

Evaluation of Muscle Oxygenation by Functional Near-Infrared Spectroscopy in Patients with Myasthenia Gravis During Rest and Exercise

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ABSTRACT

Introduction: Myasthenia gravis (MG) is an autoimmune disease that is caused by autoantibodies targeting the neuromuscular junction. A few studies in the literature show that MG may negatively affect muscle metabolism. However, no current study investigates MG pathophysiology's effect on muscle oxygenation. In this study, we aimed to investigate the difference in muscle oxygenation in MG disease and to evaluate its clinical Pathophysiological implications.

Methods: 19 MG patients and 19 age, gender and body mass index (BMI) matched healthy controls participated in the study. Functional near-infrared spectroscopy (fNIRS) recordings were recorded from six channels over the biceps brachii muscles during the rhythmic elbow flexion-extension task.

Results: It was observed that oxygenated-hemoglobin (HbO) ($p = 0.008$) and total hemoglobin (HbT) ($p = 0.017$) values during exercise were significantly lower in MG patients in the motor point of the biceps

brachii muscle. In addition, at rest, deoxygenated-hemoglobin (HbR) levels were significantly lower in patients ($p < 0.05$) in the motor point and the lateral region of the biceps brachii muscles. Additionally, a difference is observed in fNIRS values between the moderate-severe MG group and healthy controls. Also, a negative correlation was observed between exercise-state HbO and rest-state HbR values and disease severity ($p < 0.05$).

Conclusion: MG patients show deterioration in muscle oxygenation values during exercise and rest. Oxygenation values show significant differences in disease severity and negatively correlate with disease severity. Based on these findings, MG disease may affect muscle oxygenation and can be monitored by fNIRS.

Keywords: Functional Near-Infrared Spectroscopy (fNIRS), Muscle Disease, Muscle Metabolism, Myasthenia Gravis, Neuromuscular Disease

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INTRODUCTION

Myasthenia Gravis (MG) is an autoimmune disease caused by autoantibodies targeting the neuromuscular junction and characterized by muscle weakness. Autoantibodies against the acetylcholine receptor (AChR), muscle-specific kinase (MUSK), and lipoprotein-related protein 4 (LRP4) are important for myasthenia gravis pathogenesis (1,2). These autoantibodies lead to impaired neuromuscular signal transmission and consequently muscle weakness and fatigue. It is characterized by weakness of almost all voluntary muscle groups such as eyes, face, chewing, swallowing, neck, and upper and lower extremities (3). Fluctuations in the severity of muscle weakness are typical. Muscle weakness worsens with effort and improves with rest. Increased weakness with continued muscle activity represents a diagnostic clue for myasthenia gravis. It is unknown what triggers the disease, but the role of circulating antibodies in the pathogenesis is well known. However, the metabolic or genetic mechanisms underlying the disease remain to be elucidated. Few studies in the literature show that the pathophysiology of MG disease may negatively affect muscle metabolism (2,4)

Highlights

- MG disease affects muscle oxygenation both during exercise and resting.
- Muscle oxygenation values show differences according to disease severity.
- fNIRS is a useful technique for evaluating skeletal muscle oxygenation in MG.

Ko et al. showed that the muscles of patients with MG use the glycolysis mechanism more than oxidative phosphorylation during exercise due to changes in muscle metabolism (2). This modification suggests that there is a change in the oxygen utilization of muscle tissues in myasthenia gravis patients. It is known that previous studies used functional near-infrared

spectroscopy (fNIRS) as an alternative measurement method of skeletal muscle oxygenation. It is demonstrated to be a monitoring technique in various neuromuscular diseases such as Facioscapulohumeral Muscular Dystrophy (FSHMD), Duchenne Muscular Dystrophy (DMD), and Becker Muscular Dystrophy (BMD), and metabolic myopathies to evaluate muscle oxygen changes (5–11). fNIRS is a rapidly developing non-invasive, cost-effective, and optically based imaging method (10).

It can provide notable information about the physiological and pathophysiological mechanisms involved in the assessment of exercise performance and exercise tolerance in healthy subjects under different environmental conditions (5,10). In addition, fNIRS is used in the monitoring of clinical symptoms, and evaluation of the effects of therapeutic or rehabilitative interventions in clinical populations (9,12–15). As mentioned before, fNIRS measurements have been used to examine patients with many neuromuscular disorders. However, no current study investigates MG pathophysiology's effect on muscle oxygenation by fNIRS. Therefore, our study aimed to investigate the differences in muscle oxygenation response to exercise in patients with myasthenia gravis compared to healthy controls and to evaluate the clinical physiopathological correlates of the disease.

