J Med Dent Sci 2019; 66: 65−73

Original Article

Use of the ^{13}C breath test to assess late dumping after esophagectomy and subsequent gastric tube reconstruction for esophageal cancer

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Abstract

Background and Aim: The aim of the present study was to evaluate the clinical usefulness of the ^{13}C breath test in postoperative patients who underwent gastric tube reconstruction following esophagectomy.
Methods: Postoperative patients (POs; n=26) and healthy volunteers (HVs; n=10) were included as subjects. Of the 26 POs, the 7 with late dumping symptoms were regarded as the dumping group (DG), and the remaining were considered the non-dumping group (NDG). Semisolid test meal mixed with 100 mg of ^{13}C-sodium acetate was given to each subject. Breath samples for the ^{13}C gas analysis and blood samples were collected.
Results: The Cmax was 37 ± 13(‰) in the HVs and 49 ± 11(‰) in POs, being significantly higher in POs (p=0.019). The Cmax was 56 ± 14(‰) for DG and 47 ± 8.9(‰) for NDG, indicating that the Cmax in the DG tended to be higher than that in the NDG, although not to a significant degree (p=0.12). The change in the C value and each glucose metabolism-related marker showed a general correlation.
Conclusion: The present results suggest that the ^{13}C-acetate breath test reflects changes in glucose homeostasis after esophagectomy, making it useful for objectively and simply assessing late dumping symptoms in postoperative esophageal cancer patients.

Key words: late dumping symptoms, 13C-acetate breath test, gastric tube reconstruction, esophageal cancer

Introduction

Gastric tube reconstruction employing stomach tissue is commonly performed after esophagectomy for esophageal cancer due to its safety and simplicity.[1-3] However, vague complaints, such as dumping syndrome and feelings of chest discomfort, can occur after surgery, often affecting half of or even more cases, and these postoperative symptoms are reported to be particularly strongly associated with a poor quality of life (QOL).[4, 5] Thus, one of the goals of esophageal cancer surgery is to mitigate postoperative sequelae and minimize the deterioration of the QOL. To this end, it is important to evaluate the gastrointestinal function and clinical symptoms after gastric tube reconstruction following esophageal cancer surgery. However, an objective and simple evaluation method has yet to be established.

Dumping syndrome is a particularly frequent postoperative issue. "Dumping" refers to a series of clinical symptoms caused by the sudden influx of food contents

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Received April 4 ; Accepted October 7, 2019

into the small intestine and can be classified as early or late dumping. In early dumping, the upper small intestine extends and expands due to food, stimulating peristaltic action, and the influx of hypertonic food into the intestine triggers extracellular fluid migration from blood vessels into the intestine, resulting in a reduction in the circulating plasma volume, and small intestinal wall extension causes excessive digestive hormone secretion, resulting in various autonomic symptoms. In late dumping, food contents are absorbed in a short period of time, causing transient hyperglycemia, which in turn stimulates excessive insulin secretion and subsequent reactive hypoglycemia, which manifests as clinical symptoms, such as dizziness, lightheadedness, and even paroxysmal unconsciousness.[6] These problems are primarily recognized as post-gastrectomy syndromes[7–9] but can also occur after gastric tube reconstruction following esophageal cancer resection and are known to be a major postoperative problem affecting the QOL. Therefore, the postoperative evaluation of the gastric tube function and absorption capacity is necessary.

The ^{13}C breath test is a method used to evaluate gastric emptying and absorption capacities.[10, 11] This method employs the stable naturally-occurring carbon isotope ^{13}C, which is given to a subject as a test meal. The ^{13}C in the test meal leaves the gastric tube as it is emptied and is then absorbed into the duodenum and small intestine, metabolized in the liver, and finally exhaled from the body as CO_2 in the breath. The ^{13}C breath test monitors ^{13}C ingested with a meal, thereby allowing for the simple determination of the gastric tube transit time and duodenal absorption rate. Although some studies are available regarding the accuracy of a ^{13}C breath test in reflecting gastric function and the relationship between food intake and change in body weight after distal gastrectomy for gastric cancer[12], only a few studies have so far evaluated the reconstructed gastric tube function following esophageal cancer surgery.[13] We previously evaluated the emptying and absorption capacities of the reconstructed gastric tube after surgery for esophageal cancer using the ^{13}C breath test in patients who underwent gastric tube reconstruction postopertively.[14]

In the present study, we discussed the ^{13}C breath test and late dumping syndrome, which are considered highly relevant to glucose metabolism. We also investigated whether or not the ^{13}C breath test is useful for evaluating late dumping symptoms after esophageal cancer surgery.

