

Effect of T6 Dermatome
Electrical Stimulation on
Gastroduodenal Motility in
Healthy Volunteers

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Title of the Study:	Effect of T6 Dermatome Electrical Stimulation on Gastroduodenal Motility in Healthy Volunteers
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Abstract

Background

Previous studies demonstrated that electrical stimulation in the upper abdomen inhibited postprandial antral motility, possibly through activation of somatovisceral stimulation or central mechanisms. Percutaneous electrical neurostimulation of dermatome T6 was associated with appetite reduction and, along with a proper diet, achieved a significantly greater weight reduction than diet alone in morbidly obese subjects. The effect on appetite and weight could be related to an effect on gastric motor functions. However, the effects of T6 dermatomal electrical stimulation on gastric motor functions are unclear.

Hypothesis

T6 dermatomal electrical stimulation treatment results in inhibition of postprandial antral motility in healthy volunteers.

Aim

We aim to compare measurements of postprandial antral motor activity in healthy participants treated with sham versus active T6 dermatomal electrical stimulation (delivered by a TENS unit).

Methods

We shall perform multilumen gastroduodenal manometry to measure postprandial antral motor activity in response to sham versus active T6 dermatomal electrical stimulation in a parallel group study design.

Significance

This study will form the foundation for the potential subsequent application of dermatome electrical stimulation for altering gastroduodenal motility.

Research Plan

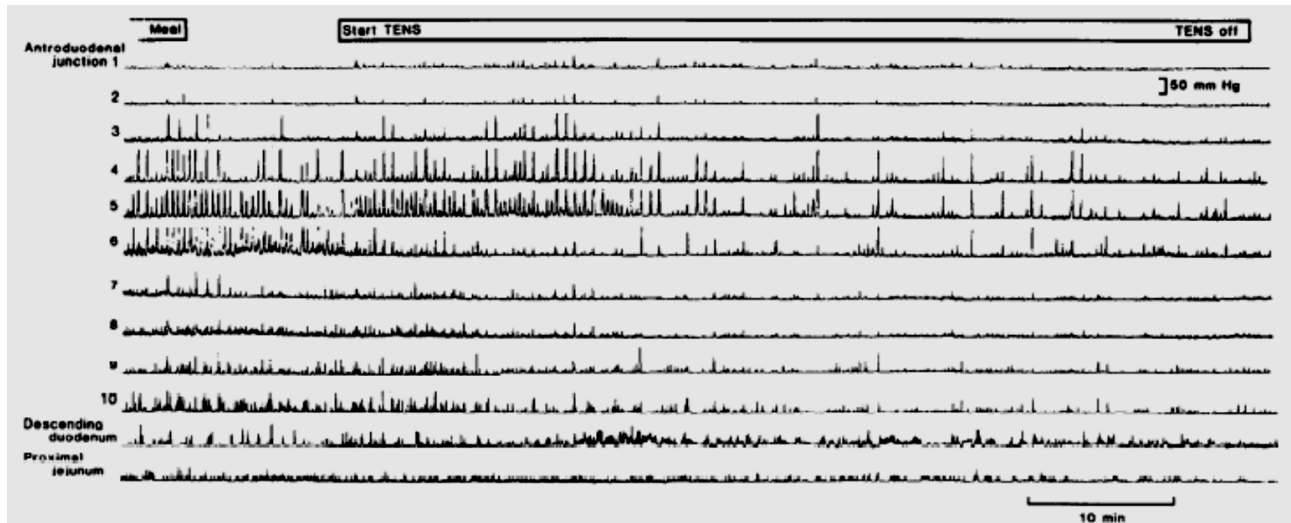
BACKGROUND

A surgically implantable gastric stimulator (gastric pacemaker) has been used to treat obesity; this achieves excess weight loss up to 40% in approximately 1 year (1). The modulation of neuronal activities and release of certain hormones with an implantable gastric stimulator may explain the reduction of appetite and the increase of satiety, such as a decrease in ghrelin levels (2).

