# Anatomical Factors Associated with Periesophageal Vagus Nerve Injury after Catheter Ablation of Atrial Fibrillation

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#### Abstract

**Background:** The periesophageal vagus nerve plexus controls the kinetics of the stomach, digestive tract, and gallbladder, and catheter ablation of atrial fibrillation (AF) can cause vagus nerve injury (VNI). We sought to clarify the incidence, clinical course, and anatomical factors related to periesophageal VNI.

**Methods:** The present study included 257 consecutive patients with AF (mean age, 62±11 years) who underwent catheter-based pulmonary vein isolation. With 64-slice computed tomographic images, the left atrium (LA)-esophageal contact length, LA diameter, and distances between each mediastinal structure were compared between patients with VNI and those without VNI.

**Results:** VNI occurred in 5 patients (1.9%), gastric hypomotility in 3 patients, and acalculous cholecystitis in 2 patients, within 3 days after ablation, and all patients recovered completely within 2 weeks. Compared with patients without VNI, those with VNI more frequently underwent ablation at the mitral isthmus (p=0.03) and inside the coronary sinus (p=0.03). On computed tomographic images, the esophagus was closer to the aorta than to the spine in 67% of patients and was defined as an aorta-sided esophagus. In patients with VNI, the distance from the LA to the spine or the descending aorta (in patients with an aorta-sided esophagus) was shorter (p=0.03), and the transverse LA-esophageal contact length was longer (p=0.01).

**Conclusion:** Acalculous cholecystitis, as well as gastric hypomotility, can develop as a result of periesophageal VNI in patients undergoing AF ablation. The anatomical relationships among the LA, esophagus, spine, and descending aorta may influence the occurrence of VNI. (J Nippon Med Sch 2014; 81: 248–257)

**Key words:** vagus nerve injury, gastric hypomotility, acalculous cholecystitis, atrial fibrillation, catheter ablation

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Journal Website (http://www.nms.ac.jp/jnms/)

# Introduction

Radiofrequency (RF) catheter ablation has emerged as a radical cure for atrial fibrillation (AF) and is increasingly being performed worldwide<sup>1</sup>. Electrical isolation of the pulmonary veins (PVs), which has been adopted as an acute procedural endpoint in many centers, requires RF energy delivery to the posterior wall of the left atrium (LA)<sup>23</sup>. The posterior wall of the LA can also be targeted in other ablation strategies: posterior inferior linear ablation<sup>4</sup>, complex fractionated atrial electrogram ablation<sup>5</sup>, and ganglionated plexi ablation<sup>6</sup>. The RF energy applied to this area can provoke esophageal complications, which range in their severity from esophageal erosion to an atrioesophageal fistula<sup>78</sup>. In addition, the RF energy can induce thermal injury of the periesophageal vagus nerve, which can result in acute pyloric spasms and gastric hypomotility after ablation<sup>9-11</sup>.

Branches of the vagus nerve arising from the periesophageal plexus descend on the surface of the esophagus and enter the abdomen to innervate the digestive organs<sup>12,13</sup>. Cholinergic neurons arising from the vagal trunk control the motility of the gallbladder as well as that of the stomach and intestines<sup>13,14</sup>, and we have observed acalculous cholecystitis and gastric hypomotility following AF ablation.

The aim of the present study was to elucidate the anatomical factors associated with the occurrence of vagus nerve injury (VNI) after catheter ablation which, to the best of our knowledge, have not been reported. The incidence and clinical course of the patients with acalculous cholecystitis, which is a newly identified complication of AF ablation, are also described.

# **Patients and Methods**

# Subjects

This study retrospectively enrolled 257 consecutive patients (194 men [75%]; mean age,  $62\pm$  11 years) with symptomatic AF who underwent an initial ablation procedure from October 2009 through

January 2013 at the Nippon Medical School Teaching Hospital. Of these patients, 93 had persistent AF (36%) and 39 had structural heart disease (15%). The mean LA dimension on echocardiography was 39.4±6.7 mm. Written consent was obtained from all patients before the ablation procedure, and computed tomography (CT) was performed within 4 days before the procedure.