Methods

Patients

A comparative study was conducted in patients who underwent subtotal esophagectomy, retrosternal gastric tube reconstruction and three-field lymph node dissection at Tokyo Metropolitan Cancer and Infectious Center Komagome hospital between 2006 and 2008 who had remained recurrence-free for at least 10 months and gave their fully informed consent for study participation. Healthy volunteers (HVs) served as comparator controls. In addition, glucose metabolism-related markers (blood glucose [BG], immunoreactive insulin [IRI], and C-peptide immunoreactivity [CPR]) were measured as indicators of dumping symptoms, and their potential correlations with the ^{13}C breath test curve results were analyzed. We excluded patients who had concomitant diabetes, as this condition was likely to affect the BG, IRI, and CPR. All procedures were approved by the Ethics and Indications Committee of Tokyo Metropolitan Cancer and Infectious Center Komagome Hospital. Written informed consent for the study was obtained from each patient. The authors have no conflicts of interest in connection with this study.

^{13}C breath test technique

A semisolid test meal (100 mL of Otsuka Racol® mixed with 100 mg of ^{13}C-sodium acetate and 1 packet of Otsuka Easygel®; Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan) was used for the ^{13}C breath test.[15,16] The test meal was total caloric content of 100 kcal. Each subject was given the test meal under 12-h fasted conditions, and the ^{13}C breath test was then performed. According to the standard method for the evaluation of gastric emptying in the ^{13}C breath test established by the Japan Society of Smooth Muscle Research (JSSMR),[10] exhaled gases were collected before test meal intake and then at 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, 120, 135, 150, 165, 180, 210, and 240 minutes after test meal intake. Dedicated sampling packets were used for the collection of exhaled gases, and the isotope ratio was expressed as Δ‰. Blood samples were also collected at these time points to evaluate the correlation between ^{13}C breath test results and glucose metabolism parameters. Glucose metabolism markers, including the BG, IRI, and CPR, were measured before and again at 20, 40, 60, and 120 minutes after the test meal intake.

Table 1. Questionnaire survey about Late dumping symptoms. (symptoms a couple of hours after a meal)

1. Do you have cold sweats?
2. Do you have dizziness?
3. Do you lose consciousness or have convulsions?
4. Do you feel general fatigue and/or languor?
5. Do you have finger tremor?

Table 2. Characteristics of the post esophagectomy patients and healthy volunteers

Characteristics	Healthy Volunteers	Dumping Group	Non-Dumping Group
Number of case (n)	10	7	19
Age (years)	36 (26–70)	52 (48–69)	66 (52–79)
Sex (male:female)	6:4	3:4	2:17
Post operative period (day)	—	513 (362–1190)	386 (351–730)

Result are given as the Median (Range)

Operation

Subtotal esophagectomy via right thoracotomy and laparotomy (including endoscopic resection), retrosternal gastric tube reconstruction, and three-field lymph node dissection (neck, chest, and abdomen) were performed for patients with esophageal cancer. Manual pyloric dilatation rather than pyloroplasty was used in all cases. The gastric tube was preserved with a large antral portion (5 cm from the pylorus, thereby preserving 3 branches of the right gastric artery), and the esophagus was anastomosed to the stomach at the left neck with a narrow gastric tube on the greater curvature with a width of approximately 3 cm. An automatic circular stapler was used for all operations. The same two surgeons performed the operations in all cases.

The evaluation of late dumping symptoms

The presence of late dumping symptoms was determined based on responses to the questionnaire (Table 1). Before starting the ^{13}C breath test, the same interviewer questioned the subjects individually in order to determine the presence of late dumping symptoms and, accordingly, divided the subjects into a dumping group (DG) and non-dumping group (NDG). Cases with positive results for one or more items were judged to have late dumping symptoms and were classified into the DG group.

