Brain Stimulation 15 (2022) 780–788

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Efficacy and safety of HD-tDCS and respiratory rehabilitation for critically ill patients with COVID-19 The HD-RECOVERY randomized clinical trial

Suellen Marinho Andrade [a,*], Maria Cecília de Araújo Silvestre [a], Eduardo Ériko Tenório de França [b], Maria Heloísa Bezerra Sales Queiroz [a], Kelly de Jesus Santana [a], Marcela Lais Lima Holmes Madruga [a], Cristina Katya Torres Teixeira Mendes [a], Eliane Araújo de Oliveira [a], João Felipe Bezerra [a], Renata Gomes Barreto [a], Silmara Maria Alves Fernandes da Silva [a], Thais Alves de Sousa [a], Wendy Chrystyan Medeiros de Sousa [a], Mariana Patrícia da Silva [a], Vanessa Meira Cintra Ribeiro [b], Paulo Lucena [b], Daniel Beltrammi [b], Rodrigo Ramos Catharino [c], Egas Caparelli-Dáquer [d], Benjamin M. Hampstead [e], Abhishek Datta [f], Antonio Lucio Teixeira [g], Bernardino Fernández-Calvo [h, i], João Ricardo Sato [j], Marom Bikson [f]

[a] Federal University of Paraíba, João Pessoa, Brazil
[b] Health Secretary, Government of Paraíba, João Pessoa, Brazil
[c] Thomson Mass Spectrometry Laboratory, Institute of Chemistry, State University of Campinas, UNICAMP, Campinas, SP, Brazil
[d] Nervous System Electric Stimulation Lab, Rio de Janeiro State University, Rio de Janeiro, Brazil
[e] Research Program on Cognition and Neuromodulation Based Interventions, Department of Psychiatry, University of Michigan & Mental Health Service, VA Ann Arbor Healthcare System, Ann Arbor, Ann Arbor, United States
[f] Department of Biomedical Engineering, The City College of New York of CUNY, New York, United States
[g] Department of Psychiatry and Behavioral Sciences, McGovern Medical School, University of Texas Health Science Center, Houston, United States
[h] Department of Psychology, University of Cordoba, Cordoba, Spain
[i] Maimonides Biomedical Research Institute of Cordoba (IMIBIC), University of Cordoba, Cordoba, Spain
[j] Center of Mathematics, Computing and Cognition. Federal University of ABC, Santo André, Brazil

A R T I C L E I N F O

Article history:
Received 9 March 2022
Received in revised form
19 April 2022
Accepted 5 May 2022
Available online 11 May 2022

Keywords:
High-definition transcranial direct current stimulation
Noninvasive brain stimulation
Coronavirus disease
Acute respiratory distress syndrome
Respiratory rehabilitation

A B S T R A C T

Background and purpose: Acute Respiratory Distress Syndrome (ADRS) due to coronavirus disease 2019 (COVID-19) has been associated with muscle fatigue, corticospinal pathways dysfunction, and mortality. High-Definition transcranial Direct Current Stimulation (HD-tDCS) may be used to attenuate clinical impairment in these patients. The HD-RECOVERY randomized clinical trial was conducted to evaluate the efficacy and safety of HD-tDCS with respiratory rehabilitation in patients with moderate to severe ARDS due to COVID-19.
Methods: Fifty-six critically ill patients were randomized 1:1 to active (n = 28) or sham (n = 28) HD-tDCS (twice a day, 30-min, 3-mA) plus respiratory rehabilitation for up to 10 days or until intensive care unit discharge. The primary outcome was ventilator-free days during the first 28 days, defined as the number of days free from mechanical ventilation. Furthermore, secondary outcomes such as delirium, organ failure, hospital length of stay and adverse effects were investigated.
Results: Active HD-tDCS induced more ventilator-free days compared to sham HD-tDCS. Patients in the active group vs in the sham group experienced lower organ dysfunction, delirium, and length of stay rates over time. In addition, positive clinical response was higher in the active vs sham group. There was no significant difference in the prespecified secondary outcomes at 5 days. Adverse events were similar between groups.

* Corresponding author. Health Center, Neuroscience and Aging Laboratory, Campus I, 58051-085, Paraíba, Brazil.
E-mail address: suellen.andrade@academico.ufpb.br (S.M. Andrade).

https://doi.org/10.1016/j.brs.2022.05.006

Conclusions: Among patients with COVID-19 and moderate to severe ARDS, use of active HD-tDCS compared with sham HD-tDCS plus respiratory rehabilitation resulted in a statistically significant increase in the number of ventilator-free days over 28 days. HD-tDCS combined with concurrent rehabilitation therapy is a safe, feasible, potentially add-on intervention, and further trials should examine HD-tDCS efficacy in a larger sample of patients with COVID-19 and severe hypoxemia.

1. Introduction

Patients critically ill with coronavirus disease 2019 (COVID-19) often require mechanical ventilation and prolonged hospitalization duration to restore adequate gas exchange and to alleviate acute respiratory distress syndrome (ADRS) [1]. There is variability between individual studies with respect to frequency of ARDS caused by COVID-19 [2–4]; individual studies for which data is available indicate that among hospitalized COVID-19 patients, approximately 1/3 (33%) develop ARDS, 1/4 (26%) require transfer to an intensive care unit (ICU), and 1/6 (16%) receive invasive mechanical ventilation [5]. Injury to the brain - whether secondary to systemic (respiratory system) dysfunction, neuro-vascular damage, or direct neural-invasion (e.g., via the olfactory nerve) [6] contributes to COVID-19 pathophysiology, symptoms, and progression [7]. Non-invasive brain stimulation approaches have been investigated for the management of disorders related to COVID-19 [8,9]. Regarding its anti-inflammatory actions, non-invasive vagus nerve stimulation has been trialed for the treatment of respiratory symptoms and inflammatory markers among patients who were hospitalized for COVID-19 [10].

High-Definition transcranial Direct Current Stimulation (HD-tDCS) is a special form on non-invasive brain stimulation that allows: 1) focal stimulation of cortical targets 2) using direct current to boost excitability and neuroplasticity [11]; 3) with minimal side-effects; and 4) in a portable way [12]. In severe COVID cases, muscle fatigue and weakness can hamper respiratory function leading to a vicious cycle requiring mechanical ventilation, which *per se*, can cause more weakness [13]. tDCS applied over the diaphragmatic motor cortex may engage not only intracortical circuits, but also spinal motor circuits, modulating the respiratory motor evoked potentials [14]. Because COVID-19 is believed to induce or exacerbate microvascular injury [15], the potential neurovascular response induced by tDCS may provide further benefit [16].

Given the potential adjuvant effect of neurostimulation, tDCS can enhance gains to the rehabilitation results on the motor and cognitive function under different clinical conditions [17,18]. For example, the motor cortex is responsible for coherent corticomuscular oscillations [19] and tDCS actions cortical networks enhance intermuscular coherence [20]. Specifically, regarding the respiratory function, tDCS paired with exercise training enhances breathing in patients with chronic stroke patients, as indicated by an increase in forced expiratory volume and forced vital capacity [21]. In healthy subjects, anodal tDCS increased chest wall intermuscular coherence during breathing [22]. Separately, tDCS actions on cerebral blood flow [23,24] have been directly linked to cortical-motor drive [25,26]. These findings indicate that tDCS can facilitate cortical activity and restore functional coupling between central and peripheral motor systems, directly or as adjuvant therapy, supporting functional recovery.

