# Blunted cerebral oxygenation during exercise in systemic lupus erythematosus patients

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## Abstract

### Objective

*Subclinical brain lesions have been reported in systemic lupus erythematosus (SLE) patients. Advanced neuroimaging techniques have revealed microstructural and microvascular alterations. Most studies examining structural or functional brain abnormalities were performed either at rest or during a mental task. Our study aimed to examine possible differences in cerebral oxygenation during exercise between SLE patients without known neuropsychiatric manifestations and age-matched controls, using near-infrared-spectroscopy (NIRS) and examine possible underlying mechanisms through evaluation of brain derived neurotrophic factor (BDNF) levels.*

### Methods

*The protocol involved a seated rest, a 3-min submaximal (30%) handgrip exercise, and a 3-min recovery. Continuous-NIRS was used to monitor changes in cerebral-oxygenated ($O_2Hb$), de-oxygenated (HHb) and total-haemoglobin (tHb). BDNF levels were measured in serum samples.*

### Results

*Twenty-six SLE patients and 27 matched controls were enrolled. No differences were observed in baseline characteristics. During exercise, cerebral-$O_2Hb$ increased in both groups. However, SLE patients exhibited a significantly lower average- ($1.20 \pm 0.89$ vs. $2.69 \pm 2.46$, $p=0.001$) and peak-$O_2Hb$ response ($2.89 \pm 1.56$ vs. $5.83 \pm 4.59$, $p=0.004$) compared to controls. Serum BDNF levels were significantly lower in SLE patients compared to controls ($p<0.01$).*

### Conclusion

*To our knowledge, this is the first study to evaluate cerebral oxygenation during exercise using NIRS in SLE patients compared to age-matched controls. Our data show that SLE patients even without overt neuropsychiatric manifestations exhibit a blunted increase in cerebral-$O_2Hb$ during a submaximal exercise stimulus. Examining brain oxygenation during a simple exercise task may assist in identifying patients with early alterations in cerebral function.*

**Key words**

systemic lupus erythematosus, brain oxygenation, near-infrared-spectroscopy, microcirculation, exercise, autoimmune disease

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## Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple body organs including the central and peripheral nervous system. The neurologic and psychiatric manifestations of SLE cover a variety of clinical syndromes from headache and mood disorders to acute confusional state and psychosis (1-3). Peripheral nervous system manifestations are not very frequent, with a rising trend, however, over the last decade (3). Less than half of neuropsychiatric symptoms (~40%) can be attributed to the disease. Neuropsychiatric manifestations occur more often at disease onset or within the first 2 years after diagnosis (2). Moreover, SLE patients have a 2.1-fold higher risk of ischaemic stroke and an increased burden of cerebral small-vessel disease (4, 5).

A growing number of studies have explored subclinical brain lesions in SLE patients. White matter hyperintensities were the most common finding (30–75%) in conventional magnetic resonance imaging (MRI) studies of patients with neuropsychiatric SLE (6). These lesions, however, are a quite common finding even in patients with SLE without overt neuropsychiatric manifestations (7, 8). White matter hyperintensities are a non-specific sign as they have also been associated with older age, smoking and hypertension (9). It is also worth mentioning that up to 40% of patients with neuropsychiatric SLE did not show any cerebral abnormalities on conventional MRI (6). Functional changes, however, especially in the microvasculature, may precede structural and permanent changes seen with conventional imaging.

To this end, advanced neuroimaging techniques including diffusion tensor imaging, have been used as additional tools and revealed significant subclinical microstructural changes in SLE patients with and without neuropsychiatric disorders compared to healthy controls (10, 11). Recent data examining brain haemodynamics with dynamic-susceptibility-contrast-MRI, showed lower cerebral-blood flow and cerebral-volume in neuropsychiatric SLE compared to controls, whereas no statistically significant differences were revealed between non-neuropsychiatric SLE (non-NPSLE) and healthy controls (8). Other studies using functional MRI (fMRI), performed mainly at rest, during a mental task, or during a simple motor task such as finger tapping, showed disturbances in attention, memory, decision making, and other functions in non-NPSLE patients (6, 11, 12).

