Experience in the Respiratory Rehabilitation Program for the Treatment of Lung Interstitial Disease in Post-COVID-19 Pneumonia by Associating Low-frequency - High Intensity - Pulsed Electromagnetic Fields (Diamagnetotherapy): A Case Series Study

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Abstract

In severe acute respiratory syndrome (SARS-Cov-2), interstitial fibrosis is one of the possible sequels of the inflammatory damage of the lung induced by the viral disease. The usual treatment of this condition includes anti-fibrotic drugs, oxygen therapy and appropriate rehabilitative programs that intend to improve the lung performance and to ameliorate the quality of life in such patients. With the aforesaid purposes and on the bases of previous experience in treating a rare case of Interstitial Lung Fibrosis secondary to an overlapping autoimmune disease, we report the experience of the combined treatment consisting in pulmonary rehabilitation and the stimulation of the respiratory muscles by the use of Diamagnetotherapy, a technology exploiting the biological effects of the Low Frequency - High Intensity -Pulsed Electromagnetic Fields.

In this analytic observational study, from May to June 2020, ten patients with respiratory failure related to Covid-19 pneumonia already addresses to daily treatments for respiratory rehabilitation, underwent to the additional stimulation of the respiratory muscles 3 times/week for 2 weeks. The outcome of this combined treatment was to improve the dyspnea, a series of functional test battery (Barthel, SPPB, 6MWT, Tinettì, Borg, MRC) and Pulse Oximetry. As demonstrated by pre and post functional scores, all the treated patients reported statistically significative functional improvement.

The compliance with the diamagnetic treatment was well-tolerated without pain or adverse events.

Keywords: Interstitial Lung Disease; Pulsed Electromagnetic Fields; Diamagnetotherapy; COVID-19 Pneumonia; Respiratory Rehabilitation Program

Abbreviations

HI-LF-PEMF: High Intensity - Low-Frequency Pulsed Electromagnetic Fields; ILF: Interstitial Lung Fibrosis; ILD: Interstitial Lung Disease; ARDS: Acute Respiratory Distress Syndrome; SARS-Cov-2: Severe Acute Respiratory Syndrome Coronavirus 2; AIPO: Italian Association of Hospital Pulmonologists; AIR: Italian Respiratory Insufficiency Rehabilitation Association; BARTHEL: Patient Functional Assessment

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Introduction

Lung damage, genetics, inflammation (cytokine triggering) and the prolonged stay under mechanical ventilation would be the origin of pulmonary fibrosis in COVID-19 patients [1]. On the other hand, pre-existing idiopathic pulmonary fibrosis is a deadly risk factor by way of acute fatal fibrosis [2-4]. Muscle, heart and nervous tissue concerns, the prolonged bedridden contribute, together with lung fibrosis, to the decline of the respiratory function in these patients [5]. Muscle weakness, as well as being a direct effect of the disease, is also a recognized consequence of the alveolar damage that alters the \( \text{O}_2 / \text{CO}_2 \) exchanges [6] while myalgia and tenderness, on their part, are additional sources of respiratory weakness and patients who develop muscle pain are more likely prone to abnormal lung imaging findings [7].

The breaking of this negative feedback may be one of the key points of the treatment of the lung fibrosis in COVID-19 patients and this should be focused, besides oxygen therapy or antifibrotic drugs, to specific programs of pulmonary rehabilitation [3,8]. Normally, this one requires the appropriate selection of the patients, suitable programs, adequate timing length of the training period and, not least, the assessment of the exercise capacity [9]. In this context, supplementary non-invasive therapeutic strategies able to support the rehabilitation programs as well to improve the recovery of the drawbacks of the lung fibrosis should be considered.

The biophysical stimulation induced by PEMF has aroused over time interest for safety and effectiveness in muscle-skeletal disorders [10]. Moreover, according to previous experiences in treating pulmonary fibrosis and chronic lymphedema [11,12] and in force anti-inflammatory and regenerative effects shown by of the high peak magnetic fields [13], the HI-LF-PEMF Diamagnetotherapy was employed to support the rehabilitation program in a series of patients with respiratory impairment Covid-19 related, to improve their functional recovery.

