Full title: Rumination syndrome: assessment of vagal tone during and after meals and during diaphragmatic breathing.

Running title: Vagal tone in Rumination syndrome

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Abstract

Background: Pathophysiology of Rumination syndrome (RS) is not well understood. Treatment with diaphragmatic breathing improve Rumination syndrome. The **aim** of the study was to characterize vagal tone in patients with Rumination syndrome during and after meals and during diaphragmatic breathing.

Methods: We prospectively recruited 10 healthy volunteers (HV) and 10 patients with RS. Subjects underwent measurement of vagal tone using heart rate variability. Vagal tone was measured during baseline, test meal and intervention (diaphragmatic (DiaB), slow deep (SlowDB), and normal breathing). Vagal tone was assessed using mean values of root mean square of successive differences (RMSSD) and area under curves (AUC) were calculated for each period. We compared baseline RMSSD, the AUC and meal-induced discomfort scores between HV and RS. Furthermore, we assessed the effect of respiratory exercises on symptom scores, and number of rumination episodes

Key Results: There was no significant differences in baseline vagal tone between HV and RS. During the postprandial period, there was a trend to higher vagal tone in RS, but not significantly ($p>0.2$ for all). RS had the higher total symptom scores than HV($p<0.011$). In RS, only DiaB decreased the number of rumination episodes during the intervention period ($p=0.028$), while both DiaB and SlowDB increased vagal tone ($p<0.05$ for both). The symptom scores with the 3 breathing exercises showed very similar trends.

Conclusions and inferences: Patients with RS do not have decreased vagal tone related to meals. DiaB reduced number of rumination events by a mechanism not related to changes in vagal tone.

Key words

- Rumination syndrome
- gastroesophageal reflux disease
- autonomic nervous system
- breathing exercises
- gastrointestinal diseases

Introduction

Rumination syndrome is characterized by the repetitive effortless regurgitation of recently ingested food into the mouth[1]. Rumination syndrome was thought to be uncommon[2,3], but recent epidemiological studies have reported a prevalence of 1-5%[4,5,6]. Furthermore, rumination can be present in patients with diagnosis of gastro-esophageal reflux disease (GERD). In a recent study including GERD patients refractory to proton pump inhibitors, postprandial high resolution impedance manometry (HRIM) detected rumination in 20% of the patients[7].

The pathophysiology of Rumination syndrome is not completely understood. Mechanically, at the beginning of a rumination episode, there are sudden unnoticed contractions of upper abdominal wall muscles, increase in intragastric pressure, and relaxation of the upper and lower esophageal sphincters (UES and LES)[8,9,10]. However, the triggering of such mechanical reaction remains unknown. Thumshirn et al proposed an association between gastric hypersensitivity and RS[11].

Diaphragmatic breathing (DiaB) is currently considered as a standard treatment for Rumination syndrome[4,5,6]. The underlying mechanism of rumination improvement by DiaB is not completely understood. One possibility is that DiaB prevents the occurrence of abdominal wall muscle contractions. An alternative possibility could be that DiaB affects vago-vagal reflexes that are probably involved in postprandial gastric motility, abdominal visceral sensations[11], and LES relaxation[12,13]. However, an effect of DiaB on gastric mechanics or LES

relaxation has not been proven.

Altered visceral sensation is an important pathophysiological factor of functional gastrointestinal disorders. Normal visceral perception is reliant on a balanced regulation of the autonomic nervous system which consists of the parasympathetic and sympathetic nervous systems.[1,14,15]. Parasympathetic nervous system activity i.e. vagal tone, can be assessed analyzing heart rate variability metrics[16]. Vagal tone has been evaluated in several functional gastrointestinal disorders[14,15,17,18]. Our group has previously shown that vagal tone and esophageal sensation are related, and we have also shown that slow deep breathing can increase vagal tone and decrease esophageal hypersensitivity. In separate studies, we have also shown that a physiological decrease in vagal tone occurs postprandially[19].

We hypothesized that patients with Rumination syndrome may have a pathological low vagal tone and that DiaB and/or SlowDB can reduce meal induced gastric discomfort and number of rumination episodes by increasing vagal tone. The **aim** of the study was to characterize vagal tone in patients with Rumination syndrome during and after meals and during diaphragmatic breathing.

