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Assessing The Autonomic Effect Of Vagal Nerve Stimulation With Low Level Lasers By Heart Rate Variability

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Abstract

Vagus nerve stimulation (VNS) has been approved to treat refractory epilepsy, and for other conditions. The invasive nature of the electrical stimulus, which requires surgical implantation of electrodes around the cervical vagus nerve, is a technical limitation. The low-level laser therapy (LLLT) is actually considered a non-invasive technique, and has been increasingly used in diverse areas of medical practice. We developed a pilot study using LLLT for VNS in normal subjects, and assessing its effect on the autonomic nervous system (ANS) by the heart rate variability (HRV) methodology. Fifteen normal participants from 22 to 46 years, divided in three groups of 5 subjects each, paired in age and gender, were studied applying VNS using LLLT by lasers of different frequencies: RED Laser (in 5 subjects); VIOLET Laser (5 subjects); and RED/VIOLET Laser (5 subjects). The study included three experimental conditions: Basal record (10 minutes), VNS (10 minutes), and Post-VNS (10 minutes). The LF/HF ratio was considered, because it provides a measurement of the parasympathetic/sympathetic balance. When the RED laser was used for VNS there was a predominance of the parasympathetic activity. On the contrary, the stimulus with VIOLET laser provoked a sympathetic prevalence. Similarly, to the stimulus with the RED laser, when the RED/VIOLET laser was applied there was a predominance of the parasympathetic activity. As a conclusion, this study showed that VNS using LLLT is a non-invasive and safe method, and should be considered for future protocols to recover prasympathetic/sympathetic nervous system balance in different conditions.

INTRODUCTION

Electrical stimulation of the cervical vagus nerve has been approved for the treatment resistant epilepsy. In Europe and the USA for over 15 years has been used to treat about 50,000 epilepsy patients.(1-4) Vagus nerve stimulation (VNS) is also an approved therapy for treatment of resistant depression, and has been investigated as a potential therapy for a wide range of conditions including heart failure, Alzheimer's disease, obesity, chronic pain, inflammation, and tinnitus.(5-13)

It is interesting that VNS has proven effective in pilot studies for the treatment of heart failure. Heart failure is a leading cause of mortality and it is estimated that 50% of people die within 5 years of diagnosis. Heart failure is characterized by decreased parasympathetic and increased sympathetic nerve activity. Therefore, if VNS can be shown to influence this autonomic balance toward parasympathetic predominance it could provide a method to correct imbalance in heart failure patients, and in other diseases.(7, 8, 14-18)

On the other hand, the use low-level laser therapy (LLLT) is actually considered a non-invasive technique, and has been also increasingly used in diverse areas of medical practice, such as prevention of tissue death, pain relief, reduction of inflammation, regenerative medicine, traumatic brain injury, , spinal cord injury, and stroke, autism, etc.(19-25)

One factor that may hinder larger trials of VNS is the invasive nature of VNS. VNS requires surgical implantation of a bipolar electrode around the cervical vagus nerve and implantation of a generator subcutaneously in the thoracic wall. This is associated with technical and surgical complications including wound infection, cardiac arrhythmia under test stimulation and electrode malfunction [9]. In addition, side effects include hoarseness, dysphagia, cough and pain.(3, 13, 17, 26, 27)

Given the number of conditions that VNS has the potential to benefit, a simpler, less invasive approach would enable treatment of significantly larger numbers, like the use of VNS using low level laser therapy (LLLT). Nonetheless, the studies using LLLT for VNS are scarce.(28)

In this study we investigated the effects of VNS on cardiovascular autonomic function in healthy participants by measuring heart rate variability (HRV), and using lasers of different frequencies.

MATERIAL AND METHODS

Fifteen normal participants from 22 to 46 years, divided in three groups of 5 subjects each, paired in age and gender, were studied applying VNS using LLLT by lasers of different frequencies: RED Laser (in 5 subjects); VIOLET Laser (5 subjects); and RED/VIOLET Laser (5 subjects). The study included three experimental conditions: Basal record (10 minutes), VNS (10 minutes), and Post-VNS (10 minutes). HRV was assessed to evaluate the autonomic system.

LLLT was applied by a neurologist (MCA) in the neck, left side. Subjects were continuously monitored by bed side monitors (Electrocardiogram, blood pressure, and body temperature) to early diagnose any complication. Participants received LLLT administration with the Erchonia® EAL Laser (RED, VIOLET and RED/VIOLET lasers).

<u>Heart rate variabiliy</u>

Electrocardiogram (ECG) was recorded with the MEDICID-05 (NEURONIC, S.A.) with disposable electrodes placed on the chest in positions CM2 and V5 and using a sampling frequency of 200 Hz. Filters were set for a band spectrum of 0.5-50 Hz. The ECG was recorded in every experimental session.

Bipolar ECG recordings were exported offline as ASCII files to a software tool developed by our staff written in our Lab. Accurate “R” peak automatic detections obtained with the software´s algorithms were always visually checked and properly corrected, when it was necessary, by a member of the staff. Pre-processing of RRI sequences were applied to the R-R series.

Selected processing parameters allowed the study of spectral frequencies from 0.02 Hz to 0.4 Hz, including the very low frequency band (VLF) band from 0.023 to 0.04 Hz, the low frequency band (LF) from 0.04-0.085 Hz; the mid-frequency band (MF) from 0,085-0.15 Hz, and for the high frequency band (HF) from 0.15-0.40 Hz. Absolute and normalized (%) values were considered for each spectral band. The ratio LF/HF was also calculated for the analysis. HRV indices calculated in the time-domain were also calculated as detailed elsewhere. The methodology for ECG recording and HRV processing can be found elsewhere. (29-33)

Informed consent was obtained for all participants. The Ethical Committee of the Institute of Neurology and Neurosurgery approved according to the “World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects”.(34)

RESULTS

Although all frequency and time domain parameters were calculated, for this pilot study we only considered the LF/HF variable, because it provides a measurement of the parasympathetic/sympathetic balance.(29-31) It is important to remark that we did not detect any cardiovascular complication with the use of bedside monitors.

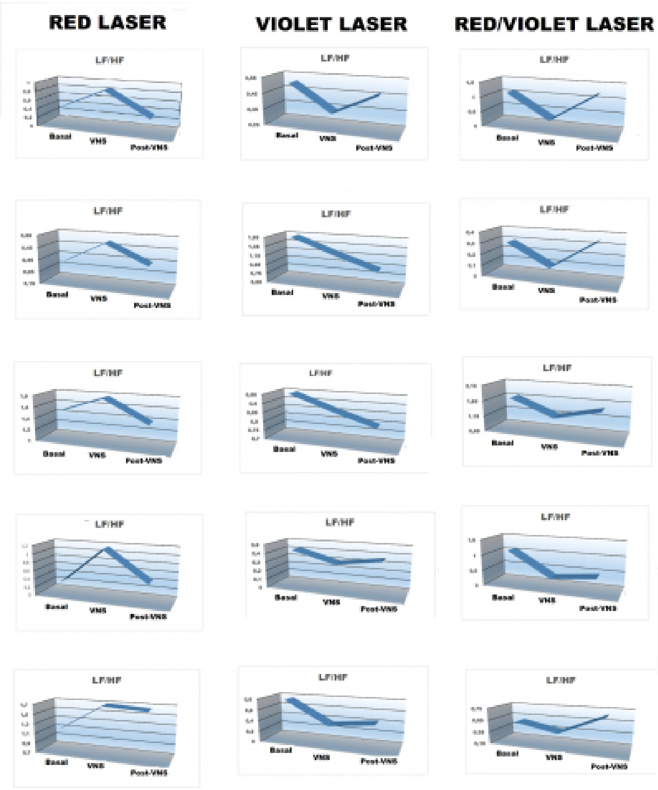
In figure 1, the ratio LF/HF values are presented for RED, VIOLET, and RED/VIOLET lasers, considering the three experimental conditions: Basal, VNS, and Post-VNS. When the RED laser was used there was a clear predominance of the parasympathetic activity when the VNS was applied in the 5 participants, compared to the Basal experimental condition (incremented values of the LF/HF ratio). This parasympathetic prevalence was afterwards almost reduced to the basal condition values. Only in one subject the parasympathetic predominance remained in the Post-VNS experimental condition.

On the contrary, the stimulus with VIOLET laser provoked a sympathetic prevalence in the VNS condition (reduced values of the LF/HF ratio), which decreased to basal values in 3 participants. In 2 subject there was a progressive sympathetic predominance from Basal, to VNS, and Post-VNS experimental conditions.