METHODS

Participants

The study included nineteen Myasthenia Gravis patients and nineteen body mass index (BMI), age, and gender-matched healthy controls (Table 1, 2). Participants' ages range from 16 to 73 years. Patients were admitted to the neurology outpatient clinic at Istanbul Medipol University Hospital (Istanbul, Türkiye). The clinical characteristics of the patients such as disease duration, MG levels, and medications are

presented in the supplementary material. (Supplementary Material). The patients' treatment regimens were not modified during the study. Inclusion criteria for patients included having a diagnosis of MG made by a neurologist. MG diagnosis was made based on anamnesis, examination findings, and, serological and electrophysiological tests. Peripheral vascular disease, congestive heart failure, chronic obstructive pulmonary disease, psychiatric disorders, a body mass index (BMI) score of greater than 32, and the presence of an elbow movement-limiting implant were the exclusion criteria for all individuals. This study was approved by the Ethics Committee of Istanbul Medipol University (Ethical Report No: 10840098–604.01.01-E.12654). The patient and the healthy participants were informed about the study protocol and a consent form was signed, and the study was conducted following the principles of the Declaration of Helsinki.

MGFA classification

The Myasthenia Gravis Foundation of America (MGFA) has created the MGFA classification, which divides the disease into subgroups according to the location of impact and severity (16). Within the scope of the current study, this classification was used to determine the clinical levels of the patients. Patients classified as MGFA class 1, 2 and 3 are included in the study.

Exercise protocol

During the experiment, participants completed repeating elbow flexion-extension tasks. The oxygenation of the biceps brachii muscle and spatial variations in the muscle oxygenation of the participants were recorded while they performed the rhythmic forearm flexion-extension exercises. Contraction-induced oxygenation changes were recorded with fNIRS optodes placed in the participants' dominant arm's biceps brachii muscles.

Table 1. Demographics and Clinical Information of MG and Control Groups.

	HC	MG
Woman (n)	16	16
Man (n)	3	3
Age (Years) Median (Min;Max)	32 (20; 68)	35 (16; 73)
BMI (kg/m ²) Median (Min;Max)	24,09 (18,21; 30,82)	25,39 (19,92; 31,65)
MGFA Class 1 (n)		5
MGFA Class 2 (n)		7
MGFA Class 3 (n)		7
Pryostigmine usage (n)		11
Antibody+ against AChR (n)		17
Antibody+ against MUSK (n)		2

BMI: Body Mass Index, HC: Healthy Control Group, MG: Myasthenia Gravis Group, MGFA: Myasthenia Gravis Foundation of America, AChR: acetylcholine receptor

Table 2. Group equivalence for age and BMI.

		N	Median (Min;Max)	MWU	p- values
BMI	MG	19	25,39 (19,92; 31,65)	161,500	0,579
	HC	19	24,09 (18,21; 30,82)		
Age	MG	19	35 (16; 73)	164,500	0,640
	HC	19	32 (20; 68)		
	Total	38			

BMI: Body Mass Index; HC: Healthy Control Group; Max: Maximum Value; Min: Minimum Value; MG: Myasthenia Gravis Group; MWU: Mann-Whitney U.

This study was conducted using the same paradigm that we applied in our previous preliminary research (17). The paradigm consisted of eight loops, each lasting 35 seconds of interval and 20 seconds of rhythmic elbow flexion-extension (Figure 1), that were presented electronically using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA).

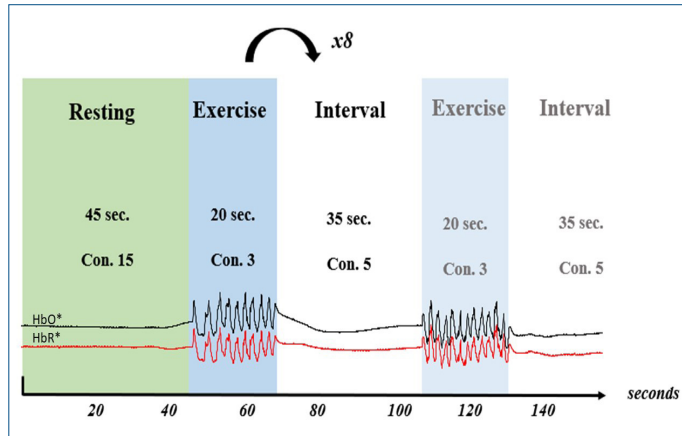


Figure 1. Study Design. Con: Condition, *Raw optical data example of oxy- and deoxyhemoglobin concentration changes for a healthy participant