However, early alterations in cerebral perfusion/oxygenation might not be evident at resting conditions and they might be revealed during physical stress. Thus, exercise has been be suggested as a stimulus to identify early functional alterations in brain oxygenation (13). Near-infrared spectroscopy (NIRS) is a valid method that can be used to non-invasively monitor rapidly occurring changes in cerebral oxygenation during exercise, in healthy participants and patients with various pathological conditions (13-15). Previous studies have reported a correlation of cerebral oxygenation (assessed by NIRS) with cerebral blood flow (assessed by transcranial Doppler) (16). In addition, simultaneous NIRS and fMRI during an event-mediated motor activity, reported a correlation of NIRS signals with the fMRI measured blood oxygen level dependent response (17).

Reduced prefrontal cerebral oxygenation during exercise has been suggested in several chronic diseases and associated with exercise intolerance (14). Thus, although exercise has been considered a therapeutic tool to improve endothelial function and cardiorespiratory capacity, alleviate fatigue, depression, and pain, without affecting disease activity and inflammation, patients with SLE, may experience trouble in regulating cerebral oxygenation during physical exertion (18-21). Patients with SLE may exhibit early, and potentially reversible, alterations in cerebral oxygenation that might be revealed during exercise, when cerebral oxygen demand and perfusion are increased.

Brain-derived neurotrophic factor (BDNF) is a known neurotrophin involved in a variety of functions including neurogenesis, neuronal differentiation and survival, synaptic transmission and plasticity (22). Importantly, BDNF has been suggested to be crucial for

the observed exercise-related improvements in cognitive function, as blocking BDNF annulled cognitive improvements induced by exercise training (23). Reduced BDNF levels have been described in aging, chronic stress, and several cognitive disorders (*i.e.* Alzheimer's disease, depression) (24). Lesions to white matter tracts can impair conduction of neural signals and result in an unfavourable neurochemical environment associated with decreased neurotrophins and neurotransmitter imbalances (25, 26). Existing data on BDNF levels in SLE are controversial (27-29). Whether alterations in BDNF levels are associated with derangements in brain oxygenation and an inability for cortical activation during exercise, to our knowledge, has not been investigated.

Therefore, the aims of this study were: i) to investigate possible changes in cerebral oxygenation during a physical task (submaximal handgrip exercise) in patients with SLE without known neuropsychiatric manifestations compared to age-, body mass index-, and cardiovascular risk-matched controls, ii) to compare BDNF levels between groups, and iii) to identify possible associations of cerebral oxygenation with BDNF levels.

## Materials and methods

*Participants*

Patients with a diagnosis of SLE, according to the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria, were recruited from the Rheumatology Outpatient Unit (30). Inclusion criteria were diagnosis of SLE made by a rheumatology specialist and age >18 years old. The control group consisted of individuals matched for age, BMI, and cardiovascular risk factors, recruited from the Outpatient clinic of the 3rd Department of Internal Medicine of Aristotle University (Papageorgiou General Hospital, Thessaloniki, Greece) and the community during the same period. Exclusion criteria for both groups were history of coronary heart disease, stroke, or other primary central nervous system disease and importantly for the SLE group any known history or symptoms of neuropsychiatric manifestations at their last rheumatologist visit according to the 1999 American College of Rheumatology classification criteria (1). None of the participants was under treatment with anti-depressants or anti-psychotic drugs. The study was approved by the Institutional Review Board committee and conducted in accordance with the Declaration of Helsinki (2013 revision) (31). All individuals signed the written informed consent prior to participating in the study. Participants were instructed to abstain from smoking, coffee, tea, or alcohol consumption for at least 4 hours before testing.

*Clinical assessment*

Participants arrived at the laboratory in the morning, after an overnight fast. A complete medical history was obtained, and a physical examination was performed. Activity of the disease was assessed at the same day, using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score (32). Office BP (office-BP) was assessed according to standard guidelines (33). Briefly, following a 10-min rest, three measurements were obtained in each participant, with a 2-min interval in-between, using a validated oscillometric device (Microlife) with an appropriate cuff size. The average of the second and third measurement was considered as the office-BP. Hypertension was defined as office systolic and/or diastolic BP ≥140/90 mmHg, and/or current anti-hypertensive medication (33).

