The Denervated Stomach as an Esophageal Substitute Is a Contractile Organ

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Objective
To determine whether the denervated stomach as an esophageal substitute is an inert conduit or a contractile organ.

Summary Background Data
The motor response of gastric transplants to deglutition suggests that the stomach pulled up to the neck acts as an inert organ.

Methods
The gastric motility of 11 healthy volunteers and 33 patients having either a gastric tube (GT) (n = 10) or their whole stomach (WS) (n = 23) as esophageal replacement was studied with perfused catheters during the fasting state, after a meal, and after intravenous administration of erythromycin lactobionate. A motility index was established for each period of recording by dividing the sum of the areas under the curves of all contractions of >9 mmHg by the time of recording.

Results
Over years, the denervated stomach recovers more and more motor activity, even displaying a real phase 3 motor pattern in 6 of the 10 WS patients and 1 of the 7 GT patients with >3 years of follow-up. Erythromycin lactobionate generates a phase 3-like motor pattern regardless of the length of follow-up. Extrinsic denervation of the whole stomach does not significantly modify the fasting motility index established >3 years after surgery (+17% on average, p > 0.05), but it reduces that in the fed period by an average of 62% (p = 0.0016). Tubulization of the denervated whole stomach lowers the fasting motility index by an average of 60% (p = 0.0248) and further impairs that in the fed period by an average of 67% (p = 0.0388).

Conclusions
The denervated stomach as an esophageal substitute is a contractile organ that may even generate complete migrating motor complexes. Motor recovery is better in the fasting than in the fed period, and it is more marked in WS patients than in GT patients.
Motor behavior of the stomach as an esophageal substitute after total or subtotal esophagectomy is poorly understood. The prevailing opinion, based on the motor response of gastric transplants to deglution, is that the stomach pulled up to the neck acts as an inert organ,1,2 so that ingested material flows down by gravity only.3,4 However, the good quality of the alimentary comfort of many of these patients living over the long term,5 especially those in whom the whole stomach was used as esophageal replacement,6 casts doubt on this classic concept. In addition, radiologic examination of gastric transplants at follow-up may show contractions in the gastric wall.7 In this setting, there was a need for an in-depth manometric study of the contractility of the stomach used as an esophageal substitute. If gastric transplants recover some motor activity, the subsequent question is whether the technical modalities of gastric tailoring may influence motor recovery.

MATERIALS AND METHODS

Population Studied and Gastric Tailoring

The 44 subjects studied belonged to one of three categories.

The first group contained 11 healthy volunteers with no previous foregut diseases or surgeries. There were 6 males and 5 females, ages 18 to 31 years (mean, 24.5 years).

The second group contained ten patients whose esophagus had been replaced by the stomach shaped into a greater curvature tube (GT patients). There were 7 males and 3 females, ages 29 to 73 years (mean, 56.9 years). Postoperative follow-up ranged from 10 days to 144 months (mean, 71 months). Tubulization8-10 was started 4 to 10 cm from the pylorus, and the cartridges of staples (GIA-50 stapler, U.S. Surgical, Norwalk, CT, or PLC-50 stapler, Johnson & Johnson, Somerville, NJ) were applied parallel to and 20 to 25 mm away from the free edge of the lesser curvature up to the left side of the cardia.

The third group consisted of 23 patients who had their whole stomach used as an esophageal substitute (WS patients).6 There were 17 males and 6 females, ages 44 to 78 years (mean, 58.1 years). Postoperative follow-up ranged from 10 days to 90 months (mean, 32.5 months). The whole stomach11 was prepared as follows. The terminal rami of both right and left gastric vessels were divided flush with the gastric wall from the pylorus up to the cardia, and the esophagus was then separated from the gastric pouch by application of a single cartridge of staples on the cardia.

Of the 33 patients who underwent surgery, 29 were operated on for cancer and 4 for a benign condition. Operations made for cancer systematically included skeletonization of the celiac axis and its three branches of division for extensive lymph node clearance.