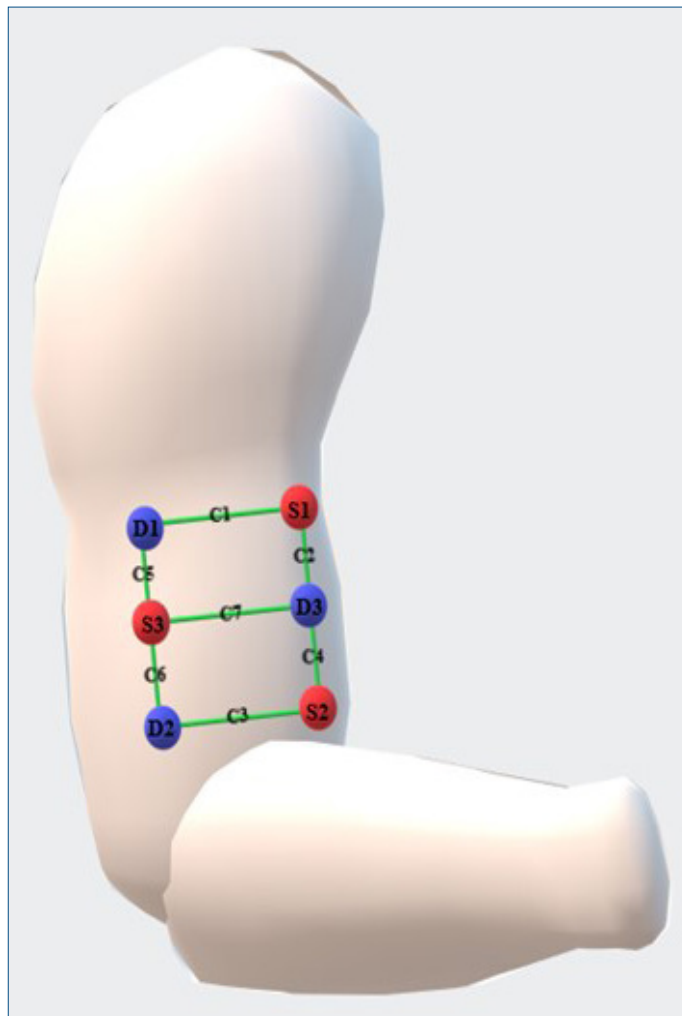


Figure 2. Armband Design and fNIRS Channels. S: Source Optode, D: Detecto Optode, Green Lines: Channel, C7: motor point of muscle, C5-6: lateral side of muscle, C2-4: medial side of muscle, C1: upper side of muscle, C3: lower side of muscle

Three conditions were established within the paradigm, and a marker was created for each of the three situations. In the first condition (Con15), a marker was made for the muscles resting state before beginning the exercise task. In the second condition (Con3), a marker was placed to indicate the beginning of the flexion-extension task, and in the third condition (Con5), a marker was placed to indicate the end of the task.

Muscle oxygenation monitoring by fNIRS

Muscle oxygenation in the biceps brachii was monitored during the paradigm by a multichannel, continuous-wave NIRS device (NIRScout, NIRx Medizintechnik GmbH, Berlin, Germany) by using NIRStar software (NIRStar/NIRStim version 14.5.). According to the working principle of the device, the light emitted at peak wavelengths of 760 nm and 850 nm are mainly absorbed by oxygenated and deoxygenated chromophores (hemoglobin (Hb)/myoglobin (Mb)) in small arterioles, capillaries, and venules within the muscle (15). The changes in optical density are converted into oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) concentration changes by using a modified Lambert-Beer law which a differential path length factor is used to correct photon scattering within the tissue. The sum of the absorbances at the two wavelengths yield the changes in local blood volume (attributed to a change in total hemoglobin (HbT)).

