 transport due to altered perfusive and/or diffusive processes during exercise are pathophysiological factors that may be associated with poor exercise capacity in SLE patients [6,8].

Importantly, aerobic exercise training has been recommended as non-pharmacological treatment for patients with a range of different comorbidities [9,10]. In this regard, recent evidence suggests that exercise training has direct effects on improving aerobic capacity and physical function in SLE patients [3,11,12]. Thus, the present review sought to clarify the physiological mechanisms associated with reduced aerobic capacity in SLE patients. Secondly, special focus was given to the role of physical training in improving aerobic capacity in these patients as well as to the underlying mechanisms.

Understanding the mechanisms related to aerobic capacity.

Physical exercise poses the greatest physiological challenge to the cardiovascular, ventilatory, and skeletal muscle system called the "oxygen transport system" (Figure 1). For instance, muscle O_2 and high energy phosphate stores are small, thus any sustained elevation of muscle adenosine triphosphate (ATP) turnover requires that O_2 be delivered to the muscle mitochondria at a rate precisely coupled to mitochondrial O_2 requirements [13].

In fact, the body´s efficiency for taking up, transporting and utilizing O_2 at a peripheral level for energy substrate oxidation during physical exertion is associated with aerobic capacity [7,13]. In this regard, the index considered the gold standard for assessing aerobic capacity is maximal oxygen consumption (VO_{2max}), defined as the highest rate at which oxygen can be taken up and utilized by the body during physical exercise. Basically, $VO_{2máx}$ can be expressed by the Fick equation (Figure 2).

Different factors can influence VO_{2max} values among individuals, such as: gender, age, heredity, body composition, disease and physical fitness status [14-16]. For instance, VO_2 max values greater than 60 ml/kg/min are more commonly observed in subjects with highest levels of aerobic capacity such as endurance athletes.

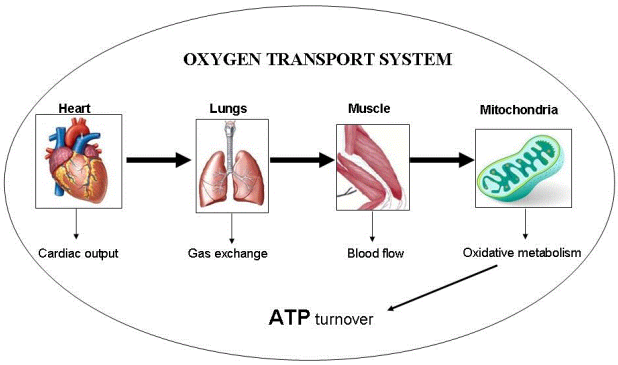

Figure 1: Oxygen transport system.

Notably, these subjects demonstrate higher body O_2 transport capacity associated with high levels of cardiac output and greater efficiency in both pulmonary gas exchange and peripheral O_2 extraction in muscles to mitochondria.

On the other hand, patients with severe heart failure show impairment in both aerobic capacity and exercise tolerance (e.g. VO_{2Max}<15 ml/kg/min). In this regard, abnormalities in cardiac output components, characterized by attenuated increase in either heart rate or stroke volume may be associated with lower VO_{2max}. Also, patients with chronic heart failure demonstrate both pulmonary gas exchange abnormalities and impaired skeletal muscle metabolism intrinsic to reduced mitochondrial oxidative capacity [7,17].

Aerobic capacity in SLE patients

There is a growing body of evidence indicating impaired aerobic capacity in SLE patients [4-7]. For instance, Keyser et al. [5] submitted 18 SLE women to a treadmill exercise test. Their findings demonstrated reduced aerobic capacity in SLE patients when compared to healthy sedentary controls (VO_{2max}=19.2 ± 4.4 vs. 27.4 ± 4.7 ml/kg/min, respectively).

$$VO_{2máx} = CO \times (a\text{-}vO_2 \text{ difference})$$

CO= cardiac output; **a- vO2 difference=** arterial- venous oxygen difference

Figure 2: Fick equation.

