Supervised physical exercise improves endothelial function in patients with systemic lupus erythematosus

Edgard Torres dos Reis-Neto¹, Aline Evelyn da Silva¹, Carlos Manoel de Castro Monteiro², Luciano Monteiro de Camargo² and Emilia Inoue Sato¹

Abstract

Objective. The objective of this study was to evaluate the effect of supervised physical exercise on endothelial function, ergospirometric test variables and disease activity in SLE patients.

Methods. We conducted a prospective study in which women with SLE who were available to perform physical exercise were allocated to the exercise group (EG) to practise supervised physical exercise for 1 h three times per week for 16 weeks. Those who were not available for this activity were allocated to the control group (CG). Intervention consisted of walking at a heart rate corresponding to the ventilatory threshold obtained from ergospirometry and monitored by a frequency meter. At baseline (T0) and after 16 weeks (T16), patients were assessed for endothelial function by brachial artery (flow-mediated dilation), ergospirometry and disease activity (SLEDAI). Statistical analysis was performed through normality tests, Student’s t-test and non-parametric tests for data with non-normal distribution. P < 0.05 was considered significant.

Results. Eighteen patients were allocated in the EG and 20 in the CG. After 16 weeks there was an increase in FMD in the EG [6.3 (6.7)% vs 14.1 (9.1)%, P = 0.006] without a change in the CG [8.4 (8.2)% vs 9.4 (5.7)%, P = 0.598]. Regarding the ergospirometric test, we found improvement in exercise tolerance [12.3 (2.4) vs 13.4 (2.6) min, P = 0.027], maximum speed [7.7 (1.0) vs 8.3 (1.2) km/h, P = 0.027] and threshold speed [5.6 (0.7) vs 6.1 (0.9) km/h, P = 0.005] in the EG without a difference in the CG. There was no difference in the SLEDAI score in both groups.

Conclusion. Physical exercise is a useful strategy to improve endothelial function and aerobic capacity without worsening disease activity in SLE patients.


Key words: systemic lupus erythematosus, exercise, endothelium.

Introduction

Endothelial dysfunction is characterized by the inability of arterial vessels to relax in response to stimuli and release nitric oxide (NO). This occurs before the development of structural atherosclerotic lesions. Disturbances in endothelial function are implicated in the pathogenesis of diseases with a vascular inflammation component of autoimmune origin, including SLE [1, 2]. Several studies have shown that cardiovascular (CV) morbidity and mortality are more frequent and premature in SLE patients than in the general population [3, 4]. Although SLE patients have a higher prevalence of traditional CV risk factors [4–6], the increased CV risk is due not only to the presence of these factors [7], but it suggests the disease itself plays an important role in the development of early atherosclerotic disease. Lima et al. [8] demonstrated for the first time that SLE patients present endothelial dysfunction even in...
the absence of traditional CV risk factors, which was confirmed by other studies [2, 9, 10].

A sedentary lifestyle increases the risk of CV disease in the general population [11] and regular physical activity has been identified as an important predictor in the reduction of CV morbidity and mortality [12, 13]. Physical exercise leads to physiological stress, including increased heat production, reactive oxygen species (ROS), antioxidants and shear stress. The latter is more related to the endothelium and increases during exercise as a result of an increase in cardiac load due to the increased demand for oxygen by the muscles [14]. Initially blood flow increases the production and release of NO through activation of endothelial mechanosensors by shear stress. Subsequently there are increases in the production of antioxidants and angiogenic factors, reducing the oxidation and increasing the production of NO, respectively [15–19]. These processes are a precondition for endothelial cells to act against mechanical or chemical damage in CV disease [14, 15, 19]. Furthermore, exercise may improve endothelial function indirectly by acting on other CV risk factors such as dyslipidaemia, hypertension and obesity [20], although this improvement can occur independent of change in these factors [21, 22].

