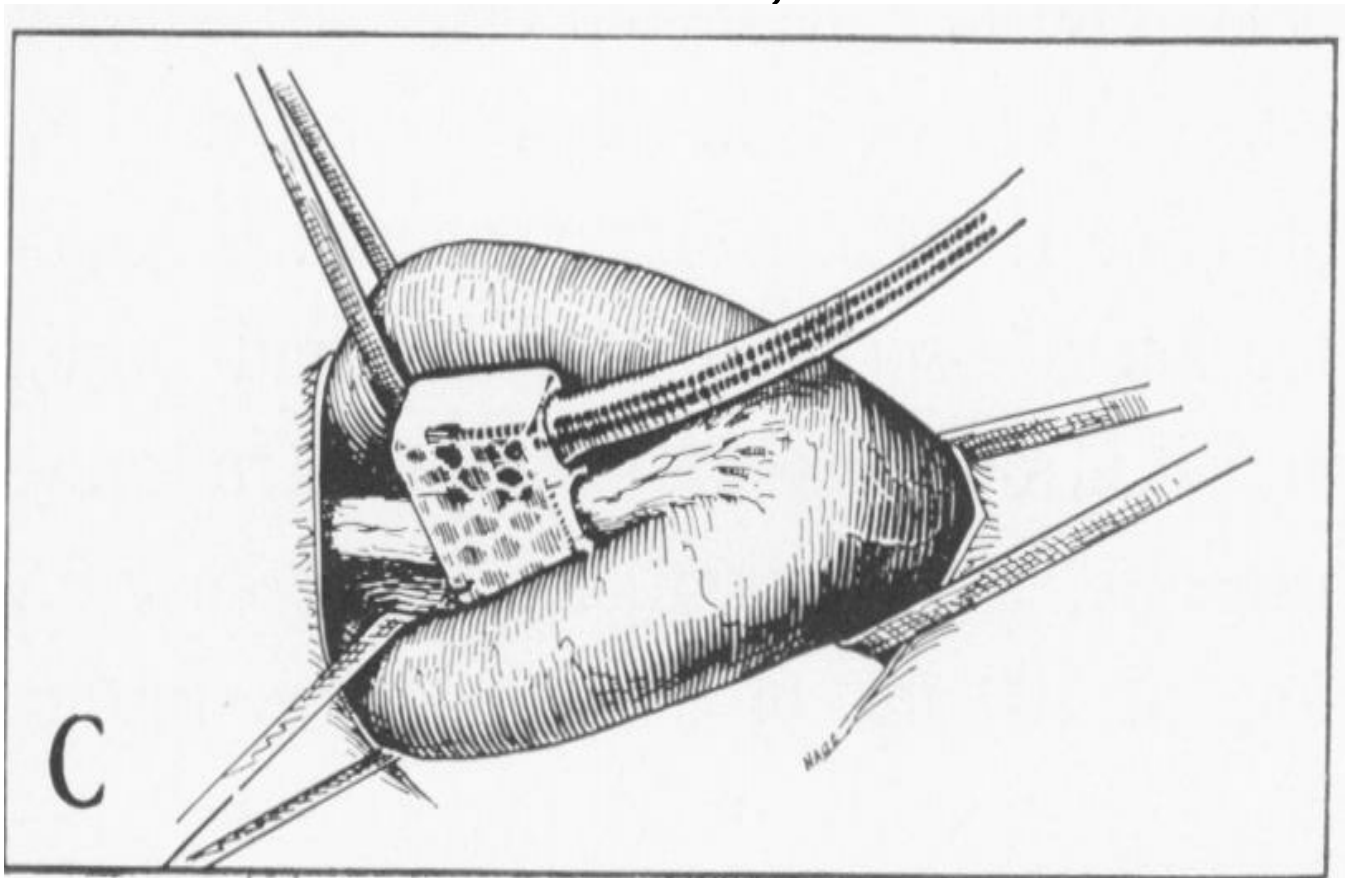
Current Neuromodulation Approaches for End-Organ Systems