Materials and Methods

We prospectively recruited 10 asymptomatic healthy volunteers (HV) aged 18-65 through advertisement and 10 patients with Rumination syndrome between April 2019 and December 2019 at Upper GI Physiology Unit, Royal London Hospital (London, UK). Inclusion criteria for patients with Rumination syndrome were: 18-65 years old, fulfilling ROME IV clinical criteria for Rumination syndrome[1], diagnosis confirmed by HRIM within 24 months prior to the study[20]. Exclusion criteria were: pregnant or lactating women, a history of GI surgeries apart from appendectomy, having diabetes, solid meal intolerances or allergies to a McDonald's Big Mac meal, known allergy to electrocardiogram (ECG) electrodes or latex, major comorbidities (i.e. significant cardiac/pulmonary disease, cancer, life-threatening conditions), relevant organic diseases detected on esophagogastroduodenoscopy performed within 2 years, evidence of major esophageal motility disorders[21], or medications taken within the last 2 weeks which may affect any of the following : vagal tone, the number of rumination episodes, or GI motility (i.e. Baclofen[22,23], anthicolinergic drugs, prokinetics, beta-blockers). All participants provided written informed consent before the study. This study was approved by South East Scotland Research Ethics Committees 01 (ref:19/SS/0054) and was registered at ClinicalTrial.gov (NCT03912636).

Measurement of Vagal tone

Continuous ECG monitoring was performed on the subjects in the sitting position. ECG electrodes (Ambu Blue Sensor VLC, Ballerup, Denmark) were placed on both sides of subclavian areas and the left side abdomen. The ECG was acquired using a biological acquisition system (3-lead ECG cable, PowerLab, and Dual Bio Amp, AD INSTRUMENTS, Sydney, Australia). We analyzed R-R intervals with dedicated software (LabChart 6.0, AD INSTRUMENTS) and the data were processed using HRVTool 1.04 (MatLab-based open-source code under MIT license, https://github.com/MarcusVollmer/HRV) and Matlab R2018a (Mathworks, Natick MA, US) to calculate mean values of root mean square of the successive differences (RMSSD) as a parameter of vagal tone, where higher RMSSD values may suggest higher vagal tone [24,25]. This was done for baseline, every 5min during the meal and intervention periods and every 1 hour during the 3-hour observation period as a parameter of vagal tone.

Training to perform DiaB and SlowDB

DiaB and SlowDB are 2 different respiratory maneuvers. DiaB involves breathing by using predominantly the abdomen. In contrast, SlowDB involves deep thoracic inspiration. In order to practice these 2 different types of breathing, the subjects exercised used a biofeedback technique that allowed them to monitor their type of breathing. During training, the subjects wore 2 respiratory belts (TN1132/ST, AD INSTRUMENTS), one at the xiphosternal level and another at the umbilical level. Belts were connected to a recording/display system (PowerLab,

LabChart 6.0, AD INSTRUMENTS) that shows "on line" screen with a distinct line tracing for either abdominal or chest movements. The subjects were instructed to perform DiaB, i.e to breath 8-10 times/min by only moving the abdomen and keeping the chest as still as possible[26]. The subjects were also instructed to perform SlowDB, i.e. to breathe using deep inspiration 6-8 times/min by moving the thorax as much as possible[14].

Meal-induced discomfort score

All subjects marked 3 Likert scales of the level of nausea, fullness and epigastric discomfort[11]. Each scale was graded from 0 to 5, where score 0 represented no perception and score 5 represented an extremely uncomfortable sensation.

