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Effects of transcranial direct current stimulation on esophageal motility in patients with gastroesophageal reflux disease

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HIGHLIGHTS

- Prolonged excitatory tDCS over the esophageal motor cortical cortex can significantly modify esophageal peristalsis in gastroesophageal reflux disease (GERD) patients.
- Anodal tDCS have shown a strong effect on distal waves mean amplitude and percentage of pathological waves in patients with non-erosive reflux disease (NERD).
- Erosive reflux disease (ERD) parameters were not significantly modified by tDCS. These data strengthen the hypothesis of a different pathophysiology and progression into a chronic (i.e. unresponsive) form in patients with ERD.

ABSTRACT

Objective: To evaluate the effects of transcranial direct current stimulation (tDCS) on esophageal peristalsis in patients with gastroesophageal reflux disease (GERD).
Methods: Patients with GERD preliminary diagnosis were included in a randomized double-blind sham-controlled study. Esophageal manometry was performed before and during transcranial direct current stimulation (tDCS) of the right precentral cortex. Half of patients were randomly assigned to anodal, half to sham stimulation. Distal waves amplitude and pathological waves percentage were measured, after swallowing water boli, for ten subsequent times. Last, a 24 h pH-bilimetry was done to diagnose non-erosive reflux disease (NERD) or functional heartburn (FH). The values obtained before and during anodal or sham tDCS were compared.
Results: Sixty-eight patients were enrolled in the study. Distal waves mean amplitude increased significantly only during anodal tDCS in NERD ($p = 0.00002$) and FH subgroups ($p = 0.008$) while percentage of pathological waves strongly decreased only in NERDs ($p = 0.002$).
Conclusions: Transcranial stimulation can influence cortical control of esophageal motility and improve pathological motor pattern in NERD and FH but not in erosive reflux disease (ERD) patients.
Significance: Pathophysiological processes in GERD are not only due to peripheral damage but to central neural control involvement as well. In ERD patients dysfunctions of the cortico-esophageal circuit seem to be more severe and may affect central nervous system physiology.

1. Introduction

Gastroesophageal reflux disease (GERD) is a widespread disorder affecting the 10–20% of population in Western countries with an increasing prevalence in the last two decades. GERD can be subdivided into erosive (ERD) and non-erosive (NERD) subtypes, the former being diagnosed if pathological acid exposure and normal endoscopic examination occur while the latter if endoscopic evidence of mucosal injury is found. Patients affected by recurrent chest pain but with negative acid exposure and normal endoscopy are usually considered as functional heartburn (FH). Clinical manifestations include esophageal (e.g. heartburn, regurgitation, dysphagia) and extraesophageal (e.g. cough, asthma,

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hoarseness) symptoms (Lacy et al., 2010). GERD can severely impair quality of life and sometimes worsen to life-threatening conditions such as Barrett's esophagus and esophageal adenocarcinoma (Shaheen and Ransohoff, 2002). Ineffective esophageal motility (IEM) is the most common manometric finding, defined as distal esophageal hypocontractility in at least 30% of wet swallows, characterized either as low-amplitude peristaltic waves (<30 mmHg), low-amplitude simultaneous or not propagated waves, or absent peristalsis (Spechler and Castell, 2001).

In early studies with transcranial magnetic stimulation (TMS) on healthy subjects, Aziz et al. (1995) suggested that stimulated cortico-esophageal pathways share the same population of brainstem motor neurons activated during swallowing and vagal stimulation, while electromyographic responses evoked by focal TMS succeeded in identifying the topographic representation of the esophagus on the cerebral cortex (Aziz et al., 1996). Transcranial direct current stimulation (tDCS) is a safe and non-invasive form of neurostimulation involving purely modulatory effects on human cortex and is burdened with fewer technical artifacts such as acoustic noise and muscle twitching in comparison with TMS, making it more suitable for double-blind, sham-controlled studies (Tanaka and Watanabe, 2009). Due to the area of surface electrodes the device ensure a wide area of cortical stimulation but, on the other hand, low spatial resolution and poorly selective effects. Anodal tDCS applied to the human cortex immediately increases cortical excitability while cathodal tDCS results in the opposite effect (Nitsche et al., 2008). Long-lasting sessions (over 10 min) can alter cortical excitability for up to 1 h, depending on the intensity of the current and the duration of the stimulation. Short-term effects are due to an action on membrane polarization thus modulating the conductance of sodium and calcium channels, while long-term effects are consequential to modulation of *N*-methyl-D-aspartate (NMDA) receptors resembling long-term potentiation and long-term depression (Nitsche et al., 2003; Antal et al., 2006). A recent study using tDCS to modulate pharyngeal motor cortex in healthy subjects showed a positive influence of anodal currents on cortico-bulbar excitability (Jefferson et al., 2009).