Manometric Study

Motor activity of the stomach was monitored using one of two polyvinyl probes (Zinetics Medical, Salt Lake City, UT). Both had a central conduit for air aspiration or insufflation and eight channels of recording; six of these were perfused and two were occluded. The distal tip of the probe used in control subjects was fitted with an inflatable balloon to facilitate passage into the duodenum. The manometry unit included microcapillary catheters, a hydraulic pump, external transducers (Peter Von Berg, Kirchseeon, Germany), a polygraphic system (PC Polygram HR, Synectics Medical, Stockholm, Sweden), an analog–digital interface (Combi-Interface 93-9506, Synectics Medical, Stockholm, Sweden), and a personal computer equipped with software (Polygram 6.30, Upper GI edition, Gastrossoft, Irving, TX) that permitted semiautomatic recognition of the best fit of each contraction using an auto-find threshold of 9 mmHg. The amplitude and duration of each contraction, as well as the area delimited by the curve and a horizontal line at the 9-mmHg level on the Y axis, were also calculated semiautomatically. In addition, it was possible retrospectively to modify the scale of the X axis (tracing speed) as well as that of the Y axis (pressure steps ranging from 0.2 to 2,000 mmHg).

The probe was introduced through an anesthetized nostril into the gastric transplant lumen under manometric or fluoroscopic control so that side holes eventually were located at a distance from the pylorus of 2, 4, 7, 12, 17, and 22 cm. The two distal holes of the probe used in control subjects were placed in the duodenum,12,13 and the four others were located in the stomach at a distance from the pylorus of 1, 2, 4, and 7 cm. Fasting motility was recorded with the patient in a reclining position for 2 to 3 hours until a solid–liquid meal of 800 calories was given. Postprandial motility was then recorded for 1 to 2 hours after the probe was repositioned at the same level as in the fasting period. By the end of the fed period, erythromycin lactobionate14 (Abbott, Chicago, IL) was perfused intravenously at a rate of 40 mg/min for 10 minutes in 13 WS patients, 6 GT patients, and 6 control subjects.

Gastric contractions were identified within the scope of the idea that the distal part of the stomach contracts at a rate of about three cycles per minute (Collard JM, Romagnoli R, Otte JB, Kestens Pj, manuscript submitted
for publication). Macrocontractions (amplitude > 9 mmHg) were detected by the semiautomatic software. Microcontractions (amplitude < 9 mmHg) were detected by reading the tracing, which used small steps of pressure (0.2 to 1 mmHg) on the Y axis. Macrocontractions were classified into three subcategories according to amplitude: 9 to 50 mmHg, 50 to 200 mmHg, and >200 mmHg. A motility index was established by dividing the sum of the areas under the curves of all macrocontractions by the time of recording (in minutes) in the best antral channel during the two most active hours of the fasting period, the most active hour of the fed period, and the 10 to 15 most active minutes of the erythromycin test. The three classic phases of the fasting migrating motor complex were identified according to the following definitions:

- **Phase 1**: period of recording just after phase 3, with no macrocontraction detectable, and lasting >10 minutes;
- **Phase 2**: fewer than 3 macrocontractions per minute for a period >10 minutes; and
- **Phase 3**: burst of macrocontractions occurring at a rate of 3 or more cycles per minute for a period longer than 3 minutes in 3 or more channels of recording. The fed pattern was defined as a phase 2–like tracing occurring just after food ingestion and lasting at least 60 minutes.

The Wilcoxon rank sum, Krusskal-Wallis, and Mann-Whitney statistical tests were used.

