ABSTRACT

Background

Gastric Electrical Stimulation (GES) has been studied for decades as a promising treatment for obesity. Stimulation pulses with fixed amplitude and pulse width are usually applied, but these have limitations with regard to overcoming habituation to GES and inter-subject variation. This study aims to analyze the efficacy of an adaptive GES protocol for reducing food intake and maintaining lean weight in dogs.

Methods

Six beagle dogs were implanted with a remotely programmable gastric stimulator. An adaptive protocol was designed to increase the stimulation energy proportionally to the excess of food consumption, with respect to the dogs' maintenance energy requirements. After surgery and habituation to experimental conditions, the dogs went through both a control and a stimulation period of 4 weeks each, in a randomized order. The stimulation parameters were adapted daily. Body weight, food intake, food intake rate, and postprandial cutaneous electrogastrograms (EGG) were recorded to assess the effect of adaptive GES.

Results

Adaptive GES decreased food intake and food intake rate ($p < 0.05$) resulting in weight maintenance. In the absence of GES, the dogs gained weight ($p < 0.05$). Postprandial EGG dominant frequency was accelerated by GES ($p < 0.05$). The strategy of adapting the stimulation energy was effective in causing significant mid-term changes.

Conclusion

Adaptive GES is effective for reducing food intake and maintaining lean weight. The proposed adaptive strategy may offer benefits to counter habituation and adapt to inter-subject variation in clinical use of GES for obesity.

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INTRODUCTION

Obesity has reached pandemic proportions in the 21st century with 710 million obese people (body mass index [BMI] above 30) worldwide, over 100 million of whom are children, and 2.1 billion overweight adults (BMI above 25) [1–4]. Obesity is associated with major health issues including diabetes, and cardiovascular, kidney, and gallbladder diseases, as well as some cancers and epigenetic changes [5]. As a result, obesity-related health problems resulted in the deaths of 4 million people in 2015 [1] and have a significant impact on healthcare system costs [1,6,7].

Bariatric surgery is the gold standard to effectively achieve weight loss in morbid obese patients (BMI > 40) [8,9]. The most commonly used procedures are the adjustable gastric banding, the Roux-en-Y gastric bypass, and the sleeve gastrectomy [10,11]. However, only a small percentage of eligible patients undergo this procedure, due to the risks of the surgery. Indeed, even though a large majority of these surgeries are now performed laparoscopically [12], reducing the invasiveness, the mortality rate was reported to range from 0.1% to 1% and the complication rate to reach up to 10%, depending on the technique [13–15]. As an alternative approach to treating obesity, gastric electrical stimulation (GES) has been investigated in the last few decades with promising pre-clinical results. If long-term clinical trials demonstrate efficacy in inducing and sustaining weight loss, GES would have the advantage of offering a minimally invasive, long-term, reversible, and adjustable alternative to bariatric surgery [12,16,17].

Various types of GES techniques have been studied over the past few decades in animals and humans [12,16]. Recently, inhibitory GES, that impairs gastric motility using trains of pulses with a width longer than 1 ms, has been considered the most promising method for inducing

weight loss [16,18–20]. In rats and dogs, the pulse width was proven to be a key parameter related to gastric emptying, and hormonal and neural alterations, leading to a decrease in food intake [21–26].

Adapting the stimulation energy for each individual also appears to be a prerequisite for optimization of GES therapy [12,16,19,20,27]. In addition, for mid-to-long-term therapy efficacy, habituation to GES (i.e. decrease in the response to stimulation over time) must be considered, as reported in dogs [19] and assumed in humans [27]. In dogs, research has demonstrated that adapting the parameters every 10 days is necessary to counter the impact of habituation [19]. This highlights the need to develop a GES therapy that can deliver stimulation pulses that are adapted to each individual [12,19,25,27] adaptable over time to overcome habituation [19], and able to induce large pulse widths (i.e. above 2 ms) [20,23–25,28]. The development of such a therapy requires a new generation of stimulators [19,23,27–29] that are remotely configurable and designed to lower the invasiveness of the implantation for widespread patient acceptance [12,20,23,28,30,31].

Our team has developed an implantable gastric stimulator (IGS) designed to deliver a more adaptable therapy. In this study, we hypothesized that an adaptive stimulation protocol, where the stimulation energy increases proportionally to the excess of food consumed with respect to the dogs' maintenance energy requirements (MER), would lead to reduced food intake and maintenance of a healthy weight, while intrinsically countering habituation and inter-subject variation in stimulation sensitivity. The IGS was implanted in six dogs to test the adaptive protocol during a 4-week period, compared to a 4-week control period. Body weight, food intake, and food intake rate were measured daily, and postprandial electrogastrograms (EGG) were recorded once per period.

METHODS

This study was approved by the Ethical Committee of the Faculties of Veterinary Medicine and Bioengineering Science of the host university (reference EC2019-56). The animals were housed in accordance with European and national regulations for the care and use of animals.

Implantable Gastric Stimulation Device

The implantable stimulator system (Figure 1a) includes (1) the IGS with the stimulation stage, the wirelessly chargeable battery, and the telecommunication module, (2) the flexible anchor to position two stimulating electrodes into the gastric wall and (3) the control box to charge and communicate with the IGS for control and adaptation of the implant parameters. The anchor body contains two stainless steel electrodes, held 1 cm apart, and is connected to the IGS with a cable ending with Craggs connectors (Finetech Medical LTD, UK) [32]. The anchor is intended to be placed in a less-invasive way through single incision percutaneous access with a single step release [33], with (1) the summarized procedure and (2) the tool illustrated in Figure 1b. The IGS is encapsulated in medical-grade silicone rubber [34] that was previously validated *in vivo* by our team [35]. The IGS delivers biphasic square current pulses from 0.5 to 15.0 mA, with a width of 0.2 to 32.0 ms, at a frequency of 20 Hz to 1 kHz. Under the use case described in the experimental protocol section, the battery is expected to last a few days to a few weeks without being charged, depending on the delivered stimulation energy. With regular charges, taking into account the body temperature that affects the life of lithium batteries, the implant battery life would theoretically range from 4.5 years (at maximum stimulation energy used in this study, 12 mA – 8 ms) to 17 years (at 5 mA – 5 ms pulses).

Surgical Procedure

Six healthy adult lean beagle dogs were selected for the experiment. After a 24h fasting period, they were premedicated with methadone 0.2 mg/kg IV (Insistor®, 10 mg/mL, Richter Pharma, Wels, Austria) and midazolam 0.2 mg/kg IV (Midazolam Mylan®, 5 mg/mL, Mylan bvba/sprl, Hoeilaart, Belgium), then induced with 2 mg/kg propofol IV (Propovet Multidose®, 10 mg/mL, Zoetis Belgium SA, Louvain-La-Neuve, Belgium), and the anesthesia was maintained through inhalation of isoflurane (Isoflo®, 100% w/w, Zoetis Belgium SA, Louvain-La-Neuve, Belgium) in oxygen given to effect. The heart rate, peripheral oxygen saturation, end-tidal CO_2 and esophageal temperature of the animals were checked throughout the procedure.

The electrodes were implanted by celiotomy 2 cm medial to the pylorus in the pyloric antrum, close to the lesser curvature, with the electrodes aligned parallel to it, as it was previously reported to be the most effective location [20]. The silicone anchoring body surrounding the electrodes was fixed onto the gastric wall by two single interrupted sutures (Prolene 4/0). Subsequently, the body wall was pierced at its right lateral aspect to allow the exit of the connecting cable towards the subcutaneous space. The silicone body was gently pulled closer to the abdominal wall and a serosal pocket was created by a gastropexy consisting of four single interrupted sutures (Prolene 4/0) between the gastric serosa and the peritoneum. The connecting cable was connected to the IGS, and placed in a subcutaneous pocket created caudal to the costal margin on the upper right quadrant. The dogs were kept in the hospitalization facility after surgery. Anti-inflammatory treatment, carprofen 4 mg/kg (Carprofen® 50 mg tablets, Zoetis Belgium SA, Louvain-La-Neuve, Belgium), was given orally for 3 days. Overall health and symptoms such as wound irritation, seroma formation or

vomiting, were checked on a daily basis until they fully recovered and returned to their kennels in the experimental unit.