# Electrophysiological Study and Catheter Ablation

An electrophysiological study and catheter performed ablation were with continuous intravenous administration of propofol. The intracardiac electrograms and surface electrocardiograms were continuously monitored and recorded with an EP-WorkMate recording system (St. Jude Medical, Minneapolis, MN, USA). After transseptal access, two 7-Fr duo-decapolar circular mapping catheters (Lasso, Biosense Webster, Diamond Bar, CA, USA, or Inquiry Optima, St. Jude Medical) and a 3.5- or 4-mm tip irrigated ablation catheter (Navistar Thermocool, Biosense Webster, or Safire BLU Duo, St. Jude Medical, respectively) were inserted into the LA. The procedures were guided with an electroanatomical mapping system (CARTO, Biosense Webster, or Ensite NavX, St. Jude Medical) in which the 3dimensional reconstructed CT images of the LA and PVs were merged with real-time anatomical maps. In 157 patients (61%), the luminal esophageal temperature was monitored with a transnasally inserted deflectable 4-mm tip ablation catheter connected to a thermocouple thermometer (Delta Ohm, Caselle di Selvazzano, Italy)<sup>15</sup>.

The RF current was delivered with an RF generator (J70 RF Generator, Stockert GmbH, Freiburg, Germany, or IBI-1500 RF generator, St. Jude Medical) targeting a maximum temperature of 41°C (for Safire BLU Duo) or 43°C (for Navistar Thermocool) and a maximum power of 30 W. For ablation within the coronary sinus (CS), the maximum power was limited to 20 W. For ΡV circumferential isolation. continuous circumferential lesions were created at the level of the LA antrum (about 10 mm from the PV ostia)

encircling ipsilateral PVs. Although the creation of additional lesions depended on the operator's decision, the standard AF ablation strategy in our laboratory was PV isolation and LA posterior wall isolation by creating roof and posterior inferior linear lesions, which connected the superior and inferior aspects of the septal and lateral PVs<sup>4</sup>. Mitral isthmus linear ablation<sup>16</sup> was also performed, especially in patients with persistent AF, patients with inducible mitral annular atrial tachycardia, and patients with AF during the procedure, which lasted even after the PV and LA posterior wall isolations. Ablation of the complex fractionated atrial electrograms or ablation targeting the foci outside the PV was performed if necessary. Ablation of the ganglionated plexi was not attempted in any patient.

# Analyses of the CT Images

Contrast-enhanced CT imaging of the LA, PVs, and aorta was performed with a 64-slice multidetector CT scanner (Brilliance 64, Philips Medical Systems, Netherland B.V., Best, the Netherlands). Images were captured during a breath hold at full expiration using cardiac gating from the caudal aspect of the aortic arch through the cranial aspect of the left hemidiaphragm. The gantry rotation speed was 420 milliseconds per rotation, and tube voltage was 120 kV. Retrospective cardiac gating was used for all examinations. The slice thickness was 0.67 mm, and reconstructed series in diastole (90% of the R-R interval) or systole (40% to 45% of the R-R interval) were chosen for analysis in all patients. The analysis of the CT images was performed with a 3-dimensional workstation (Osirix, Geneva, Switzerland) by 2 cardiologists who were not informed of the aim of the present study. Images in the sagittal, axial, and coronal planes, with or without an oblique angle, were reviewed, and offline digital calipers were used to measure the following variables (Fig. 1): 1) the maximal transverse diameter of the LA, which was the distance between the midpoint of the right and left sides of the PV; 2) the anteroposterior diameter of the LA measured at the midpoint of the transverse diameter; 3) the craniocaudal and 4) transverse contact lengths of the LA posterior wall and the anterior wall of the esophagus; 5) the distance between the LA endocardium and the most anterior luminal aspect of the esophagus; 6) the distance between the LA endocardium and the thoracic spine; and 7) the distance between the LA endocardium and the endothelium of the descending aorta. Furthermore, 8) the distance between the most posterior luminal aspect of the esophagus and the thoracic spine and 9) the distance between the most posterior luminal aspect of the esophagus and the endothelium of descending aorta were measured, and the esophagus was defined as spine-sided or aorta-sided according to the lesser of those 2 values (Fig. 1). The distance between the LA and the spine (in patients with a spine-sided esophagus) or the aorta (in patients with an aorta-sided esophagus) was also determined. The operators were blinded to the measurement results.

## Diagnosis of Conditions Caused by VNI

The diagnosis of gastric hypomotility was based on the gastroparesis: delay in gastric emptying and dilatation of the stomach despite overnight fasting in the absence of a gastric outlet obstruction<sup>17</sup>. Acalculous cholecystitis was defined as thickening of the gallbladder wall (exceeding 4 mm) and the presence of pericholecystic fluid without signs of gallstones or sludge on CT or ultrasonography<sup>18</sup>.