**RESULTS**

**Recovery of Motor Patterns**

The tracings recorded during the fasting period a few days after surgery showed weak contractile activity consisting of synchronous microcontractions occurring at a rate of about three cycles per minute, with rare macrocontractions ranging in amplitude from 9 to 50 mmHg occurring between them (Fig. 1). Patients who were studied a few months to 3 years after surgery had recovered a more marked motor activity, similar to a phase 2 pattern (Fig. 2) — that is, a mixture of sporadic, peristaltic, and variable-amplitude macrocontractions and peristaltic microcontractions at a rate of about three cycles per minute. The three classic phases of the interdigestive migrating motor complex, namely a real phase 3 (Fig. 3), were evident in 6 of the 10 WS patients and 1 of the 7 GT patients investigated >3 years after surgery. Gastric resection in the latter patient had been limited to the proximal segment of the lesser curvature, leaving intact the...
contractile part of the stomach. Tracings of the 10 remaining patients with >3 years of follow-up (4 WS, 6 GT) displayed only a phase 2 pattern. During the fed period, gastric transplant patients progressively recovered phase 2-like motor activity. Intravenous administration of erythromycin lactobionate generated a phase 3-like motor pattern after a latency period of 2 to 7 minutes in all the subjects studied, regardless of the length of follow-up (10 days to 144 months after surgery). When erythromycin lactobionate was given a few days after surgery, the high-amplitude contractions induced were peristaltic, even though spontaneous microcontractions were synchronous.

**Motility Index**

The motility index during fasting and fed periods increased progressively with time in both groups of patients (Figs. 4 and 5), but motor recovery was better in WS patients than in GT patients. The fasting motility index in WS patients beyond 3 years of follow-up was similar to that in control subjects and was significantly superior to that in GT patients (Fig. 6). In the fed period, the motility index in both groups of patients with >3 years of follow-up remained significantly lower than that of control subjects, but it was significantly higher in WS patients than in GT patients. In control subjects, food ingestion stimulated gastric motility, thus significantly increasing the motility index, but it did not in both groups of patients. The motility index after erythromycin administration was significantly higher in control subjects and WS patients than in GT patients (Fig. 7). Roughly speaking, extrinsic denervation of the stomach does not significantly modify the fasting motility index (+17% on
average, \( p > 0.05 \), but it reduces the postprandial motility index by an average of 62\% (\( p = 0.0016 \)). Tubulization of the denervated whole stomach lowers the fasting motility index by an average of 60\% (\( p = 0.0248 \)) and further impairs that in the fed period by an average of 67\% (\( p = 0.0388 \)). Compared with the intact stomach, the tubulized stomach has a motility index reduced by 54\% (\( p = 0.0057 \)) and 87\% (\( p = 0.0019 \)) on average in the fasting and fed periods, respectively.

### Frequency Distribution of Contractions

The frequency distribution of contractions in the distal antrum during the fasting period (Fig. 8) shows that beyond 3 years of follow-up, both whole stomachs and gastric tubes generate fewer macrocontractions (>200 mmHg) than stomachs of controls (\( p = 0.0486 \) and 0.0008, respectively). However, although WS patients compensated for this loss by a significant increase in the frequency of macrocontractions of 50 to 200 mmHg (\( p = 0.0124 \)), GT patients generated more macrocontractions of lower amplitude (9 to 50 mmHg; \( p = 0.0191 \)). Contractions recorded in the proximal antrum of the three categories of subjects studied are of lower amplitude than those in the distal antrum (see Fig. 8), so that, for instance, the former cannot generate any contractions of >200 mmHg (all subjects), or even of >50 mmHg (GT patients). However, the frequency of contractions of 50 to 200 mmHg and 9 to 50 mmHg, recorded in the proximal antrum of the denervated whole stomachs, was similar to that in control stomachs (\( p > 0.05 \)).

During the fed period (Fig. 9), both types of gastric transplants generated fewer macrocontractions of >200 mmHg (\( p = 0.0020 \) for WS and 0.0012 for GT) as well as fewer macrocontractions of 50 to 200 mmHg (\( p = 0.0022 \) for WS and 0.0018 for GT tubes) than control stomachs. WS patients compensated for these losses by an increase in the frequency of macrocontractions of 9 to 50 mmHg (\( p = 0.0274 \)); this was not the case in GT patients (\( p = 0.6973 \)). Food ingestion in control subjects (Fig. 10) stimulated gastric motility, increasing the frequency of both macrocontractions of 50 to 200 mmHg (\( p = 0.0002 \)) and 9 to 50 mmHg (\( p = 0.0003 \)). In gastric transplant patients with >3 years of follow-up, food ingestion significantly decreased the frequency of macrocontractions of >200 mmHg. However, unlike GT patients, WS patients compensate for this loss by a significant increase in macrocontractions of 9 to 50 mmHg.