Kip Ludwig, Ph.D.
Program Director for Neural Engineering
NIH/NINDS

National Institutes of Health

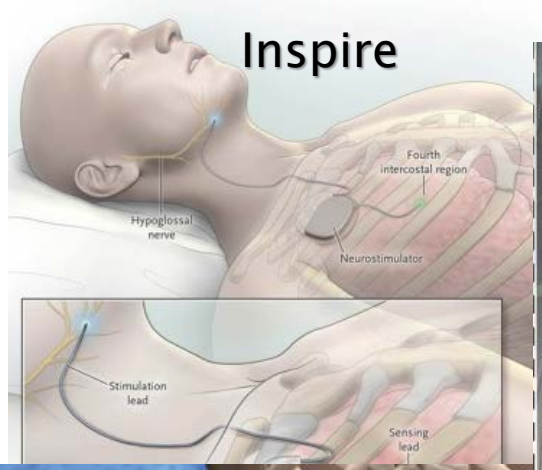
An Old Idea – New Opportunities

Braunwald,1970



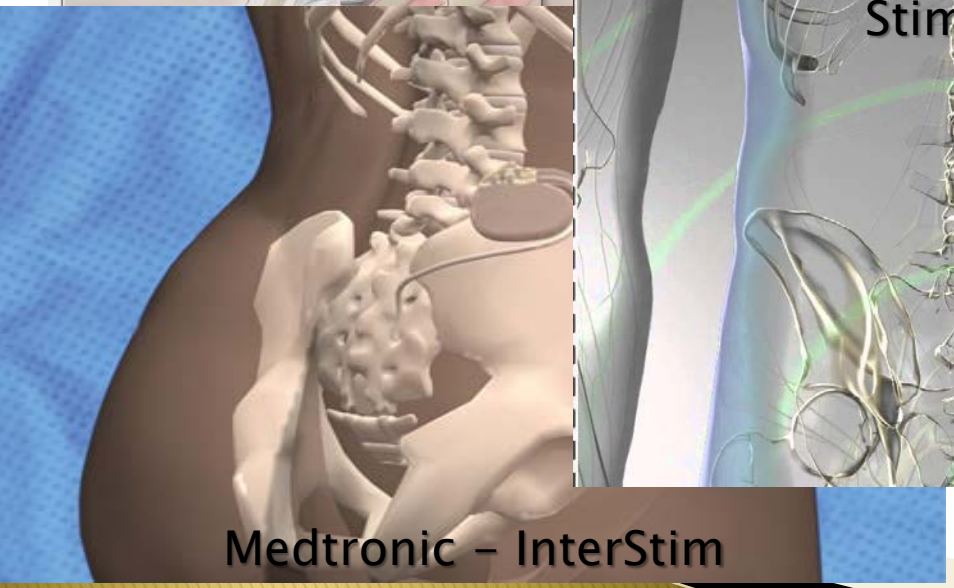
Vagal stim for mapping to spleen in 1870's & 1880's (Bulgak, Roy, Masuda)!

