AUTONOMOUS NEURAL CONTROL OF GASTROPARESIS

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# Characteristics of Gastroparesis

**Diagnosis**

- Symptoms
  - Nausea
  - Vomiting
  - Early satiety

- Delayed gastric emptying on nuclear scintigraphy

- Absence of anatomic gastric outlet obstruction

**Epidemiology**

- Incidence (per 100,000)
  - 2.4 (M)
  - 9.8 (F)

- Prevalence (per 100,000)
  - 9.6 (M)
  - 37.8 (F)

- Survival (5 year)
  - 80% (p < 0.05 vs. expected)

Jung et al. Gastroenterology 136:1225-1229, 2009

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# Etiology of Gastroparesis

- **Diabetes Mellitus:** neuropathy (?)

- **Idiopathic:** post-viral, myopathy, neuropathy, autoimmune

- **Post-surgical:** vagotomy, Nissen fundoplication
Gastroparesis Treatment Options

- Diet
- Promotility agents
- Anti-nausea medication
- GJ (gastrojejunostomy) tube
- TPN (total parenteral nutrition)
- GES (gastric electrical stimulation)

Enterra® II Gastric Electrical Stimulator
(Medtronic, Inc.)

State of Gastric Electrical Stimulation

- Mechanism unknown
- Up to six months for symptom improvement
- No correlation between symptom improvement and improvement in gastric emptying rate

- GES efficacy
  - Diabetic: 80-90%
  - Idiopathic: 60-70%
  - Post-surgical: 60%

GES device implants (FY 2013)
- Worldwide: >8,000
- United States: 1,141

Enterra® II Gastric Electrical Stimulator
(Medtronic, Inc.)
COLLABORATE AND TRANSLATE

IU GASTROENTEROLOGY/HEPATOLOGY

PURDUE BIOMEDICAL/ELECTRICAL ENGINEERING

The Gastroparesis Team

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Goals for Gastroparesis

- **Improve patient care**
  - Enhance efficacy, reduce cost-of-care
  - Simplify device tuning protocols

- **Translate promising biomedical tech to the clinic**
  - Leading physicians/investigators
  - Leading engineering school

- **Develop next-generation, personalized medicine**
  - Biomarker/response marker discovery
  - Self-optimizing therapy

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Central Hypothesis

Gastric electrical stimulation modulates nausea and vomiting through a vagal mechanism

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Problems with GES Therapy

- **Variable (often short) battery life**

- **Stimulating lead failure**
  - Dislodge from generator
  - Break

- **No measurable (“objective”) response marker**

- **No standard device tuning protocol**
Our Solution: Battery Life

- Variable (often short) battery life
- Stimulating lead failure
  - Dislodge from generator
  - Break
- No measurable (“objective”) response marker
- No standard device tuning protocol

Wireless power transfer and supercapacitor technology
Miniature, leadless stimulation and measurement technology
Noninvasive measurement of vagal nerve response to GES
Autonomous neural control technology

Demo: Wireless Power Transfer
Power Storage: Supercapacitor

- Integrated within package
- Size < 1 mm² relevant to buoy antenna design
- Capacity: 1 µW/hour for 16 hours on a single charge

Our Solution: Stimulating Leads

- Variable (often short) battery life
- Wireless powering technology

- Stimulating lead failure
  - Dislodge from generator
  - Break
- Miniature, leadless stimulation and measurement technology

- No measurable ("objective") response marker
- Noninvasive measurement of vagal nerve response to GES

- No standard device tuning protocol
- Autonomous neural control technology
Demo: Leadless Pressure Sensor

The Bionode (ZIPH Labs)

- Wireless power and data transfer
- Light (<4g) fully implantable, 5x8.5x2 mm package
- Electrical stimulator option, pulses as short as 8us, 2mA
- Fiber optic stimulator option for optogenetic research
- 1 or 2 recording channels up to 5K samples/s
- Input signal amplitude range of 35uV - 10mV
- Frequency response of 5 - 2500 Hz
- Wave Stage compatible with Windows, OS X, and Linux
Our Solution: Response Markers

