



Evaluation of muscle oxygenation by near infrared spectroscopy in patients with facioscapulohumeral muscular dystrophy

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Abstract

The purpose of the study was to determine muscle metabolism adaptation to exercise in facioscapulohumeral muscular dystrophy patients (FSHD) and to study the correlation with clinical functional status (6-min walk test).

8 FSHD patients and 15 age-matched healthy controls (Controls) performed two isokinetic constant-load knee extension exercises: (1) at 20% of their maximal extensors' peak torque (i.e. the same relative workload) and (2) at (20N·m) (the same absolute workload) for up to 4 min. All exercises consisted of rhythmic, voluntary, isokinetic, concentric contractions of the quadriceps femoris at 90°/s, whereas the flexion was performed passively at the same speed. Muscle oxygenation in the vastus lateralis was evaluated using near-infrared spectroscopy (NIRS).

The FSHD patients displayed a lower maximal peak torque than controls (~41%, $p < 0.05$). During the two-exercise modalities, deoxygenated haemoglobin (HHb) and total haemoglobin volume (tHb) were lower in the FSHD patients ($p < 0.05$). The initial muscle deoxygenation time delay was shorter in the control group (FSHD: 15.1 ± 4.1 s vs. controls: 10.4 ± 2.1 s, $p < 0.05$). Mean response time and maximal peak torque were both correlated with functional impairment (walking endurance).

The results suggest that FSHD patients present an impairment in their capacity to deliver or to use oxygen.

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1. Introduction

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant inherited muscular dystrophy and affects about 1 in 20,000 people worldwide [1]. Symptoms may develop in early childhood but generally appear after adolescence. FSHD is characterised by a progressive asymmetric muscle weakness (due to fibre degeneration) in the facial muscles, shoulder girdle and arms [2]. In addition, muscle weakness develops in other areas and the lower limbs can be affected, leading to loss of mobility in 20% of patients. Potential complications include severe muscle weakness, wheelchair use and postural problems leading to a sedentary lifestyle. Hence, the ability of patients to perform physical activity is limited and contributes to a decreased quality of life

[3,4]. Understanding the mechanisms involved in the physical weakness is thus a major issue.

The altered physical ability during exercise may result from a limited oxygen uptake within the active muscles in this population. Recent studies have shown an increased oxidative stress and mitochondrial dysfunction correlated to parameters of muscle function in patients affected by FSHD [5,6]. The impairment of one or more metabolic or mitochondrial pathways may result in an energy deficiency that could be a feature of muscle impairment. To investigate this hypothesis, near-infrared spectroscopy (NIRS) has been widely used for monitoring local muscle oxygenation in healthy subjects and in patients with various neuromuscular, metabolic, vascular or respiratory diseases [7–9]. More specifically in the field of neuromuscular disease, NIRS has been used almost exclusively to evaluate the muscular oxygen uptake capacity in patients with muscular metabolic disorders [10,11]. During an incremental exercise test, patients with muscular metabolic diseases display lower levels of deoxyhemoglobin (HHb) – perhaps as a result of a defect in oxygen uptake [7]. In patients

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with myopathies, Quaresima et al. did not observe any difference in muscle oxygen levels and muscle blood volume when comparing children suffering from Duchenne muscular dystrophy and healthy children during treadmill exercise performed at the same absolute velocity [12,13]. Sander et al. observed similar levels of muscle deoxygenation in Duchenne muscular dystrophy patients and in healthy controls during a grip strength effort performed at the same relative resistance [14]. Using a 5-min isokinetic leg extension exercise trial, Allart et al. [8] reported that patients suffering from Becker muscle dystrophy (BMD) did not differ from their healthy counterparts in terms of peak HHb levels or blood volume. In contrast, the time course of the initial muscle de-oxygenation (as measured by NIRS) appeared to be faster in BMD patients and associated with disease severity and functional impairment. The authors suggested that it may have been due to the O₂ supply defect induced by the impaired vasodilation [8]. All together, these results suggest that muscular O₂ uptake disorders reported during exercise may appear very specific to the concerned myopathy: either characterised by impaired vasodilation (oxygen delivery) or limited by muscular metabolic alterations (O₂ consumption).

While FSHD is not known to be associated with impaired vasodilation, a better understanding of the mechanisms involved in the reduced physical ability of this population will be important in developing adapted training protocols. The objective of this study was to compare muscle oxygenation kinetics between FSHD patients and healthy subjects. We hypothesised that: (i) changes in muscle oxygenation during effort in FSHD patients will differ from their healthy counterparts and (ii) muscle oxygenation kinetics will reflect the functional capacity (distance covered during a 6-min walking test).

