

The effect of sham feeding on neurocardiac regulation in healthy human volunteers

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BACKGROUND: Distension and electrical stimuli in the esophagus alter heart rate variability (HRV) consistent with activation of vagal afferent and efferent pathways. Sham feeding stimulates gastric acid secretion by means of vagal efferent pathways. It is not known, however, whether activation of vagal efferent pathways is organ- or stimulus-specific.

OBJECTIVE: To test the hypothesis that sham feeding increases the high frequency (HF) component of HRV, indicating increased neurocardiac vagal activity in association with the known, vagally mediated, increase in gastric acid secretion.

METHODS: Continuous electrocardiography recordings were obtained in 12 healthy, semirecumbent subjects during consecutive 45 min baseline, 20 min sham feeding (standard hamburger meal) and 45 min recovery periods. The R-R intervals and beat-to-beat heart rate signal were determined from digitized electrocardiography recordings; power spectra were computed from the heart rate signal to determine sympathetic (low frequency [LF]) and vagal (HF) components of HRV.

RESULTS: Heart rate increased during sham feeding (median 70.8 beats/min, 95% CI 66.0 to 77.6; $P < 0.001$), compared with baseline (63.6, 95% CI 60.8 to 70.0) and returned to baseline levels within 45 min. Sham feeding increased the LF to HF area ratio (median: 1.55, 95% CI 1.28 to 1.77; $P < 0.021$, compared with baseline (1.29, 95% CI 1.05 to 1.46); this increase in LF to HF area ratio was associated with a decrease in the HF component of HRV.

CONCLUSIONS: Sham feeding produces a reversible increase in heart rate that is attributable to a decrease in neurocardiac parasympathetic activity despite its known ability to increase vagally mediated gastric acid secretion. These findings suggest that concurrent changes in cardiac and gastric function are modulated independently by vagal efferent fibres and that vagally mediated changes in organ function are stimulus- and organ-specific.

Key Words: *Autonomic nervous system; Heart rate variability; Sham feeding; Vagus nerve*

It has been reported that pathological symptoms attributable to the upper gastrointestinal (GI) tract may be associated with abnormalities of the autonomic nervous system (ANS), but the pathways subserving the generation and perception of symptoms have not been identified (1,2). Although functional bowel diseases may be associated with changes in afferent or

Effet d'une alimentation simulée sur la régulation neurocardiaque chez des volontaires en bonne santé

HISTORIQUE : La distension et les stimuli électriques au niveau de l'œsophage influent sur la variabilité de la fréquence cardiaque (VFC), ce qui concorde avec l'activation des voies vagales afférentes et efférentes. Une alimentation simulée stimule la sécrétion d'acide gastrique par le biais des voies vagales efférentes. On ignore par contre si l'activation des voies vagales efférentes est organo-spécifique ou dépendante des stimuli.

OBJECTIF : Tester l'hypothèse selon laquelle une alimentation simulée accroît la composante haute fréquence (HF) de la VFC, indiquant une activité vagale neurocardiaque accrue en association avec l'augmentation connue de la sécrétion d'acide gastrique d'origine vagale.

MÉTHODES : Des enregistrements électrocardiographiques continus ont été obtenus chez 12 sujets en bonne santé placés en position semi-assise durant des périodes ininterrompues de 45 minutes au départ, de 20 minutes durant l'alimentation simulée (hamburger standard) et de 45 minutes de récupération. L'intervalle RR et le signal de fréquence cardiaque entre les battements ont été déterminés à partir d'enregistrements électrocardiographiques numérisés. Les spectres de puissance ont été analysés par ordinateur à partir du signal de fréquence cardiaque pour déterminer les composantes sympathiques (basse fréquence [BF]) et vagales (HF) de la VFC.

RÉSULTATS : La fréquence cardiaque a augmenté durant l'alimentation simulée (médiane 70,8 battements/minute, IC 95 % 66,0 à 77,6; $p < 0,001$), comparativement aux valeurs de départ (63,6, IC 95 % 60,8 à 70,0) et est revenue au taux de base en l'espace de 45 minutes. L'alimentation simulée a fait augmenter le ratio BF:HF (médiane 1,55, IC 95 % 1,28 à 1,77; $p < 0,021$) comparativement aux valeurs de départ (1,29, IC 95 % 1,05 à 1,46). Cette augmentation du rapport BF:HF a été associée à une baisse de la composante HF de la VFC.