*Exercise protocol*

Next, the participants underwent the exercise protocol during which brain prefrontal oxygenation (using NIRS) and beat-by-beat haemodynamics [via photoplephesmography (Finometer-Pro, Finapres Medical systems, The Netherlands)] were continuously monitored. The NIRS sensor was placed on the participants' forehead over the prefrontal cortex (contra-laterally of the dominant hand), 2 cm beside the midline and about 3 cm above the supraorbital ridge. NIRS monitored changes in cerebral oxygenation, by measuring the micromolar (μM) relative changes from baseline for oxygenated ($O_2Hb$), deoxygenated (HHb) and total haemoglobin (tHb) (34). Following a 15-min rest in the seated position (during which calibration of the equipment was performed), baseline assessments were performed. Handgrip testing was performed as previously described, using a digital dynamometer (MP150, Biopac, Goleta, CA, USA). Following evaluation of maximal handgrip strength [maximal voluntary contraction (MVC) assessed as the highest of the three maximal trials] the participant performed a 3-min submaximal handgrip exercise test (at 30% MVC). During handgrip, the participant had visual feedback to maintain force output to the predetermined MVC percentage. A 3-min recovery followed.

*Biochemical measurements*

Blood samples for laboratory tests were then obtained to quantify biochemical profile (levels of uric acid, fasting glucose and creatinine), inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), levels of complement components (C3, C4), anti-nuclear antibodies and anti-double stranded DNA antibodies. Antiphospholipid antibodies positivity (lupus anticoagulant, anticardiolipin antibody, antibody to β2 glycoprotein I) was retrieved from patients' medical history file. Glomerular filtration rate was estimated in mL/min/1.73m$^2$ using the chronic kidney disease epidemiology collaboration equation (35).

Additionally, serum from blood samples were separated and stored at -80°C. Serum BDNF levels were measured in those samples according to a standard methodology. Commercially available competitive enzyme-linked immunosorbent assay kit for BDNF (Human Free BDNF Quantikine ELISA Kit, Minneapolis, USA) was used in this study (sensitivity 20 pg/ml). All samples were analysed by the same investigator and results are shown in ng/ml.

*Statistical analysis*

Statistical analyses were performed using SPSS software (IBM SPSS Statistics 25.0, Chicago, IL, USA). Continuous variables are described as mean ± standard deviation or as median ± interquartile range, based on the normality of the distribution. Differences between

groups were examined by independent samples t-tests or Mann-Whitney for normally or non-normally distributed variables, respectively. Qualitative variables were compared by the $\chi^2$ test or Fisher's exact test when necessary and results are expressed as percentages. Pearson's and Spearman's correlations were used, based on the variable's normality of distribution. A $p<0.05$ was considered as statistically significant.

## Results

*Participants' characteristics*

Fifty-three individuals (26 SLE patients and 27 controls) aged 43.2 ± 11.5 years were included in the study. Baseline characteristics of the study participants are presented in Table I. By study design, participants in the two groups did not differ in age, sex, BMI, and smoking status. Moreover, no differences were observed between groups in office-BP and hypertension status (25.9% *vs*. 15.4%, in the control and SLE groups, respectively; $p=0.34$). Overall, 11 participants presented hypertension. From these, 8 participants had borderline newly-diagnosed hypertension and were following life-style changes (no medication; 6 in control group and 2 in SLE), and 3 participants (one in the control group and two in the SLE group) were under anti-hypertensive medication (Table I).

Participants in the SLE group (Table II) had a median disease duration of 7.5 (3.0–16.0) years. Almost 80% of the patients (76.9%) were on anti-malarial treatment and 34.6% were under treatment with immunosuppressants (mainly azathioprine 26.9%). Ten of the patients (38.5 %) were treated with corticosteroids with a median dose of 7.5 (5.0–10.0) mg of prednisolone equivalent. Two patients in the SLE group had secondary anti-phospholipid syndrome. The first patient had experienced deep vein thrombosis in the past and was under treatment with warfarin. The second patient had obstetric APS and was under treatment with low-dose aspirin.

*Blood pressure response during exercise*

The SLE group did not exhibit significantly different BP responses during the exercise protocol (*i.e*. during baseline, exercise, and recovery) compared to the control group. Blood pressure and heart rate responses of the two groups at baseline, during exercise, and recovery are presented in Figure 1.

