Vagal Nerve Blocking to Treat Obesity and the Metabolic Syndrome

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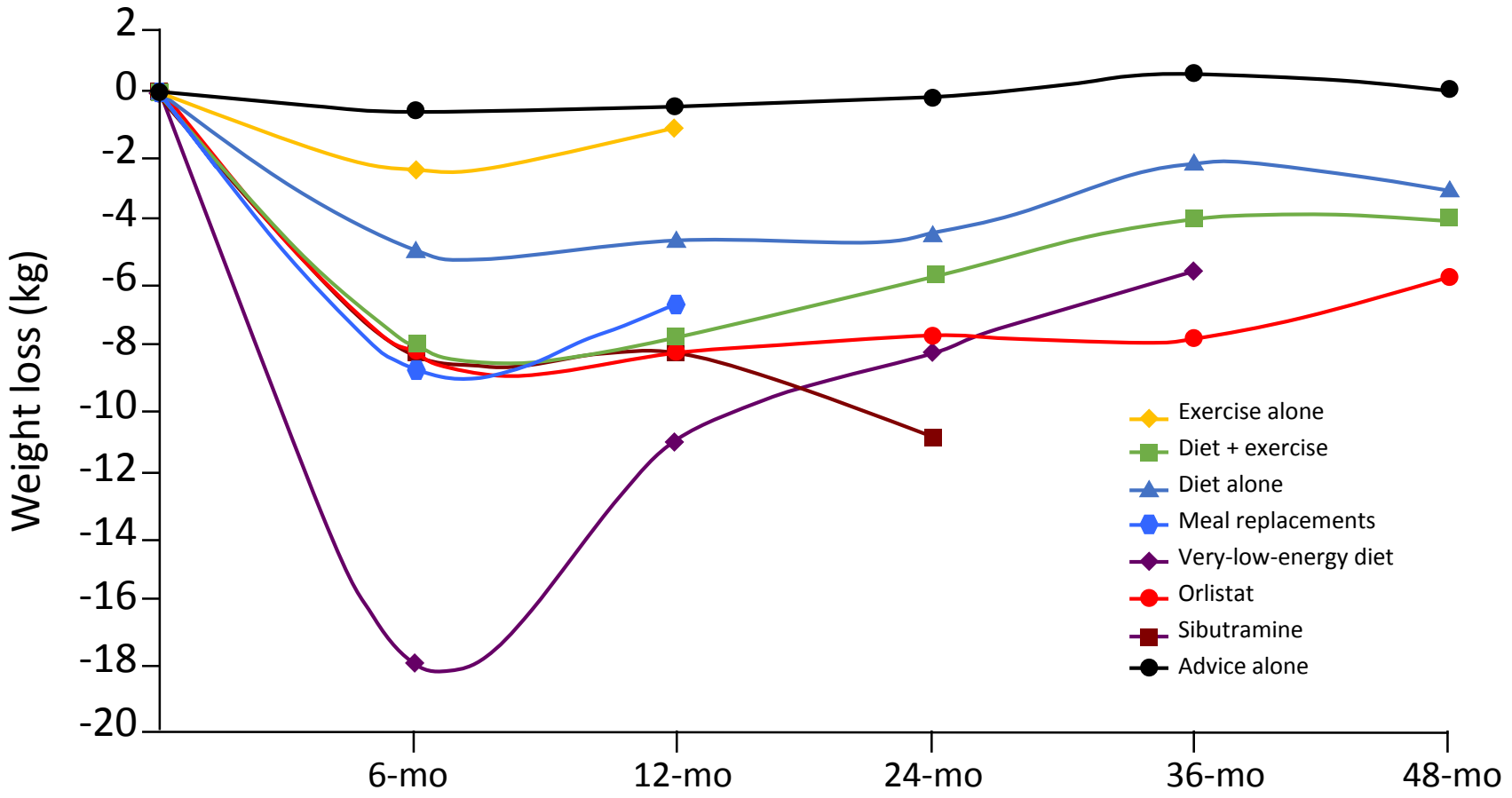
Weight loss clinical trials: Outcomes

Review of 80 studies with minimum 1 year follow-up (69% completion)



Franz MJ, et al. *J Am Diet Assoc.* 2007;107:1755-1767.

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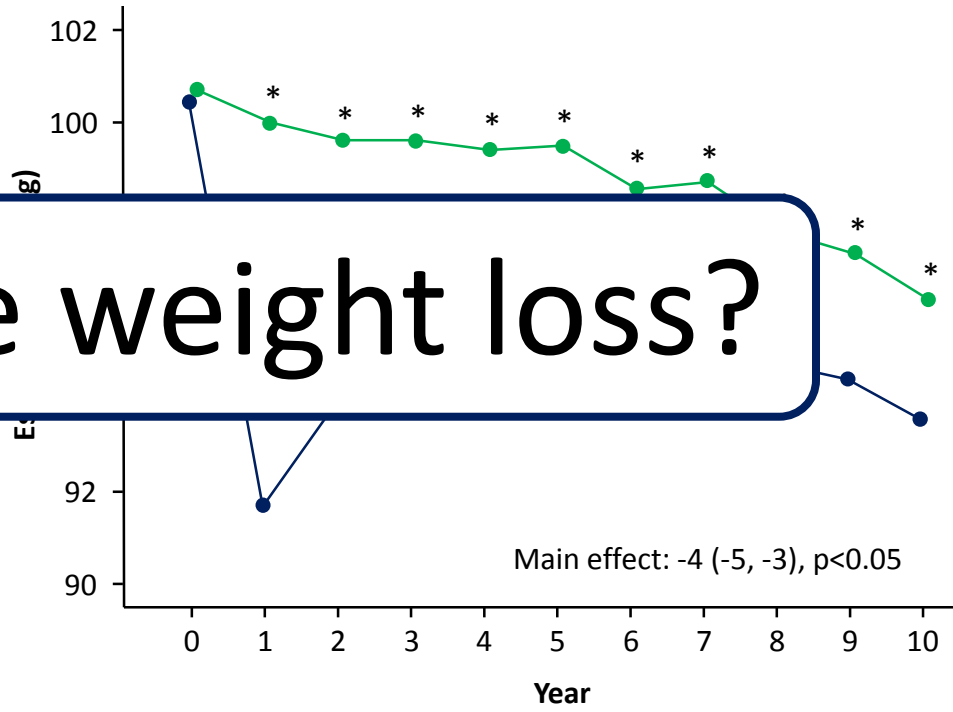
Look AHEAD trial: does weight loss reduce mortality?

- Randomized controlled trial: uses strategy of weight loss in patients with type 2 diabetes to achieve treatment goals
- Intensive Lifestyle Intervention (ILI) versus Diabetes Support and Education (DSE); 5,145 participants in 16 centers
- The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization
- Weight loss 6% in the intensive group vs 3.5% in the medical group with modest improvements in HbA_{1c}
- **No difference in primary outcome at mean follow-up 9.6 years: trial was stopped**

Do we need more weight loss?



Look AHEAD Research Group. *Arch Intern Med.* 2010;170:1566-75.
Look AHEAD Research Group. *N Engl J Med.* 2013 Jul 11;369:145-54.

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DSS: Baseline data

Patient characteristics	IMM (n=60)	RYGB (n=60)
Age, mean (SD), y	49 (8)	49 (9)
Female, no. (%)	34 (57)	38 (63)
BMI (kg/m^2), mean (SD)	34.3 (3.1)	34.9 (3.0)
Waist circumference (cm), mean (SD)	113 (12)	114 (10)
Systolic blood pressure (mmHg), mean (SD)	132 (14)	127 (15)
Laboratory values		
HbA_{1c} (%)	9.6 (1.2)	9.6 (1.0)
LDL cholesterol (mg/dL)	105 (43)	103 (36)
HDL cholesterol (mg/dL)	42 (9)	41 (1)
Taking insulin, n (%)	26 (43)	37 (62)
Medications to achieve targets, mean (SD)	4.4 (1.5)	4.1 (1.9)

BMI, body mass index; DSS, Diabetes Surgery Study; HDL, high density lipoprotein; IMM, intensive medical management; LDL, low density lipoprotein; RYGB, Roux-en-y gastric bypass

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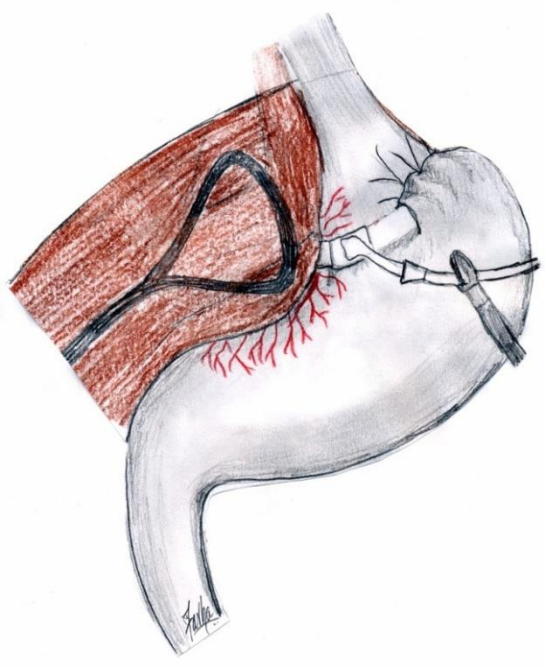
Ikramuddin S, et al. *JAMA*. 2013;309:2240-2249.

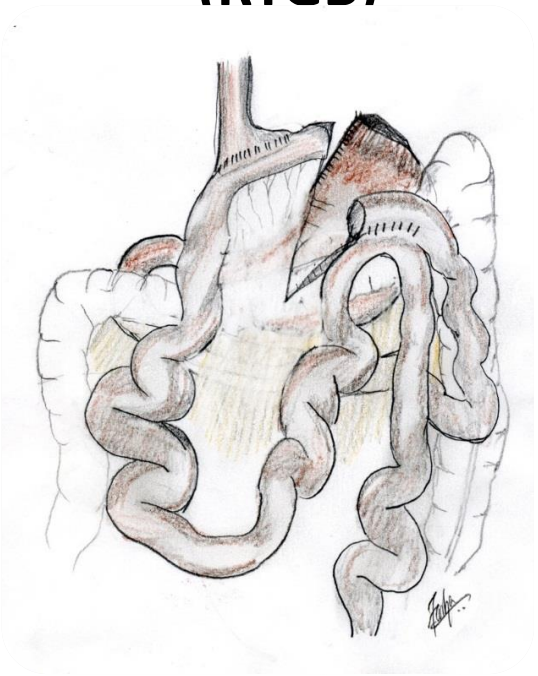
Modern surgical options

Adjustable band

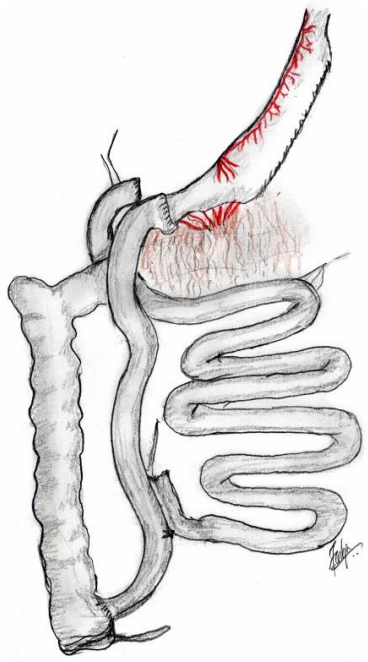


Sleeve gastrectomy

Roux-en-Y gastric bypass (RYGB)



Duodenal switch



DSS: Improvement in metabolic parameters

Glycemia	IMM	RYGB	Difference with p value
HbA1c (%)	7.8 (7.4–8.2)	6.3 (6.1– 6.5)	1.5 (1.0 – 1.9); p<0.001
HbA1c <6.0%	5 (9) [3–20]	25 (44) [31–58]	-35 [-50 – -20]; p<0.001
Fasting glucose (mg/mL)	153 (137–169)	111 103–120)	42 (23 – 60); p<0.001
LDL (mg/dL)	89 (80–97)	83 (77–90)	5 (-5 – 16); p=0.27
HDL (mg/dL)	42 (39–44)	50 (47–54)	-9 (-13 – -4); p<0.001
Triglycerides (mg/dL)	182 (142–222)	104 (92–117)	78 (36 – 120); p<0.001
Systolic blood pressure (mmHg)	124 (121–127)	115 (112–119)	8 (4 – 13); p<0.001

DSS, Diabetes Surgery Study; HDL, high density lipoprotein; IMM, intensive medical management; LDL, low density lipoprotein; RYGB, Roux-en-y gastric bypass