Viscerovisceral spinal reflexes that are thought to be relayed through sympathetic pathways appear to play an important role in the autonomic control of thoracoabdominal viscera, such as the heart and great vessels (3). However, somatic stimulation may also affect visceral function through autonomic reflexes. The best known somatovisceral response is the effect of cold pain on vasomotor reactions (4). Evidence suggests that the gastrointestinal tract may also be influenced by such somatovisceral reflexes; thus, in anesthetized rats, cutaneous stimuli applied to the abdomen and hind paw decrease and increase stomach motility, respectively. Whereas the latter reflex response appears to relay centrally and the efferent limb of the reflex is located in vagal fibers, the response to abdominal stimulation involves a somatosympathetic reflex that relays at the level of the spinal cord, being retained in cervical cord-transected rats (5).

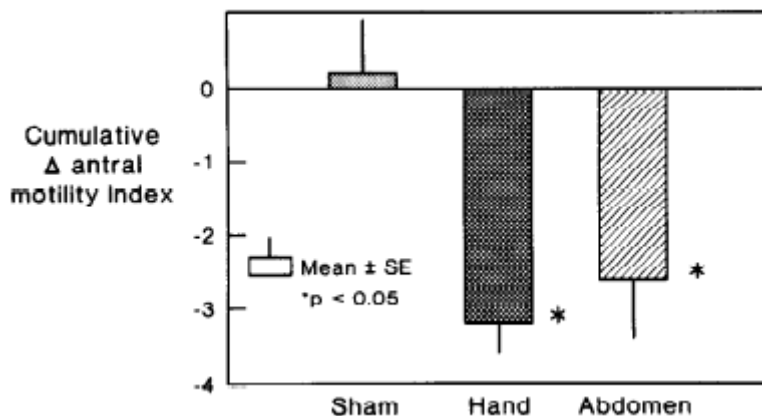
In studies performed by the Principal Investigator 30 years ago (6), sustained somatic stimulation by transcutaneous electrical nerve stimulation (TENS) was applied to the skin of human volunteers while simultaneously monitoring their upper gastrointestinal phasic pressure activity, extraintestinal vasomotor indices, and plasma levels of putative humoral mediators of autonomic reflexes (Figure 1).

Figure 1.



Stimuli were applied either to the hand (C8-T1) or to the upper abdomen (T5-T10) to determine whether impulses at these two dermatomes produced different effects on fed antral phasic pressure activity. TENS resulted in significant reduction ($p=0.007$) in antral motility index when applied to the hand and abdomen, as compared with sham stimulation (Figure 2). This was associated with increases in skin conductance (suggesting vasomotor changes) and plasma beta-endorphin levels (suggesting a central stress pathway was stimulated), but there were no changes in pulse, blood pressure, or circulating catecholamine levels. No qualitative changes in proximal intestinal pressure activity were detected. These studies suggested that sustained somatic stimuli resulted in reduced postprandial antral phasic pressure activity and the similarity in the responses to TENS applied to the hand and abdominal dermatomes suggests that the somatovisceral responses may relay at the central level. It is assumed that such a central effect results in inhibition of firing of vagal cholinergic pathways that are typically stimulated in the postprandial period by the presence of food in the stomach activating vagal afferents

Figure 2.



Electrical stimulation of the dorsal columns of the spinal cord to prevent the perception of intractable neuropathic pain signals in two patients was associated with appetite reduction and weight loss (7). In a large study, Ruiz-Tovar et al. showed that percutaneous electrical neurostimulation of dermatome T6 was associated with appetite reduction and, along with a proper diet, achieved a significantly greater weight reduction than diet alone in morbidly obese patients (8). The mechanism of appetite reduction in response to treatment is unknown, but could be explained by a possible effect on gastric motor functions.

The effects of T6 dermatomal electrical stimulation on gastric motor functions, particularly gastroduodenal motility, are unclear.

HYPOTHESIS AND SPECIFIC AIM

Hypothesis

T6 dermatomal electrical stimulation treatment results in inhibition of postprandial antral motility in healthy volunteers.

Aim

We aim to compare measurements of postprandial antral motor activity in 16 healthy participants treated with sham versus active T6 dermatomal electrical stimulation (delivered by a TENS unit).