The low aerobic capacity in SLE patients may lead to restrictions on recreational and occupational activities and exercise is a potential target for intervention in these patients [23].

There are studies showing an improvement in endothelial function with an exercise programme in patients with hypertension [24], congestive heart failure [25], coronary artery disease [26] and diabetes mellitus [27]. Although SLE patients exhibit endothelial dysfunction, there is no study evaluating the effect of physical exercise on endothelial function in these patients. This study aimed to assess the effect of supervised physical exercise on endothelial function, ergospirometric test variables and disease activity in SLE patients.

**Patients and methods**

This is a prospective study in which patients were divided into two groups according to their convenience. Those who were willing to perform training were included in the exercise group (EG) and those who were not available were allocated in the control group (CG).

**Patients**

We included female patients, 18–45 years of age, with SLE (1997 ACR criteria) [28] who signed the consent form approved by the ethics committee of the institution. Exclusion criteria were haemoglobin <10 mg/dl; neuropsychiatric, pulmonary, articular or vascular damage that would not allow the practice of exercise; coronary disease; heart failure (functional class ≥ II); pulmonary hypertension; uncontrolled hypertension; creatinine ≥ 1.4 mg/dl; BMI ≥ 35 kg/m²; diabetes mellitus; uncontrolled hypothyroidism; smoking in the last 12 months; pregnancy; menopause; use of statins or regular practice of exercise in the past 3 months and overlap with other autoimmune rheumatic diseases, except anti-phospholipid syndrome.

Patients were recruited in the rheumatology divisions of three tertiary public hospitals in the city of São Paulo, Brazil (Fig. 1). This study was approved by the Research Ethics Committee of the Universidade Federal de São Paulo (UNIFESP) and registered at www.clinicaltrials.gov (NCT01712529).

**Intervention—supervised physical exercise**

The EG subjects performed an exercise protocol three times per week for 60 min (a 10-min warm-up, 40 min of walking and a 10-min cool-down) in the morning at a public park, supervised by a physical educator or physician over 16 weeks. The walk was conducted at a heart rate corresponding to the ventilatory 1 threshold (VT1) obtained from ergospirometry and monitored by a frequency meter (Polar Electro, Kempele, Finland). In the EG, patients were excluded if they did not attend at least 75% of exercise sessions. The CG received instructions not to start any exercise programme for 16 weeks.

**Patients assessment**

All assessments were performed at baseline (T0) and after 16 weeks (T16) in both groups by blinded evaluators. In the EG, assessments were performed 72 h after the last training session in order to avoid possible effects of acute exercise.

**Endothelial function**

US of the brachial artery with flow-mediated dilation (FMD) was performed in the Lipids section of the Cardiology division of the UNIFESP by a single experienced professional using high-resolution US equipment (Hewlett Packard Image Point, USA) and a linear 7.5 MHz transducer according to guidelines previously published [29].

Patients were instructed to remain fasting and without vasoactive medications for 12 h before evaluation. The patient remained in a comfortable supine position and images of the right brachial artery located ~7 cm above the medial humeral epicondyle were recorded for measurements of blood flow velocity and arterial resting diameter. Subsequently a sphygmomanometer was placed on the forearm and inflated to a pressure of at least 50 mmHg above systolic pressure for 5 min, inducing reactive hyperaemia and increased blood flow. Forty-five to 60 s after cuff release, images were captured for FMD assessment. After 15 min of rest, new images were acquired for resting measurements and 0.4 mg of sublingual nitroglycerin spray was administered, with further measurements being taken after 4 min [nitroglycerin-mediated dilation (NitroMD)]. The different phases of the examination were recorded on DVD for later analysis. FMD%, an endothelium-dependent function, and NitroMD%, an endothelium-independent function, were calculated according
to the formulae below:

\[ \text{FMD\%} = \left( \frac{\text{Diameter after hyperaemia} - \text{Resting diameter}}{\text{Resting diameter}} \right) \times 100 \]

\[ \text{NitroMD\%} = \left( \frac{\text{Diameter after nitroglycerin} - \text{Resting diameter}}{\text{Resting diameter}} \right) \times 100 \]