Recent FDA Commercial Approvals Neuromodulation: End-Organ Systems

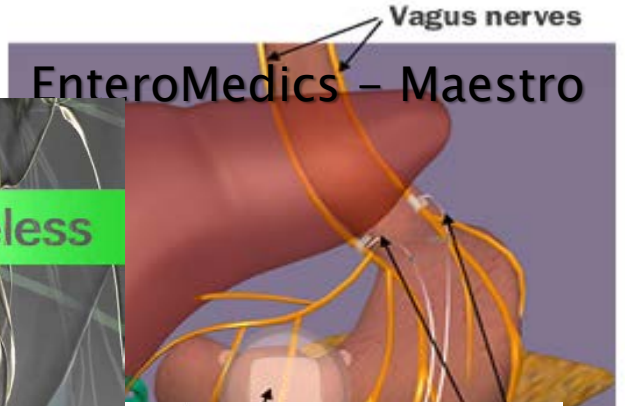


Inspire

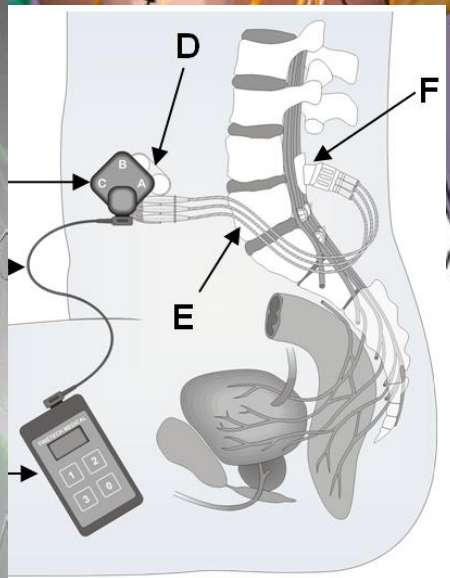
StimWave



Medtronic – InterStim



EnteroMedics – Maestro



Finetech – Brindley
VOCARE

Notable CE Marks: Neuromodulation of End-Organ Systems

- Heart Failure
  - CVRx® Neo (Baroreceptors)
  - BioControls CardioFit (Vagus)
  - Cyberonics (Vagus, submitted)
- Hypertension
  - CVRx® Neo (Baroreceptors)
  - Renal Denervation
    - Medtronic, Boston Scientific, St. Jude, Covidien, ReCor
- Obesity/Type II Diabetes
  - MetaCure Diamond (stomach muscles)

Treatments in Clinical Studies – Just the Vagus, Not Exhaustive

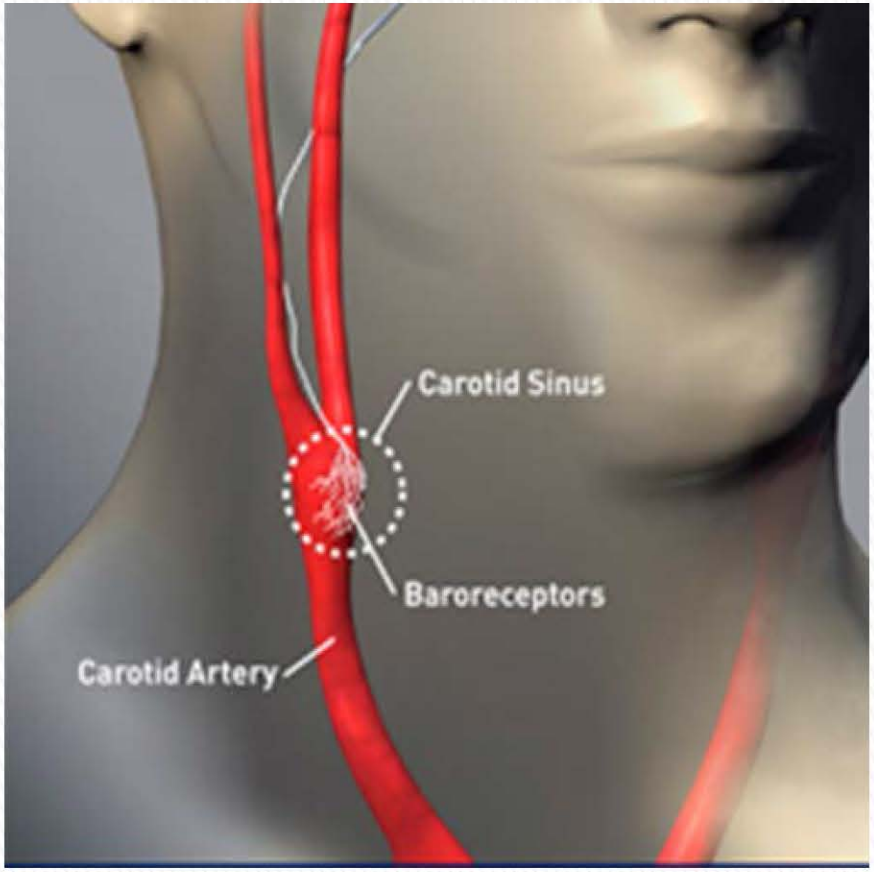
- Heart Failure
- Hypertension
- Depression
- Anxiety
- Epilepsy
- Inflammation
- Stroke Rehab/Plasticity
- Tinnitus
- World Peace
- Diabetes
- Obesity
- Bronchoconstriction/Asthma
- Pain, Migraines, Cluster Headaches