Statistical analyses

Parameters determined by the breath test were the isotope ratio Δ‰ in exhaled breath (C value), the maximum isotope ratio Δ‰ in exhaled breath (Cmax), and the time to Cmax (Tmax in minutes). Data are presented as the means ± standard deviation, based on statistical testing performed using the Welch's t-test. P values < 0.05 were considered to indicate a statistically significant difference. Correlations were statistically tested using linear regression to determine the coefficient of correlation (r). All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[17]

Results

Study subjects

The details of the study subjects are presented in Table 2. In total, 26 patients were included in the postoperative group (POs), and 10 HVs comprised the control group. Dumping symptoms were present in 7 (27%) of the 26 POs.

^{13}C Breath test in POs

Figure 1-1 shows the mean percentage curve of ^{13}C isotope for the HVs and POs. The Cmax was 37 ± 13(‰) in the HVs and 49 ± 11(‰) in the POs, being significantly higher in the latter (p=0.019). The Tmax was 59 ± 19(min) in the HVs and 53 ± 21 (min) in the POs, indicating a longer time to the Cmax in the HVs, but not significantly so (p=0.38) (Figure 1-2).

^{13}C Breath test by the presence of late dumping symptoms

Figure 2-1 shows the mean percentage curve of the ^{13}C isotope for the DG and NDG. The Cmax was 56 ± 14(‰) in the DG and 47 ± 8.9 (‰) in the NDG, showing no significant difference (p=0.12). The Tmax was 48 ± 15(min) in the DG and 54 ± 23(min) in the NDG, without a significant difference (p=0.42) (Figure 2-2).

Relationships of ^{13}C breath test curve results with BG, CPR, and IRI

Regarding the correlation of C values and changes in each parameter, at 20 minutes after the test meal intake, the changes in the C value correlated with changes in BG ($p < 0.0001$, r=0.82), IRI (p=0.0003, r=0.65), and

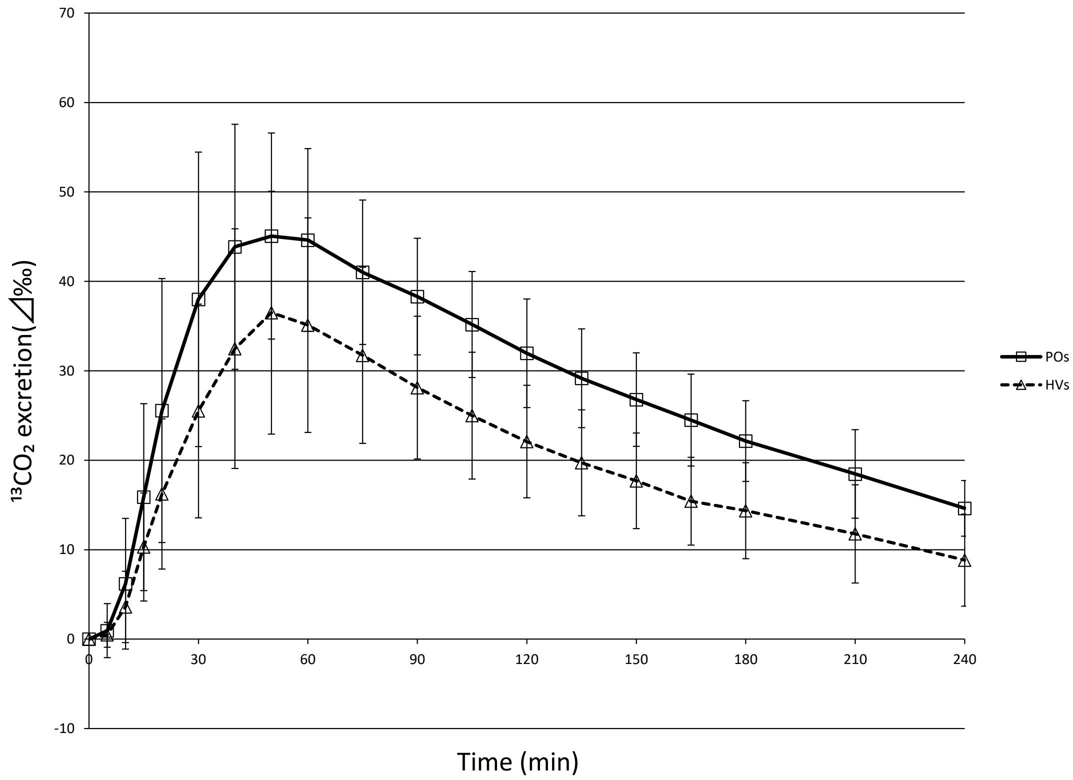

Figure 1-1. There is pulmonary $^{13}CO_2$ output curves

Error bars indicate SD.

