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Original Article

## Evaluation of periesophageal nerve injury after pulmonary vein isolation using the $^{13}\text{C}$ -acetate breath test



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### ABSTRACT

**Background:** Pulmonary vein isolation (PVI) has become an important option for treating patients with atrial fibrillation (AF). Periesophageal nerve (PEN) injury after PVI causes pyloric spasms and gastric hypomotility. This study aimed to clarify the impact of PVI on gastric motility and assess the prevalence of gastric hypomotility after PVI.

**Methods:** Thirty consecutive patients with AF underwent PVI under luminal esophageal temperature (LET) monitoring. The  $^{13}\text{C}$ -acetate breath test was conducted before and after the procedure for all patients (PVI group). Gastric emptying was evaluated using the time to peak concentration of  $^{13}\text{CO}_2$  ( $T_{\text{max}}$ ). This test was also conducted in another 20 patients who underwent catheter ablation procedures other than PVI (control group).

**Results:** The number of patients with abnormal  $T_{\text{max}}$  ( $\geq 75$  min) increased from seven (23%) to 13 (43%) and from three (15%) to five (25%) after the procedure in the PVI group and control group, respectively. The mean  $T_{\text{max}}$  was longer after PVI than before PVI ( $64 \pm 14$  min vs.  $57 \pm 15$  min,  $p=0.006$ ), whereas there was no significant difference before and after the procedure in the control group. However, no significant difference in  $\Delta T_{\text{max}}$  was observed between the two groups ( $p=0.27$ ). No patients suffered from symptomatic gastric hypomotility.

**Conclusions:** Asymptomatic gastric hypomotility occurred more often after PVI. However, the average impact of PVI on gastric motility was minimal.

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## 1. Introduction

Pulmonary vein isolation (PVI) has become an important option for treating patients with atrial fibrillation (AF) [1]. However, a few reports have described esophageal injury after PVI, including the development of lethal atrioesophageal fistulae. In addition, periesophageal nerve (PEN) injury after PVI may rarely cause pyloric spasms and gastric hypomotility [2]. These disorders lead to abdominal distension and discomfort. No quantitative or objective methods have been published for diagnosing PEN injury after PVI. The  $^{13}\text{C}$ -acetate breath test has been used to diagnose delayed gastric emptying induced by gastric hypomotility and/or pyloric spasms. This method is a noninvasive alternative to scintigraphy.

The objectives of this study were to clarify the impact of PVI on gastric motility, the prevalence of gastric hypomotility after PVI, and the relationship between *de novo* esophageal injury and gastric hypomotility following PVI. The  $^{13}\text{C}$ -acetate breath test and esophagogastroduodenoscopy (EGD) were performed before and after the procedure to achieve these objectives.

## 2. Material and methods

### 2.1. Patient population

Thirty-one consecutive patients with symptomatic paroxysmal or persistent AF were included in this prospective study. Patients with a history of PVI, the Maze procedure, gastrostomy, an eating disorder, or episodes of acute coronary syndrome, emboli, or decompensated heart failure within 3 months before enrollment were excluded. We

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enrolled 20 patients who underwent ablation procedures other than PVI as the control group.

All patients provided written informed consent prior to participation in this study. The study protocol was approved by the research ethics board of each institution.

EGD was performed in all patients within 3 months before the ablation procedure and within 3 days after the procedure. Esophageal injury was defined as a *de novo* lesion detected on the anterior wall of the midthoracic esophageal region after PVI that had not been detected before the procedure.

Administration of rabeprazole (30 mg/day) was scheduled to start the day after PVI and was re-evaluated on the day of the gastric emptying test after PVI to avoid worsening any esophageal injury. Oral medications, other than rabeprazole, that affected gastric peristalsis were initiated or changed in all patients within a month before the ablation and in the hospital.

Measurements of the gastroesophageal reflux disease symptoms scale and the gastrointestinal symptom rating scale were obtained before and after PVI. These scales are used to evaluate common symptoms of patients with gastrointestinal digestive disorders such as reflux esophagitis [3,4].

## 2.2. $^{13}\text{C}$ -acetate breath test

Gastric emptying was evaluated using the  $^{13}\text{C}$ -acetate breath test with a slight modification [5–7]. Gastric emptying is conventionally evaluated using the acetaminophen absorption test or technetium-99m scintigraphy [8]. However, the acetaminophen absorption test requires repeated collection of blood samples, and scintigraphy requires specialized instrumentation. Both examination times are approximately 4 h. In contrast, the  $^{13}\text{C}$ -acetate breath test, which is an alternative method to the acetaminophen absorption test or scintigraphy, can be performed at the patient's bedside. A strong correlation is observed between gastric emptying time measured by scintigraphy and the time to peak  $^{13}\text{CO}_2$  concentration in an expired breath ( $T_{\max}$ ) as well as half-dose recovery time ( $T_{1/2}$ ) measured by the  $^{13}\text{C}$  acetate breath test [9].  $T_{\max}$  in patients with functional dyspepsia is significantly delayed compared with that in healthy controls [9]. Therefore, we chose the  $^{13}\text{C}$ -acetate breath test, which was modified by not measuring  $T_{1/2}$ , as described previously [5,6,10]. The examination time was 90 min.  $^{13}\text{C}$ -sodium acetate administered orally with a test meal moves from the stomach and is absorbed by the intestines, where it is subsequently metabolized to  $^{13}\text{CO}_2$ , and finally expired by the lungs (Fig. 1). If a patient has gastric hypomotility, the duration between swallowing the test meal and the test meal reaching the intestines is longer than that in normal patients. As a result,  $T_{\max}$  in a patient with gastric hypomotility is longer than that in a patient without gastric hypomotility. Therefore, delayed  $T_{\max}$  reflects delayed gastric emptying.

