Background

Reflux hypersensitivity is a condition affecting the oesophagus (food pipe) and results in symptoms of chest pain, heartburn and / or regurgitation. Patients with reflux hypersensitivity are identified as having a normal endoscopic camera test (gastroscopy) and fulfil specific parameters on a 24 hour pH manometry and impedance study (1). The oesophagus is overly sensitive to normal episodes of reflux and so acid reflux per se is not responsible for the symptoms. Therefore, treatment with anti-acid medication e.g. omeprazole, is often not useful and clinicians rely on pain modulators or anti-depressant drugs to treat the symptoms that arise (2,3). Yet these drugs are unsatisfactory for many patients, either because they are ineffective or cause unpleasant side effects (4).

The Autonomic Nervous System (ANS) consists of two main branches; the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). Our research group has previously demonstrated that pain in the oesophagus triggers an increase in SNS tone and a reciprocal decrease in PNS tone. To date, stimulation of PNS tone i.e. increase, is shown to have a pain relieving effect in experimental studies on healthy volunteers.

Slow deep breathing (SDB) is a non-invasive, self-sufficient and proven method to increase PNS tone. For example, our group has shown that modulation of PNS by SDB reduced acid-induced oesophageal hypersensitivity in healthy volunteers (5). This experimental pain condition is thought to be a model for 'central sensitisation', which is thought to be the mechanism of pain in reflux hypersensitivity as well. Therefore, we hypothesise that SDB may have an effect on symptoms in patients with reflux hypersensitivity as well.

Results of interim analysis

In our interim analysis (unpublished data) that was funded by this grant, we included the Bernstein test* in the protocol to investigate the effect of SDB on patients with non-erosive gastro-oesophageal reflux disease (NERD). Thirty healthy participants with NERD were randomised to SDB arm or sham breathing part. There were equal numbers in both arms of the study, and both groups were well matched for age and sex. The median age was 55 (44 – 60) and 11 were female. Median BMI was 28.21 Kg/m2 (25.15 – 32.22).

Symptoms were evaluated by the questionnaire named Reflux Symptom Questionnaire, 7 day recall (RESQ7). We compared the lag time during the Bernstein test, cardiac vagal tone (CVT)(indicator for PNS tone), and symptoms 1 month after each breathing exercise between the 2 groups.

The analysis showed no significant results regarding the Bernstein test and symptoms (Figure 1) although ANS was successfully modulated in the SDB group (Figure 2).

* The **Bernstein test** is a method to reproduce symptoms of heartburn by perfusing acid to the oesophagus by nasogastric tube. We measured the time from the start of acid perfusing to the perception of heartburn (lag time).

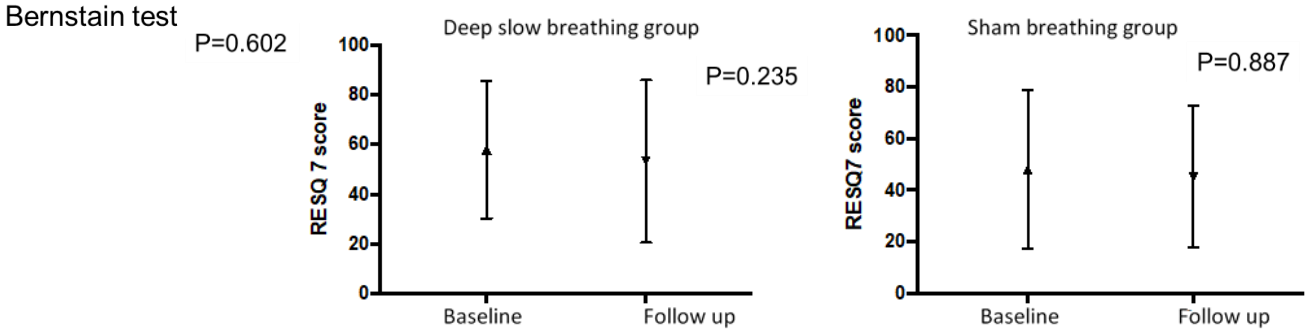

Figure 1: There were no significant differences in the lag time and symptom scores between the baseline vs follow up for either the SDB or the sham breathing group.