The HD-RECOVERY randomized clinical trial was conducted to evaluate the efficacy and safety of active or sham HD-tDCS in association with respiratory rehabilitation in patients with moderate to severe ARDS due to COVID-19. The hypothesis was that HD-tDCS combined with concurrent rehabilitation therapy would increase the number of ventilator-free days during the first 28 days, thereby reducing rates of delirium, organ dysfunction, and hospital length of stay.

2. Methods

2.1. Overview

This trial was an investigator-initiated, parallel-group, stratified, double-blinded randomized clinical trial. The protocol was approved by the independent ethics committee (Paraíba Government) and conducted in compliance with the Declaration of Helsinki [27]; it is registered in clinicaltrials.gov (NCT04844554). All patients or legally authorized representatives provided written informed consent.

2.2. Participants

Patients underwent screening and randomization between April 14 to September 2, 2021. Final follow-up was completed on October 4, 2021. Patients of at least 18 years-old with a PCR-confirmed SARS-CoV-2 diagnosis and receiving mechanical ventilation at least 48 h of meeting criteria for moderate to severe acute respiratory distress syndrome (ARDS), under weaning, were enrolled in this study. An ARDS diagnosis was made according to the Berlin Definition criteria [28]. Patients were excluded if they had a condition that could prevent adequate performance of inspiratory muscle training (e.g., neuropathy, myopathy, agitation), pregnancy or active lactation, Glasgow Coma Scale (GCS) [29] $\leq$ 8, consent refusal, and contraindications to brain stimulation (e.g., aneurysm clips) [30].

2.3. Randomization

Randomization was performed through an online web-based system using computer-generated random numbers stratified by age. Participants admitted consecutively were assigned randomly in a 1:1 ratio to receive active or sham HD-tDCS for 10 days or until ICU discharge, whichever occurred first, plus respiratory rehabilitation. Treatment assignments were concealed from patients, clinicians, investigators, trial statisticians and the data and safety monitoring committee.

2.4. Data collection and monitoring

Patients were followed up for 28 days after randomization (both hospitalized patients and those who had been discharged). Previous studies showed that severe COVID-19 can occur in otherwise healthy individuals, but certain underlying medical comorbidities have also been associated with severe illness and morbidity [31,32]. Since clinical characteristics at baseline are factors that may help to better define the risks of mechanical ventilation [33], we included the comorbidities most prevalent among these COVID-19 patients.

Data on demographic characteristics, hemodynamic variables, respiratory status, adverse events, and concomitant medications were collected. In addition, we obtained the following information at baseline (day 1): degree of comorbidity, as assessed by the Charlson Comorbidity Index (CCI) [34], and severity of acute injury throughout Simplified Acute Physiology Score III (SAPS-III) [35,36].

Trial investigators reported any serious adverse events daily through day 28. Individual patient data on infections and/or serious adverse events were adjudicated by a blinded investigator. Trial data were monitored (including consent and source data verification) by independent monitors according to a prespecified monitoring plan.

2.5. Interventions

2.5.1. HD-tDCS

HD-tDCS was delivered on 10 consecutive weekdays, with two sessions per day (in the morning and in the afternoon). For each participant, a 3-mA current was applied via a center anode using a Soterix Medical Inc. stimulator (mini-CT with 4 × 1 adaptor, Soterix Medical, New York, NY, USA). The center anode was placed at the left diaphragmatic primary motor cortex (4 cm lateral to the midline and 1 cm anterior to the binaural line) [37] and the four cathodes were spaced in a radius ~7.5 cm from the center electrode. The Soterix Medical adaptor passively splits current produced by the mini-CT among these cathodes. For those in the active group, the electrical current was delivered with a ramp-up time of 30 s, held at 3 mA for 30 min, and then ramped down over 30 s. In the sham condition, the device provided a 30-s ramp-up period to the full 3 mA, followed immediately by a 30-s ramp down. Each set of five electrodes were used for 10 sessions and the location of each electrode was rotated to where any given electrode was used as the center anode twice and ring cathode 8 times [38]. The electrodes were placed in an adapted headgear that supported the required HD-tDCS positions (Fig. 1). Brain stimulation was applied concurrently with pulmonary rehabilitation to both groups. Investigator blinding was performed by a predefined code triggered active or sham tDCS (i.e., a participant-specific code that was entered into the unit at the start of the session), thereby ensuring study team members were blind to stimulation condition. Blinding efficacy was assessed at the end point by asking staff to guess the patient's allocation group.

2.6. Respiratory rehabilitation

The inspiratory muscle training program was based upon a previous protocol applied to facilitate weaning of ventilatory support [39]. Training was based on progressive regimen: In the first session, the target was to start with a load of 30% of the participant's maximal inspiratory pressure, increasing daily by 10% (absolute), with training for 5 min, twice a day, seven days a week throughout the weaning period. Supplemental oxygen was provided as needed. During 25 remaining minutes, the session also included regular physiotherapy intervention including daily passive movement of all joints and positional therapy [40–42].

The session was interrupted if a patient had any of the following: respiratory frequency of more than 30 breaths per minute, arterial saturation below 90%, systolic blood pressure above 180 mm Hg or below 90 mm Hg, paradoxical breathing, or tachycardia above 140 beats per minute [43–45]. When any of these signs occurred during a training session, the load was maintained (i.e., not increased by 10%) at the next session.

2.7. Outcomes

The primary outcome was ventilator-free days during the first 28 days, defined as the number of days free from mechanical ventilation for at least 48 consecutive hours [46]. Patients discharged from the hospital before 28 days were considered free from mechanical ventilation at 28 days and nonsurvivors at day 28 were considered to have no ventilator-free days [47].

Secondary outcomes were assessed at baseline, and on days 5, 11, and 28, and included changes in the (1) Confusion Assessment Method for the ICU (CAM-ICU) [48] and the Sequential Organ Failure Assessment (SOFA) scale scores [49]; (2) hospital length of stay (LOS), defined as the total number of days that patients remained hospitalized from the date of randomization until the date of hospital discharge; (3) rates of adverse events; (4) clinical response (defined as a reduction from baseline SOFA score from all weeks greater than 3 points). Changes in SOFA score have been used to assess the effects of therapeutic interventions [50–53]. The delta SOFA (ΔSOFA) and delta CAM-ICU (ΔCAM-ICU) were calculated as the difference between the score on a specific day and the score on the day of admission to the ICU.

2.8. Statistical analysis

No reliable data were available at the time of trial design to allow for an accurate sample size calculation. We originally estimated that 24 patients per group or 48 patients in total were required for the trial to have 80% power to detect a difference of 3.2 (1.2 SD; margin of clinically meaningful difference 1.9) ventilator-free days between groups, assuming that 15% of patients would die at 28 days. The mean difference of ventilator-free days was calculated based on local hospital-level pilot clinical estimates, and no prior data were available on the distribution of clinical status categories over time in patients with severe COVID-19.