The NIRS cap was positioned on the top of the biceps brachii muscle once the participants had settled into a comfortable position. The recording was performed in a dark room to avoid ambient light interfering with the signal

The cap has 3 sources and 3 detector optodes. Three sources and three detector optodes were used to create seven channels for recording (Figure 2). The inter-optode distance is 3 centimeters. The channels are located along the entire biceps brachii, and Channel 7 is positioned at the level of the motor point of the muscle (18). The sampling rate of the data is 20.83 Hz. in this design.

Other assessments

Additionally, muscle strength measurements and arm circumference measurements were recorded. Participants’ biceps brachii muscle strength was scored over 5 by manual muscle testing, and arm circumference measurement was obtained at rest from the motor point level of the biceps brachii muscle.

Data preprocessing

The data received from the NIRScout device was converted to .snirf data format via the MATLAB program. The fNIRS data were preprocessed via the open-source software program Homer 3 (version 1.58) (19). In the first step, the raw data were converted to optical density. Movement artifacts were manually removed by observation. A band-pass filter was applied to the optical density data (high pass filter: 0.01 and low pass filter: 0.1) to eliminate respiratory and cardiac artifacts with the hmr_BandpassFilt function. Optical density was converted to hemoglobin concentration (ppf 3.8 3.8). Finally, grand averages were calculated for each group after taking the averages of the three conditions for each participant.

Statistical analysis

Cohen’s d value for motion and rest states for each channel was calculated using the formula below in the Excel program for every time series.

$$d = \frac{(\text{Mean [Activation]} - \text{Mean [Baseline]})}{(\text{Standard Deviation [Baseline]})}$$

Given the small sample size, the data were rank-transformed before a non-parametric analysis. Mann Whitney U test was used to determine whether there was any difference in muscle strength and arm circumference measurements between the patient and control groups. Inter-group comparisons were performed with a Kruskal-Wallis Test. The associations between NIRS and other parameters were studied using Spearman's rank correlation coefficient. All statistical analyses were performed with SPSS software (IBM, SPSS version 25). The threshold for statistical significance was set to $p < 0.05$.

RESULTS

Patient information

MG diagnosis was made by the neurologist based on anamnesis, examination findings, serological and electrophysiological tests. No distinction was made based on antibody type in patient selection and during analyses. Anti-ACh antibody was investigated primarily in serological tests. Anti-MUSK antibody was only examined for patients found negative for anti-ACh. 84% of our patients were anti-ACh antibody (+). For EMG findings, more than 10% decrement was considered positive for MG diagnosis.

As a result of clinical evaluation with MGFA classification, 5 of the MG patients participating in the study were in the MGFA-1 class, 7 in the MGFA-2 class, and 7 in the MGFA-3 class. Based on the knowledge that there is no peripheral muscle involvement in the MGFA-1 class, we separated the MGFA-1 group in our analyses and compared it with the MGFA-2-3 group (2). In this way, we aimed to investigate whether there is any difference in peripheral muscle oxygenation between ocular and generalized forms of MG.

Age and BMI were compared between groups to determine group equivalence, and there was no significant difference (Table 1, Table 2).

Muscle strength and arm circumference evaluations

Biceps brachii muscle strength was shown to be significantly lower in patients with MG (Table 3). The Spearman correlation test was used to find out if there was a link between muscle strength and arm circumference in the MG group, there is no significant relationship found.

fNIRS measurements

Table 4 and figure 3 illustrates the changes in HbO, HbR, and HbT during exercise and rest. Resting (Con15) HbR levels in channels 1, 5, 6, and 7 were significantly lower in MG patients. Furthermore, HbO and HbT changes in Channel 7 were found to be significantly lower in MG patients (Table 4) which corresponds to the motor point where increased activation is expected during exercise. There was no significant difference between the MG and control groups in any of the other channels' hemodynamic responses.

To evaluate how the disease severity affects the hemodynamic activity, participants were divided into three groups: healthy, mild MG (ocular type), and moderate-severe MG (generalized type). HbR change at rest differed significantly between healthy and moderate-severe MG in channels 1, 5, 6, and 7 (Figure 4, Table 5). HbO change in channel 7 differ significantly between healthy and moderate-severe MG patients during exercise (Figure 5, Table 6).

Correlations between muscle oxygenation and MG severity

A negative correlation was found between disease severity and HbR change of four significant channels mentioned above during rest (Ch1 $p=0.009$, $r=-0.419$; Ch5 $p=0.004$, $r=-0.456$; Ch6 $p=0.001$, $r=-0.509$; Ch7 $p=0.006$, $r=-0.438$). Additionally, a negative correlation was found between HbO change and disease severity during exercise at the motor point (Ch7 $p=0.009$, $r=-0.418$).

Table 3. Muscle strength and arm circumference result.

		N	MWU	p-value
Biceps Brachii Muscle Strength	MG	19	66.5	0,000**
	HC	19		
	Total	38		
Arm Circumference	MG	19	142	0,374
	HC	18		
	Total	37		

HC: Healthy Control; MG: Myasthenia Gravis. *significant at $p < 0.05$, **significant at $p < 0.01$.

Table 4. Δ HbO, Δ HbR, Δ HbT Statistical Results between MG and Healthy Control Group in Exercise and Resting Conditions.

			N	HbO		HbR		HbT	
				MWU	P	MWU	P	MWU	P
Con15	Channel 1	MG	19	175	0,872	88	0,007**	172	0,804
		HC	19						
	Channel 5	MG	19	152	0,405	91	0,009**	146	0,314
		HC	19						
	Channel 6	MG	19	153	0,422	76	0,002**	137	0,204
		HC	19						
	Channel 7	MG	19	86	0,53	159	0,006**	132	0,157
		HC	19						
Con3	Channel 7	MG	19	89	0,008**	126	0,112	99	0,017*
		HC	19						

HbO: Oxyhemoglobin, HbR: Deoxyhemoglobin, HbT: Totalhemoglobin, Con15: Resting, Con3: Exercise. *significant at $p < 0.05$, **significant at $p < 0.01$