Methods

From May to June 2020, 10 patients (8 male, 2 females - the average age of 69,6 yrs.) with respiratory failure related to Covid-19 interstitial pneumonia, were selected and addresses to daily treatments for respiratory rehabilitation. This, according to the Guidelines of the Italian Association of Hospital Pneumologists (AIPO) and Respiratory Insufficiency Rehabilitation Association (ARIR). The rehabilitation program included: active-assisted exercises, mobilization at the bed, analytical and global muscle reinforcement-adaptation to the exertion, postural changes, walking and postural balance; respiratory training: ventilation exercises (volume incentive), facilitating treatments in lateral and prone recumbency.

Additionally, patients underwent the treatment with an LF-HI-PEMF equipment CTU Mega 20® (Periso SA - Switzerland) CE marked in class IIA, modifying a protocol already experienced in ILF related to auto-immune pathologies [11] to stimulate the respiratory muscles. The outcome of this combined treatment was to improve the exertion dyspnoea and the functional scores in a multiple test battery.

The CTU Mega 20 machine shares the bio-active properties of HI-PEMF [14] but differs in the possibility to provide the so-called repulsive or Diamagnetic effect. This one, give rise from the force of a self-limiting, pulsed high-intensity magnetic field of 2 Tesla (max energy value of 90 J), low frequency (7 Hz) and able to move liquids and solutes from the extracellular to the intracellular space and vice versa. Besides, a wide bandwidth of electromagnetic frequencies is carried at the cellular level to implement the biological effect of PEMF [15].

The treatment area included the posterior and posterolateral thoracic region (intercostal muscles- Serratus Anterior muscle). Since the magnetic field flows through the handpiece to an extent of 7 cm it was possible to operate both in contact, using a proper conductive cream, or in contactless mode.
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The selected patients underwent a standardized cycle of 6 sessions (3 times a week) for two weeks, according to the therapeutic scheme conceived by Cell Regeneration Medical Organization (Bogotá-Colombia). The therapeutic scheme was based on selected values of the Energy (J), Magnetic Field intensity (PWD), the Repetition rate of the pulse (HZ). The duration of each treatment was 20 minutes.

The protocol is specified in table 1 and 2, corresponding respectively to the first and second week of treatment.

<table>
<thead>
<tr>
<th>Pain control</th>
<th>Endogenous biostimulation</th>
<th>Liquids movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 HZR 30 J 5’</td>
<td>MC 3 PWD 5’ FL 3 PWD 5’</td>
<td>60% INTRA/EXTRA 5’</td>
</tr>
</tbody>
</table>

PC: Pain Control (effect on pain nerve fibres) 
MC: Cell Membrane (activation of ion channels) 
FL: Slow fibres (improvement of the nerve transmission)

Liquids Movement: (Extracellular Matrix drainage, endo-cellular molecular movements)

Table 1: First week of treatment (pain control, reactivation of nerve conduction - metabolic effects on cells – the movement of liquid and solutes).

<table>
<thead>
<tr>
<th>Pain control</th>
<th>Endogenous biostimulation</th>
<th>Liquids movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 HZR 30 J 5’</td>
<td>MC 3 PWD 5’ MS 3 PWD 5’</td>
<td>60% INTRA/EXTRA 5’</td>
</tr>
</tbody>
</table>

PC: Pain Control (PC: Pain Control (effect on pain nerve fibres) 
MC: Cell Membrane (activation of ion channels) 
MS: Striated Muscle (muscle cell stimulation)

Liquids movement: (ECM drainage, endo-cellular molecular movements)

Table 2: The second week of treatment (pain control, cell stimulation- metabolic effect on muscle – movement of liquids and solutes).

Once informed consent has been given, the treatments were carried out by the rehabilitation team at Villa Gemma Clinic (Gardone Riviera- Italy) under the supervision of two specialist doctors, respectively in pneumology (R.S.) and rehabilitation (S.V.). In this clinic, the CTU Mega is normally employed for the treatment of muscle-skeletal disorders.