Ultrasound examinations were conducted on all six dogs prior to the start of the experimentation to assess the proper positioning of the electrodes. At the end of the experiment, computed tomography scans and ultrasound examinations were conducted again. Correct positioning of the electrodes is confirmed when reported to be inside the muscular layer of the stomach, in the pyloric antrum, without piercing the mucosa.

Experimental Protocol

During the whole experiment, the dogs' health was checked daily by the animal caretakers. If adverse symptoms (vomiting, diarrhea, sialorrhea, excessive licking, whimpering) were observed, the stimulation energy was reduced until disappearance of such symptoms. Body weight was checked daily and, should the dog's body condition score go below 3 or above 7/9 during clinical evaluation [36], the experiment was suspended until the dog recovered. The initial body condition score was 4 to 5/9, which represents an ideal condition.

The timeline of the experiment is shown in Figure 2. The six dogs underwent both a control period (labeled SHAM) and a stimulation period (labeled STIM) of 4 weeks each, in a randomized order. The SHAM/STIM periods are separated by a 1-week washout to avoid carry-over effects. During the washout, the food quantities were adapted for the dogs to remain in healthy body condition (following their clinical evaluations and veterinarian's advice). The first SHAM/STIM period started 5 to 6 weeks after the surgery and was preceded by 2 weeks of habituation to experimental conditions (availability of food both in amount and duration).

During the habituation, SHAM, and STIM periods, the dogs were given 600 g of commercially available food with standard nutritional composition (SPECIFIC[TM] CXD-M, Adult Medium Breed, dry diet, per 100g: 1648 kJ, 22.5 g protein, 11.0 g fat, 51.3 g carbohydrate, 1.7 g fiber), once a day for 1 hour (9-10 am), every day. This amount was calculated as being above three times the averaged MER (following FEDIAF guidelines [37]) of the dogs, and was considered to be sufficient for ad libitum feeding [19,20]. For the STIM group, stimulation started 15 min before the meal and lasted for 30 minutes afterward. No stimulation was applied in the SHAM group.

An adaptive protocol was designed to increase the stimulation pulse charge - and so the energy applied to the stomach - proportionally to the difference in food intake with respect to the MER. Thus, the MER was considered as the target for food intake, which has the benefit of being applicable to lean dogs that do not require weight loss. This approach aims at regulating the dogs' food consumption by increasing (or decreasing) the stimulation pulse charge when they eat more (or respectively less) than their MER, until this target is reached. The pulse adaptation was calculated as follows:

$$Q_d = Q_{d-1} + K * (MFI - MER) \tag{1}$$

Where

- Q_{d-1} is the charge per pulse set the previous day [C],

- Q_d is the charge per pulse to be set the considered day [C],

- MER is the Maintenance Energy Requirement based on the initial body weight (before experimentation) [g],

- MFI is the Mean Food Intake, averaged on the three previous days [g],

- $K = 0.03$ is a constant linking the charge increase with the difference between the food intake and the MER [µC/g].

As this approach is the first of its kind, no previous experience could support the choice of K, or of the number of days considered to quantify the MFI average. Therefore, K was chosen to reach the maximum pulse charge in an observable time (~ 8 days) and a 3-day averaged MFI was chosen in agreement with the nutritionists to smooth the daily variability of dogs' food intake.

The range of stimulation parameters was chosen that was wide enough to cover previously reported effective values in inhibitory GES [16,19,20]: pulse amplitude from 0.5 to 12.0 mA and pulse width from 0.2 to 8.0 ms (please note that these two ranges are more conservative than the ranges the gastrostimulator is able to provide, i.e. respectively up to 15 mA and 32 ms). A frequency of 40 Hz, and a cycle of 2 s ON, 3 s OFF, were chosen as previously proposed for inhibitory GES [20] and, in general, widely spread in gastrostimulation against obesity both in animal models (e.g. [16,19,20,22]) and in clinical trials (e.g. [27]).