**Table I.** Baseline characteristics of the study population

| | SLE (n=26) | Control (n=27) | *p*-value |
|---|---|---|---|
| Age (years), mean ± SD | 42.7 ± 10.4 | 43.6 ± 12.6 | 0.761 |
| BMI (kg/m$^2$), mean ± SD | 25.0 ± 4.4 | 25.7 ± 4.4 | 0.527 |
| Female sex, n (%) | 23 (88.5) | 21 (77.8) | 0.467 |
| Smoking, yes, n (%) | 11 (42.3) | 10 (37.0) | 0.695 |
| Hypertension, n (%) | 4 (15.4) | 7 (25.9) | 0.344 |
| Diabetes mellitus, n (%) | 1 (3.8) | 0 | 0.491 |
| Anti-hypertensive treatment, n (%) | 2 (7.7) | 1 (3.7) | 0.610 |
| Calcium channel blocker, n | 2 | 0 | |
| B-blocker, n | 1 | 0 | |
| Angiotensin II receptor blocker, n | 0 | 1 | |
| Statin use, n (%) | 2 (7.7) | 0 (n/a) | 0.236 |
| Office SBP (mmHg), mean ± SD | 116.5 ± 13.9 | 121.0 ± 13.7 | 0.241 |
| Office DBP (mmHg), mean ± SD | 76.9 ± 12.1 | 79.3 ± 9.4 | 0.426 |
| Office HR (pulses/min), mean ± SD | 75.4 ± 12.0 | 71.1 ± 10.8 | 0.180 |
| Glucose (mg/dl), mean ± SD | 84.9 ± 9.6 | 86.8 ± 9.4 | 0.512 |
| Uric acid (mg/dl), mean ± SD | 4.4 ± 0.9 | 4.5 ± 1.2 | 0.909 |
| eGFR (ml/min/1.73m$^2$), mean ± SD | 100.0 ± 11.7 | 96.1 ± 12.5 | 0.254 |

SLE: systemic lupus erythematosus; SD: standard deviation; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; eGFR: estimated glomerular filtration rate. eGFR was calculated using chronic kidney disease epidemiology collaboration equation.

**Table II.** Clinical characteristics of patients with SLE (n=26).

| Clinical characteristics | median (interquartile range)/percentage |
|---|---|
| Age (years), mean (SD) | 42.7 ± 10.4 |
| Disease duration (years), median (IQR) | 7.5 (3.0–16.0) |
| Female sex, n (%) | 23 (88.5) |
| Raynaud's phenomenon, n (%) | 16 (61.5) |
| SLEDAI-2K, median (IQR) | 2.0 (2.0–4.0) |
| Serology | |
| ANA, positive, (%) | 100.0 |
| Anti-dsDNA, (%) | 40.0 |
| ESR (mm), median (IQR) | 12.0 (5.0–19.0) |
| CRP (mg/dl), median (IQR) | 0.31 (0.17–0.6) |
| C3, mean ±SD | 76.5 ± 21.4 |
| C4, mean ±SD | 15.0 ± 6.8 |
| Comorbidities | |
| Sjögren's syndrome, n (%) | 2 (7.7) |
| Secondary APS, n (%) | 2 (7.7) |
| History aPL (%) | 26.1 |
| Anti-cardiolipin antibodies | 13.0 |
| Anti-$\beta_2$-glycoprotein I antibodies | 18.8 |
| Lupus anticoagulant | 25.0 |
| Hypertension, n (%) | 4 (15.4) |
| Diabetes mellitus, n (%) | 1 (3.8) |
| Dyslipidaemia, n (%) | 2 (7.7) |
| Hypothyroidism, n (%) | 9 (34.6) |
| Cataract, n (%) | 3 (11.5) |
| Treatment | |
| Anti-hypertensive drugs, n (%) | 2 (7.7) |
| Anti-diabetic drugs, n (%) | 1 (3.8) |
| Statins, n (%) | 2 (7.7) |
| Thyroid hormone therapy, n (%) | 7 (26.9) |

SLE: systemic lupus erythematosus; SD: standard deviation; IQR: interquartile range; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, ANA: anti-nuclear antibodies; Anti-ds-DNA: anti-double stranded DNA antibodies; APS: antiphospholipid syndrome; aPL: antiphospholipid antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; C3: complement component 3; C4: complement component 4.