2. Patients and methods

2.1. Subjects

Eight male patients and fifteen age-matched healthy male controls were enrolled in this study between February and May 2014. Patients were medically followed-up in the referral centre for neuromuscular disease at Lille University Medical Center (Lille, France). The inclusion criteria included genetically confirmed FSHD, the ability to walk with or without a technical aid and a quadriceps strength rating of at least 4/5 according to Medical Research Council scale in at least one leg. Only male subjects were included in order to compare our results to our previous study conducted with patients affected by Becker muscular Dystrophy [8]. Control subjects had to be sedentary,

Table 1

Anthropometric characteristics and extensor peak torque of the FSHD subjects and controls.

	Age (years)	Weight (kg)	Height (cm)	Peak torque (N.m)
FSHD group	36 ± 5	69 ± 5	172 ± 6	75 ± 21
Control group	38 ± 6	73 ± 6	176 ± 9	182 ± 54*

The values are expressed as mean ± SD.

* Significantly different between the FSH group and Control group ($p < 0.05$).

i.e. less than one hour of physical activity per week. Subjects presenting local knee osteo-articular pain, other neurological disease, dyspnoea above 2 according to NYHA classification, cardiovascular contraindications for exercise or peripheral arterial vascular disease were excluded from the study. Written informed consent was obtained before participation. The study was performed in accordance with the Declaration of Helsinki.

Anthropometric characteristics of patients and controls are presented in Table 1. FSHD symptoms lasted for 14 ± 8 years, the Brooke and Vignos functional scales were used to grade arm and leg function, respectively [15]. Five of 8 patients were scored either 1 or 2 for arm function (i.e. they were able to raise the arms and touch the hands together above the head) – and scored 1 in their legs (i.e. they were able to walk and climb stairs without assistance). The 3 other patients were scored 3 for the arm function (i.e. they were unable to raise the hands above the head but were able to raise an 8-oz glass of water to the mouth) and were scored 2 in the legs (i.e. they were able to walk and climb stairs with aid of railing).

2.2. Exercise protocol

Subjects performed exercise trials on a CON-TREX isokinetic dynamometer (MEDIMEX ®, Sainte Foy les Lyon, France) in knee mode. Subjects sat on the CON-TREX device with back reclined at 90° and were strapped according to the manufacturer's recommendations. The device was then calibrated according to manufacturer's instructions. The knee range of motion was set from 10 to 100° of flexion for all subjects and all assessments were made on the stronger leg. Exercise trials consisted in rhythmic, voluntary, isokinetic, concentric contractions of the quadriceps femoris at an angular velocity of 90°/s, whereas the flexion was performed passively at the same speed (Fig. 1).

Subjects were first familiarised with the experimental protocol by means of two practice runs of five submaximal repetitions, with a 30-s interval between runs. Maximal muscle

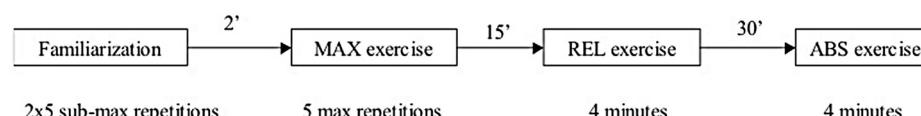


Fig. 1. Protocol design. MAX exercise: determination of the maximal peak torque; REL exercise: at the same relative load (20% of the maximal peak torque); ABS exercise: at the same absolute workload (20 N.m). The text under the boxes describes the exercise time or repetitions number and the text between the boxes indicates the rest period.

peak torque was assessed during five contractions and strong verbal encouragements were provided during each set. The highest peak torque value (highest point of the torque curve) was used thereafter as reference to calculate exercise intensity for the relative trial.

After a 15-minute rest period, subjects performed a constant load exercise trial at a rate of one cycle every two seconds performed at 20% of their maximal peak torque (i.e. same relative workload for all subjects; REL) for up to 4 minutes, adjusting their force by a visual feedback. Finally after a 30-minute rest period they performed a second exercise trial at 20 N·m (i.e. same absolute workload for all subjects; ABS) for up to 4 minutes. The criteria for stopping the exercise before the end of the 4-minute test were exhaustion, muscular pain or the occurrence of 5 successive contractions performed below the ‘target-torque’.

