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Upper Gastrointestinal Complications Following Ablation Therapy for Atrial Fibrillation

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Abstract

Background—Following ablation therapy for cardiac arrhythmias, patients may develop upper gastrointestinal (UGI) symptoms. The vagus nerve is close to the atria and may be affected by ablating energy.

Aim—To identify structural or functional complications in UGI tract following ablation for atrial fibrillation (AF) and clinical outcomes and association with vagal dysfunction.

Methods—Using natural language processing of electronic medical records and an AF ablation database of 5380 patients treated during 17 years, we identified 40 patients with UGI complications. We evaluated vagal dysfunction by electrocardiogram (ECG) showing lack of sinus arrhythmia (variation in R-R interval by ≥ 120 msec, in presence of normal sinus P waves and constant P-R interval).

Key Results—Among 40 patients: (A) 8 had structural GI complications confirmed by diagnostic tests: 7 with esophageal ulcer/erosions and no signs of UGI bleeding and 1 developed esophagopericardial fistula (and survived with treatment); (B) 15 had functional UGI complications confirmed by objective motility tests. Nine had newly developed symptoms and 6 had aggravated symptoms; and (C) the remaining 17 had GI symptoms without relevant diagnostic results. Most UGI issues resolved spontaneously or with conservative treatment. However, 2 died several weeks after ablation procedure; cause of death was suspected atriopharyngeal fistula or esophageal rupture. Vagal dysfunction persisted for 3 months in 13 and was transient in 8.

Conclusions/Inferences—Although most GI issues resolved spontaneously, there should be a high index of clinical suspicion in patients with persistent symptoms. Vagal dysfunction may serve as a marker of more extensive tissue damage.

Graphical abstract

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Keywords

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INTRODUCTION

Catheter-based ablation therapies for atrial fibrillation (AF) are part of the current guidelines recommended by major international cardiovascular societies.¹ Ablation is a complex and technically challenging procedure, requiring pulmonary vein isolation and extensive ablation in the left atrium. Because of the proximity of the left atrium to the esophagus, atrioesophageal fistula or esophageal ulceration as a result of direct injury to the adjacent esophagus has been reported as rare complications of catheter ablation procedures.²⁻⁴

In addition, the vagus nerve and its branches are anatomically close to the posterior wall of the left atrium and the pulmonary veins (Figure 1),⁵ which are the principal sites of radiofrequency ablation (RFA) in AF.^{6, 7}

The periesophageal vagus nerve plexus supplies parasympathetic control to the motor functions of the stomach, digestive tract, and gallbladder.^{8, 9} Therefore, vagus nerve injury resulting from ablation therapy for AF may rarely lead to motor disorders such as gastroesophageal reflux and gastric hypomotility as a result of the dysfunction or injury of the vagus nerve.¹⁰⁻¹² A recent multinational survey documented the incidence, clinical course over a short follow up period, and outcomes.¹³ However, there are limitations of such survey-based data with limited follow-up, and the methods of diagnosis for functional gastrointestinal (GI) complications such as gastroparesis are not standardized in such multi-center studies. Some of these limitations are overcome in a single center study especially if the sample size is large and the methods of treatment and diagnosis are standardized.

Our objectives were to identify among patients who underwent ablation treatment for AF at Mayo Clinic the occurrence of structural or functional complications in upper gastrointestinal (UGI) tract, to appraise clinical outcomes, review the association with vagal dysfunction, the probable mechanism of the functional UGI complication.

MATERIALS AND METHODS

Study Design

This study was approved by Mayo Clinic Institutional Review Board (IRB No. 15-009264). All patients included in this study provided written consent to use their medical records for research purposes.

Method for Case Identification

We tried to identify UGI complications among patients who underwent RFA or cryoablation for atrial fibrillation at Mayo Clinic between 1999 and early 2016.

First, from the AF ablation database of the Cardiac Electrophysiology Laboratory of Mayo Clinic, Rochester, MN, relevant data were collected prospectively pre-ablation. Patients received a 1 month phone follow-up inquiring for complications and current health status. At three months and yearly following the ablation procedure, questionnaires that included: quality of life assessment, recent symptom information, and self-reports of arrhythmia recurrences were requested from the patients. The database includes information about patients who underwent catheter ablation therapy and completed the post-procedural patient questionnaire. We identified patients whose questionnaire responses and additional review of medical records showed they developed any GI symptoms and/or underwent diagnostic tests following catheter ablation for AF because of clinical concern that there may be damage in the upper GI tract.