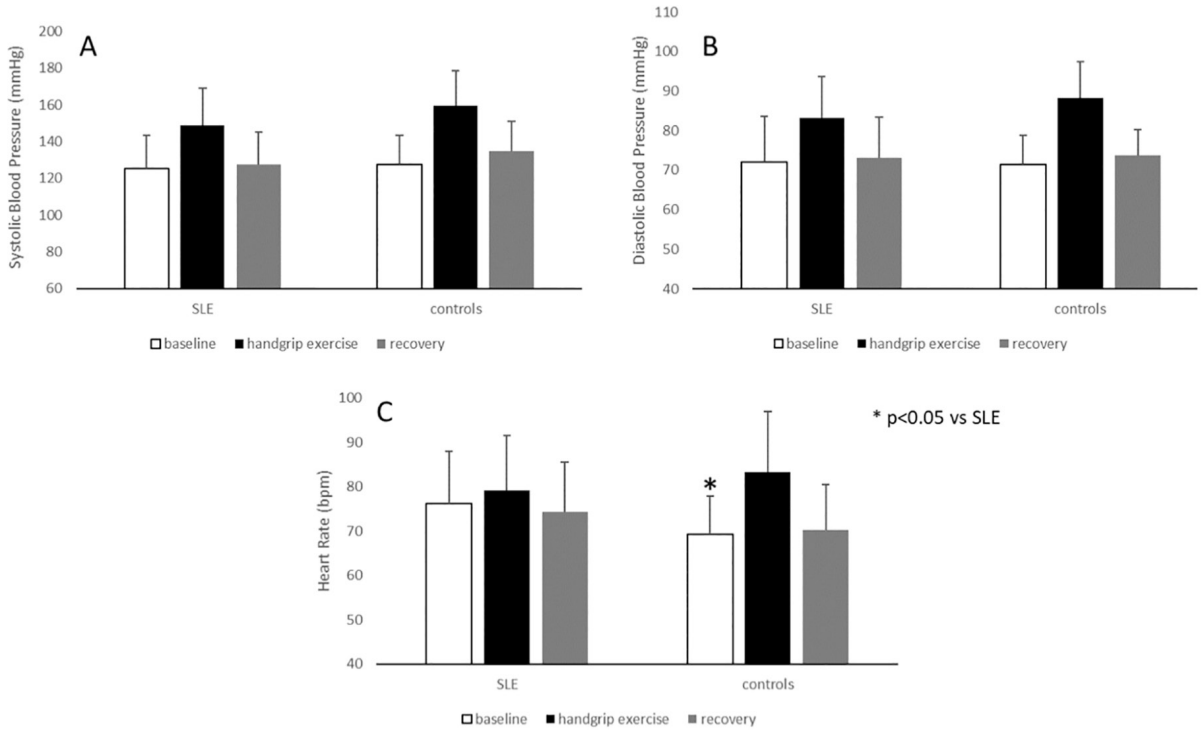


**Fig. 1.** Blood pressure and heart rate responses of the two groups during the exercise protocol. Beat-by-beat responses in systolic (**A**) and diastolic (**B**) blood pressure and heart rate (**C**) during the exercise protocol (*i.e.* 3-min average responses during baseline, handgrip exercise, and recovery) in SLE patients and controls. Data are presented as mean ± standard deviation. SLE: systemic lupus erythematosus. *$p$<0.05 *vs*. SLE in the respective period.

*Cerebral oxygenation during exercise*

Accumulative data of NIRS cerebral responses during exercise in each group are presented in Figure 2. As depicted in the figure, cerebral $O_2$Hb continuously increased during exercise in the control group, whereas the SLE group exhibited a plateau in $O_2$Hb after the first minute of exercise. The average cerebral responses in $O_2$Hb, HHb, and tHb (relative changes from rest) in each group were calculated (Fig. 3). During exercise, the SLE group exhibited significantly lower average- $O_2$Hb (1.20±0.89 *vs*. 2.69±2.46, $p$=0.001), and a lower peak -$O_2$Hb response (2.89±1.56 *vs*. 5.83±4.59, $p$=0.004) compared with the control group. No differences were detected in the average HHb responses between groups (-0.26±0.57 *vs*. -0.37±0.63, $p$=0.511). The SLE group maintained significantly lower average- and peak tHb (0.94±0.98 *vs*. 2.19±2.4 and 2.99±2.04 *vs*. 5.87±4.69, $p$=0.017 and $p$=0.005, respectively) than controls during exercise.

In order to further investigate the blunted cerebral oxygenation in SLE patients, further subgroup analysis was carried. No significant differences were found in average or peak $O_2$Hb between SLE patients with and without Raynaud's phenomenon ($p$=0.737 and $p$=0.310, respectively), corticosteroid use ($p$=0.967 and $p$=0.644, respectively), or history of antiphospholipid antibodies ($p$=0.610 and $p$=0.596, respectively).