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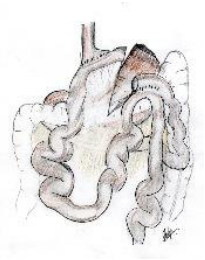
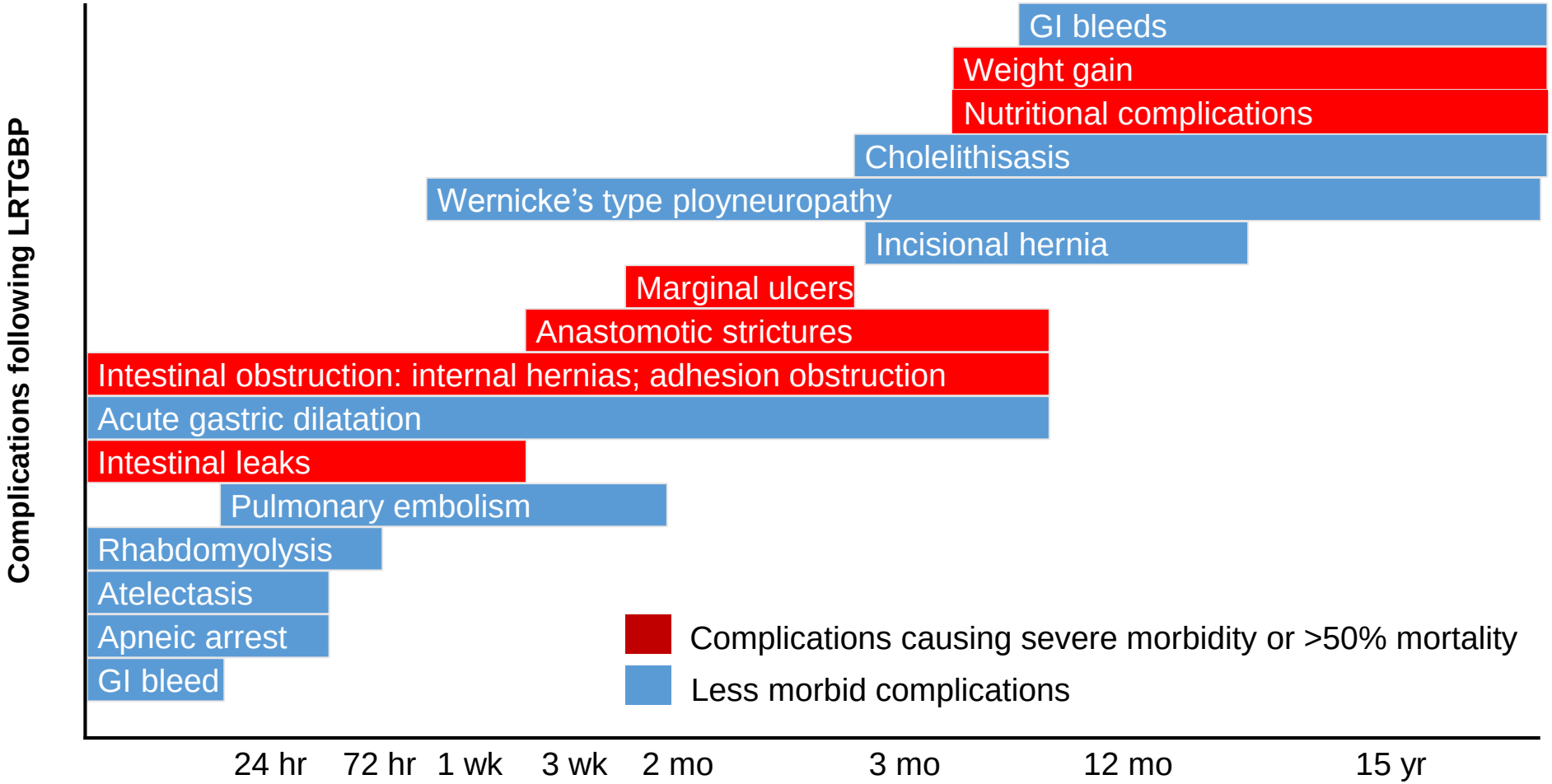
Ikramuddin S, et al. JAMA. 2013;309:2240-2249.

Complications of RYGB: Timeline





Note: Time is not represented to scale

Thodiyil PA, et al. Lippincott Williams & Wilkins. 2004.

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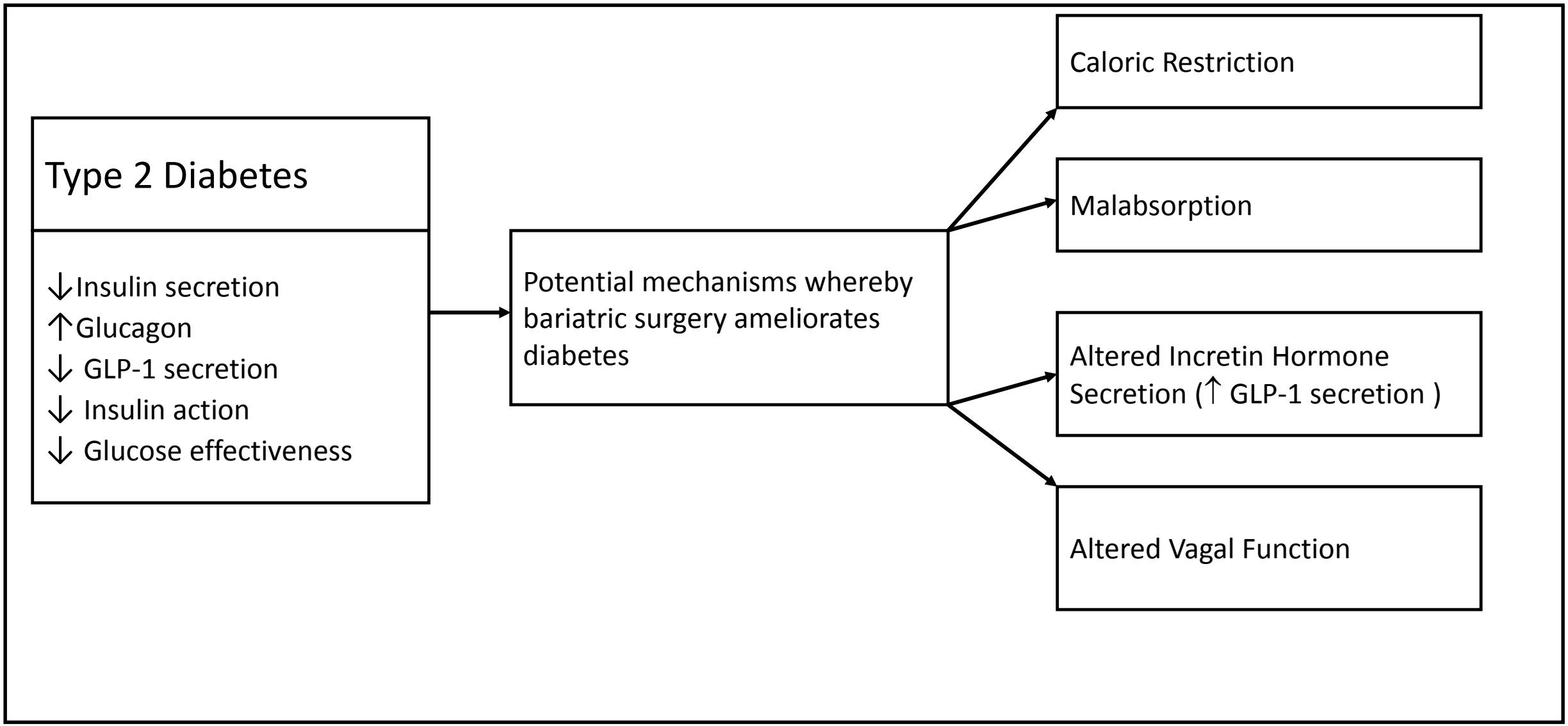
Treatment Gap

Diet, Exercise, & Lifestyle Modification	Drug Therapy		Bariatric Surgery
Difficult to achieve significant weight loss Difficult to maintain weight loss	Lack of compliance Difficult to maintain weight loss Risks: • Serotonin syndrome • Pulmonary hypertension • Cognitive effects • Birth defects • Drug-drug interactions	**LARGE TREATMENT GAP** **MOST PATIENTS RECEIVE SUB OPTIMAL TREATMENT**	Significant dietary restrictions Risks: • Vomiting • Leaks • Bleeding • Bowel obstruction • Band erosion • Malabsorption • Constipation • Dumping syndrome



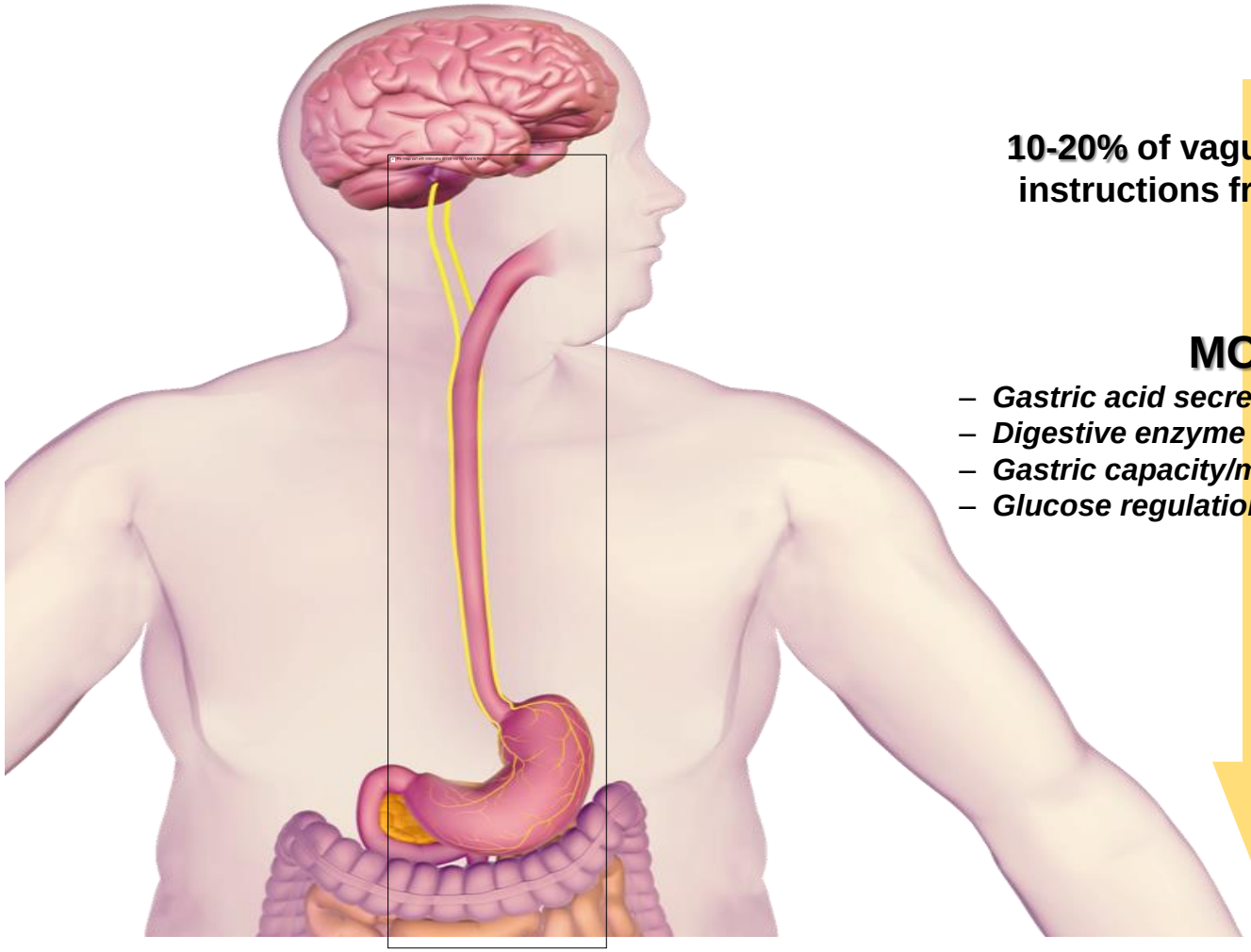
Courtesy of Adrian Vella, Mayo Clinic

Effects of surgical vagotomy

- On satiation and weight loss are often transient
- In experimental animals, accommodation reflex recovered 4 weeks post-vagotomy, through unclear metabolic or neural pathways

Kral JG. Lancet 1978; 1(8059):107-108
Takahashi T, Owyang C.. J Physiol 1997;504:479-488

Science Underlying Vagal Block



10-20% of vagus nerve fibers send instructions from the brain to the gut

MOTOR

- ***Gastric acid secretion***
- ***Digestive enzyme secretion***
- ***Gastric capacity/motility***
- ***Glucose regulation***