Protocol

Healthy volunteers (HV) and patients with RS attended 3 separate times the GI Physiology Unit with at least 1-week intervals (figure 1). All subjects underwent an 8-hour fast for solids and 2-hour fast for liquids prior to the visit. At each visit, they performed a different breathing exercise in a random order (i.e. visit1: no respiratory intervention as a control, visit2: DiaB and visit3: SlowDB). The order of these breathing exercises was randomized using www.randomization.com. The protocol was as follows: a) screening for subclinical anxiety and depression using the validated Hospital Anxiety and Depression Scale (HADS)[27]; b) placement

of ECG electrodes and respiratory belts; c) instructions and training of DiaB or SlowDB; d) 15min baseline measurement of ECG; e) test meal (McDonald's Big Mac meal: 953kcal, 42g fat) for 15 minutes[19], and marking of the meal-induced discomfort score every 5 minutes from onset of meal; f) respiratory intervention for 15 minutes soon after the meal and the meal-induced discomfort score at the end of the intervention period; g) postprandial ECG measurement for 3 hours with normal breathing and recording of the meal-induced discomfort score every 30 minutes during the postprandial period; h) the number of rumination episodes reported by patients in each period of baseline, meal, intervention, and every 30min during the 3h observation period was recorded. During ECG measurements, subjects were instructed to keep as still as possible in the sitting position.

The primary outcome was to compare the baseline, prandial and postprandial vagal tone together with meal-induced discomfort scores during normal breathing between patients with RS and HV. The secondary outcome was to investigate the effect of the respiratory exercises on vagal tone, meal-induced discomfort scores, and the number of rumination episodes.

Statistical analysis

All data were expressed in median and interquartile ranges. Fisher's exact test was used to compare proportions; Mann–Whitney U test and Kruskal–Wallis test were used to compare

continuous variables; Wilcoxon signed-rank test was used for paired data. To compare changes in RMSSD values (vagal tone) and meal-induced discomfort scores over time, we calculated the area under curves (AUC). When we compared RMSSD values and AUC of RMSSD between HV and patients with RS, Linear Regression Model was performed with coefficients [age, gender, Body Mass Index(BMI)][25]. P-values <0.05 were considered statistically significant. All statistical analyses were performed with EZR (Ver 1.36; Saitama Medical Center Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)[29].

Results

Baseline characteristics

Table 1 shows baseline characteristics in both groups. Patients with RS had their symptoms for 6.5 years [3.63-9.75]. Patients with RS had higher BMI than HV. Patients with RS had higher scores for anxiety and depression.

Vagal tone in Healthy volunteers and patients with RS

One low-quality ECG tracing from 1 HV was excluded, so ECG tracing from 10 patients with RS and 9 HV were analyzed. The baseline RMSSD values did not show a significant difference between HV (0.0436 seconds [0.0327-0.0552]) and RS (0.0372 seconds [0.0291-0.0485]) ($p=0.696$). During the postprandial period, we observed a drop and slow recovery in RMSSD in HV as reported previously[19], this was not the case in patients with patients with RS. Furthermore, RMSSD in patients with RS tended to increase after the first 10-min postprandial period. No significant differences in AUC of RMSSD during meal, intervention, and each 1-hour observation periods were observed ($p>0.2$ for all) [Figure 2].

Meal-induced abdominal sensation in HV and RS

Patients with RS had higher scores compared to HV in all the evaluated symptoms, especially nausea and abdominal discomfort over the whole observation period. The AUC of the total

score over the whole period in patients with RS was significantly higher than that in HV (p=0.0111) [figure 3].

Effect of respiratory exercises in patients with RS

Both DiaB and SlowDB increased RMSSD (vagal tone) soon after the initiation of the exercises, while control (normal breathing) showed a small spike in RMSSD at the postprandial 10min [figure 4]. The AUC of RMSSD values with both DiaB and SlowDB during the intervention and first 30min observation periods were significantly larger than those with normal breathing ($p<0.05$ for all).

DiaB (not slow DB) significantly decreased the number of rumination episodes during the breathing period compared to normal breathing (from 7 [3.5-8] to 3.5 [1.25-4.75], p=0.0278) [figure5]. 8 patients showed decrease in number of rumination events with DiaB compared to 4 with SlowDB (p=0.17). During the 3-hour observation period, there were no significant differences in the number of rumination episodes between all breathing exercises.

There was no significant correlation between changes in AUC during DiaB and SlowDB and number of rumination events.

meal-induced abdominal sensation with breathing exercises in patients with RS

No significant differences in the meal-induced discomfort score were observed during the

intervention and 3-hour observation period with 3 breathing exercises.