In accordance with previous studies [5,6], we considered  $T_{\max} \geq 75$  min to reflect abnormal gastric emptying. This duration has been validated on the basis of a mean and standard deviation value of  $43.9 \pm 10.3$  min and a median value of 70 min in patients with advanced Parkinson's disease, which is commonly associated with dyspepsia [7].

Patients undergoing catheter ablation were tested after an overnight 12-h fast. First, a breath sample was obtained after ingestion of a liquid test meal (Racol, 200 kcal/200 mL; Otsuka Pharmaceutical Co., Ltd., Otsuka, Japan) which contained 100 mg of  $^{13}\text{C}$ -sodium acetate (Sigma-Aldrich, St. Louis, MO, USA). The test meal was consumed in < 5 min, and breath samples were collected after 5, 10, 15, 20, 30, 40, 50, 60, 75, and 90 min. Patients remained in a seated position throughout the examination. All breath samples were analyzed using infrared isotope spectrometry (POC one; Otsuka Electronics Co., Ltd., Otsuka, Japan). Gastric emptying was evaluated by the peak time of  $^{13}\text{CO}_2$  excretion ( $T_{\max}$ ) [5,6]. The  $^{13}\text{C}$ -acetate breath test was conducted

early in the morning before catheter ablation and was repeated early in the morning 1–3 days after catheter ablation.

## 2.3. Computed tomography (CT)

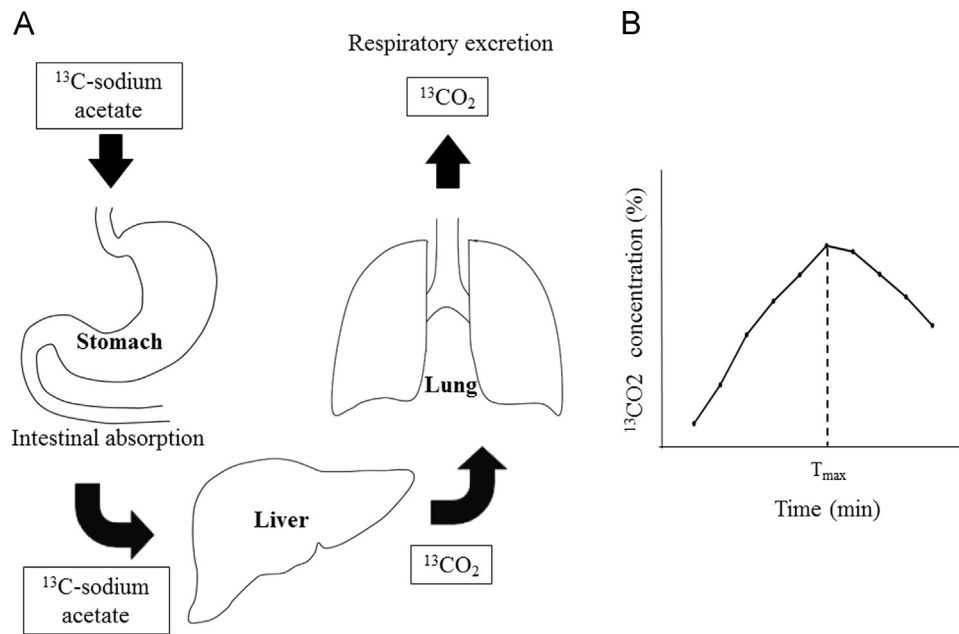
Cardiac-enhanced CT (CCT) was performed before the procedure to obtain three-dimensional images of the heart, thoracic vessels, and esophagus. This was to exclude the presence of a thrombus and to avoid transesophageal echocardiography, which may increase the burden in patients with a low CHADS2 score (< 2).

## 2.4. Ablation procedure and monitoring of luminal esophageal temperature (LET)

All antiarrhythmic drugs were discontinued for at least five half-lives before the day of the ablation procedure. Warfarin and dabigatran were discontinued for 5 days and on the day preceding the ablation procedure, respectively, and were substituted with intravenous unfractionated heparin (15,000 units/day). The electrophysiological study and ablation were performed under continuous dexmedetomidine hydrochloride infusion. We adjusted the dose between 0.2 and 0.7  $\mu\text{g}/\text{kg}/\text{h}$ . A deflectable quadripolar electrode catheter was positioned in the coronary sinus. When the baseline heart rhythm showed AF, sinus rhythm was restored by external cardioversion. After trans-septal catheterization, intravenous heparin was administered to maintain an activated clotting time of 250–300 s. A three-dimensional reconstruction of the LA was performed using an electroanatomical mapping system (Carto3™, Biosense Webster, Diamond Bar, CA, USA). The electroanatomical map was integrated with the CT image (Carto Merge™, Biosense Webster). A 7-Fr ablation catheter with a 3.5-mm open-irrigated distal tip (Thermocool Navistar™, Biosense Webster) was used for mapping and ablation. An esophagram was obtained after oral administration of 10 mL of gastrografin before PVI. After esophagraphy and venography, an LET monitoring probe (Sensi Therm; St. Jude Medical, St. Paul, MN, USA) with three metal thermocouple electrodes (5-mm distance) was placed within the esophagus under fluoroscopic guidance, directly posterior to the LA at a level covering the antra of the left PVs. The ipsilateral left and right PVs were encircled at the antrum in a single lesion line by circumferential PVI using a dragging technique. The end-point of PVI was defined as the elimination of all PV potentials on the circular mapping catheter during sinus rhythm, while an exit block was confirmed by pacing from inside the PV using the circular mapping catheter. If PV potentials continued after creating the circumferential lesion, additional radiofrequency applications were delivered to the carina between the PVs. The radiofrequency generator (Biosense Webster) was set at 30–35 W and 42 °C. The power and duration of the radiofrequency applications were limited to 25 W and 30 s, respectively, on the posterior wall adjacent to the esophagus according to the esophagram or the merged CT image. Ablation energy was stopped when the LET reached 40 °C. After a period of waiting until the LET decreased to  $\leq 39$  °C, RF was resumed at 15–20 W. If the lower and shorter applications did not create a lesion, another part of the linear lesion was dragged further from the esophagus.

## 2.5. Statistical analysis

Continuous variables are reported as means  $\pm$  standard deviations and discrete variables as percentages. Continuous variables were compared with the *t*-test. Categorical variables were compared using the chi-square test. Correlations were tested with the nonparametric Spearman's rank correlation test. All statistical analyses were carried out using SPSS 21 for Windows software (SPSS Inc., Chicago, IL, USA). *p*-Values of < 0.05 were considered statistically significant.



**Fig. 1.** Schematic process of metabolism and respiratory excretion of  $^{13}\text{C}$ . (A)  $^{13}\text{C}$ -sodium acetate administered orally with a test meal moves from the stomach and is absorbed from the digestive tract, where it is subsequently metabolized to  $^{13}\text{CO}_2$ , and finally expired by the lungs. (B)  $^{13}\text{CO}_2$  gradually increases in association with metabolism. It reaches the peak of excretion ( $T_{\text{max}}$ ) and then decreases.  $T_{\text{max}}$ , time to peak concentration of  $^{13}\text{CO}_2$  in expired breath.

### 3. Results

#### 3.1. Patient characteristics

After obtaining informed consent, a thrombus was detected in the LAA of one AF patient by CCT; this patient was excluded from the study. Thirty out of 31 patients with AF and all 20 patients in the control group completed the required procedures and were analyzed. No patient suffered from stroke or hemopericardium requiring pericardiocentesis. The baseline characteristics of both the PVI and control groups are shown in Table 1. No significant differences were observed in baseline characteristics between groups, except history of heart failure and stroke. The mean CHADS2 score was  $0.67 \pm 0.76$  in the AF group, with a maximum score of 2.0.

#### 3.2. The $^{13}\text{C}$ -acetate breath test

The number of patients with abnormal  $T_{\text{max}}$  ( $\geq 75$  min) increased from seven (23%) to 13 (43%) after the procedure in the PVI group (Fig. 2A). The seven patients with abnormal  $T_{\text{max}}$  before PVI also had abnormal  $T_{\text{max}}$  after PVI. No significant differences were observed between the histories of these seven patients and those of the other patients (Table 2). The number of patients with abnormal  $T_{\text{max}}$  increased from three (15%) to five (25%) after the procedure in the control group (Fig. 2B). The mean  $T_{\text{max}}$  was longer after PVI than before PVI ( $64 \pm 14$  min vs.  $57 \pm 15$  min,  $p=0.006$ ; Fig. 2C). On the other hand, the mean  $T_{\text{max}}$  in the control group was not significantly different after the procedure ( $56 \pm 16$  min vs.  $53 \pm 16$  min,  $p=0.35$ ; Fig. 2D).

Proton pump inhibitor (PPI) administration was initiated between the first and second  $^{13}\text{C}$ -acetate breath test in five patients with AF. The mean  $T_{\text{max}}$  was significantly longer after PVI than before PVI when the effects of the PPI on gastric emptying were considered, even after excluding these five patients ( $58 \pm 16$  min vs.  $64 \pm 15$  min,  $p=0.039$ ).

The mean difference between  $T_{\text{max}}$  before and after the procedure ( $\Delta T_{\text{max}}$ ) was 7.7 min in the AF group and 3.3 min in the control group ( $p=0.27$ ).

**Table 1**

Baseline characteristics of patients in the AF and control groups.

	AF group	Control group
Age, years	$61.8 \pm 8.3$	$61.8 \pm 13.4$
Sex, M/F (n)	21/9	12/8
Paroxysmal/persistent AF (n)	26/4	–
LVEF, %	$62 \pm 9$	$62 \pm 10$
Left atrial diameter, mm	$40 \pm 7$	$38 \pm 5$
Body height, cm	$166 \pm 9$	$162 \pm 9$
Body weight, kg	$68 \pm 13$	$61 \pm 11$
BMI, kg/cm <sup>2</sup>	$24.6 \pm 4.1$	$23.4 \pm 3.2$
Diabetes mellitus, n	4 (13%)	3 (15%)
Hypertension, n	11 (37%)	7 (35%)
Congestive heart failure, n	2 (7%)	0 (0%)
Stroke history, n	3 (10%)	0 (0%)
CHADS2 score, n	$0.67 \pm 0.76$	$0.55 \pm 0.69$
Peptic ulcer history, n	0 (0%)	0 (0%)
PVC, n	–	6
PSVT, n	–	8
AT/AFL, n	–	6

Data are expressed as means  $\pm$  SDs or n (%).

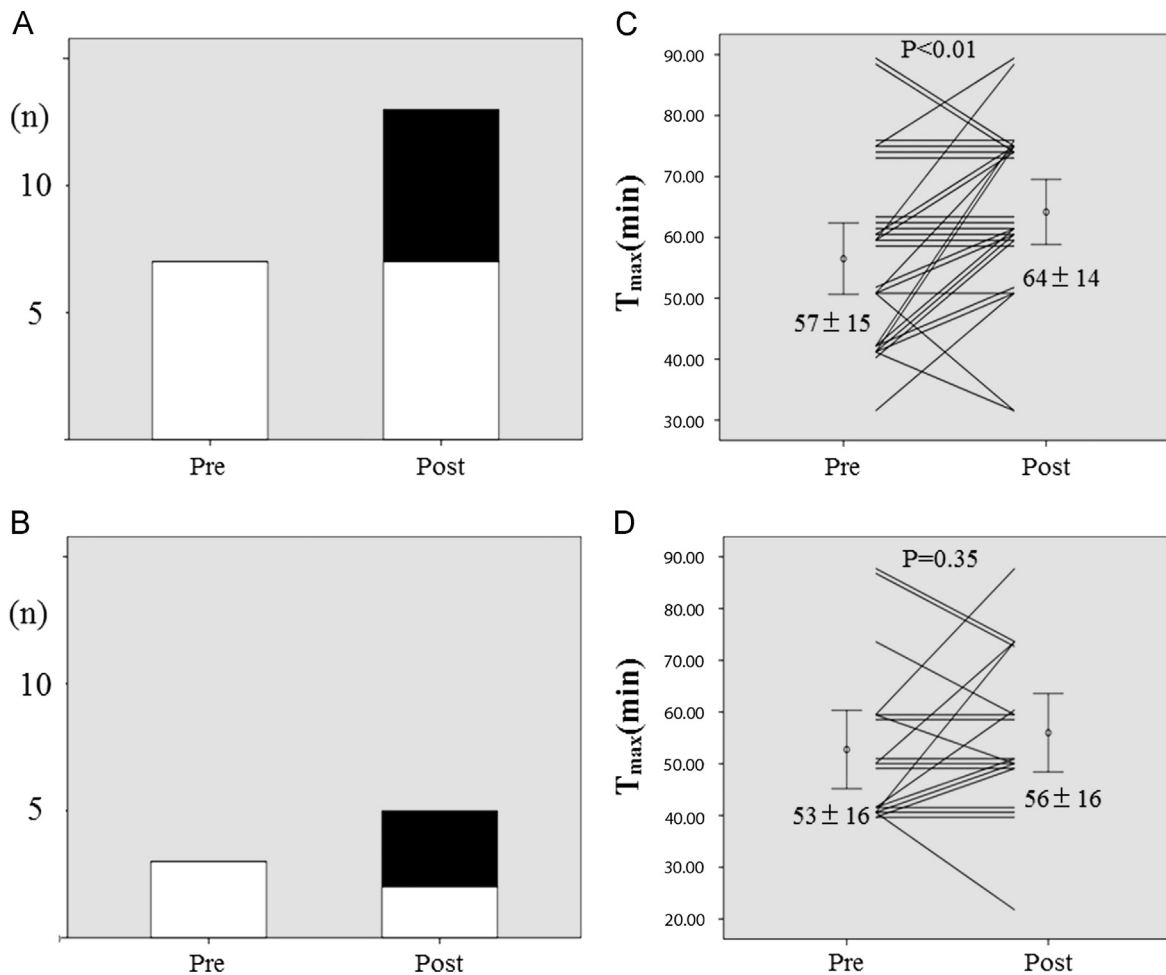
AF, atrial fibrillation; AT, atrial tachycardia; AFL, atrial flutter; BMI, body mass index; PSVT, paroxysmal supraventricular tachycardia; PVC, premature ventricular contraction; LVEF, left ventricular ejection fraction.

The left atrial diameter is measured in the parasternal view.

No significant difference was observed in the quantity of the radiofrequency energy applied to the left side of the posterior wall of the LA or the number of points of LET  $> 39$  °C between the groups (normal  $T_{\text{max}}$  to normal  $T_{\text{max}}$  vs. normal  $T_{\text{max}}$  to abnormal  $T_{\text{max}}$ ; Table 2). In addition, there was no correlation between  $\Delta T_{\text{max}}$  and the quantity of radiofrequency energy applied to the left side of the posterior wall of the LA ( $p=0.82$ ) or the number of points of LET  $> 39$  °C ( $p=0.30$ ).

#### 3.3. EGD findings and clinical symptoms

Reflux esophagitis and hernia were detected in seven (23%) and nine (30%) patients, respectively, before PV (Table 3). No patients had food residue in the stomach or esophageal mucous membrane lesions before the procedure. Furthermore, no patient suffered from digestive



**Fig. 2.** Results of the  $^{13}\text{C}$ -acetate breath tests before and after the ablation procedure. (A) Number of patients with abnormal  $T_{max}$  in the PVI group. (B) Number of patients with abnormal  $T_{max}$  in control group. White parts represent the patients who had abnormal  $T_{max}$  before the procedure. Black parts represent the patients who have new abnormal  $T_{max}$  after the procedure. (C, D) The longitudinal axis represents the peak time of  $^{13}\text{C}$  excretion ( $T_{max}$ ) measured by the  $^{13}\text{C}$ -acetate breath test. Each patient's  $T_{max}$  results from before and after the procedure are linked by a line. (C) Mean  $T_{max}$  in all patients before and after PVI. (D) Mean  $T_{max}$  in all patients before and after the procedure in the control group.  $T_{max}$ , time to peak concentration of  $^{13}\text{C}$  in an expired breath; PVI, pulmonary vein isolation.

symptoms such as nausea, vomiting, bloating, epigastric pain, or dyspepsia after the procedure. Three patients exhibited erosion of the esophagus (Fig. 3), but only one of these patients exhibited prolonged  $T_{max}$ . Food residue in the stomach was detected in another three patients, but only one had an abnormal  $T_{max}$  after PVI. Of the other 24 patients with no EGD findings, 13 had an abnormal  $T_{max}$ . Furthermore, no patient developed a symptomatic PEN injury after PVI during their hospital stay.

## 4. Discussion

### 4.1. Major findings

This study demonstrated significantly, although only slightly, prolonged gastric emptying after PVI compared with that before the procedure. Asymptomatic gastric hypomotility was demonstrated more frequently after PVI. These findings may represent the inhibitory effects on PEN. However, the average impact of PVI on gastric motility under monitoring of the LET was small. The vagus nerve modulates the secretion of gastric acid and gastric peristalsis. In the thoracic cavity, the left vagus nerve forms the mesh-like anterior esophageal plexus after traveling behind the left pulmonary hilum and enters the abdomen through the esophageal diaphragmatic opening (Fig. 4). Inside the abdominal cavity, the anterior vagus nerve from the

esophageal plexus lies extremely close to the outer muscle of the abdominal esophagus and divides near the esophageal end of the lesser curvature into the gastric and pyloric branches. Therefore, the anterior vagal nerve is responsible for coordinated relaxation of the pyloric sphincter and gastric peristalsis during gastric emptying [11]. Because radiofrequency energy may injure the esophagus, it is possible that the esophageal nerve plexus situated between the left atrium and esophagus can also be injured. However, if the radiofrequency energy injures any part of the plexus, although rare, PEN injury may occur. Because the plexus surrounds the entire circumference of the esophagus, the nerve rarely becomes completely blocked.

Kuwahara et al. recently reported the characteristics of PEN injuries that complicate PVI [12]. They reported that patients with PEN injuries were defined as those with symptoms of delayed gastric emptying, such as nausea, vomiting, postprandial fullness, and bloating, associated with gastric hypomotility as assessed by gastrointestinal fluoroscopy. Eleven of 3538 patients (0.3%) were diagnosed with a periesophageal vagus nerve injury. They only described patients with severe symptoms. The average impact of RF energy on PEN and the prevalence of asymptomatic or slight PEN injury were previously unknown. This study demonstrates the minimal average impact and shows a very low incidence of severe PEN injury.

Using electrogastronomy, Lo et al. showed that the periesophageal vagus plexus may be injured after PVI [13]. Similar to the

**Table 2**  
Clinical characteristics and gastric emptying in the AF group patients.

	Normal $T_{\max}$ before PVI	Abnormal $T_{\max}$ before PVI	p Value	Normal $T_{\max}$ before PVI		p Value
	(N=23)	(N=7)		Normal $T_{\max}$ after PVI	Abnormal $T_{\max}$ after PVI	
				(N=17)	(N=6)	
Age, years	61.0 ± 8.9	64.7 ± 5.7	0.49	60.3 ± 9.0	62.8 ± 9.2	0.55
Sex, M/F (n)	18/5	3/4	0.07	13/4	5/1	0.82
Paroxysmal/persistent AF	19/4	7/0	0.24	14/3	5/1	0.57
LVEF, %	63 ± 10	61 ± 5	0.58	64 ± 9	58 ± 13	0.97
Left atrial diameter, mm	40 ± 8	40 ± 8	0.98	41 ± 8	36 ± 6	0.23
Body height, cm	167 ± 9	160 ± 8	0.07	166 ± 8	170 ± 10	0.51
Body weight, kg	68 ± 14	67 ± 14	0.94	70 ± 14	63 ± 11	0.26
BMI, kg/cm <sup>2</sup>	24.3 ± 4.3	25.6 ± 3.3	0.18	25.2 ± 4.3	21.9 ± 3.7	0.06
Total RF energy for PW, J	38,459 ± 11729	35,643 ± 20297	0.44	35,398 ± 15517	40,720 ± 8068	0.26
Procedure time, min	167 ± 38	169 ± 32	0.88	165 ± 38	171 ± 42	0.83
Radiofrequency time, min	82 ± 27	81 ± 19	0.93	82 ± 28	80 ± 27	0.67
Point of LET > 39 °C, n	4.5 ± 3.7	7.8 ± 7.1	0.20	4.5 ± 3.6	4.7 ± 4.1	0.94
HPIGG (positive/negative)	9/14	3/3	0.63	5/9	4/2	0.43
FSSG						
Pre, pt	3.9 ± 4.3	6.2 ± 6.7	0.68	4.8 ± 4.8	1.7 ± 1.2	0.12
Post, pt	5.0 ± 7.0	4.2 ± 5.9	0.65	6.1 ± 8.0	2.2 ± 1.6	0.26
GSRS						
Pre, pt	22.9 ± 6.1	24.0 ± 8.2	0.98	23.9 ± 6.5	20.5 ± 4.7	0.21
Post, pt	23.5 ± 7.8	26.9 ± 9.9	0.51	24.5 ± 8.6	20.7 ± 4.6	0.39

Data are expressed as means ± SDs or n (%).

$T_{\max}$ , time to peak concentration of <sup>13</sup>CO<sub>2</sub> in an expired breath; normal baseline, patients with normal  $T_{\max}$  before pulmonary vein isolation (PVI); abnormal baseline, patients with abnormal  $T_{\max}$  before PVI; AF, atrial fibrillation; BMI, body mass index; HPIGG, *Helicobacter pylori* IgG; PW, posterior wall; LVEF, left ventricular ejection fraction; RF, radiofrequency.

We defined  $T_{\max}$  of equal to or longer than 75 min as abnormal  $T_{\max}$ .

<sup>13</sup>C-acetate breath test, electrogastrography is noninvasive and may be a surrogate measure of gastric emptying.

We observed a discrepancy between the presence of food residue as detected during EGD and abnormal  $T_{\max}$  in the gastric emptying test.

One reason is that we used a liquid meal for the test; therefore, the results were representative of liquid gastric emptying. In contrast, food residue indicated a delay in gastric emptying of solid material. We consider that this difference may lead to conflicting results. The secretion of pepsin is evoked by vagus nerve stimulation. Decomposition in the stomach was probably affected by RF energy through the PEN injury. The additive effect may result in the formation of solid residue, even when the PEN is slightly affected by RF energy. When a patient complains of gastroparesis-like symptoms but has normal findings of EGD after AF ablation, the <sup>13</sup>C-acetate breath test may be helpful to diagnose the possible periesophageal vagal nerve injury.

In addition to the direct effects of RF energy, mental stress, fatigue, and other factors may also have a considerable influence. In the control group, some patients exhibited delayed  $T_{\max}$  after the procedure compared with that before the procedure. This finding indicates that not only a direct effect of RF energy but also mental or other stress can influence gastric emptying after the procedure, including PVI.

Dexmedetomidine has previously been shown to affect gastric emptying [14,15]. Some reports also indicated that PPIs influence  $T_{\max}$  [16–18]. Takahashi et al. reported that rabeprazole may delay  $T_{\max}$  to a greater extent than H<sub>2</sub> receptor antagonists, although this difference was not significant. Rabeprazole suppresses gastric emptying of liquid nutrients after the ingestion of a meal. Even after exclusion of patients for whom PPI administration was initiated between the first and second <sup>13</sup>C-acetate breath tests, the mean  $T_{\max}$  was significantly longer after PVI than before PVI.

Irola et al. showed that dexmedetomidine administered at the upper limit of the recommended dose (0.7 µg/kg/h) inhibited gastric emptying, whereas Memis et al. reported that doses administered at the lower limit did not affect gastric emptying. These reports evaluated gastric emptying several minutes after intravenous

**Table 3**

Gastrointestinal findings in the AF and control groups.

	AF group		Control group	
	Pre-PVI	Post-PVI	Pre-PVI	Post-PVI
$T_{\max}$ , min	57 ± 15	64 ± 14	53 ± 16	56 ± 16
FSSG, pt	4.5 ± 5.0	4.9 ± 6.7	6.3 ± 5.4	4.6 ± 5.4
GSRS, pt	23.2 ± 6.5	24.3 ± 8.3	28.3 ± 10.7	26.4 ± 10.6
GERD, n (%)	7/30 (23%)	7/30(23%)	–	–
Hiatal hernia, n (%)	9/30 (33%)	8/30 (27%)	–	–
Residue of food, n (%)	0	3/30 (10%)	–	–
Erosion of esophagus, n (%)	0	3/30 (10%)	–	–
PPI, n (%)	5/30 (17%)		0/20	

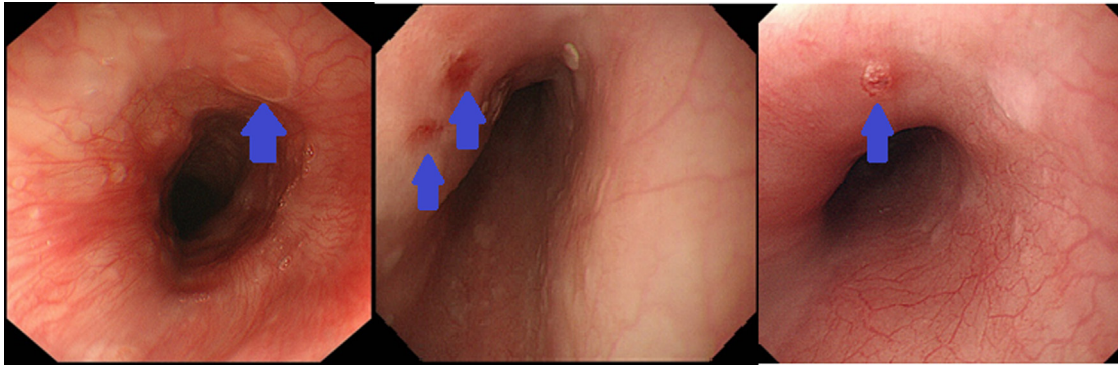
Data are expressed as means ± SDs or n (%).

$T_{\max}$ , time to peak concentration of <sup>13</sup>CO<sub>2</sub> in expired breath; PVI, pulmonary vein isolation; FSSG, frequency scale for symptoms of gastroesophageal reflux disease; GERD, gastroesophageal reflux disease; GSRS, gastrointestinal symptom rating scale; HPIGG, *Helicobacter pylori* immunoglobulin G; PPI, administration of a proton pump inhibitor at the time of enrollment.

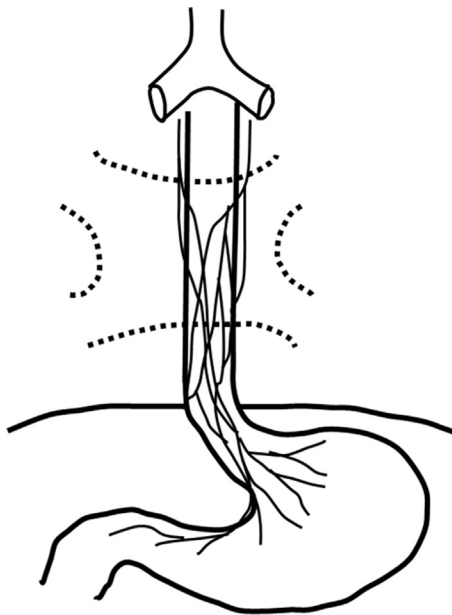
injection. In the present study, we used a low to medium dose of dexmedetomidine and evaluated the effect 1–3 days after the intravenous injection. Because the half-life of dexmedetomidine is extremely short (2 h), we predicted that it would barely influence gastric emptying in our study.

Before PVI, reflux esophagitis and hernia were detected in 23% and 30% of patients, respectively. As already described in Table 2, PPI was administered at the time of enrollment in 20% patients with AF and may potentially have led to a risk of symptomatic delayed gastric emptying and esophageal injury after PVI. The possibility that the PPI may have influenced gastric emptying in some of the patients with AF at baseline also cannot be ruled out.

Low air infiltration occurred in some patients during the procedure. However, this was transient and patients recovered by decreasing sedation dose. Adaptive servo ventilator or airway devices were not used, but it cannot be denied that these patients might have potential sleep apnea syndrome (SAS).



**Fig. 3.** Endoscopic findings of esophageal injuries after pulmonary vein isolation. In each panel, variable erosions (arrow) are shown on the anterior wall of the esophagus of different patients.



**Fig. 4.** Image of the vagus nerve innervating the stomach. The broken line represents the left atrium and pulmonary vein antrum. The vagus nerve forms the mesh-like anterior esophageal plexus after traveling behind the left pulmonary hilum, and enters the abdomen through the esophageal diaphragmatic opening.

Respiratory failure is associated with the presence of reflux esophagitis [19]. Continuous positive airway pressure (CPAP) reduces reflux esophagitis with respiratory failure [20]. Respiratory support device such as CPAP may preserve gastric motility.

#### 4.2. Study limitations

This study had some limitations. First, we investigated a small group of patients only during the acute phase. Therefore, it is necessary to evaluate a larger number of patients from multiple centers with a longer follow-up for further clarification of the clinical implications.

Second, because we used the modified  $^{13}\text{C}$  acetate breath test, we measured excretion only up to 90 min. In patients with peak times of  $^{13}\text{CO}_2$  excretion  $> 90$  min,  $T_{\text{max}}$  may be considered as 90 min. In our study, two patients out of 30 had a  $T_{\text{max}}$  of 90 min before ablation. In both patients, this was 75 min after ablation. If patients have a greater degree of gastric hypomotility than this, we may overestimate the impact of RF energy. Likewise, another two patients had a time of 90 min after ablation. One of them marked 60 min before ablation and the other 75 min. If they had more gastric hypomotility, we may underestimate the impact of RF energy.