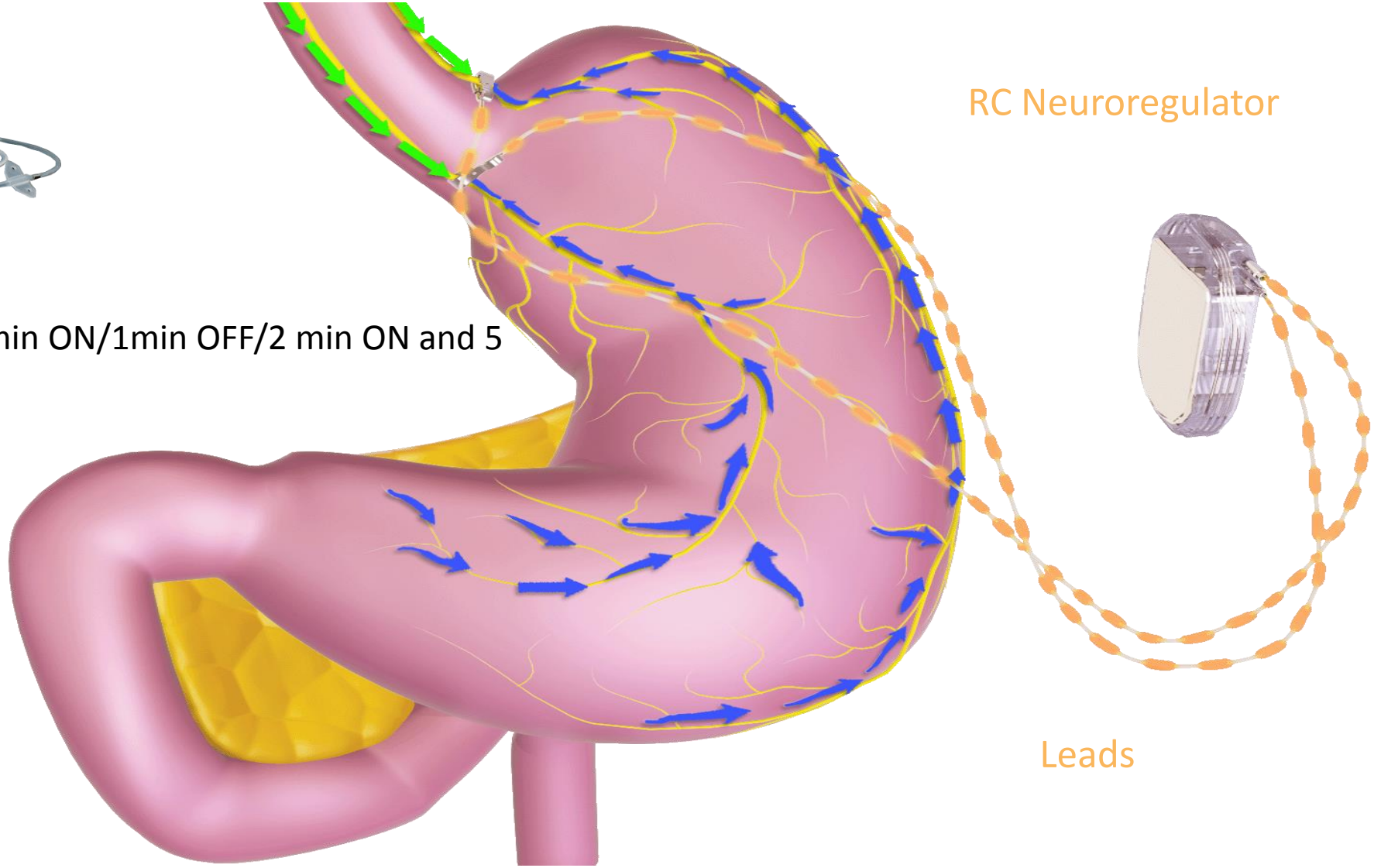
SENSORY

- ***Satiety (Hunger)***
- ***Satiation (Fullness)***
- ***Energy metabolism***
- ***Blood pressure regulation***

80-90% of vagus nerve fibers send instructions from the gut to the brain

Maestro® RF and Rechargeable Systems

RF Neuroregulator

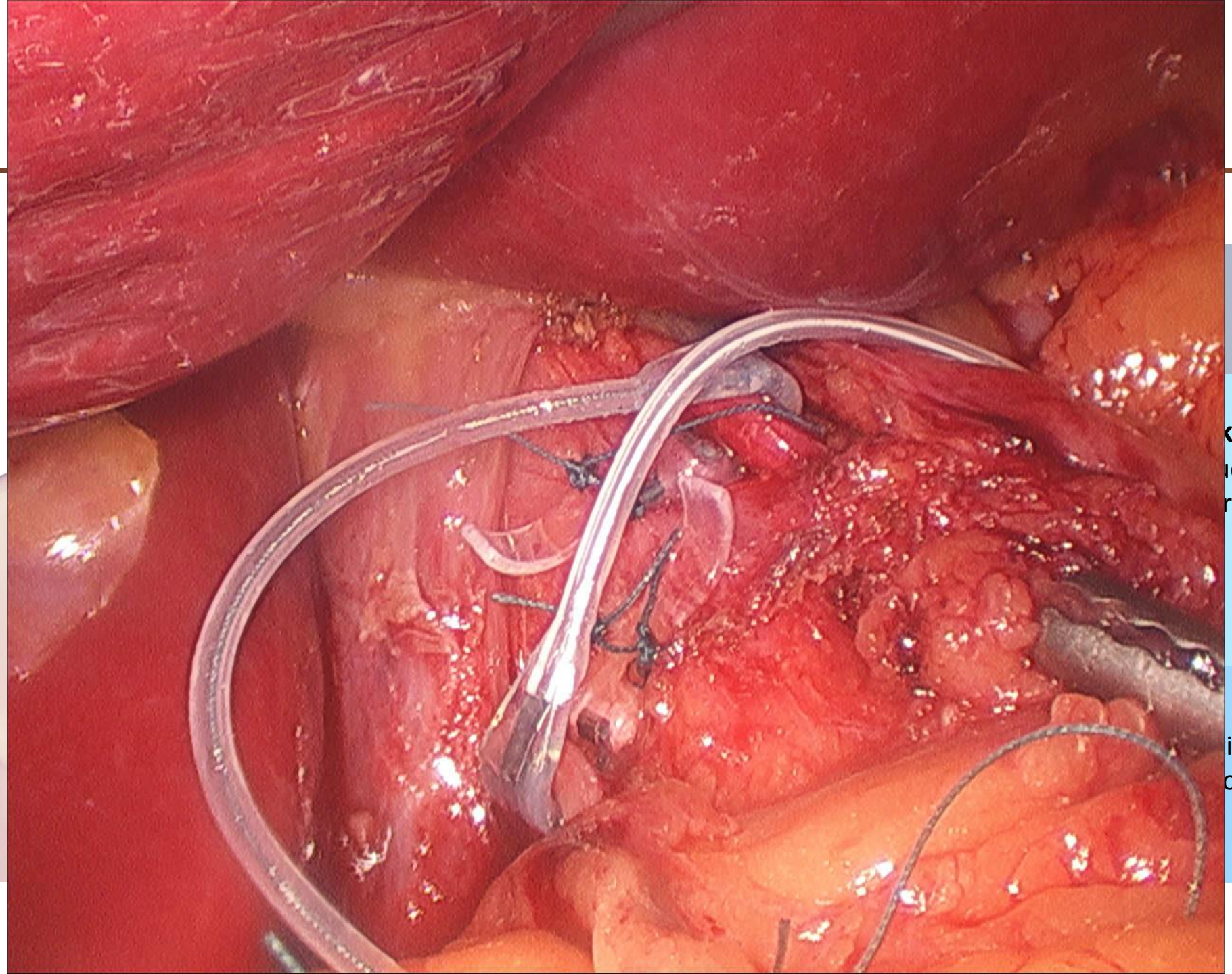


RC Neuroregulator

- Delivers intermittent 5kHz pulses 2 min ON/1min OFF/2 min ON and 5 min OFF 12 hrs/day
- Laparoscopic vagal lead placement
- Subcutaneous neuroregulator

Lead head

Leads



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Vbloc therapy: Ongoing RCT Studies

EMPOWER (2008-2013)

- **Prospective, double blind, placebo controlled randomized trial in 294 Subjects**
- **BMI range 35 to 39.9 with co-morbidity; 40 to 45 with or without**
- **Used 1st generation device with external power source**
- **3 % device or implant SAE rate, no therapy SAEs**
- **Clinically significant weight loss was observed in patients who used the device ≥ 9 hours per day in both arms**
- **An unanticipated therapeutic effect appeared to have been delivered to subjects in the control arm**

ReCharge (2011-2016)

- Prospective, double blind, placebo controlled, randomized trial in 233 subjects, same BMI range as EMPOWER
- Built on previous trial learning
  - Uses 2nd generation device with internal power source, 12+ hrs therapy delivery
  - No charge delivered to vagus nerve in surgical sham control arm
- Showed superior weight loss in VBLOC group compared to control (p=.002) and significant level of responders
- Met safety endpoint (safer than AGB)
- Published in JAMA Fall 2014
- CE marked, TGA approval and FDA approved (as of Jan 14, 2015)

Baseline Demographics

	VBLOC	Sham Control
Age (Mean ± SD)	47.1 ± 10.3	46.6 ± 9.4
Female	87.0%	80.5%
Race		
Caucasian	92.0%	94.8%
African American	4.9%	3.9%
Other	3.1%	1.3%
Type 2 Diabetic	5.6%	7.8%
Obese before Adulthood	44%	52%

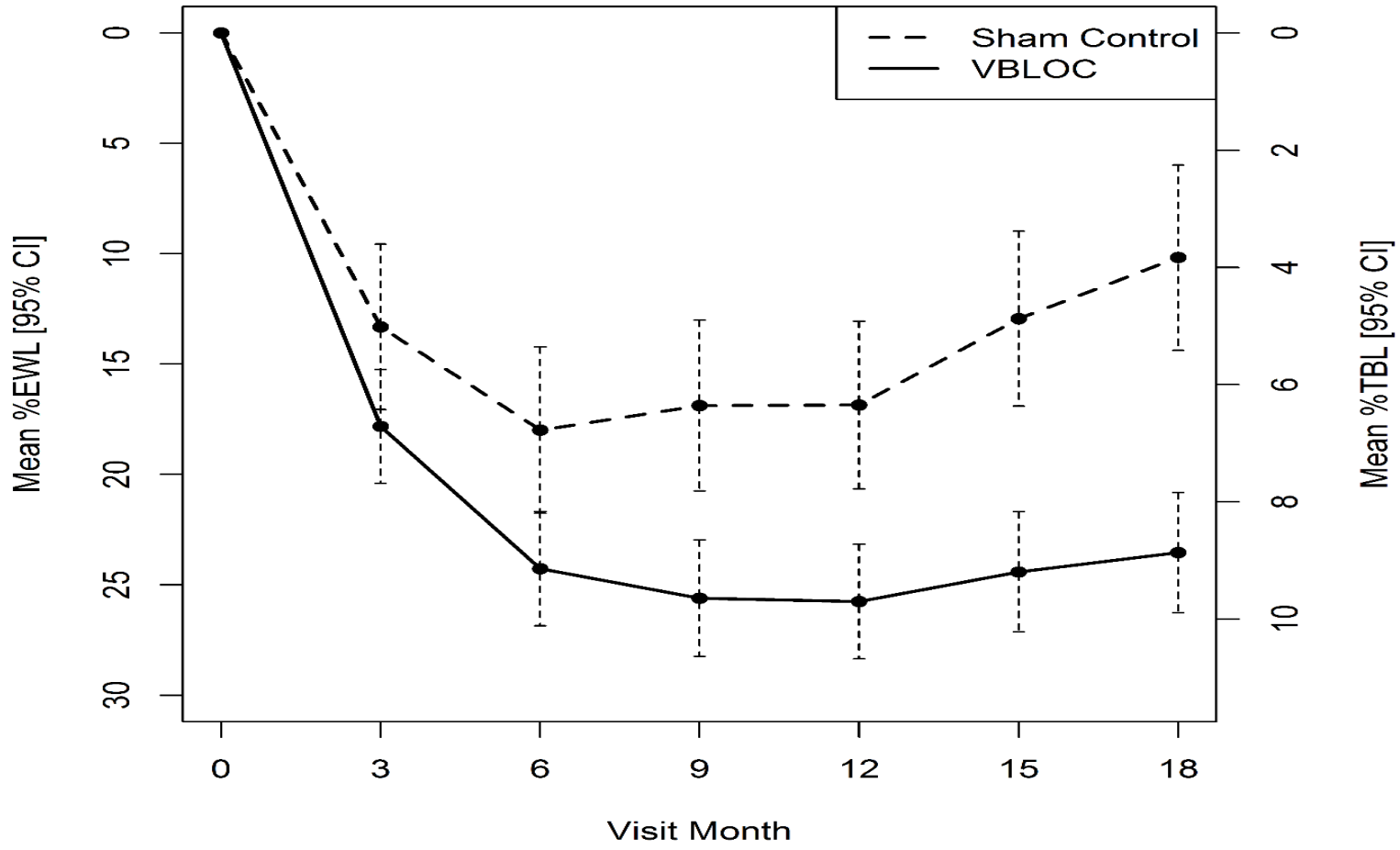
JAMA.2014;312(9):915-922.doi:10.1001/jama.2014.10540

Baseline Demographics

	VBLOC Mean ± SD (Range)	**Sham Control** Mean ± SD (Range)
BMI (kg/m²)	**41 ± 3** (34-46)	**41 ± 3** (35-48)
Weight (lbs)	**247 ± 29** (175-349)	**254 ± 31** (196-352)
Excess weight, BMI method (lbs)	**96 ± 19** (51-161)	**99 ± 21** (59-145)
Waist circumference (in)	**48 ± 5** (36-60)	**48 ± 4** (39-58)

JAMA.2014;312(9):915-922.doi:10.1001/jama.2014.10540

Sustained Weight Loss with Vagal Nerve Blockade but Not with Sham: 18-Month Results of the ReCharge Trial



In Press, 2015.