The patients underwent to CT scan or X-ray examination of the chest before and at the end of the treatments. Furthermore, the following functional scales have been applied at the same time: BARTEL (Performance in activities of daily living -ADL), SPPB (Short Physical Performance Battery to assess lower extremity function and mobility), WALKING TEST (6 minutes test for exercise tolerance in chronic respiratory disease and heart failure), TINETTI (gait, balance, stability and fear of falling in older adults ) – BORG (rating of perceived exertion) - MRC – (Dyspnoea Scale) and Pulse Oximetry(Sat/O₂).

Results

All patients showed good compliance with the individual rehabilitative program that was accomplished in the respect of the safety measures provided for COVID-19. The addition of the Diamagnetic treatment has been well-tolerated without pain or adverse events.

At the end of the treatments, the patients showed speedy and progressive improvement in dyspnea and fatigue as well as in the functional skills.

The X-ray examination and CT scan imaging did not show significant changes (only 3 patients exhibited a limited decrease in the interstitial pattern of the lung). This is coherent with the short time interval between the first and the second x-ray exam, also according

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to the usual latency necessary to observe possible changes in the lung structure. Further imaging study and clinical follow up have been scheduled at three months after the discharge of the patients. Anyway, no X-ray worsening has been recorded.

The preliminary analysis of the functional scales results shows that only at the Tinetti and at the MRC test all the patients were able to complete the pre- and post-assessment score. For the Barthel test, 9/10 were able to do it while 7/10 were able to perform the SPPB (2 patients only the post-treatment assessment). Finally, 6/10 of the patients accomplished the Walking Test (1 patient only the post-treatment test) and the Borg Test. In general, the better functional improvement occurred for Barthel, MRC and SPPB and less relevant were the results of the Borg Test (perceived exertion). The Oxygen saturation improved in 100% of patients.

The statistical analysis included the sum of the scores for each assessed functional test as mean difference values ± standard deviations for discrete numeric variables. The Student’s «t» test for normal distribution of the data was chosen to determine the statistical significance between the pre- and post-treatment. The significance level has been chosen for p < 0,05.

In detail, for the 6 min Walking Test the improvement pre- and post-treatment ranged from 0 to 570 meters (133 meters ± 81,4 SD, p < 0,02), in the Tinetti Test, from 2 to 19 points (6 points ± 5,9 SD, p < 0,02) while for the Borg Test the values ranged from 6 to 0 points (1,14 points ± 1,22 SD, p > 0,05). The Barthel score improvement ranged from 0 to 33 points (16,78 points ± 14,09 SD, p < 0,01) and for SPPB scale the improvement score ranged from 2 to 7 points (4 points ± 2,04 SD, p < 0,01). The Dyspnoea (MRC questionnaire) and the Oxygen saturation showed respectively the variation from 5 to 2 points (0,9 ± 0,74 SD, p < 0,01) and the change from 88 to 99(-2 ± 2,21 SD, p < 0,02). These results are summarized in table 3 and demonstrate the efficacy of the joint treatment in a short time.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>6MWT</th>
<th>Tinetti</th>
<th>Borg</th>
<th>Barthel</th>
<th>SPPB</th>
<th>MRC</th>
<th>Sat/O2</th>
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<td>395 - 530</td>
<td>8 - 27</td>
<td>0 - 0</td>
<td>68 - 103</td>
<td>5 - 12</td>
<td>5 - 3</td>
<td>97 - 98</td>
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<tr>
<td>2</td>
<td>195 - 340</td>
<td>26 - 27</td>
<td>6 - 3</td>
<td>105 - 105</td>
<td>9 - 12</td>
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<td>97 - 93</td>
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<td>96 - 98</td>
</tr>
<tr>
<td>4</td>
<td>305 - 360</td>
<td>23 - 28</td>
<td>3 - 0</td>
<td>62 - 85</td>
<td>5 - 12</td>
<td>4 - 2</td>
<td>95 - 98</td>
</tr>
<tr>
<td>5</td>
<td>NE - NE</td>
<td>2 - 17</td>
<td>3 - 0</td>
<td>38 - 65</td>
<td>0 - 6</td>
<td>5 - 4</td>
<td>95 - 96</td>
</tr>
<tr>
<td>6</td>
<td>NE - 300</td>
<td>21 - 25</td>
<td>0 - 0</td>
<td>79 - 97</td>
<td>6 - 10</td>
<td>3 - 3</td>
<td>96 - 95</td>
</tr>
<tr>
<td>7</td>
<td>NE - NE</td>
<td>8 - 13</td>
<td>4 - 2</td>
<td>43 - 58</td>
<td>N - N</td>
<td>4 - 4</td>
<td>93 - 97</td>
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<tr>
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<tr>
<td>10</td>
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<td>26 - 28</td>
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<td>100 - 100</td>
<td>10 - 12</td>
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<tr>
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<td>P &gt; 0,05</td>
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<td>p &lt; 0,01</td>
<td>p &lt; 0,02</td>
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</tr>
</tbody>
</table>

Table 3: Pre and post - treatment values (first and second columns for each test) for the multiple functional scores.

The Walking Test shows the improvement in 7 patients, the remaining failed to complete the test pre or post - treatment (NE= not executed), the best improvement was for patients No 6 (0 - 300 meters). The Tinetti test was accomplished by all the patients, the best performance was for patient No 1 (+19 points). 3 subjects were not been able to complete the exertion Borg test and not meaningful improvement was appreciated in the subjects that completed the pre and post - test. For the SPPB test, patient No 7 was not able to run it anyway statistical analysis is significative as improvement in the short performances. In the Barthel Group, 3 patients showed a full score at the beginning of the treatments and, globally, 60% showed good result in term of autonomy in ADL.

Discussion

In muscle-skeletal disorders, the effects of the biophysical impulse originated from PEMFs, combined with a rehabilitative program, have attracted a certain interest for safety and effectiveness [10]. This would depend on a series of biological effects ranging from anti-inflammatory, due to the cytokine modulation, regenerative effects mediated by specific growth factors, neo-angiogenesis [13-16], mesenchymal stem cell differentiation and muscle cell proliferation [17,18]. These properties are shared with another type of biophysical stimulation such as Extracorporeal Shock Waves [17] and for this reason, biophysical treatments are worldwide becoming potential support, or therapeutic alternative, in many medical conditions.

As reported in a preceding experience [11], LF-HI-PEMF showed effectiveness in the treatment of ILF accompanying a rare case of overlapping connective disease. In the present study, non-invasive Diamagnetic treatment contributed to ameliorating the respiratory function and the quality of life in post-SARS-Cov-2 pneumonia in terms of oxygen saturation, improvement of dyspnea and muscle performance.

Various can be the causes of muscle weakness in such patients. Primarily, the altered $O_2/CO_2$ alveolar gas exchange due to the local anatomical alterations that include: inflammatory exudation in alveoli, interstitial inflammation, thickening of the alveolar epithelium, the buildup of jalone membranes, dense patchy perilobular fibrosis, honeycomb remodeling and bronchial metaplasia [2,6]. Ground-glass opacity (GGO), parenchymal density and thickening of the interstitial septae with diffuse fibrosis have been also described in CT scan of ILF [19]. These lesions affect the respiratory function which may be worsened by muscle, heart and nervous tissue concerns together with the effects of prolonged bedridden or the undesired ventilatory – induced lung injury (VILI) [2,5]. Not least myalgia, secondary to myositis and present in 35% to 50% of COVID 19 patients [20] has been considered as a further cause of respiratory weakness. Once more, the patients who develop muscle pain more likely exhibit abnormal lung imaging findings [7].

In COVID-19, the lung infection is more lethal in patients suffering from idiopathic pulmonary fibrosis (IPF) or with comorbidities such as high blood pressure, diabetes, ischemic heart disease and a history of cigarette smoke exposure [3]. However, the possibility that pulmonary fibrosis could be a consequence of the infection is real mainly for ARDS [1,2,4] and as reported by Bandirali., et al. abnormalities highly suspicious for COVID-19 pneumonia have been observed at the X-rays chest examination, in asymptomatic or little symptomatic subjects [21].

The pathogenesis of pulmonary fibrosis during COVID-19 is not well understood, although the consequences of the alveolar damage, the overexpression of pro-inflammatory cytokines, the activation of fibroblasts and myofibroblasts, the deposit of collagen in the extracellular matrix plus the dysfunction of the cardiorespiratory nuclei in brainstem would have a noteworthy role [22,23]. Furthermore, the disadvantages of ICU stay in the prone position, at the origin of the post-intensive care syndrome, share the muscle weakness, the joint stiffness, the impaired mobility and balance, the neuropathy and myopathy that are proper of the viral infection [24,25], worsening the morbidity and the mortality in such patients [26].

Antifibrotic drugs such as pirfenidone and nintedanib have been proposed to slow down the deterioration of the lung function [3]. However, there are no adequate studies that endorse the routine use of these drugs or evidence that these therapies impact severe lung fibrosis. Incidentally, adverse effects of these drugs and several symptoms of COVID-19 (diarrhoea, fatigue, loss of taste) are similar and this is a confounding factor [27].

For all these reasons, as stated by Curci., et al. post-acute COVID-19 patients need early -personalized rehabilitative care that should take into account the disability status, vital and functional parameters and comorbidities. For example, a low threshold for dyspnea reflects on the performance of 6-MWT [28] and any reduction of the exercise capacity, such the baseline walks distance and the contempo-
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...ratory desaturation $\leq 88\%$ are respectively, a prognostic factor and risk factor of subsequent mortality [29]. Add to this, muscle dysfunction and impairment of the gas alveolar exchanges hinder the efficacy of the rehabilitation.

Given the above, the selection of the patients, the timing and the elements of the rehabilitation programs, the training and exercise assessment are mandatory [9]. Consequently, safe and non-invasive therapeutic strategies able to support the rehabilitative programs, not entailing efforts for these fragile patients, may represent a valid tool, and this is a recognized property of the biophysics stimulation induced by PEMF.

In our study, 4/10 subjects (40%) were unable to perform the 6MWT before to start the treatments, and at the end 15 days after, 3/10 (30%) were. In these subjects, the combined treatment produced in 15 days suggestive positive changes in the skill to carry out the test (mean range from 284.2 to 417.8 meters $p < 0.02$) that, in the light of the above [28,29] can be interpreted as a favourable prognostic index. The same applies to other functional items, except for the more challenging exertion Borg test (Table 3).

Although it was not possible to use a control group, the joint results of the rehabilitation and Diamagnetic treatment are remarkable. This is confirmed by the short time necessary to observe a significant improvement at the functional test battery and this could be attributed also to the bio-inductive and anti-inflammatory effects of PEMF [13-18], capable to stimulate properly the respiratory muscles.

We recognize that further assessments in the long term and adequate RCT are necessary to validate these results and, as reported in a previous experience [11], we can't still know if this improvement correspond to changes in the lung parenchyma. The answer to the question could derive from the radiographic and functional follow up scheduled at three months.

Conclusion

10 hospitalized patients with a confirmed diagnosis of post-COVID-19 pulmonary fibrosis were treated, in addition to their conventional rehabilitation therapy, with the Cell Regeneration Medical Organization protocol that employs a machine delivering Low-Frequency Pulsed Electromagnetic Field (CTU Mega 20) capable of stimulating muscle tissue.

This pilot test based on a longitudinal descriptive observational study evidence significant clinical and functional quantitative improvements in most of the scales applied to each patient, and no side effects have been reported.

The improvement was common for the parameters of respiratory function, muscle efficiency and tolerance to exercise more quickly and effectively. The Diamagnetic treatment demonstrated also to be safe for the patients.

More comparative studies are needed to affirm that diamagnetic therapy applies routinely to all patients with post-Covid19 pulmonary fibrosis.

Conflict of Interest

Dr Pietro Romeo declares to have a scientific collaboration with Periso SA.

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Bibliography


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