# Statistical Analysis

The data are expressed as the mean±standard deviation for continuous variables and as absolute frequencies and percentages for categorical variables. For continuous variables, differences between the groups were compared by means of the Mann-Whitney U-test and Student's t-test. Because the results were similar, only the latter are presented. Categorical variables were evaluated with Fisher's exact test. All tests were 2-sided, and a p value of <0.05 was considered to indicate statistical significance. To assess the effect of intraobserver and interobserver variability, the CT images of 10 randomly selected patients were remeasured on a different day by 2 examiners who were given no clinical information. The measured data were evaluated with Pearson correlation coefficient analysis. All statistical analyses were

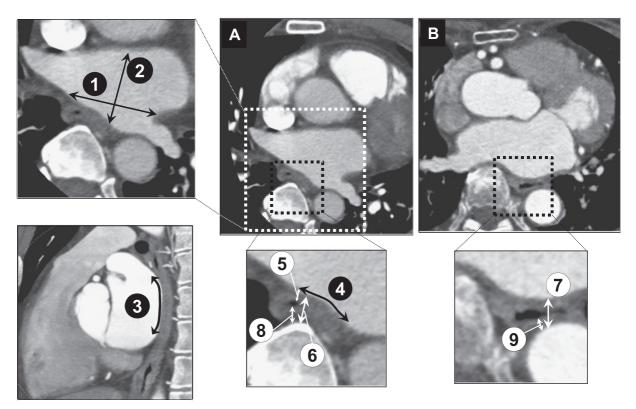


Fig. 1 The anatomical variables measured in computed tomographic images.

1: Transverse diameter of the left atrium (LA). 2: Anteroposterior diameter of the LA. 3: Craniocaudal contact length of the LA posterior wall and the anterior wall of the esophagus. 4: Transverse contact length of the LA posterior wall and the anterior wall of the esophagus. 5: Distance between the LA and esophagus. 6: Distance between the LA and thoracic spine, 7: Distance between the LA and the aorta. 8: Distance between the esophagus and the thoracic spine. 9: Distance between the esophagus and the aorta. Panel A shows a representative case of a spine-sided esophagus, and panel B shows an aorta-sided esophagus. For details, see the text.

performed with the software package SPSS for Windows 11.0 J (SPSS Inc., Chicago, IL, USA).

#### Results

### **Incidence and Clinical Course of VNI**

Among the 257 patients, VNI developed in 5 patients (1.9%): acalculous cholecystitis in 2 (patients 1 and 2), and gastric hypomotility in 3 (patients 3, 4, and 5), which were all symptomatic. **Table 1** compares the clinical characteristics of the patients with and without VNI, which were similarly distributed between the 2 groups.

# **Acalculous Cholecystitis**

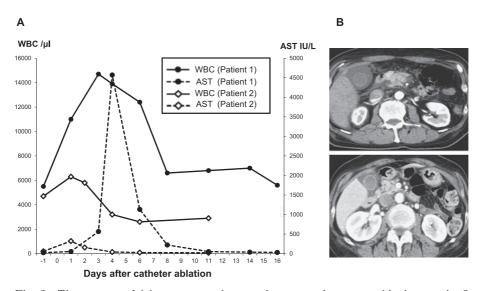
Two patients (patients 1, a 68-year-old man, and patient 2, a 75-year-old woman) had acalculous cholecystitis 3 days and 1 day, respectively, after the session. In both patients, the procedure consisted of bilateral PV isolation, LA posterior wall isolation, and mitral isthmus linear ablation. Ablation inside the CS was also required in patient 1. A luminal esophageal temperature monitor in patient 1 showed a maximal temperature of 41.5°C during the session. These patients complained of epigastralgia and vomiting and had elevated white blood cell counts and liver enzyme levels (Fig. 2A). Abdominal CT revealed a thickening of the gallbladder wall and pericholecystic fluid (Fig. 2B). There was no sign of gallstones or sludge, and acalculous cholecystitis was diagnosed. In patient 1, percutaneous transhepatic gallbladder drainage was performed, and cefoperazon and sulbactam were administered intravenously. The symptoms had resolved by 10 days after ablation, and the laboratory data had normalized by 14 days after ablation. Patient 2 was treated with intravenous cefotaxime. The symptoms had resolved by 4 days after ablation, and laboratory