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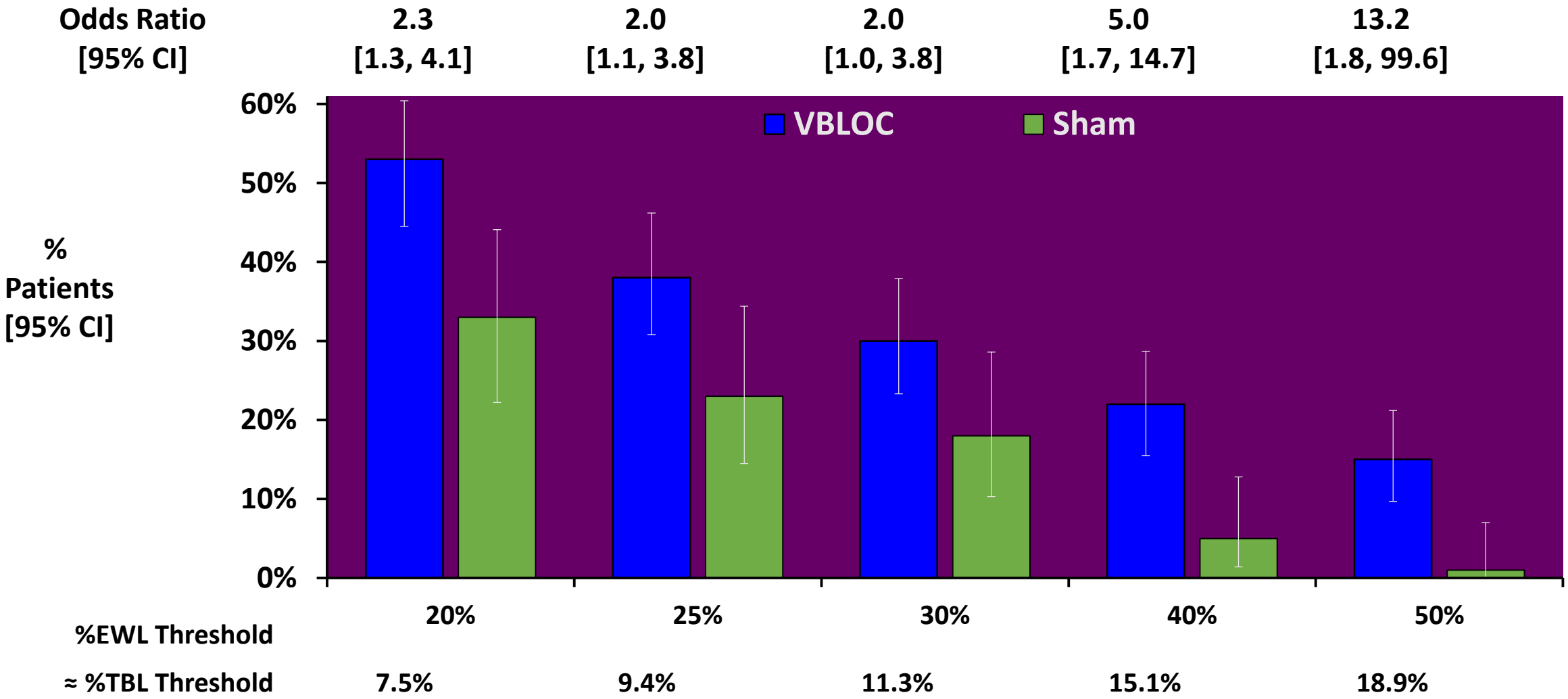
VBLOC Patients Achieved Higher %EWL at 12 Months



ITT Population, LOCF

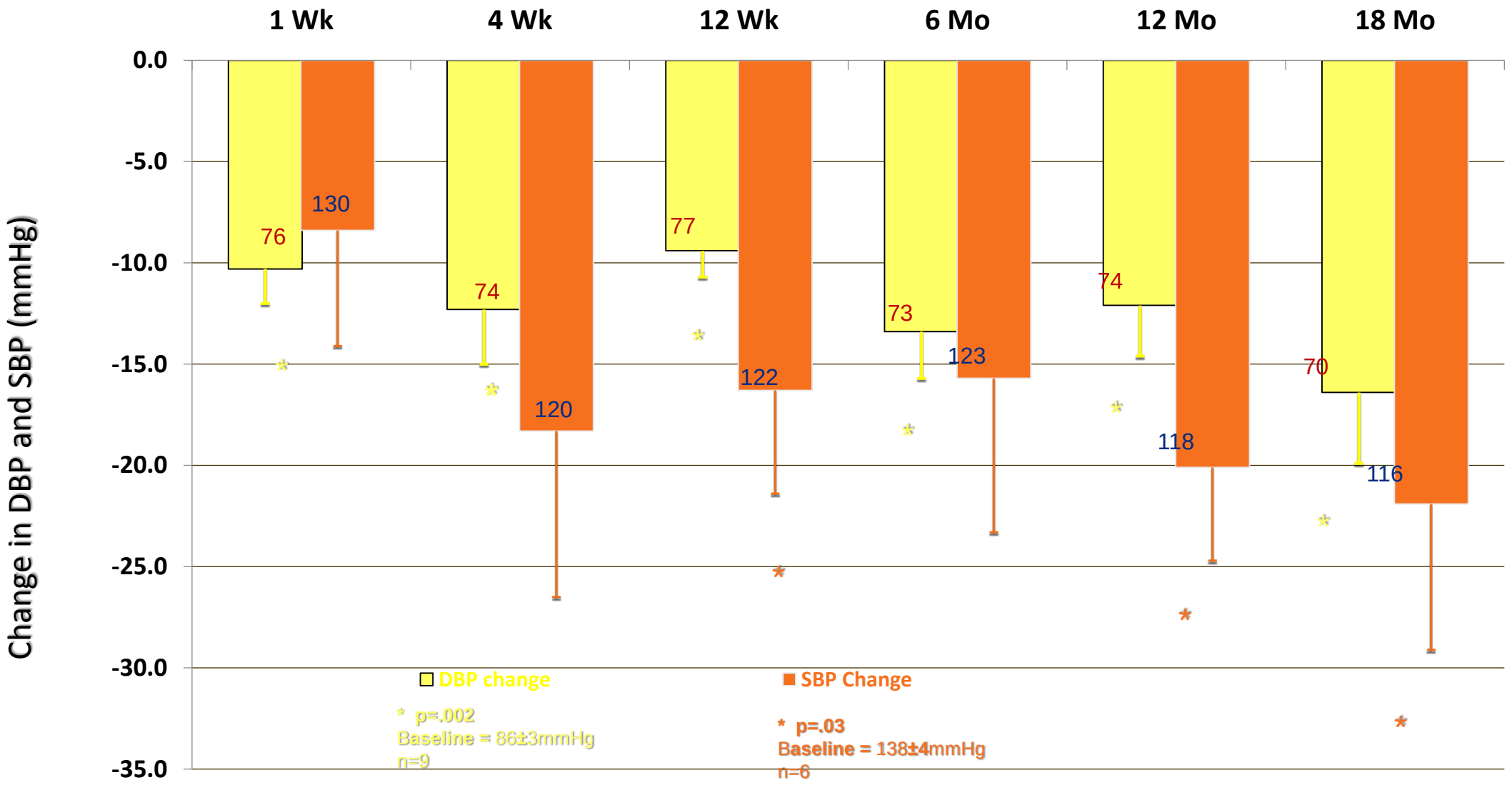
JAMA.2014;312(9):915-922.doi:10.1001/jama.2014.10540

Clinically Relevant Changes in Risk Factors for VBLOC Patients Achieved

Risk Factor	VBLOC Mean Change		
	All Patients	7.5% TBL	10% TBL
Systolic BP (mmHg)	-5	-8	-9
Diastolic BP (mmHg)	-3	-5	-6
Heart Rate (bpm)	-4	-4	-6
Total Cholesterol (mg/dL)	-9	-12	-15
LDL (mg/dL)	-5	-8	-9
Triglycerides (mg/dL)	-21	-32	-41
HDL (mg/dL)	1	2	3
Waist circumference (inches)	-4	-6	-7
HbA1c (%)	-0.3	-0.5	-0.5