Additionally, Robb-Nicholson et al. [18] showed that SLE patients performed at 45% of expected VO_{2max}, while Tench et al. [19] concluded that SLE women exhibited poor exercise capacity, having a VO_{2max} 62% of the average expected value in healthy females of the same age (normality>85% VO_{2max} predicted) (Table 1) [20,21].

Study	Sample	$VO_{2\ max}$
[5]	18 women (35 years)	↓ 19.2 ± 4.4 ml/kg/min
[8]	13 women (29 years)	↓ 1098 ± 7.4 ml/min
[21]	21 women (43.5 years)	↓ 810.7 ± 7.4 ml/min
[4]	93 women (39 years)	↓ 23.2 ml/kg/min
[20]	20 women (28.8 years)	↓ 26.8 ± 1.2 ml/kg/min
[8]	22 women (29.5 years)	↓ 27.6 ± 0.9 ml/kg/min
Abbreviations and symbols: ↓=decrease when compared with healthy control.		

Table 1: Studies that evaluated aerobic capacity in SLE patients.

Furthermore, in a more recent study on childhood-onset SLE, Prado et al. [22] observed both lower exercise tolerance and aerobic capacity when compared with healthy control children. Taken together, these findings suggest that the aerobic capacity impairment observed in SLE patients may be associated with a reduced capacity to engage in both daily occupational activities and recreational tasks.

What are the physiological mechanisms involved in lower aerobic capacity in SLE patients? As outlined previously, aerobic capacity depends on several multi-organ interactions involving the heart, lungs, respiratory/peripheral muscles and autonomic nervous systems. In this regard, impairments in either convective O_2 transport (product of arterial O_2 content x blood flow) to the working locomotor muscles or O_2 diffusive transport from muscle capillaries to mitochondria during physical exercise are the major determinants of reduced aerobic capacity [23,24] (Figure 3).

A growing number of investigations have shown cardiorespiratory abnormalities during exercise in SLE patients [6,8,17,20]. In this sense, Prado et al. [6] observed abnormal chronotropic response during cardiorespiratory exercise testing in SLE women. Moreover, prior evidence [21,25] has demonstrated lower oxygen pulse during cardiorespiratory exercise tests in SLE woman suggesting blunted inotropic response. Therefore, it seems reasonable to speculate that an attenuated increase in both heart rate and systolic volume during exercise may be associated with lower cardiac output (e.g. decrease in convective O_2 transport) and consequently with reduced VO_{2max} in SLE patients.

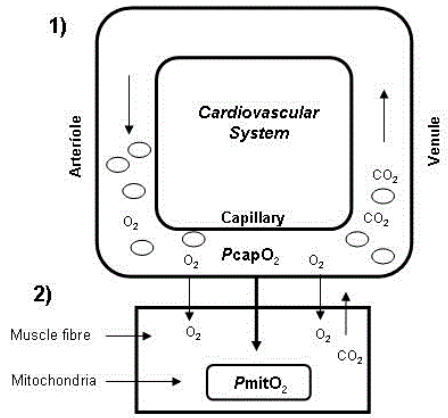

Figure 3: Schematic representation of the interaction between the convective and diffusive components of O_2 transport. Abbreviations: $PcapO_2$=partial pressure for oxygen in capillaries; $PmitO_2$=partial pressure for oxygen in mitochondria.

Concerning ventilatory abnormalities, it has been demonstrated that patients with SLE have an increased ventilatory response for a given metabolic demand during exercise, otherwise recognized as reduced ventilatory efficiency (increased VE/VCO_2) when compared with healthy subjects [8,20]. For instance, Forte et al. [8] observed greater values of ventilatory equivalent for carbon dioxide at anaerobic threshold (VE/VCO_2 AT) in SLE woman than healthy peers (pre=31 ± 1 vs. post=24 ± 1 units, respectively). Likewise, Prado and coworkers [20] demonstrated ventilatory inefficiency during treadmill cardiorespiratory exercise test in SLE patients. It is noteworthy that in the same investigation, the authors observed abnormalities in the pattern and timing of breathing in SLE patients, characterized by more rapid and shallower breathing pattern. Importantly, these findings resemble the pattern observed in patients with other pulmonary disorders (e.g. chronic obstructive lung disease). Similarly, Scano et al. [26] observed both erratic breathing patterns and mild inspiratory muscle weakness in a subset of SLE patients with normal baseline lung function.