For the primary outcome (ventilator-free days during the first 28 days) and secondary outcomes (delta SOFA, delta CAM-ICU and LOS), we performed a generalized linear model, adjusted for age and partial pressure of arterial blood oxygen to fraction of inspired oxygen (Pao_2:Fio_2) ratio at randomization. The effect size was estimated as the mean difference (95% confidence interval) for the primary outcome and LOS, and as the number needed to treat (NNT) for the secondary outcomes.

Clinical responses of the interventions at 28 days after randomization were compared using Kaplan-Meier survival curves. The Cox model was used to estimate the hazard ratio and its confidence interval associated with the intervention [54].

We performed exploratory analysis to identify whether the variables age, Pao2:Fio2 ratio, CCI score, Simplified Acute Physiology Score III (SAPS III) are moderators of the primary outcome. Additionally, we performed linear model analyses to estimate the interactions for these baseline outcomes (age, CCI, Pao2:Fio2 and SAPS score) and the length of stay.

Adverse events are expressed as counts and percentages and compared between groups using the χ^2 test. All patients who were randomized and received at least 1 HD-tDCS session were assessed for efficacy and adverse events. There was no loss to follow-up, and data on the clinical outcomes and mortality within 28 days were available for all patients. Missing values on individual outcome components were imputed as normal. One patient was declared by a physician on day 8 as being well enough to hospital discharge. To test the integrity of blinding, investigator's responses when asked to guess the treatment group of patients were compared for active and sham groups using a χ^2 test. A 2-sided P value of less than 0.05 was considered statistically significant. All analyses were performed using the R software version 4.0.2 (R Core Team) and the

Fig. 1. HD-tDCS setup and montage. A. 4x1 HD-tDCS device. B. Soterix neurostimulator delivering the current on the 5 electrodes in a 4x1 HD-tDCS montage positioned around a circle of 7.5 cm of diameter centered to the target electrode position (the left diaphragmatic motor cortex).

GraphPad Prism software version 8.0 for Mac (GraphPad Software, San Diego, CA, USA).

3. Results

3.1. Participants

Of 168 patients who consented and were assessed for eligibility, 112 were excluded (97 did not meet eligibility criteria and 15 withdrew consent). Of the enrolled patients, 28 were randomly assigned to receive active HD-tDCS and 28 to the sham group (Fig. 2).

3.2. Trial and concomitant interventions

Both groups received pulmonary rehabilitation daily during HD-tDCS. Baseline characteristics were well balanced between groups, including severity of ARDS. The use of respiratory, circulatory, and kidney support and the use of other anti-inflammatory, antiviral, and antibacterial drugs were similar between groups at baseline (Table 1).

3.3. Primary outcome

Multiple linear model analysis revealed that the mean number of days free from mechanical ventilation during the first 28 days was significantly higher in the active group than in sham group ($\beta_{interv} = 7.47$; 95% CI, 3.95–10.99; $P < .001$; mean difference = 7.42; 3.90 to 10.95) (Table 2). The cumulative frequency of ventilator-free days according to the study group is shown in Fig. 3.

3.4. Secondary outcomes

3.4.1. Organ dysfunction and clinical response

Organ dysfunction was similar between groups at baseline and on day 5 ($P > .05$). However, patients in the active group experienced significantly greater improvement over time compared with those in the sham group at 11 days ($\beta_{int} = 5.43$; 95% CI, 3.37 to 7.57; $P < .001$) and 28 days ($\beta_{int} = 7.21$; 95% CI, 4.86 to 9.57; $P < .001$) (Table 2) (Fig. 4).

Respectively for the active and sham groups, 24 and 11 patients presented positive clinical responses (i.e., a change from baseline in SOFA score of ≥3 points) at 28 days. Kaplan–Meier analysis showed a cumulative survival (positive clinical response) of 83.33% (standard error = 8.7%) and 52.80% (standard error = 9.7%), respectively for the active and sham groups. The Cox proportional hazards ratio associated with active group was 2.00 (95% CI, 0.96–4.146; $P = .0009$). The corresponding NTT was 2 and the relative risk reduction associated with active group was 0.91 (95% CI, 0.37–0.98; $P < .05$) (Fig. 5).

3.5. Length of stay and delirium

The median length of stay was shorter in the active group compared with the sham group (βint = 7.03; 95% CI, 4.44 to 9.61; $P < .001$; mean difference, 7.75; 4.89 to 10.60) (Table 2). As suggested by the earlier discharge date, the mean Delta CAM-ICU score at 11 days after randomization was significantly lower in the active group (βint = −2.79; 95% CI, −3.79 to −1.79; $P < .001$) when delirium cleared in 13 patients from the active group but only 5 in the sham group (NNT = 3.3, Relative risk reduction 0.36; 95% CI, 0.04–0.58) (Table 2; Fig. 4B). At 28 days, there was no significant difference between the groups in the Delta CAM-ICU score

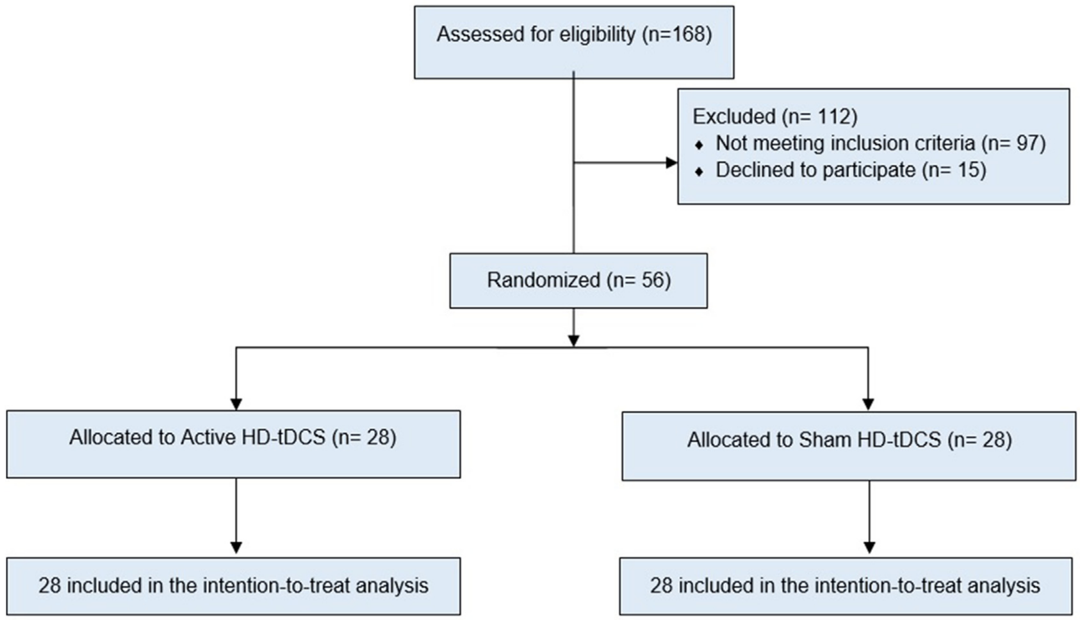

Fig. 2. Screening, Randomization, and Follow-up of Patients in the HD-RECOVERY trial. HD-tDCS indicates High-definition transcranial direct current stimulation.

