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Low-field thoracic magnetic stimulation increases peripheral oxygen saturation levels in coronavirus disease (COVID-19) patients

A single-blind, sham-controlled, crossover study

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Abstract

Severe acute respiratory syndrome coronavirus-2 may cause low oxygen saturation (SpO_2) and respiratory failure in patients with coronavirus disease (COVID-19). Hence, increased SpO_2 levels in COVID-19 patients could be crucial for their quality of life and recovery. This study aimed to demonstrate that a 30-minute single session of dorsal low-field thoracic magnetic stimulation (LF-ThMS) can be employed to increase SpO_2 levels in COVID-19 patients significantly. Furthermore, we hypothesized that the variables associated with LF-ThMS, such as frequency, magnetic flux density, and temperature in the dorsal thorax, might be correlated to SpO_2 levels in these patients.

Here we employed an LF-ThMS device to noninvasively deliver a pulsed magnetic field from 100 to 118 Hz and 10.5 to 13.1 milliTesla (i.e., 105 to 131 Gauss) to the dorsal thorax. These values are within the intensity range of several pulsed electromagnetic field devices employed in physical therapy worldwide. We designed a single-blind, sham-controlled, crossover study on 5 COVID-19 patients who underwent 2 sessions of the study (real and sham LF-ThMS) and 12 patients who underwent only the real LF-ThMS.

We found a statistically significant positive correlation between magnetic flux density, frequency, or temperature, associated with the real LF-ThMS and SpO_2 levels in all COVID-19 patients. However, the 5 patients in the sham-controlled study did not exhibit a significant change in their SpO_2 levels during sham stimulation. The employed frequencies and magnetic flux densities were safe for the patients. We did not observe adverse events after the LF-ThMS intervention.

This study is a proof-of-concept that a single session of LF-ThMS applied for 30 minutes to the dorsal thorax of 17 COVID-19 patients significantly increased their SpO_2 levels. However, future research will be needed to understand the physiological mechanisms behind this finding.

The study was registered at ClinicalTrials.gov (Identifier: NCT04895267, registered on May 20, 2021) retrospectively registered. https://clinicaltrials.gov/ct2/show/NCT04895267.

Abbreviations: COVID-19 = coronavirus disease of 2019, LF-ThMS = low-field thoracic magnetic stimulation, mT = milliTesla, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2, SpO_2 = oxygen saturation.

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We declare that all relevant ethical guidelines have been followed, and ethics committee approval has been obtained. All necessary patient/participant consent has been obtained. STROBE-Checklist was included. The study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee of the Institutional Review Board (IRB) of the Faculty of Medicine from Benemérita Universidad Autónoma de Puebla, Mexico (protocol: Oficio No. SIEP/C.I./065A/2020; book number: 2; sheet number: 133; registration number: 818; date: July 3, 2020). The study was registered at ClinicalTrials.gov (Identifier: NCT04895267, registered on May 20, 2021) retrospectively registered. All subjects voluntarily participated with full understanding and signed informed consent.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Although recent studies on the structure and function of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may help develop new targeted treatments against the coronavirus disease of 2019 (COVID-19), there is still no universally approved treatment for this illness.[1,2] For instance, some pharmacological treatments include the controversial use of azithromycin, ivermectin, oseltamivir, remedesivir, favipiravir, tocilizumab, ribavirin, lopinavir, interferon β-1b, lopinavir/ritonavir, hydroxychloroquine, or chloroquine phosphate (for review, see[1,3,4]). However, many of them are based mainly on case studies or prospective or retrospective observational studies, with a low number of randomized controlled trials and low quality of study design to guarantee their efficacy and safety.[5] Moreover, in severe cases, many countries employ empiric antimicrobial therapy, mechanical ventilation, convalescent plasma therapy, or combinations of antiviral and anti-inflammatory drugs.[6,7] In addition, because fever and acute respiratory failure are common symptoms, the management of these patients includes antipyretics and oxygen therapy to increase oxygen saturation (SpO_2) levels during respiratory distress. Hence, developing new methods to increase SpO_2 levels in COVID-19 patients could become a potential complement to oxygen masks, ventilators, or other modalities to improve oxygenation.

This study aimed to present a proof-of-concept that a 30-minute single session of dorsal low-field thoracic magnetic stimulation (LF-ThMS) can be employed to increase SpO_2 levels in COVID-19 patients significantly. In addition, we hypothesized that the variables associated with LF-ThMS, such as frequency, magnetic flux density, and temperature in the dorsal thorax, might be correlated with SpO_2 levels in these patients. Our proof-of-concept research could help design future randomized controlled trials intended to develop plausible LF-ThMS treatments for the successful management of these patients.

We acknowledge that several magnetic field interventions are controversial, but others are gaining an excellent reputation as transcranial magnetic stimulation. This controversy could be due to the low quality of study designs alongside the exaggerated promotion of alternative therapies intended only for lucrative practices. Therefore, to avoid misinterpretations with our research, we included a single-blind, sham-controlled, crossover study on 5 COVID-19 patients who underwent 2 sessions of the study (real and sham LF-ThMS) and 12 patients who underwent only the real LF-ThMS. Moreover, we applied LF-ThMS in a short time range, in a 30-minute single intervention to measure SpO_2 values, after an adaptation condition of at least 35 minutes of resting in a prone position. In this form, we avoided confounding factors related to the change from supine to prone position or spontaneous recovery by natural immunity, common in many COVID-19 patients several days after the infection.