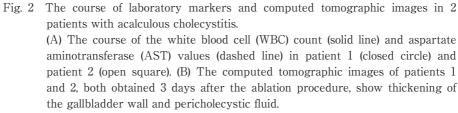
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	With vagus nerve injury (n=5)	Without vagus nerve injury (n=252)	p-value
Age, years	$67.6 \pm 6.3$	$61.6 \pm 11.2$	0.23
Female patients	1 (20)	62 (25)	0.81
Body weight, kg	$65.8 \pm 11.0$	$66.5\pm13.1$	0.86
Body-mass index, kg/m <sup>2</sup>	$23.6 \pm 2.7$	$24.3\pm3.4$	0.92
Persistent atrial fibrillation	2 (40)	91 (36)	0.86
Structural heart disease	0 (0)	39 (15)	0.34
Valvular heart disease	1 (20)	30 (12)	0.58
Comorbidities			
Hypertension	4 (80)	146 (58)	0.32
Dyslipidemia	2 (40)	90 (36)	0.84
History of stroke/transient ischemic attack	0 (0)	11 (4)	0.63
Smoking	3 (60)	129 (51)	0.70
Left atrial diameter, mm	$42.0 \pm 3.7$	$39.4 \pm 6.1$	0.81

Table 1 Clinical characteristics of the study subjects

a) Values are mean  $\pm$  SD or n (% of n).





data had normalized by 6 days after ablation, without invasive procedures.

# **Gastric Hypomotility**

Gastric hypomotility developed in 3 patients (patients 3, 4, and 5: aged 64, 59, and 72 years, respectively) 3 to 5 days after ablation (**Fig. 3**). All 3 patients had undergone PV isolation and a posterior

LA isolation. Mitral isthmus linear ablation requiring ablation inside the CS was also performed in patients 3 and 5. Luminal esophageal temperatures were monitored in patients 3 and 4, and the maximum temperature during the session was 41.3°C and 42.5°C, respectively. After 3 to 14 days of fasting, the abdominal bloating had resolved in all patients, even after resumption of a normal diet, and these 3 patients were discharged without residual symptoms. Gastric hypomotility did not recur in any of these patients.

# **Procedural Details**

Table 2 compares ablation procedures between patients with and without VNI. There was no difference between the groups, except for the higher rate of mitral isthmus linear ablation in patients with VNI (80% vs 29%, p=0.03). In addition, the rate of ablation inside the CS for mitral isthmus block was higher in patients with VNI (60%) than in those without (16%, p=0.03). The rate of VNI did not differ on the basis of whether the esophageal temperature during the ablation procedure was monitored (3 of

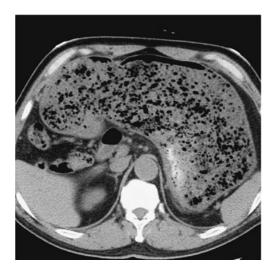


Fig. 3 Representative presentation of gastric hypomotility in patient 3. Computed tomographic image of the abdomen obtained 5 days after ablation reveals a stomach with a large amount of retained food. 157 patients [2%]) or was not monitored (2 of 100 patients [2%], p=1.00).

# Analysis of CT Images

The anatomical variables measured on CT images in patients with and without VNI are shown in Table 3. Although the craniocaudal contact length of the LA and esophagus (No. 3 in Fig. 1) did not differ (p=0.40), the transverse contact length (No. 4 in Fig. 1) was significantly greater in patients with VNI (p= 0.01). Measurement of the distance from the esophagus to the spine and to the descending aorta (No. 8 and 9 in Fig. 1) showed an aorta-sided esophagus in 3 patients with VNI (60%) and 169 patients without VNI (67%). Although neither the distance from the LA to the spine nor the distance from the LA to the descending aorta (No. 6 and 7 in Fig. 1, respectively) differed between the groups, the distance from the LA to the spine (in patients with a spine-sided esophagus) or to the aorta (in patients with an aorta-sided esophagus) was significantly shorter in patients with VNI (6.2±1.0) than in those without VNI (7.4±1.9 mm, p=0.03; Table 3).

The intraobserver correlation coefficient for the measurement in the 10 selected patients was r=0.97 (95% confidence interval, 0.96 to 0.98), and the interobserver correlation coefficient was r=0.94 (95% confidence interval, 0.91 to 0.96).