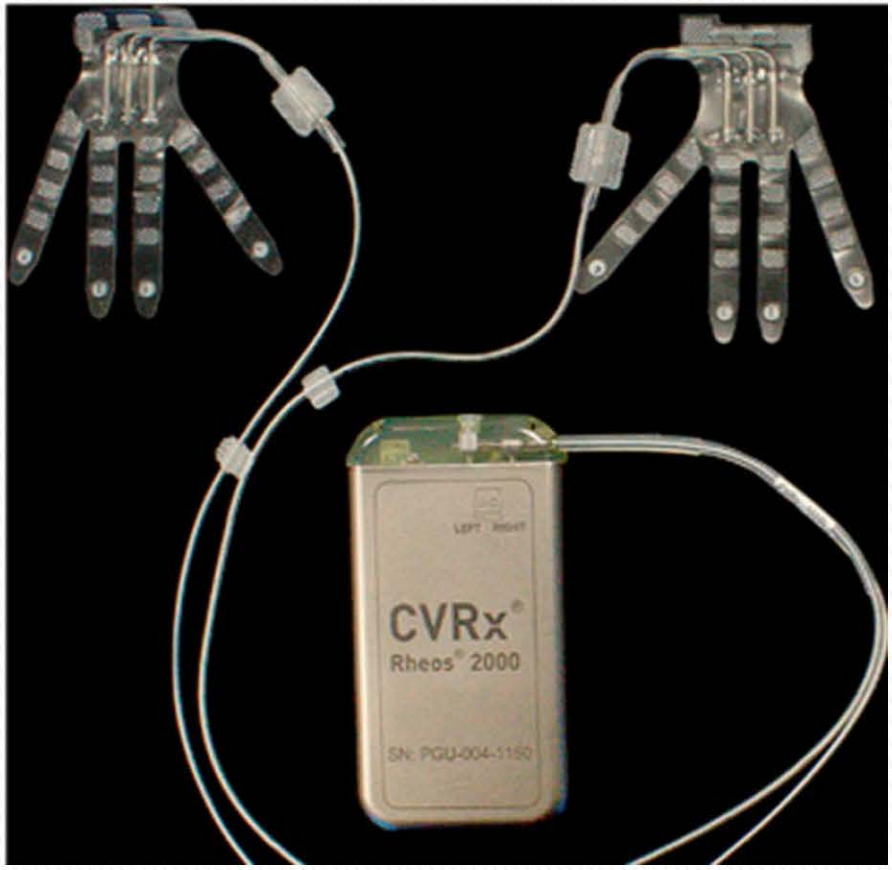
Note: I only made one of these up

RCTs Not Meeting Primary Efficacy Endpoint after CE Mark

- Enteromedics EMPOWER
  - 24.4% Excess Weight 'On' versus 15.9% 'Sham'
  - Primary endpoint >10% difference
  - FDA Panel in June: 8 to 1 safety, 4 to 5 efficacy; 6 to 2 for approval (1 abstention)
- Medtronic SYMPLICITY
  - 14 mmHg SAP Drop versus 12 mmHg in Sham Arm
- Boston Scientific NECTAR Trial
  - Cardiac remodeling 'Open Label' = CE Mark
  - No difference between 'On' and Sham Arm
- BROADEN/RECLAIM (Depression)
- SANTE Trial (Epilepsy)