EXPERIMENTAL DESIGN

Healthy volunteers will be recruited for this one-day study that will take place in our gastric functions laboratory at the Clinical Research Trials Unit (CRTU) at Mayo Clinic. Participants will have a multilumen gastroduodenal manometry tube placed transnasally after overnight fasting.

In a parallel group design, all 16 participants will receive a standardized breakfast meal to assess baseline post-prandial gastric motility followed by ingestion of the same standardized meal as lunch (500 kcal, see Appendix 1) at 4 hours after the ingestion of the first (breakfast) meal. Prior to the lunch meal, the subjects will receive either sham or active T6 Dermatome cutaneous stimulations with a wireless TENS unit applied 15 minutes before ingestion of the lunch meal, and immediately after completing ingestion of this meal for a duration of 60 minutes. Participants will be randomized to either sham or active treatment at the lunch meal. Hence, 8 participants will receive one set of sham stimulations (pre and post prandial in relation to lunch time meal) and 8 participants will receive one set of active stimulations (pre and post prandial in relation to lunch time meal). Participants randomized to sham will have a TENS unit connected without activation of the electrodes.

Gastroduodenal manometry will be performed to assess gastroduodenal motility during the postprandial phase of each meal, with the primary measurement being the antral motility index during the first postprandial hour.

METHODS

Participants

At least 16 healthy volunteers will be recruited for the study. We may screen up to 24 participants in order to ensure 16 fulfill eligibility criteria and complete the study. Additional participants from our list of eligible candidates will be recruited to replace early withdrawals, in the event that participants withdraw on testing day before having completed all investigative testing. Participants will be randomized in blocks of four.

Inclusion Criteria

- a. Healthy volunteers with BMI ≤ 34.99 kg/m² residing within 125 miles of Mayo Clinic in Rochester, MN; these will be healthy individuals with no unstable psychiatric disease and not currently on treatment for cardiac, pulmonary, gastrointestinal, hepatic, renal, hematological, neurological, or endocrine (other than hyperglycemia on diet) disorders.
- b. Age: 18-65 years.
- c. Gender: Men or women. Women of childbearing potential will be using an effective form of contraception, and have negative pregnancy tests within 48 hours of the test day.
- d. Subjects must have the ability to provide informed consent before any trial-related activities.

Eligible individuals will be asked to avoid taking additional medications and supplements for one week before and after the test day, unless reviewed and approved by the study team.

Exclusion Criteria

- a. Abdominal surgery other than appendectomy, Caesarian section or tubal ligation.
- b. Positive history of chronic gastrointestinal diseases, systemic disease that could affect gastrointestinal motility, or use of medications that may alter gastrointestinal motility.
- c. Positive history of spinal cord injury and/or chronic back pain.
- d. Significant untreated psychiatric dysfunction based upon screening with the Hospital Anxiety and Depression Inventory (HAD) (9) If such a dysfunction is identified by a HAD score >11 on either Anxiety or Depression or difficulties with substance or eating disorders, the participant will be excluded and given a referral letter to his/her primary care doctor for further appraisal and follow-up.
- e. Intake of medication, whether prescribed or over the counter (except multivitamins), within 7 days of the study. Exceptions are birth control pill, estrogen replacement therapy, thyroxine replacement therapy, low dose analgesia or anti-inflammatory medications (Acetaminophen and Ibuprofen) and any medication administered for co-morbidities as long as they do not alter gastrointestinal motility.
- f. Subjects may also be excluded from participation for other factors at the discretion of the principal investigator.

T6 Dermatomal Stimulation

T6 dermatomal stimulation will be achieved by utilizing an Elira TENS device (Elira Therapeutics, Inc., St. Louis, MO), following the company's device protocol. The Elira device provides a broad range of options for stimulation parameters. In particular, pulse width is programmable from 25 μ sec to 400 μ sec, pulse amplitude from 1 mA to 45 mA, pulse frequency from 1 Hz to 200 Hz, session duration from 5 min to 60 min, and number of sessions per day from 0 to 8 sessions.