Post-operative group: POs (squares), Healthy volunteers (control): HVs (triangles)

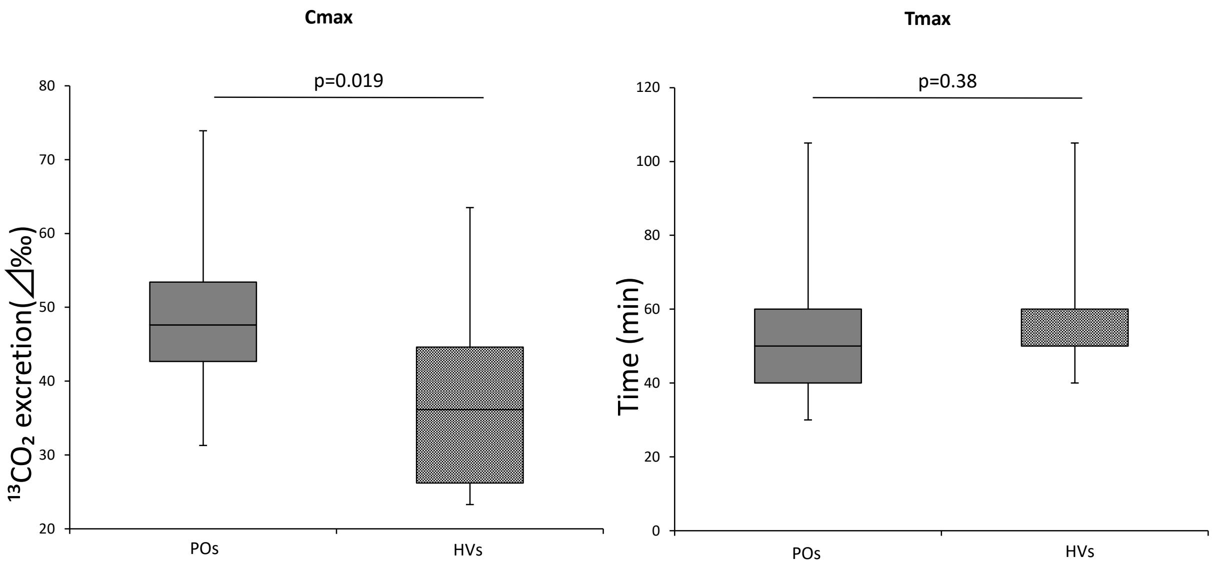

Figure 1-2. Box-and-whisker plot of Cmax and Tmax in each group (HVs vs. POs)

Welch's t-test showed that mean value of Cmax was significantly high ($p=0.019$) and mean time of Tmax was not significantly difference ($p=0.38$).

Box plot: median and 25&75 percentile, Whisker: maximum and minimum.

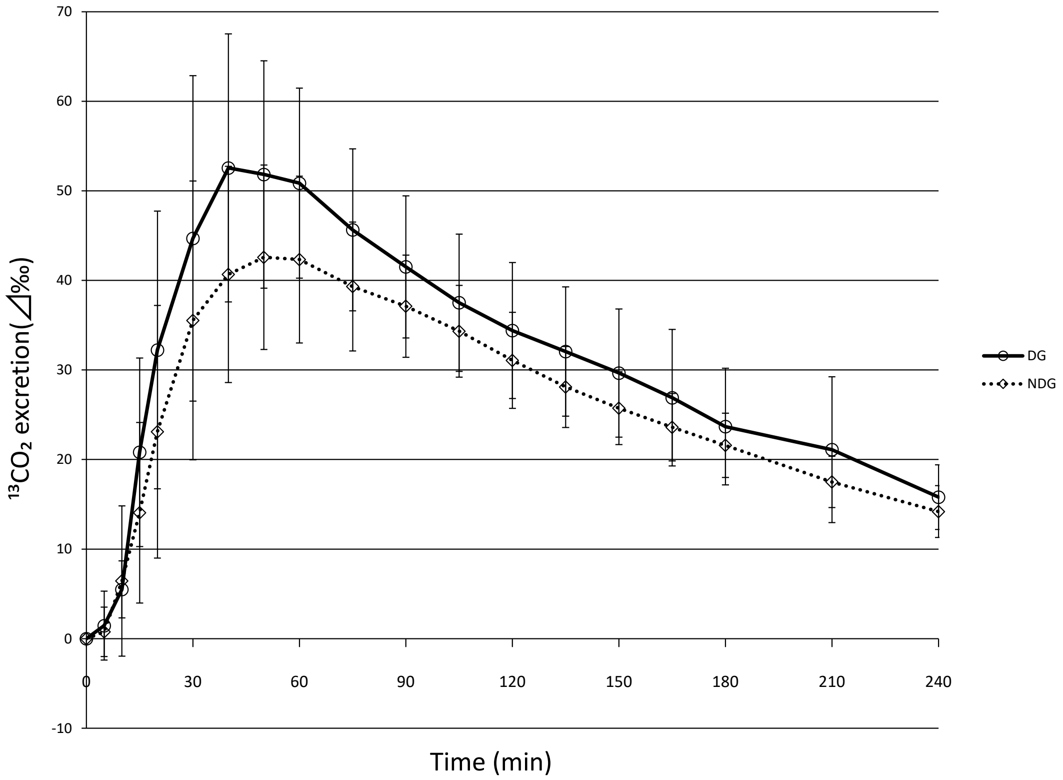

Figure 2-1. There is pulmonary $^{13}CO_2$ output curves

Error bars indicate SD. Dumping group: DG (circles), Non-dumping group: NDG (diamonds)

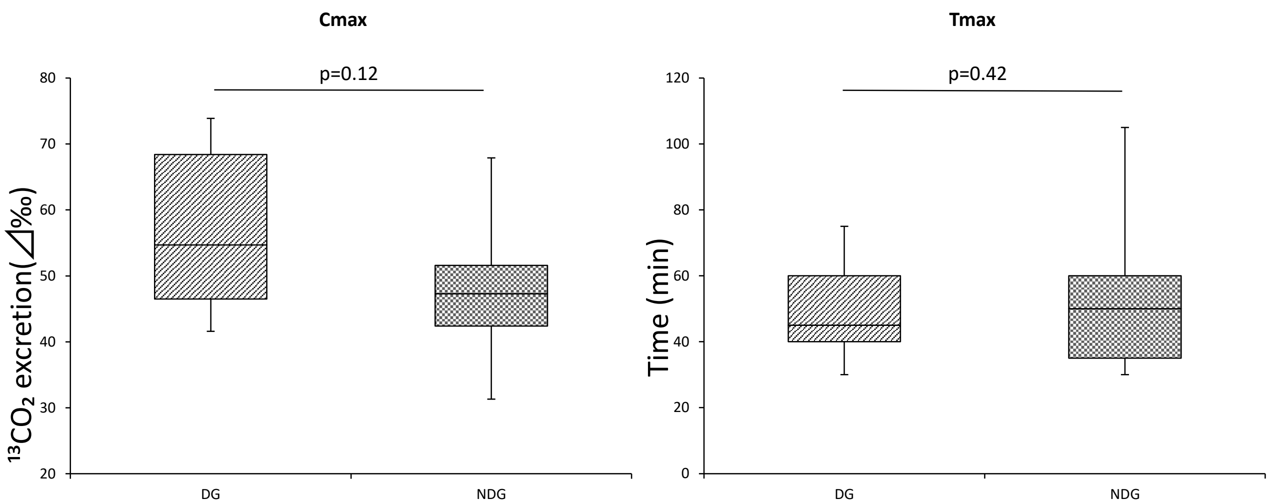

Figure 2-2. Box-and-whisker plot of Cmax and Tmax in each group (DG vs. NDG)

Welch's t-test showed that mean value of Cmax was not significantly difference (p=0.12) and mean time of Tmax was not significantly difference (p=0.42).

Box plot: median and 25&75 percentile, Whisker: maximum and minimum.

Figure 3-1.