### DISCUSSION

The stomach used as an esophageal substitute is a contractile organ, even though it is disconnected from the extrinsic innervation pathways after truncal vagotomy in the chest and partial gastric sympathectomy along the branches of division of the celiac axis. Early in the postoperative period, the gastric wall exhibits weak microcontractions at the pacemaker’s rate of about three cycles per minute (Collard JM, Romagnoli R, Otte JB, Kestens PJ, manuscript submitted for publication).15–16 These microcontractions are recorded by intraluminal sensors as synchronous because of the chamber effect produced by the postoperative intraluminal stasis of gas-
tric juice. Administration of erythromycin lactobionate suppresses this chamber phenomenon, unmasking peristalsis by generating high-amplitude macrocontractions. With time, the amplitude of contractions increases, and peristalsis and the three phases of the classic migrating motor complex spontaneously reappear. Such a motor reorganization depends on the myenteric plexus in the gastric wall,\textsuperscript{18} which is capable of acting as a local brain that coordinates contractions of muscle fibers. Induction of a phase 3–like motor pattern by intravenous administration of erythromycin as early as 10 days after surgery attests to the inborn presence of this organizational potential in ganglionic cells.\textsuperscript{19} Over time, these cells can progressively and spontaneously express these properties outside of any extrinsic nervous influence.

However, analysis of the motor response to food ingestion indicates that motor recovery after extrinsic denervation is far from complete: unlike the intact stomach, the gastric transplant reacts poorly to the arrival of food material into its lumen. Fed motor activity is thus more dependent on vagal impulses than that in the fasting state. However, the difference in antral contractility between the denervated whole stomach and the intact stomach is more marked just proximal to the pylorus than in the proximal antrum. This indicates that the distal branches of the two Latarjet’s nerves in the crow’s foot carry the most important motor fibers of the vagus nerves.

Motor recovery is much more marked in WS patients than in GT patients. Indeed, unlike WS patients, GT patients recover a fasting motility index that is much lower than that of control subjects. Tubulization of the denervated whole stomach further depresses motility an average of two thirds in both periods of recording. Moreover, the loss in macrocontractions of very high amplitude (>200 mmHg) that results from extrinsic denervation is better compensated for in WS patients than in GT patients.

Resection of the proximal 75\% of the lesser curvature for tubulization obviously destroys in part both the organizer and effector of the contractions—that is, the myenteric plexus and muscle mass in the proximal antrum, respectively. This is why the response to erythromycin given as a booster of gastric motility is significantly weaker in GT patients than in WS patients. The role of the myenteric plexus is made still more significant by the fact that depression of gastric contractility was observed not only at the level where the lesser curvature had been removed but also in the distal antrum, where the gastric muscle had been maintained intact. The existence of very long ganglionic fibers and interneurons all over the gut\textsuperscript{20} allows us to hypothesize that the reduced contractility in the distal antrum is related to removal of ganglionic cells that were located in the resected lesser curvature segment but whose axonal processes extended down to the distal antrum. In this respect, it has been shown in the animal\textsuperscript{21} that the vast majority of the vagus-dependent "command ganglia" containing the motor programs of the myenteric plexus are located within the wall of the lesser curvature. As a consequence, the neural injury to the stomach that results from tubulization with resection of the lesser curvature extends beyond the staple line over the remaining gastric wall.

Our study confirms that the stomach maintained in its entirety is a better esophageal substitute than the gastric tube\textsuperscript{6}. If the stomach is tubulized for resection of the subcardial area, as for a lower-third tumor, it would be wise to skeletonize the lower two thirds of the lesser curvature for lymph node clearance and to limit stapling resection to the proximal third. In this way, the contractile part of the stomach is maintained intact and, as in one of our patients, recovery of migrating motor complexes, including phase 3, may be expected. Of course, removal of a tumor centered on the cardia must include either more extended proximal or total gastrectomy\textsuperscript{22} to achieve cancer-free histologic margins.

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References