(βint = 0.23; 95% CI, −0.98 to 1.45; *P* = .69) when only 1 patient in each group remained in delirium.

3.6. Safety outcomes

All 7 [12.5%] but one death through day 28 (3 in the active group and 4 in the sham group) occurred in patients aged 69 years or older, but none was attributed to HD-tDCS treatment. A total of 5 and 3 mild adverse events (i.e., transient skin redness) were recorded in the active and sham groups, respectively (P = .44). More patients in the sham group experienced secondary infections (11 patients) compared with patients in the active group (8 patients) during the study period (P = .05). Apart from deaths, 2 serious adverse events were reported, all in the sham group: 1 episode of stroke possibly related to SARS-CoV-2 (on day 17), 1 episode of cardiac dysfunction related to a pulmonary embolism (on day 23). No serious adverse events were attributed to the study treatment. No serious adverse events occurred in the active group.

Table 1
Baseline characteristics.[a].

Characteristic	Active HD-tDCS	Sham HD-tDCS
Age, mean (SD), y	67.25	68.92
Women, n (%)	9 (32.14)	10 (35.71)
SAPS III, median (IRQ)[b]	58 (51.5–68.25)	61 (50–65)
CCI, median (IRQ)[c]	3 (1.75–4.25)	4 (3–5)
PaO2/FiO2 ratio, mean (SD)	167.6 (41.74)	168.7 (34.40)
Comorbidities and risk factors, n (%)		
Hypertension	14 (50)	16 (57.14)
Chronic ischemic heart disease	8 (28.57)	7 (25)
COPD	3 (10.71)	5 (17.85)
Chronic kidney disease	2 (7.14)	3 (10.71)
Diabetes	8 (28.57)	5 (17.85)
Chronic liver disease	3 (10.71)	2 (7.14)
Concomitant Medications, n (%)		
Convalescent plasma or serum	7 (25)	7 (25)
Steroids	15 (53.57)	16 (57.14)
Antibiotics	21 (75)	23 (82.14)
Adrenergic agents	16 (57.14)	14 (50)

Abbreviations: SAPS III, Simplified Acute Physiology Score III; CCI, Charlson Comorbidity Index; PaO2/FiO2, Partial Pressure of Arterial Oxygen; COPD, Chronic obstructive pulmonary disease.

[a] Continuous variables are presented as mean (SD) unless otherwise indicated.

[b] The Simplified Acute Physiology Score III ranges from 0 to 217. High scores indicate a higher risk of death, and it is calculated from 20 variables at admission of the patient.

[c] Express as sum of the weights, with higher scores indicating not only a greater mortality risk but also more severe comorbid conditions.

3.7. Exploratory analyses

In subgroup analyses, tests for effect were not statistically significant for subgroups defined by age (*P* = .35), CCI (*P* = .40), Pao_2:Fio_2 ratio (*P* = .79) and SAPS III (*P* = .60). No significant effect was found between baseline clinical status (age, CCI, PaO_2:FiO_2 and SAPS score) and length of stay (P >. 42).

3.8. Integrity of blinding

Investigators were unable to guess the participant's actual group beyond chance. The stimulation groups did not differ in this regard ($\chi 2(2) = 0.157$; P = .71).

4. Discussion

In this randomized clinical trial involving 58 adults with moderate to severe ARDS due to COVID-19, active HD-tDCS plus respiratory rehabilitation significantly increased the number of days free of mechanical ventilation during the first 28 days. This outcome suggests a clinically meaningful benefit of HD-tDCS in patients with severe COVID-19. Furthermore, HD-tDCS combined with concurrent rehabilitation therapy was associated with improvement in other parameters (clinical status, delirium, length of hospital stay) without increasing adverse events in this population of critically ill COVID-19 patients.

The observed clinical benefit from HD-tDCS in the present study may be explained by several underlying mechanisms. A first plausible explanation relates to the interplay between the altered respiratory drive during mechanical ventilation and the corticospinal

Table 2
Clinical outcomes.

Primary Outcome[a]	Active (n = 28)	Sham (n = 28)	P value[b]
Ventilator-free days			.01
Mean (95% CI)	16.57 (14.20–18.94)	9.14 (6.72–11.55)	
Median (IQR)	18 (16.75–19.25)	9.5 (3–12)	
Secondary Outcomes			
Organic Dysfunction, Mean (95% CI) [c]			
Baseline	11.64 (10.78–12.50)	10.85 (9.89–11.82)	.24
Day 5	10.81 (9.63–11.99)	11 (9.88–12.11)	.82
Day 11	4.62 (3.45–5.80)	9.28 (7.90–10.66)	.01
Day 28	1.04 (0.64–1.43)	7.5 (6.54–8.45)	.01
Delirium, Mean (95% CI) [d]			
Baseline	4.75 (4.03–5.46)	4.35 (3.60–5.11)	.46
Day 5	4.29 (3.65–4.94)	4.32 (3.50–5.13)	.96
Day 11	0.88 (0.52–1.25)	3.35 (2.62–4.08)	.01
Day 28	0.04 (0.03–0.11)	0.15 (0.13–0.43)	.50
Length of Stay Mean (95% CI)	15.11 (13.27–16.93)	22.86 (20.81–24.89)	.01
Median (IQR)	15 (12–17)	22 (19–26)	

[a] Express as the number of days alive and free from mechanical ventilation for at least 48 consecutive hours.
[b] P value for the treatment group comparison were estimated using general linear models.
[c] Measured in 6 organ systems (cardiovascular, hematologic, gastrointestinal, renal, pulmonary, and neurologic), with each organ score from 0 to 4, resulting in an aggregated score that ranges from 0 to 24, with higher scores indicating grater dysfunction. An initial SOFA score up to 9 predicts a mortality risk of less than 33%.
[d] Final CAM-ICU-7 score ranges from 0 to 7 with 7 being most severe. CAM-ICU-7 scores were further categorized as 0–2: no delirium, 3–5: mild to moderate delirium, and 6–7: severe delirium.

control of respiratory muscles [55]. Previous studies have shown supra-threshold brain stimulation activates cortical projections directly stimulating the diaphragm [56–58]. Mechanical ventilation reduces the excitability of the motor cortex supplying the diaphragm [59]. Thus, considering that modulation of motor cortex excitability is the canonical neurophysiological outcome of tDCS [60,61], our intervention may restore excitability of the diaphragmatic primary motor cortex. Second, is the boosting of motor learning and motor rehabilitation efficacy when paired with tDCS [62]. Third, enhancement of cerebral blood flow by tDCS may have a neuroprotective function and/or counteract COVID-19 microvascular injury [63–65].