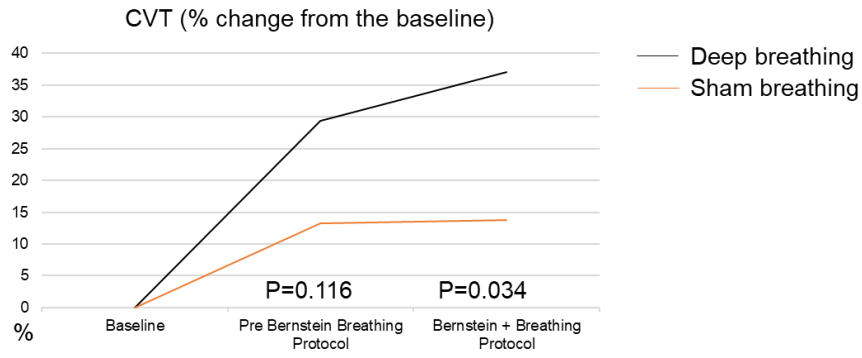

Figure 2: The percent change of CVT tended to be higher in the deep breathing group during pre-Bernstein breathing protocol (p=0.116). Furthermore, CVT was significantly increased during the Bernstein plus breathing protocol in the deep breathing group compared to the sham breathing group (p = 0.032).

Rationale for the present study

We considered that the negative results regarding the symptoms in the previous study might be due to the fact that NERD patients can be a heterogeneous group of patients with many different reasons for symptoms. For instance, some patients may have symptoms to excessive acid reflux despite, while others may have symptoms without experiencing any acid reflux, and still others can experience symptoms with normal levels of acid reflux. Hence we modified our protocol to look at patients with reflux hypersensitivity only.

Aims

The primary aim of this study is to evaluate the feasibility of slow deep breathing versus sham breathing in patients with reflux hypersensitivity. A secondary aim is to establish the impact of slow deep breathing on reflux symptoms and autonomic tone.

Objectives:

1. To assess compliance rates, subjective acceptability, recruitment, retention and completion rates.
2. To assess change in Reflux Symptom Questionnaire – 7 day (RESQ7), State-Trait Anxiety Inventory (STAI) and Hospital Anxiety and Depression Scale (HADS) scores from baseline to week 4 in sham vs SDB.
3. To correlate Big Five Questionnaire (BFQ) with baseline RESQ7 scores.
4. To correlate BFQ correlation with heart rate variability (HRV) at baseline.
5. To assess change in HRV – root mean square of successive differences (rMSSD) from baseline to week 4.

Recruitment target

40 patients with reflux hypersensitivity

Methods (Figure 3)

Patients are enrolled remotely for a period of 4 weeks. A video chat on day 1 will consist of confirming eligibility, after which the patient will be randomised to follow either the slow deep breathing protocol or the sham breathing protocol in a single-blinded fashion. That is, the patients will be unaware of whether they are performing the active breathing exercise. Once randomised on visit 1, they will undergo baseline heart rate recording using a smartphone based mobile app. Heart

rate recordings will be done on day 1, 8, 15, 22, and 29 before and after the breathing exercise to determine if there is a serial change in vagal tone over time.

For the assessment of symptoms, acceptability of the breathing exercise, and mental status, we will use questionnaires including Big Five Inventory, Hospital Anxiety and Depression Scale, State and Trait Anxiety Inventory, Global or General acceptability of treatment, and Reflux Symptom Questionnaire, 7 day recall. These questionnaires are set up on our electronic data capture system (Research Electronic Data Capture: REDCap).