To evaluate intraobserver reproducibility, eight healthy individuals were assessed twice by the same examiner, with an interval of 1 week. In both measurements there was no difference between the resting diameter (mean (s.d.) 3.35 (0.63) vs 3.45 (0.62) mm, \( P = 0.753 \)), hyperaemia diameter (3.74 (0.56) vs 3.95 (0.70) mm, \( P = 0.513 \)) and FMD (12.6 (7.7\%) vs 14.8 (5.9\%), \( P = 0.522 \)). Regarding variance, there was no difference between the two measurements of resting diameter (\( P = 0.915 \)), hyperaemia diameter (\( P = 0.757 \)) and FMD (\( P = 0.568 \)). The intraclass correlation coefficients were 0.896 (95% CI 0.639, 0.973, \( P < 0.001 \)) for the resting diameter, 0.838 (95% CI 0.388, 0.965, \( P = 0.002 \)) for hyperaemia diameter and 0.608 (95% CI −0.099, 0.907, \( P = 0.041 \)) for FMD.

**Ergospirometric assessment**

Ergospirometry was performed at the laboratory of the Center for Studies in Psychobiology and Exercise using a Quark PFT ergospirometric testing device (Cosmed, Italy). After gas analysis, for 3 min in the standing position, participants completed the protocol on the treadmill, with an initial speed of 3 km/h. After the first 3 min, the speed was maintained at 4 km/h for 2 min and progressively increased 0.5 km/h every minute until exhaustion, with 1% of fixed inclination. After maximum effort, the test was stopped and the speed of 3 km/h was maintained for 2 min for recovery and for another 1 min for vital signs control in the standing position, with gas analysis.
At least two criteria were considered for VO$_{2\text{max}}$ (maximal oxygen consumption), including VO$_2$ plateau or stabilization, gas exchange ratio ($R > 1.10$, maximum heart rate achieved and physical exhaustion. For determination of VT$_1$, the inflection point of the ventilatory equivalent [pulmonary ventilation (VE)/VO$_2$] and the non-linear increase of the exhaled gas at the previous point in which $R > 1.0$, without loss of linearity between CO$_2$ production and O$_2$ consumption (VO$_2$/VE) was considered [30].

We analysed the following variables: exercise tolerance (duration of the test), resting heart rate, VT$_{1\text{max}},$ VO$_{2\text{max}},$ VE$_{\text{max}},$ VO$_2$ of VT$_1$, maximum speed, speed of VT$_1$ and gas exchange ratio. Disease activity was assessed using the SLEDAI [31].

**Statistical analysis**

We used the software package SPSS for Windows version 20.0 (IBM-SPSS, Chicago, IL, USA). Data are presented as mean and standard deviation or median with minimum and maximum values for continuous variables, or frequencies and percentages for categorical variables. The Shapiro-Wilk test was used to assess the normality of the variables. To compare continuous variables, Student’s $t$-test, Mann-Whitney $U$ test or Wilcoxon test were used. Categorical data were analysed by chi-square test, Fisher’s exact test or McNemar’s test. The difference between T0 and T16 values [$\Delta$T16−T0] between groups was assessed by Student’s $t$-test or Mann-Whitney $U$ test. For correlation analysis, a Pearson correlation test or Spearman’s rank correlation was performed. $P < 0.05$ was considered significant.

**Results**

**Clinical and demographic data**

Among the 38 participants, 16 (42.1%) were White. The mean (s.d.) age was 33.2 (7.8) years and the mean (s.d.) disease duration was 94.2 (80.5) months. Only one patient had secondary anti-phospholipid syndrome. There was no difference in the frequency of ACR criteria for SLE, or in the clinical features, demographic characteristics or medication between the groups at baseline (Table 1). Regarding CV risk factors, only the level of diastolic blood pressure was higher in the EG compared with the CG, however, the mean values were within normal range (Table 2). No patient had a coronary event or stroke previously.