The definition of clinical response used in this study (3 points grades on the SOFA scale) essentially translates to a change in clinical condition requiring invasive mechanical respiratory support, sepsis or death [66]. The difference between groups was associated with a large effect size and this reduction is clinically relevant, in which a tolerable, safe, and widely available intervention like HD-tDCS increase the number of ventilator-free days and may reduce the risk of pulmonary complications, hospital length of stay, organ dysfunction and burden to the health care system.

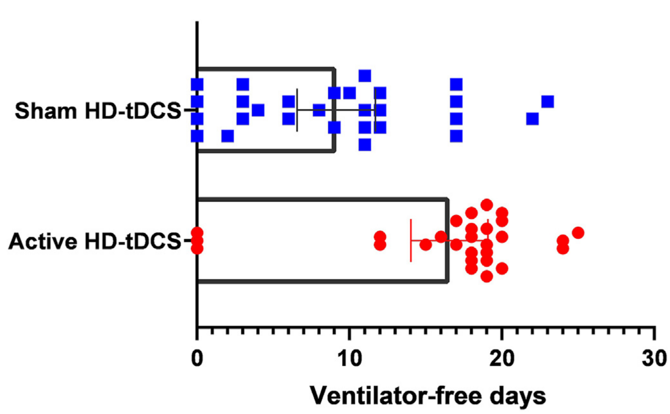

Fig. 3. Ventilator-Free Days at 28 Days. Panels showing individual changes in ventilator-free days from baseline to treatment slopes (follow-up) are displayed with box plots for groups (mean, central line; SD, boxes) overlaid with dots for single patients.

Active HD-tDCS was superior to sham HD-tDCS to delirium at 11 days, but not on day 28. These time points reflect different clinical concepts and the presence of 'a ceiling' effect may explain these findings. Often physicians and nurses are reluctant to discharge patients with delirium from the ICU [67]. In our study, after 28 days

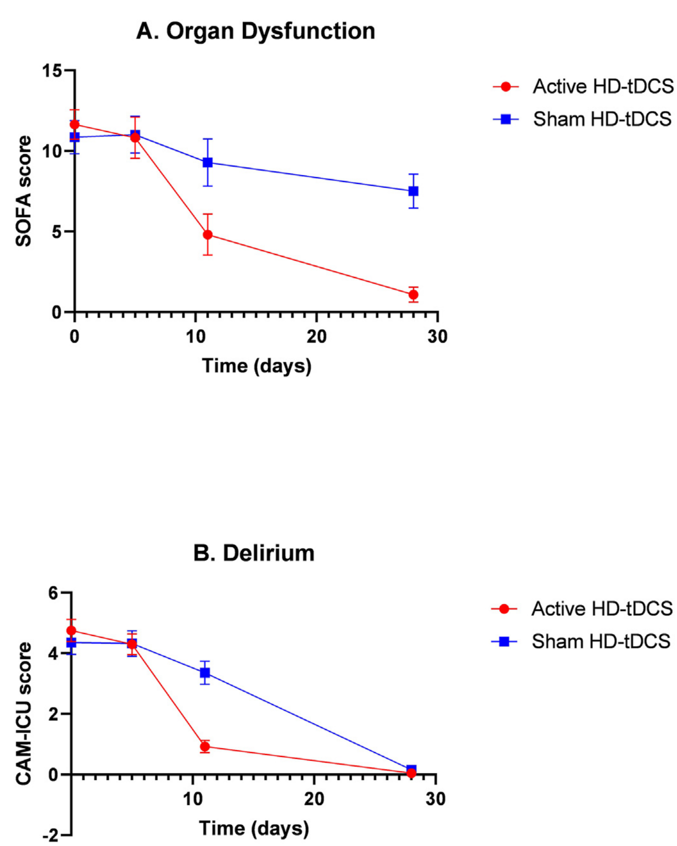

Fig. 4. Organ Dysfunction and Delirium Rates. Distributions of the Secondary Outcomes Organ Dysfunction, SOFA score, (A) and Delirium, CAM-ICU score, (B) from baseline to endpoint. Active High-definition transcranial direct current stimulation (HD-tDCS) was superior to sham. Intention-to-treat analysis. Error bars indicate 1 SD.

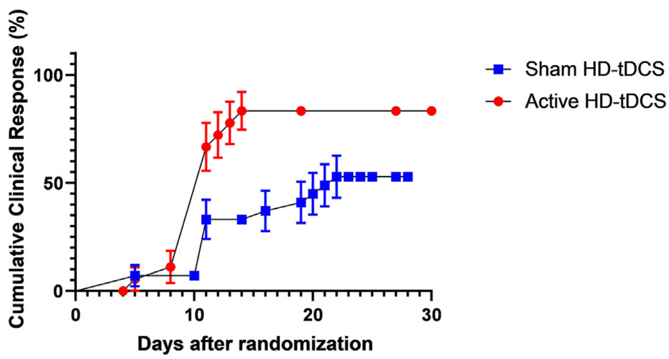

Fig. 5. Clinical Response. Distributions of the Secondary Outcomes Organ Dysfunction, SOFA score, (A) and Delirium, CAM-ICU score, (B) from baseline to endpoint. Active High-definition transcranial direct current stimulation (HD-tDCS) was superior to sham. Intention-to-treat analysis. Error bars indicate 1 SD.

of enrollment, most of the active group patients have been discharged from ICU and lower rates of delirium were found in the remaining patients from both groups. Future trials should consider monitoring delirium patients whose critical illness has resolved.

HD-tDCS plus respiratory rehabilitation was tolerable and safe, with both groups presenting similar adverse events. Mild and transient scalp erythema was the only adverse event associated with Active HD-tDCS, which is consistent with the general population non-significant-risk profile of tDCS [68]. HD-tDCS was selected based on its established tolerability, portability, and focal cortical modulation [69] — and shown here to be deployable to intensive care units.

The strengths of this trial include the pragmatic protocol, representative of a real word setting, allocation concealment and blinding and the high percentage of follow-up at 28 days. Also, adverse events data regarding HD-tDCS use among patients with COVID-19 were prespecified secondary safety outcomes and accurately provided, along with detailed data on ARDS treatment, and clinical variables.

This study has several limitations. First, because of the urgent circumstances in which the study was conducted, the in-hospital study setting may limit the generalizability of these results to patients with COVID-19 in other settings. Second, other laboratory/clinical parameters that are not routinely collected could elucidate the effect of intervention on various pathophysiological (e.g., inflammatory, oxidative stress, Body mass index evaluation and vaccination status) pathways. Third, since these patients did not receive any specific COVID-19 medication, for example, the monoclonal antibodies, but only medical support, changes in the treatment of COVID-19 during the study (such as adjusting medication dose) may have influenced the results. Fourth, this clinical trial cannot distinguish between alternative therapeutic mechanisms that have been identified in pre-clinical models and non-COVID trials, including enhancement of diaphragmatic neuromuscular drive [56] or neuro-vascular modulation [64,65,70,71]. Fifth, the conditions of the trial did not allow leveraging techniques such as image guided targeting [72] or additional study arms (e.g., tDCS alone). Sixth, this study was conducted prior to both widespread vaccination and circulation of the Delta (B.1.617.2) and Omicron (B.1.1.529) variants.