CONCLUSION : L'alimentation simulée produit une augmentation réversible de la fréquence cardiaque qui est attribuable à une baisse de l'activité parasympathique neurocardiaque, malgré sa capacité connue à faire augmenter la sécrétion d'acide gastrique d'origine vagale. Ces observations donnent à penser que les variations concomitantes des fonctions cardiaque et gastrique subissent une influence indépendante des fibres vagales efférentes et que les variations fonctionnelles d'origine vagale sont spécifiques aux stimuli et aux organes.

efferent autonomic signalling, it is not known whether this reflects a generalized autonomic dysfunction, or changes affecting specific afferent or efferent pathways. It would, therefore, be useful if the integrity and function of these different pathways could be tested to assess whether they are abnormal in the presence or absence of GI symptoms.

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Power spectral analysis of beat-to-beat, heart rate variability (HRV) data, derived from electrocardiography (ECG) recordings, has provided useful insights into ANS function (3) in animal models and in clinical physiology (4,5). It is now generally acknowledged that changes in heart rate signals indicative of ANS activity are due to its effect on the sinoatrial node. A power spectral plot of an HRV signal derived from a short, 2 min to 5 min ECG recording, yields two distinct peaks. One peak in power, observed in the low frequency (LF) part of the HRV spectrum (0.05 Hz to 0.15 Hz), is attenuated partially by beta-adrenergic blockers and is considered, therefore, to be an index of sympathetic activity; the other peak, observed in the high frequency (HF) part of the spectrum (0.20 Hz to 0.50 Hz), is atropine sensitive, and is considered to be an index of vagal activity (3,5). The combined effects of sympathetic and parasympathetic activity on HRV are summarized as the LF to HF area ratio, calculated as the ratio of the areas under the curve for the LF and HF segments of the HRV power spectral plots. Neural regulatory aspects of ANS function can, therefore, be studied by means of power spectral analysis of HRV; this has been shown to be a sensitive technique for monitoring neuroregulatory cardiac activity (3-5), and because it is derived from standard ECG recordings, it has the added attraction of being completely noninvasive. In the absence of techniques that permit direct monitoring of the ANS and its effects on individual GI organs, such as the liver, stomach and intestine, investigators have used power spectral analysis of HRV as a surrogate indicator of overall sympatho-vagal balance within the human body (3-5).

Stimulation of the esophagus increases vagal efferent activity, identifiable by power spectral analysis of the HRV signal (6-10). It is not known, however, whether the increase in HF power is confined to the neurocardiac fibres or whether there is generalized upregulation of vagal activity. Similarly, it is not known whether the vagally mediated heart rate changes are precipitated only by cardiotropic vagal afferent activity or if they can be induced by any stimulus that can evoke a vagal efferent response in other parts of the body.

Sham feeding invokes the cephalic phase of gastric acid secretion by way of afferent sensory stimuli (related partly to taste and smell), mediated by the facial and glossopharyngeal nerves, which then lead to gastric acid secretion mediated by vagal efferent pathways. The studies by Pavlov (11) documented this mechanism in dogs; subsequent studies in man (12,13) led to the development of a modified sham feeding technique ('chew and spit') to document the role of the vagus nerve in healthy subjects, with and without anticholinergic medication (14,15). Sham feeding has also been used to study acid secretion and the effect of the vagotomy in control subjects and duodenal ulcer patients (16,17), the role of the vagus nerve in mediating gastric myoelectrical activity (18) and the effect of acupuncture on gastric acid secretion (19). A more recent study (20) in patients with a past history of duodenal ulceration, after *Helicobacter pylori* eradication, and in healthy controls indicated that the ulcer patients had greater resting vagal tone than controls; they also reported a correlation between resting vagal tone and sham feeding-induced gastric acid secretion in ulcer patients, suggesting that vagal modulation of heart rate in ulcer patients was linked to indices of neurally mediated gastric acid secretion. However, in this study, there was no recording of heart rate or cardiac response during the sham feeding period and it was not, therefore, possible to

determine whether the sham feeding-induced increase in gastro-tropic vagal activity was accompanied by an increase in cardiotropic vagal activity.

The aim of the present study was to test the general hypothesis that there is a nonspecific increase in vagal efferent activity in response to sham feeding; the specific hypothesis was that sham feeding would produce an increase in HF activity on power spectral analysis of the HRV signal, indicating increased centrally mediated cardiotropic vagal activity accompanying the known, vagally mediated, increase in gastric acid secretion.

PATIENTS AND METHODS

Subjects

The study was approved by the McMaster University Research and Ethics Board (Hamilton, Ontario). Twelve healthy volunteers (seven men and five women; age range 21 to 44 years), with no history of GI or cardiorespiratory disease, were studied after an overnight fast. Subjects lay semirecumbent in a darkened room, and a standard, lead II ECG was recorded. The ECG signals were sampled at 500 Hz using a 12-bit analogue-to-digital converter (Dataq Instruments Inc, USA) and stored on a hard disk for subsequent analysis.

Lead II ECG recordings were obtained during the baseline resting (45 min), sham feeding (20 min) and recovery (45 min) periods. Subjects were made comfortable and were asked to move as little as possible during the study. During sham feeding, subjects remained semirecumbent and were fed small portions of a standard hamburger and bun that had previously been cut into 10 pieces. The subjects were instructed to chew each portion of the hamburger steadily for 2 min, without swallowing, after which they spat the residue into a container held in place by the investigator, such that the subject would not have to sit up. The subjects were monitored by the investigator throughout the study.

Signal processing and statistical analysis

The technique of power spectral analysis, applied to HRV signals, is well documented in the literature (4,5) and will, therefore, be described in brief. The HRV signals were derived from standard, lead II ECG recordings that must be at least 2 min to 5 min in duration with no ectopic activity. The ECG recordings were obtained with the subject at rest and with no sudden changes due to subject activity or other interventions. Because the recordings for each session were 20 min to 45 min in duration, they were divided into shorter segments (each of them 2 min to 5 min) for analysis; summary statistics were then calculated for each session. Power spectra for each of the sessions were plotted, sequentially one above the other, for visual inspection in a pseudo-three-dimensional format.

To generate the HRV signal from the ECG recording, the R-wave for each QRS complex was located and a continuous R-R interval series was formed; this was re-sampled at a rate of 2 Hz, using linear interpolation, to produce a heart rate signal. Successive 128 s data sets (256 data points) from the heart rate series were analyzed using autoregressive power spectral analysis (10). The LF and HF components of HRV were characterized after identification of the respective peaks in each of the power spectral plots and the associated area under the curve was computed by numerical integration of the curve. From these data, mean HF area, mean LF area and mean LF to HF area ratio were computed for each baseline, sham feeding and recovery period. The mean heart rate during each recording

TABLE 1
Heart rate and results of power spectral analyses during baseline, sham feeding and recovery periods (n=12)

	Baseline		Sham feeding		Recovery	
	Median	Range	Median	Range	Median	Range
Heart rate, beats/min	63.6	60.8–70.0	70.8*	66.0–77.6	64.4**	58.9–78.0
LF area, (beats/min) ²	6421	5768–6693	6784	6490–7168	6853	6109–7283
HF area, (beats/min) ²	5017	4403–5372	4494***	3674–5065	4426	4065–5169
LF to HF ratio	1.29	1.05–1.46	1.55†	1.28–1.77	1.54	0.76–1.77

*P<0.001 compared with rest; **P=0.001 compared with sham feeding period; ***P=0.021 compared with rest. HF High frequency; LF Low frequency

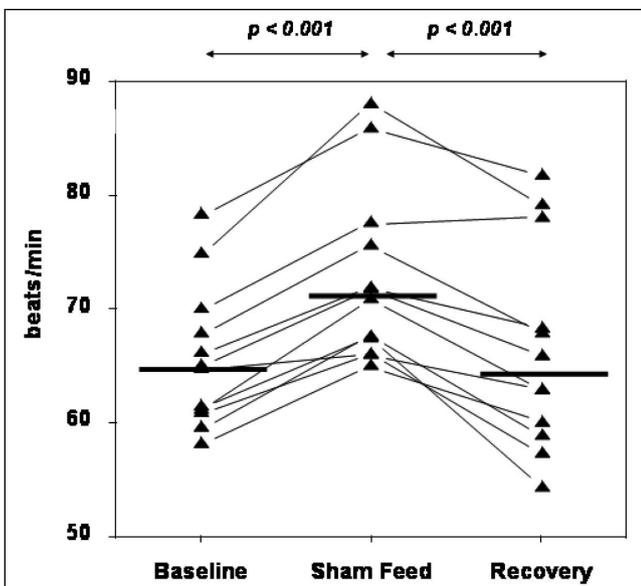


Figure 1) Mean heart rate during the baseline, sham feeding and recovery recording periods for each subject (n=12). Horizontal bars indicate the group median heart rate during each recording period

period was also calculated. All data are presented as medians with 95% CIs. To test the hypothesis that sham feeding produces an increase in cardiotropic vagal activity, LF to HF area ratios during the sham feeding and baseline periods were compared using the Wilcoxon test for paired data. Additional statistical testing, also performed using the Wilcoxon test for paired data, was descriptive.

RESULTS

Studies were completed by all subjects and the results are summarized in Table 1.

Heart rate

During the baseline period, the median heart rate was 63.6 beats/min (95% CI 60.8 to 70.0), increasing to 70.8 beats/min (95% CI 66.0 to 77.6; P<0.001 versus baseline) during the sham feeding period and falling again to 64.4 beats/min (58.9 to 78.0; P<0.001 versus sham feeding period) during the recovery period (Figure 1).

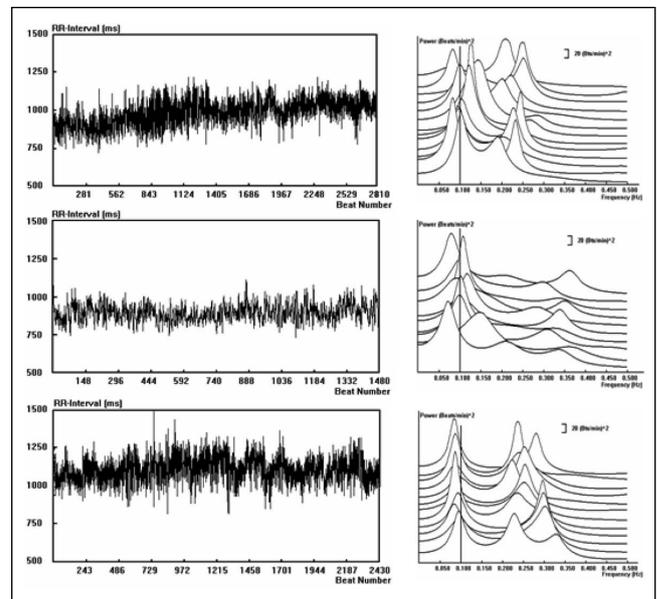


Figure 2) Results from one subject, showing R-R interval series (left hand panels) and power spectral analyses (right hand panels) for the baseline (top two panels), sham feeding (middle two panels) and recovery (bottom two panels) periods. During sham feeding, the R-R interval (ms) decreases, consistent with an increase in heart rate, while the area under the curve for the high frequency peaks decreases and the area ratio increases, indicating a reduction in the vagal modulation

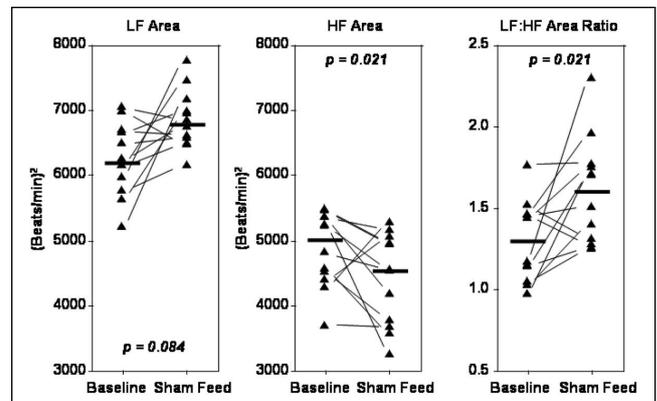


Figure 3) Changes in low frequency (LF) area, high frequency (HF) area and LF to HF area ratios produced by sham feeding, compared with baseline for each subject (n=12). Horizontal bars indicate group median values for each recording period