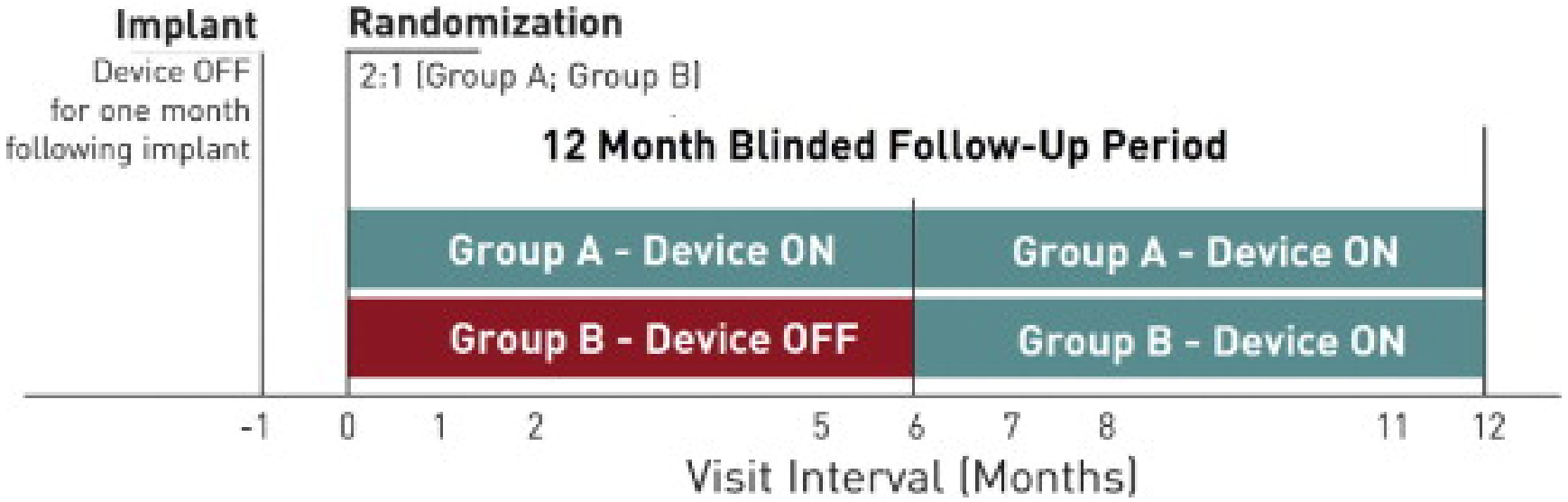
CVRx®: Stimulation of the Baroreflex





Gassler, 2014

U.S. Pivotal Trial Design

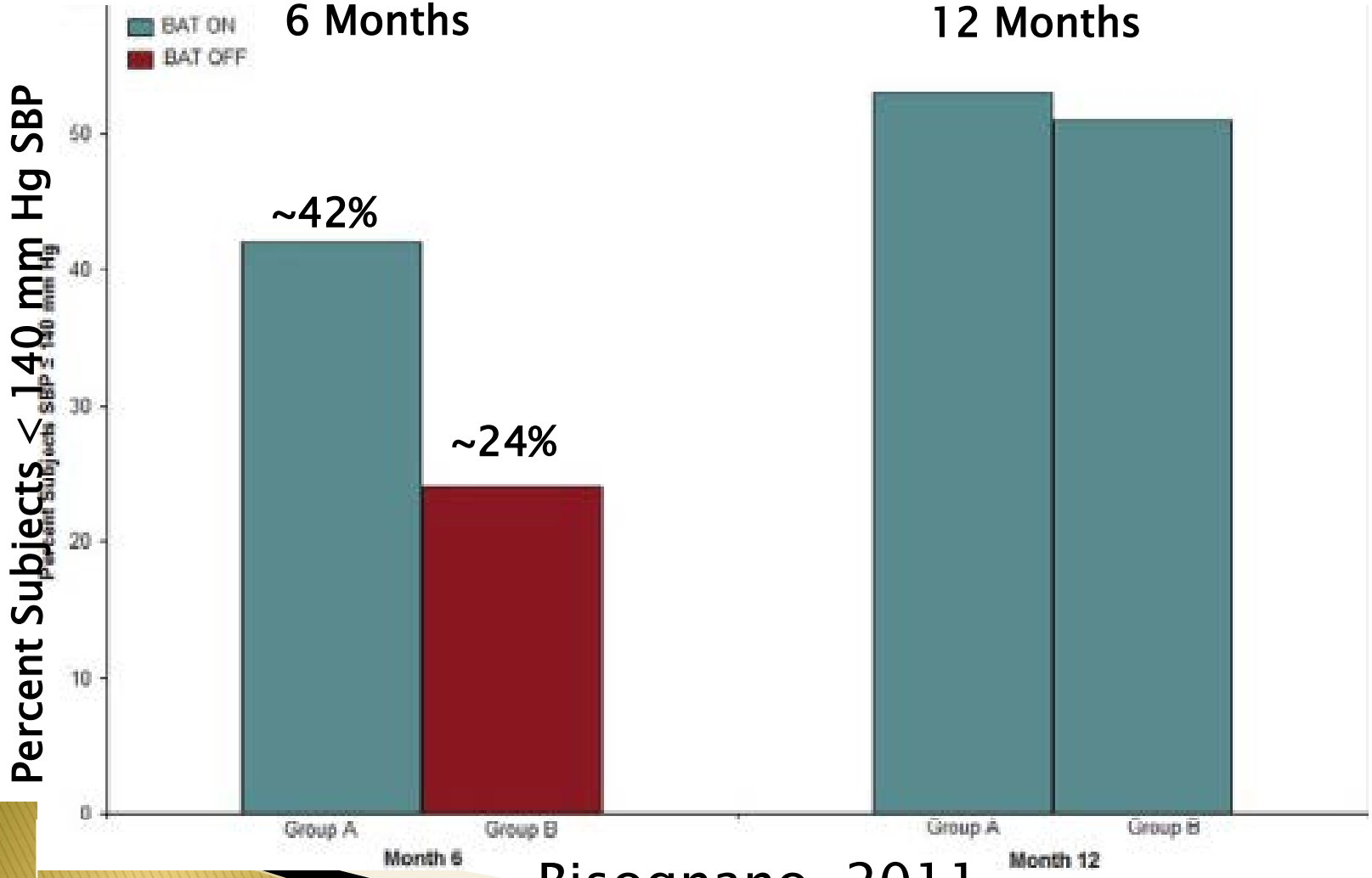


Bisognano, 2011

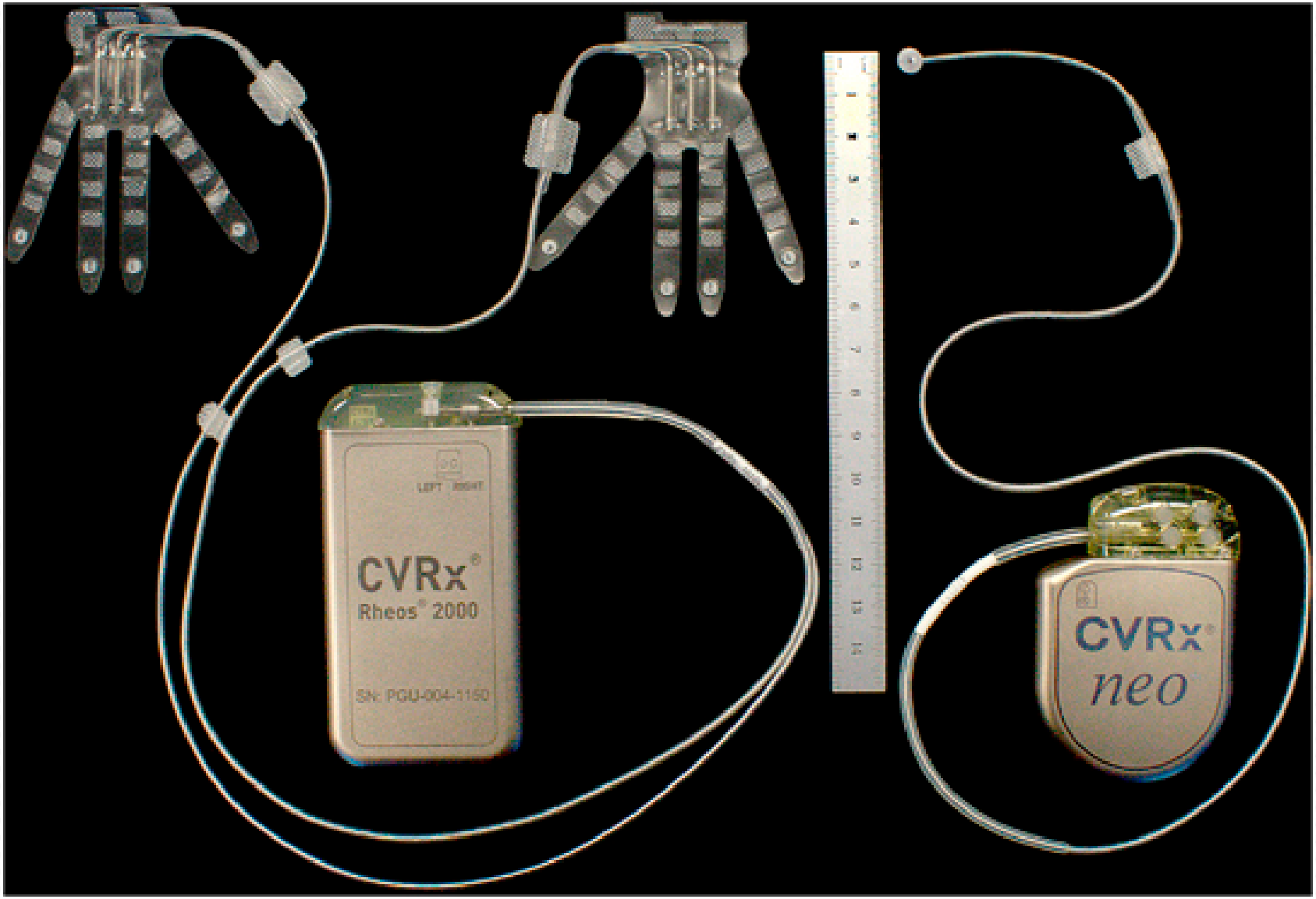
U.S. Trial Results

- 265 patients randomized
- Failed Procedural Safety Endpoint (74.8%, 82% goal)
- Failed Acute Efficacy – Percent in 'On' and 'Sham' with >10mmHg SBP Drop at 6 months (54% vs. 46%)

% of Patients with Controlled Hypertension



Bisognano, 2011



Gassler, 2014

Biology Unknowns for Designing Next-Gen Electrode

Stimulating for effect? (Baroreceptors, SIZ, Proximal Afferents or CSN)?

Stimulating to cause side effects (Pain)?

Minimum functional unit to create these effects?

Locations/densities of each in the canine and human?

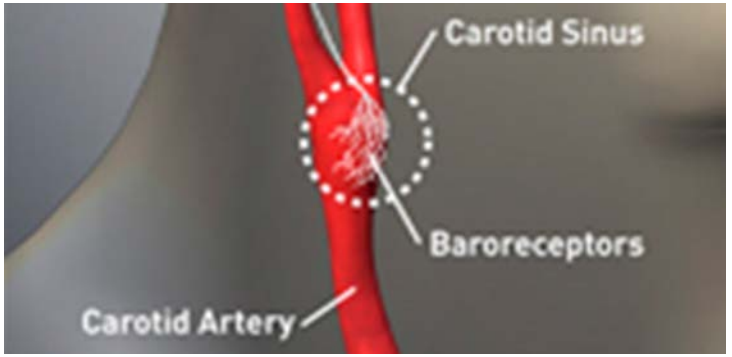
Variance in anatomy from subject to subject?

Anchoring technique prevent electrode movement?

Effectiveness given multiple medications and pathologies?

Impact of anesthesia and edema on surgical mapping?