Regarding safety, our LF-ThMS device applied to the dorsal thorax produces low-intensity magnetic flux densities in a safe range from 10.5 to 13.1 milliTesla (mT) and 100 to 118 Hz. Such magnetic fields are within the intensity range of pulsed magnetic stimulators employed in physical therapy worldwide. Moreover, they are within the frequency range of extremely low-frequency (0-300 Hz) magnetic fields to study the interaction between extremely low-frequency magnetic fields and neuronal systems.[8–10]

Our LF-ThMS device also produces heat with a safe temperature range from 27.5 to 44 °C, consistent with the well-known tolerance of the isolated and perfused dog lung to hyperthermia in this temperature range.[11,12] Rickaby et al[11] found that temperatures below 44.4 °C for 2 hours had no detectable influence on the following measured variables of lung weight, extravascular water, vascular volume, serotonin uptake, urea permeability, surface area product, perfusion pressure, and lung compliance. In line with such findings, Cowen et al[12] confirmed that the isolated dog lung with perfusion was tolerant to hyperthermia up to approximately 44 °C for 1 hour. Other studies claimed that hyperthermia in this range is beneficial and enhances the immune response.[13–15]

Our results demonstrate that LF-ThMS locally applied to the dorsal thorax of COVID-19 patients is safe, allowing increased SpO_2 levels during a single LF-ThMS intervention of 30 minutes. This is in line with models predicting the electrical[16] or thermal inactivation of SARS-CoV-2[17] in the environment, or with the hypothesis that hydro-thermotherapy or photobiomodulation could help in the treatment of COVID-19 patients.[18,19]

2. Materials and methods

2.1. Study design

We designed a single-blind, sham-controlled, crossover study on 5 COVID-19 subjects who underwent 2 sessions of the study (sham or real LF-ThMS) and 12 subjects who underwent only the real LF-ThMS stimulation. The study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee of the Institutional Review Board (IRB) of the Faculty of Medicine from Benemérita Universidad Autónoma de Puebla, Mexico (protocol: Oficio No. SIEP/C.I./065A/2020; book number: 2; sheet number: 133; registration number: 818; date: July 3, 2020). The study was registered at ClinicalTrials.gov (Identifier: NCT04895267, registered on May 20, 2021) retrospectively registered. All subjects voluntarily participated with full understanding and signed informed consent.

2.2. Setting

The study was performed on patients voluntarily self-isolated at home, with continuous clinical treatment and medical staff visits. In addition, we completed a follow-up on the health conditions of all patients up to 6 months after the LF-ThMS intervention. Data analysis was performed at the "Universidad Veracruzana" and the "Benemérita Universidad Autónoma de Puebla."

2.3. Patients

We applied LF-ThMS on the dorsal thorax to 17 patients (25-81 years of age, Table 1) who were selected according to the following criteria. The inclusion criteria were: adult patients diagnosed with mild to moderate COVID-19 disease without

Table 1

Control SpO_2 (%) levels at time 0 (before the LF-ThMS intervention), comorbidity, and symptomatology for all patients participating in the study.

Patients	Sex	Age (yrs)	Weight (kg)	Height (m)	Comorbidity	First day COVID-19 symptomatology	Control SpO_2
Patient 1	Male	53	110	1.73	Diabetes, hypertension	Sore throat, fever, chills and fatigue	88
Patient 2	Male	56	54	1.55	Diabetes, glaucoma	Fever, chills, fatigue, dizziness, headache and fatigue	86
Patient 3	Male	46	95	1.7	Asthma	Fever, chills, sore throat, backache and fatigue	89
Patient 4	Female	45	62	1.6	–	Fever, chills, sore throat, backache and fatigue	90
Patient 5	Female	71	55	1.58	Hypertension, glaucoma	Fever, backache, chills, sore throat, sickness, abdominal pain and fatigue	87
Patient 6	Male	42	92	1.71	Hypertension, diabetes	Fever, backache, sickness, chills and sore throat	90
Patient 7	Female	41	76	1.59	–	Fever, backache, chills, sore throat, sickness, fatigue, and abdominal pain	87
Patient 8	Male	46	90	1.7	Anxiety, panic disorders	Chills, fever, backache, sore throat, abdominal pain, and fatigue	88
Patient 9	Female	44	86	1.59	–	Sore throat, backache and headache, and fatigue	87
Patient 10	Female	44	74	1.7	–	Fever, chills, headache, sore throat, abdominal pain, vomit, and fatigue	86
Patient 11	Female	81	51	1.5	Hypertension, diabetes	Backache, sore throat, headache, fever, abdominal pain, and fatigue	84
Patient 12	Male	25	70	1.65	–	Backache, sore throat, headache, abdominal pain, and fatigue	83
Patient 13	Male	56	75	1.7	Diabetes	Backache, chills, sickness and fatigue	84
Patient 14	Male	48	75	1.65	–	Backache, chills, sickness and fatigue	85
Patient 15	Male	48	75	1.72	Hypertension, diabetes	Backache, sore throat, headache, fever, abdominal pain, and fatigue	88
Patient 16	Female	52	65	1.62	–	Backache, sore throat, headache, fever, abdominal pain, and fatigue	83
Patient 17	Male	48	65	1.68	–	Backache, fatigue	88

COVID-19 = coronavirus disease of 2019, LF-ThMS = low-field thoracic magnetic stimulation, SpO_2 = oxygen saturation.

pneumonia. The COVID-19 disease severity was interpreted by the clinical assessment of physicians from the Mexican Institute of Social Security or physicians from private hospitals, who followed the interim guidance for the clinical management of COVID-19 from the World Health Organization, May 27, 2020. Patients with a SpO_2 level of less than or equal to 90% and difficulty breathing, but were not intubated. The physicians selected this set of patients because they had a low risk of developing a severe clinical condition with pneumonia or with a chance of being intubated. Patients had similar pharmacological treatments for COVID-19. All patients were medicated with azithromycin (500 mg), ivermectin (6 mg), and oseltamivir (75 mg) by physicians in respiratory medicine. The most prevalent comorbidities in these patients were diabetes and hypertension.