Power spectral analysis

Sham feeding produced changes in the R-R interval series and the accompanying power spectra, which reverted to normal baseline pattern during the subsequent recovery period; an example of these changes is shown, for one subject, in Figure 2. The areas under the curve for the LF peaks did not change in response to sham feeding (P=0.084) but those for the HF peaks decreased (P=0.021) and the LF to HF area ratios increased (P=0.021) compared with baseline (Figure 3). However, during the recovery period, there were no consistent changes in the LF area, HF area or LF:HF area ratio (Table 1), despite the normalization of the heart rate.

DISCUSSION

The results of the present study have refuted the hypothesis that sham feeding would increase the HF power of the HRV, indicative of increased cardiotropic vagal activity accompanying the known, vagally mediated increase in gastric acid secretion (11-19). In contrast, the results indicate that sham feeding actually produced a decrease in centrally mediated cardiotropic vagal activity. Sham feeding produced a clear increase in heart rate in all subjects; the results of the power spectral analyses indicate that there was no significant increase in the sympathetically mediated LF component of HRV. Instead, there was a significant decrease in the parasympathetically mediated HF component of the HRV. Thus, the increase in heart rate was most probably due to a decrease in cardiotropic vagal activity, despite the fact that sham feeding is known to increase gastric vagal activity and acid secretion (11-19). It is also possible that the increase in heart rate was related, at least in some subjects, to an increase in sympathetic activity albeit that the increase in LF area was not statistically significant in the present study. It is, of course, possible that the increase in LF area would have been statistically significant, had more subjects been studied. Our observations are consistent with those of Stern et al (21) who reported increases in heart rate when subjects were presented with appetizing food. On the other hand, Lucini et al (20) have suggested that a vagally modulated decrease in heart rate is linked to a vagally mediated increase in gastric acid secretion. However, the correlation that they reported is not directly comparable to the relationship reported in our study and, furthermore, the study protocols were quite different. Lucini et al (20) studied patients with a past history of duodenal ulcer disease – a condition that is recognized to be associated with an increased acid secretory capacity – and, although the authors assessed HRV, they did so only under resting conditions, in comparison with normal subjects. Thus, their evaluation of the effect of sham feeding on gastric acid secretion was not accompanied by concurrent HRV monitoring and it was not compared with the effect of stimulated gastric acid output in a control group. Even if duodenal ulcer patients were comparable to normal healthy subjects – and the data from Lucini et al (20) suggest that they are not – their study does not address the concurrent effects of sham feeding on gastric and cardiac activity in ulcer patients. It would, nonetheless, be important to determine whether the autonomically mediated responses to sham feeding are similar in ulcer patients and healthy subjects, and whether the presence of ulcer-related symptoms, the presence or absence of *H pylori* and the persistence of inflammation after *H pylori* eradication have an effect on ANS activity and the cardiac response to a challenge such as sham feeding.

The absence of a consistent HRV response during the recovery period, despite the normalization of the heart rate, was unexpected; however, it is possible that this is due to the marked interindividual differences in baseline values for each individual, combined with differences in autonomic and psychological responses to sham feeding. It is probable that the sympathetic and parasympathetic elements of ANS activity are highly dynamic and responsive to external and internal stimuli, and that their relative contributions to final effect on cardiovascular and GI effector mechanisms are state-dependent. Subjects will have differed not only with respect to the extent of hunger and acid secretion induced by sham feeding, but also with respect to the initial extent of change in

sympathetic and parasympathetic activity and, hence, the extent to which subsequent changes might occur to effect a poststimulation normalization of heart rate. This interpretation is consistent with the observation that there were changes in both sympathetic and parasympathetic activity, manifested as changes in the LF and HF areas, albeit that the changes in sympathetically mediated LF areas were not evident in all subjects and were not statistically significant in the group analysis. Future studies should, therefore, evaluate concurrent changes in acid secretion, hunger and satiety, and blood pressure, for example, in conjunction with the HRV analyses; subsequently, pharmacological interventions to modulate sympathetic, parasympathetic and acid secretory responses would lead to a clearer understanding of the role of the ANS in controlling gastric and cardiorespiratory function.

