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Development of a Porcine Roux-en-Y Gastric Bypass Survival Model for the Study of Post-Surgical Physiology

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Background: Rodents have been used to examine physiologic changes after bariatric surgery, but differences in gastric/vagal anatomy may limit their utility. Swine may be a more appropriate animal model because of anatomic and physiologic similarities to humans. The aim of this study was to establish a survival model of Roux-en-Y gastric bypass (RYGBP) in swine and to evaluate its potential in studies of physiology.

Methods: 13 miniature swine, 5 Yucatan [26.4 ± 1.6 kg], 4 Hanford [28.3 ± 0.6 kg] and 4 other breed [54.9 ± 6.2 kg] underwent open RYGBP, and were kept alive to 30 (n=4), 60 (n=1) or 90 (n=2) postoperative days.

Results: 4 early animals had staple-line leakage within 7 days from surgery and 1 animal experienced unmanageable pain at 42 days after surgery. One animal experienced immediate cardiopulmonary collapse. 58% of animals survived to their projected endpoint. Necropsy of 1 animal at its 90-day endpoint revealed a gastro-gastric fistula. Anatomic features in swine that differ from humans, such as thick perigastric membranes, required adjustment to the standard RYGBP technique used in humans to achieve satisfactory results. Caloric intake decreased in some but not all animals, and was linked to feeding regimen. By postoperative day 30, animals weighed 5.7-29.1% less than their projected, non-operative weight. Serum assays of ghrelin and PYY were conducted, with results consistent with the procedure.

Conclusions: The use of swine as a model for bariatric surgery has promise, but also has associated pitfalls that must be addressed for this to be an effective model.

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Introduction

Roux-en-Y gastric bypass (RYGBP) is the most commonly performed bariatric operation in the United States. The procedure exerts a dramatic impact on patients, but its mechanisms of action are unclear. Weight loss is believed to result from mechanisms including restriction in gastric capacity and mild malabsorption due to bypass of the first few feet of the small intestine. RYGBP also appears to circumvent the normal homeostatic responses of weight loss that normally stimulate hunger and "calorie-seeking" behavior.[1-3] RYGBP also dramatically improves type 2 diabetes, and this effect typically precedes significant weight loss.[4] These effects are consistently observed in large groups of patients, but the effect in any given patient is quite variable and difficult to predict. The physiological mechanisms involved in diabetes resolution, anorexia, and the degree to which RYGBP is really malabsorptive have yet to be fully explored. The specific components of the operative technique that influence these mechanisms of action and in the observed variability of these effects also remain to be determined. An appropriate animal model for bariatric surgery may be helpful in isolating and understanding these effects.

The use of large animal models in bariatric surgery has been invaluable in the development of novel bariatric operations.[5] Small animal models have been used to test the metabolic derangements that follow these procedures.[6,7] but swine may be a more appropriate model to study bariatric surgical changes because of anatomic similarity[8] and gut peptide responses to fasting and feeding, relative to humans.[9,10] Swine have been utilized in several recent animal models evaluating RYGBP, but few have been survival experiments and none have focused on gut peptide and physiologic changes after surgery. The aim of this project was to establish a postoperative survival model of RYGBP in swine and to evaluate its feasibility for use as a model in physiologic research after gastrointestinal surgery.

Materials and Methods

All experimental procedures involving animals were approved by the Institutional Animal Care and Use Committee at the University of Washington.

Animals and Environment

Thirteen pigs (Yucatan, Hanford and other breed) progressed through phased group studies over ~1 year. All animals were acclimated to the research environment an average of 13.5 (± 8.2) days prior to surgery, to confirm that they were not losing weight in captivity. Animals were given access to water at all times, maintained on a 12:12-h light:dark cycle and were removed daily for cleaning of pens.

Yucatan Swine

Five 7-month-old miniature Yucatan swine (26.4 ± 1.6 kg) were obtained from Sinclair Research Center, Inc. (Columbia, MO). Animals were fed a maintenance diet (Prolab Mini-Pig Formula, PMI Nutrition International, St. Louis, MO), containing 22% total kcal from protein, 10% from fat, and 67% from carbohydrate (for a total of 3855 kcals daily).[11] To assess eating responses to twice daily, limited time feeding, Yucatan swine were provided portioned meals (750 g) in the morning and afternoon, with food removed once the animals appeared to lose interest in eating (1-2 hours).

Hanford Swine

Four 8-month-old miniature Hanford swine (28.3 ± 0.6 kg) were obtained from Sinclair Research Center, Inc. Animals were fed the Pro-lab Mini-Pig maintenance diet. To assess the response to a typical feeding pattern for swine, Hanford swine were provided one morning meal (1500 g). The animals were allowed free graze of feed over ~8 hours per day, and then the food (if any remained) was removed.

Other Breed Swine

Four 6-month-old other breed swine (54.9 ± 6.2 kg) were obtained from a University School of Medicine laboratory. To promote weight gain, animals were fed a specialized high-fat diet for 9 weeks prior to arrival, and they continued on a matched TestDiet (PMI Nutrition International, St. Louis, MO) upon arrival. The TestDiet contained 12.1% total kcal from protein, 45.7% from fat, and 42.2% from carbohydrate (7595 kcals). These swine were provided 2-hour feedings with portioned meals (875 g) in the morning and afternoon.

Surgical Procedures

Yucatan and Hanford animals were restricted from food and water for at least 12 hours prior to procedures. Other breed animals were provided 1500 calories in liquid meal (Ensure, Abbott Laboratories, Abbot Park, IL) within 48 hours prior to procedures, then restricted from all food within 24 hours with water restricted for at least 12 hours prior to procedures. Anesthesia was induced with 4 mg/kg of Telazol and Xylazine and 5% Isoflurane inhalation, and then maintained with .01 mg/kg of Glycopyrolate and 1-2% Isoflurane inhalation. An antibiotic (Cetifour, dose 3-4 mg/kg) was administered with anesthesia induction. Veterinary staff monitored the animal's heart rate, respiratory rate, core temperature, oxygen saturation, and corneal reflexes throughout the procedure. A continuous intravenous drip of Lactated Ringer solution was administered at 10-15 ml/kg/hr. Heating pads, warming fluids and blankets were used to maintain body temperature.

Surgical procedures in Yucatan and Hanford groups were completed utilizing United States Surgical (Norwalk, CT) stapling devices (i.e. GIA), while the other breed group was completed utilizing Power Medical Interventions (Langhorne, PA)

SurgASSIST system (PCL). The skin was prepped using a Betadine solution, and through a midline incision the small bowel was mobilized and measured from the ligament of Treitz to the cecum. An alimentary limb and biliopancreatic limb were fashioned of similar lengths and measured to be a total of either 1/3 or 1/4 of the total small bowel length. A standard 90-150 cm Roux limb was not felt to be appropriate, given the long and variable length of the animals' small bowel. The jejuno-jejunostomy anastomosis was created as a side-to-side anastomosis using a GIA or PCL stapler and 3-0 Maxon (United States Surgical, Norwalk, CT) reinforcement suture. An orogastric tube was placed, the esophagus dissected circumferentially, and a Penrose drain was placed for traction as the gastrohepatic ligament was dissected and the lesser curve identified. A gastric pouch was created using a 4.5-mm GIA or PCL stapler around the anvil of a 25-mm circular stapler placed in the gastric pouch. In the first 9 animals, the pouch was configured as a square and measured 3x3 cm, and the gastric remnant and pouch staple-lines were reinforced with suture material. In the other breed group, a V-shaped application of the two staple-lines was used to create a pouch with a narrower distal component than proximal component, to take advantage of the small lesser sac in the pig. An antecolic, antegastric anastomosis of alimentary limb and gastric pouch was completed using the circular stapler placed through the cut end of the jejunal limb. The gastric pouch was inflated with air using the esophageal tube to test the anastomosis in a bath of saline. Subcuticular stitches and tissue glue (United States Surgical, Norwalk, CT) were used for skin closure.

Post-Surgical Management

Fentanyl transdermal patches (100 μg) were placed on the dorsal thorax at the end of the surgical procedure for pain relief, and removed on postoperative day 3. Buprenorphine (0.05 mg/kg) was also administered for analgesia 1-2 times per day in the first 24 postoperative hours and utilized as necessary for breakthrough pain in the first 5 postoperative days. Feeding was restarted on the 1st postoperative day. The first other breed animal developed a low-grade wound infection and was given 375 mg amoxicillin trihydrate / clavulanate potassium. Subsequently, the remaining three other breed swine were given extended prophylaxis to prevent wound infection.

Termination was planned at random time points [days 30 (n=7), 60 (n=4) and 90 (n=2)]. Animals were euthanized using a method consistent with the recommendation of the Panel on Euthanasia of the American Veterinary Medical Association.[12] Necropsy was performed by veterinary pathologists on all animals.

Weight and Food Intake Measurement

Weight was monitored on at least three separate days preoperatively and at least once weekly postoperatively using a digital scale (Waypig 15, Vittetoe Inc., Keota, IA). Food consumption was determined at similar times utilizing a scale and recording the quantity of feed provided and the quantity remaining at the end of the feed period. Yucatans' and Hanfords' consumption was assessed during the morning feeding, while other breed's consumption was measured during the morning and afternoon feeding to record total daily intake.

Blood Sampling for Gut Peptide Measurements

Yucatan and Hanford swine underwent pre- and postprandial blood sampling preoperatively and on postoperative days 7, 30, 60, and 90 to assess plasma ghrelin, peptide YY (PYY), and glucagon-like peptide 1 (GLP-1). After an overnight fast, blood was drawn into EDTA tubes prior to meal (time 0) and after meal initiation (time 30, 60, 90, and 120 min). After meal initiation, animals had free access to their food and water throughout the blood sampling series. Serial blood samples on Yucatan swine were collected through auricular or femoral catheters, while animals were resting in a humane restraint sling.[11] In 9 of 20 completed blood draws, the peripheral vessels were inadequate for access, and animals were sedated[11] with isoflurane (3-5% induction and 1-3% maintenance) so that catheterization could be performed. To avoid this intervention, the Hanford swine underwent implantation with intravascular ported catheters (Vascular Access Port, Access Technologies, Skokie, IL) into the left and right external jugular veins prior to the initiation of the study.[13] During blood sampling through the port, animals were confined within a gated cart.

Each sample was mixed with aprotonin before being centrifuged at 1000 g for 15 minutes. Plasma was aliquoted into 250-μL tubes and frozen at -80˚C until analysis. Plasma samples were analyzed by commercially available radioimmunoassay kits (Phoenix Pharmaceuticals, Belmont, CA).

Statistical Analyses

Data analyses were descriptive rather than comparative, given the exploratory nature of this pilot project and the small number of animals involved in these analyses. Ghrelin and PYY area under the curve (AUC) were calculated using the trapezoid method.

Results

All 13 animals underwent successful open RYGBP with an average operative time of 127.1 ± 24.3 minutes. The length of the small bowel from ligament of Treitz to cecum was 786.4 ± 164.1 cm (range 600-1193 cm). Ten animals had a 1/3 small bowel bypass and 3 animals received a 1/4 bypass.

Intraoperative Complications

During one procedure, the diaphragm was penetrated during dissection of the midline fascia and was suture repaired. An anastomotic leak was detected by an air test in one procedure, requiring suture closure of the defect. Two procedures were complicated by the finding of massive gastric distension with both air and food that was not helped by decompression through a gastrotomy. In these cases, a partial gastrectomy was necessary to expose the angle of His for completion of the gastric pouch. This prompted a re-evaluation of the preoperative fasting period by the animal husbandry care team to avoid this complication in future procedures by increasing the preoperative fast from 12 to 24 hours and, in other swine, liquid diet from 24 to 48 hours preoperatively. Thickened perigastric membranes and an obliterated lesser sac made for difficult pouch creation. Stomach thickness that exceeded the capacity of the staple height also required suture reinforcement in almost all animals. One animal experienced cardiopulmonary collapse upon extubation and could not be resuscitated. Necropsy indicated that the GI procedure was not the immediate cause of death, and an anesthetic event was speculated, but not proven.

Postoperative Events

Seven of the remaining 12 animals (58.3%) survived to their projected time points of 30 (n=4), 60 (n=1) or 90 (n=2) postoperative days. Four Yucatan and Hanford animals died within 7 postoperative days and one was terminated at 42 postoperative days. Of these five animals, one died unobserved and all others were selectively terminated by euthanasia based upon clinical deterioration. Three of the five terminated animals appeared to have a staple-line leakage at the level of the gastric pouch, resulting in a caudal mediastinitis. Clinically, these animals presented with respiratory distress. One animal was euthanatized 7 days after surgery due to clinical signs of pain. On gross examination, severe peritonitis with extensive adhesions and a staple-line leakage at the level of the bypassed stomach was revealed. The other animal was euthanatized 42 days after surgery due to signs of pain that did not respond to usual care. No leak or serious intra-abdominal condition was identified. Necropsy of one animal at 90 days revealed a gastro-gastric fistula. This animal gained considerable weight after surgery. It is noteworthy that each of the third group of swine (other breed) survived to their projected time points, and there were no internal or anatomical problems detected at necropsy.

Weight and Food Intake

Food intake and weight are reported on all animals that survived >1 week postoperatively and were without gastro-gastric fistulas at necropsy (Table 1). Yucatan swine decreased body weight 17.4% on average by postoperative day 30. Growth projections suggest that this represented 29.1% less body weight than expected at that age (Figure 1). The first Yucatan animal continued to decrease body weight by 19% from day 30 to 90. The two surviving Hanford swine increased body weight by 6.7% by day 30. Growth projections for Hanford swine suggest that this was 5.7% less body weight than expected at that age. Expected growth curves for

Table 1. RYGBP procedure and outcomes summary table

	Group 1 Yucatan n=5	Group 2 Hanford n=4	Group 3 Other Breed n=4
		Surgical Procedures	
Small bowel length	705 ± 119.1	602 ±279	723 ± 83.4
Roux length	1/3 bypass	1/4 bypass	1/3 bypass
Pouch cut	Traditional	Traditional	V Cut
Anastomotic leak	1	0	0
Intraoperative death	0	0	1
		Postoperative Complications	
Staple-line leak	2	2	0
Mediastinitis and/or peritonitis	2	2	0
Gastro-gastric fistula	1	0	0
Postoperative death	2	3	0
		Food Consumption*	
Calories offered / day (kcals)	3855	3855	7595
Feed schedule	2 hr am/pm	24 hr am	2 hr am/pm
Preoperative food intake / day (kcals)	1147.2 ± 96.1	3836.2 ± 30.6	5402.4 ± 1470.4
Day 30 food intake / day (kcals)	1732.2 ± 1453.6	3855 ± 0	4313.9 ± 3086.6
		Weight	
Preoperative weight (kg)	30.45 ± 2.8	30.4 ± 1.3	56.6 ± 7
Body weight change at day 30	-17.4%	6.7%	-9.0%
Difference in day 30 actual weight and expected weight	-29.1%	-5.7%	-21.5%

*Food consumption and weight reported on surviving animals (n = 2 Yucatan, 2 Hanford including animal euthanized 42 days after surgery, and 3 other breed).

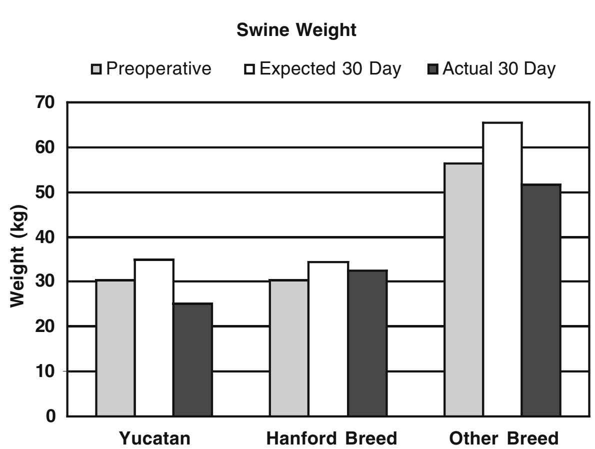

Figure 1. Swine weight. Preoperative weight represents age 8 months in Yucatan, 7 months in Hanford and 6 months in other breed swine. Expected weight at Day 30 represents the anticipated growth within 1 month for Yucatan (5 kg), Hanford (4 kg) and other breed (9 kg) swine.

each animal species were obtained from the supplier and projected for Yucatan and Hanford animals. The other breed swine uniformly decreased body weight by approximately 9% by day 30. From previous research on other swine,[14] we deduced that the animals may be expected to gain ~2.2 kg per week, or 9 kg in 30 days. At 30 days, our study animals weighed 21.5% less than their expected weight.

Gut Hormones

Data on gut peptides are reported for the 4 Yucatan and Hanford swine that survived to their planned time points. Preoperatively, animals demonstrated the expected meal-related response in ghrelin and PYY. Ghrelin (fasting levels: 515.7 ± 499.6 pg/mL) decreased by 30.4% (358.9 ± 247.8 pg/mL) at 120 minutes after meal initiation. PYY (fasting levels: 70.7 ± 11.7 pg/mL) rose by 60.6% (113.6 ± 49.3

pg/mL) at 120 minutes after meal initiation. Post-surgical ghrelin responses were evaluated in the 2 of 4 animals (both Yucatan swine) that were not gastrectomized during surgery. Because the stomach is the primary source of circulating grhelin, gastrectomy would be expected to impact ghrelin levels. Among non-gastrectomized swine, fasting levels of ghrelin at postoperative day 30 (2072.3 ± 1987.9 pg/mL) were greater than at baseline (239.7 ± 205.1 pg/mL). RYGBP in these selected animals seemed to be associated with an increase in postprandial ghrelin response, as determined by area under the curve. Plasma ghrelin was assayed in the 2 gastrectomized animals and as expected, ghrelin levels were undetectable in these animals. Fasting levels of PYY for all four animals at day 30 (73.9 ± 13.8 pg/mL) did not appear to differ from baseline values (70.7 ± 11.7 pg/mL). RYGBP did not appear to change overall meal-related PYY response in Yucatan swine, as determined by area under the curve.

Discussion

Swine may be a more appropriate model to study bariatric surgical changes than small animal models, because of similarities with this species and humans in anatomic features and physiologic responses to fasting and feeding. Swine have occasionally been utilized in evaluating the feasibility of RYGBP, but not to study mechanisms of post-surgical physiological changes. Preliminary swine model development has not been reported in a complete fashion, so the true rate of complications for a developing model may be underestimated by the published literature.

Thirteen miniature swine underwent successful open RYGBP. Like other porcine bariatric investigations,[15,16] we experienced one immediate peri-operative death, most likely due to anesthetic complications. We also identified pitfalls unique to this model that will be important for others who are developing swine surgery programs. For example, thickened stomach walls make use of standard staplers problematic[15-18] and required suture buttress. A set of other anatomic features necessitated adjustments to the standard RYGBP technique used in humans. These included an exaggerated gastric cardia, thick perigastric membranes, obliteration of the lesser sac, gastric distention with food despite preoperative food restriction, narrow small bowel caliber, and small bowel length occasionally in excess of 8 meters. We found that these pitfalls were overcome with procedure modifications, such as changing the Roux limb length to accommodate an appropriate percentage bypass of the intestine, subtotal gastrectomy in 2 animals, over-sewing of the staple-lines in 7 animals, and dilation of the small bowel to accommodate standard staplers. Lastly, the problem of leaking from the gastric pouch was overcome by utilizing a V-shaped staple application for the creation of a "virtual" gastric pouch.

A review of the published literature revealed 5 RYGBP porcine survival studies, all completed laparoscopically, with postoperative follow-up ranging from 1 week to 6 months.[15,16,19-21] Of these studies, 2 reported intraoperative deaths[15,20] and two reported similar postoperative complications leading to untimely death.[15,19] Laparoscopic bariatric surgical investigations in swine have found anastomotic leaks in 53%-91%[18,22] of animals, and several of the animals experienced staple-line or other leakage at the gastric pouch in the present investigation. Additionally, Nocca et al[23] and Potvin et al[19] both reported unexpected postoperative deaths in swine due to peritonitis, and Potvin et al[19] and Waage et al[16] reported gastro-gastric fistulae. As in humans, the communication between the gastric pouch and distal stomach renders the restrictive components of the RYGBP procedure ineffective.

Of the 5 prior survival swine studies, only one reflected on body weight changes and none discussed caloric intake. In that study,[20] all animals weighed less at termination than their expected weight despite stable levels of food consumption which is comparable to results of our swine groups. In an open vertical banded gastroplasty study, Nocca et al[23] reported an average weight loss of 3.42 kg after 4 weeks, and, in a model using reinforced RYGBP, researchers found 12-15 kg weight loss at 3 months.[15] This is similar to our experience of weight loss among the first and third group of swine (Yucatan and other breed) but is more than what we observed with the second group (Hanford) that were fed *ad libitum*. Prior RYGBP studies have not detailed how food was provided to animals or the time course of feeding allowed. We explored two approaches to feeding and caloric intake in swine. One approach was twice-daily feeding and removal of food once animals lost interest. The other was 24-hour *ad libitum* exposure to food and periodic assessments of 24-hour intake. We studied this issue because limited feeding times may parallel human feeding where eating to satiety in a limited period is the norm. The third swine group (other breed) were returned to a 2-hour twice-daily feeding approach and experienced ~16% decrease in caloric intake and ~9% body weight loss at postoperative day 30. Our findings suggest that this limited feeding time approach may be the only way to promote reductions in caloric intake, and believe this should be a component of the model in future physiologic testing. Exposing animals to *ad libitum* caloric intake may circumvent the effects of gastric pouch restriction or possible neurologic clues of hunger and satiety on caloric intake.

We also sought to demonstrate the feasibility of gut peptide assessments before and after bariatric surgery within the swine model. The small numbers of animals included in these analyses and the variation in surgical technique, feeding patterns and weight loss preclude a meaningful assessment of peptide changes after surgery. However, some findings suggest that gut peptide analyses in swine will be worthwhile in future physiologic studies. For example, gastrectomized swine produced virtually no ghrelin. Animals demonstrated a typical ghrelin response to fasting and meal ingestion but this response did not decrease after surgery. In fact, in selected animals, ghrelin area under the curve appears to increase despite an ~25% body weight loss. This type of response has been witnessed with non-surgical weight loss in humans but is not expected after weight loss induced by RYGBP. Future studies will explore the response in pigs undergoing standard procedures and nutritional intake along with the effects of bypassed stomach size, pouch size and vagal nerve disruption on post-surgical ghrelin release. Lastly, assays for porcine GLP-1 are limited at this time but are commercially available and under evaluation by our group. The evaluation of gut peptides after RYGBP may be critical to understand the changes in appetite that induce massive weight loss as well as those that explain why diabetic patients improve in glycemic control even before significant weight loss occurs.[24]

Current speculation has promoted the "distal intestinal hypothesis" that RYGBP anatomical rearrangement of the bowel brings nutrients in direct contact with distal sensors that elicit the ileal break, perhaps promoting over-expression of GLP-1. In a recent study, Rubino and colleagues[25] found that non-obese type 2 diabetic rats improved glucose tolerance with a stomach-preserving duodeno-jejunal bypass, but not with a gastrojejunostomy, which acts as a shortcut for ingested nutrients from the preserved stomach to the distal bowel while still keeping the proximal bowel intact. A well developed large animal model with similar anatomic function to humans will be essential in understanding if these hypotheses are relevant in clinical care. If so, their implication in more targeted "metabolic" procedures may be considerable.

In conclusion, we found that the use of swine as a model for RYGBP has both promise and associated pitfalls that may limit its utility. The knowledge to be gained from having an animal model with similar anatomic characteristics to humans is critical. Performing standardized procedures that allow for adjustment in Roux lengths, pouch size, vagal nerve inclusion and other factors will be essential to more targeted procedures in the future and in understanding the critical elements of a successful RYGBP. Future studies utilizing this model will clarify these technique-related elements and also their impact on gut peptides, clinical course and co-morbid conditions such as diabetes.

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