Esophageal Injury and Atrioesophageal Fistula Caused by Ablation for Atrial Fibrillation

ABSTRACT: Esophageal perforation is a dreaded complication of atrial fibrillation ablation that occurs in 0.1% to 0.25% of atrial fibrillation ablation procedures. Delayed diagnosis is associated with the development of atrial-esophageal fistula (AEF) and increased mortality. The relationship between the esophagus and the left atrial posterior wall is variable, and the esophagus is most susceptible to injury where it is closest to areas of endocardial ablation. Esophageal ulcer seems to precede AEF development, and postablation endoscopy documenting esophageal ulcer may identify patients at higher risk for AEF. AEF has been reported with all modalities of atrial fibrillation ablation despite esophageal temperature monitoring. Despite the name AEF, fistulas functionally act 1 way, esophageal to atrial, which accounts for the observed symptoms and imaging findings. Because of the rarity of AEF, evaluation and validation of strategies to reduce AEF remain challenging. A high index of suspicion is recommended in patients who develop constitutional symptoms or sudden onset chest pain that start days or weeks after atrial fibrillation ablation. Early detection by computed tomography scan with oral and intravenous contrast is safe and feasible, whereas performance of esophageal endoscopy in the presence of AEF may result in significant neurological injury resulting from air embolism. Outcomes for esophageal stenting are poor in AEF. Aggressive intervention with skilled cardiac and thoracic surgeons may improve chances of stroke-free survival for all types of esophageal perforation.

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Catheter ablation of atrial fibrillation (AF) is an increasingly used modality of treatment.[1] A dreaded complication of left atrial (LA) ablation is atrial-esophageal fistula (AEF). Whereas increased operator experience is associated with lower overall complications, the occurrence of AEF seems to be independent of operator case load.[2] AEF has so far been reported for surgical and catheter AF ablation (including radiofrequency and cryoballoon ablations).[3] Information on the development, presentation, diagnosis, and management is sparse, but delayed diagnosis is associated with a high mortality. This review aggregates knowledge ascertained by retrospective data published in this evolving field.

EPIDEMIOLOGY AND PREVALENCE TRENDS OF AEF

The epidemiology of AEF is difficult to describe accurately, largely as a result of its rarity. It is estimated to occur in <0.1% to 0.25% of AF ablation procedures.[1] AEF has been reported to be more prevalent in men than women.[4]

In a survey aggregating 191 215 AF ablations, symptom onset for esophageal perforation or fistula was reported on postprocedural day 19.3±12.6 (range, 6–59 days). Of the 28 patients with esophageal perforation or fistula, 20 (71%) had an AEF, 4 (14%) had a pericardial-esophageal fistula, and 4 (14%) had esophageal perforation without fistula formation.[5] Among causes of death after AF ablation, AEF is the second most common along with stroke, with acute cardiac tamponade being the leading cause of mortality.[6]

PATHOPHYSIOLOGY OF ESOPHAGEAL INJURY AND FISTULIZATION

Anatomy

Key to the development of esophageal injury is the anatomic proximity of the esophagus to the LA. The esophagus descends in the mediastinum posterior to the LA and to the right of the descending aorta; however, as it descends more inferiorly, it tends to run anterior and