- Participants randomized to active treatment will undergo 2 stimulation sessions related to lunch meal, 4 hours after consuming a standardized breakfast meal and acquiring baseline assessment of post-prandial gastric motility. The stimulation session will occur as follows: A 15-minute pre-prandial session (starting 15 minutes before the meal) and a 60-minute post-prandial session (starting immediately after completing ingestion of the meal)
- The stimulation parameters will be: 200 μ sec pulse width at 30 Hz and 40mA to achieve a stimulation goal amplitude range of 18-30 mA (depending on the subject's skin impedance and pain threshold). Each stimulation will begin at 0 mA and increase quickly to achieve the 18-30 mA.

Clinical trial stimulation will be limited to an accumulated maximum of 20.25 Joules on the test day; one 15-minute and one 60-minute stimulation sessions at 200 μ sec pulse width, 30 Hz and 40 mA deliver an accumulated 20.25 Joules.

Antral Motor Activity

On the test day, participants will attend Mayo Clinic Clinical Research Trials Unit at a prescheduled time after an 8-hour fasting period, and the following validated test will be performed following both the standardized breakfast and lunch meals.

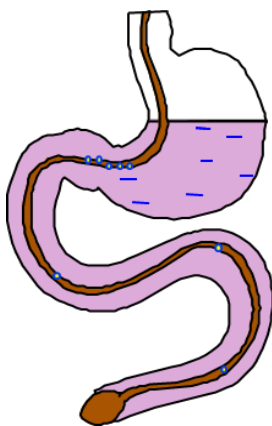
Gastroduodenal manometry

Gastroduodenal tube placement: Participants will undergo an overnight (8 hours) fast. Trained technologist (DB) and staff physician (MC) will perform the placement in accordance with standard practice over the past 25 years. A 4-meter Teflon (green) guidewire will be placed in the duodenum in order to facilitate placing the combined manometry tube into the duodenum.

The position of the manometry tube will be verified using fluoroscopy.

Figure 3. Multilumen manometric assembly in the upper gastrointestinal tract to measure distal antral motility in postprandial period

Gastroduodenal manometry: Gastrointestinal manometry will be performed after an overnight fast with a multiple-lumen perfusion tube



(external diameter: 6mm) that is introduced along a guidewire placed with aid of fluoroscopy. Each of the fifteen perfusion channels of the manometric tube will be perfused with distilled water via a pneumohydraulic pump (perfusion rate: 0.15ml/min, perfusion pressure: 14psi) and attached to a strain gauge transducer (model PX-MK099, Edwards Lifesciences, Irvine, CA.). One side opening was made in each channel of the multi-lumen tube, and the positions of these openings were at the tip of the tube will be fluoroscopically placed across the antroduodenal region; thus, the tip of the tube lies near the ligament of Treitz. Fasting pressure activity will be recorded in each volunteer for 1 hour while they are fasting. Then, each individual will ingest a 500 Kcal mixed solid-liquid meal consisting of scrambled egg, bread, pudding, and milk at each test meal (Appendix 1). Pressure activity will be recorded after each test meal (10). The participant will be seated at a 45 degree angle during this test.

The gastroduodenal tube will remain in place and the gastrointestinal manometry test will be performed again 4 hours later at the lunch meal. The lunch GDM measurements will be performed while sham or active TENS treatment is taking place.