2.3. Muscle oxygenation monitoring by NIRS

Muscle oxygenation was monitored in vastus lateralis during the two constant load exercise trials with a 3-channel portable continuous-wave NIRS device (PORTAMON, Artinis Medical systems®, Zetten, The Netherlands). NIRS is a widely used validated technique to monitor muscle oxygenation in health and disease [16,17]. Emitted light (peak wavelength 750 and 850 nm) is mainly absorbed by oxygenated haemoglobin (HbO_2) and deoxygenated haemoglobin (HHb) in small muscular blood vessels (small arterioles, capillaries and venules) [18]. The optical density is converted into concentration of HbO_2 and HHb using a modified Lambert–Beer law in which a differential pathlength factor is incorporated to correct for scattering of photons in the tissue. The sum of absorbencies at the 2 wavelengths gives the change in local blood volume that is attributed to change in total haemoglobin volume (tHb). HHb signal has been preferred to characterise muscle oxygenation because it can be regarded as being essentially blood volume insensitive during exercise compared to HbO_2 and it represents a reliable criterion of changes in O_2 extraction in the field of interrogation [19]. At the beginning of a constant load exercise, HHb rises up rapidly after a time delay (TD) before maintaining at a steady-state value (Fig. 2). This signal can be fitted by the monoexponential function $\text{HHb}_{(t)} = \Delta \text{HHb} \times (1 - e^{-(t-TD)/\tau})$, where ΔHHb represents the HHb amplitude between resting and steady-state values, TD the Time Delay and τ the time constant, i.e., the time taken to reach 63% of the steady-state response [20,21]. The sum of TD and τ represents the Mean Response Time (MRT) (Fig. 2). Signal has been arbitrarily set to 0 at rest so the equation did not include baseline HHb. Skinfold thickness at the site of application of the NIRS probe was determined (at the end of the exercise protocol) with a Harpenden caliper. The calculated value of skin and subcutaneous tissue thickness was not different in the two groups (6.1 ± 2.1 mm in FSHD patients vs. 5.5 ± 2.2 mm in controls). These values enabled efficient measurement of muscle tissue oxygenation because the probe’s 2.5–3.5 cm source-to-detector separation allows a minimum 1.25–1.75 cm depth measurement [22].

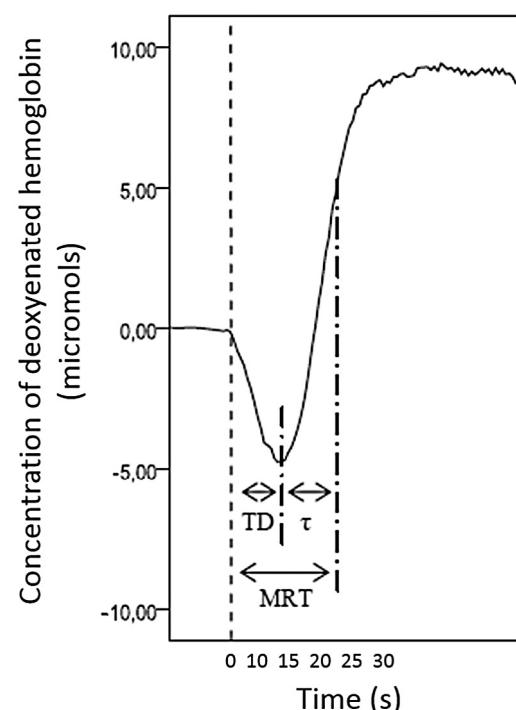


Fig. 2. Focus on the initial deoxygenation parameters occurring at the start of exercise trials. TD: time delay; τ : time constant; MRT: mean response time.

NIRS probe was placed on the belly of vastus lateralis midway between the lateral epicondyle and the great trochanter of the femur in order to obtain a same relative position between subjects because vastus lateralis oxygenation has been proved to be spatially heterogeneous [23]. To avoid interference with ambient light, a sleeve of opaque, black cloth surrounded the probe. The signal was sampled at 10 Hz by the computer software provided by the manufacturer and the data were filtered by a 2 s-moving average.

2.4. Cardiorespiratory parameter measurements

The gas exchange parameters, O_2 uptake (VO_2), carbon dioxide production, (VCO_2), and minute ventilation (V_E), were continuously measured breath-by-breath with a cardiopulmonary exercise test system (Metamax 3b, Cortex, Germany). VO_2 outlier values over the exercise ($\pm 4\text{SD}$) were removed as per Lamarra et al. [24] and signal was averaged over 5-s periods. Respiratory exchange ratio (RER) was defined as VCO_2 divided by VO_2 over 5-s periods.

2.5. Global exercise tolerance

In order to assess the global tolerance of exercise, we measured rate of perceived exertion (RPE) by a Borg scale [25]. The RPE scale consisted of 15 levels between 6 and 20 associated with verbal information (from “very very light” to “very very hard”). This scale was presented to the subjects at the end of each exercise.

2.6. Assessment of functional capacity

Functional capacity was measured with a 6-min walking test on a circular walkway marked at 10-m intervals. Patients were

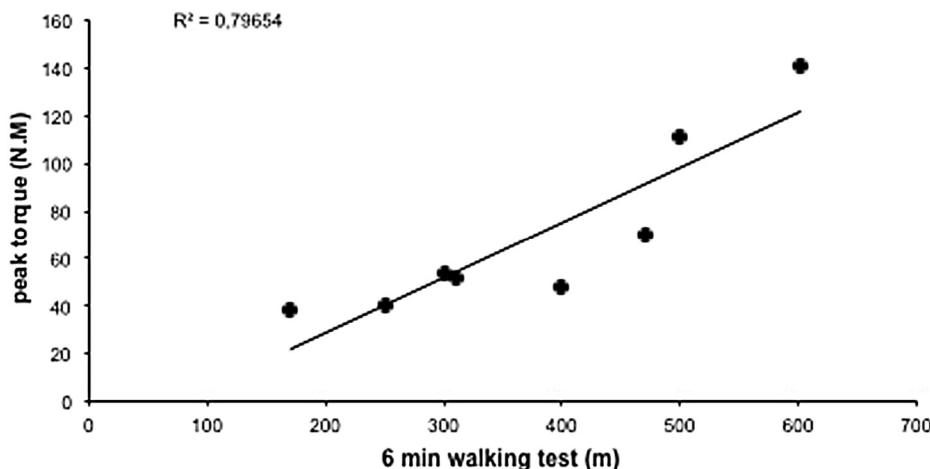


Fig. 3. Correlations between the leg extensor peak torque and the 6-min walking test in FSHD patients.

not verbally encouraged or advised and only the 2-min and 4-min time points were announced.

2.7. Statistical analysis

Results are expressed as mean \pm SD. NIRS parameters were tested with a linear mixed model with group for fixed effect and pairing block for random effect. Data have been transformed before into rank to realise a non-parametric analysis that fit to the small population. Intra-group comparisons were made with a Wilcoxon Signed-rank test. The links between NIRS parameters and the other assessments were studied using a Spearman's rank correlation coefficient. Analyses were performed with SPSS software v18 (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered as statistically significant.

3. Results

3.1. Overall exercise tolerance

As expected, the FSHD group exhibited a lower maximal leg extensor peak torque than the control group (peak torque: 75 ± 21 N·m vs. 182 ± 54 N·m, respectively; $p < 0.05$; Table 1). Peak torque was correlated with the 6-min walking test ($r^2 = 0.79$, $p < 0.05$, Fig. 3). The RPE was greater in FSHD group for the two exercise modalities ($p < 0.05$, Table 2).

3.2. Cardiorespiratory data

The 5-s averaged cardiorespiratory data are presented in Table 2. After cessation of exercise, the RER and the peak minute ventilation (peak V_E) were higher in FSHD patients ($p < 0.05$). Nevertheless, heart rate (HR), oxygen uptake (VO_2) did not differ between the two-groups for either exercise modality (Figs. 4 and 5).

3.3. Muscle oxygenation

The changes over time in HHb and tHb during relative and absolute exercise trials are shown in Figs. 4 and 5 respectively. In the two-exercise modalities, HHb and tHb were lower in the FSHD group ($p < 0.05$). Parameters concerning the initial deoxygenation kinetics during the two-exercise modalities are presented in Table 3. For the relative exercise trial, the mean response time was similar in the two groups, but the initial muscle deoxygenation (TD) was shorter in the control group (FSHD group: 15.1 ± 4.1 s vs. control group: 10.4 ± 2.1 s; $p < 0.05$). For the absolute exercise trial, TD, τ and MRT parameters were similar between the two-groups.

In addition, there was, in the FSHD group, a negative relationship between the walking distance achieved during the 6-min walking test and the MRT duration ($r^2 = 0.72$, $p < 0.05$, Fig. 6).

Table 2

Comparisons of cardiorespiratory values and rate of perceived exertion between the FSHD patients and healthy controls subjects for both exercises.

	Resting V_E (L/min)	Peak V_E (L/min)	Resting VO_2 (mL/min/kg)	Peak VO_2 (mL/min/kg)	Resting HR (bpm)	Peak HR (bpm)	Peak RER	RPE
20% peak torque								
FSHD group	10.1 ± 1.7	27.1 ± 6.8	4.6 ± 0.8	8.9 ± 2.8	76 ± 7	108 ± 12	1.12 ± 0.26	14 ± 2
Control group	11.2 ± 2.6	$21.6 \pm 3.8^*$	4.5 ± 1.4	9.7 ± 1.9	74 ± 11	101 ± 13	$0.81 \pm 0.18^*$	$11 \pm 1^*$
20 N.m								
FSHD group	10.3 ± 1.2	33.2 ± 7.2	4.3 ± 0.5	10.4 ± 2.8	74 ± 5	109 ± 15	1.11 ± 0.24	15 ± 1
Control group	11.2 ± 2.9	$19.7 \pm 3.1^*$	4.5 ± 0.9	8.98 ± 2.3	73 ± 8	95 ± 11	$0.84 \pm 0.2^*$	$11 \pm 1^*$

The values are expressed as mean \pm SD. V_E : minute ventilation; VO_2 : oxygen uptake; HR: heart rate; RER: respiratory exchange ratio; RPE: rate of perceived exertion.

* Significantly different between the FSHD group and Control group ($p < 0.05$).

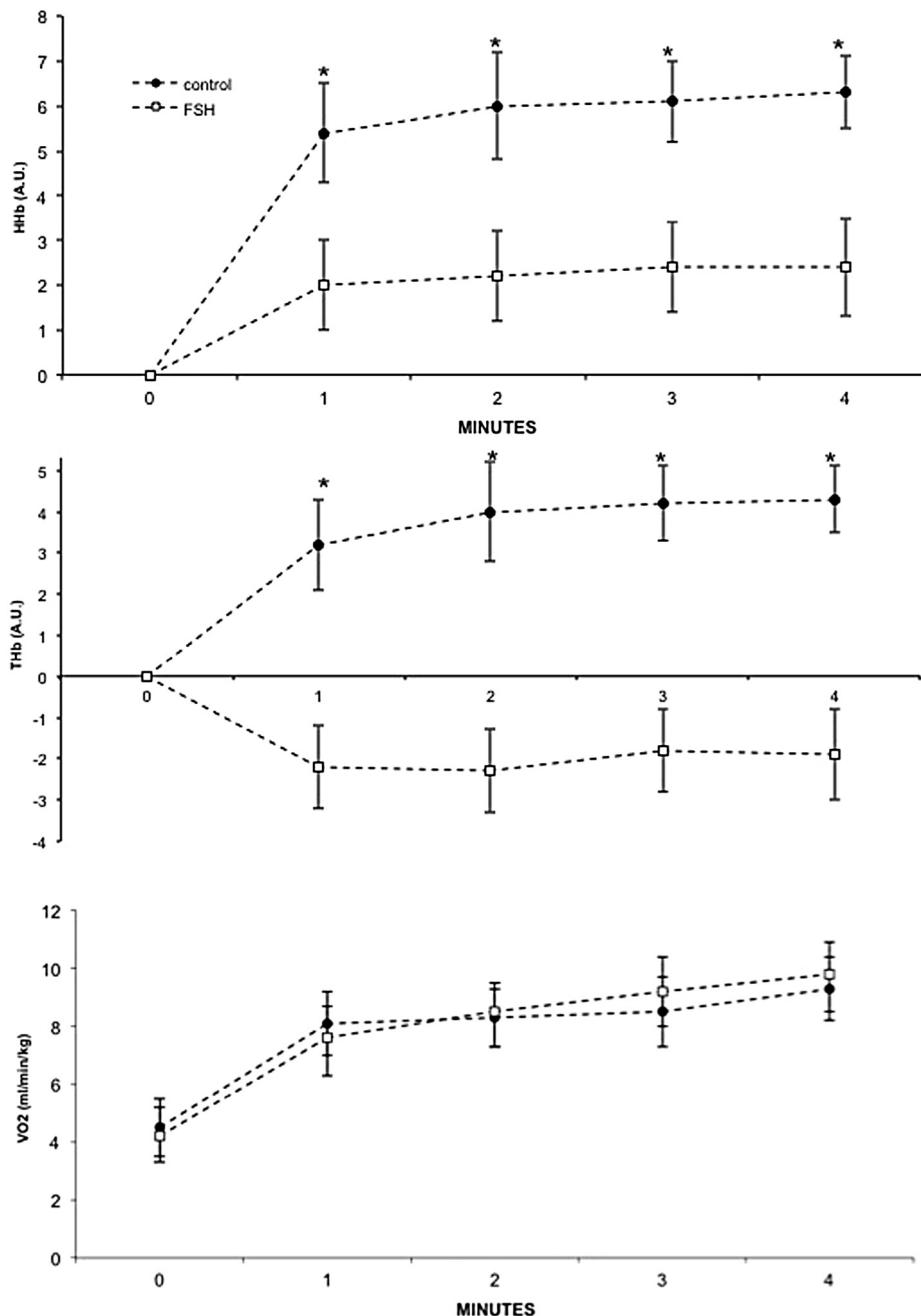


Fig. 4. Evolution of the mean deoxygenated haemoglobin (HHb), total haemoglobin (tHb) and O₂ consumption (VO₂) parameters during the relative exercise trial (20% of their respective peak torque) in FSHD patients and healthy controls. A.U., arbitrary units. *Significantly different between the FSHD group and the control group ($p < 0.05$).

4. Discussion

The purpose of this work was to determine exercise-induced changes in muscle oxygenation in FSHD patients and to study a possible association with functional capacity assessed by a 6-min walking test. Our results showed that during both exercise modalities the peak HHb and total haemoglobin (tHb) levels were lower in FSHD patients. The mean response time (MRT) and peak torque were respectively negatively and positively correlated with the functional capacity of FSHD patients.

4.1. Absolute load exercise (20N·m)

The change in HHb levels is often used to estimate muscle O₂ uptake (Grassi et al. [21]), and so this latter process may have been more efficient in the controls. During exercise trial, the tHb level increased in the control group but decreased in the FSHD group (Fig. 5). The literature data on cycle ergometer or leg extension exercise show that tHb should normally increase [8,26,27]. This increase is generally explained by capillary recruitment, local vasodilation and/or an increase in muscle blood flow. In contrast, a decrease in tHb occurs when there is

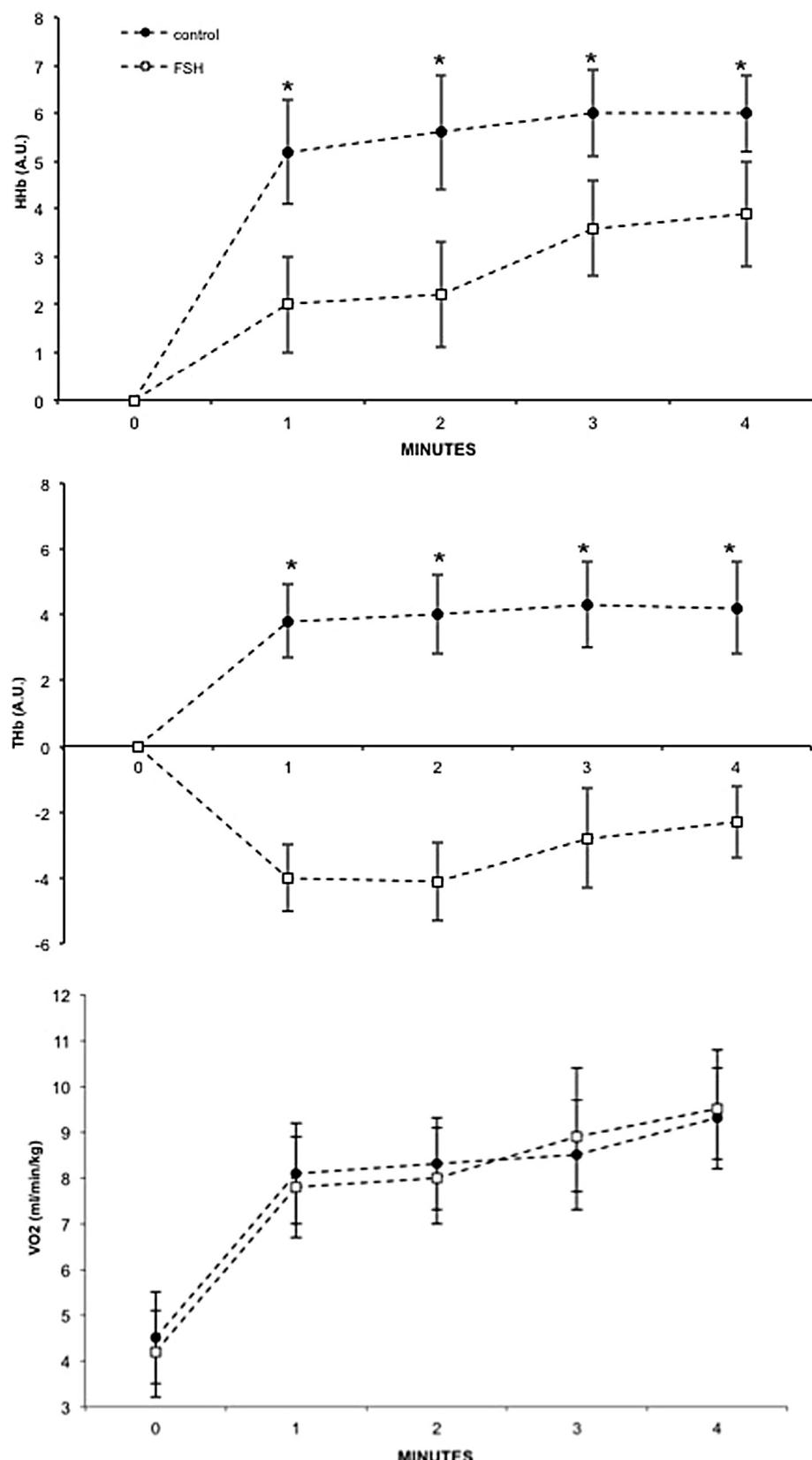


Fig. 5. Evolution of the mean deoxygenated haemoglobin (HHb), total haemoglobin (tHb) and O₂ consumption (VO₂) parameters during the absolute exercise trial (20 N.m) in FSHD patients and healthy controls. A.U., arbitrary units. *Significantly different between the FSHD group and the control group ($p < 0.05$).

Table 3

Parameters of initial deoxygenation kinetics between FSHD patients and healthy control subjects for both exercises.

	TD (seconds)	τ (seconds)	MRT (seconds)
20% peak torque			
FSHD group	15.1 ± 4.1	14.6 ± 3.5	27.2 ± 4.5
Control group	10.4 ± 2.1*	15.2 ± 3.8	25.1 ± 4.9
20 N.m			
FSHD group	14.3 ± 4.2	16.5 ± 6.2	30.3 ± 8.5
Control group	10.2 ± 3.9	17.3 ± 3.1	25.5 ± 3.7

The values are expressed as mean ± SD. TD: time delay; τ : time constant; MRT: mean response time.

* Significantly different between the FSHD group and Control group ($p < 0.05$).

an increase in muscle pressure and vascular compression associated with muscle contraction [28]. The much higher relative exercise intensity in the FSHD group may have accentuated the effects of muscle pressure and vascular compression and thus prompted a fall in tHb. In our study, in the absolute load exercise, the two groups did not differ in terms of the time delay (TD), τ , and the MRT (Table 3). Our time course data for the healthy controls are similar to those reported by Allart et al. [8]. However, the authors reported that peak HHb values obtained with the BMD patients were markedly lower than our present values for FSHD patients [8]. This disparity may have been due to a lower O₂ supply in BMD as a result of impaired vasodilation.

During the exercise test, we also recorded gas exchange and heart rate parameters (Table 2). To the best of our knowledge, these parameters have not previously been studied during this type of effort in this patient population. At the end of the exercise test, the two groups displayed similar heart rate and VO₂ values. However, the RER and the peak ventilation

were higher in FSHD patients (Table 2). A similar VO₂ and a higher RER indicate a greater VCO₂, which may lead to hyperventilation [29]. The same absolute workload of 20 N.m corresponded to 27% of the maximum leg extensor peak torque in the FSHD group, but ~11% in the control group (Table 1). The difference in the mean Borg rating of perceived exertion shows that the FSHD group found it more difficult to perform the 20 N·m exercise (Table 2). These differences may be due to the muscle acidosis induced by exercise and/or the low peak force.

4.2. Relative load exercise (20% of maximum peak torque)

The changes over time in HHb during exercise at the same relative load (20% of maximum peak torque, Fig. 4) in the control group were similar to those found during the exercise at the same absolute load (20 N.m). The fact that difference in intensity between the two exercise sessions was only small explains this result and also shows that the measurements were reproducible (Tables 2 and 3). At the beginning of the exercise bout, THb levels fell in FSHD group whereas it increased in control group. Allart et al. also observed this decrease in HHb in patients with BMD, which may be due to (i) a delayed muscle oxygen consumption and (ii) greater muscle pump activity (which would favour perfusion). In fact, the TD at the start of the exercise is related to the inertia of oxidative metabolism [28]. This parameter was higher in our FSHD group than in our control group (15.1 ± 4.1 s vs. 10.4 ± 2.1 s, respectively). Moreover, the mean TD was much shorter in Allart et al.'s BMD group than in our FSHD group (respectively 5.8 ± 2.1 s vs. 15.1 ± 4.1 s for relative load, and 5.5 ± 2 s vs. 14.3 ± 4.2 s for absolute load) [9]. Given that the FSHD and BMD groups displayed the same muscle performance, this difference is probably due to impaired vasodilation in BMD.

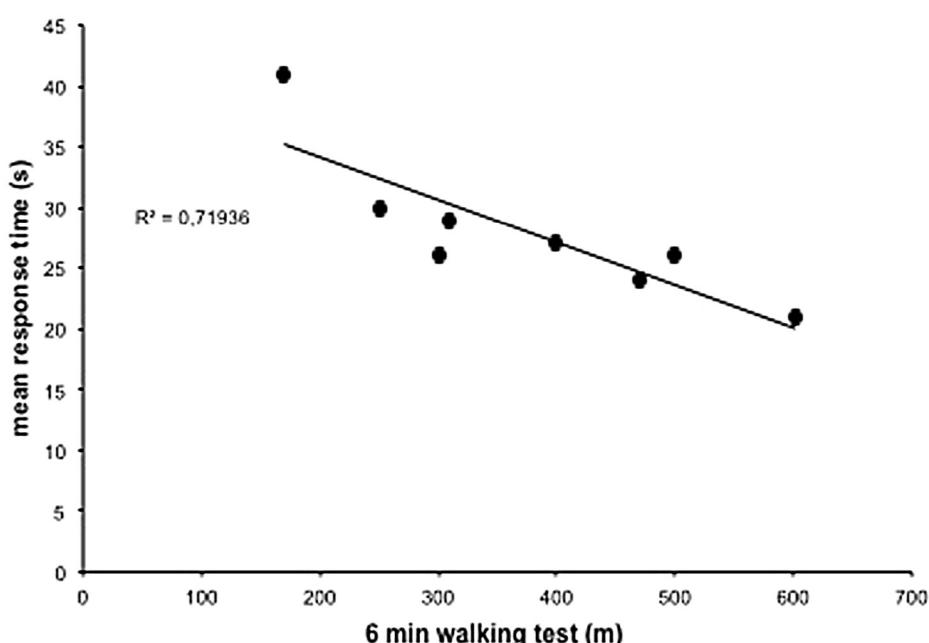


Fig. 6. Correlations between the mean response time during the relative exercise trial (20% of maximal peak torque) and the 6-min walking test in FSHD patients.

The change over time in tHb levels differed in the two groups, with an increase in the control group and a decrease in the FSHD group (Fig. 4). It must be borne in mind that tHb is only a marker of blood volume; it would be interesting to obtain more detailed information on femoral blood flow by using Doppler ultrasound.

We also recorded gas exchange parameters during the relative load (Table 2). There were no intergroup differences in VO₂ and heart rate at the end of the session. These findings are expected, as the exercise was performed at 20% of peak torque for all subjects. However, the RER was significantly higher in FSHD patients, suggesting that anaerobic glycolysis (which favours the production of lactate and hydrogen ions and increases CO₂ production) is used to a greater extent during exercise in these patients [30,31]. Therefore for an exercise realised at a same relative intensity, the greater RER measured during the exercise in FSHD patients indicate that they use in a greater extent the anaerobic glycolysis. This energy process favours the production of lactate and hydrogen ions, which increase CO₂ production and the RER.

4.3. Association with the functional capacity

The 6-min walking test is a well-validated measurement of cardiac and respiratory retraining that is related to the level of personal independence in activities of daily living [32]. However, the test's functional relationship with activities of daily living has yet to be defined for FSHD patients. In our study, the walking distance was correlated with peak leg extensor peak torque (Fig. 3); the lower the peak torque and the lower the walking distance. There was also a negative relationship between the walking distance achieved by FSHD patients and the MRT (Fig. 6) ($p < 0.05$). Taken together, these data suggest that there may be a link between the muscle ability to extract oxygen rapidly and the functional capacity. These results challenge the interest of retraining programs in these patients. Neuromuscular electrical stimulation strength training and moderate aerobic programs appear to be safe and associated with positive effects on muscle function, strength and capacity for daily activities [33,34].

4.4. Methodological limitations

We have to read our results with caution since the sample size is very small due to the rarity of the disease. Nevertheless, we decided to include subjects who were less affected (i.e. patients who were still able to walk), comparing to the globality of patients affected by FSHD in our clinic, in order to have a more homogeneous population. Furthermore, the NIRS signal was collected from the vastus lateralis, which can be more or less affected in FSHD. Since all participants had an MRC score of at least 4/5 in the evaluated muscle, we effectively limited this variability. Moreover, female patients were excluded in our experiment which limits the generalisation of the results. Complementary experiments including female patients will help to obtain a complete overview of physical limitations in FSHD patients.

The semi-quantitative NIRS parameters (changes in HHb, HbO₂ and tHb) would have been more sensitive if expressed as

a percentage of peak deoxygenation during an arterial ischaemia challenge [35]. Although this technique enhances inter-individual comparisons, it is painful and would probably have been poorly tolerated by our patients. Moreover, each subject performed only one single evaluation session for each modality, and so we could not evaluate a possible intra-individual variability across sessions. The inclusion of a Doppler arterial blood flow measurement in our protocol [36] would have been useful for confirming our hypotheses, i.e. whereby O₂ uptake is impaired in FSHD patients despite a sufficient O₂ supply. Finally, although we strictly applied the same exercise and NIRS measurement protocol in the present study and the one we conducted on BMD patients, the absence of a third group composed of BMD patients didn't allow direct comparisons and made our conclusions on the difference between BMD and FSHD muscle oxygenation partially speculative.

5. Conclusion

The present study confirmed the value of NIRS for evaluating FSHD patients. It may constitute a selection criterion for clinical trials of (i) symptomatic or targeted drugs or (ii) exercise-based therapy. Our results revealed that muscle oxygen levels were lower in FSHD than in controls. The findings in this study suggest that FSHD patients exhibit impairment in their capacity to deliver or to use oxygen at the level of active muscles that may reflect and help point to the underlying pathophysiology of FSHD; but may also, at least in part, be the consequences of the deconditioning syndrome. Future studies should include investigating the ability of aerobic exercise and muscle strengthening retraining programs to mitigate the skeletal muscle capacity to deliver or to use oxygen.

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