There was no difference in the SLEDAI score at T0 and after 16 weeks in the EG [mean (s.d.) 2.0 (2.1) vs 2.4 (2.3), $P=0.196$] or in the CG [2.4 (2.3) vs 3.1 (3.3), $P=0.833$]. There was also no difference in this score between groups at T16 ($P=0.652$). There were no intragroup and intergroup differences in the EG and CG assessed at T0 and T16 with respect to BMI, abdominal circumference and waist:hip ratio (data not shown).

**Assessment of endothelial function**

At baseline there was no difference between the EG and CG in relation to resting diameter, hyperaemia diameter and FMD. Patients of the EG had lower NitroMD at T0 compared with the CG ($P=0.011$). At the end of 16 weeks there was a significant increase in FMD in the EG. No other variables showed significant changes in the EG or CG. (Table 3; Fig. 2). The EG showed a significant increase in FMD when compared with the CG at the end of 16 weeks [7.8 (8.8)% vs 1.1 (8.8)%], $P=0.026$.

The analysis of all patients regarding medications showed no difference in FMD at T0 and T16 when comparing patients with and without prednisone ($P=0.723$), antimalarials ($P=0.135$) or immunosuppressive drugs ($P=0.849$).

When assessing all patients at T0, the mean FMD was 7.4 (7.5)% and no correlation was found between FMD and disease duration, age, BMI, blood pressure, abdominal circumference, waist:hip ratio, history of hypertension and dyslipidaemia and use of immunosuppressive drugs, antimalarials and steroids. There was a positive correlation between FMD and NitroMD ($r=0.410$, $P=0.011$) and a negative correlation between NitroMD and diastolic blood pressure ($r=-0.331$, $P=0.042$). No correlation with other variables was observed.

**Ergospirometric assessment**

With regard to the variables of ergospirometry, there was no difference between the groups at T0. In the EG after 16 weeks there was a significant improvement in exercise tolerance, maximum speed and VT$_1$ speed. In the CG there was no difference in any variable (Table 4). The EG showed a significant increase in exercise tolerance [1.1 (1.8) vs $-0.2$ (1.6) min, $P=0.026$], maximum speed [0.6 (1.0) vs $-0.1$ (0.8) km/h, $P=0.019$] and VT$_1$ speed [0.5 (0.5) vs $-0.2$ (0.6) km/h, $P=0.002$] compared with the CG at the end of 16 weeks. There was no correlation between FMD and ergospirometric test variables.

**Discussion**

This is the first study evaluating the effect of physical exercise on the endothelial function in SLE patients. Our study demonstrated that a supervised physical exercise programme is capable of improving endothelial function in these patients as other studies had shown in patients with CV risk factors. Our previous study showed SLE patients had endothelial dysfunction, even in the absence of traditional CV risk factors [8]. Since then, several authors have confirmed endothelial dysfunction in these patients [2, 9, 10, 32–38], including a recent meta-analysis [39]. Although a wide range of mean FMD has been reported in healthy individuals, varying from 5.8% to 15.8% [2, 9, 10, 32–38], in our service, using the same protocol, we found a similar FMD in healthy individuals in the present study [12.6 (7.6)%] and in the previous study [12 (6)%] [8]. In the literature the FMD in SLE patients varied from 2.4% to 10.9% [2, 9, 10, 32–38].