- Variable (often short) battery life
- Wireless powering technology

- Stimulating lead failure
  - Dislodge from generator
  - Break
- Miniature, leadless stimulation and measurement technology

- No measurable (“objective”) response marker
- Noninvasive measurement of vagal nerve response to GES

- No standard device tuning protocol
- Autonomous neural control technology

The Compound Nerve Action Potential


Experimental Setup: Gastric Electrical Stimulation in Rat

Autonomous Neural Control System [1]

Preliminary Observations in Rat

- Reproducible bioelectric activity from left cervical vagus (antral stimulation)
  - Smooth muscle component
  - Nerve component

- Activation threshold depends on stimulating electrode placement

- Response latency is inversely related to stimulus pulse amplitude

- The response marker is measurable from the nerve and skin surface

- Response averaging required to enhance signal-to-noise ratio
No GES-evoked Response Following Vagotomy

Vagal CAP Measurement with Cutaneous Electrodes in Rat

Black trace: Cuff electrode recording (N = 20)
Red trace: Cutaneous electrode recording (N = 20)
Vagal CAP Measurement with Cutaneous Electrodes in Human Subjects

Ex. Summary of 15-min Recording Session
Our Solution: Objective Tuning

- Variable (often short) battery life
- Stimulating lead failure
  - Dislodge from generator
  - Break
- No measurable (“objective”) response marker
- No standard device tuning protocol

Wireless powering technology
Miniature, leadless stimulation and measurement technology
Noninvasive measurement of vagal nerve response to GES
Autonomous neural control technology

The Gold Standard in Neurostimulation

- Increase stimulus until:
  1. Adverse effects occur
  2. Average setting is reached
  3. Patient reports symptom relief
- Repeat every few weeks
- Major limitations:
  1. Body ignores stimulus over time
  2. No control over target neuron type
  3. No true “dosing” method
**Parameters:**

- $I_{st} = 0.5$ mA
- $t_{st} = 0.4$ ms
- PRF = 5 Hz
- $t_{train} = 30$ s

**Ex. Response to 30s of Constant Stimulation**

The New Standard: Autonomous Neural Control

- Personalized medicine
- Amenable to any:
  - Patient
  - Nerve
  - Neuron type
- Therapy based on activation level maintenance
  - e.g., 0 to 100% activation
- Utilizes a nerve activation prediction model
Ex. Response to 140s of Constant Activation

Parameters:
• $I_{st}$ = Variable
• $t_{st}$ = 0.5 ms
• PRF = 1 Hz
• $t_{train}$ = 140 s

Constant Activation with Variable Stimulation Strength


Solutions for GES Therapy

- Variable (often short) battery life
- Stimulating lead failure
  - Dislodge from generator
  - Break
- No measurable ("objective") response marker
- No standard device tuning protocol

- Wireless power transfer and supercapacitor technology
- Miniature, leadless stimulation and measurement technology
- Noninvasive measurement of vagal nerve response to GES
- Autonomous neural control technology
Dynamic Control of Gastroparesis

Approach

• Innovate with the end user in mind

• Fit device to patient, not patient to device

• Use ANC to link vagal response marker to:
  – Patient symptom surveys
  – Gastric output
  – Blood biomarkers
  – Exams
  – Other health data?

Summary of Collaboration

Clinical Study (IUSM)

Classify GES-evoked vagal nerve compound action potentials

Correlate vagal nerve response to gastric stimulation efficacy

Animal Study (Purdue)

Compare VNS to GES in animal model of diabetic gastroparesis

Use algorithm to replicate human action potential patterns in rat

New intellectual property

Develop new diagnostic and therapeutic tools for gastroparesis

Design clinical study to evaluate new tools and treatments

Aim 1

Aim 2

Aim 3

Scope of Work

Apply for extramural funding

Apply for extramural funding

Publish

Publish
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