Long-term impact of adaptation?



Limitations of the Animal Model

- Electrodes don't scale linearly
  - Electric field fall off from a dipole is $1/r^2$
    - (if '1' at 10 microns, $1/4^{th}$ strength at 20 microns, $1/16^{th}$ at 40 microns)
  - Edge effects more pronounced at smaller sizes
  - Insulation to steer current depends on size
  - Anode/cathode spacing
- Differences in orientation/size/degree of myelination of nerve fibers matter
- Fundamental differences in physiology
- Side effects are difficult to assess
- Range of pathologies that cause the same symptoms, drug interactions

Limitations of Surgical Mapping in Humans

- Limited time means art, not science
- n = 1
- Engagement at point of interface difficult to assess
  - Surrogate biomarkers of effect
  - Biomarkers with high variance
    - Blood Pressure, Heart Rate
  - Anesthesia impacts circuit function
  - Bloody field = E-field not going where it will chronically

Location, Location, Location

- Techniques to selectively activate by fiber type:
  - Size
  - Degree of myelination
  - Receptor types may be frequency responsive
- Techniques to selectively activate by location:
  - Asymmetrical pulses
  - Blocking currents
  - Chronaxie chasing
- Techniques tested via modeling and acute demonstrations, little published chronic validation
- Difference in threshold $1/5^{th}$ to 5x
- Distance from an electrode still biggest driver ($1/r^2$)!

'Neural Language of Love' – Milton Morris™

Why Weren't My Biological Unknowns 'Known'

Tools didn't exist

- No baroreceptor specific stain
- Difficult to record baroreceptor, SIZ, afferents, CSN specifically, and chronically
- Difficult to record nerves for side effect at all
- No way to determine extent of recruitment (can't see e-field)
- No tools to modulate with finer spatial resolution and cell-type specificity
- Functional anatomical maps with variance don't exist in animals, much less humans
- Limited opportunity to establish animal relevance with human data

SPARC – These problems are tractable in the near-term

Thank You!
Questions?

Kip.Ludwig@nih.gov