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Research Article

Transcutaneous Auricular Vagus Nerve Stimulation (tVNS) can Reverse the Manifestations of the Long-COVID Syndrome: A Pilot Study

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Abstract

Background: SARS-Cov2 has caused unprecedented morbidity, and mortality across the world. Clinically, acute SARS-Cov2 infection ranges from asymptomatic disease to severe pneumonia with respiratory failure, acute kidney and/or cardiac injury. These severe manifestations are induced by hyperinflammation. After the acute phase, a chronic COVID syndrome can occur. Until now, there is no treatment for this chronic syndrome. We first suggested that the syndrome could be due to protracted intensity inflammation. In that way, we decided to test tVNS (transcutaneous Vagal Nerve Stimulation) on the syndrome because this procedure could reduce inflammatory processes. **Methods:** 20 patients suffering from chronic COVID syndrome were selected. The symptoms were carefully recorded, and a personal intensity scale was constructed for each patient. They received 10 daily tVNS stimulations using a Parasym device. Clinical assessments and measures of blood inflammatory factors were performed on days 0, 5 and 10. The data were analyzed using non-parametric statistical methods. **Results:** All the patients completed the study. The clinical manifestations of the disorder were globally similar for each patient: a wax-and-waning syndrome combining fatigue, pain, digestive problems and cognitive difficulties. All the patients improved dramatically during treatment. We did not observe a modification of the blood inflammatory circulating factors, invalidating the hypothesis of an effect of tVNS on a remaining inflammatory state. **Conclusions:** In this study, we showed that tVNS is an interesting tool for patients with chronic COVID syndrome. Even if this preliminary study did not confirm the hypothesis of protracted inflammation, it helped to propose an alternate explanation, based on the clinical observations supporting COVID-induced dysautonomia. We suggest that tVNS improves chronic COVID syndrome through a "sympathetic reset".

Keywords: *Long COVID syndrome, treatment, vagal nerve, tVNS, dysautonomia*

Introduction

The World Health Organization (WHO) announced on March 2020 that COVID-19, a novel coronavirus named officially SARS-CoV-2, provoked a pandemic that initially started in Asia. The characteristics of the virus and the pathophysiology of infection in humans are reported in good state-of-the-art papers [1,2]. Like other respiratory coronaviruses, SARS-CoV-2 is transmitted primarily via respiratory droplets. The first step of infection is virus binding to angiotensin-converting enzyme-2 (ACE2). ACE2 is a crucial SARS-CoV receptor in vitro and in vivo [3] that is expressed in the airways in epithelial cells, vascular endothelium cells and macrophages. The binding of SARS-CoV-2 to the receptor reduces ACE2 receptor expression in lung cells, maybe through down regulation; this provokes an acute lung injury because Sars-CoV-2 infection and the destruction of lung cells trigger a local immune response recruiting macrophages and monocytes that release cytokines and prime adaptative T and B cell immune responses. This can

resolve the infection; however, in some cases, a dysfunctional immune response occurs ("Cytokines storm") which causes severe lung and even other organs destruction [4,5]. This can cause septic shock and multi-organ failure. Older people and people with co-morbidities seem to be more likely to develop such dysfunctional immune responses. Extensive descriptions of the clinical characteristics of infected people were published in China and New York City [6,7]. In the American cohort, the most common presenting symptoms were cough, fever, dyspnea, myalgias, diarrhea and vomiting. Most of the patients had lymphopenia, and many had increased liver-function values and inflammatory markers. The profile of symptoms was similar in China, but with fewer digestive manifestations.

After infection, the clinical consequences have been classified in four categories: asymptomatic, mild, medium and severe. These categories were proposed by some authors after scoring the severity of the disease [8]. Commonly, the patients with medium and severe clinical states are hospitalized because they have acute respiratory insufficiency. Usually, patients with mild symptoms remain at home. As a consequence, there are consistent follow-up studies in survivors after discharge from the hospital, but only very few for patients who were not hospitalized. The cohort studies showed that 60 days after the recovery from the acute phase, only about 15% were completely free of any symptom [9]. Among the others none had fever or any signs or symptoms of acute illness. But the worsened quality of life was observed among 44% of patients; the most frequent symptoms were fatigue, dyspnea, joint pain and chest pain. The symptoms seem to be present for as much than 12 weeks after the onset of COVID-19 infection in between 5% and 35% of patients [10]. There is evidence that many patients, even those with initially "mild" illness, have a more complex course of illness than suggested by initial reports from Wuhan [11]. More and more authors report that COVID-19 infection can have long-term health consequences, even for initially asymptomatic people [12]. The situation of COVID-19 is uncertain until now, but there are examples of long-term effects, and even life-long consequences of infections with viruses. The best-known example is the infection by the Epstein-Barr virus [13]. We have no definite certitude about the course of COVID in the long term, but long COVID appears more and more to be an important concern [14]. The pathophysiology of this syndrome is unknown, but we formulate as a first hypothesis that it could be due to a protracted low-intensity hyperinflammatory process.

This is why we decided to organize an assay testing the effect of vagus nerve stimulation in patients suffering from long COVID. The rationale for this is that, besides to regulation of homeostasis by controlling heart rate, gastrointestinal motility, pancreatic endocrine and exocrine secretion, hepatic glucose production, and other visceral functions, the vagus nerve is also a major constituent of a neural reflex cholinergic mechanism that controls immune response and inflammation during pathogen invasion and tissue injury. It was also demonstrated that stimulation of efferent vagus nerve could inhibit inflammatory processes. This is called the cholinergic anti-inflammatory pathway [15,16]. Non-invasive vagus nerve stimulation (tVNS) can reduce pathologic inflammatory processes by inhibiting cytokine production. It was demonstrated to have clinical usefulness: tVNS was shown to attenuate the disease severity of inflammatory diseases like rheumatoid arthritis [17] and of Crohn disease [18]. In that way, tVNS has been proposed as a useful tool to prevent the consequences of COVID associated with hyperinflammation [19-22]. In other clinical situations than COVID, tVNS has shown to be a useful therapeutic tool to reduce acute respiratory distress syndrome [23]. In COVID-19 infection, there is only limited experience of the putative usefulness of tVNS. Staats et al. [24] reported that tVNS can reduce respiratory symptoms related to acute COVID infection in 2 patients. Furthermore, Boezaart and Botha [25] reported that in two other cases of stage 3 COVID-19 tVNS reduced drastically Interleukin-6 blood level.

In the present paper, we report the clinical and biological effects of tVNS in 20 patients suffering from a long COVID syndrome.

Materials and Methods

Selection of patients

Patients were recruited on a voluntary basis through the communication of the protocol on social networks. All of them were infected by COVID-19 for at least 12 weeks and continue to experiment with symptoms of the illness for all the period. The age was between 20 and 60 years. All the patients were free of major health problems before the infection.

Timetable of the study

Patients received 10 consecutive daily tVNS sequences of 35 minutes each on the left ear. They were clinically assessed before the first stimulation (day 0), and after 5 (day 5) and 10 (day 10) stimulations. They were also clinically assessed 7 days after the last stimulation (follow-up).

On day 0, 5 and 10, the physiological and biological parameters were also measured.

Procedure of stimulation

The stimulation was performed by using transcutaneous vagus nerve stimulation (tVNS) (Parasym device of Parasym Health, London, United Kingdom). The electrodes are included in a clip fixed at the left ear and more precisely at the tragus.

The delivered frequency of the current is 25 Hz and the pulse width is 250μs. The form of the signal is a square wave. The amplitude of the applied current is customized below the sensitivity of the patient to avoid slight discomfort. Depending on the sensitivity of the patient the applied current is varying between ±13 and ±35 mA measured at 3.65 Ohm. The duration of the stimulation is 45 minutes [26].

Assessment of the patient situation across the study

Clinical evaluation

Each patient was interviewed three times by independent investigators (including a physician). The clinical history was accurately reported, and all the symptoms at the intake in the survey were recorded. On the basis of those symptoms, we construct for each patient a personal evaluation by scoring the intensity of each symptom on a visual analogic scale rating from 0 to 10. The scores for each symptom were added and this cumulated score was used as a measure of the intensity of the syndrome for every single patient. The evolution of this score during the survey was chosen as the primary evolution criterion.

Secondary clinical criteria were the scores on the Beck Depression Inventory [27] and on the Pichot Fatigue Scale [28] that was chosen because all the patients were French-speaking. The Pichot Scale is widely used in medical practice and health psychology in France. Although initial development was aimed at examining depression through fatigue and anxiety responses, data have shown that the scale has a specific in evaluating fatigue as an isolated event.

Physiological parameters

The strength of the dominant hand ("grip test") was measured using a dynamometer (Electronic Hand Dynamometer Model EH101).

Blood oxygen saturation was estimated by a finger oximeter (Contec ™ pulse oximeter – Model CMS 50D1).

Biological parameters

The levels of 16 inflammatory cytokines (interleukin-1 α (IL-1α), IL-1β, IL-2, IL-6, IL-8, IL10, IL-12p70, IL-13, MCP-1, MIP1 α, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), IL1-RA, IL2-RA, IL6-R and GMCSF) were measured in serum samples using an electrochemiluminescence plate multiplex method (Q-Plex™ Human Cytokine Release Syndrome (16-Plex) Quansys Biosciences (Logan, UT, USA). Serum levels of ferritin and CRP and complete blood counts were determined using routine laboratory methods.

Statistical analysis

All the data were computed and analyzed using Prism 9 for Mac OS, GraphPad Software, LLC. Parametric and non-parametric tests were used.

Ethical concerns

The work has been carried out following the Code of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from all the patients and the privacy rights of human subjects have been observed.

The protocol was approved by an official medical Ethical Committee (CHU Brugmann, Ref.: CE 2020/154).

Results

Demographical data

A total of 20 outpatients were enrolled in the study, 12 females and 8 males. They had a mean age of 44 years (range: 20-59 years). All of them were free of significant medical history, with the exception of 1 man with a long-term stabilized bipolar I disorder. Before COVID 19 infection, 19 were professionally active, and 17 had a regular physical activity.

At the moment of the study, the mean delay from acute infection was 22 weeks (range: 12-32 weeks). Out of the 20 patients, only 6 were briefly hospitalized (less than 7 days), and none was admitted into an intensive care unit. The diagnosis was confirmed by PCR in 10 patients and on serological basis in 3 others; the remaining 7 patients were diagnosed only on a clinical basis, because at the beginning of the pandemic, PCR was performed only in hospitalized patients.

Clinical data

Symptoms before treatment

The most prominent symptoms during the week before the beginning of the treatment were systematically recorded for each patient. Their occurrence is shown in Figure 1. Fatigue was reported by all patients to be "abnormal", more like a feeling of exhaustion. 17 reported cognitive problems: difficulties to concentrate, memory problems, dysorthography were reported. Some reported that they became unable to speak previously known foreign languages. Pain was also frequently reported, mainly headache, thoracic pain and burning feelings in the limbs. Mild to moderate dyspnea was reported in 13 patients. Digestive problems (mostly acute diarrhea) were reported in 10 subjects. The other symptoms were reported with a lower prevalence.

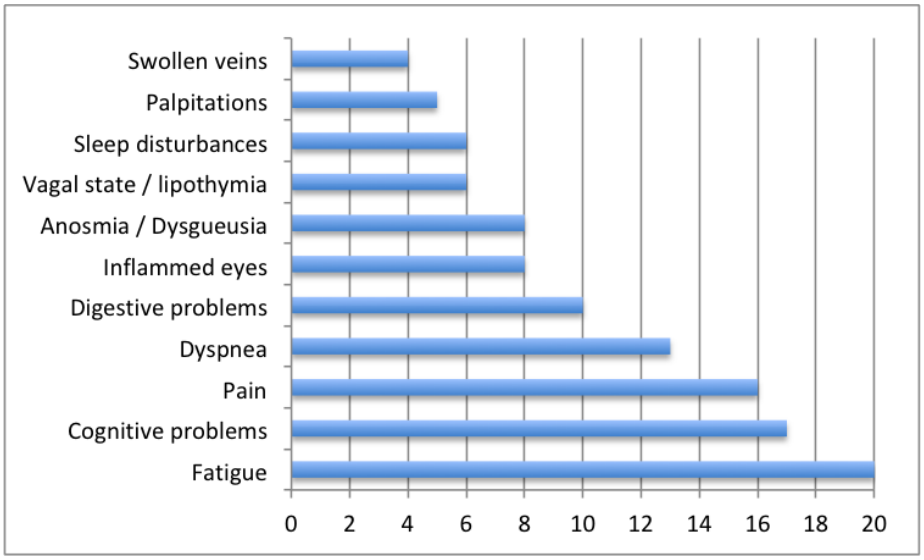
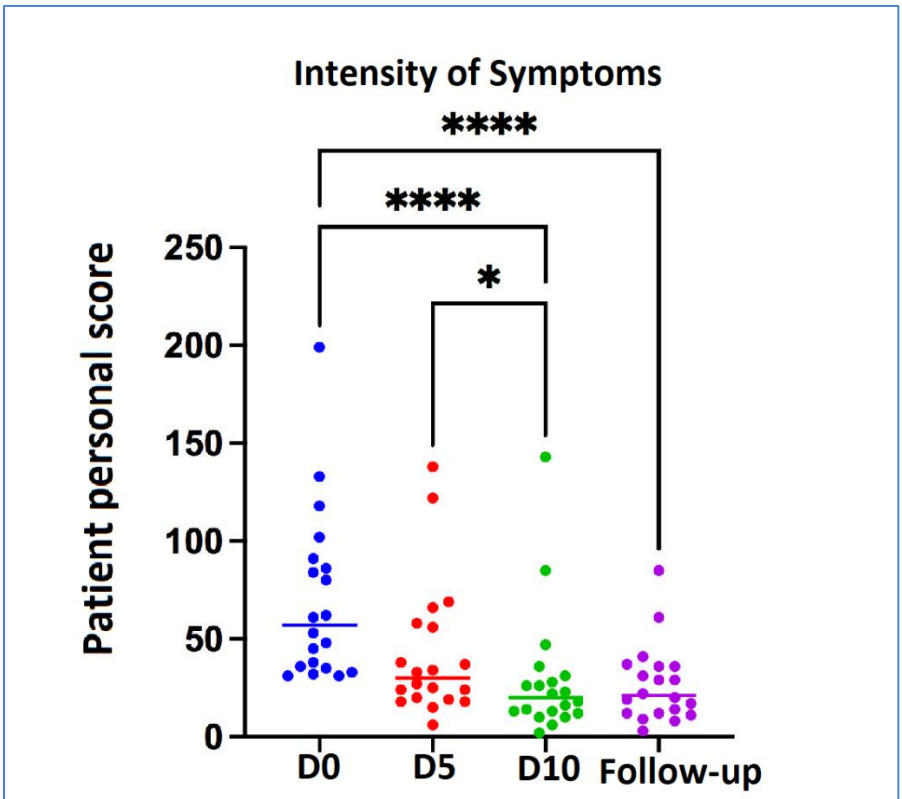


Figure 1. Prevalence of symptoms the week before starting the treatment (N=20 patients)

Evolution of the severity of the syndrome during and after treatment

As previously described, we asked each patient to compute each symptom before intake (day 0) according to a visual analogic scale rating from 0 to 10. The sum of all values permits the construct of a personal score considered as the evaluation of the severity of the syndrome. A similar evaluation was done after 5 stimulations (day 5) and after 10 stimulations (day 10). Furthermore, an additional rating was performed 7 days after the last stimulation (follow up). The evolution of the intensity of the syndrome is shown in Figure 2. A very significant improvement was observed after 10 stimulations (D0 *vs.* D10: $p<0.0001$). This improvement remains after ending stimulations (D0 *vs.* follow-up: $p<0.0001$).



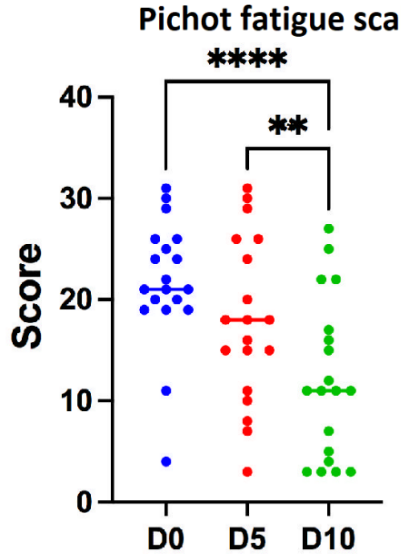
Friedman test	
P value	<0.0001
Exact or approximate P value?	Approximate
P value summary	****
Are means signif. different? (P < 0.05)	Yes
Number of groups	4
Friedman statistic	41.31

Dunn's multiple comparisons test	Rank sum diff.	Significant?	Summary	Adjusted P Value	
D0 vs. D5	20.50	No	ns	0.0723	A-B
D0 vs. D10	46.00	Yes	****	<0.0001	A-C
D0 vs. Follow-up	41.50	Yes	****	<0.0001	A-D
D5 vs. D10	25.50	Yes	*	0.0107	B-C
D5 vs. Follow-up	21.00	No	ns	0.0607	B-D
D10 vs. Follow-up	-4.500	No	ns	>0.9999	C-D

Figure 2. Evolution of the severity of the syndrome (personal scale), during treatment (day 0, day 5and day 10), and 1 week after ending stimulation (follow-up). The individual values and the median are shown. Non parametric Friedman statistics for paired comparisons were used and followed by post-hoc Dunn's multiple comparisons test.

Evolution of fatigue

Fatigue, the most prominent complain was measured by using the Pichot Fatigue Scale. As shown in Figure 3, there was a highly significant improvement after the treatment (D0 *vs.* D10, $p<0.0001$). The patients reported that, subjectively, the improvement remains 1 week after stopping the treatment.



Friedman test	
P value	<0.0001
Exact or approximate P value?	Approximate
P value summary	****
Are means signif. different? (P < 0.05)	Yes
Number of groups	3
Friedman statistic	28.48

Dunn's multiple comparisons test	Rank sum diff.	Significant?	Summary	Adjusted P Value	
D0 vs. D5	12.00	No	ns	0.1547	A-B
D0 vs. D10	31.50	Yes	****	<0.0001	A-C
D5 vs. D10	19.50	Yes	**	0.0047	B-C

Figure 3. Evolution of fatigue estimated by Pichot fatigue scale during treatment (day 0, day 5 and day 10). The individual values and the median are shown. Non parametric Friedman statistics for paired comparisons were used and followed by post-hoc Dunn's multiple comparisons test.

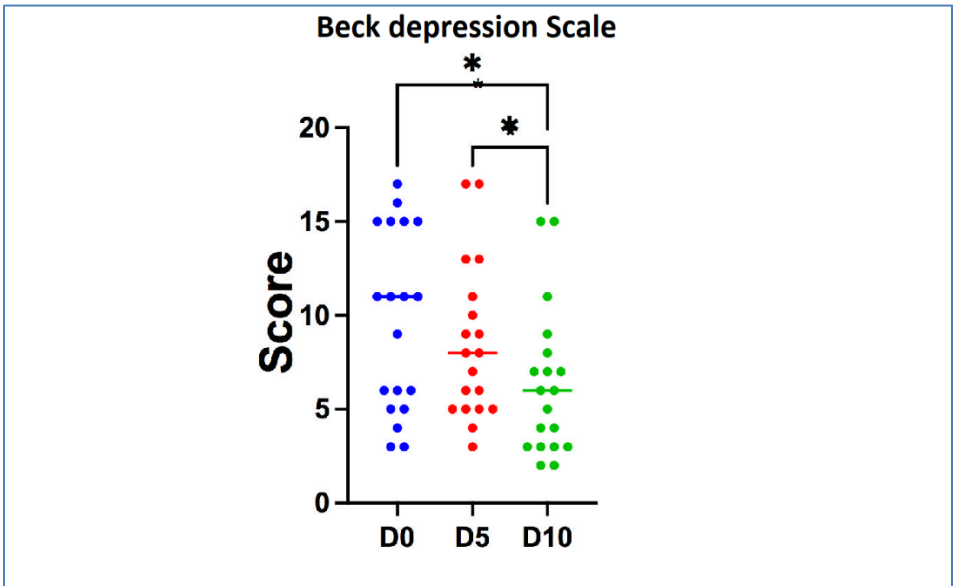
Evolution of depressive feelings

The data are shown in Figure 4. A significant decrease of the score on the Beck depression scale was observed (D0 *vs.* D10, $p<0.05$). Interestingly, none of the subjects reported subjectively to be "depressed" at the beginning of the study, but rather "sad" or "preoccupied". At the end of the study, they reported not to be "less depressed", but rather "more optimistic".

Physiological parameters

The arterial pressure and the cardiac rate were measured on lying and standing position before and after each session of tVNS. No significant modifications were observed.

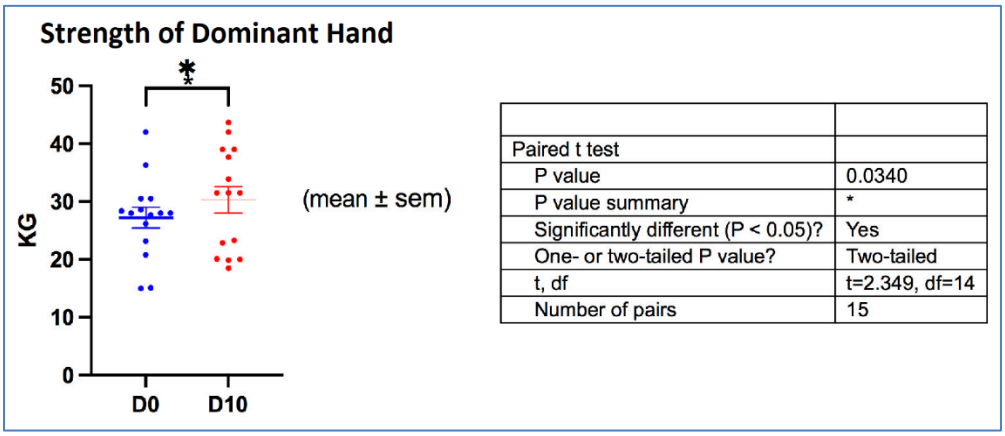
In Figure 5 is shown the evolution of the strength of the "grip" of the dominant hand. A moderate but significant increase between day 0 and day 10 was observed ($p<0.05$). Similarly, we observed a small but definite increase of arterial blood O_2 saturation (D0 *vs.* D10, $p<0.05$) (figure 6).



Friedman test	
P value	0.0031
Exact or approximate P value?	Approximate
P value summary	**
Are means signif. different? (P < 0.05)	Yes
Number of groups	3
Friedman statistic	11.57

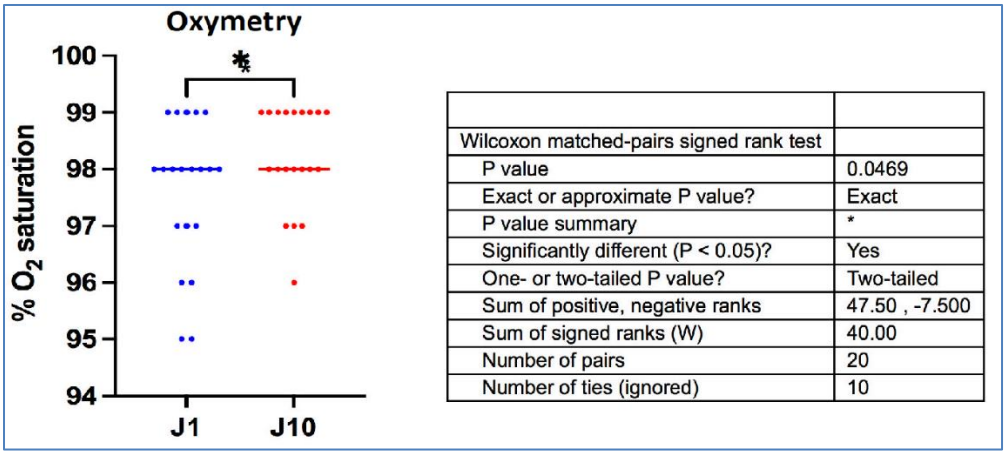
Dunn's multiple comparisons test	Rank sum diff.	Significant?	Summary	Adjusted P Value
D0 vs. D5	1.500	No	ns	>0.9999
D0 vs. D10	18.00	Yes	*	0.0105
D5 vs. D10	16.50	Yes	*	0.0223

Figure 4. Evolution of the Beck depression scale scores during treatment (day 0, day 5 and day 10). The individual values and the median are shown. Non parametric Friedman statistics for paired comparisons were used and followed by post-hoc Dunn's multiple comparisons test.



Paired t test	
P value	0.0340
P value summary	*
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
t, df	t=2.349, df=14
Number of pairs	15

Figure 5. Comparison of the strength of the dominant hand (grip test) before and after treatment (day 0 and day 10). Wilcoxon matched-pairs signed rank test was used for comparisons.



Wilcoxon matched-pairs signed rank test	
P value	0.0469
Exact or approximate P value?	Exact
P value summary	*
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
Sum of positive, negative ranks	47.50 , -7.500
Sum of signed ranks (W)	40.00
Number of pairs	20
Number of ties (ignored)	10

Figure 6. Evolution of arterial blood oxygen saturation before and after treatment (in % O_2 arterial blood saturation). The means were compared by using paired *t*-test.

Biological data

The measures of the concentrations of inflammatory cytokines at day 0, day 5 and day 10 are shown in Table 1 [29]. The details of the analysis are not shown, but there were no significant differences between the groups. The pro-inflammatory cytokine levels measured did not allow us to demonstrate an inflammatory state in the patients and were comparable at the three times of the study. Furthermore, CRP and ferritine were also measured for each patient at day 0 and were for all of them in the normal range (data not shown).

Table 1. Blood inflammatory factors concentrations at day 0, day 5 and day 10. Reference values in healthy controls using an equivalent method (Multiplex electrochemiluminescence). IQR: Interquartile Range

		Healthy Controls	Visit 1			Visit 2			Visit 3			
	Limit of quantification	IQR*	N	Median	IQR		N	Median	IQR		N	Median	IQR	
hIFNy (pg/ml)	0.18	1.5-3	20	1.26	0.95	2.03	20	1.21	0.92	2.02	19	1.23	0.95	2.43
hIL-1b (pg/ml)	13.72	4- 4.54	20	<LOQ	<LOQ	<LOQ	20	<LOQ	<LOQ	<LOQ	19	<LOQ	<LOQ	<LOQ
hIL-1ra (pg/ml)	12.48	79.9-97.6	20	281.7	198.6	382.6	20	249	187.5	357.1	19	251.6	178.1	429.8
hIL-2 (pg/ml)	0.11	9.4-15.9	20	3.01	1.87	4.66	20	3.19	2.04	4.65	19	2.89	2.12	3.7
hIL-2Ra (pg/ml)	28.5	32.2-79.7	20	342.2	300.9	425.6	20	333.9	270.9	366.6	19	325.4	280.7	368.3
hIL-6 (pg/ml)	0.59	9.87-13.3	20	2.2	1.17	3.95	20	1.85	1.15	2.32	19	2.18	1.47	3.39
hIL-8 (pg/ml)	3.6	26.5-33.3	20	11.91	7.63	15.98	20	10.35	8.39	16.81	19	9.48	8.07	15.35
hIL-10 (pg/ml)	4.78	4.34-8.34	20	6.47	5.64	11.67	20	6.43	5.64	9.63	19	6.77	5.64	9.23
hIL-12p70 (pg/ml)	5.35	19.6-56.3	20	30.24	30.24	30.24	20	30.24	30.24	30.24	19	30.24	30.24	30.24
hIL-13 (pg/ml)	0.59	7.19-9.29	20	1.61	0.93	3.22	20	1.72	1.16	2.43	19	1.56	1.16	3.25
hMCP-1 (pg/ml)	3.6	17.8-26.7	20	312.2	230.4	469.2	20	311	226.7	452.5	19	298.6	233.9	470.7
hMIP-1a (pg/ml)	3.57	7.26-9.42	20	30.74	20.26	66.47	20	24.89	20.43	39.79	19	27.07	20.59	35.23
hTNFa (pg/ml)	1.18	5.11-7.23	20	6.08	4.74	7.58	20	5.18	4.55	6.37	19	4.98	3.95	7.54

Safety data

All the patients completed the study (no drop-out).

The side effects of tVNS are presented in Figure 7. We consider as a side effect a new symptom that occurs 0 to 24 hours after the last tVNS. Most patients report no side effect at all during the whole stimulation period. All the reported

symptoms resolved spontaneously before the following stimulation, except for swelling of the popliteal fossa experienced by one patient.

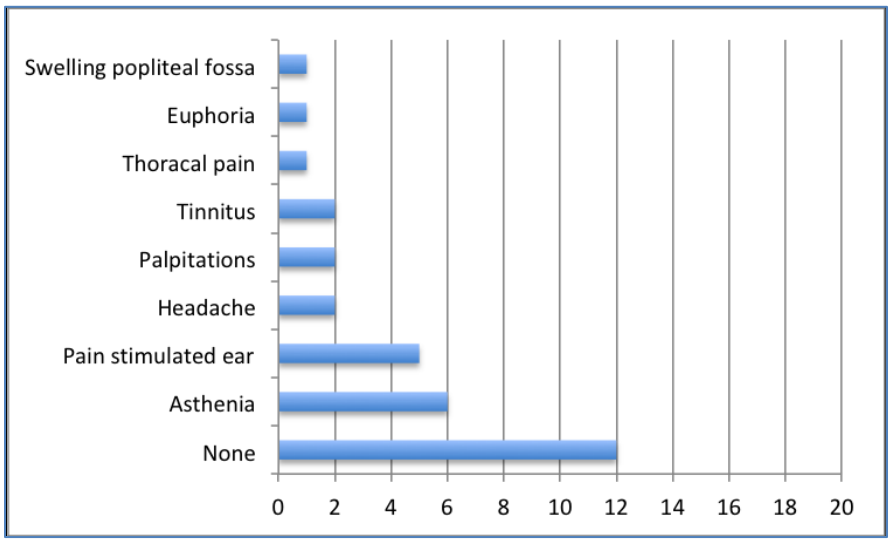


Figure 7. Side effects: new symptom occurring 0 to 24 hours after last stimulation (N=20).

Discussion

This study was the first one to explore the putative therapeutic effect of tVNS in the long-COVID syndrome. The rationale was that if hyper inflammation is an important mechanism of the pathophysiology of the acute phase of COVID infection, it could be possible that the long-term remaining symptoms are consequences of protracted low-intensity chronic inflammation. In that way, we decided to test the efficacy of tVNS that has anti-inflammatory effect. The main observation is the dramatic remission of the invalidating symptoms in all the 20 patients of the study.

For ethical reasons, the trial was organized as a pilot study. Therefore, it is necessary to question the part of a placebo effect in the observed clinical improvement. The psychosocial conditions commonly related to a placebo effect are present, especially important expectations of efficacy of a new innovative treatment, and also an empathic attitude of the research team [30]. We cannot exclude such a placebo effect, but we believe that, if present, it represents only a minor part of the therapeutic response. The first reason is the fact that tVNS does not alleviate the symptoms of post-COVID immediately, but only after 6 to 10 stimulations. Secondly, the remission remains stable even 7 days after ending stimulation. And thirdly, there was not only a remission of symptoms reported subjectively through questionnaires, but there was also a moderate but definite improvement of physiological parameters like muscular strength and blood oxygen saturation. Moreover, all the patients showed an impressive improvement that allows most of them to return to their previous professional and physical activities. Therefore, our study demonstrated unequivocally that tVNS is an effective tool for the treatment of post-COVID syndrome, even if empathy and psychosocial support are important in the same way than for medical interventions in general.

Fatigue, or more precisely an overwhelming sensation of exhaustion, was reported by all patients to be the key problem inducing a feeling of helplessness. Fatigue decreased dramatically during treatment; this was a major determinant for the sensation of remission. The treatment was effective for all symptoms, even if some of them remain longer than others: especially, abdominal pain and diarrhea were commonly the last to improve.

We observed a decrease in mood symptoms during the trial. We do not believe that this is due to a specific antidepressant effect of tVNS. In our opinion, but also in the opinion of the subjects, depressive symptoms disappeared as the consequence of the remission of the invalidating manifestations of long-COVID.

The study was constructed on the hypothesis that protracted inflammation could be responsible for the symptoms of post-COVID syndrome. This is supported by a very recent publication of Sun et al. [31]. They found an increase of plasma cytokine IL-4 in patients with long-COVID syndrome and also a correlation between IL-6 concentration and age of the participants and severity of the symptoms. We were unable to replicate their observations, but we did not use a similar methodology. More precisely, we did not observe a decrease of any plasma inflammatory factor during tVNS protocol; however, unfortunately, we did not measure IL-4 concentrations.

If tVNS can reduce long-COVID syndrome without affecting peripheral inflammatory factors through a "top-down" mechanism, an alternate hypothesis could be that it affects the brain through a "bottom-up" stimulation of ascending fibers of the vagal nerve. The first authors who pointed the effect of vagal nerve on the brain were Bailey and Bremer in 1938 [32]. Such brain effects have major therapeutic implications: vagal nerve stimulation has been proven to be useful in the treatment of refractory epilepsy [33,34] and of drug-resistant depression [35,36]. Even if most publications reported the need for implantable material for those purposes, non-invasive transcutaneous methods are effective as well [37].

If tVNS does not correct a protracted inflammatory process, a direct effect on the brain could be an alternate explanation of the efficacy of tVNS in long-COVID. This should be in accordance with observations showing an involvement of the nervous system including the brain in COVID-19 infection [38-40]. The neurological symptoms related to COVID-19 are multiple and heterogeneous, not only in the acute phase, but also in the long-COVID syndrome. COVID-induced dysautonomia is evoked [41,42] and would be related to the frequent occurrence of symptoms like fatigue, brutal modifications of the heart rhythm, acute episodes of diarrhea, fainting, and sleep disturbances. We typically observed such symptoms in the present study, as reported in Figure 1. It is important to mention that dysautonomia can be provoked by other viruses, like hepatitis C [43], Epstein-Barr virus [44], and HIV [45].

Conclusion

Long-COVID syndrome appears more and more as a new epidemic problem that follows the acute infection with COVID19. According to recent data, it concerns about one-third of all the persons who were infected, even those who had only moderate symptoms during the acute phase of the disease. In many patients, this long COVID syndrome is a very invalidating situation with uncertain spontaneous improvement. The causes of the syndrome are unknown, but it seems to be due, at least partly, to a long-lasting impairment of the nervous system, maybe through the persistence of the virus in neural tissue. In most patients, this impairment does not appear to be related to any inflammatory condition. Until now, there were no validated therapeutic tools for long COVID. We present here the first evidence that auricular transcutaneous vagal nerve stimulation (tVNS) is a potent therapeutic tool in that instance. In a group of 20 patients suffering of long-COVID, without definite comorbidity, we observed that tVNS dramatically alleviates most of the symptoms in less than 14 days.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

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Highlights

- Long-COVID syndrome is a frequent invalidating manifestation of COVID 19 infection.
- The common course of the syndrome is a long-term fluctuating situation with several symptoms suggesting a dysautonomic situation.

- Until now, there was no efficacious therapeutic approach for this clinical situation.
- In this study, we showed, for the first time, that transcutaneous vagal nerve stimulation (tVNS) is a simple, safe, and effective treatment for this syndrome.

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