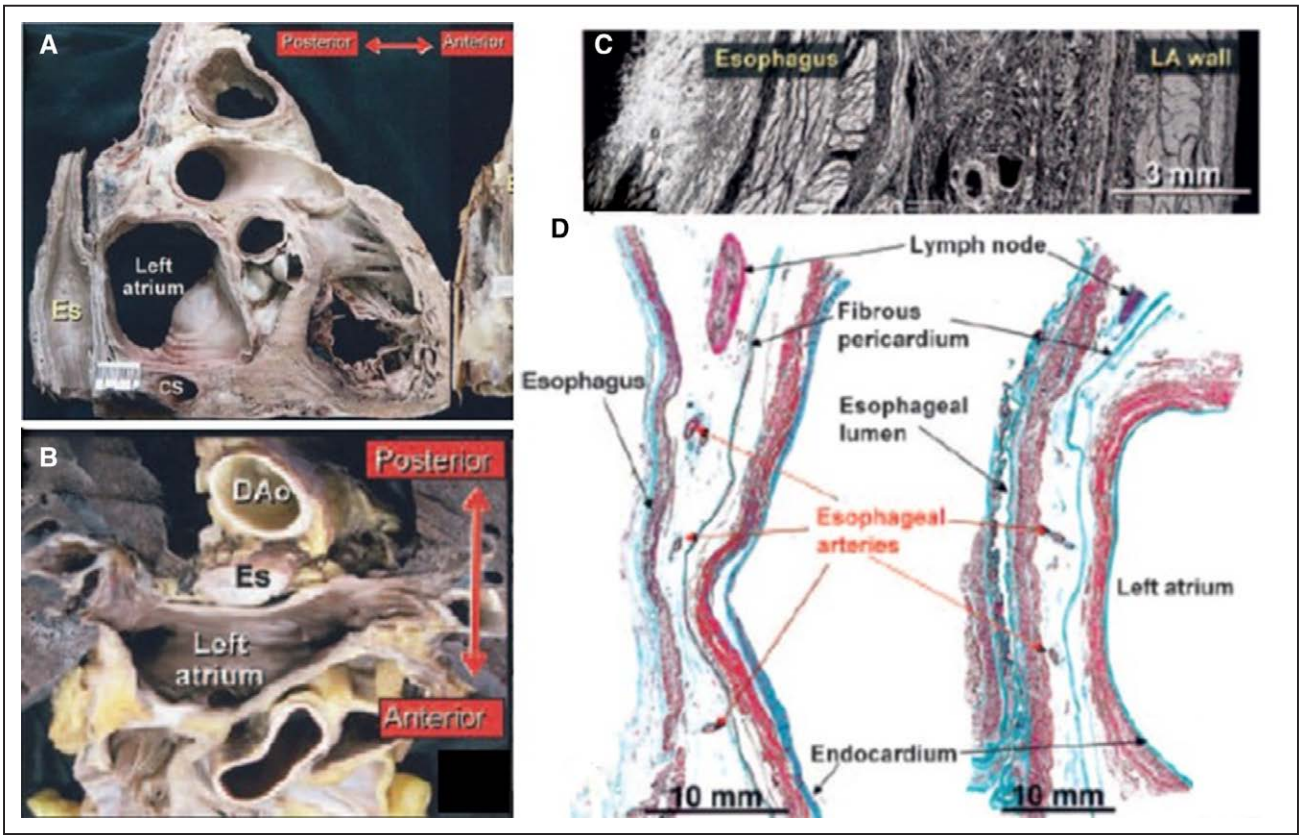

Figure 1. Atrial/esophageal anatomy.
A, Sagittal section through the heart and esophagus (Es) showing a middle section between the left and right pulmonary veins (note close proximity). **B**, Transverse sections through the left atrium (LA) and esophagus show the esophagus related to the middle of the posterior atrial wall. **C**, Scanning electron microscopy of a sagittal section. **D**, Histological sections in similar orientation showing the fibrous pericardium between the LA wall and the esophageal wall and the fatty tissue plane containing lymph nodes and esophageal arteries immediately behind that (Masson trichrome stain). DAo indicates descending aorta. Reproduced from Sánchez-Quintana et al[7] with permission of the publisher. © 2005 American Heart Association, Inc.

slightly to the left of the aorta before it passes through the diaphragm into the abdomen.[7,8] Esophageal anatomy is highlighted in Figure 1. The relationship of the esophagus to the LA posterior wall and pulmonary veins is variable. It tends to be located farthest from the right superior pulmonary vein, but it can be close to any of the others, depending on its course, and may be within a few millimeters at the point of closest proximity. Moreover, there is clear evidence that the esophagus can shift, even while the ablation is performed. In a study assessing esophageal position change during AF ablation under conscious sedation with serial, biplane digital cine-fluoroscopic imaging after barium paste ingestion, 67% of patients had a shift ≥2 cm and 4% had a shift ≥4 cm of lateral movement.[9] The mobility of the esophagus is important when considering esophagus deviation as a potential strategy to avoid thermal damage.

Beyond the body of the esophagus, periesophageal nerves are at risk of injury when ablation is performed in these areas. Branches of the vagus nerve control peristalsis, the pyloric sphincter, and motility in the gastric antrum. Two branches descend on the anterior surface of the esophagus to form the anterior esophageal plexus, which enters the abdomen through the esophageal diaphragmatic opening. The anterior plexus passes external to the pericardium but within 2.5 to 6.5 mm of the posterior atrial wall or the junctions of the pulmonary veins and the posterior LA.[10] The vagus nerve mediates gastric antral contraction followed by pyloric relaxation in the late phase of gastric emptying.[11]

Mechanism of Injury

Although the precise mechanism of esophageal injury is not completely understood, potential mechanisms of injury include direct thermal injury, acid reflux exacerbated or caused by ablation, infection from the lumen, and ischemic injury through thermal occlusion of end arterioles.[12] Table 1 summarize the key mechanisms proposed for AEF formation. More significant esophageal injury has been found to have later symptom onset than self-resolving injury and is therefore less likely to be related to immediate thermal injury.

Table 1. Possible Mechanisms of Atrial-Esophageal Fistula Formation

Mucosal damage
Caused by thermal injury
Concurrent thermal damage to the anterior esophageal arteries→ischemic lesions
1°C increase in endoluminal temperature increases odds of an esophageal lesion by 1.4
Ulceration seems to be precursor to AEF
Gastroesophageal reflux
Ablation may damage vagal fibers→impair lower esophageal sphincter→increase reflux
Potentially aggravates mucosal injury
Canine studies in which AEF formation was observed show severe esophagitis in addition to ulceration (rationale for proton pump inhibitor use)
Esophageal dysmotility
Preexisting or exacerbated by nerve injury in ablation
Exacerbated by general anesthesia

AEF indicates atrial-esophageal fistula.

Progression of Fistula Formation

Both components, the posterior wall of the LA and the anterior esophagus, may be weakened by endocardial catheter ablation. However, the primary insult seems to be to the esophageal wall, with fistulization occurring from the esophagus toward the atrium. Necrosis and perforation of the LA in the absence of an AEF have not been reported as complications of AF ablation, whereas esophageal perforation alone is a well-known complication. Furthermore, as the esophageal ulceration penetrates into the LA, a 1-way valve is created with leakage into but not out of the LA in the majority of cases. In addition, case reports document esophageal-pericardial fistulas preceding esophageal-atrial fistulas[13] and have shown serial computed tomography (CT) chest scans with progressive ulceration of the esophagus, connection to the mediastinum and the pericardial space, and ultimately perforation into the LA.[14] Although all esophageal ulcerations may not communicate with the pericardium before rupturing into the LA, the better survival associated with atriopericardial fistula formation and esophageal perforation without fistula formation underlines the urgency in diagnosing esophageal perforation in its earliest stage.[5]

Esophageal Lesions/Ulcerations

A number of gastrointestinal symptoms can be observed after AF ablation (Table 2). Esophageal ulcerations are commonly seen during endoscopic esophageal evaluation after AF ablation. In a study of endoscopy after cryoablation, up to 17% of patients had esophageal injury.[15] Similarly, in a recent endoscopy study in 267 patients who underwent AF ablation with radiofrequency energy, 2.2% had either erythema or a necrotic ulcer on endoscopy. Multivariate analysis revealed that the distance between the LA and esophagus was the only independent predictor.[16] Survey data suggest that 73% of patients diagnosed with esophageal ulcer after AF ablation ultimately have complete resolution of ulcer symptoms.[5]

The prevalence of esophageal abnormalities after AF ablation was demonstrated in a study of 425 patients who underwent upper gastrointestinal endoscopy 1 to 3 days after AF ablation. Findings included gastral erosions (22%), esophageal erythema (21%), gastroparesis (17%), hiatal hernia (16%), reflux esophagitis (12%), thermal esophageal lesion (11%), and suspected Barrett esophagus (5%).

Table 2. Gastrointestinal Symptoms of Atrial Fibrillation Ablation Beyond Atrial-Esophageal Fistula

Gastroparesis/dysmotility
Injury of vagal anterior esophageal plexus→pyloric spasm+gastric hypomotility
Common symptoms include nausea, vomiting, bloating, and abdominal pain
The incidence may be as high as 1%
Symptoms develop within a few hours to a few weeks after the ablation procedure
Most patients (≈95%) recover within 2 weeks; rarely a protracted course
Case reports of esophageal hypermotility (jackhammer esophagus)
Evaluation may include
Endoscopy or a barium swallow study to look for residual food
CT looking for gastric dilation
Solid food labeled with technetium-99 looking for delayed gastric emptying
Real-time MR imaging assessing gastric motility and pyloric spasm
Gastric reflux
Injury of vagus controlling lower esophageal sphincter and diaphragm→reflux
Occurs in ≈20% of patients as measured by leadless pH-metry
Esophageal lesions/ulcerations
Esophageal ulcerations are commonly seen after ablation
Symptoms include odynophagia, dysphagia, chest discomfort
Estimated prevalence of 2%–20%
Dependent on ablation characteristics and distance between the LA and esophagus
Majority resolve by 6–8 wk
Possibly dependent on preexisting pathology

CT indicates computed tomography; LA, left atrium; and MR, magnetic resonance.