The stimulation pulse charge was then adapted for each dog, every day, as per equation 1. When the pulse charge needed to be increased, first the pulse width was increased. When the maximum pulse width (8 ms) was reached, the amplitude was increased. The pulse width was increased first since it has been shown to be a key parameter that impacts gastric motility and reduces food intake compared to pulse amplitude [16,18–20,29,38].

Finally, no change in pulse charge was made (1) during the first three days of the STIM period, (2) if any sign of discomfort was observed or (3) if the maximum stimulation parameters fixed

for this study (8 ms – 12 mA) were reached. If discomfort symptoms persisted over 2 consecutive days, the stimulation pulse charge was reduced back to a comfortable value.

Weight and Food Intake Monitoring

The dogs were weighed daily before their meal and any food remaining after the 1-hour mealtime was removed and recorded to measure the food consumed that day.

Video cameras were placed in the kennel to observe (online) any adverse symptoms and to measure (offline) the duration needed for each dog to eat their food portion. The recording started 30 minutes before the meal (15 minutes before the stimulation started) and lasted for 3 hours. Food intake rates were evaluated daily as the amount of kibbles eaten divided by the effective meal duration (based on the videos).

Electrogastrogram

The EGG was recorded once per period (STIM and SHAM). The signal was recorded by cutaneous electrodes connected to a dedicated biopotential amplifier (BIOPAC MP150, with wireless Bionomadix 2 EGG, BIOPAC Systems, Inc., Santa Barbara). This setup has the benefit of being noninvasive (i.e. cutaneous rather than percutaneous electrodes), which minimizes the impact of the measurements on the dogs' well-being, as opposed to most previous studies [20,22,29,39]. However, the signal was expected to have a lower SNR compared to percutaneous electrodes and to be highly impacted by GES stimulation artefacts. Consequently, only postprandial EGG was considered, i.e. 30 minutes recording after meal and GES ended.

The recorded signal was initially sampled at 1 kHz then numerically bandpass filtered from 0.03 Hz to 0.2 Hz and then down sampled to 2 Hz. Corrupted parts of the signal, containing

motion artefacts, were removed from the analysis. The dominant EGG frequency, i.e. the frequency with maximum power, was computed on a 5-minute sliding window during a 30-minute postprandial period.

Statistical Analysis

All data and graphs are presented as mean and standard deviation. A prior normality test was performed on the variables to check the normally distributed sample population required for the t-test. After data processing, statistical significance was calculated by paired t-test to answer the following questions:

1. Were there significant changes in the dogs' weight and/or food intake in the STIM period with respect to a reference baseline?

2. Were there significant changes in the dogs' weight and/or food intake in the SHAM period with respect to a reference baseline?

3. Did the stimulation significantly affect the dogs' weight and/or food intake (STIM vs SHAM)?

The data was averaged over each week. While the first two tests compared the weekly averages of each period (STIM or SHAM) to a baseline, the third one compared the weekly averages of both periods (STIM vs SHAM) to each other. A difference with a p value of < 0.05 was considered statistically significant in all the tests.

For every dog, the baseline for food intake was selected as the average over the last three days of the habituation period and the baseline for weight was selected as the weight at the beginning of the considered period (see Figure 2). We chose to compute the baseline for food intake only once during the entire study (i.e. during the habituation period) and not before

each considered period (i.e. during habituation or washout), because food intake was regulated during washout (i.e. adapted for the dogs to remain in healthy body condition), which would have caused a considerable bias. We chose to select the baseline for weight at the beginning of the considered period to consider the weight variation due to SHAM / STIM. Even if the washout period allowed the dogs to nearly recover their initial weight, small variations remained (0.7 ± 0.6 kg between the two baselines).

Significance of the paired t-test on the food intake rate estimations (the weekly averages of STIM vs SHAM) and the EGG postprandial frequencies (STIM vs SHAM) are also reported.