5. Conclusions

Among critically ill patients with COVID-19 and moderate to severe ARDS, active HD-tDCS significantly increased the number of ventilator-free days over 28 days. The results of this trial support the early use of HD-tDCS associated with respiratory support of severe COVID-19 patients and encourage further trials to examine the efficacy of brain stimulation in a large sample with pulmonary disease.

Funding

This trial was funded and supported by Governo do Estado da Paraíba (Brazil) and by the National Institutes of Health - NHI (1R01NS112996; 1R01NS101362).

CRediT authorship contribution statement

Suellen Marinho Andrade: designed the experiment, performed data analysis, prepared the manuscript and figures. **Maria Cecília de Araújo Silvestre:** performed the clinical experiments and data analysis. **Eduardo Ériko Tenório de França:** designed the experiment. **Maria Heloísa Bezerra Sales Queiroz:** performed the clinical experiments, prepared the manuscript and figures. **Kelly de Jesus Santana:** performed the clinical experiments, prepared the manuscript and figures. **Marcela Lais Lima Holmes Madruga:** performed the clinical experiments, prepared the manuscript and figures. **Cristina Katya Torres Teixeira Mendes:** designed the experiment and conducted critical revision of the manuscript. **Eliane Araújo de Oliveira:** designed the experiment and conducted critical revision of the manuscript. **João Felipe Bezerra:** designed the experiment and conducted critical revision of the manuscript. **Renata Gomes Barreto:** designed the experiment and conducted critical revision of the manuscript. **Silmara Maria Alves Fernandes da Silva:** performed the clinical experiments, prepared the manuscript and figures. **Thais Alves de Sousa:** performed the clinical experiments, prepared the manuscript and figures. **Wendy Chrystyan Medeiros de Sousa:** performed the clinical experiments, prepared the manuscript and figures. **Mariana Patrícia da Silva:** performed the clinical experiments, prepared the manuscript and figures. **Vanessa Meira Cintra Ribeiro:** designed the experiment and conducted critical revision of the manuscript. **Paulo Lucena:** designed the experiment and conducted critical revision of the manuscript. **Daniel Beltrammi:** designed the experiment and conducted critical revision of the manuscript. **Rodrigo Ramos Catharino:** designed the experiment and conducted critical revision of the manuscript. **Egas Caparelli-Dáquer:** designed the experiment and conducted critical revision of the manuscript. **Benjamin M. Hampstead:** designed the experiment and conducted critical revision of the manuscript. **Abhishek Datta:** designed the experiment. **Antonio Lucio Teixeira:** designed the experiment and conducted critical revision of the manuscript. **Bernardino Fernández-Calvo:** designed the experiment and conducted critical revision of the manuscript. **João Ricardo Sato:** performed the data analysis and conducted critical revision of the manuscript. **Marom Bikson:** designed the experiment and prepared the manuscript.

Declaration of competing interest

The City University of New York holds patents on brain stimulation with MB as inventor. MB has equity in Soterix Medical Inc. MB consults, received grants, assigned inventions, and/or serves on the SAB of SafeToddles, Boston Scientific, GlaxoSmithKline, Biophysics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Humm, Allergan (Abbvie), Apple. AD is an employee and has equity in Soterix Medical Inc.

References

[1] Ramani C, Davis EM, Kim JS, Provencio JJ, Enfield KB, Kadl A. Post-icu covid-19 outcomes. Chest 2021;159(1):215−8. https://doi.org/10.1016/j.chest.2020.08.2056.

[2] Elsayed HH, Hassaballa AS, Ahmed TA, Gumaa M, Sharkawy HY, Moharram AA. Variation in outcome of invasive mechanical ventilation between different countries for patients with severe COVID-19: a systematic review and meta-analysis. PLoS One 2021 Jun 4;16(6):e0252760. https://doi.org/10.1371/journal.pone.0252760.

[3] Zirpe KG, Tiwari AM, Gurav SK, et al. Timing of invasive mechanical ventilation and mortality among patients with severe COVID-19-associated acute respiratory distress syndrome. Indian J Crit Care Med 2021 May;25(5):493−8. https://doi.org/10.5005/jp-journals-10071-23816.

[4] Zeiser FA, Donida B, da Costa CA, et al. First and second COVID-19 waves in Brazil: a cross-sectional study of patients' characteristics related to hospitalization and in-hospital mortality. Lancet Reg Health Am 2022 Feb;6:100107. https://doi.org/10.1016/j.lana.2021.100107.

[5] Tzotzos SJ, Fischer B, Fischer H, Zeitlinger M. Incidence of ARDS and outcomes in hospitalized patients with COVID-19: a global literature survey. Crit Care 2020 Aug 21;24(1):516. https://doi.org/10.1186/s13054-020-03240-7.

[6] DosSantos MF, Devalle S, Aran V, et al. Neuromechanisms of sars-cov-2: a review. Front Neuroanat 2020;14:37. https://doi.org/10.3389/fnana.2020.00037.

[7] Steardo L, Steardo L, Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiol 2020;229(3). https://doi.org/10.1111/apha.13473.

[8] Baptista AF, Baltar A, Okano AH, et al. Applications of non-invasive neuromodulation for the management of disorders related to covid-19. Front Neurol 2020;11:573718. https://doi.org/10.3389/fneur.2020.573718.

[9] Gómez L, Vidal B, Cabrera Y, Hernández L, Rondón Y. Successful treatment of post-covid symptoms with transcranial direct current stimulation. Prim Care Companion CNS Disord 2021;23(6). https://doi.org/10.4088/PCC.21cr03059.

[10] Tornero C, Pastor E, del Mar Garzando M, et al. Non-invasive vagus nerve stimulation for respiratory symptoms of covid-19: results from a randomize controlled trial(Savior i). Respir Med 2021. https://doi.org/10.1101/2021.09.24.21264045.

[11] Jackson MP, Rahman A, Lafon B, et al. Animal models of transcranial direct current stimulation: methods and mechanisms. Clin Neurophysiol 2016;127(11):3425−54. https://doi.org/10.1016/j.clinph.2016.08.016.

[12] Villamar MF, Volz MS, Bikson M, Datta A, DaSilva AF, Fregni F. Technique and considerations in the use of 4x1 ring high-definition transcranial direct current stimulation(HD-tDCS). JoVE 2013;(77):50309. https://doi.org/10.3791/50309.

[13] Azabou E, Roche N, Sharshar T, Bussel B, Lofaso F, Petitjean M. Transcranial direct-current stimulation reduced the excitability of diaphragmatic corticospinal pathways whatever the polarity used. Respir Physiol Neurobiol 2013;189(1):183−7. https://doi.org/10.1016/j.resp.2013.07.024.

[14] Kadosh RC, Zaehle T, Krauel K. In: Non-invasive brain stimulation (Nibs) in neurodevelopmental disorders. first ed. Elsevier; 2021.