Worse endothelium-dependent function in SLE patients was associated with several factors, including systolic
TABLE 1 Demographic and clinical characteristics and medications of SLE patients in the EG and CG at baseline

<table>
<thead>
<tr>
<th>Variables</th>
<th>EG (n = 18)</th>
<th>CG (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years&lt;a&gt;</td>
<td>35.3 (6.8)</td>
<td>30.8 (7.2)</td>
<td>0.093</td>
</tr>
<tr>
<td>Disease duration, months&lt;a&gt;</td>
<td>78.9 (65.0)</td>
<td>107.9 (91.3)</td>
<td>0.251</td>
</tr>
<tr>
<td>White colour, n (%)</td>
<td>7 (38.9)</td>
<td>9 (45.0)</td>
<td>0.703</td>
</tr>
<tr>
<td>SLEDAIb</td>
<td>2.0 (2.1)</td>
<td>2.4 (2.3)</td>
<td>0.534</td>
</tr>
<tr>
<td>SLICC/ACR-DIb</td>
<td>0 (0–1)</td>
<td>0 (0–2)</td>
<td>0.837</td>
</tr>
<tr>
<td>Current prednisone use, n (%)</td>
<td>10 (55.6)</td>
<td>13 (65.0)</td>
<td>0.552</td>
</tr>
<tr>
<td>Current prednisone dose, mg&lt;a&gt;</td>
<td>2 (0–40)</td>
<td>5 (0–30)</td>
<td>0.815</td>
</tr>
<tr>
<td>Current antimalarial use, n (%)</td>
<td>13 (72.2)</td>
<td>16 (80.0)</td>
<td>0.359</td>
</tr>
<tr>
<td>Current immunosuppressive drug use, n (%)</td>
<td>8 (44.4)</td>
<td>14 (70.0)</td>
<td>0.111</td>
</tr>
<tr>
<td>Current antihypertensive use, n (%)</td>
<td>3 (16.7)</td>
<td>7 (35.0)</td>
<td>0.278</td>
</tr>
<tr>
<td>Current ASA use, n (%)</td>
<td>2 (11.1)</td>
<td>3 (15.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Current contraceptive use, n (%)</td>
<td>3 (16.7)</td>
<td>8 (40.0)</td>
<td>0.160</td>
</tr>
</tbody>
</table>

Table footnote: aMean (s.d.) unless stated otherwise. bMedian (minimum and maximum value). SLICC/ACR-DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus.

TABLE 2 CV risk factors in SLE patients in the EG and CG at baseline

<table>
<thead>
<tr>
<th>Variables</th>
<th>EG (n = 18)</th>
<th>CG (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²a</td>
<td>26.9 (4.7)</td>
<td>25.7 (4.0)</td>
<td>0.609</td>
</tr>
<tr>
<td>SBP, mmHg&lt;a&gt;</td>
<td>122.1 (14.4)</td>
<td>115.8 (13.0)</td>
<td>0.169</td>
</tr>
<tr>
<td>DBP, mmHg&lt;a&gt;</td>
<td>80.3 (7.4)</td>
<td>74.0 (9.3)</td>
<td>0.048</td>
</tr>
<tr>
<td>Abdominal circumference, cm²</td>
<td>87.2 (9.9)</td>
<td>86.1 (10.0)</td>
<td>0.751</td>
</tr>
<tr>
<td>Waist:hip ratio&lt;a&gt;</td>
<td>0.81 (0.06)</td>
<td>0.79 (0.06)</td>
<td>0.526</td>
</tr>
<tr>
<td>Fasting glucose, mg/dl&lt;a&gt;</td>
<td>84.6 (4.9)</td>
<td>81.3 (6.1)</td>
<td>0.076</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl&lt;a&gt;</td>
<td>161.4 (32.9)</td>
<td>164.1 (38.0)</td>
<td>0.816</td>
</tr>
<tr>
<td>HDL, mg/dl&lt;a&gt;</td>
<td>50.8 (16.0)</td>
<td>49.4 (12.3)</td>
<td>0.953</td>
</tr>
<tr>
<td>LDL, mg/dl&lt;a&gt;</td>
<td>88.3 (22.9)</td>
<td>95.1 (31.9)</td>
<td>0.590</td>
</tr>
<tr>
<td>Triglycerides, mg/dl&lt;a&gt;</td>
<td>109.9 (48.3)</td>
<td>97.2 (35.8)</td>
<td>0.262</td>
</tr>
<tr>
<td>CAD family history, n (%)</td>
<td>4 (22.2)</td>
<td>3 (15.0)</td>
<td>0.687</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>4 (22.2)</td>
<td>1 (5.0)</td>
<td>0.170</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>4 (22.2)</td>
<td>5 (25.0)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table footnote: aMean (s.d.) unless stated otherwise. SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein; LDL: low density lipoprotein; CAD: coronary artery disease. 