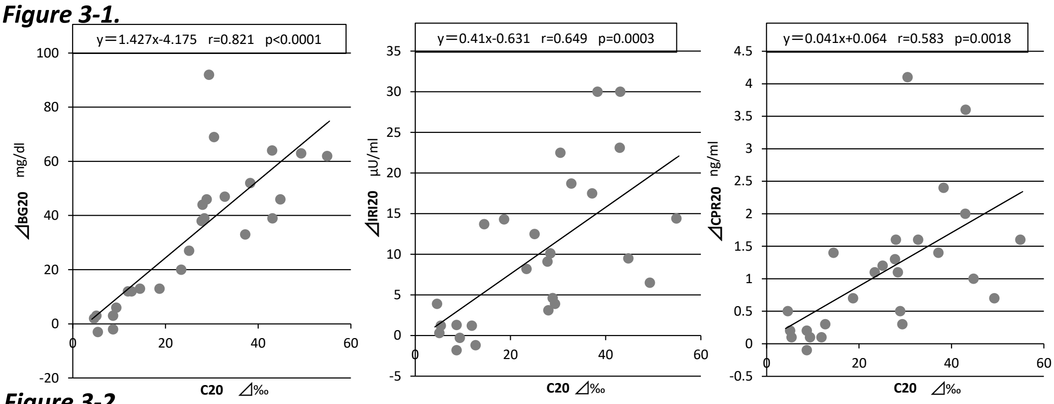

Figure 3-2.

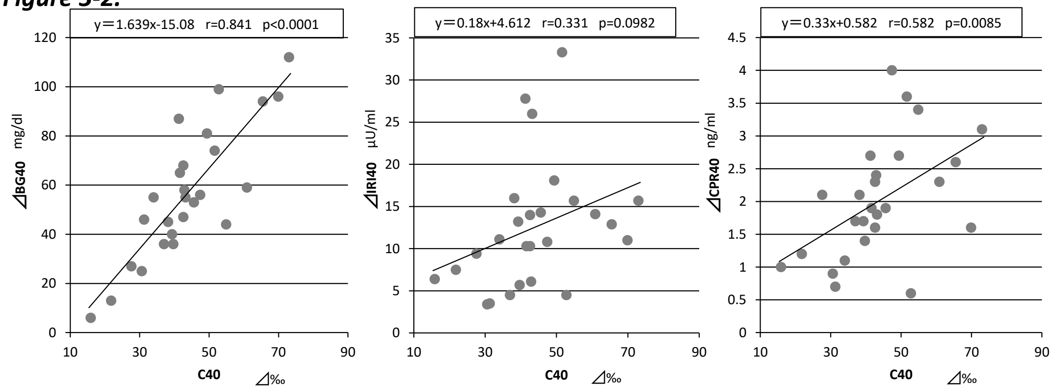

Figure 3-3.

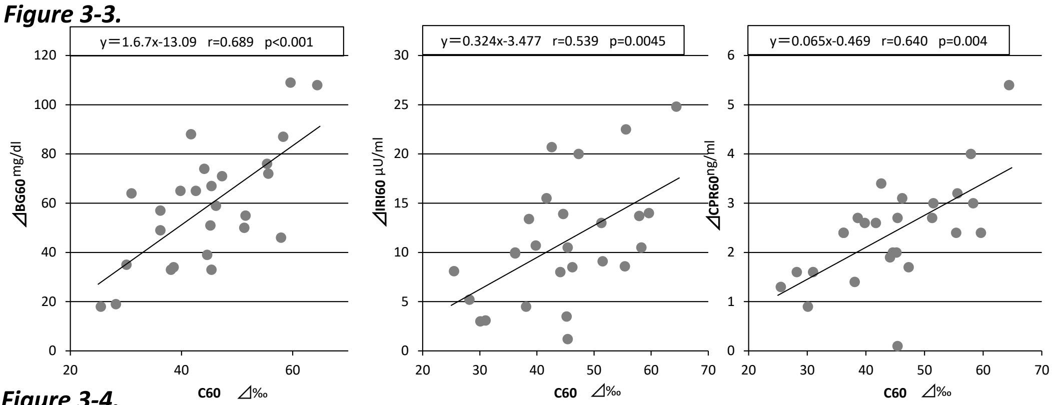

Figure 3-4.