*BDNF measurement*

Serum BDNF levels were significantly lower in the SLE group compared to the control group [17.4 (5.4–22.4) *vs*. 32.7 (19.6–40.4) ng/ml, $p$=0.006, respectively].

*Correlations of cerebral oxygenation*

Cerebral oxygenation (average and peak $O_2$Hb) during exercise was inversely correlated with age (r=-0.276, $p$=0.045 and r=-0.423, $p$=0.002, respectively) regarding the whole study sample, whereas only peak $O_2$Hb correlated with age in the SLE subgroup (r=-0.306, $p$=0.031). No significant correlations were found between average or peak $O_2$Hb with BMI, SBP, DBP or BDNF neither in the whole study sample ($p$=0.089 to $p$=0.907) nor in the SLE subgroup ($p$=0.106 to $p$=0.983). Regarding disease related parameters, no significant correlation was found between average or peak $O_2$Hb with disease duration, SLEDAI-2K or corticosteroid dose ($p$=0.156 to $p$=0.759).

## Discussion

The results of this study showed that even in the absence of a known overt neuropsychiatric history, patients with SLE presented a blunted increase in cerebral oxygenation during submaximal handgrip exercise compared to non-SLE peers with similar cardiovascular risk factors. It should be mentioned, that despite the similar increase in blood pressure during exercise, SLE patients were not able to reach the same brain oxygenation levels as individuals from the control group. Patients with SLE also presented significantly lower BDNF resting values compared to controls. However, no significant correlation between cerebral NIRS parameters with BDNF, was revealed.

To our knowledge, this is the first study to evaluate cerebral oxygenation during exercise using NIRS in a group of SLE patients without known neuropsychiatric manifestation patients compared

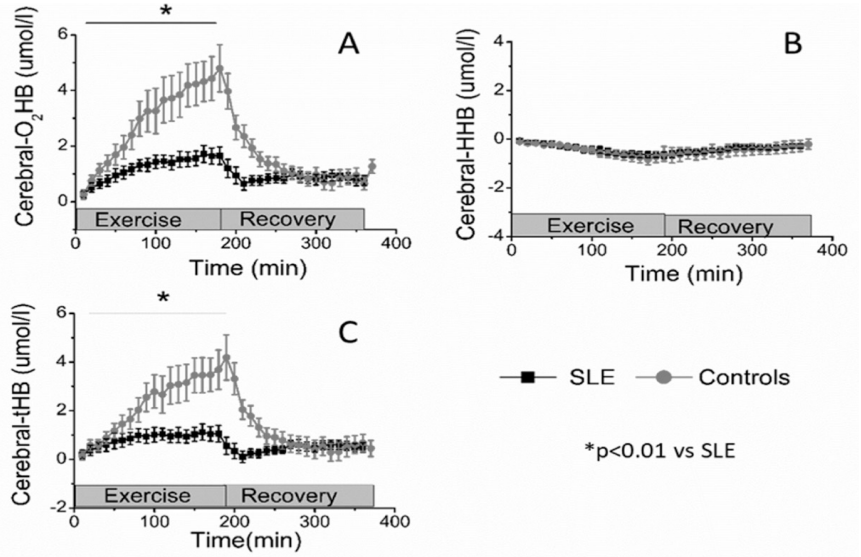


**Fig. 2.** Continuous accumulative data of NIRS cerebral responses of the two groups during handgrip exercise. Average responses in cerebral $O_2Hb$, HHb and tHb in participants with SLE and controls. Data are presented as mean ± standard error of the mean.
NIRS: near-infrared-spectroscopy; SLE: systemic lupus erythematosus; $O_2Hb$: oxygenated haemoglobin; HHb: deoxygenated haemoglobin and tHb: total haemoglobin. *$p$<0.01 *vs*. SLE in the respective period.