Aim of the present study was to investigate the effects of anodal tDCS on esophageal peristalsis in a randomized double-blind sham-controlled study in patients with GERD.

2. Methods

2.1. Patients

We recruited adults between 18 and 65 years of age with GERD symptoms according to a reflux disease questionnaire (RDQ) score >12 based on symptoms over the previous 2 weeks (Shaw et al., 2001), a positive response to a proton pump inhibitor (PPI) trial and a disease duration not inferior to 6 months. Prior to enrollment each patient underwent an esophageal endoscopy in order to differentiate ERD from NERD, and withdrew PPI therapy at least 7 days before. The severity of esophagitis was assessed according to the Los Angeles classification (Armstrong et al., 1996). Patients affected by neurological, neoplastic or systemic diseases, or taking drugs which could affect central nervous system or esophageal motility were excluded from the study. Clinical evaluations and interviews were conducted by a neurologist and a surgeon expert in digestive motility disorders, who made the final decisions with respect to eligibility.

2.2. tDCS settings

A continuous current was delivered via two electrodes measuring 5×7 cm using a battery-driven constant current stimulator (Magstim DC Stimulator). All patients comfortably seated and in a safe environment wore a tight-fitting plastic swimmer's cap to mark the optimum site of stimulation. Afterward, the cap was removed and electrodes were fixed thanks to elastic head straps placed around the head circumference, according to standard procedures as suggested in several studies (Da Silva et al., 2011). Cz was located at the vertex using the international "10–20" system (Herwig et al., 2003) and, in agreement with previous studies, the active electrode was placed with its center 4 cm in front and 5.5 cm lateral to the vertex on the right hemisphere in order to stimulate the "esophageal cortical area", while the reference electrode was placed above the contralateral mastoid (Aziz et al., 1996). The stimulation side was chosen because esophageal function on human cortex has been reported to be asymmetric, prevailing on the right rather than left side in most of studies. Nevertheless, previous studies have reported that evoked potentials can be recorded from esophageal muscles following TMS on both hemispheres, therefore stimulating the "non-dominant" hemisphere should not significantly affect esophageal response (Aziz et al., 1996; Hamdy et al., 2001). The mastoid was chosen because it ensured a wider and deeper pattern of stimulation in comparison with supraorbital montage (Datta et al., 2011). For anodal stimulation a current of 1.5 mA intensity was delivered for the whole duration of the esophageal manometry (on average 20 min). Unfortunately, the stimulation time could not be previously set because it was determined by the duration of manometry. Nevertheless, differences in stimulation time between subjects were minimal and we evaluated the on-line rather than post-tDCS off-line effects, therefore we believe this variability could unlikely affect results.

The current intensity applied for stimulation is in the range if compared with most of recent studies (Brunoni et al., 2012). For sham stimulation the device was turned off after 30 s of stimulation at the same intensity in order to give to the patients a local temporary tingling sensation and a feeling of stimulation which has been reported to be indistinguishable from anodal tDCS (Gandiga et al., 2006; Jaberzadeh et al., 2014). No adverse effects were observed during and after stimulation.

2.3. Esophageal manometric and pH-metric settings and parameters

An appropriate flexible probe (Mui Scientific, E4555) closed tip, 4 radial ways with bearing point, has been used for the tests; perfusion equipment involves an azotes infusion pump: "International Biomedical Inc. mod. 745–0100"; recording of data by an auto-calibrating polygraph "Narco Bio System MMS 200" connected to a PC by a dedicated software for automatic analysis of acquired data. Lower esophageal sphincter (LES) pressure was obtained thanks to four pressure sensors separated by intervals of 5 cm and placed internally at different sides of the probe, the distal esophageal body was assessed 3 cm over the LES: both these parameters were measured in mmHg. Regarding 24 h pH-metry, a Microdigitrapper or a Digitrapper pH recorder were randomly used for each patient. Probes (placed 5 cm above the manometrically determined upper border of LES) were calibrated in a standard buffer solution (pH = 7 and 1) either before and after monitoring. A pH Software Analysis Program was used for data analysis. A Bilitec 2000 fibreoptic probe was used to detect bile reflux.

2.4. Study protocol

The study was conducted in the digestive motility section in a safe and quiet environment, in accordance with the declaration of Helsinki and was approved by local ethics committee (Rickham, 1964). A written informed consent was obtained from each patient before starting the protocol. Eligible patients were randomly assigned in a 1:1 ratio to one of the two groups: one group