TABLE 3 Assessment of endothelial function at baseline (T0) and after 16 weeks (T16)

<table>
<thead>
<tr>
<th>Variables</th>
<th>EG (n = 18)</th>
<th>T0</th>
<th>T16</th>
<th>P</th>
<th>CG (n = 20)</th>
<th>T0</th>
<th>T16</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal diameter, mm</td>
<td>3.07 (0.46)</td>
<td>3.09 (0.68)</td>
<td>0.748</td>
<td></td>
<td>3.24 (0.39)</td>
<td>3.26 (0.37)</td>
<td>0.726</td>
<td></td>
</tr>
<tr>
<td>FMD, mm</td>
<td>0.19 (0.18)</td>
<td>0.39 (0.20)</td>
<td>0.002</td>
<td></td>
<td>0.27 (0.24)</td>
<td>0.30 (0.19)</td>
<td>0.531</td>
<td></td>
</tr>
<tr>
<td>FMD, %</td>
<td>6.3 (6.7)</td>
<td>14.1 (9.1)</td>
<td>0.006</td>
<td></td>
<td>8.4 (8.2)</td>
<td>9.4 (6.7)</td>
<td>0.598</td>
<td></td>
</tr>
<tr>
<td>NitroMD, mm</td>
<td>0.65 (0.21)</td>
<td>0.76 (0.24)</td>
<td>0.105</td>
<td></td>
<td>0.88 (0.26)</td>
<td>0.83 (0.19)</td>
<td>0.488</td>
<td></td>
</tr>
<tr>
<td>NitroMD, %</td>
<td>20.9 (6.1)</td>
<td>24.3 (7.9)</td>
<td>0.147</td>
<td></td>
<td>26.7 (7.1)</td>
<td>26.1 (7.0)</td>
<td>0.782</td>
<td></td>
</tr>
</tbody>
</table>

Table footnote: Unless otherwise indicated, values are mean (s.d.). aIntragroup difference between T0 and T16.
blood pressure [2, 32], age [2, 37], CV complications [2], cholesterol levels [10, 35], BMI, abdominal circumference, use of corticosteroids and immunosuppressive drugs [35], disease activity, disease duration, anti-dsDNA and aCL antibodies, anti-phospholipid syndrome, CYC pulse therapy [37] and duration of steroid use [40]. The various factors found to be associated with endothelial dysfunction in SLE patients are likely due to the difference in characteristics and sample size in each study. Endothelial dysfunction in these patients is probably multifactorial and, beyond the disease itself, includes the presence of CV risk factors, some of which may be secondary to SLE or its treatment [8].

Many SLE patients were contacted, but <50% expressed an interest in performing physical activity. Exclusion criteria were restrictive and were designed to exclude factors that could interfere with the exercise practice or endothelial function assessment. In the end, few patients remained with the availability to perform the exercise programme for 16 weeks, and those formed the EG.

The most frequent exclusion criteria were the regular physical exercise practice, current use of a statin, menopause status and overlap with other autoimmune rheumatic disease. Although it was already known that exercise training is beneficial for patients with SLE, only 15.2% of contacted patients had practised regular physical activity in the past 3 months.