The interpretation that increased heart rate is primarily due to reduced vagal activity presumes that the vagal fibres innervating the heart subserve only one function. Conversely, increased vagal activity would lead only to a decrease in the heart rate and an increase in the HF component of HRV. Such results would also be consistent with the hypothesis that there are efferent vagal fibres innervating the heart which, when activated, will decrease both heart rate and HRV; one might then postulate that activation of vagal efferent fibres to the GI tract is accompanied by both activation of vagal fibres and by the suppression of excitatory fibres, innervating the sinus node. This hypothesis is supported by previous observations that direct stimulation of the efferent and afferent vagal nerves causes a decrease in gastric contractions (22,23). A decrease in gastric contractions has also been associated with increases in heart rate (21,24).

In an attempt to minimize stress during the present study, we did not confirm that sham feeding had produced a concomitant increase in gastric acid secretion by gastric aspiration or pH monitoring. However, the subjects were all quiet and relaxed during the study and none had a past history or abnormality of GI or autonomic function. Thus, we were confident that these subjects would have had a normal gastric response to sham feeding and we wished to avoid the possibility that gastric intubation would produce effects on autonomic function and heart rate unrelated to the effect of sham feeding (11-19), similar to the effects documented by esophageal stimulation (7,10,25,26).

Our study had the following limitations: we did not monitor blood pressure variability, which may have helped to identify sympathetically mediated changes in the blood pressure variability. Furthermore, respiration was not studied, due to interruptions that would have been produced in the respiratory signals during chewing; in addition, there was concern that the stress of enforcing a regular respiratory rate might affect cardiotropic autonomic neural activity (6,27).

Studies on the effect of gastric stimulation during feeding in the absence of vagal feedback (eg, after vagotomy) (28,29) or through external vagal stimulation in the absence of feeding and digestion (30), show that isolation or stimulation of a single pathway does not necessarily have an appreciable effect on the overall process. This suggests that sham feeding alone may not be sufficient to generate all of the gastric responses normally associated with ingestion and digestion.

Hibino et al (31) found a consistent increase in the HF power of the power spectra of the HRV following the intake of beverages containing caffeine. However, in their study, subjects' breathing frequency was regulated during the experiment,

whereas our subjects breathed spontaneously. It is known that regulating the breathing can increase the HF power in the power spectra of the HRV signal (6,27).

Increased heart rate and blood pressure have also been associated with jaw movement (32). Shiba et al (33) found that mastication increases the LF component of the HRV power spectrum and suppresses the HF component. However, the objectives assessed by Shiba et al differed substantially from the objectives of our study. The study by Shiba et al (33) used mastication as the primary stimulus whereas, in the present study, the primary hypothesis related to the effect of sham feeding on efferent neurocardiac activity; as a result, in the study by Shiba et al, subjects received chewing gum (1.5 g) instead of a standard hamburger meal; the subjects' breathing rate was regulated at 15 breaths/min (33), whereas our subjects breathed normally; and the recording period was only 3 min, rather than 20 min.

The results of the present study strongly suggest that vagally mediated changes in organ function are stimulus- and organ-specific. Concurrent changes in cardiac and gastric function are modulated independently by vagal efferent fibres

and an increase in parasympathetic activity observed in one organ system may be accompanied by a decrease in parasympathetic activity in another organ system. These findings indicate that the sympathetic and parasympathetic divisions of the autonomic nervous system cannot be considered in toto when assessing autonomic function in patients with GI disturbances. Power spectral analysis of HRV is a sensitive technique for assessing neurocardiac function in patients with GI disorders such as noncardiac chest pain, dyspepsia and irritable bowel syndrome; as such, it may help determine whether there are organ-specific abnormalities of autonomic innervation or function that may play a role in the generation or perception of visceral stimuli in other conditions affecting the GI tract (34).

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