How can ventilatory inefficiency limit exercise tolerance and aerobic capacity? Previous investigations in different comorbidities [27-29] have observed that, during exercise, an increase in work of breathing produced by lower ventilatory efficiency may cause sympathetic mediated vasoconstriction of limb musculature via a supraspinal reflex. Specifically, these effects may limit limb blood flow and promote a corresponding reduction in O_2 delivery to working muscle, thus leading to a decrease in both exercise tolerance and aerobic capacity [27,28]. Thus, it follows that in pathological conditions, the respiratory and peripheral muscles might actively compete for the available cardiac output, where the ability to further increase O_2 delivery during exercise is impaired.

Lastly, with regard to peripheral abnormalities, previous studies have demonstrated oxidative metabolism impairment in SLE patients compared with healthy controls [21,30]. Kayser et al. [30], for instance, found prolonged VO_2 on-kinetics on the square wave test in SLE patients. In addition, the authors observed that VO_2 at anaerobic threshold was 27.9% lower in women with SLE compared to controls (VO_{2AT}=12.9 ± 2.9 vs. 17.9 ± 3.1 ml/kg/min, respectively). These findings, suggest impaired microcirculatory dynamics and mitochondrial function during exercise, resulting in decreased a-vO_2 difference [30]. In this regard, previous studies have demonstrated that pathological adaptations in the muscle capillary bed of patients with SLE could impair microvascular reactivity and O_2 diffusive transport from muscle capillaries to mitochondria [31,32].

Taken together with the aforementioned results, it is reasonable to suggest that peripheral abnormalities may also be associated with reduced aerobic capacity in SLE patients (Figure 4).

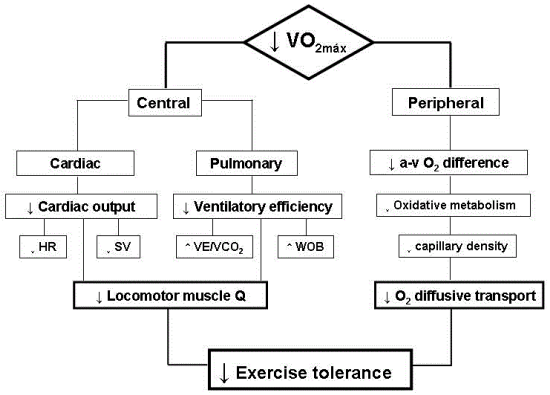

Figure 4: Potential mechanisms suggested for the reduction of aerobic capacity in SLE patients. Abbreviations and symbols: HR=Heart Rate; SV=Stroke Volume; WOB=Work of Breathing; Locomotor muscle Q=Locomotor muscle blood flow; ↓=decrease.

Exercise training and aerobic capacity

Adherence to a physical training program results in both physiological and metabolic adaptations that characterize the specific adaptive responses [33,34]. In this context, studies have shown that aerobic exercise training may increase VO_{2max} by between 4 and 93% [35]. However, increases in VO_{2max} of between 10 and 20% are more typical when sedentary individuals are subjected to a specific period of aerobic exercise training. Moreover, previous investigations have demonstrated an increase in aerobic capacity after aerobic exercise training in patients with different comorbidities such as cardiovascular [9,10] and autoimmune diseases [36].

Effect of exercise training on aerobic capacity in SLE patients: Previous studies have shown that when SLE patients are submitted to aerobic exercise training their aerobic capacity improves (by up to 19%) and exercise endurance increases (by up to 18%) [37]. Carvalho et al. [11] also demonstrated a significant increase in aerobic capacity after 12 weeks of aerobic exercise training in SLE woman. Additionally, Robb- Nicholson and coworkers [18] showed a 19% improvement in aerobic capacity after 8 weeks of exercise training. Importantly, in the same investigation the authors observed that an increase in aerobic capacity significantly correlated with decreased

fatigue, as measured by visual analogue scales (VAS). Likewise, Prado et al. [12] explored the effect of a 12-week aerobic exercise training program on a 15 year- old boy with juvenile SLE and antiphospholipid syndrome. The authors observed that after intervention, the patient significantly ameliorated both $VO_{2máx}$ (pre: 30.6 vs. post: 41.6 ml/kg/min, Δchange=36%) and exercise endurance (pre: 7.15 vs. post: 12.0 min, Δchange=67.9%).

