Severe Delayed Gastric Emptying Induces Non-acid Reflux up to Proximal Esophagus in Neurologically Impaired Patients

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Background/Aims

The aim of this study is to investigate the degree of delayed gastric emptying (DGE) and evaluate how the severity of DGE affects gastroesophageal reflux disease (GERD) in neurologically impaired (NI) patients utilizing 24-hour multichannel intraluminal impedance pH measurements (pH/MII) and ^{13}C-acetate breath test (^{13}C-ABT) analyses.

Methods

^{13}C-ABT and pH/MII were conducted in 26 NI patients who were referred to our institution due to suspected GERD. At first, correlation analyses were performed to investigate the correlation between the ^{13}C-ABT parameters and the clinical or pH/MII parameters. Thereafter, all patients were divided into 2 groups (DGE and severe DGE [SDGE] group) according to each cut off half emptying time ($t_{1/2}$, 90-170 minutes). Each pH/MII parameter was compared between the 2 groups in each set-up cutoff $t_{1/2}$.

Results

The mean $t_{1/2}$ of all patients was 215.5 ± 237.2 minutes and the $t_{1/2}$ of 24 (92.3%) patients were > 100 minutes. Significant moderate positive correlations were observed between both $t_{1/2}$ and lag phase time and the non-acid reflux related parameters. Furthermore, the patients in the SDGE group demonstrated higher non-acid reflux related parameters than those of the DGE groups when the cutoff was $t_{1/2} \geq 140$ minutes.

Conclusion

The present study demonstrated that GE with $t_{1/2} \geq 140$ minutes was related to an increase of non-acid exposure reaching up to the proximal esophagus in NI patients, and indicating that NI patients with SDGE might have a high risk of non-acid GERD.
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Key Words

Breath test; Disabled patient; Gastric emptying; Gastroesophageal reflux; Multichannel intraluminal impedance measurements

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Introduction

Gastroesophageal reflux disease (GERD) has been one of the most critical conditions for neurologically impaired (NI) patients with a high incidence.[1,2]

Although the relationship between delayed gastric emptying (DGE) and GERD is still controversial, with some authors reporting a significant association between the 2 conditions[3,4] and others reporting no correlation,[5,6] several authors have described that the presence of DGE increases the probability and rate of gastroesophageal reflux (GER) episodes.[7-10] DGE has also been documented with an increasing frequency in infants and children with symptoms of GERD. In particular, DGE is common in patients with esophageal atresia or NI[11-14] at an incidence of > 50.0%. As an empirically acceptable pathophysiology, it has been suggested that DGE could be an important contributor to GER by increasing esophageal exposure in the postprandial period,[3,4] indicating the accentuation of postprandial reflux is likely due to an increased volume of refluxate per episode of reflux through an underlying incompetent lower esophageal sphincter (LES).[3] A reduction in meal size or adding pyloroplasty to fundoplication with the aim of reducing the postoperative complications and recurrence of GERD[10,15,16] have been used in clinical practice as therapeutic options for GERD accompanying DGE.

As mentioned above, it is well recognized that DGE contributes to the aggravation of GERD in NI patients. However, most reports have only referred to the relationship between acid GERD and DGE according to pH monitoring, which only examines acid GERD. Indeed, a previous report evaluated by pH monitoring indicated that although a large proportion of NI patients manifest moderate to severe GERD and its complications, they do not have DGE.[5] Moreover, it remains unclear how the severity of DGE affects the aggravation of GERD.

Twenty-four hour multichannel, intraluminal impedance pH measurements (pH/MII) have recently emerged as a novel technique to evaluate GERD irrespective of the pH value. As pH/MII has recently been introduced for clinical use, non-acid GERD has received attention and a close relationship between non-acid GERD and NI has been suggested. Additionally, a previous study reported that more than half of the reflux events in NI children were non-acidic detected by pH/MII.[17]

Although the presence of non-acid reflux is potentially related to DGE in NI patients, to the best of our knowledge, only one report thus far has investigated the relationship between non-acid

reflux and DGE in NI patients.[18] Thus, the detailed pathophysiology of DGE in NI patients with GERD including non-acid reflux remains controversial.

The aim of this study is to investigate the degree of GE in NI patients and to evaluate how the severity of DGE affects GERD, including both acid and non-acid reflux, in NI patients by utilizing both 24-hour pH/MII and ^{13}C-acetate breath test (^{13}C-ABT) analyses.

Materials and Methods

This retrospective study included NI patients, who underwent gastrointestinal examinations between 2011 and 2014 at the Kurume University hospital. Medications for GERD were stopped at least 3 days before entering the study, and upper gastrointestinal endoscopy and barium swallowing were performed in all cases—there were no abnormal findings that affected gastric emptying. All enrolled NI patients were evaluated using both GE measurements and 24-hour pH/MII. The study protocol was approved by the Kurume University Ethical Committee (No. 2575 and 11049). Informed consent was obtained from their families before their enrollment in this study.

GE was evaluated using the ^{13}C-ABT (the Breath ID system; Oridion Breath ID Ltd, Jerusalem, Israel) after the ingestion of a liquid meal (Racol; Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan), which is a semi-digested (osmotic pressure: 330-360 mOsm/L) as a test meal. The nutrient compositions of 100 mL of the liquid meal (100 kcal/mL) were 4.4 g of protein extracted from casein and soybean, 15.6 g of carbohydrate, and 2.2 g of fat. The test meal was administered via a nasogastric tube in 24 patients, and via gastrostomy in 2 patient within 5 minutes. The breath test was performed by accumulating each subject's exhaled gas via a nasal cannula for breath testing. After a baseline collection of the patient's breath, all patients were administered 10 mL/kg (maximum dose 100 mL) of the test meal, in which 100 mg of ^{13}C-labeled sodium acetate was dissolved, and were tested in the semi-Fowler's position after more than 6 hours of fasting. The test meal was processed and emptied by the stomach. After absorption and metabolism, ^{13}C was derived and exhaled in the breath as CO_2. The device continuously measures the ratio of ^{13}C and ^{12}C in the CO_2 of the exhaled breath for 4 hours using molecular correlation spectroscopy. The Breath ID device measures the ratio and the ^{13}C substrate and dose, and provides the percentage dose recovery and cumulative percentage dose recovery. It then calculates the half emptying time ($t_{1/2}$, minute), the lag phase time (t_{lag}), and the gastric emptying coefficient

(GEC), based on a non-linear analysis as described by Ghoos et al.[19] GE was expressed as $t_{1/2}$. t_{lag} and GEC was also evaluated as automatically analyzed parameters. $t_{1/2}$ is the time required for half of the gastric contents to be emptied. t_{lag} is the time at the point of inflection of the curve after mathematical integration, and GEC is an index of the global gastric emptying rate. A shorter $t_{1/2}$ and t_{lag} and a higher GEC suggest accelerated gastric emptying.

In the analysis of 24-hour pH/MII, a multiple intraluminal impedance catheter (outer diameter, 2 mm) with 2 pH antimony electrodes and 7 impedance electrodes (Sandhill Scientific, Inc, Highlands Ranch, CO, USA) was used. This technique can assess the esophageal flow by measuring changes in conductivity (impedance value) of the esophageal content between multiple electrode pairs on a catheter. The main advantage of this device is its ability to detect not only acid, but also non-acid reflux episodes and the height of refluxate. The catheter was inserted transnasally through the esophagus, and pH sensor placement was confirmed by radiography. Obtained data from the 24-hour pH/MII was automatically evaluated using the BioVIEW analysis software program (Sandhill Scientific, Inc, Highlands Ranch, CO, USA) and each tracing was manually reviewed by the same investigators (S.I. and S.F.). Liquid reflux was defined as a fall in impedance more than or equal to 50.0% from the baseline occurring in at least 2 consecutive channels in an abnormal direction. Each type of reflux was defined as follows: acid reflux, associated pH drop to ≤ 4, and non-acid reflux, associated pH value above 4. The pH index was defined as the percentage of time with a pH value ≤ 4. A high cut-off value was defined as 4.0% according to the definition of the Working Group of Japanese Society for Pediatric Alimentary Motility.[20] The bolus exposure index (BEI) was defined as the percentage of time with retrograde movement of intraluminal esophageal material. A high cut-off value was defined as 1.4% (higher than the 95th percentile of normal 24-hour pH/MII values, as suggested by Shay et al[21] in an adult series of healthy patients). Pathological GERD was defined as a pH index > 4.0% or a BEI > 1.4%.

At first, correlation analyses were performed to investigate the correlation between the ^{13}C-ABT parameters ($t_{1/2}$, t_{lag}, and GEC) and the clinical parameters (age, gender, height, body weight, causal disorders of NI [congenital or acquired], and the degree of scoliosis) or the pH/MII parameters (BEI [total, acid, and non-acid], and the number of reflux and proximal reflux episodes [total, acid, and non-acid]), respectively.

Thereafter, all patients were divided into 2 groups (the DGE group and the severe DGE [SDGE] group) according to each set-up cut off $t_{1/2}$ (90, 100, 110, 120, 130, 140, 150, 160, and 170 min-

utes). Each of the pH/MII parameters were compared between the 2 groups in each set-up cutoff $t_{1/2}$.

All statistical analyses were performed with the JMP Pro 11 software program (SAS Institute Inc, Cary, NC, USA). The numerical data were expressed as the mean ± standard deviation and range. A Spearman's correlation analysis was used to investigate the correlation between the ^{13}C-ABT and the clinical or pH/MII parameters. The Mann-Whitney U test was used for nonparametric analyses. *P*-values less than 0.05 were considered to be statistically significant.

Results

Twenty-six NI patients were enrolled in this study (male/female, 12/14; mean age, 17.11 ± 15.59 years [range, 11 months-41 years]; mean height, 1.16 ± 0.32 [range, 0.70-1.58] m; mean body weight, 20.47 ± 12.21 [range, 5.00-44.00] kg; mean body mass index, 13.86 ± 3.06 [range, 8.61-20.09] kg/m^{2}). All patients had profound NI due to a congenital disorder (cerebral palsy [n = 15], chromosomal anomaly [n = 5]) or acquired disorder (hypoxic brain damage [n = 6]), and were referred to our institution due to symptoms of suspected GERD. Feeding was achieved orally (n = 1) or enterally (n = 25) (nutrients were continuously administered for more than an hour, 3 to 5 times a day), via a nasogastric tube (n = 23) and via a gastrostomy (n = 2). The mean Cobb angle of all NI patients was 38.89 ± 34.81 degrees.

Based on the GERD examination by 24-hour pH/MII analyses, 14 patients were diagnosed with pathological GERD (53.8%), and 12 were diagnosed with non-pathological GERD (46.2%). The above data for the clinical parameters and details results of pH/MII parameters in all NI patients are shown in Tables 1 and 2, respectively.

In the GE measurements by ^{13}C-ABT in all NI patients, the mean $t_{1/2}$, t_{lag}, and GEC for all NI patients were 215.5 ± 237.2 (range, 105.4-1061.6) minutes, 81.7 ± 67.9 (range, 26.2-316.9) minutes, and 3.2 ± 0.6 (range, 2.0-3.9), respectively. The $t_{1/2}$ of 24 (92.3%) patients was over 100 minutes (Figure).

The correlation analyses between the ^{13}C-ABT and clinical parameters revealed no significant correlations between the ^{13}C-ABT parameters and the clinical parameters (Table 1). The correlation analyses between the ^{13}C-ABT parameters and the pH/MII parameters revealed significant moderate positive correlations between both $t_{1/2}$ and t_{lag} and the non-acid related parameters (BEI [non-acid] and the numbers of total and non-acid reflux and total and non-acid proximal reflux episodes). In contrast, no significant correlation

Table 1. The Correlation Analyses Between the Clinical and ^{13}C-acetate Breath Test Parameters

Clinical parameters	No. or mean ± SD	t_{lag} (P-value)	$t_{1/2}$ (P-value)	GEC (P-value)
Age (yr)	17.11 ± 15.59	0.609	0.583	0.489
Gender (M/F)	12/14	0.939	0.738	0.980
Height (m)	1.16 ± 0.32	0.822	0.599	0.294
Body weight (kg)	20.47 ± 12.21	0.270	0.164	0.630
Causal disorder (C/A)	20/6	0.879	0.692	0.605
Scoliosis (Cobb angle, degree)	38.89 ± 34.81	0.370	0.176	0.500
Pathological GERD (+/−)	14/12	0.625	0.625	0.898

t_{lag}, lag phase time; $t_{1/2}$, half-emptying time; GEC, gastric emptying coefficient; M/F, male/female; C/A, congenital (cerebral palsy and chromosomal anomaly)/acquired (hypoxic brain damage); GERD, gastroesophageal reflux disease.

Table 2. The Correlation Analyses Between ^{13}C-acetate Breath Test and Multichannel Intraluminal Impedance pH Measurement Parameters

Parameters	Mean	Median	t_{lag}		$t_{1/2}$		GEC	
	Mean ± SD	Median (range)	r	P-value	R	P-value	r	P-value
pHI (%)	6.07 ± 8.94	2.15 (0.0-39.1)	-0.076	0.714	-0.043	0.836	0.322	0.109
BEI (total, %)	2.21 ± 4.03	1.1 (0.1-20.4)	0.226	0.267	0.216	0.289	-0.020	0.925
BEI (acid, %)	1.58 ± 3.87	0.65 (0.0-20.2)	0.060	0.772	0.035	0.865	0.082	0.691
BEI (non-acid, %)	0.62 ± 1.24	0.25 (0.0-6.4)	0.412	0.036[a]	0.450	0.021[a]	-0.264	0.193
REs (total, n)	43 ± 22	45 (1-80)	0.466	0.016[a]	0.445	0.023[a]	-0.310	0.124
REs (acid, n)	26 ± 18	25 (0-69)	0.221	0.278	0.181	0.375	-0.071	0.730
REs (non-acid, n)	17 ± 13	13 (1-59)	0.463	0.017[a]	0.466	0.016[a]	0.305	0.130
PREs (total, n)	15.27 ± 15.05	13.5 (0-76)	0.315	0.117	0.403	0.041[a]	-0.237	0.244
PREs (acid, n)	9.58 ± 9.33	7 (0-42)	0.177	0.387	0.228	0.263	-0.013	0.949
PREs (non-acid, n)	5.69 ± 7.52	3 (0-34)	0.324	0.106	0.429	0.029[a]	-0.315	0.117

[a]$P < 0.05$.

t_{lag}, lag phase time; $t_{1/2}$, half emptying time; GEC, gastric emptying coefficient; pHI, pH index; BEI, bolus exposure index; REs, reflux episodes; PREs, proximal reflux episodes.
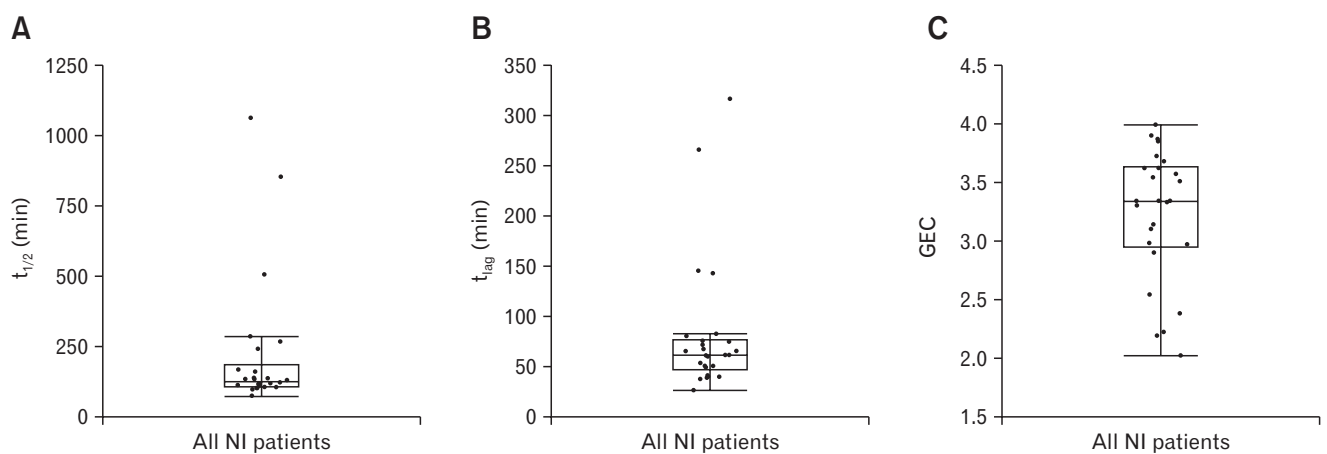

Figure. In the gastric emptying measurements by ^{13}C-acetate breath test (^{13}C-ABT) in all neurologically impaired (NI) patients, the mean half emptying time ($t_{1/2}$), lag phase time (t_{lag}), and gastric emptying coefficient (GEC) for all NI patients were 215.5 ± 237.2 (range, 105.4-1061.6) minutes (A), 81.7 ± 67.9 (range, 26.2-316.9) minutes (B), and 3.2 ± 0.6 (range, 2.0-3.9) (C), respectively. The $t_{1/2}$ of 24 (92.3%) patients was over 100 minutes.

was observed between the acid-related parameters (pH index, BEI [total/acid], and the number of acid reflux and acid proximal reflux episodes) and any ^{13}C-ABT parameters. GEC showed no significant correlations with any pH/MII parameters (Table 2).

The detailed pH/MII parameters of the patients classified into the DGE and SDGE groups according to each cutoff $t_{1/2}$ are shown in Table 3.

In the comparison of the pH/MII parameters between the DGE and SDGE groups at each set-up cutoff $t_{1/2}$ value, a significant difference in the BEI (non-acid) values and the number of total reflux episodes was observed between the DGE and SDGE groups when the cutoff $t_{1/2}$ was set to ≥ 130 minutes. Furthermore, when it was set to ≥ 140 minutes, there were significant differences between the 2 groups in the numbers of non-acid reflux episodes and the numbers of proximal total and non-acid reflux episodes (Table 3).

Discussion

The present study investigated gastric emptying using the ^{13}C-ABT and the liquid test meal because most NI patients receive enteral feeding via a nasogastric tube or gastrostomy. Several reports thus far have evaluated the normal value of $t_{1/2}$ in neurologically normal subjects analyzed by technetium-99m scintigraphy or ^{13}C-octanoic acid breath test analysis.[5,19,22-24] Regarding the normal range of gastric emptying analyzed by the ^{13}C-ABT, Gatti et al[22] reported that the mean $t_{1/2}$ with milk as the test meal was 74 ± 12 minutes in healthy children. Hauser et al[25] reported that the median $t_{1/2}$ value in 21 healthy children was 81 (65-112) minutes. These previous reports set a longer threshold of $t_{1/2}$ at 90 minutes. Additionally, several reports have attempted to investigate GE of NI patients, although no report has demonstrated the normal range in NI patients. Kawahara et al[12,13] examined GE of 30 NI patients and their $t_{1/2}$ ranged from 75-204 minutes; 16 (53.0%) patients had a $t_{1/2}$ longer than 100 minutes. Okada et al[26] examined 5 NI patients and their mean $t_{1/2}$ was 1.8 hours.

In the present study, the mean $t_{1/2}$ of all patients was 215.5 minutes and the $t_{1/2}$ of 24 (92.3%) patients were over 100 minutes. These results appear to be longer than those that previously reported. The mechanisms of DGE in NI patients, similar to GERD, might be considered as the cause of aggravated gastric emptying via affected gastric motility, such as abnormal modulation of extrinsic innervations due to a damaged central nervous system or hypoxic-ischemic damage to the enteric nerves.[27] Moreover, a combination of several factors, such as scoliosis, horizontal position and long-

Table 3. The Comparison Analyses of Multichannel Intraluminal Impedance pH Measurement Parameters Between Delayed Gastric Emptying and Severe Delayed Gastric Emptying Groups According to Each Cutoff Half Emptying Time

Cutoff $t_{1/2}$ (min)	90		100		110		120		130		140-160		170	
Parameters	DGE(1)	SDGE(25)	DGE(2)	SDGE(24)	DGE(7)	SDGE(19)	DGE(12)	SDGE(14)	DGE(14)	SDGE(12)	DGE(18)	SDGE(8)	DGE(20)	SDGE(6)
pHI (%)	0.0	6.3	2.8	6.3	4.9	6.5	5.6	6.5	4.8	7.5	7.2	3.6	7.6	1.1
BEI (total, %)	0.1	2.3	1.4	2.3	1.4	2.5	1.3	3.0	1.2	3.4	2.2	2.1	2.1	2.5
BEI (acid, %)	0.0	1.6	0.9	1.6	1.1	1.8	1.0	2.1	0.9	2.4	2.0	0.7	1.8	0.7
BEI (non-acid, %)	0.1	0.6	0.5	0.6	0.3	0.8	0.3	0.9	0.3	1.0[a]	0.3	1.4[b]	0.3	1.8[b]
REs (total, n)	1.0	44.3	25.0	44.1	33.6	46.0	34.2	49.9	32.7	54.3[b]	37.1	55.1[a]	38.6	56.2
REs (acid, n)	0.0	27.0	13.0	27.1	20.9	27.9	21.9	29.5	20.9	31.9	25.8	26.5	26.9	23.0
REs (non-acid, n)	1.0	17.3	12.0	17.0	12.7	18.1	12.3	20.4	11.8	22.3	11.3	28.6[b]	11.7	33.2[b]
PREs (total, n)	0.0	15.9	8.5	15.8	9.7	17.3	10.8	19.1	10.6	20.8	11.2	24.4[a]	11.5	27.8[a]
PREs (acid, n)	0.0	10.0	3.5	10.1	7.0	10.5	7.3	11.5	6.9	12.7	8.0	13.1	8.5	13.3
PREs (non-acid, n)	0.0	5.92	5.0	5.8	2.7	6.8	3.5	7.6	3.6	8.1	3.2	11.3[a]	3.1	14.5[b]

[a]P < 0.05 vs DGE, [b]P < 0.01 vs DGE.

$t_{1/2}$, half emptying time; DGE, delayed gastric emptying; SDGE, severe delayed gastric emptying; pHI, pH index; BEI, bolus exposure index; REs, reflux episodes; PREs, proximal reflux episodes.

term anticonvulsant use potentially delays GE. Gatti et al[22] also indicated that severe NI in children is associated with a high probability of DGE. We speculated that the patients enrolled in the present study were complicated by more of the above-mentioned factors that affect GE than the patients in previous studies.

The relationship between the clinical parameters, such as causal disorders and scoliosis and the $t_{1/2}$ and t_{lag} values in NI patients was evaluated. However, no significant difference was observed. As a consequence, the present study could not detect the cause of SDGE according to the clinical parameters. Furthermore, no significant difference was observed in any ^{13}C-ABT parameters between GERD (+) and GERD (-), findings which were the opposite of what was expected. We suspect that other factors, such as the proximal gastric accommodation, reported to be closely related to an increase in the transient LES relaxation,[28] which is known as the main mechanism of GERD, might have affected the present results. GEC is an index, equivalent to the slope in the early phase of the velocity curve of GE, and a higher GEC suggests an accelerated GE. Previous studies also measured the GEC, but did not mention its significance. In the present study, GEC did not demonstrate a significant relationship with any parameters, so we were unable to clarify its meaning.

Following the introduction of pH/MII in clinical practice, studies evaluating non-acid reflux have increased, gradually clarifying its pathophysiology. Regarding the relationship between non-acid reflux and NI, Del Buono et al[17] reported that more than half of the reflux events in NI children were non-acid; we also indicated that NI patients fed via a nasogastric tube suffered more non-acid reflux episodes than those fed orally.[29]

Few reports thus far have analyzed the relationship between gastric emptying and non-acid GERD using pH/MII, although a close relationship between DGE and GERD in both adults and children has been reported from a considerable number of studies. Emerenziani et al[30] reported a significant relationship between reflux acidity and gastric emptying; namely, the slower the emptying, the higher the pH of the refluxate. To the best of our knowledge, Kawahara et al[12,13] are the only investigators who reported the relationship between DGE and GERD in NI patients by utilizing both pH/MII and ^{13}C-ABT analyses; they concluded that there was no significant relationships between DGE and GERD.

The primary findings in the present study were that significant moderate correlations were observed between all of the non-acid related parameters and the $t_{1/2}$ or t_{lag} values. Moreover, in the comparison analyses of the pH/MII parameters and the cutoff values of $t_{1/2}$ in the DGE and SDGE groups, significant increases

were observed in the non-acid related parameters of the patients of the SDGE group when the cut off $t_{1/2}$ was set to ≥ 140 minutes. These findings indicate that $t_{1/2} \geq 140$ minutes potentially increases the exposure of non-acid reflux in the distal as well as the proximal esophagus in NI patients. Our oppositional findings from that of Kawahara et al[12,13] might be due to the high proportion of DGE in the present study. It has been suggested that long-term retained enteral feeding buffers gastric juice; when the gastric pressure is higher than the LES, such as in the condition of seizures or the presence of transient LES relaxations, then the buffered gastric content flows into the esophagus. Schwizer et al[31] reported that the severity of GERD in patients with DGE was lower than that in patients without DGE, indicating that buffering of the gastric juice due to the presence of DGE changes acid reflux to weakly-acid reflux, which reduces damage to the esophageal mucosa.

Rebound acid hypersecretion after the discontinuation of proton pump inhibitor has been reported to be a factor affecting the pH.[32] In the present study, four patients received proton pump inhibitors before stopping the medication, while 21 did not. No significant difference was observed between these 2 groups with regard to the percentage of time for which the gastric pH was < 4 ($P = 0.972$).

A previous study described a close relationship between non-acid reflux reaching the proximal esophagus and aspiration in children.[33] This suggests that a certain percentage of NI patients are likely at risk of aspiration due to non-acid reflux.

Based on the present results, improving the SDGE detected by ^{13}C-ABT might reduce the risk of aspiration due to non-acid GER reaching the proximal esophagus in NI patients requiring enteral feeding. Therefore, as these patients cannot complain their symptoms, the administration of prokinetic drugs with enteral feeding may be beneficial, although ideally, gastric emptying of all NI patients should be evaluated by ^{13}C-ABT, regardless of symptoms.

In summary, a considerably high proportion of NI patients demonstrated DGE with $t_{1/2}$ above 100 minutes, and the patients with $t_{1/2} \geq 140$ minutes suffered more non-acid exposure reaching up to the proximal esophagus, whereas no obvious clinical causes of SDGE were detected in the present study. Generally, NI patients tended to show a higher frequency of DGE in comparison to healthy individuals. As a result, it remains debatable whether a comparison of gastric emptying between NI patients and neurologically normal patients is appropriate. Considering that most NI patients spend the majority of their lives under abnormal circumstances, such as feeding via a nasogastric tube in the supine position compared to neurologically normal patients, the normal range of gastric

emptying in NI patients might be defined separately from that of neurologically healthy subjects.

There are several limitations associated with the present study. First, the age of the enrolled patients ranged from children to adults because gastric emptying of children has been reported to be the same as that of adults.[19,22-24] Therefore, we did not take age distribution into consideration. However, the possibility that the age difference affected the gastric emptying cannot be ruled out. Second, the dosage of the test meal was calculated according to the body weight of each patient because in NI patient, it might be difficult to determine the optimal dose due to the presence of growth failure and wasting, compared to neurologically normal subjects of the same age. However, several reports have determined the optimal dose according to the body surface area[11,12] or recommended as a dose of 200 mL for adults. Such limitations in the present study might have affected the results.

In conclusion, the present study demonstrated that GE with $t_{1/2} \geq 140$ minutes was related to an increase of non-acid exposure reaching up to the proximal esophagus in NI patients, indicating that NI patients with SDGE might have a risk of non-acid GERD. Further studies enrolling a large number of subjects are required to elucidate the precise pathophysiological mechanism involved in the relationship between non-acid GERD and SDGE in NI patients.

Conflicts of interest: None

Author contributions: Shinji Ishii performed the experiments and data analysis, and prepared the manuscript; Suguru Fukahori, Kimio Asagiri, and Yoshiaki Tanaka supervised the planning and execution of the experiments and statistical analysis, and reviewed the manuscript; Nobuyuki Saikusa assisted with conducting some of the experiments; Naoki Hashizume, Motomu Yoshida, Daisuke Masui, Naoko Komatsuzaki, Naruki Higashidate, Saki Sakamoto, Tomohiro Kurahachi, Shiori Tsuruhisa, and Hirotomo Nakahara assisted with the execution of the experiments and reviewed the manuscript; and Minoru Yagi supervised the planning and execution of the experiments, and reviewed the manuscript.

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