The exclusion criteria were as follows: COVID-19 patients with acute respiratory failure requiring urgent intubation; COVID-19 patients with impaired consciousness or during pregnancy; patients with metallic implants in the thorax, abdomen or arms, or electronic medical devices such as pacemakers, and children.

The criteria for discontinuing the LF-ThMS intervention were the request of the participant, SpO_2 decrease, or any discomfort reported by the patient during the intervention. The strategy for achieving adequate participant enrollment to reach the target sample size was to describe favorable results obtained from other patients.

2.4. Procedures to avoid confounding factors and efforts to prevent potential sources of bias

To avoid confounding factors or sources of bias, we performed a crossover study in a short time of 30 minutes, in which the SpO_2 levels could not be spontaneously improved. The rationale for this decision is that COVID-19 is a disease that is not spontaneously resolved in a short time window of 30 minutes. Hence this study can also be classified as a nontherapeutic trial. This research was aimed to obtain physiological knowledge that may contribute toward the design of new treatments or therapies.

There is evidence that a change from supine to prone position improves oxygenation, which occurs significantly within the first 10 minutes after the positional change.[20] Therefore, to avoid confounding factors due to differences in SpO_2 levels between supine and prone positions, we obtained all SpO_2 measurements (during sham and real LF-ThMS) in the prone position at least 35 minutes after the patients rested in the prone position. Hence, only SpO_2 numerical values in the prone position after such resting intervals were used for comparison.

Moreover, the single-blind, sham-controlled, crossover study followed here has the advantage that the influence of confounding factors is reduced because each COVID-19 patient serves as their own control. In the same context, the number of patients required to test for statistical significance was reduced compared to the noncrossover designs.

2.5. LF-ThMS device

Dominguez-Nicolas developed the first custom-designed LF-ThMS device (Mexican patent pending by Dominguez-Nicolas SM, 2020) to modulate alternating current in a coil pair to generate low magnetic flux densities and magnetic hyperthermia for COVID-19 patients. Previous patents and experimental studies also induce magnetic hyperthermia,[21–24] but they reach up to 71 °C (160 °F), not suitable for our application. Instead, we employed an electronic circuit in our LF-ThMS device to limit the temperature and magnetic flux density levels up to 44 °C and 13.1 mT for safe use in the dorsal thorax of COVID-19 patients. In this form, we avoided harm or adverse effects.

The LF-ThMS device consisted of a virtual instrument, a PCI-DAS6031 acquisition board (Measurement Computing), an electronic board for the coupling between the digital signal and power, a power source of 0-15 Vcc, and 6-30 A, and 2 rings made of coils to generate LF-ThMS. In addition, we used 1.7 cm of a cotton cloth disk between the LF-ThMS rings and the patient's skin to allow homogeneous heat diffusion.

We used alternating current from 100 to 118 Hz to generate the magnetic field with a peak amplitude of 8 A, polarized at

Table 2

Variables associated with LF-ThMS (frequency, magnetic flux density, temperature) and the mean SpO_2 levels in 17 COVID-19 patients.

Time (min)	Frequency (Hz)	Magnetic flux density (mT)	Temperature °C	SpO_2 (%) mean ± SD	Number of patients
0	0	0	27.5 ± 0.2	86.6 ± 2.2	17
5	100	10.5 ± 0.01	29.3 ± 0.07	86.7 ± 2.0	17
10	103	10.7 ± 0.04	35.2 ± 0.08	88.0 ± 2.1	17
15	105	11.1 ± 0.12	41.4 ± 0.3	88.8 ± 2.2	17
20	110	11.6 ± 0.02	43.3 ± 0.2	90.1 ± 2.4	17
25	115	12.2 ± 0.2	44 ± 0.05	91.4 ± 2.5	17
30	118	13.1 ± 0.15	43.9 ± 0.01	92.2 ± 3.2	17

COVID-19 = coronavirus disease of 2019, LF-ThMS = low-field thoracic magnetic stimulation, SpO_2 = oxygen saturation.

12 Vcc with a regulated power source of 0 to 15 Vcc and 6 to 30 A. We fabricated a couple of rings for LF-ThMS with an internal diameter of 9.5 cm and 130 turns. The LF-ThMS device emitted magnetic flux densities in the range of 10.5 to 13.1 mT. These were calculated theoretically with Biot-Savart law and physically with a magnetic field sensor (475 DSP Gaussmeter, Lakeshore). We also used a thermocouple sensor (model NTC 10k) to monitor the temperature changes due to the LF-ThMS. Both the Gaussmeter and thermocouple sensors helped calibrate the magnetic flux densities and temperatures in a safe range (Table 2).

The main electronic components of the LF-ThMS device consisted of a power relay RL of 2 poles, a 12 Vcc coil, silver alloy contacts of Vcc/10 A or 250 Vca/10 A, Q NPN 2N2222 transistor, 10 kOhms resistance at 0.25 Watts, and a IN4007 semiconductor diode. We also employed a PCI-DAS6031 board to energize the RL at 10 Vcc and a virtual instrument developed in Delphi Borland 7. Figure 1 shows the electronic circuit of our LF-ThMS device, and Table 2 shows the frequency, magnetic flux density, and temperature associated with the LF-ThMS during a single 30-minute session.