Post Hoc Analysis, As-Observed

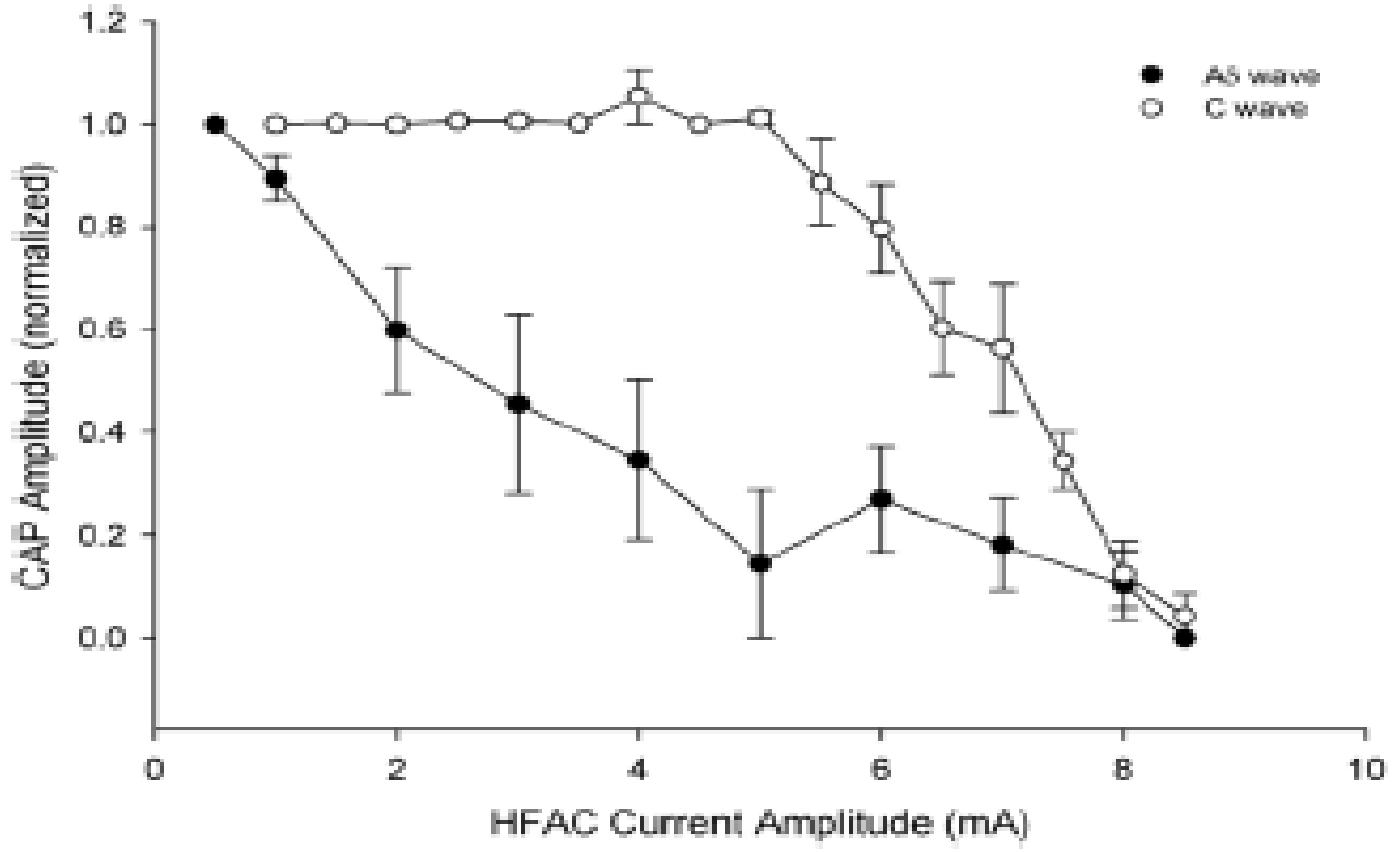
Change in Elevated DBP and SBP



Toouli et al. OSSANZ conference, April 11-13, Darwin, Australia, 2012

Reversibility and Impact on nerve histology

Isolated Rat Vagal Nerve Preparation: Block and Recovery of Abdominal Vagus

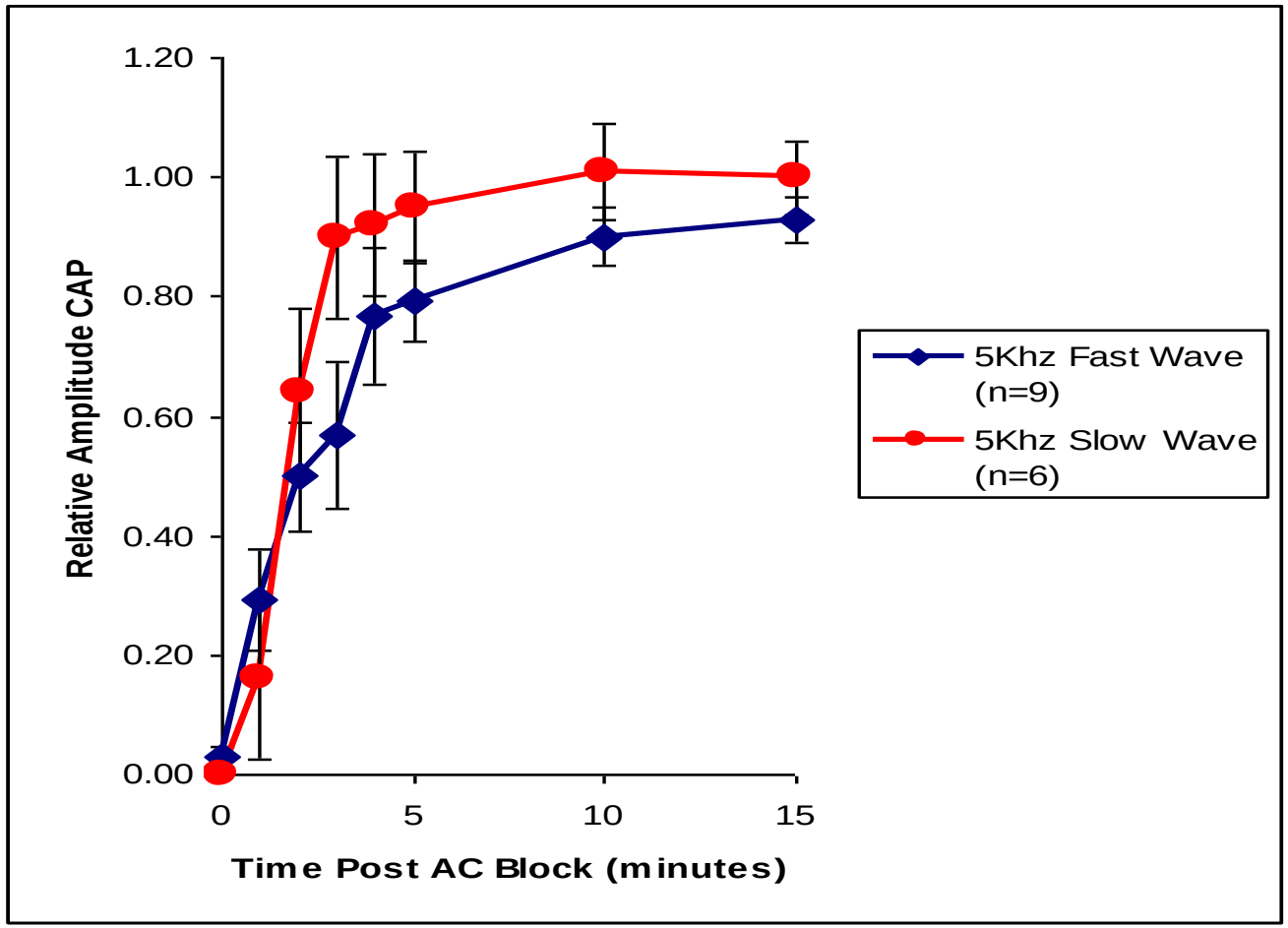


Aδ: 2mA<EC_{50}<3 mA

C: 7mA<EC_{50}<7.5 mA

Waataja et al. J Neural Eng 2011

CAP Recovery Post-block



- Electrode: Monopolar nerve cuff with Pt-Ir contact (humans, pigs), bipolar hook with Pt-Ir (rats)
- Waveform: 5 kHz charge-balanced square wave, 90µsec pulse width
- Typical Amplitudes: 1-8 mApp
- Preparation: Isolated rat vagus nerve (primarily)
- Outcome Measure: Compound action potential (typically)
- Onset observed? Not tested
- Prolonged effect (post HFAC)? Minutes of recovery
- Nerve fiber selectivity? Perhaps

- **Fast and slow waves of CAP blocked at 5000 Hz and 2-4 mA**
- **CAP recovered to 50% by 2 min and 90% by 10 min**

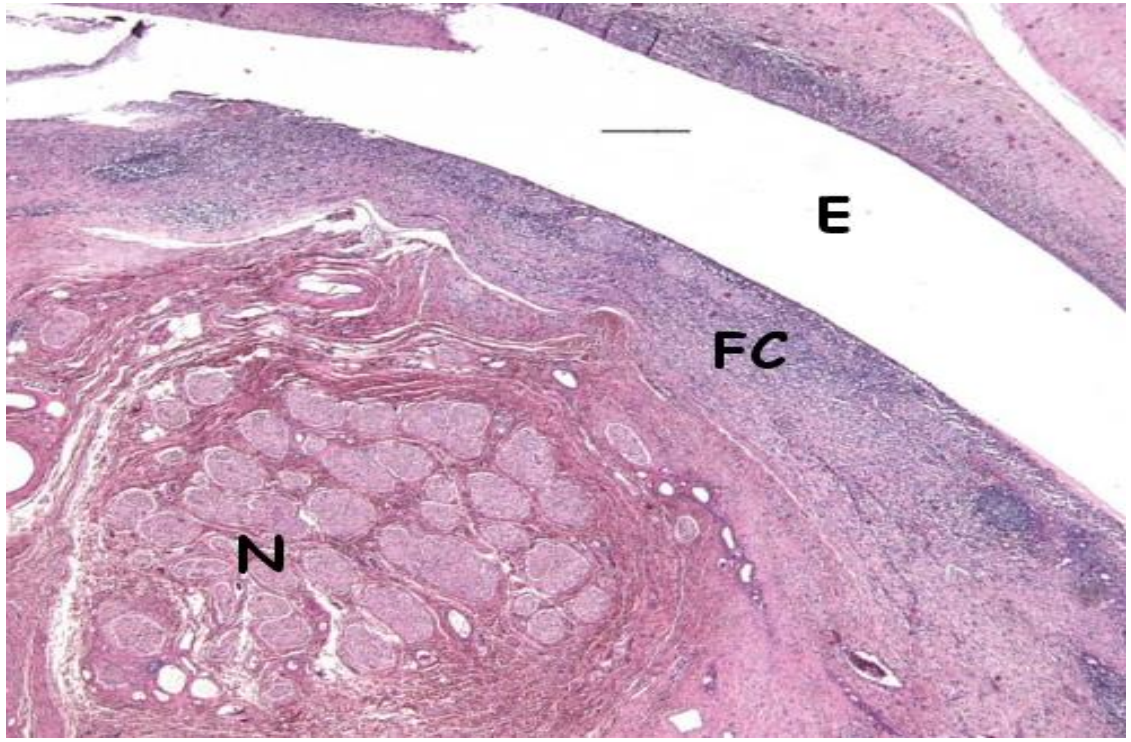
Tweden et al. Gastroenterology 2006;130:A148

Porcine Safety Models

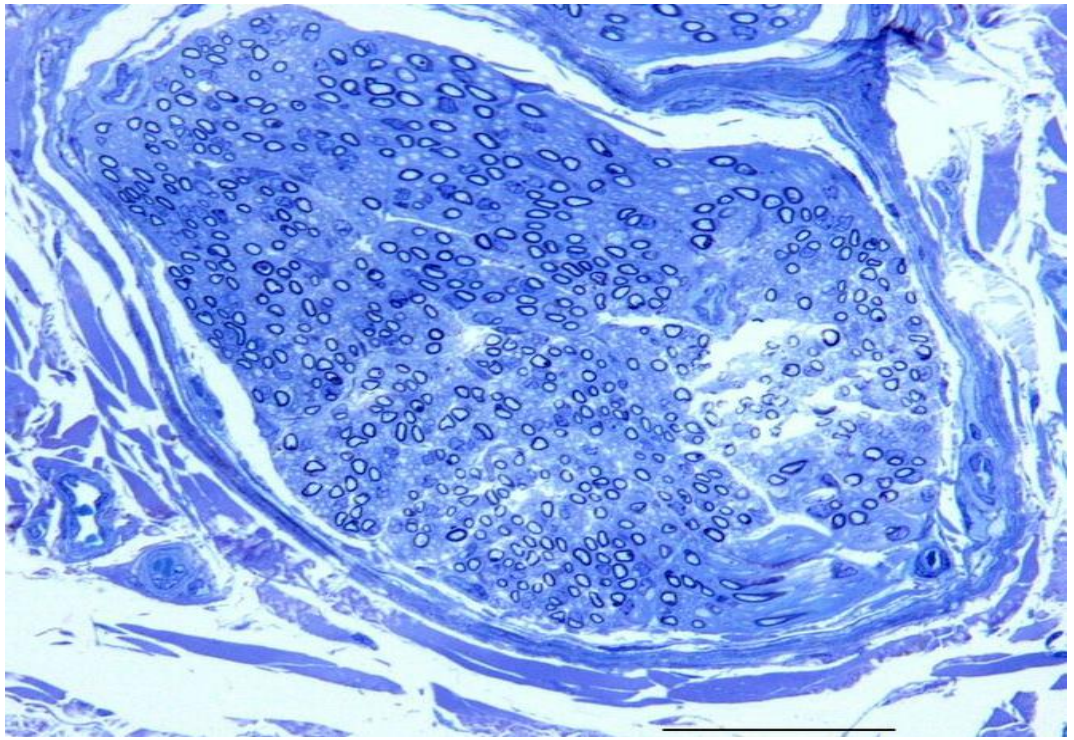
Chronic 1-12 wk Safety Model (71 pigs, 142 leads)

- Placed electrodes on posterior and anterior vagal trunks at EGJ via laparotomy
- Applied vagal block for 5 min “on”/ 5 min “off” cycles for 24 hrs per day out to 12 weeks at up to 8 mA
- Evaluated:
  - Fibrous capsule formation between the electrode and the nerve (300µm at 12 wk)
  - Histologic response of the vagal fascicles and axons to the electrode and electrical algorithm
  - Maintenance of nerve function
  - Gross and histologic response of gastrointestinal organs

Histology Results



H&E, bar = 200 µm

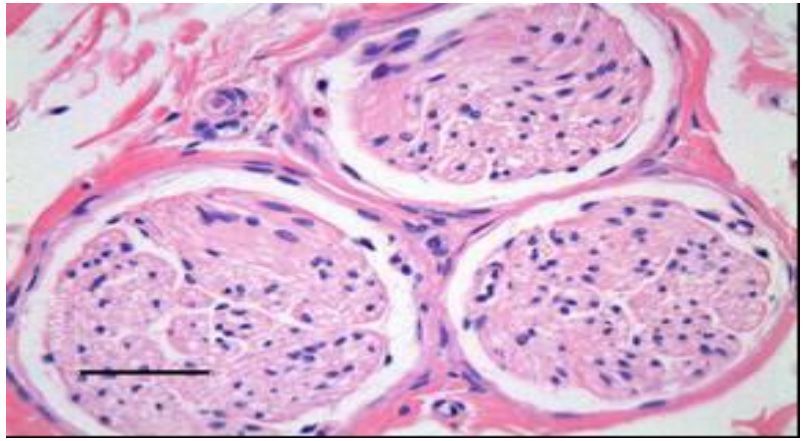


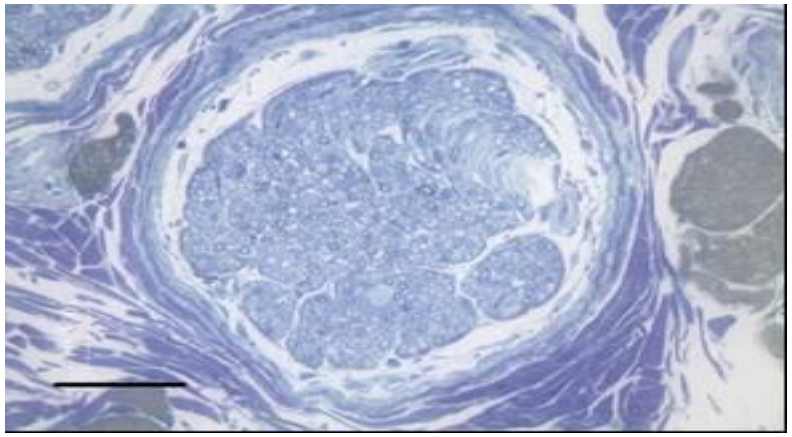
T-blue, bar = 50 µm

E=electrode, FC= fibrous capsule, N=nerve fascicle

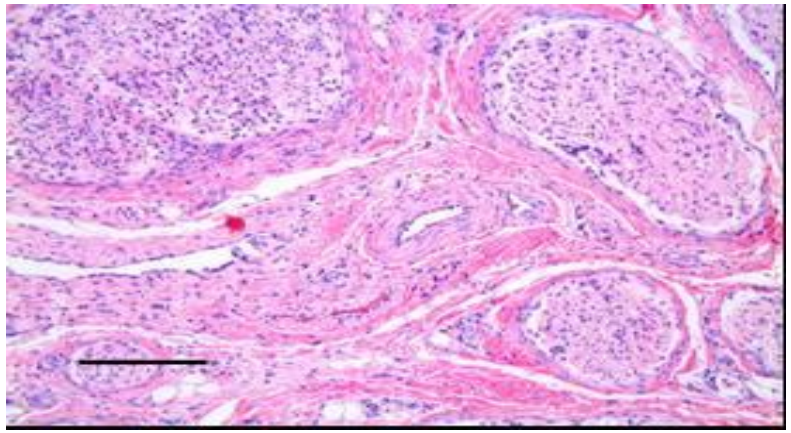
Representative Vagal Trunk Histopathology, Porcine Model, 90 days post-block