Discussion

In this study, we have shown that (i) during the baseline, vagal tone was similar in patients with RS and HV. During the postprandial period, there was a trend to higher vagal tone in patients with RS but the difference did not reach statistical significance; (ii) patients with RS reported higher meal-induced discomfort scores than HV both during the meal and postprandial periods; (iii) Only DiaB reduced the number of rumination episodes during the intervention period in spite of the fact that both DiaB and SlowDB significantly increased vagal tone; (iv) DiaB or SlowDB did not significantly affect postprandial abdominal discomfort.

The pathophysiology of Rumination syndrome has been investigated. Sudden increase in intragastric/intestinal pressure accompanies contractions of abdominal wall muscles preceding rumination[8],[10],[20],[30]. The relaxation of the UES and EGJ and a possible upward displacement of the EGJ were observed during rumination[10],[31]. The sudden increase in gastric pressure was not always followed by the EGJ relaxation[10]. Reduction of the LES tone during gastric distention was greater in patients with RS than in HV[11], and the EGJ pressure decreased prior to rumination episodes[10]. Significant differences in gastric emptying or gastric accommodation were not reported, but one study showed no gastric accommodation in half of the patients[11],[32]. So far, the triggering mechanisms underlying abdominal wall muscle

contractions, increase in intragastric pressures and the abnormal EGJ functions remain unknown. We initially hypothesized that a lower vagal tone could underlie prandial and postprandial abdominal discomfort leading to subconscious abdominal straining and also cause alteration in EGJ functions. Additionally, we hypothesized that the positive clinical effect of DiaB could be through enhancement of vagal tone. Our results do not support these hypotheses.

RMSSD is a surrogate parameter of vagal tone which cannot be measured directly in human. Reliability of heart rate variability parameters (i.e. RMSSD, High-Frequency) for assessment of vagal tone in the gut is controversial[14,19]. However, there is no other available non-invasive method to assess vagal tone in human. A relationship between RMSSD parameters and gut functions or conditions (i.e. motility, inflammation in patients with inflammatory bowel diseases, and abdominal sensations) has been reported[14,15,17,33,34]. In this study, both DiaB SlowDB significantly increased RMSSD, while only DiaB decreased the number of rumination episodes during the intervention period. We could not find a correlation between changes in RMSSD and number of rumination events. Therefore, it is unlikely that DiaB improves rumination by increasing vagal tone above normal basal values. It is possible that DiaB affects more specifically the increased contractility of abdominal wall muscles. Anxiety and depression were higher in Rumination syndrome compared to healthy volunteers. DiaB might reduce anxiety and thereby, have an effect on rumination events. Another possibility is that DiaB improves rumination by increasing the EGJ pressure/resistance. It was reported that DiaB

increased the EGJ pressure, possibly by increasing in the crural diaphragm activity[35]. A 4-week DiaB treatment improved esophageal acid exposure and reflux symptoms in patients with GERD[36]. However, SlowDB training increased the EGJ pressure as well[37], so the reason why SlowDB did not decrease the number of rumination episodes remains unclear.

Our study has several limitations. The small number of subjects might cause type 2 error in our results. However, the RMSSD values tended to be higher in patients with RS than in HV, so even with a small of patients, it is unlikely that vagal tone is lower in patients with RS. We adopted very stringent inclusion criteria for diagnosis of RS which required both typical symptoms and results of objective testing with HRIM. Most of the Rumination syndrome patients had significant dyspeptic symptoms during and after the meal. It is possible therefore, that many of them could have, together with rumination, some degree of gastroparesis. In our study we did not measure gastric emptying rate. We could not investigate the association between changes in vagal tone and manometric findings. Although all patients had confirmed initial diagnosis of rumination based on HRIM, we could not repeat the HRM-impedance study during or after meals due to ethical constrains. The number of rumination episodes was reported by patients (not by objective testing). In our previous report[38],24-hour impedance pH-metry showed that patients with RS reported their symptoms quite accurately. This study aimed to understand pathophysiological mechanisms in patients with rumination but does not include long term evaluation of the effect of DiaB treatment on vagal tone and rumination events.