RESULTS

Surgical Procedure and Recovery

The surgical implantations were carried out without any complications. All dogs recovered well from surgery and were back in the kennel after 3 to 6 days. Based on the CT scan and ultrasound analyses, experts concluded the electrodes were positioned as intended before and after the experiment.

Preliminary GES Evaluation

During the preliminary evaluation, discomfort symptoms were observed between pulse parameters of 8 ms – 5 mA and 8 ms – 8 mA, depending on the dog. A starting set of stimulation parameters of 5 ms – 5 mA, i.e. a "middle of the range" stimulation charge that is below the discomfort level, was selected for all dogs.

Follow-up

During the experimental periods, few signs of discomfort from stimulation were observed. The most frequent adverse symptom was vomiting with 13 observations gathered for all the dogs during their STIM periods (140 observations in total). Whimpering and sialorrhea were recorded over two consecutive days for a specific dog. The stimulation energy was thus decreased to a comfortable value. No discomfort was reported during the SHAM periods.

One dog out of six had to be excluded during the habituation period because of non-recoverable malfunction of the device during the experiment. The results thus include data from the five remaining dogs. In addition, a subcutaneous repair surgery was performed in four out of the five dogs because of a weakness in the cable connecting the electrodes. These

surgeries were performed during the washout periods and the latter was extended to have full recovery of the dog and second habituation to experimental conditions.

Food Intake

Figure 3 (left) compares the dogs' food intake during the STIM and SHAM periods over the 4 weeks. During the STIM period, the dogs significantly reduced their food intake with respect to the baseline (food intake reduction of 229 ± 193 g, $p < 0.05$). In the SHAM period, the dogs did not significantly modify their food intake with respect to the baseline during the whole experimentation (food intake reduction of 95 ± 117 g, $p > 0.05$).

Comparing STIM and SHAM, dogs significantly reduced their food intake when they were stimulated (STIM) compared to when they were not (SHAM) until the third week (256 ± 183 g VS 27 ± 63 g, $p < 0.05$). Statistical significance was, however, lost in the 4th week.

Food Intake Rate

Figure 3 (right) compares the dogs' food intake rate during the STIM and SHAM periods over the 4 weeks. Stimulation significantly reduced the food intake rate during the whole experimentation (26 ± 8 g/min VS 65 ± 32 g/min at week 4, $p < 0.05$).

Weight Variation

Figure 4 compares the dogs' weight gain during the STIM and SHAM periods over the 4 weeks. During the STIM period, a slight weight loss trend was observed. However, the dogs' body weight was not significantly modified over the 4 weeks with respect to baseline (weight loss of 0.55 ± 1.15 kg, $p > 0.05$). During the SHAM period, the dogs' body weight significantly increased over the 4 weeks with respect to baseline (weight gain of 1.51 ± 0.93 kg, $p < 0.05$).

Over the 4 weeks, a significant difference in the weight variations was observed between the STIM and SHAM periods ($p < 0.05$).

Electrogastrogram

Table 1 compares the postprandial EGG frequency during the STIM and SHAM periods. The frequency was stable during the 30-minute analysis window. For one of the five dogs, it was not possible to extract a 30-minute window free from motion artefacts out of the 1-hour recording in the postprandial period, and it was, therefore, excluded from the analysis. A significant increase ($p < 0.05$) was observed, for the remaining four dogs, in the postprandial EGG frequency during the STIM period with respect to the SHAM period. An illustration of the postprandial EGG frequency during the STIM and SHAM periods is given in Figure 5.

Adaptive Stimulation Protocol

The dogs' reaction to stimulation differed among individuals. The evolution of the stimulation pulse charge (µC per pulse) and food intake according to time is, for each dog, shown in Figure 6. In the 4th week of the STIM period, the stimulation parameters stabilized around 7.7 ± 0.6 ms and 9.8 ± 3.2 mA. Three dogs (dogs #1, 4, 5) reached the maximum stimulation pulse charge (8 ms – 12 mA) in 12 ± 2 days, without showing signs of discomfort. One of them (dog #4) reached its MER at the end of the 4-week STIM period and the two others (dog #1 and #5) only decreased slightly their food consumption. Of the two dogs that did not reach the maximum pulse charge, one dog (dog #3) stabilized at a pulse charge of 8 ms – 8 mA and the other (dog #2) reduced its food consumption below its MER during the last two weeks, such that we decreased the pulse charge (as per equation 1).

