A randomized single blinded parallel study to investigate the effect of physiological modulation of the ANS using deep slow breathing on oesophageal pain hypersensitivity in patients with NERD – INTERIM ANALYSIS

Modulation of the autonomic nervous system (ANS) as a therapeutic measure for the treatment of pain is well described in the literature (1-3). Work in our group by Botha et al (4) showed that ANS modulation by slow deep breathing had an effect on pain thresholds in healthy volunteers. Our group has also shown that transcutaneous vagal nerve stimulation (tVNS) did the same in healthy volunteers (5).

This study takes this work a step further, by investigating the effect of deep slow breathing compared to sham breathing on oesophageal pain hypersensitivity in a group of patients with non erosive reflux disease (NERD).

Primary objective - To evaluate the effect of slow deep breathing and sham breathing on oesophageal pain hypersensitivity during experimental acid infusion in patients with NERD.

Secondary objectives

- A pilot follow-up study to evaluate the effect of slow deep breathing as a self-administered therapeutic measure for oesophageal symptoms measured using validated RESQ7 questionnaire in patients with NERD
- To evaluate the effect of slow deep breathing and sham breathing following oesophageal acid perfusion on APSS (acid perfusion sensitivity score).
- To determine ANS changes before and after slow deep breathing/sham breathing.

Primary endpoint - Difference in lag time to first sensation of discomfort following oesophageal acid perfusion between the slow deep breathing group and the sham breathing group.

Secondary endpoints

- Change in validated reflux symptom questionnaire (RESQ7), before and after 4 weeks, between the slow deep breathing and sham breathing groups.
- Difference in APSS (acid perfusion sensitivity score) following oesophageal acid perfusion between the slow deep breathing group and the sham breathing group.
- Comparison of ANS changes before and after slow deep breathing versus sham breathing in visit 1.

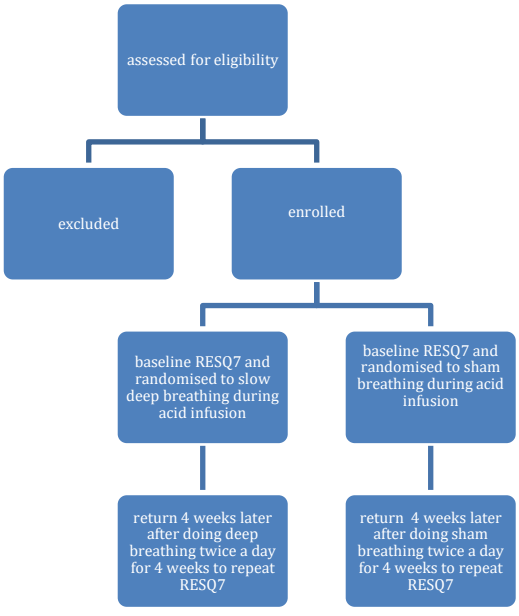

Figure 1: Schematic diagram of study design.

Results

116 eligible patients were approached and 30 were randomised, completing visit 1. There were no drop-outs and 24 of the 30 patients completed visit 2 of the study. The reason for declining was informally noted, with reluctance to undergo further non-essential invasive tests (after having completed their clinically indicated High Resolution Manometry (HRM) and 24 hour pH studies) being the predominantly sited reason. There were equal numbers in both arms of the study, and both groups were well matched for age and sex. Median age was 55 (44 – 60). 11 were female. Median BMI was 28.21 Kg/m2 (25.15 – 32.22).

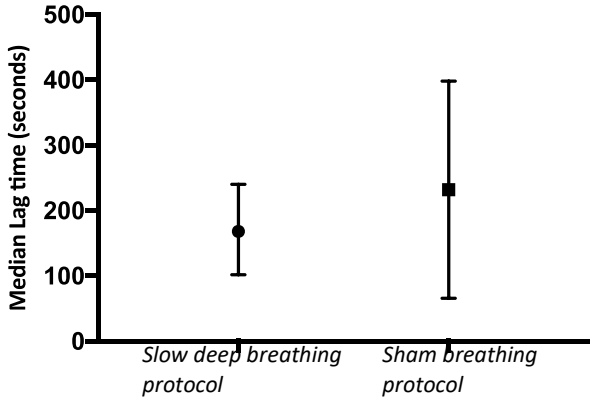

Figure 3: No significant difference between the two groups was seen (p = 0.6022).

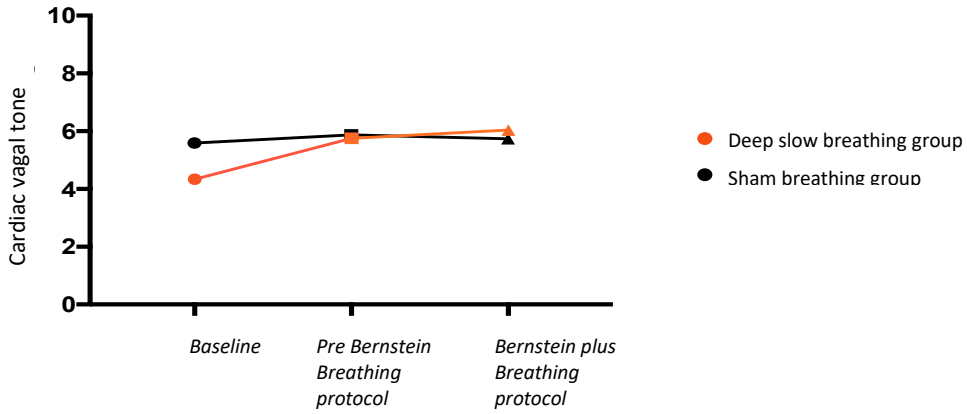

Figure 4: A significant rise from mean baseline CVT was seen in the SDB group with deep slow breathing alone (p = 0.0052) and deep slow breathing during a Modified Bernstein test (p = 0052). This was not shown in the sham breathing group (p = 0.5245 and p = 0.7197).