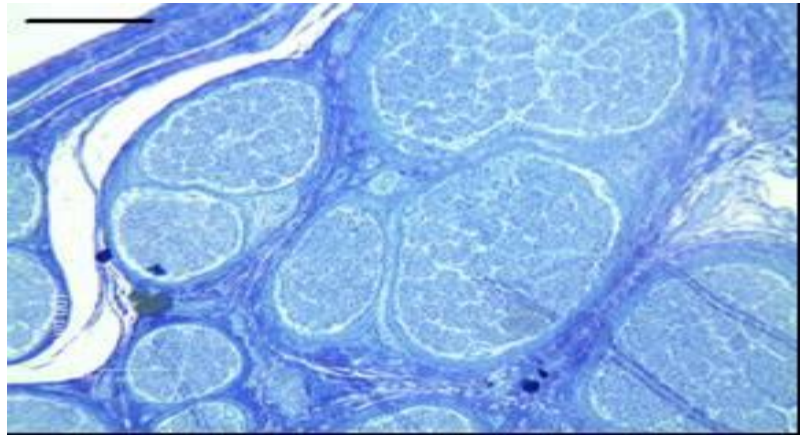
Control- vagus, 400x





Active- vagus, 200 - 400x



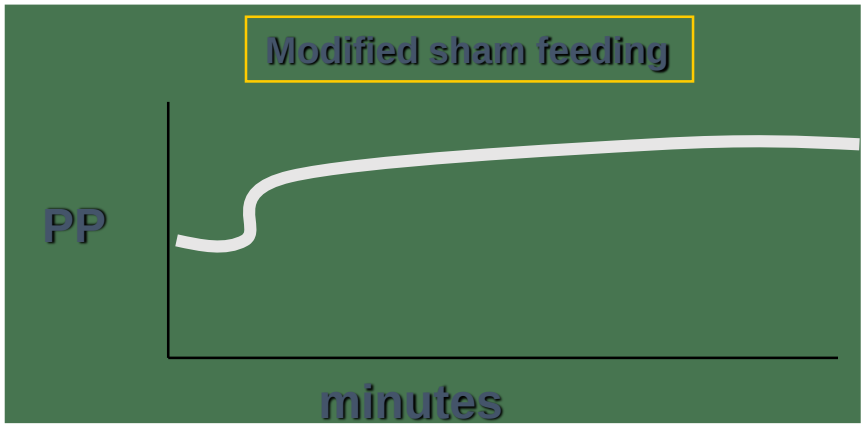


No evidence of necrosis, Wallerian degeneration, eosinophilic change/early axonal degeneration of the axons

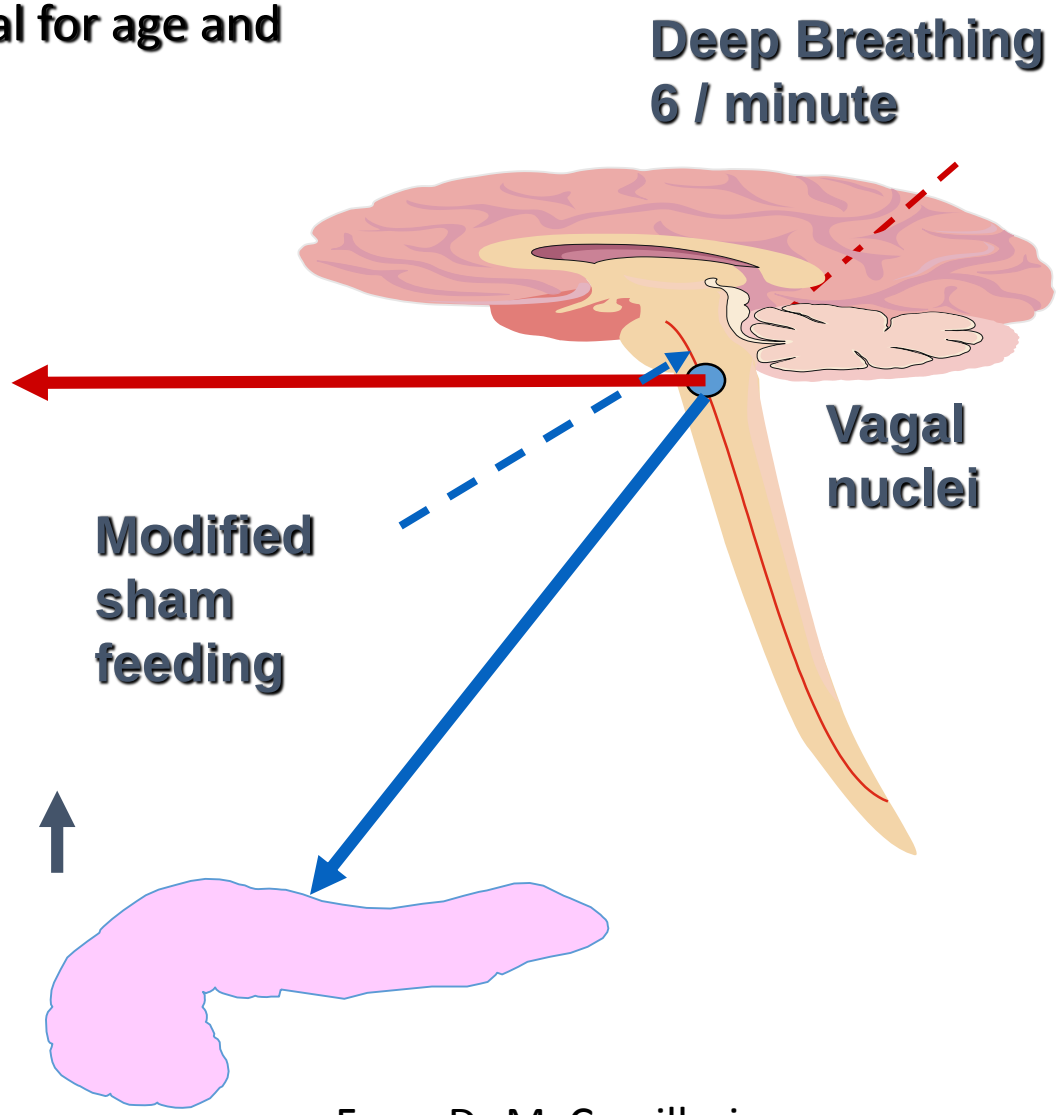
Internal data

Testing Vagal Function

- Heart period change to deep breathing: 6 per min, normal for age and gender >10 / min
- Pancreatic polypeptide response to sham feeding

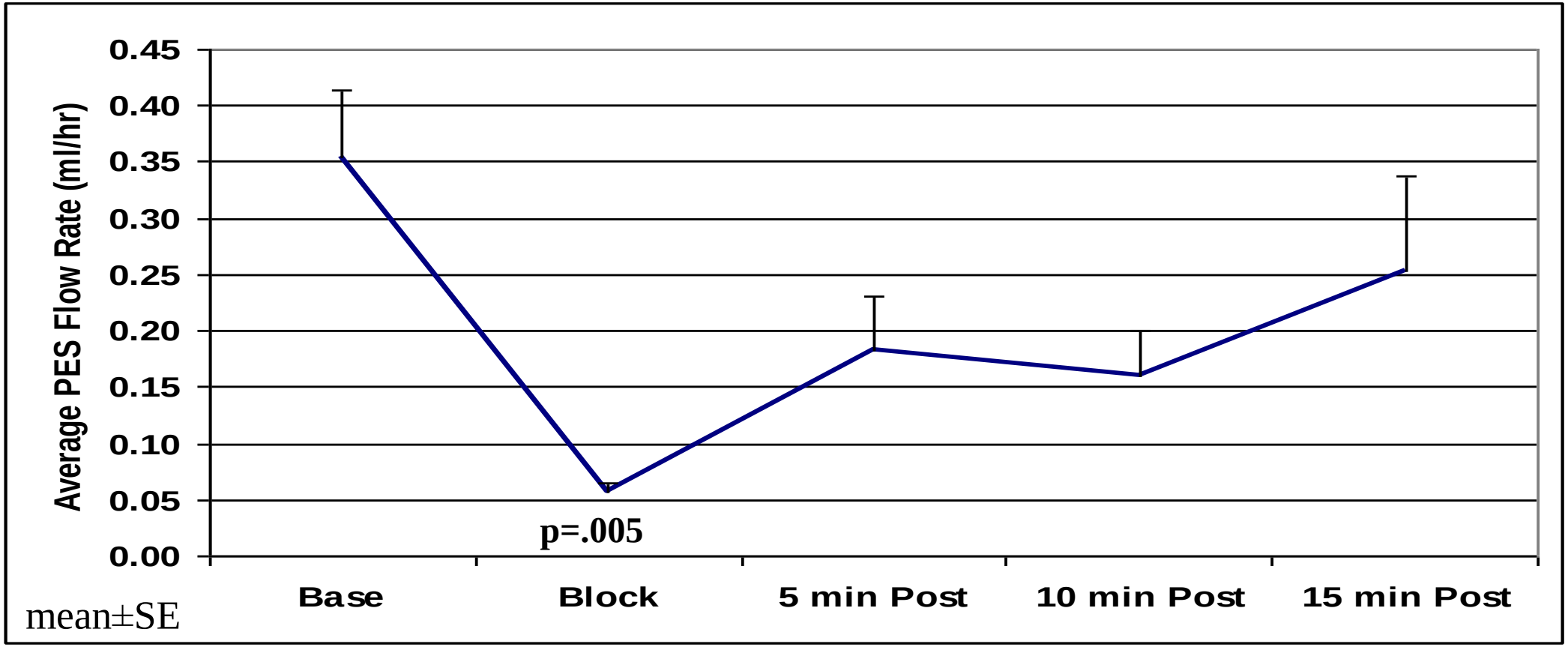


Normal: by 25 pg/ml



From Dr M Camilleri

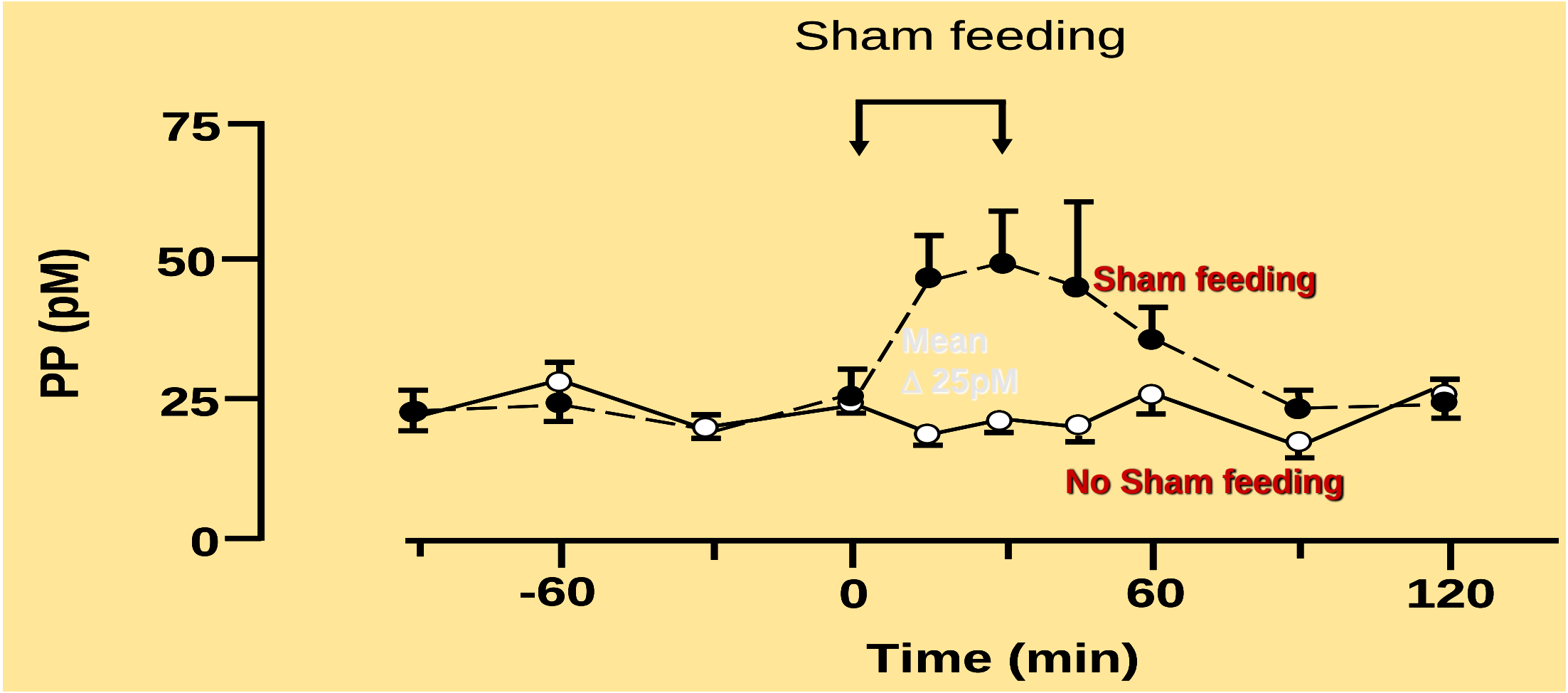
Block and Recovery of Pancreas
Porcine PES Model (n=6)