Dog #3 showed discomfort symptoms (whimpering and sialorrhea) during its STIM period (days 13 and 14, represented in Figure 6). The pulse charge was decreased back to comfortable values (8 ms – 6 mA). From day 20, discomfort on the increase of pulse charge disappeared, and so the stimulation parameters were increased again as per equation 1, which led to an observable decrease in food consumption from day 21 to 28 (end of STIM period).

DISCUSSION

In this study, we have shown that the use of an adaptive GES protocol, that aimed to regulate food intake with MER as a target, was suitable for significantly reducing food intake in dogs with respect to baseline (- 42% by week 4), resulting in weight maintenance. In comparison, significant increases in weight (+ 10% by week 4) were observed compared to baseline without stimulation. In addition, GES significantly reduced the food intake rate during the STIM period compared to the SHAM (- 60% at week 4), and significantly increased the postprandial frequency of the gastric slow waves (+11% STIM vs SHAM), as measured with a noninvasive cutaneous system.

While the satiety-related action of GES is not fully understood, the development of our gastrostimulator system and adaptative stimulation protocol was based on previous evidence.

The impact of GES on gastric motility depends on the type of stimulation. In particular, the frequency at which the train of pulses is delivered is a key parameter for GES. When this frequency is the same as (or slightly higher than) the frequency of the intrinsic gastric slow waves, they enhance antral contractions and speed up gastric emptying [40–42]. However, when this frequency is higher than the frequency of the intrinsic gastric slow waves, they inhibit gastric motility such as gastric tone, contractions, and/or emptying [16]. In this study, we have chosen to use inhibitory GES, which corresponds to the second type of stimulation described above, where higher stimulation frequency implies inhibition of gastric motility. Due to its ability to impact gastric motility, inhibitory GES has been reported in recent reviews to be the most appropriate method to reduce food intake and treat obesity [16,18]. Indeed, gastric motility inhibition has been linked to reduced food intake in obese rats [31], in dogs

[29,43–45], and in healthy volunteers [38,46]. Moreover, this kind of GES was also observed to affect hormonal and neural activities both in animals and humans [22,23,44,47,48].

For this study, we developed a fully implantable and adjustable gastrostimulator to deliver inhibitory GES, based on previous evidence. The design of an IGS capable of delivering the required inhibitory GES is a challenge, given the relatively high energy demand necessary for efficient GES therapy [12,16,20,23,38]. Some teams have used external stimulators with transabdominal wires [20,29,39,44,49], which has the drawback of being invasive. Others have used implantable devices [12,19,30,45,50–53]. These are usually adapted nerve or cardiac stimulators [23], delivering fixed parameters with limited pulse width, unsuitable to stimulate with the longer pulses (i.e. higher energy) reported to be more effective in recent studies on inhibitory GES [16,19,20,27]. There is a growing interest in developing fully implantable systems capable of delivering an individualized and adjustable GES therapy with pulses longer than 2 ms [18,19,27,40,54,55]. Compared to emerging devices, our IGS can deliver a similar (and even larger) reprogrammable range of stimulation parameters, including pulse width (up to 32 ms), amplitude (up to 15 mA), and frequency (up to 1 kHz), which enables the investigation of other stimulation protocols.

In our experiment, we coupled standard analyses of food intake, weight, and gastric slow-wave pace, with a newly introduced estimation of the food intake rate. This latter modality allowed us to add more detailed insights on the reduction of appetite. Even though loss of significance of food intake was observed in the 4th week, food intake rate variation was significant that week, suggesting a clearer longer-lasting change in behavior.

GES induced tachygastria has been linked to impaired coordination, which in turn impairs gastric motility, delays gastric emptying, and reduces food intake, consequently leading to

weight loss [22,43]. The postprandial EGG frequency increased by about 10% with GES (STIM vs SHAM periods). Similar GES parameters (5 mA, 2 ms, 40 Hz, 2 s ON 3 s OFF) have previously shown to induce an acceleration on the slow waves in dogs, increasing their frequency from 5.3 ± 0.3 cpm at baseline to 6.4 ± 0.5 cpm during GES [22]. This tachygastria was correlated to a diminution of the dominant power, producing a lower gastric entrainment. However, the acceleration rapidly wore off when the GES was interrupted, and the EGG returned close to the baseline value during the recovery period. In our study, the increase in slow-wave frequency persisted after the end of the daily GES session, suggesting a longer-lasting effect.

The present study obtained encouraging results, further supporting GES, individualized and adaptive, as a solution to overcome obesity. Nonetheless, several limitations have been experienced in our experiment.

The theoretically computed MER – used in the protocol as the target value – was observed to be underestimated for four out of five dogs. Indeed, those dogs maintained or slightly decreased their body weight even when eating more than their MER. In practice, the targeted food intake may largely vary between individuals (up to 40% MER variation was observed in dogs of the same breed) [37,56]. In this regard, the target could be revised in future adaptive stimulation protocols and further adapted for human use.

Besides adapting the MER, the arbitrary constant K and the number of days to average the food intake MFI can be fine-tuned to adapt the therapy dynamics for the needs of future trials. Increasing K decreases the time required to reach optimal stimulation parameters, hence, the daily targeted food consumption. However, increasing K also makes stimulation parameters very sensitive to slight variations of food intake. There is, therefore, a tradeoff when choosing K and the number of days to average the MFI. Both K and the MFI were set in this study so as

to investigate high energy parameters within the stimulation period if the MER was not reached. As desired, our choices resulted in reaching maximum parameters or stabilization in 12 ± 2 days. For future use in humans, these constants will have to be adapted. Altogether, our adaptive protocol could be an adequate and elegant answer to the need for an individualized and dynamic therapy emphasized in recent GES studies [12,16,19,20,27].

Also, our adaptive GES protocol tackles at the same time (1) weight stabilization (to a given target – here MER), (2) habituation and (3) individualization (since stimulation parameters are automatically adapted to each individual). Further study could focus on only one of these objectives. For instance, varying the stimulation parameters in a stochastic way (but within safe boundaries) could be sufficient to tackle the habituation. Further interesting work could include optimization of stimulation parameters that were fixed in this study, i.e. the stimulation frequency (40 Hz) and the frequency at which the train of pulses is delivered (2 s on, 3 s off, i.e., 0.2 Hz). These could be optimized, for instance, by maximizing the impact of the stimulation on stomach activity, as evaluated through acute EGG measurements. Besides, in this study, no stimulation was applied in the SHAM group. In this regard, we were able to assess the benefits of adaptive GES protocol (in terms of food intake, food intake rate, and weight maintenance) against the absence of stimulation, and best estimate the usefulness of implanting such an IGS. In a further study, we could also compare different kinds of stimulation protocols (e.g. this adaptive protocol, stochastic stimulation, stimulation with fixed parameters, etc.) to assess the added value of a given protocol against another.

Unfortunately, one anchor migrated into the stomach lumen in one dog two months after the completion of the experiment and was explanted. This event did not influence the results of our study because the absence of migration was confirmed by CT images taken 2 weeks after

study completion. The hypothesis is that the gastropexy pocket may have been too tight around the anchor during the implantation surgery, leading to chronic excess pressure working towards the migration of the anchor into the lumen by pressure necrosis. Similar anchoring devices remained in place in six dogs for almost 3 years, without any complications [33]. It is likely that the minimally invasive implantation procedure, the intended electrode placement technique, will cause a lower pressure on the gastric wall, further reducing the risks of such a migration event.