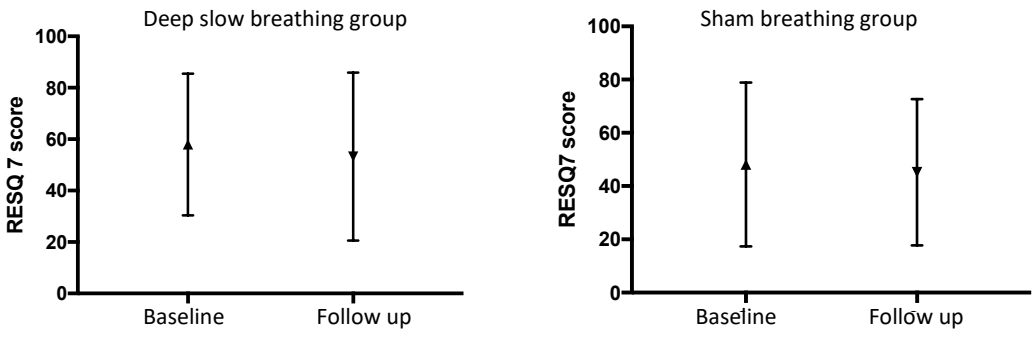

Figure 5: There was no significant difference between the baseline vs follow up scores on RESQ7 questionnaire for either the slow deep breathing group (p = 0.2354) or the sham breathing group (p = 0.8867).

Conclusions and discussion

In this study we have shown that a slow deep breathing protocol produced a significant rise in parasympathetic tone from baseline when compared to a sham breathing protocol. This rise was similar to the study in healthy volunteers by Botha et al (4). We were not able to show a significant difference in lag time. Both groups were equally matched with regards to symptom scores, which did not significantly change after 4 weeks of self-administered slow deep breathing.

The power calculation used in this study was aimed at detecting a difference in lag time of 20% between the 2 groups. Using a 5% significance level and 80% power, it was calculated that I required 34 patients in each group to detect a reduction of 20% in the primary outcome. The sample size was not achieved due to difficulties in recruitment.

Therefore, a ***change in the protocol is proposed*** as follows:

- Removal of the invasive component of the study i.e. acid perfusion test in view of a lack of a signal seen with lag time and also because the invasive nature of this part of the study affected recruitment.
- We will however continue with the second half of the study as we did see a signal in cardiac vagal tone but as yet we do not have sufficient power to see a difference in symptom scores.
- We do still believe in the utility of assessing change in reflux symptom scores as the ultimate aim of our research is to develop therapeutic strategies to address an unmet need in a population of patients with NERD. Improvement in reflux symptoms as measured by the RESQ 7 questionnaire will be the new primary end point of the study.

Request for no cost extension

- Because our clinical research fellow's contact finished we have had difficulty in identifying a new research fellow to take on the project. However, as the study now does not require intubation but is based on autonomic assessment and symptoms therefore it can be conducted by a research nurse who we have identified.
- Amendment to the ethics application is in progress and will be submitted within the next 2-3 weeks
- *We would like to request a 1 year no cost extension to the grant to enable us to complete the next phase of the proposed research.*

1.Bonaz B, Picq C, Sinniger V, Mayol JF, Clarencon D. Vagus nerve stimulation: from epilepsy to the cholinergic anti-inflammatory pathway. Neurogastroenterol Motil. 2013;25(3):208-21.
2.Johnson RL, Wilson CG. A review of vagus nerve stimulation as a therapeutic intervention. J Inflamm Res. 2018;11:203-13.
3.Lange G, Janal MN, Maniker A, Fitzgibbons J, Fobler M, Cook D, et al. Safety and efficacy of vagus nerve stimulation in fibromyalgia: a phase I/II proof of concept trial. Pain Med. 2011;12(9):1406-13.
4.Botha C, Farmer AD, Nilsson M, Brock C, Gavrila AD, Drewes AM, et al. Preliminary report: modulation of parasympathetic nervous system tone influences oesophageal pain hypersensitivity. Gut. 2015;64(4):611-7.
5.Adam D. Farmer GA, Jacob Juel, Maria Moller, Geeth Silva, Christina Brock, Daniel Sifrim, Asbjorn Drewes. 520 Randomized Controlled Trial: Transcutaneous Electrical Vagal Nerve Stimulation Prevents the Development of Acid Induced Esophageal Hyperalgesia. Gastroenterology,. April 2016; Vol. 150(Issue 4,):S107.