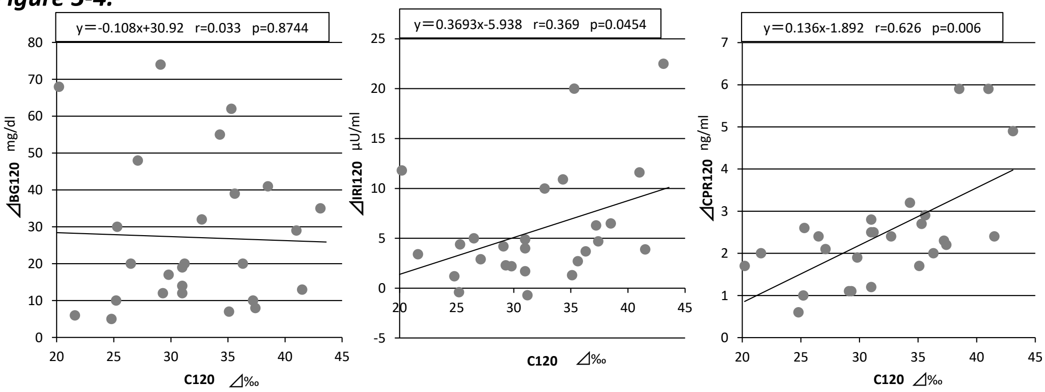

Figure 3-1, 3-2, 3-3, 3-4.

Correlation between the value of $^{13}CO_2$ excretion in the ^{13}C-acetate breath test and the amount of change of each parameter in each measurement time (20, 40, 60 and 120 min). Circles: individual data, n=26

CPR ($p=0.0018$, $r=0.58$), demonstrating a particularly strong correlation with BG (Figure 3–1). At 40 minutes after the test meal intake, the changes in the C value correlated with changes in BG ($p < 0.0001$, $r=0.84$), IRI ($p=0.33$, $r=0.098$), and CPR ($p=0.0085$, $r=0.58$), demonstrating a particularly strong correlation BG but a weak correlation with IRI (Figure 3–2). At 60 minutes after the test meal intake, the changes in the C value correlated with changes in BG ($p < 0.001$, $r=0.69$), IRI ($p=0.0045$, $r=0.54$), and CPR ($p=0.004$, $r=0.64$) (Figure 3–3). At 120 minutes after the test meal intake, the changes in the C value showed no correlation with changes in BG ($p=0.87$, $r=0.033$) but did correlate with IRI ($p=0.045$, $r=0.37$) and CPR ($p=0.006$, $r=0.63$) (Figure 3–4).

Discussion

Generally, dumping symptoms significantly and adversely impact the postoperative QOL. Dumping symptoms are classified as early or late and are caused by the rapid entry of food into the small intestine.[6-9] Dumping symptoms are clearly associated with dysfunctional emptying of the reconstructed gastric tube after esophageal cancer surgery,[18-20] but the relationship between the emptying function and severity of dumping symptoms is poorly understood. Some reports indicated that late dumping symptoms are caused by delayed gastric tube transit[21-24] and recommended improving gastric tube emptying by applying endoscopic balloon dilatation to the postoperative gastric tube in order to reduce complications, such as aspiration and suture rupture.[23] However, worsening of late dumping symptom and bile reflux have also been noted in association with stimulation of gastric tube emptying by pyloric dilatation,[4, 24, 25] and whether or not pyloric dilatation and emptying stimulation are favorable for the reconstructed gastric tube has yet to be determined. It is therefore very important to evaluate the gastric tube emptying capacity and severity of associated symptoms. Because the morphology and route of the reconstructed gastric tube are also known to influence gastric tube emptying and the onset of dumping symptoms,[26-28] we limited our study subjects to patients who had undergone the same procedure and route of gastric tube reconstruction.

We used a simple ^{13}C breath test for the evaluation in this study. This test monitors a compound labeled with ^{13}C, a stable isotope of ^{12}C, as it is emptied from the stomach, absorbed in the small intestine, metabolized in the liver, and exhaled as $^{13}CO_2$ in the breath. The test is mainly used to evaluate gastric emptying, and the standard method is recommended by the JSSMR protocol for multicenter investigations in Japan.[10] This is an indirect method, in contrast to a direct method utilizing imaging techniques, such as the conventional invasive RI method.[29] However, few studies have assessed the feasibility and validity of the ^{13}C breath test for evaluating the gastrointestinal function after surgery. Safety is particularly important, considering the risk of aspiration and other complications after esophageal cancer surgery, and the ^{13}C breath test is said to be safer and less invasive than the RI method.[29-31] It is also regarded as being safe and applicable to the evaluation of gastric tube emptying and absorption after esophageal cancer surgery. Because the standard method could not be directly performed in our study subjects after esophageal cancer resection, we used a semisolid test meal[14,32] with a small portion,[14] in order to avoid aspiration. All subjects swallowed the entire test meal without experiencing aspiration.

We first compared gastric tube emptying capacity between postoperative and healthy subjects. The Cmax was significantly higher and the Tmax lower in POs than in HVs, indicating that gastric tube emptying was increased in POs. Our results are consistent with the findings reported for patients who had undergone surgery for gastric cancer, who also showed a lower Tmax[33, 34] and higher Cmax than healthy individuals. The findings in surgically treated gastric cancer patients were attributed to a decreased gastric retention, and our results may also reflect a reduced gastric retention, which is known to occur after gastric tube reconstruction following esophageal cancer resection. The present study also demonstrated a significant increase in gastric emptying and early entry of food into the small intestine in patients who had undergone esophageal cancer surgery compared with HVs. These are, in fact, the primary causes of late dumping symptoms. Based on these results, we considered a possible correlation between late dumping symptoms and the ^{13}C breath test curve and thus performed further analyses based on the presence of late dumping symptoms.

The subjects with late dumping symptoms had a higher Cmax and a lower Tmax than those without such symptoms, suggesting gastric tube emptying to be increased in subjects with late dumping symptoms. In other words, late dumping symptoms were apparently attributable to increased gastric tube emptying, which is a particularly significant finding. However, in the subjects with late dumping symptoms, while the increase in Cmax and the Tmax decrease was not statistically significant. This indicates that late dumping symptoms after esophageal cancer surgery cannot be explained by the reduced gastric tube transit rate alone and that these symptoms are related to postoperative changes in the gastrointestinal absorption capacity, particularly an increase in the absorption. Furthermore, subjects with late dumping symptoms may have increased gastrointestinal absorption postoperatively. In addition, in the subjects with an increased gastrointestinal absorption, rapid transient hyperglycemia and associated excessive insulin secretion, which are known to cause postoperative late dumping symptoms, were also likely to have been involved.

We therefore next measured the glucose metabolism markers of BG, IRI, and CPR at the same time in order to investigate whether or not the ^{13}C breath test curve indicates not only the gastric tube emptying capacity but also the respiration capacity, as well as its association with late dumping symptoms. We found that the breath test curve correlated with all 3 glucose metabolism markers up to 60 minutes and with CPR and IRI up to 120 minutes after the start of the test. These results support the idea that the breath test curve reflects these changes in glucose markers and therefore correlates with the presence or absence of dumping, particularly late dumping symptoms. Furthermore, a strong correlation was seen at 20 minutes after test meal intake, indicating meal absorption and an associated BG increase, probably because the influence of the BG reduction by insulin secretion was minimal in this early phase.

In addition, the correlation between insulin and the breath test curve can also be explained by the relationship between insulin secretion and acetic acid metabolism. Piloque et al. reported that insulin secretion stimulated acetic acid metabolism.[35] The C value in the breath test curve ultimately indicates the amount of metabolized acetic acid, and the observed correlations of the C value with IRI and CPR raise the possibility that the breath test curve is consistent with the insulin secretion.

Furthermore, the DG had a higher Cmax than the NDG. This finding, coupled with the fact that the breath test curve correlated with BG as well as IRI and CPR, suggests that the DG patients were likely to have had hyperglycemia and increased insulin secretion at an early stage following meal ingestion.

The present study showed that the ^{13}C breath test after esophageal cancer surgery was useful for evaluating the gastric tube emptying capacity as well as the severity of dumping symptoms simply and objectively. The results of the ^{13}C breath test revealed late dumping symptoms to be due mainly to increased gastric tube emptying. The ^{13}C breath test curve correlated with BG, IRI, and CPR and therefore correlated with late dumping symptoms. In addition, the evaluation of the gastric tube function using this test was shown to be safe, simple, and effective. Further studies should be conducted in order to establish the cut-off value of each parameter and clarify the positive and negative predictive values. We would then be able to evaluate universal late dumping symptoms with only objective test values. In the future, the ^{13}C breath test might be applied after esophageal cancer surgery not only for the objective evaluation of the gastric tube emptying capacity but also for detecting potential late dumping symptoms, essentially serving as a “glucose-insulin metabolism test.” Further studies will be needed in order to establish a procedure aimed at QOL improvement, which is the ultimate therapeutic goal.

Acknowledgments

The authors thank Masako Akiyama, Department of University Research Administration, Tokyo Medical and Dental University, for help with the statistical analysis.

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