What physiological mechanisms underlie increased aerobic capacity in SLE patients after aerobic exercise training? Considering the physiological mechanisms responsible for increasing aerobic capacity after exercise training programs, these may be dependent on central (cardiac output) as well as peripheral components (a-vO_2 difference). Supporting this notion, a pioneering study in healthy individuals conducted by Ekblom et al. [38] revealed that 16 weeks of aerobic exercise training increased $VO_{2máx}$ from 3.15 to 3.68 L/min, respectively. Interestingly, the improvement in aerobic capacity was explained by the 8% increase in cardiac output (22.4 to 24.2 L, respectively) and 3.6% in a-vO_2 difference (138 to 148 mL/L-1, respectively) observed.

With regard to SLE patients, accumulating evidence [11,12,22] suggests that either central or peripheral components are involved in improved aerobic capacity after exercise training programs. A study by Carvalho et al. [11] in SLE patients reported an increase in O_2 pulse at $VO_{2máx}$ (pre: 7.8 vs. post: 8.6 ml/beats, respectively). In addition, a randomized controlled trial study by Prado et al. [22] demonstrated an increase in chronotropic response (Δ heart rate response rest- peak exercise) in childhood-SLE patients after three-month aerobic exercise training. Likewise, Miossi et al. [39] showed an improvement in chronotropic reserve after an exercise training program in women with SLE.

In a case report, Prado et al. [12] submitted a juvenile SLE patient to a 6-min square-wave test to evaluate metabolic response during submaximal exercise. After an intervention, results on the square-wave test indicated that exercise training had led to both a reduction in metabolic cost of movement and an increase in oxidative metabolism. It was believed these outcomes might have a beneficial impact on the physical capacity and activities of daily living of the patient. In support of this speculation, the patient showed clinically relevant improvements in physical functioning, as assessed by the VAS.

In addition, Carvalho et al. [11] demonstrated an improvement in VO_2 at anaerobic threshold after 12 weeks of the aerobic exercise training in the SLE patient. Collectively, these findings suggest an improvement in O_2 extraction and utilization by the peripheral muscle during exercise (Table 2).

Cardiac output	↑
Systolic volume	↑
Arterial- venous oxygen difference	↑
Heart rate at rest condition	↓
Δ Heart rate response (rest-peak exercise)	↑
Microcirculation (capillary-to-muscle fibre ratio)	↑
Mitochondrial density (mitochondria number)	↑
Activity and concentration of oxidative enzymes	↑

↑=increase; ↓=decrease; Adapted from Jones et al. [33]; Negrão et al. [40]. Prado et al. [12,22].

Table 2: Physiological mechanisms suggested for the increase aerobic capacity after exercise training program.

Perspectives and conclusion

Systemic lupus erythematosus is an autoimmune disease of unknown origin affecting cardiorespiratory and skeletal muscle systems. In this sense, an impairment in both convective O_2 transport to the working locomotor muscles or in O_2 diffusive transport from muscle capillaries to mitochondria may be associated with reduced aerobic capacity in SLE. Substantial evidence supports the benefits of aerobic exercise training for increasing aerobic capacity in patients with different comorbidities. In addition, a growing number of studies have shown the positive benefits of exercise training programs toward improving aerobic capacity and exercise tolerance in SLE patients. However, the optimal exercise training protocol for improvement in aerobic capacity in SLE remains to be clarified. Furthermore, long-term randomized controlled trials are necessary to elucidate the main physiological mechanism that is associated with improvement in aerobic capacity in SLE patients. Finally, it is important to emphasize that the studies cited in this review did not report that exercise training program provoke any adverse events including disease exacerbation.

In conclusion, these findings suggest that improved aerobic capacity in SLE patients is associated with enhanced capacity to engage in daily occupational activities and recreational tasks.

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