# Discussion

#### **VNI and Acalculous Cholecystitis**

The present study identified acalculous cholecystitis as a new complication of AF ablation.

	With vagus nerve injury (n=5)	Without vagus nerve injury (n=252)	p-value
Pulmonary vein isolation	5 (100)	252 (100)	1.00
Pulmonary vein isolation only	0 (0)	26 (10)	1.00
Roof line	5 (100)	226 (90)	1.00
Posterior inferior line	5 (100)	203 (81)	0.57
Mitral isthmus line	4 (80)	72 (29)	0.03
Ablation inside coronary sinus	3 (60)	40 (16)	0.03
Posterior complex fractionated atrial electrogram	0 (0)	4 (2)	1.00

Table 2 Ablation procedures in the 2 patient groups

a) Values are n (% of n).

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	With vagus nerve injury (n=5)	Without vagus nerve injury (n=252)	p-value
(1) Transverse LA diameter, mm	$59.1 \pm 6.6$	$54.1 \pm 8.0$	0.14
(2) Anteroposterior LA diameter, mm	$45.5\pm7.4$	$40.7\pm19.9$	0.09
(3) Craniocaudal LA-esophageal contact, mm	$65.1\pm13.4$	$60.3\pm8.5$	0.40
(4) Transverse LA-esophageal contact, mm	$26.5\pm6.9$	$19.1\pm4.9$	0.01
(5) LA to the esophagus distance, mm	$3.5\pm0.4$	$4.1 \pm 2.4$	0.30
(6) LA to the spine distance, mm	$7.2 \pm 0.3$	$8.9 \pm 2.6$	0.051
(7) LA to the aorta distance, mm	$11.5\pm7.9$	$8.8 \pm 4.0$	0.44
LA to the spine or aorta distance, mm	$6.2 \pm 1.0$	$7.4 \pm 1.9$	0.03
(8) Esophagus to the spine distance, mm	$6.2 \pm 3.2$	$6.4 \pm 2.8$	0.76
(9) Esophagus to the aorta distance, mm	$8.0 \pm 9.3$	$5.6 \pm 3.6$	0.49
Esophagus to the spine or aorta distance, mm	$3.3 \pm 1.2$	$4.5 \pm 1.3$	0.03
Eesophagus location			0.67
Spine-sided esophagus	2 (40)	83 (33)	
Aorta-sided esophagus	3 (60)	169 (67)	

Table 3 Anatomical variables in computed tomographic images

a) Values are mean  $\pm$  SD or n (% of n).

b) The numbers correspond to the locations shown in Figure 1.

LA=left atrium

We believe that the mechanism of acalculous cholecystitis is thermal injury to the periesophageal plexus, which is also thought to be a mechanism of gastric hypomotility and pyloric spasm after AF ablation<sup>9-11</sup>. The branches of the vagus nerve arising from the periesophageal plexus form a network on the surface of the esophagus, enter the esophageal hiatus, and innervate the digestive organs, including the stomach, duodenum, liver, and gallbladder<sup>12-14</sup>. Injury to the periesophageal nerve plexus can cause dysfunction of these upper-abdominal digestive organs. Acalculous cholecystitis is a rare, lifethreatening condition that most frequently develops after gastrointestinal surgery<sup>19-21</sup>. The pathogenesis of acalculous cholecystitis after surgery remains unclear, but bile stasis and ischemia are the 2 principle proposed mechanisms<sup>19,20</sup>. Vagotomy during esophageal or gastric surgery is reported to be a risk factor for postoperative acalculous cholecystitis<sup>20,21</sup>, indicating the importance of vagus nerve innervation for contraction of the gallbladder.

#### **Clinical Variables Associated with VNI**

In a earlier study<sup>11</sup> of periesophageal nerve injury and luminal esophageal damage after AF ablation, the only independent clinical variable for predicting these complications was lower body-mass index:  $22.0\pm0.5$  kg/m<sup>2</sup> versus  $24.6\pm3.4$  kg/m<sup>2</sup>. In the present study, however, the body-mass index in patients with VNI was  $23.6\pm2.7$  kg/m<sup>2</sup> and did not differ from that in patients without VNI. The reason for this discrepancy is not clear but is probably due to a difference in the complications observed. In contrast to those in the present study, all complications in the earlier study<sup>11</sup> were asymptomatic, indicating that the degree of thermal injury to the esophagus or periesophageal vagus nerve might be less severe than that in our subjects with VNI. We speculate that substantial damage, which provokes symptomatic VNI, is not influenced by patient physique.