After answering the questionnaires on day 1, the patients will then be trained to self-administer the video breathing exercise to be used twice a day, for 10 minutes over the next 4 weeks. The patients record their compliance with the exercise on a log sheet. After day 29, all the results will be compared between the 2 groups (SDB group vs sham breathing group)

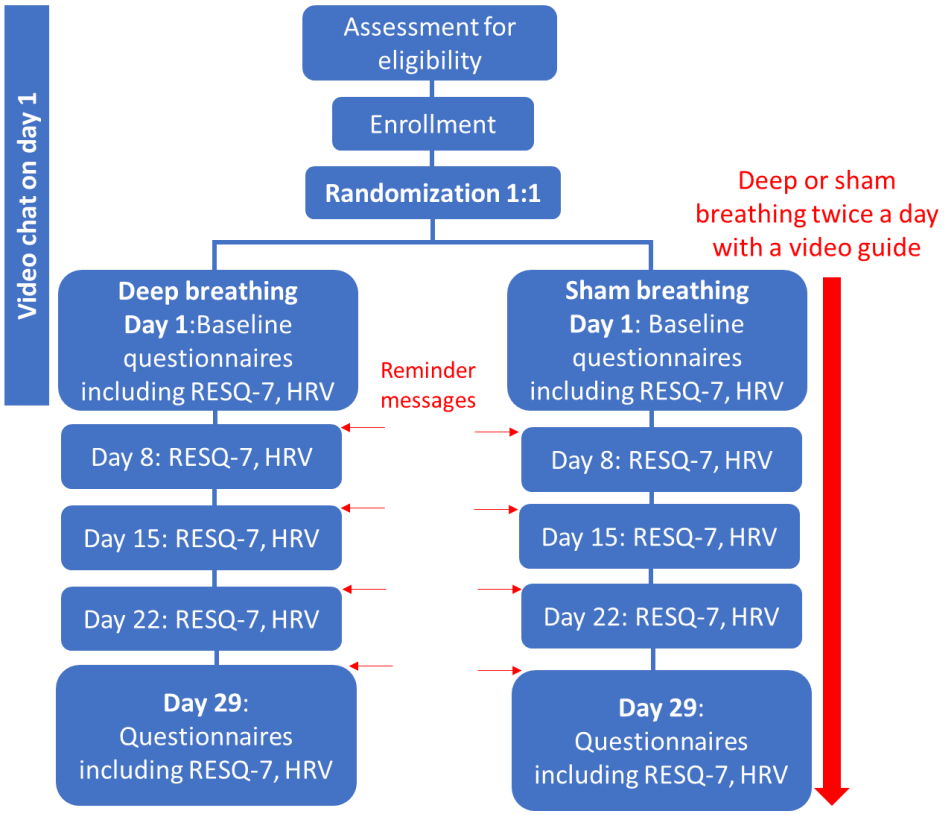

Figure 3: schematic diagram of the study design

Study progress **(updated as of 12/5/2020)**

This study was given final approval by the Research Ethics Committee on 6th April 2020. Since then, we have recruited and randomised 19 patients across 3 hospital sites (Royal London Hospital, University College London Hospital & St Georges NHS Trust). A fourth site has just been approved to recruit (Guys & St Thomas' Hospital) which should increase our yield exponentially.

Having performed interim analysis of our current data we can confirm that our objectives are being satisfactorily reached. The compliance rates are 95.1% and 99.1% for the slow deep breathing and sham breathing arm respectively. Subjective acceptability is high and completion rates for the study

are 89% and 80% for the slow deep breathing arm and sham breathing arm respectively. These results provide a positive indication for us to complete recruitment and prove feasibility for future studies to occur.

Due to the COVID-19 Pandemic, the capacity of the GI Physiology units are limited, and we are having to await newly diagnosed patients. Obtaining ethical approval at each site also prevented us from progressing with our timeline. However, we are now in a position to approach more potential participants and hope to complete our recruitment by December 2021. Therefore we request the final extension of the grant until this date to reach our target.

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