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

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

Central Hypothesis
Gastric electrical stimulation modulates nausea and vomiting through a vagal mechanism

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

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

\[\leftrightarrow\] 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
- 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
Demo: Leadless Pressure Sensor

• 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

Pre-Vagotomy

Post-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
Ex. Response to 30s of Constant Stimulation

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

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


Ex. Response to 140s of Constant Activation

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

A fibers

C fibers
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

Scope of Work

- Design clinical study to evaluate new tools and treatments
- Compare VNS to GES in animal model of diabetic gastroparesis
- Use algorithm to replicate human action potential patterns in rat

Aim 1

- Clinical Study (IUSM)
  - Classify GES-evoked vagal nerve compound action potentials

Aim 2

- Correlate vagal nerve response to gastric stimulation efficacy

Aim 3

- Animal Study (Purdue)
  - Develop new diagnostic and therapeutic tools for gastroparesis

New intellectual property

Apply for extramural funding

Publish

Apply for extramural funding

Publish
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