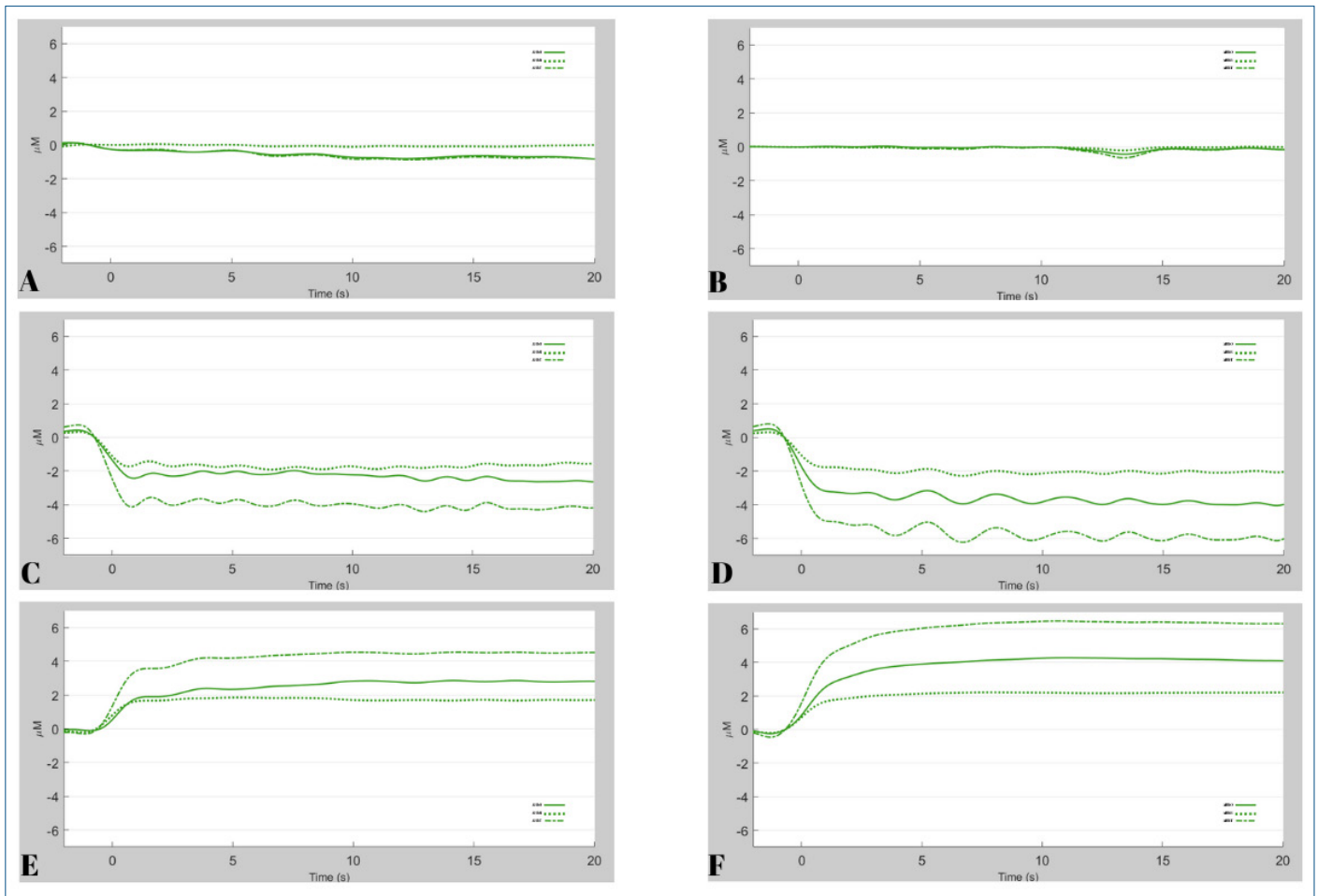


Figure 3. ΔHbO , ΔHbR , ΔHbT values during rest, exercise and recovery periods from one MG and one HC participant's fNIRS recordings. (A) HC, rest; (B) MG, rest; (C) HC, exercise; (D) MG, exercise; (E) HC, recovery; (F) MG, recovery. HC: Healthy Control; MG: Myasthenia Gravis Group; HbO: Oxyhemoglobin, HbR: Deoxyhemoglobin, HbT: Totalhemoglobin

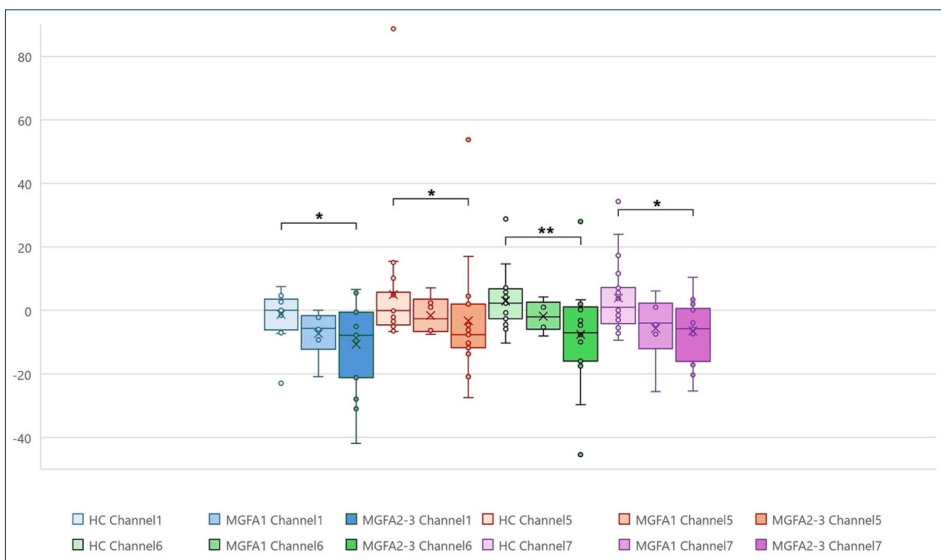


Figure 4. ΔHbR values at rest according to disease severity in Channels 1, 5, 6, and 7. HC: Healthy Control; MGFA1: Mild MG; MGFA2-3: Moderate-Severe MG; x: Mean values; Hollow Dots: Individual data points; Filled Dots: Outliers; *: Significant at $p < 0.05$; **: Significant at $p < 0.01$.

DISCUSSION

A few studies have shown that the pathophysiology of MG disease may have a negative impact on muscle metabolism (2). However, to our best knowledge, no study investigating the effects of MG on muscle oxygenation by fNIRS exists in the literature. Thus, the primary goal of our study is to compare muscle oxygenation parameters during isotonic

exercise in MG patients and healthy controls, as well as to observe the effects of MG disease severity.

Firstly, our findings showed that arm circumference measurements were similar in MG patients and healthy controls, and as expected, biceps brachii muscle strengths were significantly lower in MG patients. Many studies on

Table 5. Comparisons of ΔHbR values during rest condition between groups.

Independent-Samples Kruskal-Wallis Test; Pairwise Comparisons of Groups - ΔHbR , Rest (Con15)					
	Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Adj. Sig. ^a
Channel 1	Mild-Modarete&Severe	-.586	5.790	-.101	1.000
	Modarete&Severe-Healthy	9.583	3.914	2.448	.043*
	Mild-Healthy	10.168	5.586	1.820	.206
Channel 5	Modarete&Severe -Mild	5.443	5.790	.940	1.000
	Modarete&Severe-Healthy	10.853	3.914	2.773	.017*
	Mild-Healthy	5.411	5.586	.969	.998
Channel 6	Modarete&Severe -Mild	3.529	5.790	.609	1.000
	Modarete&Severe-Healthy	11.929	3.914	3.047	.007**
	Mild-Healthy	8.400	5.586	1.504	.398
Channel 7	Modarete&Severe -Mild	.643	5.790	.111	1.000
	Modarete&Severe-Healthy	10.117	3.914	2.585	.029*
	Mild-Healthy	9.474	5.586	1.696	.270

a. Significance values have been adjusted by the Bonferroni correction for multiple tests

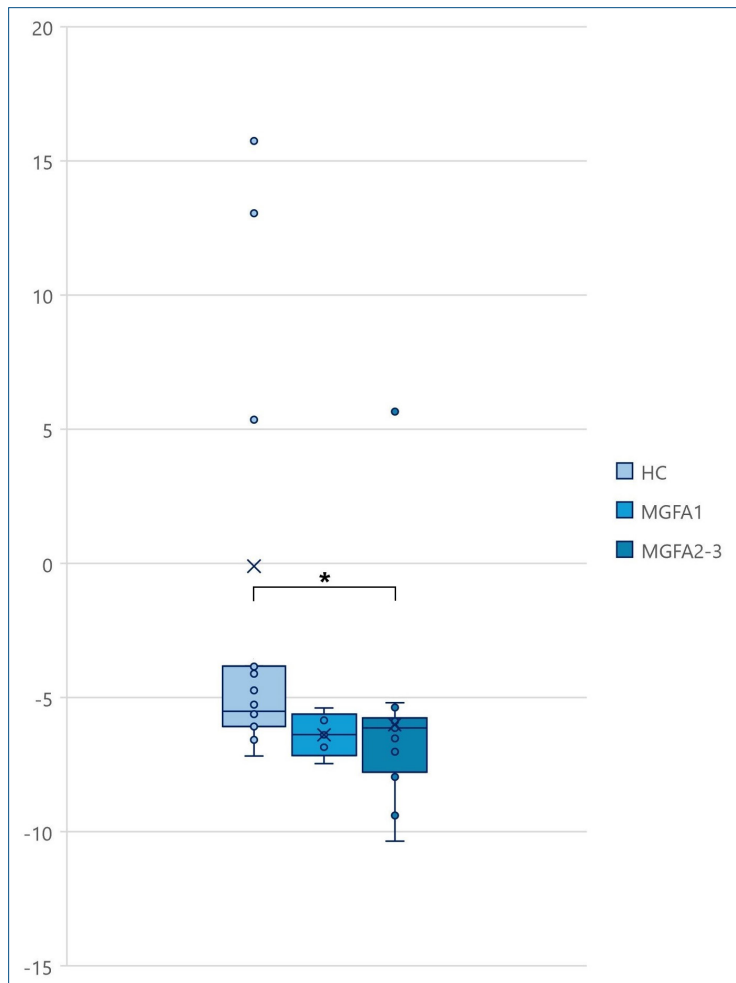


Figure 5. ΔHbO values during exercise according to disease severity in Channel 7 (Motor point of M. Biceps brachii). HC: Healthy Control; MGFA1: Mild MG; MGFA2-3: Moderate-Severe MG; x: Mean values; Hollow Dots: Individual data points; Filled Dots: Outliers; *: Significant at $p < 0.05$. One outlier data is not shown in the figure, not shown data value is 47,232.

Table 6. Comparisons of ΔHbO values during exercise condition between groups.

Independent-Samples Kruskal-Wallis Test; Pairwise Comparisons of Groups - ΔHbO , Exercise (Con3)					
	Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Adj. Sig. ^a
Channel 7	Mild-Modarete&Severe	-.114	5.790	-.020	1.000
	Mild-Healthy	9.716	5.586	1.739	.246
	Modarete&Severe-Healthy	9.602	3.914	2.453	.043*

a. Significance values have been adjusted by the Bonferroni correction for multiple tests.

MG patients have found that muscle weakness is one of the most common symptoms of the disease, which is consistent with our findings (1).

The changes in HbR levels are frequently used to estimate muscle oxygen uptake (9). In our study, HbR changes of MG patients were significantly lower than the healthy control group at rest. This low HbR level was shown in the biceps brachii motor point and three other channels (7 and 1, 5, 6). When the studies on muscle diseases using the fNIRS method were examined in the literature, it was found that the hemodynamic response between patients and healthy controls was compared in several studies at rest. One of these studies, Weng et al., showed that HbR levels were lower at rest in DMD patients than in healthy individuals (11). They also showed that HbR levels decreased as disease severity progressed. It has been discussed that this result shown in the study may occur due to impaired microvascular perfusion. Although Weng et al. used a venous occlusion method, we observed similar findings without applying vascular restriction. We also found that HbR levels are negatively correlated with disease severity. This finding could indicate decreased oxygen consumption and impaired muscle metabolism in MG patients.

Studies revealed that the deoxygenation-reoxygenation patterns of healthy and patient groups differ (14,20,21). Our findings show that HbO and HbT levels are significantly lower in MG patients than in healthy controls during exercise. We also demonstrated that HbO levels are negatively associated with disease severity. Previously, Ko et al. proposed that MG patients use glycolysis rather than oxidative phosphorylation as an oxygen source during exercise due to deterioration in their mitochondrial metabolism (2). Our findings may support Ko et al.'s hypothesis that MG patients use less oxygen and obtain more energy from glycolysis during exercise. In addition, the decrease in oxidative capacity that occurs in various diseases has been shown in studies that cause fatigue symptoms in the muscle (22–24). In experiments conducted with healthy participants, it has been reported that muscle fatigue is associated with a decrease in the amount of HbO in the muscle (25). We suggest that the lower amount of HbO in patients compared to controls during exercise may be related to the mechanism underlying MG disease-related fatigue.

Another study with FSHMD patients discovered that HbO levels were lower in the patient group (9). Considering there have been no studies on patients with MG, this study presents results that do not contradict the oxygenation changes highlighted in other muscle diseases. Weng et al also investigated oxygenation during exercise in DMD patients with fNIRS, and similar to the data of the current study, it was observed that HbT concentration during exercise was significantly lower in patients compared to healthy individuals (11). They showed that the HbT was lower in the DMD group during exercise suggesting less muscular blood supply occurs in DMD patients. The decrease in HbT and HbO during exercise observed in the current study may be due to the reduced oxygen levels that the muscle receives.

Muscle oxygenation tends to differ from the healthy control group in myasthenia gravis patients with ocular type. Although no significant difference was found between the ocular type and healthy controls, a gradually decreasing trend of oxygenation parameters was observed from the healthy to the severe type. Based on these results, patients with ocular involvement may also have biceps brachii involvement that is not clinically evident. A similar situation was reported in the study by Olivier et al (9). In FSHMD patients, oxygenation differences were observed in the physically unaffected quadriceps muscle. In light of this information, deterioration of muscle oxygenation may be an indicator of muscle diseases before they appear clinically.

Based on these findings, we demonstrated that the muscle oxygenation parameters of MG patients differ from the healthy group. Our findings

suggest that fNIRS may provide a promising non-invasive tool for monitoring muscle oxygenation in MG.

Limitations

The current study has a few limitations. Our first limitation is the study's small sample size. The second limitation is that only one type of exercise (isotonic) was used in the study, which prevented the effects of other types of exercise such as isometric and isokinetic from being investigated. Future studies can be designed to include these limitations.

As a result, the current study's findings show that oxyhemoglobin and total hemoglobin measurements during movement, as well as deoxyhemoglobin at rest, are lower in MG patients' biceps brachii muscles than in healthy controls. These muscle oxygenation parameters are negatively correlated with disease severity. Based on these findings, MG disease may affect muscle oxygenation and can be monitored by fNIRS. This method might be adapted to clinical diagnostic and follow-up processes.

Ethics Committee Approval: This study was approved by the Ethics Committee of Istanbul Medipol University (Ethical Report No: 10840098-604.01.01-E.12654).

Informed Consent: The patient and the healthy participants were informed about the study protocol and a consent form was signed, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

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