In 2020, Paulus et al. [27] studied a novel IGS (Exilis system) for one year in 20 patients suffering from morbid obesity. They chose a fixed stimulation pulse width of 5 ms and individually adapted the amplitude between 6 and 10 mA based on preliminary titration visits (10 mA being the limit of the device). The stimulation was active 16 hours per day and no adaptation of the initial parameters was made during the whole year. Interestingly, significant excess weight loss was obtained in 28 weeks, but not at the end of the 52 weeks (EWL was 12.8% ± 3.7%, and 14.2% ± 4.5%, respectively) [27], suggesting a habituation phenomenon. No reduction in food consumption was observed by the end of the study. This again highlights the need to adapt the stimulation parameters individually, but also to counter the habituation that arises with time, as has also been observed in animals [19].

Taken together, we believe that new long-term clinical trials should be undertaken using a minimally invasive device that delivers individualized parameters and adaptive patterns over time to counter habituation, that is applied during mealtimes, and has a large pulse capability (> 2 ms). Several major steps are still required before reaching clinical use of our device. Approval from the competent authorities must be sought, for which safety will require significant investment. In particular, inhibitory GES uses long pulses (> 2 ms), and their impact

on the electrode-body interface should be addressed. It should be noted that the Abiliti™ from IntraPace [57] and the Exilis™ from Medtronic [27], which deliver pulse width up to respectively 2ms and 5 ms, have been approved for use in clinical trials, and therefore have proven to be safe. Clinical use of the proposed adaptive stimulation method will also require several adaptations. In this study, the MER based on the initial body weight (before experimentation) was chosen as the target food intake. In clinical practice, target food intake should be adapted to each single individual, depending on the therapy outcome that is both reasonable to target and desirable (weight reduction or maintenance), with the help of a trained nutritionist. In this study, the food intake was weighted and used as an input for stimulation parameter adaptation. While weighing food may be time-consuming in practice, entering calories into a smartphone seems easier to implement and a viable alternative. The arbitrary constant K and the number of days to average the food intake MFI can be fine-tuned to adapt the therapy dynamics, as stated above. The present study provides additional evidence in favor of individualized and adaptive GES therapy. We believe this is a step towards clinical trials to evaluate the long-term effects in humans, with a hope to one day offer this therapy to obese patients.

SUPPLEMENTARY MATERIAL

An appendix with the details about the battery life estimation is also provided.

STATEMENT OF ANIMAL RIGHTS

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

All procedures performed in studies involving animals were in accordance with the ethical

standards of the institution or practice at which the studies were conducted.

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Table 1: *EGG dominant postprandial frequencies in contractions per minutes (mean ± SD), the difference between the STIM and SHAM periods is significant (p < 0.05).*

Dog	STIM	SHAM
#1	4.14 ± 0.09	3.87 ± 0.35
#2	/	/
#3	4.56 ± 0.12	4.09 ± 0.09
#4	4.22 ± 0.22	3.84 ± 0.15
#5	4.27 ± 0.10	3.69 ± 0.16
Mean ± SD	**4.30 ± 0.18**	**3.88 ± 0.17**

FIGURES

Figure 1: (a) System overview with (1) the implantable gastric stimulator, (2) the flexible anchor with electrodes and (3) the external control box for wireless charge and communication. (b) Minimally invasive anchoring placement with (1) major steps proposed for implantation procedure and (2) related implantation tool.

Figure 2: Timeline of the experiment with key periods and the baselines used for the statistical computations.

Figure 3: Evolution of the weekly averaged food intake (left) and food intake rate (right) in both STIM and SHAM periods (mean & SD); "" and "*{" indicate significance with respect to the baseline and between STIM and SHAM, respectively ($p < 0.05$).*

Figure 4: Evolution of the weekly averaged weight gain in both STIM and SHAM periods (mean ± SD); "" and "*{" indicate significance with respect to the baseline and between STIM and SHAM, respectively ($p < 0.05$).*

Figure 5: Illustration of the postprandial EGG frequency during the STIM (in red) and SHAM (in blue) periods. An increase in the postprandial EGG frequency during the STIM period with respect to the SHAM period is visible.

Figure 6: Evolution of the stimulation pulse charge (µC per pulse) and food intake according to time, for each dog.