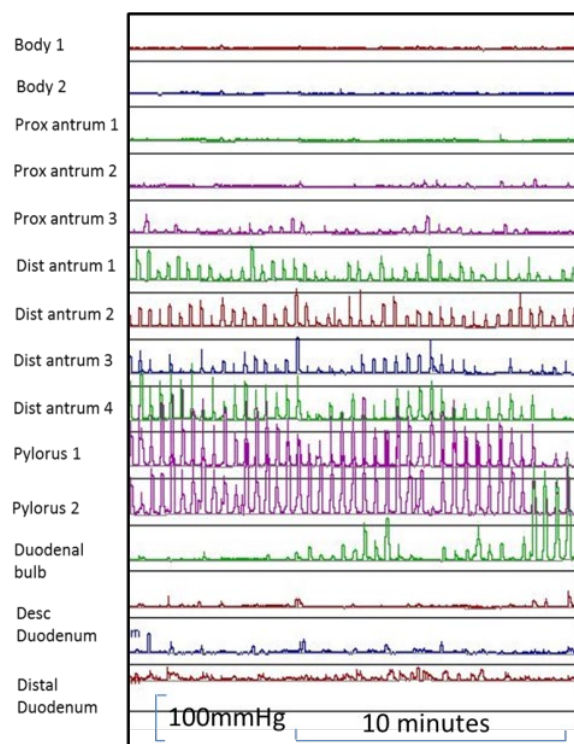
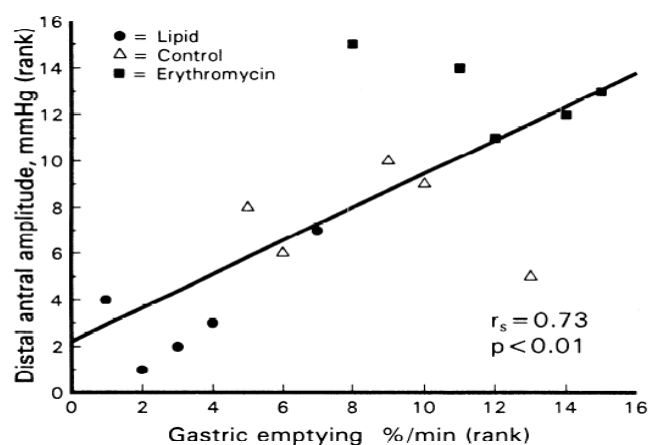


Figure 4 shows the postprandial gastric motility following ingestion of a solid-liquid meal. Note the increased frequency of distal antral phasic contractions and coordination with pyloric and duodenal motility. Reproduced from ref. 11.

Figure 5 shows a correlation between distal antral contraction amplitude and rate of gastric emptying (12).



Analysis of manometric recordings

Antrum: Phasic pressure activity in the distal antrum recorded on the manometric tracing is quantified manually. The most distal antral site will be identified as a site recording up to three waves per minute, which is (a) just proximal (1cm) to a site recording duodenal-type wave or

(b) just proximal to a site exhibiting a mixture of antral-type and duodenal-type waves associated with baseline elevation (pyloric-type activity). For each sequential 15-minute period and for the 1-hour postcibal period, a motility index (MI) will be calculated using the formula: $MI = \log(\text{sum of amplitude} \times \text{number of contractions} + 1)$. The average 15-minute antral MI will be calculated, as previous studies showed that the cumulated slope of antral motility indices is linear (13).

Statistical Analysis

Sample size assessment - The standard deviation used for the sample size calculations was calculated from the observed value of distal antral activity in healthy volunteers in the absence of any treatment: 14.3 ± 0.66 (SD) (10,13). Comparison of 8 Participants in the active vs. sham treatment arms will have sufficient power to detect a difference between the 2 groups (Unpaired t-test; Parallel group design) of distal antral MI of 0.995 units or 7.0% relative to controls (10,13). It is to be noted that the antral MI measurement is on a logarithmic scale and, therefore, a 10% reduction in **antral** motility index is clinically relevant since it is associated with reduction in gastric emptying rate.

Response	Mean	SD	Predicted detectable effect size (%(absolute #)), n=8 per group unpaired analysis
Postprandial distal antral motility index	14.3	0.66	7.0% (0.995 MI units)

Data obtained from ref. 10; predicted detectable effect size is shown with 80% power, $\alpha=0.05$.

Statistical Methods

It is anticipated that the primary endpoint (the logarithmically transformed antral MI) will be normally distributed. We shall use an unpaired student's t-test to compare the antral MI in the sham versus active treatment groups.

An interim analysis will be performed for **“futility” assessment** after the first 8 participants. In such an analysis, we would have 4 patients per group, assessed in unpaired t test based on parallel group design. Using the same SD of 0.66, a comparison of 4 patients per group would have sufficient power to detect a significant difference in antral motility index of 1.572 (11 %). If the interim analysis shows that the antral MI difference between the 2 groups is <0.75 (~5%), we would consider whether it would be futile to continue the study and completing 16 participants. On the other hand, if the difference in mean antral MI is >0.75 in the two groups, we would complete the study. Since this interim analysis is conducted for “futility” rather than for efficacy, we will **not** correct the α statistic from 0.05 (e.g. to 0.025) on completion of the pre-specified sample of 16 subjects.