[15] Østergaard L. SARS CoV-2 related microvascular damage and symptoms during and after COVID-19: Consequences of capillary transit-time changes, tissue hypoxia and inflammation. Physiol Rep 2021;9(3):e14726. https://doi.org/10.14814/phy2.14726.

[16] Siddiqi HK, Libby P, Ridker PM. COVID-19 − a vascular disease. Trends Cardiovasc Med 2021;31(1):1−5. https://doi.org/10.1016/j.tcm.2020.10.005.

[17] Andrade SM, Batista LM, Nogueira LL, de Oliveira EA, de Carvalho AG, Lima SS, Santana JR, de Lima EC, Fernández-Calvo B. Constraint-induced movement therapy combined with transcranial direct current stimulation over premotor cortex improves motor function in severe stroke: a pilot randomized controlled trial. Rehabil Res Pract 2017:6842549. https://doi.org/10.1155/2017/6842549. 2017.

[18] Ministro G, Castaño JB, Barboza CA, Moura EG, Ferreira-Melo SE, Mostarda CT, Fattori A, Moreno-Junior H, Rodrigues B. Acute transcranial direct current stimulation (tdcs) improves ventilatory variability and autonomic modulation in resistant hypertensive patients. Respir Physiol Neurobiol 2022 Mar;297:103830. https://doi.org/10.1016/j.resp.2021.103830.

[19] Gerloff C, Braun C, Staudt M, Hegner YL, Dichgans J, Krägeloh-Mann I. Coherent corticomuscular oscillations originate from primary motor cortex: evidence from patients with early brain lesions. Hum Brain Mapp 2006 Oct;27(10):789−98. https://doi.org/10.1002/hbm.20220.

[20] Power HA, Norton JA, Porter CL, Doyle Z, Hui I, Chan KM. Transcranial direct current stimulation of the primary motor cortex affects cortical drive to human musculature as assessed by intermuscular coherence. J Physiol 2006 Dec 15;577(Pt 3):795−803. https://doi.org/10.1113/jphysiol.2006.116939.

[21] Lee DJ, Lee YS, Kim HJ, Seo TH. The effects of exercise training using transcranial direct current stimulation (tDCS) on breathing in patients with chronic stroke patients. J Phys Ther Sci 2017 Mar;29(3):527−30. https://doi.org/10.1589/jpts.29.527.

[22] Tomczak CR, Greidanus KR, Boliek CA. Modulation of chest wall intermuscular coherence: effects of lung volume excursion and transcranial direct current stimulation. J Neurophysiol 2013 Aug;110(3):680−7. https://doi.org/10.1152/jn.00723.2012.

[23] Stagg CJ, Lin RL, Mezue M, Segerdahl A, Kong Y, Xie J, Tracey I. Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. J Neurosci 2013 Jul 10;33(28):11425−31. https://doi.org/10.1523/JNEUROSCI.3887-12.2013.

[24] Zheng X, Alsop DC, Schlaug G. Effects of transcranial direct current stimulation (tDCS) on human regional cerebral blood flow. Neuroimage 2011 Sep 1;58(1):26−33. https://doi.org/10.1016/j.neuroimage.2011.06.018.

[25] Mosayebi-Samani M, Jamil A, Salvador R, Ruffini G, Haueisen J, Nitsche MA. The impact of individual electrical fields and anatomical factors on the neurophysiological outcomes of tDCS: a TMS-MEP and MRI study. Brain Stimul 2021 Mar-Apr;14(2):316−26. https://doi.org/10.1016/j.brs.2021.01.016.

[26] Paquette C, Sidel M, Radinska BA, Soucy JP, Thiel A. Bilateral transcranial direct current stimulation modulates activation-induced regional blood flow changes during voluntary movement. J Cerebr Blood Flow Metabol 2011 Oct;31(10):2086−95. https://doi.org/10.1038/jcbfm.2011.72.

[27] Bahr-Hosseini M, Bikson M. Neurovascular-modulation: a review of primary vascular responses to transcranial electrical stimulation as a mechanism of action. Brain Stimul 2021;14(4):837−47. https://doi.org/10.1016/j.brs.2021.04.015.

[28] World medical association declaration of helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310(20):2191. https://doi.org/10.1001/jama.2013.281053.

[29] Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2(7872):81−4. https://doi.org/10.1016/s0140-6736(74)91639-0.

[30] Woods AJ, Antal A, Bikson M, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol 2016;127(2):1031−48. https://doi.org/10.1016/j.clinph.2015.11.012.

[31] Zeiser FA, Donida B, da Costa CA, et al. First and second COVID-19 waves in Brazil: a cross-sectional study of patients' characteristics related to hospitalization and in-hospital mortality. Lancet Reg Health Am 2022 Feb;6:100107. https://doi.org/10.1016/j.lana.2021.100107.

[32] Iftimie S, López-Azcona AF, Vicente-Miralles M, et al. Risk factors associated with mortality in hospitalized patients with SARS-CoV-2 infection. A prospective, longitudinal, unicenter study in Reus, Spain. PLoS One 2020 Sep 3;15(9):e0234452. https://doi.org/10.1371/journal.pone.0234452.

[33] Izcovich A, Ragusa MA, Tortosa F, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: a systematic review. PLoS One 2020 Nov 17;15(11):e0241955. https://doi.org/10.1371/journal.pone.0241955.

[34] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40(5):373−83. https://doi.org/10.1016/0021-9681(87)90171-8.

[35] Metnitz PGH, Moreno RP, Almeida E, et al. SAPS 3–From evaluation of the patient to evaluation of the intensive care unit. Part 1: objectives, methods and cohort description. Intensive Care Med 2005;31(10):1336−44. https://doi.org/10.1007/s00134-005-2762-6.

[36] Moreno RP, Metnitz PGH, Almeida E, et al. SAPS 3–From evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. Intensive Care Med 2005;31(10):1345−55. https://doi.org/10.1007/s00134-005-2763-5.

[37] Acute respiratory distress syndrome: the berlin definition. JAMA 2012;307(23). https://doi.org/10.1001/jama.2012.5669.

[38] Azabou E, Bao G, Heming N, et al. Randomized controlled study evaluating efficiency of low intensity transcranial direct current stimulation (Tdcs) for dyspnea relief in mechanically ventilated covid-19 patients in icu: the tdcs-dysp-covid protocol. Front Med 2020;7:372. https://doi.org/10.3389/fmed.2020.00372.

[39] Hampstead BM, Ehmann M, Rahman-Filipiak A. Reliable use of silver chloride HD-tDCS electrodes. Brain Stimul 2020;13(4):1005−7. https://doi.org/10.1016/j.brs.2020.04.003.

[40] Cader SA, de Vale RGS, Castro JC, et al. Inspiratory muscle training improves maximal inspiratory pressure and may assist weaning in older intubated patients: a randomised trial. J Physiother 2010;56(3):171−7. https://doi.org/10.1016/S1836-9553(10)70022-9.

[41] Clinic E, Holand A, Pitta F, Troosters T. Textbook of pulmonary rehabilitation. Springer Nature; 2018.