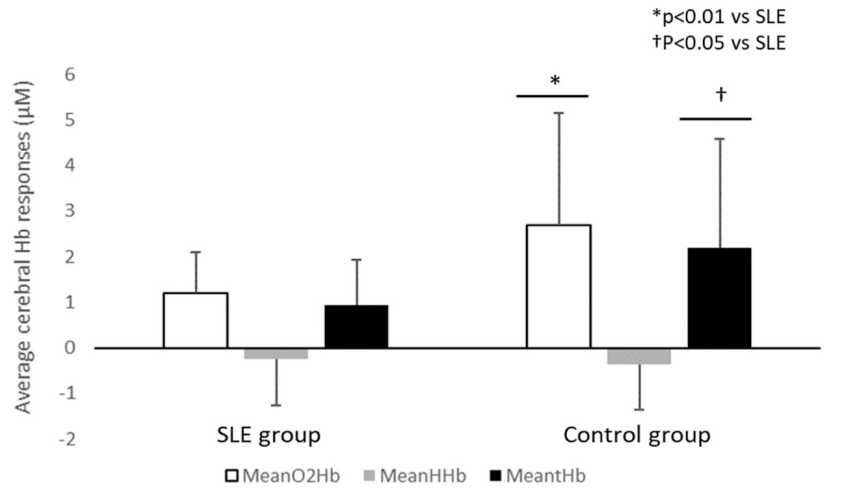


**Fig. 3.** Average cerebral responses of the two groups during the submaximal handgrip exercise. Average cerebral responses in O2Hb, HHb and tHb in the SLE and the control group during handgrip exercise (changes from rest). Data are presented as mean ± standard deviation.
SLE: systemic lupus erythematosus; O2Hb: oxygenated haemoglobin; HHb: deoxygenated haemoglobin and tHb: total haemoglobin. *$p$<0.01 *vs*. SLE in the respective period. †$p$<0.05 *vs*. SLE in the respective period.

to controls. By study design, the two groups were matched for age, sex, and BMI minimising the possible confounding effect of those parameters. Taking into account that BP and smoking status may affect microvascular function, groups with similar BP levels and smoking status were included in the study. Moreover, acute smoking can delay O2Hb recovery and, therefore, smokers were instructed to abstain from smoking for at least 4 hours before exercise testing (36). The exercise type and intensity used in this study (30% MVC), is a frequently used protocol in studies evaluating the exercise pressor reflex, since it stimulates both the mechanoreflex and metaboreflex, and elicits a significant increase in sympathetic stimulation in a short time (37, 38).

Our data showed that the SLE group presented a blunted cerebral oxygenation response during exercise. In accordance with our findings, earlier studies using single-photon emission tomography (SPECT) revealed hypoperfusion lesions in SLE patients even without neuropsychiatric manifestations (39). However, classical neuroimaging techniques require longer time and have a significantly higher cost. On the other hand, investigating cerebral oxygenation using NIRS may be a useful non-invasive alternative method, having additional advantages the lack of radiation and the use of contrast media.

A recent necrotomic study in SLE patients with and without neuropsychiatric manifestations revealed signs of brain injury compared to controls. Vasculopathy (both focal and diffuse), macroinfarction, microinfarction and vasculitis were observed in non-NPSLE patients, although in lower frequency compared to NPSLE (40). In the same study complement deposits (classical complement components, as well as the membrane attack complex) were also found on endothelial cells of small brain vessels of both SLE groups (40). Brain macro- and microcirculation alterations could impair the ability of vessels to dilate or constrict in response to different stimuli and therefore lead to hypoperfusion during a physical stress such as exercise. To this direction, SLE is characterised by macro- (increased arterial stiffness) and microcirculation (blunted microvascular reactivity) alterations in various vascular beds, possibly as part of a state of generalised vascular dysfunction (41, 42).

Previous data have suggested a possible link between cerebral oxygenation and exercise intolerance. Normally, during exercise an increase in both cerebral

$O_2$HB and tHb (an index of regional blood volume) is observed (13, 43). Chronic disease, however, can alter the ability of the brain to increase brain oxygenation and activation during exercise (13,14). Brain function is impaired when its oxygenation is reduced more than 10% (44). Moreover, reduced cerebral oxygenation during exercise may play a role in the development of central fatigue and therefore reduce the ability to maintain force output (14, 44, 45). To this direction, SLE patients are more likely to develop sarcopenia related to physical inactivity, disease activity, inflammation and smoking (46, 47).