- **Vagal block→ PES ↓ > 80%**
- **Mean PES recovery 19±8 min**

Tweden et al. Obesity Surgery 2006;16:988

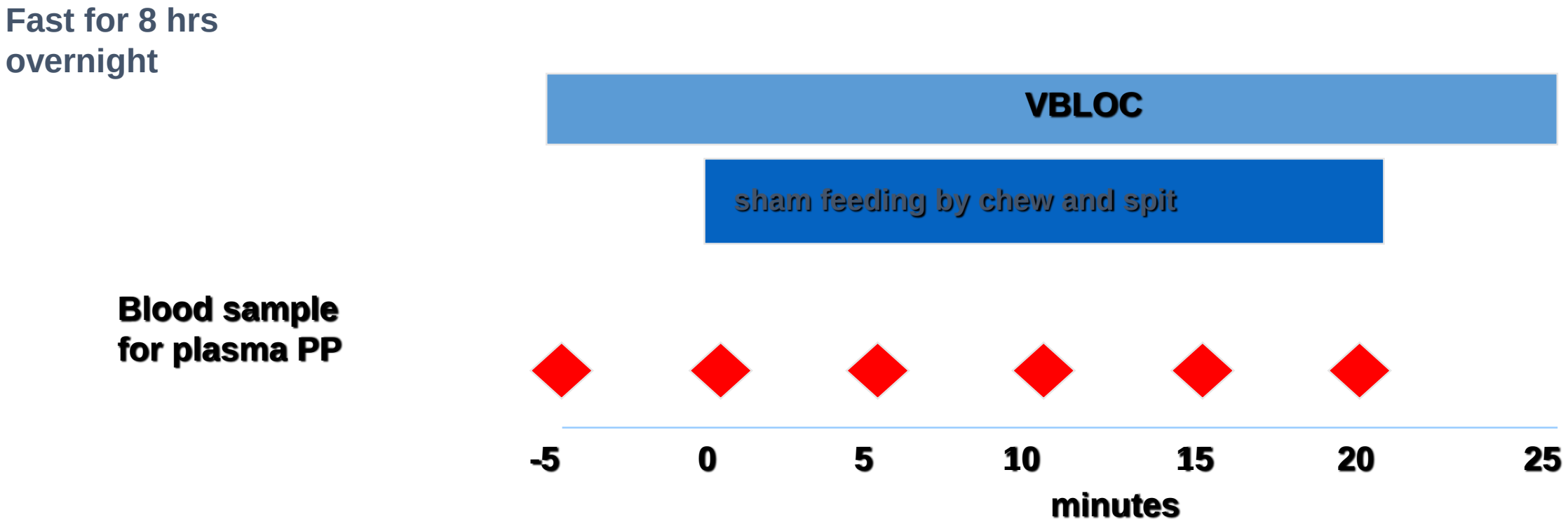
Effect of Sham Feeding (SF) on Plasma PP During Fast



Taylor IL, Feldman M. J Clin Endocrinol Metab. 1982; 55: 1114-7.

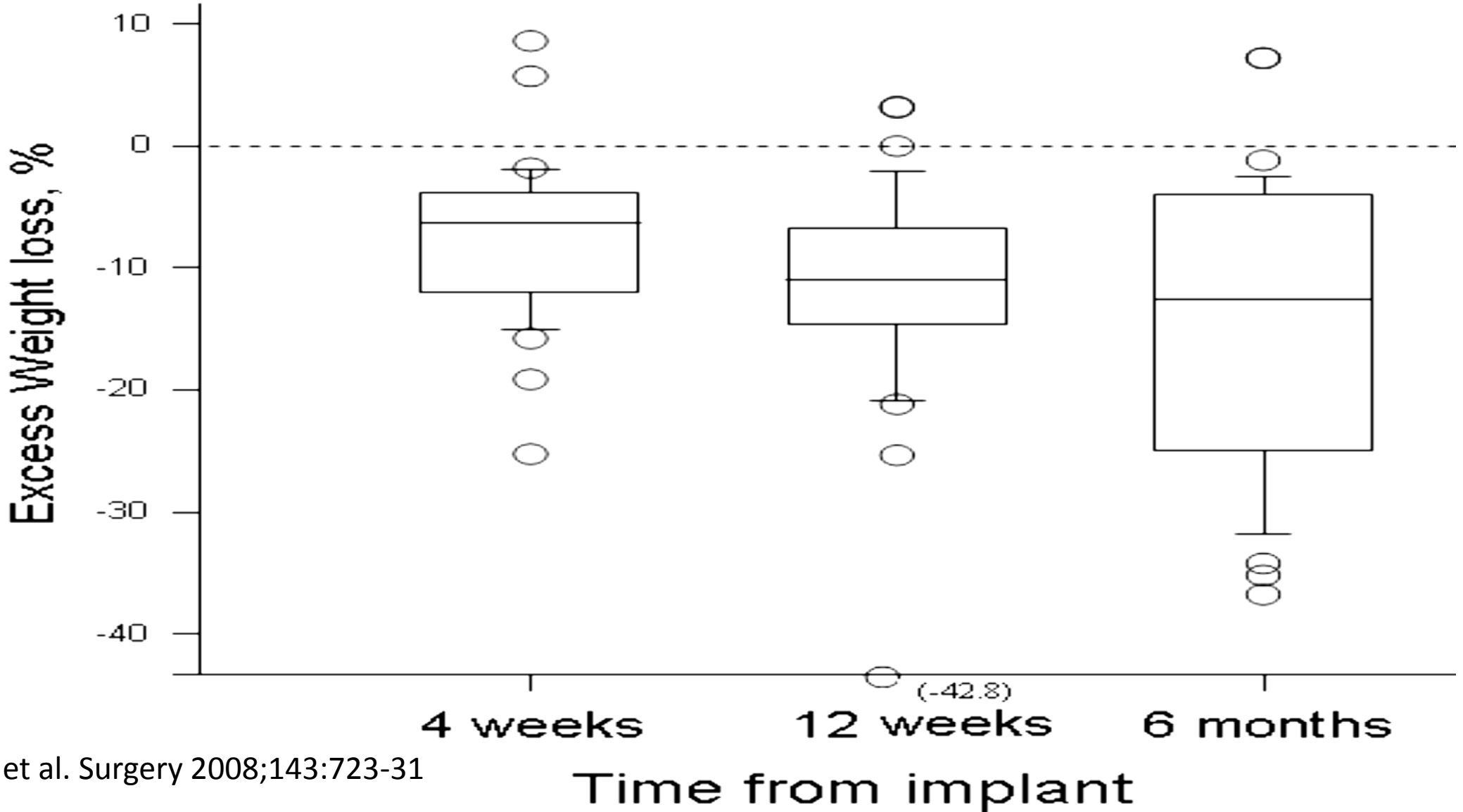
Methods

- 25 obese pts (age: 30-58 yrs; BMI: 33-48 kg/m^2; 20 F, 5M)
- Sham feeding after 12 wks of VBLOC therapy
- 10 patients also had pre-implant SF
- Maestro RF1 System



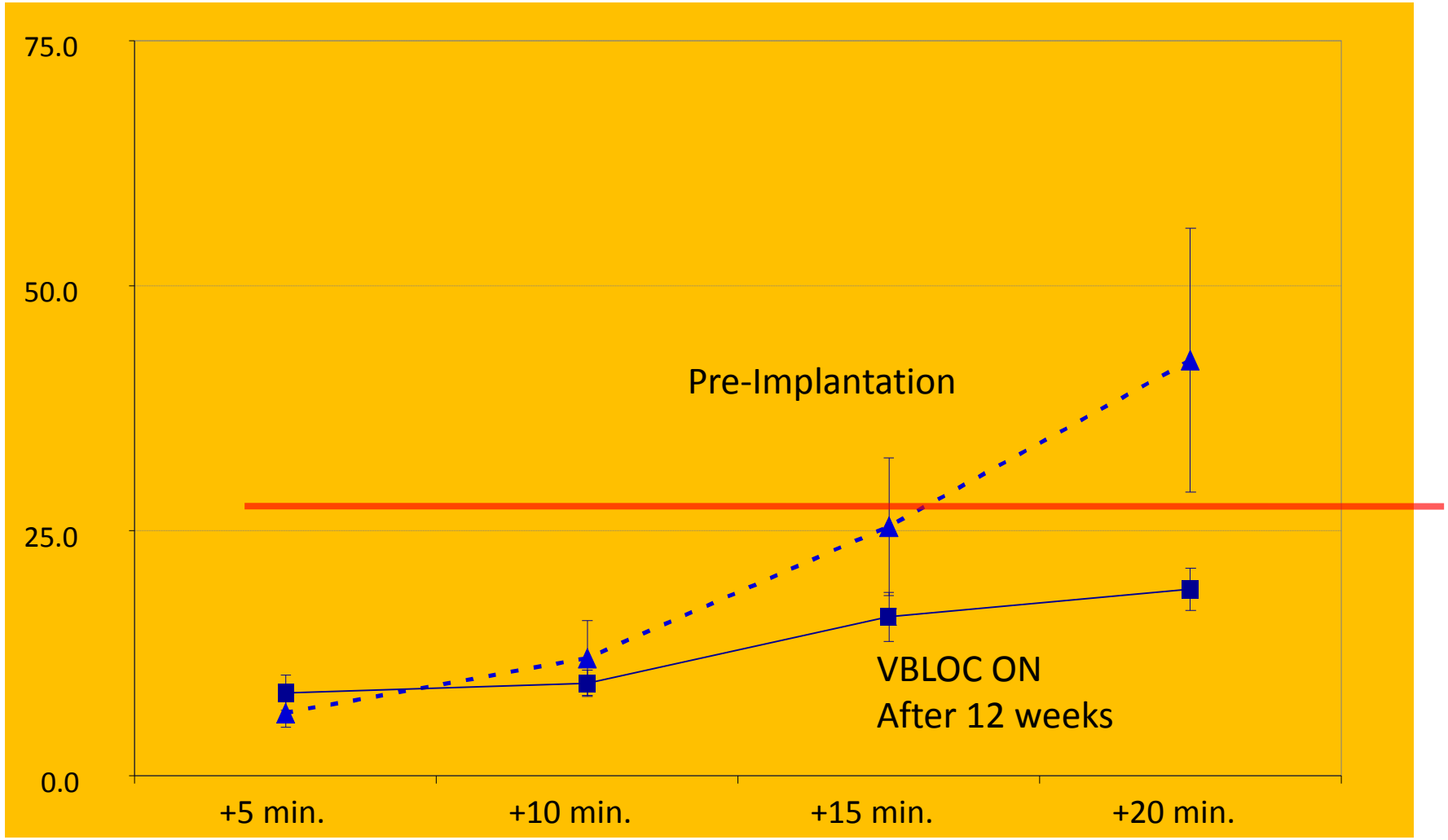
Camilleri et al. Surgery 2008;143:723-31.