Similarly, to the stimulus with the RED laser, when the RED/VIOLET laser was applied the values of the ratio LF/HF a clear predominance of the parasympathetic activity in the 5 participants, compared to the Basal experimental condition (increment values of the LF/HF ratio). This parasympathetic prevalence was reduced almost to the basal condition values in the Post-VNS phase. Only in one subject the parasympathetic predominance remained in the Post-VNS experimental condition.

Figure 1

In figure 1, the ratio LF/HF values are presented for RED, VIOLET, and RED/VIOLET lasers, considering the three experimental conditions: Basal, VNS, and Post-VNS.



DISCUSSION

VNS is currently used to treat refractory epilepsy and is being investigated as a potential therapy for a range of conditions, including heart failure, tinnitus, obesity and Alzheimer's disease. (1-4) However, a taking in consideration the number of conditions that VNS has the potential to benefit, a simpler, less invasive method would enable treatment of significantly larger numbers, like the use of VNS using LLLT.(19, 22, 25, 35, 36)

Some authors have shown that VNS can alter cardiovascular autonomic control in healthy humans and highlights the role of the parasympathetic/sympathetic nervous system balance in mediating VNS effects.(17, 37-41)

Increased sympathetic activity and/or reduced parasympathetic nerve activity as indicated by HRV is not only a powerful and independent predictor of poor prognosis in patients with cardio vascular disease, but also a risk factor for mortality in healthy populations. Lower vagal (HF) and higher sympathetic (LF) tone are considered to be predictors of morbidity and mortality in cardiovascular samples. (18, 42-44)

We recently demonstrated that HRV is a reliable method to assess the integrity of the neural control of the caudal brainstem centers on the hearts of patients in coma and to predict patient mortality. HRV indices showed that they can efficiently predict mortality in these patients in coma. The LF/HF index resulted reduced in non-survivors.(45, 46)

The HF component is considered to be a marker of the parasympathetic activity, meanwhile LF is a marker of sympathetic function, and relatively low of parasympathetic activity. Nonetheless, the sympatho-vagal balance is accurately reflected by the fractional distribution of power across the frequency spectrum. This balance can be assessed by the relation between LF and HF components. Hence, an increase of the LF/HF ratio indicates a sympathetic predominance, meanwhile a decrement of its values signposts a parasympathetic prevalence.(29-31, 33, 45, 46)

Clancy et al. reported, using electrical stimulation of the auricular branch of the vagus nerve distributed to the skin of the ear, that VNS can increase HRV and reduce sympathetic nerve outflow, which is desirable in conditions characterized by enhanced sympathetic nerve activity, such as heart failure. These authors explained these findings on the issue that VNS could activate the caudal ventrolateral medulla to inhibit the rostral ventrolateral medulla and thus reduce sympathetic output. In addition, an activation of the dorsal motor nucleus of the vagus and the nucleus ambiguous to increase parasympathetic activity. (17) Yiloski et al., also using electrical stimulation of the auricular branch of the vagus nerve distributed to the skin of the ear, reported that VNS induced a shift in autonomic function from sympathetic preponderance towards parasympathetic predominance.(41) Some authors have emphasized that the cardiovascular system is under deep sympathetic influence in children with epilepsy, and that VNS seems to provide a substantial improvement by achieving increased parasympathetic effects in short-term therapy.(47-49) Several authors have stated that an autonomic imbalance demonstrating an increased sympathetic activity and a reduced parasympathetic activation is involved in the development and progress of epileptic seizures. Therefore, activation of the parasympathetic by VNS is a powerful tool for the treatment of intractable epilepsy.(1, 4, 42, 50-52)

It was interesting that according to our results when the RED and RED/VIOLET lasers were used for VNS used was a clear predominance of the parasympathetic activity (incremented values of the LF/HF ratio)., meanwhile with the VIOLET laser, a predominant sympathetic function was found. These findings should be considered for future protocols of VNS using LLLT.

Of course, the limitations of this pilot study is the reduce sample of participants. Nonetheless, we have not found any publication using LLLT for VNS.

As a conclusion, this study showed that VNS using LLLT is a non-invasive and safe method, and should be considered for future protocols to recover parasympathetic/sympathetic nervous system balance.

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