2.6. LF-ThMS protocol

The LF-ThMS was applied locally to the dorsal thorax while the patients were kept in a prone position. In the same way, the single-blind sham-controlled stimulus was also applied locally to the dorsal thorax while the patients were kept in a prone position. To guarantee stability in SpO_2 level measurements in sham and control conditions, the SpO_2 levels were taken at least 35 minutes after the patients changed from the supine to the prone position. The LF-ThMS intensity was successively increased every 5 minutes during a single session of 30 minutes, following the values of frequency, magnetic flux density, and temperature. Table 2 shows quantitative variables used in the analyses. The protocol for the proof of concept consisted of a single LF-ThMS session of 30 minutes. However, daily sessions in 3 or 4 other consecutive days were applied to verify its reproducibility. The

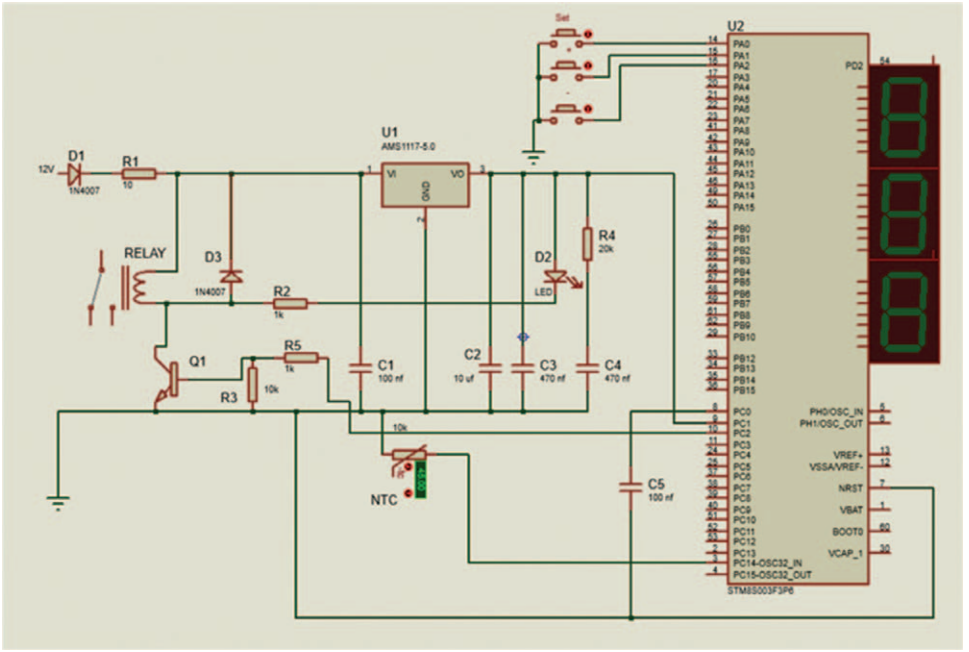

Figure 1. Electronic circuits employed in the LF-ThMS device. These circuits modulate the intensity and frequency of the alternating current producing the magnetic fields, limiting the maximum temperature to 44 °C, and the magnetic flux density up to 13.1 mT at 118 Hz. LF-ThMS = low-field thoracic magnetic stimulation.

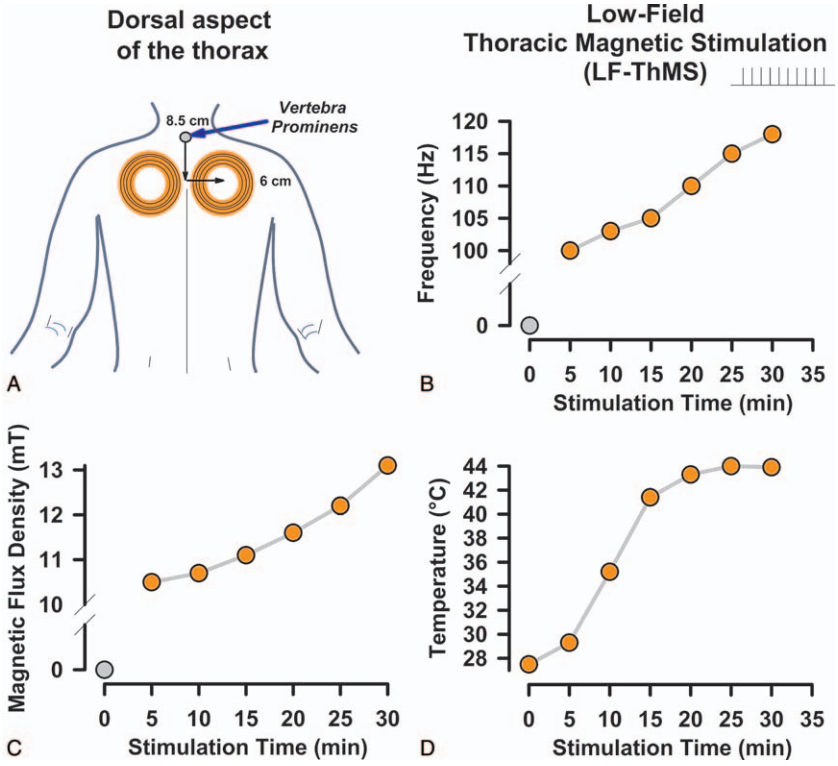

Figure 2. Experimental arrangement. A. Anatomical landmarks for the positioning of LF-ThMS coils on the dorsal thorax of COVID-19 patients. The gray circle indicates the anatomical landmark called the "spinous process of C7" or "*vertebra prominens*". B-D. Gradual increase (every 5 min) from 0 to 30 min of pulsed stimulus frequency, magnetic flux density, and temperature during the application of LF-ThMS to COVID-19 patients. The stimulation consisted of applying LF-ThMS for 30 min on the dorsal aspect of the thorax. COVID-19 = coronavirus disease of 2019, LF-ThMS = low-field thoracic magnetic stimulation.

rationale for presenting only the results from the first session was to avoid bias due to confounding factors and to evaluate the hypothesis that SpO_2 levels in COVID-19 patients are significantly correlated with the magnetic flux density and temperature during 30 minutes of LF-ThMS intervention (see Discussion section).

Figure 2A illustrates anatomical landmarks and coordinates of the LF-ThMS rings. We positioned the center of these LF-ThMS rings using palpable skeletal landmarks. We employed the spinous process of C7 (i.e., *vertebra prominens*) as zero landmarks (see the gray circle in Fig. 2A). The center of these rings was positioned 8.5 cm below this landmark and bilaterally ±6 cm on the dorsal thorax (see black arrows in Fig. 2A).

The device allowed a gradual increase in the frequency, magnetic flux density, and temperature, as illustrated in Figures 2B, 2C and 2D, respectively. The patients rested for 3 hours after the session, and they did not report any discomfort during or after the magnetic stimuli. In contrast, they felt more comfortable, mainly because the LF-ThMS improved their breathing.

We checked the health conditions of all patients after receiving the LF-ThMS. In addition, in 11/17 patients, we monitored their SpO_2 levels at the end of 6 months (see Results section).

2.7. Sham stimulation

For sham exposure, the coils were positioned in the same coordinates, but the pulse generator was not turned on. The subjects were blinded to the real LF-ThMS or sham stimulation conditions.

2.8. Peripheral oxygen saturation (SpO_2) level, magnetic flux density, and temperature monitoring

The peripheral oxygen saturation (SpO_2) level was monitored with a conventional fingertip pulse oximeter (model C101H1) every 5 minutes during the 30-minute LF-ThMS session. Thus, 7 SpO_2 measurements, including the control (time 0, at 27.5 °C and 0 mT, without LF-ThMS and compensating the terrestrial magnetic field), were obtained for each subject. In this way, we were able to quantify the repeatability of the effects of LF-ThMS in different patients.

2.9. Statistical analysis

We analyzed the statistical differences among SpO_2 levels related to each LF-ThMS intensity. For normally distributed data (Kolmogorov-Smirnov normality test, $P > .05$) with homogeneity of variances, we used parametric 1-way repeated-measure ANOVA under the null hypothesis that the dependent variables "SpO_2 levels" were the same across the different LF-ThMS intensities. We also employed the Mauchly test to verify that the assumption of sphericity was not violated. We performed a pairwise post-hoc test using the corrected Bonferroni adjustment. All effects were reported to be significant if $P < .001$.

Moreover, a Pearson product-moment correlation coefficient was employed to examine whether there was a statistically

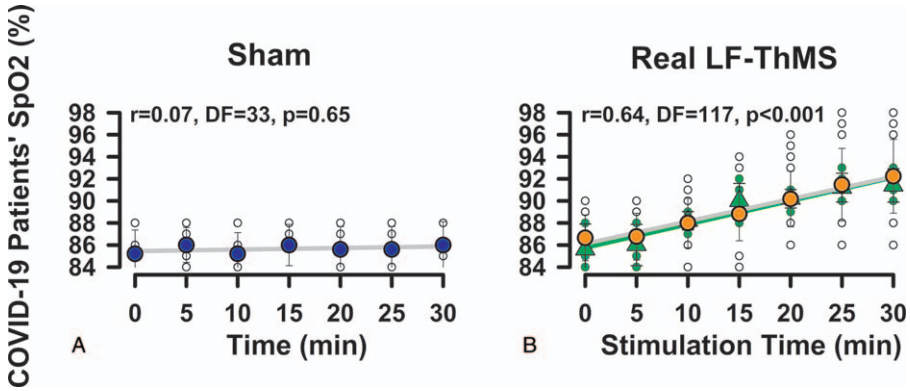

Figure 3. Comparative results obtained from the sham-controlled study and the real LF-ThMS intervention. A. Peripheral oxygen saturation (SpO_2) levels vs time during the sham stimulation for 5 COVID-19 patients. Blue circles represent the grand average of these SpO_2 levels B. SpO_2 levels vs time during LF-ThMS stimulation. The green triangles represent the grand average of SpO_2 values during real LF-ThMS in the same 5 patients that received sham stimulation in A. The orange symbols illustrate the grand average of SpO_2 levels in 12 COVID-19 patients vs time during a single session of LF-ThMS. The green and gray circles (raw data) show the SpO_2 values obtained for all the patients (every 5 min) vs the time in minutes. A statistically significant correlation ($P < .001$, Pearson product-moment correlation) was found for "SpO_2 values" vs "stimulation time" during real LF-ThMS but not during sham stimulation. All SpO_2 measurements in the control and sham conditions were taken at least 35 min after the patients rested in a prone position. Therefore, only SpO_2 measurements in the prone position were used for comparison. COVID-19 = coronavirus disease of 2019, LF-ThMS = low-field thoracic magnetic stimulation, SpO_2 = oxygen saturation.

significant linear correlation between SpO_2 levels and frequency, magnetic flux density, and temperature changes during the LF-ThMS intervention. The sample size was n = 35 SpO_2 measurements during 7 LF-ThMS levels (including the control) in 5 patients in the sham-controlled experiment and n = 119 SpO_2 values in another 12 patients. The correlation coefficient was calculated for n-2 = 33 or n-2 = 117 degrees of freedom (DF), and the correlation was reported as significant if $P < .001$. Data are expressed as mean ± standard deviation in the main text and figures.

3. Results

We measured the SpO_2 level in all patients before the LF-ThMS intervention. To avoid confounding factors due to differences in SpO_2 levels between supine and prone positions, we obtained all SpO_2 measurements (during sham and real LF-ThMS) in a prone position at least 35 minutes after the patients rested in a prone position. We found that COVID-19 patients had similar symptoms (Table 1). On the first day of magnetic stimulation, we found that the patients experienced difficulty breathing with a low SpO_2 level of 86.6% ± 2.2% (N = 17 patients), consistent with COVID-19 signs and breathlessness symptoms. However, we found that during LF-ThMS, the patients exhibited a gradual increase in their SpO_2 levels. No adverse events or discomfort were reported during or after LF-ThMS.

3.1. Comparisons between the SpO_2 levels of COVID-19 patients in the sham and real LF-ThMS

In the controlled study, we observed no statistically significant changes in SpO_2 levels during sham stimulation (5 subjects, Fig. 3A). We performed One-way repeated measures ANOVA to examine statistical significance between SpO_2 levels during sham stimulation in all patients. The differences in the mean values among the sham groups were not significant enough to exclude the possibility that the difference is due to random sampling variability; that is, there was no statistically significant difference ($F = 0.165$, $DF = 6$, $P = .984$).

However, during the real LF-ThMS, we observed statistically significant changes in SpO_2 levels in response to real LF-ThMS in 5 subjects who previously underwent sham stimulation (green triangles and green line; Fig. 3B) and in the other 12 subjects who underwent only the real LF-ThMS (orange circles and gray line; Fig. 3B). We performed one-way repeated measures ANOVA to examine statistical significance between groups: "control SpO_2 levels" and "SpO_2 levels during the LF-ThMS interventions" in all patients (17 subjects). The differences in the mean values among the treatment groups were more significant than would be expected by chance ($F = 13.872$, $DF = 6$, $P < .001$). The post-hoc test indicated that the significant main effect exhibited significant differences ($P < .001$) between the "control SpO_2 levels" and the "SpO_2 levels obtained after 20 min of LF-ThMS interventions" (Table 3). In contrast, no statistically significant differences ($P > .05$) were found before 20 minutes of LF-ThMS intervention (Table 3). This indicates that the LF-ThMS at the frequency and magnetic flux density employed produces changes in SpO_2 levels only after 20 minute of LF-ThMS application.

Table 3

One-way repeated measures ANOVA for SpO_2 values of 17 COVID-19 patients in control conditions (0 min) and during LF-ThMS at 10, 15, 20, 25, and 30 min. The Bonferroni *t* test was used for multiple comparisons vs the control group. All SpO_2 measurements in control (0 min) and sham conditions were taken at least 35 min after the patients rested in a prone position. Only SpO_2 measurements in the prone position were used for comparison.

Comparison	Difference of means	t	*P*	Significance
SpO_2 (0 min) vs SpO_2 (30 min)	5.588	6.655	<.001	Yes
SpO_2 (0 min) vs SpO_2 (25 min)	4.824	5.745	<.001	Yes
SpO_2 (0 min) vs SpO_2 (20 min)	3.529	4.203	<.001	Yes
SpO_2 (0 min) vs SpO_2 (15 min)	2.176	2.592	.065	No
SpO_2 (0 min) vs SpO_2 (10 min)	1.353	1.611	.66	No
SpO_2 (0 min) vs SpO_2 (5 min)	0.118	0.14	1	No

COVID-19 = coronavirus disease of 2019, LF-ThMS = low-field thoracic magnetic stimulation, SpO_2 = oxygen saturation.

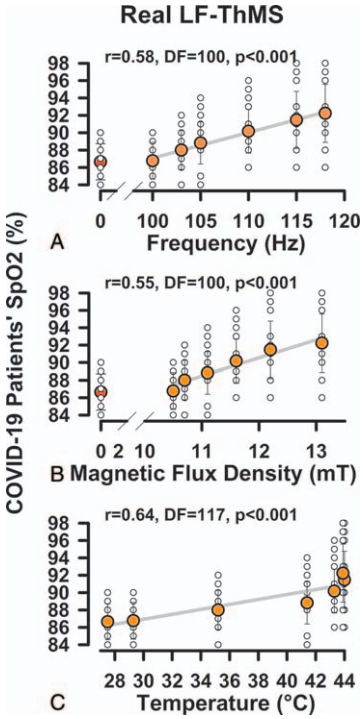

Figure 4. The same as Figure 3B, but it refers to the correlation between SpO2 levels and the variables related to the real LF-ThMS applied to 17 patients. The Pearson correlation coefficients (r), degrees of freedom (DF), and *P* values ($P < .001$) are shown above each graph. LF-ThMS = low-field thoracic magnetic stimulation, SpO_2 = oxygen saturation.

3.2. Correlations among the frequency, magnetic flux density, and temperature elicited by the LF-ThMS vs the SpO_2 levels of COVID-19 patients

In the controlled study, we also examined whether SpO_2 levels were correlated with the sham session time. We observed no statistically significant correlation between SpO_2 levels and session time in the sham condition (Pearson product-moment correlation coefficient r = 0.07, DF = 33, $P = .65$, gray regression line, Fig. 3A). However, we obtained a statistically significant correlation between SpO_2 values and session time in the real LF-ThMS applied to the same 5 subjects that had previously undergone sham stimulation (Pearson product-moment correlation coefficient r = 0.81, DF = 33, $P < .001$, green regression line, Fig. 3B).

Finally, we examined whether the SpO_2 levels were correlated with the LF-ThMS session time, frequency, magnetic flux density, and temperature for all patients. Figures 3B, 4A, 4B, and 4C show significant correlations between these measurements. Pearson product-moment correlation method was used to test for significant correlations. We obtained a $P < .001$ with 117 or 100 degrees of freedom and correlation coefficients r = 0.64, 0.58, 0.55, and 0.64, respectively (see Fig. 3B, and Figures 4A, 4B, and 4C). These statistically significant results suggest that the changes in SpO_2 levels during a 30 minutes LF-ThMS session are related to their associated variables: frequency, magnetic flux density, and temperature. These findings support our hypothesis.

3.3. Adverse events

We did not find adverse effects during or after the LF-ThMS intervention. We also followed up on the health conditions of all patients. Five days after LF-ThMS, we found that the mean SpO_2 level was 98.3% ± 0.7% for 17 patients (Table 4). We also found a mean SpO_2 level of 98.4% ± 0.8% for 11 patients 6 months after the LF-ThMS intervention (Table 4). Such average SpO_2 ranks indicate that LF-ThMS did not produce adverse events in oxygen saturation. In the follow-up on the general health conditions after 5 days or 6 months, the physicians confirmed that the patients did not exhibit any adverse events or secondary effects after the LF-ThMS intervention. These findings indicate that 30 minutes of LF-ThMS intervention on the dorsal thorax of COVID-19 patients is safe at the frequencies, magnetic flux densities, and temperatures of 100 to 128 Hz, 10.5 to 13.1 mT, and 27.5 to 44 °C, respectively.

Table 4

Follow-up on the SpO_2 values for all the patients after LF-ThMS. Six months after LF-ThMS intervention, the patients reported no adverse events, and they exhibited normal SpO_2 levels.

Patients	Before LF-ThMS SpO_2 (%)	30 min after sham stimulus SpO_2 (%)	30 min after LF-ThMS SpO_2 (%)	5 d after LF-ThMS SpO_2 (%)	6 mo after LF-ThMS SpO_2 (%)
Patient 1	88	–	98	98	99
Patient 2	86	–	97	98	97
Patient 3	89	–	96	98	97
Patient 4	90	–	97	99	99
Patient 5	87	–	91	98	99
Patient 6	90	–	93	99	99
Patient 7	87	–	91	97	98
Patient 8	88	–	93	98	98
Patient 9	87	–	91	99	99
Patient 10	86	–	90	98	99
Patient 11	84	–	88	97	99
Patient 12	83	–	86	99	–
Patient 13	84	85	93	99	–
Patient 14	85	86	90	99	–
Patient 15	88	88	93	99	–
Patient 16	83	83	90	98	–
Patient 17	88	88	91	99	–
	86.6 ± 2.2	86 ± 2.1	92.2 ± 3.2	98.3 ± 0.7	98.4 ± 0.8

d = days, LF-ThMS = low-field thoracic magnetic stimulation, mo = months, SpO_2 = oxygen saturation.

4. Discussion

We found statistically significant correlations between SpO_2 levels in COVID-19 patients and LF-ThMS variables in a time range of 30 minutes, but not in the sham-controlled study.

4.1. Reproducibility

Our findings were reproducible in all patients in a time range of 30 minutes of LF-ThMS intervention. Interestingly, our results were reproducible in 4 other subsequent sessions. However, to avoid bias due to confounding factors, we did not present such data because the changes could be associated with an ongoing daily recovery of the patients due to unknown immune mechanisms and not necessarily due to the daily LF-ThMS intervention. Hence, future randomized controlled trials with 2 groups (placebo and experimental) will be necessary to examine the potential use of this LF-ThMS application as therapy during consecutive daily sessions in covid-19 patients. Therefore, the principal value of our results is that in the sham-controlled crossover study, we found a reproducible and significant correlation between LF-ThMS-associated variables and SpO_2 levels in a short time range of 30 minutes.

4.2. Interpretation

At this stage, we cannot provide a physiological interpretation of our results. Specifically, we can acknowledge that the main limitation of our study is that we do not know the mechanisms of SpO_2 increase by the LF-ThMS intervention. However, besides this limitation, we can only speculate with caution by describing possible physical interferences by the magnetic heat energies on the virus-host interactions. Hence the rationale of the following speculations is not intended to interpret our findings but to open future avenues of research.

4.3. Possible interference of LF-ThMS hyperthermia with the virus-host protein interactions

It is well known that several viral protein complexes mediate the entry and replication of SARS-CoV-2 into the cells, manipulating host mRNA translation, subsequent viral protein production, antiviral immunity, and inflammation response to induce lung infection and pneumonia. This pathogen is a single-stranded ribonucleic acid virus with gene fragments expressing structural and nonstructural proteins.[25–27] Therefore, several viral protein complexes are involved in the entry and replication of this virus into cells, such as the virus spike protein and the nonstructural protein 1. The spike protein mediates cell entry via binding with angiotensin-converting enzyme 2 in host cells, and the nonstructural protein 1 is crucial for virus-host interaction.[28,29] Furthermore, there is evidence that an increase in tissue temperature can affect proteins and enhance the immune response[14,15]; hence, it is tempting to speculate that hyperthermia produced by the LF-ThMS may acutely interfere with these viral proteins and improve respiratory function.

4.4. Possible interference of LF-ThMS magnetic flux with the virus-host electrical interactions

Another possibility is that the magnetic stimuli could also directly interfere with the positively charged site in the SARS-CoV-2 spike protein, disturbing the electrical binding between the virus protein and the negatively charged human cell receptors. This is consistent with recent simulation studies, which reported a positively charged site (called polybasic cleavage site) positioned 10 nm from the actual binding site on the SARS-CoV-2 spike protein.[30] These authors found that the positively charged site allows strong bonding between the virus protein and negatively charged cell receptors.

In their simulation, Qiao and Olvera de la Cruz[30] designed a negatively charged molecule to bind to the positively charged cleavage site, with the idea that blocking this site inhibits the virus from binding to the host cell.[30] Therefore, it is tempting to speculate that interfering with the electrostatic interaction during the binding action of the SARS-CoV-2 spike protein and the ACE2 receptors or the nonstructural protein 1 could mitigate the viral infection. This possible mode of action of the LF-ThMS is also consistent with the claim that electrostatic precipitators are also valuable for eliminating airborne virus particles.[31,32]

4.5. Possible interference of LF-ThMS hyperthermia with the immune response and interferon activity

Another mechanism by which the LF-ThMS up to 44 °C could improve SpO_2 levels in COVID-19 patients is the enhanced immune response due to the increased temperature of the dorsal thorax during the intervention. This is consistent with reports that hyperthermia potentiates the immune response against cancer by activating immune cells.[15,33,34] Some of the immune cells activated by hyperthermia are natural killer cells, dendritic cells, and cytotoxic T-lymphocytes, which alter the cell-surface molecules on cancer cells and modify adhesion molecules on immune cells and endothelial cells.[33]

Previous studies claimed that interferons could have a potential role in treating COVID-19 patients.[35] However, recent investigations demonstrated that the SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells.[36] This means that interferons could help or damage depending on the infection stage for each COVID-19 patient. In this context, we suggest that LF-ThMS should be applied at the first stages of the COVID-19 infection. This simple action could enhance interferon activity by increasing the temperature, in which the interferons may confer an antiviral state on the cells.

4.6. Possible interference of LF-ThMS in inflammation and cytokine storm

Finally, because inflammation and cytokine storms are the main factors contributing to breathing, ventilation, and oxygenation in COVID-19 patients, it will be necessary to examine in future studies whether the LF-ThMS has an impact on these factors. A blood test for cytokines after successive LF-ThMS interventions could help investigate correlations among these variables.

4.7. Advantages and limitations

The first potential advantage of dorsal LF-ThMS is that the subjects did not require oxygen therapy with face masks, mainly because during the LF-ThMS session, the patients significantly increased their SpO_2 levels 20 minutes after the LF-ThMS ($P < .001$, Table 3). The second advantage is that the device for LF-ThMS is easy to reproduce, and the electronic components are not expensive. Moreover, it may be possible that several pulsed electromagnetic field devices employed in physical therapy

worldwide could be adapted to emit magnetic fields at 100 to 118 Hz, 10.5 to 13.1 mT (105 to 131 Gauss), and 27.5 to 44 °C.

The main limitations of our study are as follows. First, we do not know the physiological mechanisms through which the administered LF-ThMS during a 30-minute single session improved SpO_2 levels in COVID-19 patients. Second, we did not explore whether the LF-ThMS intervention enhances the patients' immune response or impacts the SARS-CoV-2 electrical charges or the inflammation and cytokine storm in COVID-19 patients. However, our study will motivate future investigations in this field.

Another limitation of our study is that it is necessary to know the real temperature in the lungs associated with variations in the external dorsal thorax temperature by LF-ThMS. Such temperatures should be expected to be lower than those on the external dorsal thorax due to the diffusion processes of heat transfer occurring in the skin, muscle, and scapula. In the same context, it will be necessary to examine the magnetic flux density reaching the lungs, which should be attenuated as a function of depth.

An additional limitation of our study is that the age of our participants followed a normal distribution with a mean age of 49 ± 12 years old, with just 1 patient on the left (25 years old) and 2 participants on the right (71 and 81 years old) of this distribution. In future studies, it would be convenient to increase the number of participants in the age groups around 25 to 40 and 60 to 80 years old to allow comparisons of SpO_2 recovery among these different age groups.

Finally, although there is a consensus that repetitive magnetic stimulation is helpful in the noninvasive modulation of brain neural activity in humans, similar interventions in other regions of the human body are still controversial. However, we found a significant experimental correlation of LF-ThMS variables: magnetic flux density, frequency, and temperature with SpO_2 levels in 17 COVID-19 patients, 5 of them in a single-blind, sham-controlled, crossover study.

4.8. Perspectives

Although the increased SpO_2 levels may be attributed to the altered perfusion resulting from warming or the impact of magnetic factors inactivating the SARS-CoV-2 virus, these are only speculations. Therefore, future studies are necessary to examine the physiological mechanisms underlying these significant correlations.

Because previous studies suggested that magnetic stimulation could be helpful in chronic obstructive pulmonary disease[37] and phrenic nerve activation,[38] future research examining this issue using the LF-ThMS in humans or animal preparations will also be necessary. Other future perspectives include developing wearable and portable devices for LF-ThMS with oximeters and respiratory magnetograms.[39] Such devices could help examine respiratory improvements after dorsal LF-ThMS in COVID-19 patients.

Here our LF-ThMS protocol is not intended to demonstrate its use as therapy but is designed to examine the hypothesis that LF-ThMS could help increase SpO_2 levels in COVID-19 patients in a short-range from 0 to 30 min. In this context, our findings are relevant because they could motivate future randomized clinical trials to examine whether LF-ThMS could be helpful as a potential therapy.

5. Conclusions

We conclude that our findings are relevant at this stage, mainly because they provide evidence that the LF-ThMS variables (frequency, magnetic flux density, and temperature) exhibit a statistically significant correlation with SpO_2 levels in the short time range of 30 minutes, thus showing that the LF-ThMS significantly increased peripheral oxygen saturation levels in COVID-19 patients. We also conclude that 30 minutes of LF-ThMS on the dorsal thorax at 100 to 118 Hz, 10.5 to 13.1 mT (105 to 131 Gauss), and 27.5 to 44 °C is safe in COVID-19 patients.

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Author contributions

SMDN conceived the therapeutic application of magnetic stimuli in COVID-19 patients, developed the first LF-ThMS prototype, and performed the experiments. EM and SMDN conceived the proof-of-concept and hypothesis of this study. SMDN and EM performed the data analysis. EM designed the single-blind, sham-controlled, crossover study on 5 COVID-19 patients, wrote the paper, and contributed to calibrate and improve the safeness of the original LF-ThMS prototype.

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