In conclusion, our findings suggest that patients with RS do not have decreased vagal tone related to meals. DiaB reduced number of rumination events by a mechanism not related to changes in vagal tone. Further studies are needed to better understand the pathophysiology of Rumination syndrome in order to improve treatment outcomes.

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Authorship:

YH study concept and experimental work, interpretation of the results, and drafting the manuscript; HF analyzed the electrocardiogram data and calculate heart rate variability blinded to subjects' conditions; RS, SS, SK, AF, EY recruited potential patients and referred them to our clinic for clinical tests; KI,QA study concept and revised the draft; DS study concept performed interpretation of the results, and drafting the manuscript. All authors approved the final version of the draft.

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[tables]

		RS†(n=10)	HV‡ (n=10)	
age		23.5 [21-25.8]	28.5 [24.5-33]	P=0.0746
Gender(female%)		80%	70%	P=1
BMI§		25.5 [22.2-30.1]	21.5 [20.5-21.8]	P=0.0433
HADS¶	anxiety	4.5 [4-8]	2.5 [1.25-3]	P=0.00749
	depression	5 [2.8-6.8]	0 [0-4]	P=0.00872

Table 1. baseline characteristics

Median values with interquartile range were shown.

† patients with Rumination syndrome, ‡ healthy volunteers, § body mass index, ¶ Hospital Anxiety and Depression Scale

[Figure legends]

Figure 1. Protocol

At each visit, subjects performed a different breathing exercise in a random order (i.e. visit1: no respiratory intervention as a control, visit2: DiaB and visit3: SlowDB). The protocol was as follows: a) screening for subclinical anxiety and depression using the validated Hospital Anxiety and Depression Scale (HADS); b) placement of ECG electrodes and respiratory belts; c) instructions and training of DiaB or SlowDB; d) 15min baseline measurement of ECG; e) test meal for 15 minutes, and marking of the meal-induced discomfort score every 5 minutes from onset of meal; f) respiratory intervention for 15 minutes soon after the meal and the meal-induced discomfort score at the end of the intervention period; g) postprandial ECG measurement for 3 hours with normal breathing and recording of the meal-induced discomfort score every 30 minutes during the postprandial period; h) the number of rumination episodes reported by patients in each period of baseline, meal, intervention, and every 30min during the 3h observation period was recorded.

HADS, Hospital Anxiety and Depression Scale; DiaB, diaphragmatic breathing; SlowDB, slow deep breathing; normal, normal breathing

Figure 2. Changes in RMSSD values (vagal tone) with normal breathing in HV and RS

Median values with interquartile ranges were shown. There were no significant differences in

the baseline RMSSD value and AUC during the meal, intervention, each 1h observation periods.

RS, patients with Rumination syndrome; HV, healthy volunteers; DiaB, diaphragmatic breathing; SlowDB, slow deep breathing; RMSSD, root mean square of the successive differences.

Figure 3. meal-induced abdominal sensation in HV and RS

Median scores with the interquartile ranges were shown. RS had higher scores in all the symptoms, and the total score in RS was significantly higher than those in HV.

RS, patients with Rumination syndrome; HV, healthy volunteers.

Figure 4. Changes in RMSSD values (vagal tone) with 3 breathing exercises in RS

Median values with interquartile ranges were shown. DiaB and SlowDB significantly increased AUC of RMSSD during the intervention and first 30min observation periods ($p<0.05$ for both).

RS, patients with Rumination syndrome; HV, healthy volunteers; DiaB, diaphragmatic breathing; SlowDB, slow deep breathing; RMSSD, root mean square of the successive differences

Figure 5. Effect of DiaB and SloDB on the number of rumination episodes during the intervention period

DiaB significantly reduced the number of episodes from 7 [3.5-8] to 3.5 [1.25-4.75] (p=0.0278), while SlowDB did not significantly decreased the number (from 7.0 [3.5-8] to 6 [4.5-6.75], p=0.395).

RS, patients with Rumination syndrome; DiaB, diaphragmatic breathing; SlowDB, slow deep breathing