In the present study the EG presented the worse NitroMD compared with the CG at baseline. Although a previous meta-analysis did not demonstrate a NitroMD compromise in SLE patients [39], studies showed a worse NitroMD in the subgroup of SLE with positive aCL antibodies [8] or with carotid plaque [36]. Adams et al. [41] showed healthy individuals with risk factors for coronary artery disease had worse NitroMD, suggesting that in the early atherosclerotic process, changes in the arterial wall are not limited to the endothelium and decreased response to NO and nitroglycerin may result in changes of vascular smooth muscle cells. We do not believe the fact that the EG presented a worse NitroMD than the CG at baseline influenced the results of our study. The higher diastolic pressure in the EG may have contributed to the worse NitroMD since we found a negative correlation between NitroMD and diastolic blood pressure.

Few studies have evaluated the effect of therapeutic intervention on endothelial function in SLE patients. There are two controlled studies that show the use of atorvastatin [42] or omega-3 polyunsaturated fatty acid supplementation [43] improves the endothelium-dependent function in SLE patients.

Studies have shown SLE patients are physically inactive or insufficiently active [44] and have a lesser ability to perform exercise [45]. Thus physical exercise may be a useful

### Table 4: Ergospirometric test in SLE patients in the EG and CG at baseline and after 16 weeks

<table>
<thead>
<tr>
<th>Variable</th>
<th>EG (n = 18)</th>
<th>CG (n = 20)</th>
<th>P&lt;sup&gt;ab&lt;/sup&gt;</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise tolerance, min</td>
<td>T0</td>
<td>T16</td>
<td>T0</td>
<td>T16</td>
</tr>
<tr>
<td>Resting HR, bpm</td>
<td>12.3 (2.4)</td>
<td>13.4 (2.6)</td>
<td>0.027</td>
<td>12.3 (2.0)</td>
</tr>
<tr>
<td>VO&lt;sub&gt;2&lt;/sub&gt;max, ml/kg/min</td>
<td>25.5 (4.4)</td>
<td>28.0 (4.5)</td>
<td>0.062</td>
<td>25.1 (4.6)</td>
</tr>
<tr>
<td>HR&lt;sub&gt;max&lt;/sub&gt;, bpm</td>
<td>175.8 (13.5)</td>
<td>175.1 (12.2)</td>
<td>0.773</td>
<td>179.3 (13.3)</td>
</tr>
<tr>
<td>VE&lt;sub&gt;max&lt;/sub&gt;, l/min</td>
<td>66.1 (16.4)</td>
<td>68.5 (13.2)</td>
<td>0.521</td>
<td>71.6 (18.3)</td>
</tr>
<tr>
<td>Maximum speed, km/h</td>
<td>7.7 (1.0)</td>
<td>8.3 (1.2)</td>
<td>0.027</td>
<td>7.7 (0.9)</td>
</tr>
<tr>
<td>VO&lt;sub&gt;2&lt;/sub&gt; VT&lt;sub&gt;1&lt;/sub&gt;, ml/kg/min</td>
<td>17.3 (4.7)</td>
<td>19.9 (4.9)</td>
<td>0.052</td>
<td>16.3 (2.7)</td>
</tr>
<tr>
<td>HR VT&lt;sub&gt;1&lt;/sub&gt;, bpm</td>
<td>137.2 (12.6)</td>
<td>142.0 (14.5)</td>
<td>0.203</td>
<td>139.5 (15.6)</td>
</tr>
<tr>
<td>Speed VT&lt;sub&gt;1&lt;/sub&gt;, km/h</td>
<td>5.6 (0.7)</td>
<td>6.1 (0.9)</td>
<td>0.005</td>
<td>5.6 (0.6)</td>
</tr>
<tr>
<td>Gas exchange ratio</td>
<td>1.18 (0.14)</td>
<td>1.18 (0.13)</td>
<td>0.775</td>
<td>1.27 (0.20)</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, values are mean (s.d.). HR: heart rate; VO<sub>2</sub>: oxygen consumption; max: maximum; VE: pulmonary ventilation. P<sup>a</sup>: intragroup difference between T0 and T16.
strategy for improving the aerobic capacity in these patients [23, 46]. However, more studies are necessary to evaluate the best modality, duration, intensity and frequency of exercise to improve endothelial function. The impact of exercise at different ages and diseases, including SLE, as well as effector mechanisms, is not fully understood. While studies show benefits of moderate exercise in older individuals with CV disease or CV risk factors, its benefits in young healthy subjects are seen only in exercises that are more intense and for longer periods [15].