Effect of VBLOC on weight loss



Camilleri et al. Surgery 2008;143:723-31

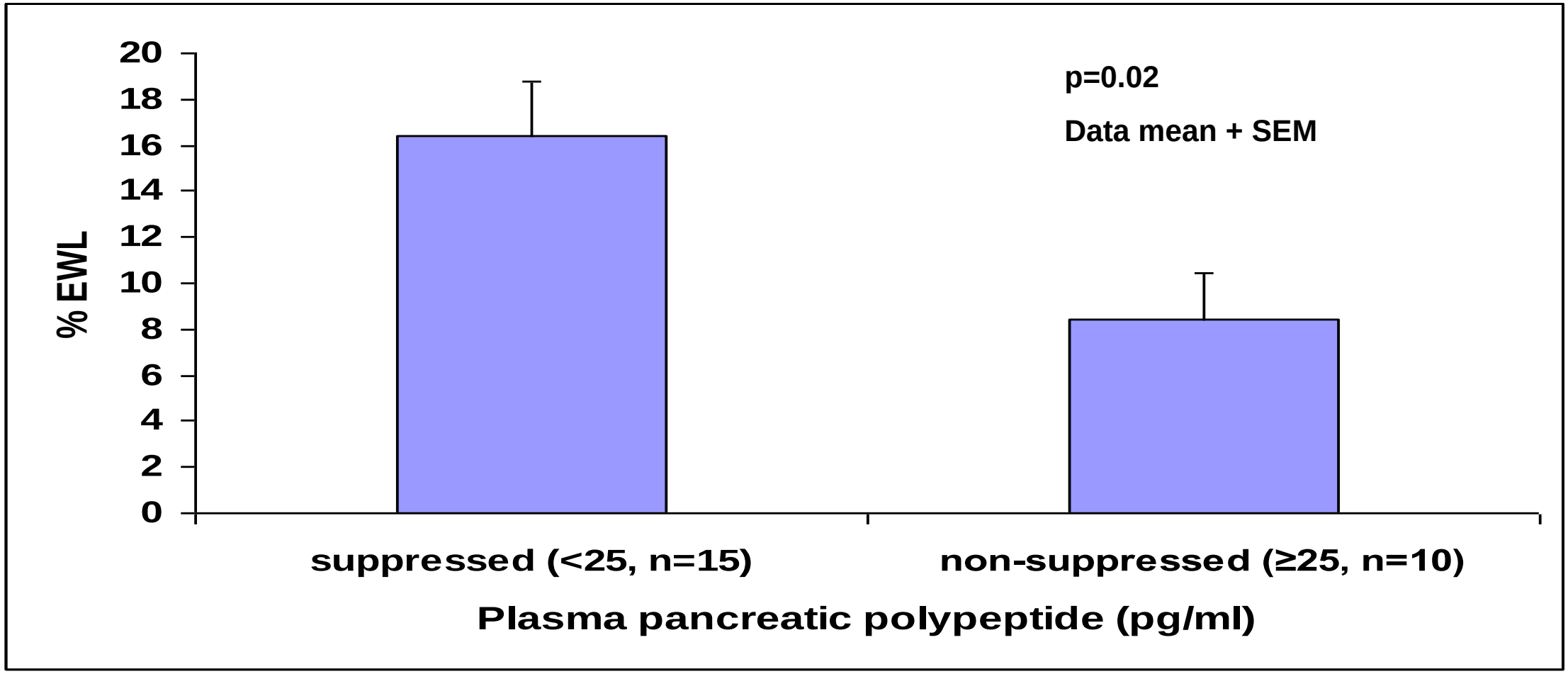
Effect of VBLOC on Vagal Function



Prior data had established Δ plasma PP <25pg/ml = vagal inhibition

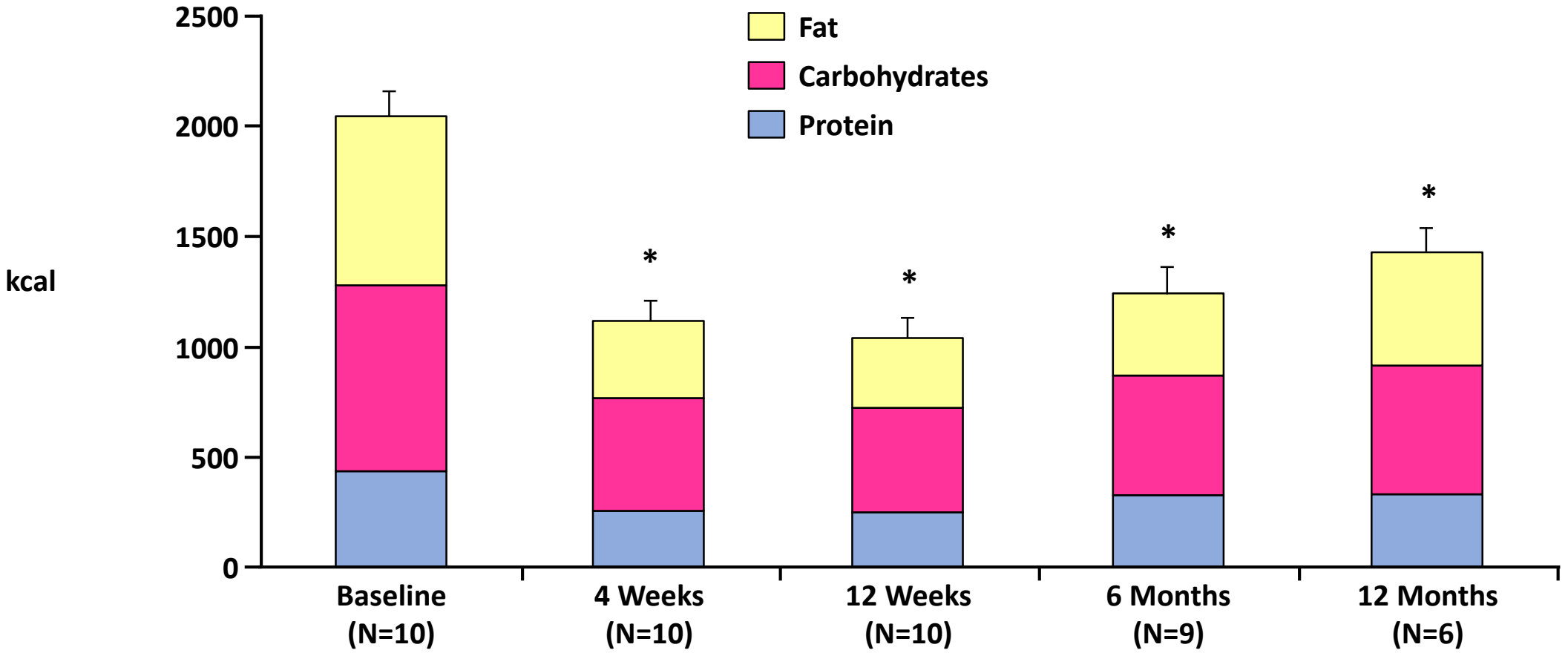
Camilleri et al. Surgery 2008;143:723-31

Greater Weight Loss in Patients with Suppression of PP on VBLOC



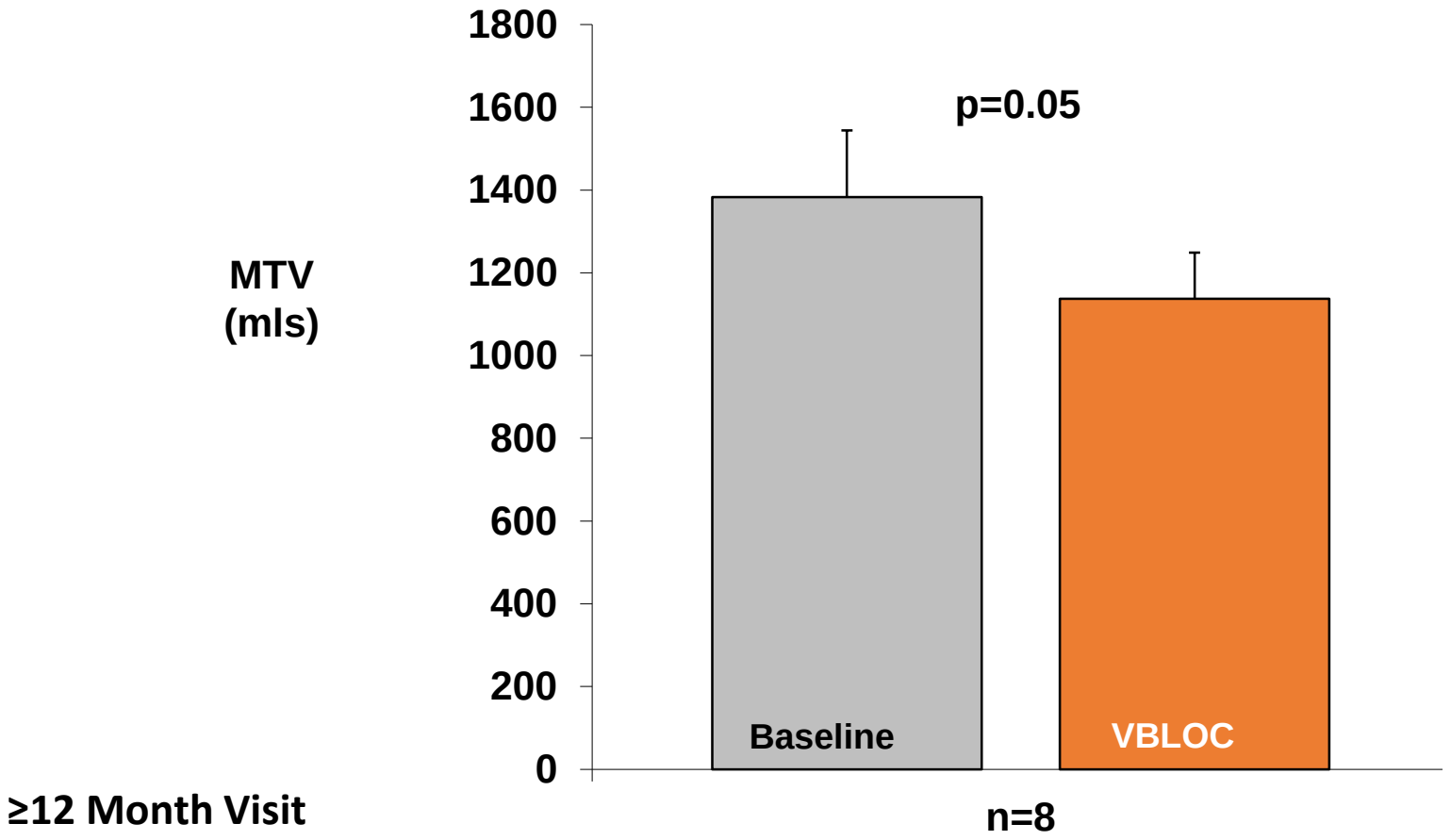
Camilleri et al. Surgery 2008;143:723-31

VBLOC Reduces Calorie Intake Without Changing Dietary Composition



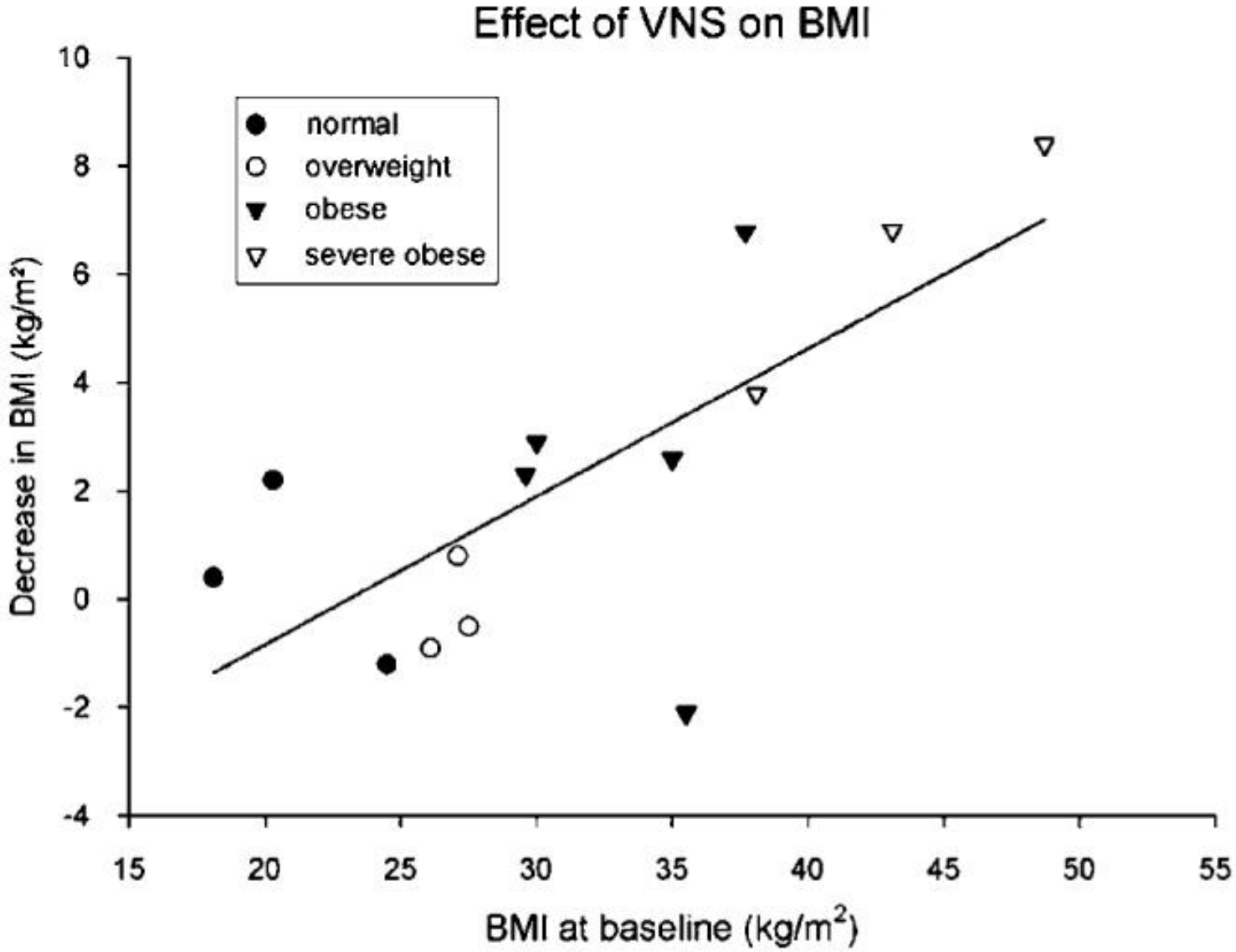
Camilleri *et al.* Surgery 2008; 143: 723-31
Wray *et al.* Obesity 2011; 19:5150
*Each visit shows a significant reduction from baseline (all p=.02)

VBLOC Results in Early Fullness in MTV Study in Humans



Herrera *et al.* Gastroenterology 2009; 136: A-386

Weight loss during chronic, cervical vagus nerve stimulation in depressed patients with obesity: an observation



31, 1756–1759;
online 12 June 2007