Second, we used a natural language processing to interrogate electronic medical records of all adults to identify AF ablation patients who had developed any GI symptoms and underwent objective diagnostic tests in the gastroenterology clinic.

After identification, we categorized patients into three groups:

- a. Patients with structural complications (e.g. any esophageal injury) confirmed by diagnostic tests;
- b. Patients with functional GI complications (any GI symptoms without associated structural problem) confirmed by objective motility test,
- c. Patients with UGI symptoms and no relevant diagnostic tests.

Method for Assessing Vagal Function

A 12-lead electrocardiogram was performed in all patients, not only in those with GI symptoms, to evaluate heart rhythm after ablation therapy in order to check on the heart rhythm response to the ablation therapy. With the patient in the supine position, a 12-lead electrocardiogram was recorded and displayed in conventional form on paper, run at a speed of 25mm/s. Using the electrocardiogram tracing, with at least 10 QRS complexes evaluable, we sought evidence of sinus arrhythmia, which was defined as variation in the R-R interval by 0.12 seconds (120msec) in the presence of normal sinus P waves and constant P-R interval assessed by manual measurement.¹⁴ The absence of sinus arrhythmia was used as evidence of vagal dysfunction. We examined electrocardiograms in the medical record for

the absence of sinus arrhythmia on 1st day of ablation therapy and at 2nd -3rd months following ablation therapy.

RESULTS

Gastrointestinal Manifestations

The overall incidence of UGI complications following AF ablation was 0.74% (40/5380). Patients were identified from two search strategies. First, from the AF ablation database consisting of 5380 patients, we identified 27 patients, of whom 16 had only UGI symptoms. Second, in the same AF ablation database, there were 11 patients with objective diagnostic tests suggestive of upper GI damage identified following catheter ablation for AF. Third, we identified 13 other patients with UGI symptoms and objective diagnostic tests in the gastroenterology clinic from the review of the entire Mayo Clinic electronic medical record database. Among these 40 patients, there was suspicion of upper GI damage based on observations during the RFA (n=38) or cryoablation procedures (n=2).

Among the 40 patients, 8 had structural GI complications confirmed by diagnostic tests such as esophagogastroduodenoscopy (EGD) or esophagogram (Table 1). Fifteen patients had functional GI complications confirmed by objective motility tests (Table 2). The remaining 17 patients had GI symptoms without relevant diagnostic results (either because tests were not done or there were no diagnostic findings on tests performed, Table 3).

1) Clinical manifestations of post-ablation patients with structural UGI complications confirmed by objective tests—There were 8 patients with esophageal erosion/ulcer or fistulous formation confirmed by EGD or esophagogram. Among 27 patients identified in the ‘AF-ablation database’, 13 underwent esophagogastroduodenoscopy (EGD) or endoscopic ultrasonography (EUS) one to seven days after the RFA procedure. There were 7 patients with esophageal ulcers/erosions and no signs of GI bleeding; among these 7 patients, 4 were symptomatic and 3 asymptomatic. Six patients had no mucosal abnormalities on EGD. Even though one patient (#8) had no abnormal mucosal findings on EGD, this patient developed esophagopericardial fistula which was confirmed by esophagogram on day 19 after ablation therapy (Table 1).

Pleuritic chest discomfort was the most common symptom post ablation. EGD showed the esophageal ulcers were located at 25~35 cm from the incisors, in the segment of the esophagus corresponding to the level of the cardiac ablation. Six patients received PPIs after ablation therapy, and two patients used PPI before ablation therapy. One patient (#8) with pneumopericardium due to esophageal perforation resolved after pericardiocentesis and primary repair of the esophageal perforation.

2) Clinical manifestations of patients with functional UGI complications confirmed by objective motility test—There were 15 patients (2 patients from the ‘AF-ablation cohort’ and 13 patients evaluated in the GI clinic) who underwent motility tests (such as gastric emptying by radioscinigraphy and esophageal manometry) for investigation of gastrointestinal symptoms that were either new after ablation therapy or represented aggravation from previously experienced symptoms. Details are provided in Table 2.

Among the 15 patients who underwent gastrointestinal motility tests for evaluation of unexplained UGI symptoms after ablation therapy for AF, 9 patients had newly developed upper GI symptoms, which resolved in all patients. Six patients had recent aggravation of previous upper GI symptoms; 2 patients (#7 and 11) with dysphagia prior to the intervention were diagnosed with esophageal achalasia and their symptoms resolved after pneumatic balloon dilatation or esophageal myotomy; the remaining 3 patients had previously diagnosed membranous glomerulonephritis (#9), systemic amyloidosis (#12), and asthma (#15), respectively. Finally, one patient (#2) was diagnosed with vasomotor dysfunction during work-up for UGI symptoms. Upper GI symptoms persisted in 2 patients (#2 and 12) who had evidence of autonomic dysfunction.

Among 9 patients who underwent gastric emptying scintigraphy, 3 women had delayed gastric emptying, 4 men had accelerated gastric emptying, and 2 women normal gastric emptying.

3) Clinical manifestations of UGI symptoms without diagnostic results—There were 17 patients with UGI symptoms without relevant diagnostic results (Table 3). Seven patients suffered from swallowing discomfort and 6 had nausea and/or vomiting. Most symptoms resolved over time in 15 patients.

Unfortunately, 2 patients (#16 and 17) with suspected atrioesophageal fistula or esophageal rupture died at 4 weeks and 5 weeks after the ablation procedure. Patient #16, a 47-year old man experienced heartburn after the ablation procedure. Chest CT and esophagogram performed 2 weeks after ablation therapy showed no specific abnormal findings. However, he presented abruptly to another hospital with septic shock due to bacteremia and GI bleeding. Patient #17, who was a 71 year old man, experienced mild dysphagia and pleuritic chest pain; chest CT showed no specific abnormal findings; he also presented to another hospital acutely with septic shock and streptococcal bacteremia about 5 weeks after the RFA procedure

Electrocardiogram Evidence of Sinus Arrhythmia after Ablation Therapy

In 5 patients, electrocardiograms were not available for review at day 1 and 2-3 months post-ablation. Assessing the data available (Table 4), the proportion of patients with no sinus arrhythmia on electrocardiogram was 80% (28/35) within 1 day and 59.3% (16/27) 2-3 months after ablation therapy. Excluding 13 of the 40 patients with limited information of electrocardiogram for sinus arrhythmia after ablation therapy at 2-3 months (4 with pacemakers, 2 with AV block, 2 with recurrent atrial fibrillation, and 5 with no follow-up electrocardiogram), we were able to evaluate 27 patients. Of these 27 patients, 21 showed 'no sinus arrhythmia' on electrocardiogram within 1 day after ablation therapy, suggesting vagal dysfunction. Among these 21 patients, 8 patients (4 functional GI symptoms with dysmotility demonstrated, 1 structural/mucosal disease, and 3 GI symptomatic without mucosal or motility abnormality) had restored 'sinus arrhythmia' (suggesting normal vagal function) and 13 had 'no sinus arrhythmia' on electrocardiogram in 2-3 months after ablation therapy (Table 4), suggesting persistent vagal dysfunction. Six patients showed 'sinus arrhythmia' on electrocardiogram within 1 day after ablation therapy.

DISCUSSION

Radiofrequency and cryoablation for atrial fibrillation can be life-saving procedures that can also prevent important complications particularly embolization resulting in stroke. Here we record that, among 5380 patients who underwent catheter ablation of the conducting pathways in the left atrial posterior wall that result in AF, a very small minority (0.74%, 40 patients) developed structural or functional complications in the UGI tract. The course of UGI complications ranges from mild to severe, and rarely fatal. Our experience is consistent with a recent multicenter, randomized trial to compare the cryoballoon ablation therapy with radiofrequency ablation; this trial showed only one patient with esophageal ulcer and two patients with unknown cause of death and sepsis.¹⁵ In the prior literature (summarized in Table 5), there is limited information about vagal nerve injury or abnormal motor functions, such as gastroparesis or esophageal dysmotility. In our study, 13 patients underwent EGD after ablation therapy and 7 patients had esophageal erosions and/or ulcers. Among those 7 patients, 3 patients were asymptomatic. Previous prospective observational studies suggested that the prevalence for asymptomatic esophageal ulcer or erythema ranged from 3.8 to 14.6%.^{16, 17} However, another prospective observational study showed 47.0% prevalence of esophageal ulcer or erythema with correlation between reflux-like symptoms and esophageal wall change.¹⁸ Therefore, it is important for clinicians to suspect such complications especially if patients are symptomatic, or develop unexplained or occult bleeding.

In our study, one patient with a pneumopericardial fistula had no mucosal lesion on EGD on the 18th day after ablation therapy and another patient with suspicious atrio-esophageal fistula had no mucosal defects on EGD on the second day after ablation therapy. Thus, screening for localized esophageal lesion by EGD might be insufficient to predict the risk of significant delayed complications such as atri-esophageal fistula.

Our study demonstrates the development of *de novo* or aggravation of symptoms suggestive of functional GI morbidity in patients after undergoing ablation therapy for AF. The prevalence of such symptoms appears to be very low and two of the patients' symptoms were proven to be caused by achalasia. The studies on extra-esophageal autonomic dysfunction in idiopathic achalasia have reported contradictory results.¹⁸⁻²² Kravitz et al. showed, in the opossum, that extrinsic vagal damage induced by thoracic vagotomy at the level of heart eliminated esophageal peristalsis and LES relaxation by swallowing, consistent with findings in achalasia.²³ However, Herreros et al. demonstrated that there were no differences in autonomic cardiovascular tests and pancreatic response to vagal stimulus between patients with idiopathic achalasia and healthy controls.²⁴ Therefore, it is unclear whether the achalasia diagnosed on 2 of our series was a result of the effects of the cardiac intervention which would be expected to affect the extrinsic neural supply to the esophagus, rather than the intrinsic inhibitory nerves in the myenteric plexus of the esophagus and lower esophageal sphincter, which are considered the prime disorders innervation that result in achalasia.

Among the other patients in this category of functional GI problems associated with impaired motor functions, the symptoms were generally reversible over time, except in 2

patients one of whom had evidence of more general autonomic dysfunction and one systemic amyloidosis, which were likely the result of the generalized neuropathy rather than the effects of the RFA ablation on local innervation of the UGI tract.

Table 5 summarizes recent literature that showed vagus nerve injury after ablation therapy for AF. The studies reviewed in the table used different definitions or criteria of vagus nerve injury, from presumed injury based on symptoms consistent with new onset gastroparesis and acalculous cholecystitis²⁵; findings of gastric retention or dilatation on upper gastrointestinal endoscopy or abdominal computed tomography;^{26, 27} or objectively delayed gastric emptying by scintigraphy.²⁸ In other studies, more definitive prospective observations were conducted at defined times before and after ablation therapy in a small number of subjects who underwent esophageal manometry, gastric emptying study, and responses to sham feeding test, corresponding to esophageal, gastric, and abdominal vagus evaluations.²⁹ We used electrocardiogram in the post-ablation period (immediate and delayed) to identify evidence of vagal dysfunction. Thus, the absence of sinus arrhythmia is suggestive of vagal dysfunction,²⁶ and we have evidence from follow-up that the vagal dysfunction was reversed in several patients, since sinus arrhythmia was re-established on follow-up evaluation. In the clinical setting, 24-hr Halter monitoring was usually performed 2-3 month after ablation therapy to appraise the restoration of sinus rhythm or recurrence of arrhythmia. Even though 24-hr Halter ECG monitoring could provide more accurate and abundant information about heart rate variability (sinus arrhythmia), it might still not demonstrate that the symptoms were associated with vagal nerve injury because most upper GI dysfunctions were transient and resolved with conservative treatment (Table 5). Review of the literature suggests that most changes could be resolved within 1 week after ablation.^{30, 31}

ECG could provide information of presence of sinus arrhythmia right after ablation therapy. However, its accuracy in detecting vagal dysfunction may be increased by incorporating vagal stimulation during the recording of the ECG (e.g. deep breathing). The sensitivity of sinus arrhythmia as a measurement of vagal dysfunction is not likely to be 100%. In fact, in this study, 2 patients had sinus arrhythmia within 1 day ECG and no sinus arrhythmia in 2-3 months after ablation therapy. Therefore, ECG with maneuvers of adequate vagal stimulation might increase sensitivity of this simple measurement to predict vagal dysfunction. Respiratory sinus arrhythmia has been used to appraise vagal function in diverse clinical situations, including as an index of emotional regulation in people with substance use disorder³² or a marker of the vagal tonic inhibition of the release of proinflammatory cytokines in patients with ischemic heart disease³³ or as a monitor of emotional control in patients with psychiatric illness treated with biofeedback.³⁴

There is limited data of prevalence of vagal nerve injury after ablation therapy for atrial fibrillation. Most studies were retrospective and used different diagnostic criteria. Yamasaki et al showed that prevalence of vagal nerve injury after ablation therapy was 5.8%.¹⁷ They defined gastric hypomotility as a marker of vagal nerve injury when retained food was observed by EGD despite an overnight period of fasting, irrespective of symptoms. In that study, all patients with assumed gastric hypomotility were asymptomatic. However, gastric retention of non-digestible food is not a specific sign of vagal dysfunction, as it may occur

even in healthy people if the overnight migrating motor complexes (MMC) had not included a gastric component, which may occur in >50% of healthy people, based on intraluminal pressure studies which showed that only approximately one-third of MMCs began in the gastroduodenal region.³⁵

Another prospective observational study showed that 74% patients had at least one new abnormal UGI function test.²⁹ It is presumed that tissue edema or microhematomas affecting the neighboring mediastinal structures during ablation therapy may have caused compression of the vagus nerve, resulting in injury. Therefore, the presence of vagal nerve injury could provide useful information about possible periesophageal injury that may predispose to esophageal fistula with an adjacent organ. Thus, it is advisable to seek for the evidence of vagal nerve injury even though the patients may have no GI symptoms.

The risks to vagal injury could be reduced by the same techniques used to prevent other esophageal complications, such as esophageal temperature monitoring and mechanical esophageal displacement.^{36, 37} However, several recent studies showed no correlation of esophageal temperature monitoring and esophageal damage.^{29, 38, 39}

In summary, catheter ablation therapy for AF may result in UGI complications and the clinical course may be quite variable. The vast majority of patients do not experience long-standing symptoms, and the vagal dysfunction may spontaneously resolve. However, there are also rare, fatal complications such as atriopharyngeal fistula or esophageal perforation. Even though conservative management is recommended for upper GI symptoms, there should be a high index of clinical suspicion of possible complications in patients with ablation therapy for atrial fibrillation. Monitoring for the absence or presence of respiratory sinus arrhythmia provides a simple approach to screen for vagal dysfunction which may serve as a marker of more extensive tissue damage.

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KEY POINTS

- Following ablation therapy for atrial fibrillation (AF), patients may develop upper gastrointestinal (UGI) symptoms secondary to structural damage or vagal nerve dysfunction affected by the ablation energy.
- We aimed to identify the structural or functional complications in UGI tract following ablation for atrial fibrillation (AF) and clinical outcomes and association with vagal dysfunction.
- The overall incidence of UGI complications following ablation therapy for AF was extremely low (0.74% of the patient cohort) in a single center AF ablation database with highly experienced experts.
- Most UGI issues resolved spontaneously or with conservative treatment.

Figure 1.

The positions of the left atrium, trachea and main stem bronchi, esophagus, and vagus nerve are shown.⁵ There are many vagal nerve fibers (shown in yellow) that cross the esophagus close to the regions relevant to ablation of bundles of conducting fibers in the left atrium. Thus, the vagus nerve and its branches are anatomically close to the posterior wall of the left atrium and the pulmonary vein, and may be injured during ablation treatment required to normalize cardiac arrhythmias such as atrial fibrillation.

Clinical manifestations in patients with structural upper gastrointestinal complications after ablation therapy for atrial fibrillation

Table 1

Case #, Age (y), Gender	Co-morbidity	Pre-existing GERD	UGI symptoms	Timing of EGD/esophagogram	EGD	Esophagogram	PPI or sucralfate post-RFA	Outcome
#1, 67 F, cryo		no	heartburn, pleuritic chest pain	7 days(EGD) 9 days (esophagogram)	Non-bleeding ulcer at mid-ESO	Ulcer in mid ESO	PPI and sucralfate pre and post	Resolved
#2, 44 M	s/p resection of melanoma	no	pleuritic chest pain	2 days	ESO ulcer (+ adherent blood clots) 35 cm from incisors	ND	PPI	Resolved
#3, 59 M	colon cancer in remission	no	No	2 days	ESO ulcer with adherent blood clots 35 cm from incisors	ND	no	Resolved
#4, 64 M	DM	yes	No	1 day	ESO erosions at 26, 36 cm from incisors; EUS: pen- ESO inflammation	ND	PPI	Resolved
#5, 57 M		no	pleuritic chest pain, dyspepsia	1 day	ESO erosion at 32 cm from incisors, hiatal hernia	ND	PPI	Resolved
#6, 56 M		no	heartburn	4 days	Non-bleeding deep ESO ulcers at 30 cm from incisors; large amount of food in stomach	ND	PPI	Resolved
#7, 61 F		no	No	2 days	Non-bleeding superficial ESO ulcer at 30 cm from incisors.	ND	no	Resolved
#8, 72 M, cryo		no	pleuritic chest pain	18 days	No mucosal defect	Pneumo- pericardium due to ESO perforation	PPI pre and post	Pericardio- centesis, repair of ESO perforation

cryo=cryoablation therapy; EGD=esophagogastroduodenoscopy; ESO=esophagus; EUS=endoscopic ultrasound; GERD=gastroesophageal reflux disease; ND=not done; PPI=proton pump inhibitor;

RFA=radiofrequency ablation; y=years

Table 2

Clinical manifestations in patients with functional upper gastrointestinal complications after ablation therapy for atrial fibrillation

Case #, Age (yr), Gender	Co-morbidity	Sinus arrhythmia post ablation		UGI symptoms after RFA	Time of motility test	Motility results	Progression/Outcome
		1 day	2-3 months				
		Acute (within 4 weeks)					
#1, 74 M	DM, hypothyroidism	yes	Yes	dysphagia	3 days	ESM: NEMD	resolved in 5 days
#2, 44 F	depression, fibromyalgia	yes	Yes	nausea, abdominal bloating, fullness, belching worse after RFA	2 wks	delayed GE at 2hr and 4hr; 5wks post RFA; antral hypomotility (neuropathic)	no improvement
#3, 57F	breast cancer, diverticulosis, infantile pyloric stenosis, anxiety, fibromyalgia	no	No	chest discomfort, swallowing discomfort	4 wks	delayed GE	resolved
Subacute (4 weeks - 12 weeks)							
#4, 78M	hypothyroidism, cholecystectomy	no	Yes	dysphagia, nausea, belching, heartburn	11 wks	accelerated GE at 1hr	resolved
Chronic (over 12 weeks)							
#5, 59 M	cardiac pacemaker due to SSS, Barrett's esophagus	NA due to pace-maker		unexplained chest pain	19 wks	ESM and impedance pH: elevated LES pressure (47.9 mmHg); increased distal esophageal acid exposure	resolved
#6, 68M	coronary artery disease, and spasm	yes	Yes	dysphagia, chest pain, especially solid food	20 wks	ESM: low LES pressure	resolved
#7, 80 M	non-melanoma skin cancer, diabetes, CKD, s/p renal transplant	NA due to pacemaker		dysphagia, vomiting worse after RFA	24 wks	esophagogram and ESM, achalasia type I	improved post-dilatation, death from CKD
#8, 40 M	fibromyalgia, cholecystectomy, lipoma	no	NA	unexplained epigastric pain	35 wks	accelerated GE at 1hr; decreased gastric accommodation	resolved
#9, 62 M	membranous glomerulonephritis	no	no	nausea, dysphagia worse after RFA	46 wks	accelerated GE at 1hr	resolved
#10, 47 F	Cowden's syndrome, thyroid cancer	yes	no	nausea, heartburn, patulous LES	65 wks	normal GE	resolved
#11, 63M		no	yes	dysphagia worse after RFA	93 wks	ESM: Achalasia type II	myotomy + fundoplication
#12, 41 F	cardiac amyloidosis, stem cell and kidney transplant, autonomic dysfunction	no	yes	bloating, chest pain, dysphagia worse after RFA	113 wks	(1) GE normal. (2) ESM: NEMD normal LES tone.	no improvement

Case #, Age (yr), Gender	Co-morbidity	Sinus arrhythmia post ablation		UGI symptoms after RFA	Time of motility test	Motility results	Progression/Outcome
		1 day	2-3 months				
#13, 63 M	mild asthma, anxiety, Barrett's esophagus	no	yes	dyspepsia, nausea, postprandial fullness	162 wks	accelerated GE at 1hr	resolved
#14, 69 M	UC, s/p cholecystectomy	no	no	dysphagia, belching, heartburn	165 wks	ESM: NEMD, Schatzki ring <13mm	resolved
#15, 54 F	mild asthma	yes	yes	longstanding, worse after RFA	207 wks	delayed GE	resolved

AF=atrial fibrillation; DM=diabetes mellitus; CKD=chronic kidney disease; ESM=esophageal manometry; GE=gastric emptying; NA=not analyzable; NEMD=nonspecific esophageal motor disorder; RFA=radiofrequency ablation; normal GE at 1 h: 11-39%; SSS=sick sinus syndrome

Clinical manifestations in patients with upper gastrointestinal symptoms without diagnostic results

Table 3

Case #, Age (yr), Gender	Co-morbidity	Pre-existing GERD	UGI after RFA	Sinus arrhythmia post ablation therapy		Ancillary findings	PPI or sucralfate after ablation Rx	Progression/Outcome
				in 1 day	2-3 months			
#1, 66 M		no	dyspepsia	no	no	CT suggestive of gastroparesis	no	resolved
#2, 58 F		no	belching, swallowing discomfort with cold water on 5 th day after RFA	no	yes	esophagogram on 6 th day showed hiatal hernia	no	spontaneously resolved in 6 days
#3, 53 M		no	swallowing discomfort with liquid diet	NA due to AV block		not done	no	resolved in 2 weeks
#4, 72 F		yes	chest discomfort worse after RFA, nausea after double dose PPI	yes	NA due to recurrent AF	not done	PPI	chest discomfort resolved in 6 weeks; nausea resolved after PPI dose reduced
#5, 82 F	anxiety	no	nausea/ vomiting on opioid drug at 3 months	no	Yes	not done	no	resolved (with cessation of opioid)
#6, 75 M		yes	throat discomfort and dysphagia	NA due to AV block		esophagogram: normal peristalsis and hiatal hernia	PPI*	resolved
#7, 41 M	anxiety		nausea/vomiting at 2 months	NA due to pacemaker		not done	no	resolved (w/o change of drug)
#8, 61 F		yes	odynophagia on 2 nd day	no	No	EGD and CT: no perforation	PPI	resolved
#9, 27 F	thyroid cancer	no	nausea/vomiting, fever	no	No	esophagogram: no ESO fistula, perforation	no	resolved
#10, 47 M		no	abdominal discomfort, nausea	no	No	large volume of bilious content in stomach during RFA	PPI*	resolved
#11, 51 F		no	dysphagia only	no	No	esophagogram and CT: normal peristalsis and no perforation	no	resolved in 4 days
#12, 31 M		no	reflux-like symptoms	no	No	esophagogram and CT: showed no leakage	no	resolved by taking H2R blocker
#13, 52 M	hyper-thyroidism	no	odynophagia and pleuritic chest pain	no	No	not done	no	resolved

Case #, Age (yr), Gender	Co-morbidity	Pre-existing GERD	UGI after RFA	Sinus arrhythmia post ablation therapy		Ancillary findings	PPI or sucralfate after ablation Rx	Progression/Outcome
				in 1 day	2-3 months			
#14, 63 M	lymphoma, anxiety	no	throat discomfort	no	N/A (no follow-up ECG)	not done	PPI	resolved
#15, 63 M	anxiety, depression and asthma	no	nausea worse	no		not done	PPI	resolved after reduction of PPI dose
#16, 47 M	hepatitis B	no	heartburn	no		chest CT and esophagogram: normal at 2 weeks	no	septic death due to suspected perforation
#17, 71 M		no	dysphagia, odynophagia, pleuritic chest pain	no		not done	no	septic death due to suspected perforation

AF=atrial fibrillation; AV=atrioventricular; CT=computerized tomography; ESO=esophageal; GERD=gastroesophageal reflux disease; NA=not analyzable;

*=PPI use before and after ablation therapy; RFA=radiofrequency ablation; y=years

Table 4

Electrocardiogram evidence of sinus arrhythmia after ablation therapy

N=40	1 day after ablation therapy	2-3 months after ablation therapy	Interpretation
13	Absence of sinus arrhythmia	Absence of sinus arrhythmia	Vagal dysfunction
8	Absence of sinus arrhythmia	Presence of sinus arrhythmia	Transient vagal dysfunction
7	Absence of sinus arrhythmia	Not available	Early vagal dysfunction
3	Presence of sinus arrhythmia	Absence of sinus arrhythmia	Late vagal dysfunction
3	Presence of sinus arrhythmia	Presence of sinus arrhythmia	Normal vagal function
1	Presence of sinus arrhythmia	Not available	Normal early vagal function
5	Not available	Not available	Not analyzable

There were thirteen patients with limited information of electrocardiogram for sinus arrhythmia after ablation therapy (4 with pacemakers, 2 with AV block, 2 with recurrent atrial fibrillation, and 5 with no follow-up ECG).

Table 5

Literature review documenting vagus nerve dysfunction after ablation therapy

# patients	Mean age, y	Procedure for AF and radiofrequency power when specified	Gastrointestinal manifestations	Evidence of vagal dysfunction	Timing and evolution	Ref. #
257 consecutive pts	62±11	RFA with catheter-based pulmonary vein isolation	5 patients (1.9%); gastric hypomotility (3 pts) and acalculous cholecystitis (2 pts)	gastroparetic symptoms and acalculous (CT or ultrasonography)	within 3 days of ablation; all recovered completely within 2 wk	24
535 consecutive pts	64±10.3	RFA with sole pulmonary vein antrum isolation; power 20-30 W	13 patients (2.4%) had gastric hypomotility	symptoms and abdominal x-ray	initial period; 12/13 full recovery with conservative Rx within 4 months; higher BMI reduced risk	25
3695 pts;	60±11	RFA ± irrigation; power 25-40 W	11 pts: gastric hypomotility (10 pts) and pyloric spasm (1 pt), 4/157 pts did not have esophageal temperature monitoring, and 7/3,538 did (p=0.0007)	fluoroscopy and/or endoscopy	8 pts almost fully recovered within 40 days; 3 pts severe symptoms for 3-12 months	26
27 pts prospective, observational study	60±12	RFA with sole pulmonary vein antrum isolation; power 30-40 W	20 pts had new onset abnormal ESM, GES, or MSF. Mean PAGI-SYM scores increased 24 hr post-ablation	ESM, GES, and MSF	new onset abnormalities; 70% at 24h, persisted in 33% pts at 3 months and normalized in all pts at 6 months.	28
104 pts; prospective study	57±12	pulmonary vein isolation by CBA (56 pts) or RFA with irrigation (46 pts)	gastroparesis symptoms in 7 cases (6 cases CBA, and 1 case RFA). abnormal GES in 5 cases (4 CBA, 1 RFA)	symptoms, fluoroscopy of stomach during procedure, and confirmed GES	all within 4 days of procedure; resolved in 6/7 at 6 months	27
30 consecutive pts	61.8±8.3	RFA with pulmonary vein isolation under esophageal temperature monitoring	13 (43%) delayed GE liquid after RFA; no symptomatic gastric hypomotility	modified ¹³ C-acetate breath test before ablation and 1-3 days after catheter ablation	NA	39

AF=atrial fibrillation; CBA=cryoballoon ablation; CT=computerized tomography; ESM=esophageal manometry; GES=gastric emptying scan; MSF=modified sham-feeding test; NA=not available; RFA=radiofrequency ablation; y=years; ¹³C-acetate breath test measures gastric emptying of liquids.