[42] Vitacca M, Carone M, Clini EM, et al. Joint statement on the role of respiratory rehabilitation in the covid-19 crisis: the Italian position paper. Respiration 2020;99(6):493−9. https://doi.org/10.1159/000508399.

[43] Ambrosino N, Venturelli E, Vagheggini G, Clini E. Rehabilitation, weaning and physical therapy strategies in chronic critically ill patients. Eur Respir J 2012;39(2):487−92. https://doi.org/10.1183/09031936.00094411.

[44] Caruso P, Denari SD, Ruiz SA, et al. Inspiratory muscle training is ineffective in mechanically ventilated critically ill patients. Clinics 2005;60(6). https://doi.org/10.1590/S1807-59322005000600009.

[45] Conti G, Montini L, Pennisi MA, et al. A prospective, blinded evaluation of indexes proposed to predict weaning from mechanical ventilation. Intensive Care Med 2004;30(5):830−6. https://doi.org/10.1007/s00134-004-2230-8.

[46] Béduneau G, Pham T, Schortgen F, et al. Epidemiology of weaning outcome according to a new definition. The wind study. Am J Respir Crit Care Med 2017;195(6):772−83. https://doi.org/10.1164/rccm.201602-0320OC.

[47] Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and covid-19: the codex randomized clinical trial. JAMA 2020;324(13):1307. https://doi.org/10.1001/jama.2020.17021.
[48] Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the intensive care unit (CAM-ICU). Crit Care Med 2001;29(7):1370–9. https://doi.org/10.1097/00003246-200107000-00012.
[49] Vincent JL, Moreno R, Takala J, et al. The sofa (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure: on behalf of the working group on sepsis-related problems of the european society of intensive care medicine. Intensive Care Med 1996;22(7):707–10. https://doi.org/10.1007/BF01709751.
[50] Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med 1998;26(11):1793–800. https://doi.org/10.1097/00003246-199811000-00016.
[51] Sakr Y, Lobo SM, Moreno RP, et al. Patterns and early evolution of organ failure in the intensive care unit and their relation to outcome. Crit Care 2012;16(6):R222. https://doi.org/10.1186/cc11868.
[52] Cruz DN, Antonelli M, Fumagalli R, et al. Early use of polymyxin b hemoperfusion in abdominal septic shock: the euphas randomized controlled trial. JAMA 2009;301(23):2445. https://doi.org/10.1001/jama.2009.856.
[53] Jabre P, Combes X, Lapostolle F, et al. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. Lancet 2009;374(9686):293–300. https://doi.org/10.1016/S0140-6736(09)60949-1.
[54] Spruance SL, Reid JE, Grace M, Samore M. Hazard ratio in clinical trials. Antimicrob Agents Chemother 2004;48(8):2787–92. https://doi.org/10.1128/AAC.48.8.2787-2792.2004.
[55] Pilloni G, Bikson M, Badran BW, et al. Update on the use of transcranial electrical brain stimulation to manage acute and chronic covid-19 symptoms. Front Hum Neurosci 2020;14:595567. https://doi.org/10.3389/fnhum.2020.59556.
[56] Gandevia SC, Rothwell JC. Activation of the human diaphragm from the motor cortex. J Physiol 1987;384(1):109–18. https://doi.org/10.1113/jphysiol.1987.sp016445.
[57] Khedr E, Trakhan M. Localization of diaphragm motor cortical representation and determination of corticodiaphragmatic latencies by using magnetic stimulation in normal adult human subjects. Eur J Appl Physiol 2001;85(6):560–6. https://doi.org/10.1007/s004210100504.
[58] Welch JF, Argento PJ, Mitchell GS, Fox EJ. Reliability of diaphragmatic motor-evoked potentials induced by transcranial magnetic stimulation. J Appl Physiol 2020;129(6):1393–404. https://doi.org/10.1152/japplphysiol.00486.2020.
[59] Sharshar T, Ross ET, Hopkinson NS, et al. Depression of diaphragm motor cortex excitability during mechanical ventilation. J Appl Physiol 2004;97(1):3–10. https://doi.org/10.1152/japplphysiol.01099.2003.
[60] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527(Pt 3):633–9. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x.
[61] Jeffery DT, Norton JA, Roy FD, Gorassini MA. Effects of transcranial direct current stimulation on the excitability of the leg motor cortex. Exp Brain Res 2007;182(2):281–7. https://doi.org/10.1007/s00221-007-1093-y.
[62] Reis J, Fritsch B. Modulation of motor performance and motor learning by transcranial direct current stimulation. Curr Opin Neurol 2011;24(6):590–6. https://doi.org/10.1097/WCO.0b013e32834c3db0.
[63] Mosayebi-Samani M, Jamil A, Salvador R, Ruffini G, Haueisen J, Nitsche MA. The impact of individual electrical fields and anatomical factors on the neurophysiological outcomes of tDCS: a TMS-MEP and MRI study. Brain Stimul 2021;14(2):316–26. https://doi.org/10.1016/j.brs.2021.01.016.
[64] Wachter D, Wrede A, Schulz-Schaeffer W, et al. Transcranial direct current stimulation induces polarity-specific changes of cortical blood perfusion in the rat. Exp Neurol 2011;227(2):322–7. https://doi.org/10.1016/j.expneurol.2010.12.005.
[65] Bahr-Hosseini M, Bikson M. Neurovascular-modulation: a review of primary vascular responses to transcranial electrical stimulation as a mechanism of action. Brain Stimul 2021;14(4):837–47. https://doi.org/10.1016/j.brs.2021.04.015.
[66] Ferreira FL. Serial evaluation of the sofa score to predict outcome in critically ill patients. JAMA 2001;286(14):1754. https://doi.org/10.1001/jama.286.14.1754.
[67] Pisani MA, Murphy TE, Araujo KLB, Van Ness PH. Factors associated with persistent delirium after intensive care unit admission in an older medical patient population. J Crit Care 2010;25(3):540.e1–7. https://doi.org/10.1016/j.jcrc.2010.02.009.
[68] Bikson M, Grossman P, Thomas C, et al. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul 2016;9(5):641–61. https://doi.org/10.1016/j.brs.2016.06.004.
[69] Minhas P, Bansal V, Patel J, et al. Electrodes for high-definition transcutaneous DC stimulation for applications in drug delivery and electrotherapy, including tDCS. J Neurosci Methods 2010;190(2):188–97. https://doi.org/10.1016/j.jneumeth.2010.05.007.
[70] Khadka N, Bikson M. Neurocapillary-modulation. Neuromodulation 2020 Dec 19. https://doi.org/10.1111/ner.13338.
[71] Stagg CJ, Lin RL, Mezue M, Segerdahl A, Kong Y, Xie J, Tracey I. Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. J Neurosci 2013 Jul 10;33(28):11425–31. https://doi.org/10.1523/JNEUROSCI.3887-12.2013.
[72] Dmochowski JP, Datta A, Bikson M, Su Y, Parra LC. Optimized multi-electrode stimulation increases focality and intensity at target. J Neural Eng 2011 Aug;8(4):046011. https://doi.org/10.1088/1741-2560/8/4/046011.