BDNF is a neurotrophin that plays an important role during the developmental years, as well as, in the maintenance of the adult brain function (24). Only a few previous studies have explored the role of BDNF in SLE, especially in non-NPSLE. The results, however, remain conflicting. More specifically, Tamashiro *et al*. and Zheng *et al*. reported increased serum BDNF levels in SLE patients compared to controls (28, 48). On the other hand, Noris-García *et al*. and Tian *et al*. found lower BDNF levels in SLE patients compared to controls (27, 29). In accordance to Tian *et al*., our results showed significantly lower BDNF levels in non-NPSLE compared to controls. It should be also noted that median values of controls in the present study is similar to those found in a validation study of 259 volunteers (49). Methodological issues related to sample collection and storing, as well as measuring of BDNF may be responsible for the conflicting results. (29). Apart from the neuronal cells, BDNF is also synthesised by vascular endothelial cells (29). In this context, low levels of BDNF along with the blunted cerebral oxygenation response during exercise, may reflect a more generalised endothelial dysfunction and microvascular damage rather than a vascular dysregulation in the CNS only, in our cohort. It is possible, therefore, that early microvascular alterations are present before the clinical manifestations of the disease in CNS or in other vascular beds in patients with SLE. Despite the interesting findings no significant correlation was found between BDNF levels and cerebral oxygenation, possibly due to the small sample size.

Despite the interesting, novel and first reported findings of our study, there are some unavoidable limitations. Firstly, its relatively small sample size, which can be partly explained by the epidemiology of the disease itself and partly by the strict inclusion criteria (without overt neuropsychiatric manifestations or other significant comorbidities, groups with similar age, BMI, hypertension status). On the other hand, those criteria allowed the elimination of possible confounding factors. Next, although groups were matched for office blood pressure and hypertension status, not all hypertensive participants were under the same anti-hypertensive medication. In the control group, one participant was under a renin-angiotensin blocker and in the SLE group, the one participant was under a calcium channel blocker and the second one under a calcium channel blocker and a low dose b-blocker. Different class of anti-hypertensive medication could exert differential responses in brain oxygenation during exercise. More specifically, studies have shown that b-blockers have little impact on cerebral circulation in the chronic setting (50). However, a reduction in cerebral blood flow velocity and frontal lobe oxygenation during maximal exercise has been reported in young healthy individuals, in response to an acute administration of b-blocker, mainly associated with a blunted increase in cardiac output at maximal effort (51). The submaximal handgrip test used in this study, involves a relatively small muscle mass and does not require maximal increases in cardiac output. In addition, this patient was also under calcium channel blockade. Chronic administration of calcium channel and renin-angiotensin blockers have been reported to improve CBF and oxygenation (50). However, the small number of participants using anti-hypertensive medication was equally distributed and affected both groups. For this reason, we believe that it did not affect the results in the whole cohort. Other limitations include the cross-sectional design of the study and the fact that we did not include patients with established NP-SLE as an extra control group. Cerebral oxygenation was assessed with NIRS, a noninvasive technique that provides reliable measures of brain function and oxygenation, during rest and exercise (13-15). Cerebral-NIRS measurements were obtained from the contralateral pre-frontal cortex. Although an excellent agreement between NIRS prefrontal lobe oxygenation indices and direct measurements of cerebral capillary oxygenation has been shown, oxygenation responses in other brain areas require further studies (52).

Exercise may be a useful non-pharmacological intervention in SLE. Recent studies showed a beneficial effects of exercise training in lupus patients, without an adverse effect on disease activity, while low physical fitness, and inactivity has been associated with muscle pro-inflammatory cytokines expression in rheumatic diseases (19, 20, 53). However, Margiotta *et al*. (2018) showed that more than 60% of lupus patients lead a sedentary life (54). Information on cerebral oxygenation during exercise is important, as reduced cerebral oxygenation can result in premature fatigue, early termination of the exercise session, exercise intolerance, and reduced adherence to exercise programs. Examining cerebral oxygenation can identify patients with a greater risk for cerebrovascular events and cognitive decline, but also could assist in exploring exercise training modalities that can improve cerebral oxygenation.

## Conclusions

Our novel data show that SLE patients even without overt neuropsychiatric manifestations exhibit a blunted increase in cerebral-$O_2$Hb during a submaximal exercise stimulus compared to matched controls. The examination of brain oxygenation during a simple exercise task by a non-invasive and reliable technique may assist in identifying patients with early alterations in cerebral function. However, larger and perspective studies are needed to confirm the results, explore possible underlying mechanisms, and investigate the role of reduced brain oxygenation during exercise in future cerebrovascular events or other neuropsychiatric manifestations.

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