Third, the precise number of patients who underwent transmural ablation in this study remains unknown. The use of a contact force catheter could have facilitated more reliable investigations.

Fourth, we did not evaluate SAS in the present study. SAS is not only related to AF, but also related to reflux esophagitis. Some papers have inferred that SAS is related to reflux esophagitis [19]. However, another paper has found that SAS is not related to reflux esophagitis [21]. In this paper, Ju et al. reported that poor subjective sleep and depressive symptoms are associated with the presence of reflux esophagitis with no association between SAS, BMI and reflux esophagitis.

#### 5. Conclusions

Asymptomatic gastric hypomotility was demonstrated to occur more frequently after PVI. However, the average impact of PVI on gastric motility under monitoring of the LET was minimal.

#### Conflict of interest

There are no conflicts of interest to declare.

#### References

- [1] Cappato R, Calkins H, Chen SA, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;3:32–8.
- [2] Shah D, Dumonceau JM, Burri H, et al. Acute pyloric spasm and gastric hypomotility. An extracardiac adverse effect of percutaneous radiofrequency ablation for atrial fibrillation. *J Am Coll Cardiol* 2005;46:327–30.
- [3] Kusano M, Shimoyama Y, Sugimoto S, et al. Development and evaluation of FSSG: frequency scale for the symptoms of GERD. *J Gastroenterol* 2004;39:888–891.
- [4] Svedlund J, Sjodin I, Dotevall G. GRSR—a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci* 1988;33:129–34.
- [5] Sanaka M, Nakada K. Stable isotope breath tests for assessing gastric emptying: a comprehensive review. *J Smooth Muscle Res* 2010;46:267–80.
- [6] Tanaka Y, Kato T, Nishida H, et al. Is there a delayed gastric emptying of patients with early-stage, untreated Parkinson's disease? An analysis using the  $^{13}\text{C}$ -acetate breath test. *J Neurol* 2011;258:421–6.
- [7] Arai E, Arai M, Uchiyama T, et al. Subthalamic deep brain stimulation can improve gastric emptying in Parkinson's disease. *Brain* 2012;135:1478–85.
- [8] Willemms M, Quartero AO, Numans ME. How useful is paracetamol absorption as a marker of gastric emptying? A systematic literature study. *Dig Dis Sci* 2001;46:2256–62.
- [9] Braden B, Adams S, Duan LP, et al. The  $^{13}\text{C}$  acetate breath test accurately reflects gastric emptying of liquids in both liquid and semisolid test meals. *Gastroenterology* 1995;108:1048–55.
- [10] Chapman MJ, Besanko LK, Burgstad CM, et al. Gastric emptying of a liquid nutrient meal in the critically ill: relationship between scintigraphic and carbon breath test measurement. *Gut* 2011;60:1336–43.
- [11] Gatzoulis MA. Heart and mediastinum. In: Standring S, editor. *Gray's anatomy*. 40th ed. UK: Elsevier; 2008. p. 939–57.

- [12] Kuwahara T, Takahashi A, Takahashi Y, et al. Clinical characteristics and management of periesophageal vagal nerve injury complicating left atrial ablation of atrial fibrillation: lessons from eleven cases. *J Cardiovasc Electro-physiol* 2013. <http://dx.doi.org/10.1111/jce.12130> [E-pub ahead of print].
- [13] Lo LW, Lu CL, Lin YJ, et al. A novel finding – impairment of gastric myoelectricity after catheter ablation of atrial fibrillation. *Circ J* 2013;77: 2014–2023.
- [14] Iiro T, Vilo S, Aantaa R, et al. Dexmedetomidine inhibits gastric emptying and oro-caecal transit in healthy volunteers. *Br J Anaesth* 2011;106:522–7.
- [15] Memis D, Dokmeci D, Karamanlioglu B, et al. A comparison of the effect on gastric emptying of propofol or dexmedetomidine in critically ill patients: preliminary study. *Eur J Anaesthesiol* 2006;23:700–4.
- [16] Takahashi Y, Amano Y, Yuki T, et al. Influence of acid suppressants on gastric emptying: cross-over analysis in healthy volunteers. *J Gastroenterol Hepatol* 2006;21:1664–8.
- [17] Sanaka M, Anjiki H, Yamamoto T, et al. Rabeprazole delays gastric emptying of a nutrient liquid. *J Gastroenterol Hepatol* 2007;22:1806–9.
- [18] Sanaka M, Yamamoto T, Kuyama Y. Effect of proton pump inhibitors on gastric emptying; a systematic review. *Dig Dis Sci* 2010;55:2431–40.
- [19] Fass R, Quan SF, O'Connor GT, et al. Predictors of heartburn during sleep in a large prospective cohort study. *Chest* 2005;127:1658–66.
- [20] Kurabayashi S, Kusano M, Kawamura O, et al. Mechanism of gastroesophageal reflux in patients with obstructive sleep apnea syndrome. *Neurogastroenterol Motil* 2010;22:611–72.
- [21] Ju G, Yoon IY, Lee SD, et al. Relationships between sleep disturbances and gastroesophageal reflux disease in Asian sleep referrals. *J Psychosom Res*. 2013;75:551–5.