Anticipated Results and Significance

We anticipate a lower antral motility index with active T6 dermatomal TENS treatment compared to sham treatment. This physiological study will provide information about the potential effect of T6 dermatomal stimulation on gastroduodenal motility, that could play a role in inducing other effects currently under investigation (appetite reduction, gastric emptying etc).

Device Safety: Designation of Non-Significant Risk

Based on the FDA guidance on Significant Risk and Nonsignificant Risk Medical Device Studies (14), the proposed study does not meet the definition for a significant risk (SR) device study and hence is a non-significant risk (NSR) clinical study.

Moreover, the Elira TENS device is regarded as an NSR device on the following basis:

- It is not implantable
- It does not support or sustain human life
- It is not for use of substantial importance in diagnosing, curing, mitigating or treating a disease (no claims related to obesity have been made by the manufacturer)
- It does not present a potential for serious risk to the health, safety or welfare of the participant

It is important to note that the Elira TENS device is essentially similar to commercially-available, over-the-counter TENS units that can be purchased at local pharmacies and are commonly utilized for self-administered therapy.

Appendix 1

Test meal nutritional information:

Item	Amount	Unit	Weight (g)	Kcal	g Carbohydrate	g Protein	g Fat
Egg, Extra Large	2	Item	112	160	2	14	10
Bread, Whole Wheat	1	Slice	36	100	17	5	2
Jell-O® Vanilla Pudding	1	Item	110	110	23	1	1.5
Milk- 2%	1	Item	240	130	12	8	5
TOTAL	N/A	N/A	498	500	54	28	18.5

REFERENCES

1. Chen J. Mechanisms of action of the implantable gastric stimulator for obesity. *Obes Surg* 2004;14(Suppl. 1):S28-S32
2. De Luca M, Segato G, Busetto L, et al. Progress in implantable gastric stimulation: summary of results of the European multicenter study. *Obes Surg* 2004;14:33-39
3. Brown AM, Malliani A. Spinal sympathetic reflexes initiated by coronary receptors. *J Physiol* 1971;212:685-705
4. Wolff, H. The mechanism and significance of the cold pressor response. *Q J Med* 1951;20:261-273
5. Sato A, Schmidt RF. Somatosympathetic reflexes: afferent fibers, central pathways, discharge characteristics. *Physiol Rev* 1973;53:916-947
6. Camilleri M, Malagelada JR, Kao PC, Zinsmeister AR. Effect of somatovisceral reflexes and selective dermatomal stimulation on postcibal antral pressure activity. *Am J Physiol* 1984;247(6 Pt 1):G703-G708
7. Pereira E, Foster A. Appetite suppression and weight loss incidental to spinal cord stimulation for pain relief. *Obes Surg* 2007;17:1272-1274
8. Ruiz-Tovar J, Oller I, Diez M, Zubiaga L, Arroyo A, Calpena R. Percutaneous electrical neurostimulation of dermatome T6 for appetite reduction and weight loss in morbidly obese patients. *Obes Surg* 2014;24:205-211
9. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361-370
10. Camilleri M, Brown ML, Malagelada J-R. Relationship between impaired gastric emptying and abnormal gastrointestinal motility. *Gastroenterology* 1986;91:94-99
11. Nelson AD, Camilleri M, Acosta A, Busciglio I, Linker Nord S, Boldingh A, Rhoten D, Ryks M, Burton D. Effects of ghrelin receptor agonist, relamorelin, on gastric motor functions and satiation in healthy volunteers. *Neurogastroenterol Motil* 2016;28:1705-13.
12. Prather CM, Camilleri M, Thomforde GM, Forstrom LA, Zinsmeister AR. Gastric axial forces in experimentally-delayed and accelerated gastric emptying. *Am J Physiol* 1993;264:G928-G934
13. Camilleri M, Malagelada J-R, Brown ML, Becker G, Zinsmeister AR. Relation between antral motility and gastric emptying of solids and liquids in humans. *Am J Physiol* 1985;249:G580-G585, 1985

14. U.S. Food and Drug Administration. Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies. FDA 2006. Silver Spring, MD.
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf>