

# One-Year Experience with Tantalus™: a New Surgical Approach to Treat Morbid Obesity

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**Background:** Increased caloric density in modern processed foods may be an important factor underlying the prevalence of obesity, because low-volume, high-caloric food intake may delay activation of volume-dependent gastric mechanical activity known to induce the feeling of fullness. We therefore hypothesized that enhancement of gastric contractions by electrical stimulation at an early stage of the meal will reduce food intake and body weight in morbidly obese subjects.

**Methods:** The study was a prospective, non-randomized, open-label, single-center trial. 12 subjects (age  $36.1 \pm 2.8$  years, BMI  $43.2 \pm 2.7$  kg/m<sup>2</sup>, weight  $128.8 \pm 5.2$  kg, means $\pm$ SEM) underwent laparoscopic implantation with the Tantalus™ system. A pulse generator with 3 bipolar leads was implanted: 2 pairs in the antrum and a 3rd pair in the fundus. The system was activated at week 6. All subjects were followed for 20 weeks and 9 of them for 52 weeks.

**Results:** All subjects finished the initial 20-week observation period. Following activation of the Tantalus™ System, a reduction ( $P < 0.05$ ) in hunger and an increase in cognitive control ( $P < 0.05$ ) as assessed by the Three-Factor Eating Questionnaire (TFEQ) could be observed. Body weight decreased ( $P < 0.05$ ) from  $128.8 \pm 5.2$  to  $119.9 \pm 5.9$  (17.6 $\pm$ 4.3% EWL, N=12) after 20 weeks (14 weeks of treatment). In the 9 subjects continuing for 52 weeks (46 weeks of treatment), body weight further decreased to  $112.4 \pm 3.8$  kg (26.6  $\pm$  8.5 %EWL, N=9). Blood pressure decreased ( $P < 0.05$ ) from  $142 \pm 6.1/91 \pm 3.2$  to  $125.5 \pm 4.0/83 \pm 2.6$  mmHg by week 20 and  $128.8 \pm 3.8 / 86.3 \pm 3.6$  mmHg after 1 year. The frequency and severity of device and/or procedure-related adverse events indicate that the method is safe and well-tolerated.

**Conclusion:** This data suggests that gastric stimulation by the minimally invasive Tantalus™ System is safe and leads to favorable changes in eating behavior, clinically significant weight loss and reduction in blood pressure. Treatment with the Tantalus™ System is therefore a promising minimally invasive treatment for obesity.

**Key words:** Obesity, morbid obesity, gastric pacemaker, laparoscopy, weight loss, gastric contractility modulation

**Abbreviations:** EWL = excess weight loss; TFEQ = Three-Factor Eating Questionnaire; BMI = body mass index; GCM = gastric contractility modulation

## Introduction

Obesity is a global problem affecting almost 300 million individuals worldwide. In addition, the dramatic increase in BMI in several populations during the last 40 years has led to a sharp rise in morbid obesity.<sup>1</sup> Conservative procedures such as diet or pharmacological treatment result in a reduction in body weight, which in morbidly obese subjects usually is insufficient and not adequately maintained.<sup>2,3</sup> Bariatric operations lead to substantial and sustained weight loss, and consequently, to a pronounced decrease in obesity-associated co-morbidities.<sup>4,5</sup> Procedures such as the Roux-en-Y gastric bypass or the biliopancreatic diversion, however, have a profound effect on gastrointestinal anatomy and may be associated with side-effects such as marginal ulceration and vitamin deficiencies. This might contribute to the fact that about 200,000

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bariatric operations are performed annually in the U.S., which serves only a small fraction of the subjects qualifying for bariatric surgery.<sup>6</sup>

Recently, gastric electrical stimulation has been evaluated for its role in the treatment of obesity<sup>7-10</sup> and other medical conditions.<sup>11</sup> The minimal side-effects, reversibility, and safety profile appear to be clear advantages of this procedure. Encouraging results achieved in small studies.<sup>9,10</sup> were, however, not confirmed by recent trials in larger populations.<sup>12</sup> In addition, the scientific rationale and the mechanism of action of the currently used techniques still have to be determined.

Meals induce gastric distension and gastric contractility, and lead to withdrawal from food in normal physiological conditions<sup>13</sup> due to activation of vagal afferent signals involved in peripheral signaling to the central nervous system (CNS) for food intake.<sup>14</sup> Recent research in rats revealed that nonexcitatory antral electrical stimulation is able to increase the antral contraction amplitude and vagal afferent firing to the CNS, similar to passive distension.<sup>15</sup> When applied to dogs, chronic gastric electrical stimulation resulted in a reduction in food intake and weight loss without a change in gastric contractions or emptying.<sup>16</sup> The results of these studies in animals prompted the development of an innovative implantable Tantalus™ system (Metacure NV), capable of delivering *gastric contractility modulation* (GCM) signals triggered by food intake.

Unlike conventional gastric pacing, where electrical signals are continuously delivered, typically at rates higher than that of the intrinsic pacemaker, the Tantalus™ System enhances smooth muscle contractions by delivering signals in synchrony with sensed spontaneous electrical activity. Stimulation is applied on demand using a specialized algorithm to detect the onset of a meal by measurements of electro-mechanical parameters in the gut. By enhancing spontaneous gastric contractions in an early stage of the meal before reaching full gastric distension, early satiety is induced through stimulation of distal stretch receptors, eliciting an increased afferent input to the CNS to convey satiety. Thus, the Tantalus™ System should lead to an early activation of a physiological early satiety mediated by gastric distention and contractions. Because GCM signals are triggered by native electrical activity, the treatment is not expected to interfere with the normal slow-wave rhythm in the antrum.

This study was undertaken to evaluate the safety of the procedure, device functionality, and the effect on eating behavior and body weight in morbidly obese human subjects.

## Methods

### Subjects

Twelve morbidly obese, non-diabetic subjects (9 female, 3 male) were enrolled in this non-randomized, open-label study over 20 weeks with an additional extension period up to 52 weeks (14 and 46 weeks of active treatment, respectively). Mean age was  $36.1 \pm 2.8$  years, mean weight was  $128.8 \pm 5.2$  kg, and mean BMI was  $43.2 \pm 2.7$  kg/m<sup>2</sup>. The study was conducted in compliance with ISO 14155 and approved by the local Ethics Committee of the Medical University of Vienna (IRB/EC 301/2003). Inclusion and exclusion criteria are listed in Table 1. Subjects with alcohol or drug abuse, or psychopathological diseases (depression, psychosis, personality disorders) who postoperatively were deemed unable or unwilling to cooperate or comply with study requirements were excluded. Subjects with eating disorders including, but not limited to, binge eating, bulimia nervosa, and night-eating syn-

**Table 1. Inclusion/exclusion criteria**

#### Inclusion criteria

- 18-50 years, male and female
- BMI between 35-50 kg/m<sup>2</sup>, stable for 3 months
- 5 years of obesity history
- Energy expenditure >1200 kcal/day (app. 5000 kJ/day)
- Compliant to participate in the technical and medical visits

#### Exclusion criteria

- Previously placed permanent electro-stimulation device
- Previous bariatric surgery
- Unstable weight ( $\pm 1$  BMI unit) during 4-week screening period
- Antidepressant drugs, eating disorders (bulimia, binge eating)
- Endocrine-related obesity
- Weight-loss medication within the last 3 months
- Motility disorders of the GI tract

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drome were also excluded. Included subjects were not required to follow a particular diet, although the dietician provided them with information about the caloric content of foods and healthy diet. After signing the informed consent, eligible subjects were enrolled in the study that consisted of a 4-week observation period to demonstrate weight stability, followed by implantation of the Tantalus™ System.

After enrollment, subjects were followed for BMI stability ( $\leq 1$  BMI unit/4 weeks). A 6-week stabilization period followed device implantation to allow observation and stabilization of electrical signals from the stomach, which were used to program customized parameters for eating detection and therapy. Subjects' weight was obtained during the 4 weeks of the screening period prior to the implant, again during the post-implant, non-stimulated stabilization period (6 weeks), and during the treatment period (up to 46 weeks).

Adverse events were analyzed on both the System Organ Class level and Preferred Term level using the standard MedDRA coding dictionary.

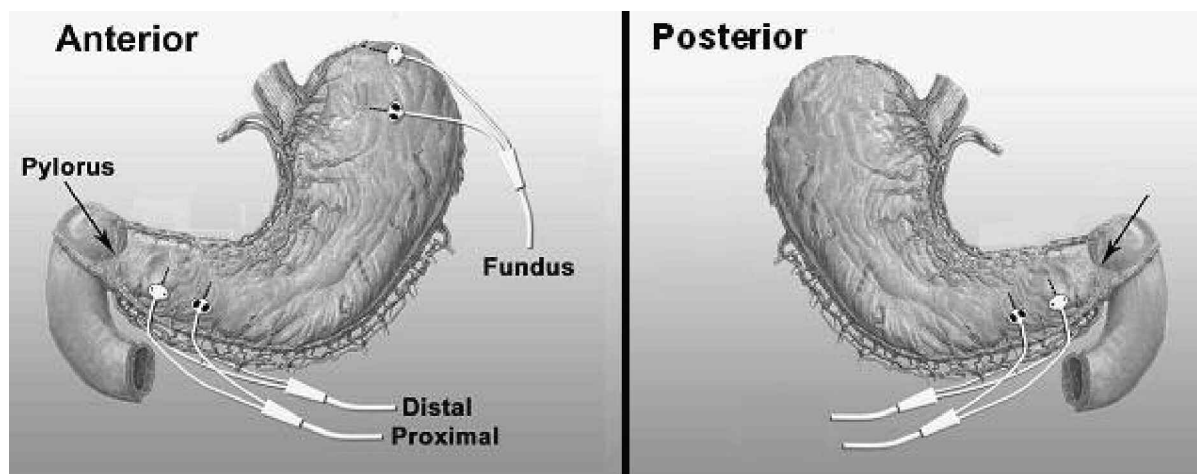
#### Implant Procedure

The Tantalus™ System consists of three sets of bipolar stitch electrodes that are placed in the sub-serosa of the gastric wall by means of laparoscopy. One lead is placed in the fundus to detect food intake, and two leads are placed in the antrum for slow-wave rate detection and signal delivery (Figure 1). The leads were fixed with 2 clips distally to avoid dislodgement and proximally sutured using non-

absorbable sutures. Once the leads were positioned, the impedance between each bipolar electrode was assessed with an external device to ensure position within the muscular layer. Endoscopic assessment of lead placement to rule out perforation of the gastric wall was performed during the procedure. In the event of a perforation of the stomach wall, the lead was withdrawn and repositioned. Leads were connected to an implantable pulse generator (IPG), which was placed in a subcutaneous pocket on the left side of the abdomen. The median duration of the procedure was 2.5 hours (mean  $3.14 \pm 0.04$  hours).

#### Device Functionality

Two aspects of the Tantalus™ device functionality were assessed: a) the performance of the automatic eating detection algorithms in identifying the initiation of a meal, and b) the accuracy of the device in detecting spontaneous electrical activity in the gastric antrum. Automated eating detection was tested four times per subject during selected follow-up visits when the ingestion of a meal (turkey sandwich and 250 cc water) was timed and recorded. A successful detection was defined as detection of meals within 5 minutes after eating started. The accuracy of electrical activity recognition was assessed offline by manually counting device slow-wave detections and comparing them with actual electrical events recorded from the gastric antrum for 1 hour in each subject.



**Figure 1.** Schematic view of lead placement. Leads in the antrum are able to detect incoming slow-waves and deliver currents to the smooth muscle. Leads in the fundus detect distension during meals.

## Enhancement of Contractility in the Antrum

The enhancement of contractions in the antrum is a component of the current working hypothesis, which in addition to gastric distension, participates in the generation of an early satiety.<sup>15</sup> Furthermore, assessment of contraction enhancement derives from GCM synchronization with native slow-waves, and with the delivery of sub-threshold electrical currents. These tests were performed 20 min after the subjects were asked to ingest a standard meal during the second half of the stabilization period (weeks 4-6). Control and test periods of 10 min were performed in all subjects. If a sensation such as pain or discomfort occurred, the current amplitude was reduced. Peak to peak amplitude was assessed manually, with a minimum amplitude of 3 ohm. At least 2 sessions (average 3.25, range 2-5) were performed in all subjects before the start of the therapy period, recording  $33.4 \pm 4.6$  control and  $43.3 \pm 6$  test contractions per patient. Enhancement is given as the percent of increased amplitude in the contractions compared to control. The validity of impedance as a measure of contractility was demonstrated previously in pre-clinical studies, where impedance changes showed a significant linear correlation with variation in the amplitude of serosal strain-gauge recordings.<sup>17</sup>

## Eating Behavior

Psychometric questionnaires were used to assess the effect of the Tantalus™ System on eating behavior of obese subjects. The Three Factor Eating Questionnaire (TFEQ) is a validated instrument that

has been used reliably in other studies of eating behavior.<sup>18,19</sup> This test was developed to measure three dimensions of human eating behavior: cognitive restraint of eating, disinhibition, and hunger.

## Statistical Analysis

Excess Weight was calculated as the difference between the weight with BMI  $25 \text{ kg/m}^2$  and the actual weight. Excess Weight Loss is presented as the percent of the excess weight loss (%EWL).<sup>20</sup> Statistical analysis was performed using a *t*-test: two-sample assuming equal variances. A *P*-value  $<0.05$  was considered significant. Data are presented as mean  $\pm$  SEM.

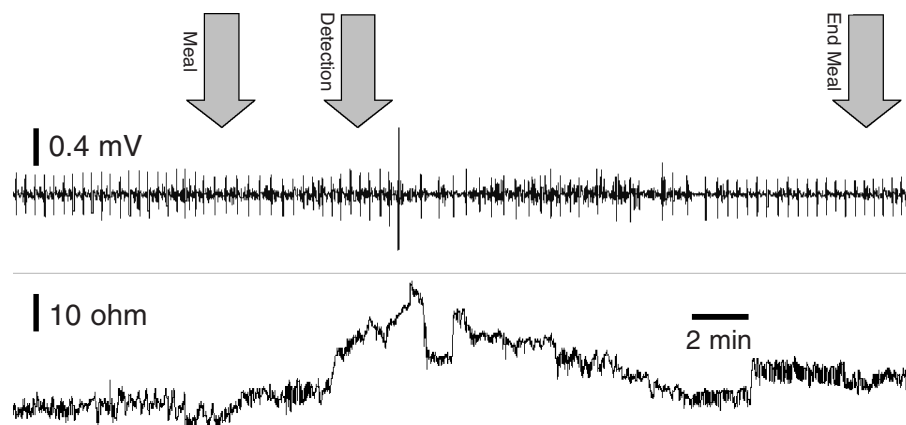
## Results

### Functional Tests

Automated eating detection by the Tantalus™ System was demonstrated in at least three of the four tests in all subjects (Figure 2). Accurate detection of spontaneous slow-waves was  $97.46 \pm 1.05\%$ . This value guaranteed a high level of synchronization between electrical activity and electrical signals.

### Enhancement of Antral Contractions

Contractions of the antrum developed 2 to 5 seconds after slow-wave detection, representing the antral contraction wave moving distally toward the pylorus. Not all slow-waves were accompanied by



**Figure 2.** Automatic eating detection. Recording of antral slow-waves (upper trace) and fundus impedance (lower trace) from a human patient. At onset of the meal, a transient reduction in slow-waves rate and a rise in fundus impedance (ohm) are visible. These parallel changes are required by the eating detection algorithm to initiate therapy.

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contractions, but their occurrence increased after food ingestion. Effects of the electrical signal on antral impedance were apparent only when contractions were present. The mean enhancement of peak-to-peak amplitude was for all subjects  $43\% \pm 4.9\%$  (median enhancement was 39.1%). Figure 3 shows a representative example of enhanced contractions.

#### Body Weight

All 12 subjects finished the initial observation period of 20 weeks. Two subjects decided not to continue for another 32 weeks because of lack of efficacy, and one subject because of personal reasons at week 28. Body weight decreased ( $P < 0.05$ ) from  $128.8 \pm 5.2$  to  $119.9 \pm 5.9$  at week 20 and to  $112.4 \pm 3.8$  kg in the remaining 9 subjects, corresponding to an excess weight loss (EWL) of  $17.6 \pm 4.3\%$  and  $26.6 \pm 8.5\%$ , respectively. Figure 4 shows the EWL and the number of subjects over time. Three out of 12 subjects obviously did not respond to the therapy (EWL of  $-0.8\%$  at week 20). One of them decided to remain in the study, however, but failed to achieve weight loss. In the group responding to therapy, one patient dropped out. In the remaining 8 subjects, we could observe a sustained weight loss over the 52-week period leading to a marked EWL of  $30.5 \pm 8.5\%$ . There were no apparent differences in the characteristics between those subjects who responded to therapy and those who failed to lose weight.

#### Blood Pressure

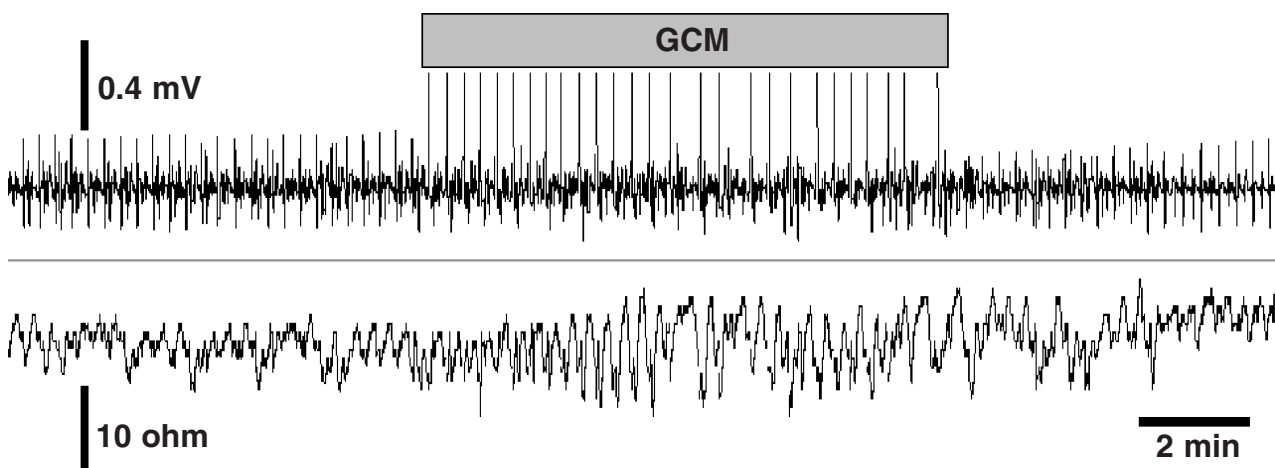
Four subjects were pre-diagnosed and were being treated for hypertension. Two of these subjects experienced changes in their medication regimen during the study and were excluded from statistical analysis. In the remainder, blood pressure decreased from  $142 \pm 6.1 / 91 \pm 3.2$  to  $125.5 \pm 4.0 / 83 \pm 2.6$  mmHg at week 20 ( $P < 0.05$ ;  $N = 10$ ), and to  $128.8 \pm 3.8 / 86.3 \pm 3.6$  mmHg ( $P < 0.05$ ;  $N = 8$ ) at 1-year follow-up.

#### Eating Behavior

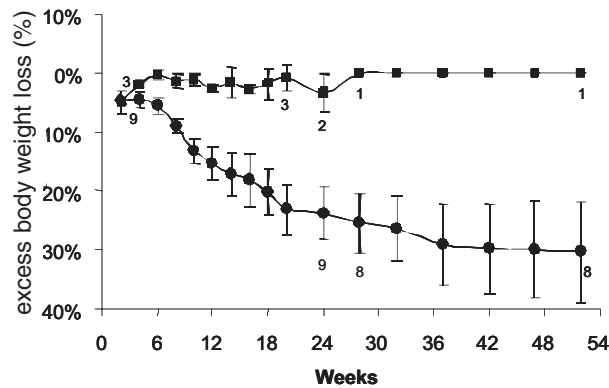
The TFEQ was administered five times to the subjects, twice before the onset of the therapy on week 0 (prior to implant) and on week 6 (at the end of the baseline period). During the therapy period, questionnaires were administered on weeks 20, 36 and 52. Subjects showed a significant ( $P = 0.05$ ) reduction in the score for hunger, while the score for cognitive control increased significantly ( $P = 0.05$ ) (Figure 5). Separate evaluation of scores for subjects who did not lose weight failed to reveal specific differences as regards to basal TFEQ values.

#### Safety Analysis

Five lead failures occurred during the study in four subjects, all manifested by continuous or intermittent high impedance values. One failure occurred at the onset of the study in a fundus lead and was cor-

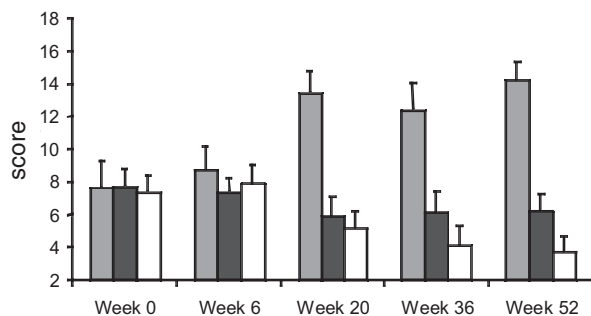


**Figure 3.** Enhanced antral contractions. Recording of antral slow-waves (upper trace) and antral contractions (lower trace) during a 10-min period of GCM delivery. Peak to peak amplitude increases gradually by delivery of GCM during the initial drop of impedance at each individual contraction. Safety mechanisms prevent delivery of GCM too early in each cycle, preventing arrhythmias or significant changes in the slow-wave rate.



**Figure 4.** Excess weight loss relative to baseline with the Tantalus™ System. Weight loss distributed by response on group A (n=9; circles) and group B (n=3; squares). Three subjects dropped out of the study on weeks 20 (N=2) and on week 28 (N=1).

rected by a simple procedure performed under local anesthesia. Antrum lead failures occurred: one after 4 months (attributed to a personal accident affecting the abdominal region); three additional failures occurred after 9 and 10 months of the implant and were not corrected until the end of the study. Delivery of treatment on those leads was suspended. No lead dislodgement was observed throughout the study. This was verified by comparison of abdominal X-rays between day 1 after the implant and those performed on week 20 and at the end of the study. Furthermore, basal impedances increased steadily and stabilized between weeks 10 and 14. There was one intra-operative gastric penetration that was detected by gastroscopy. The lead was



**Figure 5.** Eating behavior assessed by the TFEQ test. Subjects showed a significant ( $P=0.05$ ) reduction in the score for hunger and augmented cognitive control at weeks 20, 36 and 52 vs week 0 (†), and vs week 6 (‡). Bars represent scores at different times throughout the study: cognitive control (light gray), disinhibition (dark gray) and hunger (white).

repositioned without further consequence. Two subjects complained about discomfort and sensation during stimulation. Both events were resolved by decreasing the current amplitude.

Eight subjects complained of discomfort or pain in the pocket area. These events were anticipated and were considered of mild to moderate severity, occurring on average 3.2 months after implantation. All were eventually resolved or subsided without consequence. These symptoms might be explained by the position of the device under the skin (3-4 cm) at the level of the lowest left rib in a vertical position.

Two subjects experienced serious adverse events during the study. A 39-year-old male had severe rhabdomyolysis<sup>21</sup> and blood loss in combination with pulmonary insufficiency on the day of implantation. These events were attributed to the procedure and led to prolonged hospitalization. A 34-year-old female had a moderate pulmonary embolism/dyspnea >4 months after implantation that lasted 14 days. It was considered unrelated to either the device or the procedure. In both cases, the events resolved without sequelae and the subjects were able to complete the study. Altogether, the type, frequency and severity of device and/or procedure-related adverse events demonstrated that the device and its implantation appear to be safe and well-tolerated.

The most frequent types of adverse events in terms of System Organ Class were “gastrointestinal disorders” and “injury and procedural complications”, each of these classes having 11 reported events. One gastrointestinal (GI) disorder, dyspepsia, was resolved during the study without intervention although the therapy continued. Mild constipation in one subject that lasted 16 days was also noted. Apart from these events, all remaining GI disorders were considered unrelated to either the device or the procedure. Some additional events, considered possibly related to either the procedure or the stimulation, were generally mild in severity, resolved during the study, and did not result in premature study discontinuation. The subjects were not required to take any medication, vitamins or supplements as a consequence of the application of the device.

Other assessments of safety, including ongoing measurements of vital signs (body temperature, pulse and heart rates, and blood pressure measurements), clinical laboratory evaluations, and urinalysis failed to detect any clinically or medically relevant findings or trends in these subjects. The upper GI radiological

examinations in one patient revealed a clinically insignificant abnormal form of the cardia. Upper GI examinations of all other 11 subjects were negative.

## Discussion

Enhancement of gastric contractions during meals is a novel approach to reduce food intake in morbidly obese subjects and was successfully applied for the first time using the Tantalus™ System. The implantation of the system appears to be a safe procedure well-tolerated by the subjects. The stimulation led to a significant change in eating behavior resulting in a substantial loss of excess weight accompanied by a decrease in systolic and diastolic blood pressure in most subjects.

Limitations of current bariatric surgical operations have led to the development of less invasive gastric pacing devices that have the advantage of not altering the normal anatomy of the GI tract, and thus avoiding the complications of restrictive and mal-absorptive interventions. The devices examined to date, however, have demonstrated inconsistent results with regard to the amount of weight loss<sup>7-10,12</sup> and their exact mechanism of action has not yet been identified. The Tantalus™ System was developed on the basis of pre-clinical animal experiments that demonstrated that on demand gastric electric stimulation following food intake enhances the antral contraction amplitude, and produces a controllable neural effect similar to gastric distention. Intra-meal satiety has been differentiated from post-absorptive satiety, and is thought to be mediated by afferent vagal signaling.<sup>15</sup> In addition, delivery of GCM during and after meals limits the influence on antral contractions to the initial gastric period of the meal, when contractions may have a role in early satiety. The analysis of contraction amplitude was performed with data obtained during follow-up visits, before the activation of the therapy. Further recordings of the contractions in advanced stages of the study could elucidate chronic effects of the therapy in antral contractility. In contrast to currently available devices for gastric stimulation, the Tantalus™ System is activated only following food ingestion and can therefore adapt to specific eating behavior and its changes. The delivery of this therapy for constrained intervals during and after a meal

for 46 weeks resulted in a mean EWL of 26.6% (30.5% in responders), which was associated with individually reported extended inter-meal periods. Indeed, the mode of action demonstrated in animal experiments is aligned with the reported decrease in hunger and the reported increase in cognitive control as assessed with the TFEQ in the study subjects.

Weight loss achieved by the Tantalus™ System over the duration of the study is comparable to gastric banding for the period of time studied (52 weeks), but inferior to gastric bypass and other mal-absorptive procedures. The weight loss was accompanied by a decrease in blood pressure comparable to the extent described in the literature.<sup>22</sup> Weight loss was more apparent in the first weeks after the therapy was initiated, then stagnated for a period of time and continued to progress at a slower rate. A lower rate of weight loss during the first months after the implant is also observed with gastric banding.<sup>23,24</sup> Lack of weight loss in three subjects became apparent soon following activation and is still under study.

The present study includes a relatively small group of subjects and is limited by the absence of subject and investigator blinding, a control group or the use of a cross-over design. However, the amount of weight loss maintained over a relatively long observation period makes it unlikely that the observed effects are solely caused by participation in the study. Moreover, the participants did not receive any specific weight loss counseling apart from general nutritional information. Taken together, the observed effects of the Tantalus™ System strongly suggest a specific action of the device which is based on a scientific rationale and is supported by the results of preclinical trials. The data definitively encourage further controlled trials to establish the exact role of this innovative technique in the context of obesity therapy.

In conclusion, the Tantalus™ System was safely implanted in a minimally invasive laparoscopic procedure which was well-tolerated by the subjects and resulted in few adverse events. The delivery of signals intermittently with food ingestion, in synchrony with the natural gastric activity using the native enteric muscular-neural transmission, results in a non-adaptive, efficient method for improved control of food intake. The results on weight loss and the effect on blood pressure with this system encourage further studies to eventually include it among the options for the treatment of obesity.

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