Regarding the variables of ergospirometry, we observed an improvement of exercise tolerance and threshold velocity after training, as had been observed by other authors [46, 47]. Daltroy et al. [48] found no improvement in exercise tolerance; however, some data in this study are difficult to interpret because of the inclusion of 37 RA patients. Furthermore, exercise was performed for only 30 min three times per week with 60% VO2max, which may lack the explain of improvement in aerobic capacity. Tench et al. [49] found no difference in exercise tolerance, peak VO2, maximum ventilation and maximum heart rate. However, the supervision of exercise in this study occurred every 2 weeks by phone, which puts in doubt whether the patients actually performed the exercise in accordance with the proposed programme.

The differences found between this study and those reported in the literature can be justified in part by differences in the modality, intensity, frequency and duration of the exercise. Additionally, personal supervision increases the reliability in the performance of the physical activity to achieve the proposed objective.

Regarding disease activity, we found no worsening of the SLEDAI score, which reveals the safety of the modality and intensity of the exercise performed, corroborating data from other studies in patients with mild to moderate disease activity [47–50].

The main limitations of the study are the small sample size and the lack of randomization. These occurred due to the restrictive exclusion criteria and the lack of availability of many patients to participate. After contacting more than 500 SLE patients, only 224 patients were interested in participating in the study. Among those, 99 patients presented exclusion criteria. Seventy-six patients quit for personal reasons and only 23 agreed to participate in the exercise programme over 16 weeks. Therefore we preferred to include all available patients in the EG and include the others in the CG. The most frequent reason for inability to participate was personal reasons, such as work, the distance from home to the place of the exercise programme and the need to take care of their children. The lack of statistical differences between groups concerning some characteristics, such as disease duration or antihypertensive and immunosuppressive drug use, could be due to the small sample. The formation of groups on the basis of personal choice might have introduced a bias; however, the FMD at baseline was similar between groups and the intergroup analysis showed improvement only in the EG. Finally, these results should not be extrapolated to SLE patients with severe disease activity.

Conclusions

In conclusion, physical exercise is a useful strategy for improving endothelial function and aerobic capacity without worsening disease activity in SLE patients with mild disease. The benefits of physical exercise should be promoted among health professionals and patients to encourage their continued use. Furthermore, exercise may contribute to reducing CV morbidity and mortality in these patients and this needs to be confirmed by a prospective long-term study.

Rheumatology key messages

- SLE patients present with early and severe atherosclerosis.
- Physical exercise improves endothelial function in SLE patients.
- Physical exercise improves exercise tolerance without worsening disease activity in SLE patients.

Acknowledgements

We are grateful to the Centro de Estudo em Psicobiologia e Exercicio (CEPE) da UNIFESP, especially to Prof Marcos Túlio de Mello and the Lipids Section of the Cardiology Division of UNIFESP, especially to Francisco Helfenstein, MD, for permission to use their laboratories. We also thank Willian H. Chahade, MD and Luis C. Latorre, MD, for allowing patient recruitment at their services.

Funding: This study was supported by the São Paulo State Research Foundation [FAPESP; grants 2008/09295-5 (research EIS) and 2008/07350-9 and 2010/09743-8 (scholarship ETRN)].

Disclosure statement: The authors have declared no conflicts of interest.

References


Exercise improves endothelial function in SLE