On the other hand, the present study showed that the rate of mitral isthmus linear ablation and the rate of ablation inside the CS to achieve conduction block in that region were significantly higher in patients with VNI than in patients without. Another report<sup>22</sup> has also demonstrated that these procedures are associated with esophageal ulceration after AF ablation. The delivery of RF energy inside the CS is often required to complete mitral isthmus conduction block<sup>16</sup> but might also injure the esophagus or periesophageal plexus. Studies<sup>23,24</sup> investigating the anatomy around the CS by means multidetector CT or intracardiac of

echocardiography have demonstrated that the esophagus is near the CS in many patients. The results of the present study reinforce the notion that special care, i.e., limiting the RF power and closely monitoring the luminal esophageal temperature, must be taken when performing ablation inside the CS.

#### **Anatomical Considerations**

In the present study, the transverse contact length of the LA and esophagus was significantly greater in patients with VNI than in patients without. It is plausible that the vagus nerve is more likely to be present between the LA and the esophagus during ablation to the posterior LA in patients showing a greater area of contact of these 2 structures, because the periesophageal plexus frequently descends on the anterior aspect of the esophagus12. A similar result was reported in an study 22 examining the earlier anatomical characteristics of the patients with esophageal ulcerations after AF ablation. In contrast to that study<sup>22</sup>, however, the present study did not show a significant difference in the distance from the LA to the esophagus between patients with VNI and patients without VNI. The reason of this discrepancy is not clear. The anatomical factor contributing to the development of the esophageal ulceration might differ from that contributing to the development of VNI. The earlier study<sup>22</sup> also showed a significant difference in the distance from the LA to the spine between patients with and without esophageal complications; this difference was not found between patients with and without VNI in the present study. We speculate that the variability in the location of the mediastinal structures is the reason for this result. As clearly shown in Figure 1, the esophagus is not always located between the LA and the spine or sandwiched between them during the delivery of RF energy to the LA posterior wall. In such cases, the distance from the LA to the spine is not a reliable predictor of VNI. To deal with this issue, the descending aorta should be considered a structure that, with the LA posterior wall, could surround the esophagus<sup>25</sup>. The present study showed that more than half of the patients had an

aorta-sided esophagus and that the distance from the LA to the spine or to descending aorta, in patients with an aorta-sided esophagus, was significantly shorter in patients with VNI than in those without. During posterior LA ablation, the contact force of the ablation catheter on the posterior LA can compress the LA posterior wall and the esophagus to the spine or to the descending aorta. We presume that a larger amount of RF energy reaches the esophagus or periesophageal plexus in patients with a shorter distance from the LA to these posterior mediastinal structures.

### Limitations

The present study had several limitations. First, this was a retrospective study performed in a single center. A further prospective multicenter analysis including more patients with VNI is needed to determine the clinical and anatomical characteristics of the VNI in greater detail. A second limitation was that we measured anatomical variables on CT images obtained within 4 days before the ablation procedure, during which time the location of the esophagus could have been differed from that at the time of the ablation. In a study<sup>26</sup> that compared the position of the esophagus between 2 AF ablation procedures, however, the location of the esophagus did not change in more than 80% of the patients, even when the second procedures were performed  $7\pm 2$  months after the first procedure. A third limitation of the present study is that we did not calculate the amount of RF energy delivered to the posterior LA wall, which would have been larger in patients with VNI than in those without. However, an earlier study has found that the amount of the RF energy delivered to the LA posterior wall does not differ between patients with and without esophageal ulcerations after AF ablation<sup>22</sup>.

#### Conclusions

Among the 257 patients that underwent AF ablation, acalculous cholecystitis and gastric hypomotility resulting from VNI occurred in 2 and 3 patients, respectively. The patients with VNI

recovered fully within 2 weeks. Compared with the patients without VNI, those with VNI showed a shorter distance from the LA to the spine or descending aorta and wider transverse LA-esophageal contact and more frequently underwent mitral isthmus linear ablation and ablation inside the CS.

# Conflict of Interest: None declared.

**Financial Support:** This work was supported by national grant, named MEXT KAKENHI Grant Number 22790735.

**Acknowledgements:** The authors thank Mr. John Martin for his linguistic assistance.

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(Received, December 13, 2013) (Accepted, January 6, 2014)