Biopsies were performed in 70 patients (17%), showing gastritis (84%), *Helicobacter pylori* colonization (17%), mucosa-associated lymphoid tissue (17%), esophagitis (9%), and Barrett esophagus (4%). These findings resulted in further diagnostic workup or initiation of treatment in 105 patients (25%).[17] Although other means to detect esophageal injury include endoscopic ultrasound[18] or capsule endoscopy,[19] the gold standard for early detection of esophageal thermal injury related to AF ablation is esophagogastroduodenoscopy (EGD) with visualization and characterization of the degree of thermal injury. Figure 2 depicts different esophageal injury patterns seen on EGD.

Esophageal ulceration is likely the initial injury that leads to AEF formation and is probably present within hours to days of the ablation procedure. Deneke et al[20] have assessed the outcomes of >800 patients who underwent first-time catheter ablation of AF followed by EGD within 4 days of the procedure. They found that 82% of patients had EGD without esophageal lesions and no subsequent esophageal events. Of the patients with esophageal abnormalities, two-thirds had erythema with no further complications. The 5 documented esophageal perforations occurred in patients with esophageal ulceration (ratio of esophageal perforation to ulcer, 1:10) These data suggest that early endoscopy that shows no esophageal ulceration should be reassuring in terms of later esophageal perforation. Conversely, patients with an esophageal ulceration early after ablation require more intense monitoring and perhaps more aggressive therapy.

ABLATION FEATURES RELATED TO AEF

Modality of Ablation

Esophageal injury has been observed most frequently with percutaneous radiofrequency ablation, although it also has been reported with other energy sources, including cryoablation,[21] high-intensity focused ultrasound,[22] and surgical ablation[23]; however, data on consecutive patients are sparse. The low incidence of AEF formation limits a direct comparison[24] between cryoballoon and radiofrequency ablation; however, AEF formation is most often adjacent to the left inferior pulmonary vein with cryoballoon ablation.[25]

A higher incidence of esophageal injury has been reported in robotic navigation AF ablation compared with manual ablation when similar radiofrequency ablation parameters are used.[26] Although not clear, this may be due to increased catheter contact and stability, thereby resulting in more significant lesions for similar ablation parameters. Reduction of ablation power in robotic navigation AF ablation to 20 from 30 W on the LA posterior wall and termination of energy delivery at esophageal temperature of 41°C instead of 43°C significantly reduced the risk of esophageal injury. In a survey of Canadian electrophysiologists, 25 electrophysiologists accounting for 7016 AF ablations reported 5 cases of proven AEF (0.07%).[27] Operators who reported

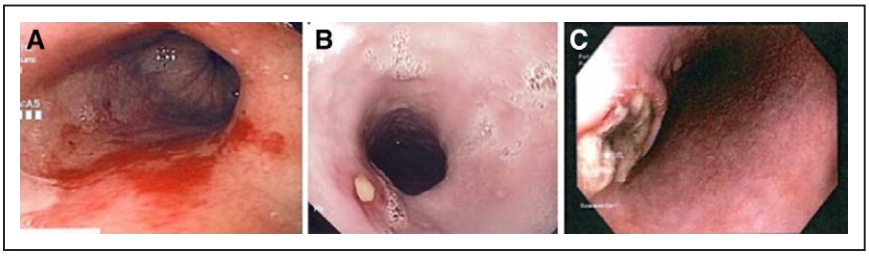

Figure 2. Different aspects of esophageal thermal lesions related to atrial fibrillation ablation as seen on upper endoscopy.
A, Erythema without disruption of the esophageal mucosa. **B**, Esophageal ulcer showing mucosal disruption and injury. **C**, Necrotizing esophageal ulcer.

AEF were more likely to use a nonbrushing technique on the posterior wall of the LA. Nonbrushing technique refers to point-by-point ablation as opposed to continuous catheter movement during ablation (brushing technique). There was a trend toward higher maximal power setting. In a small randomized study comparing post-AF ablation capsule endoscopy in procedures performed under conscious sedation with those performed under general anesthesia, esophageal tissue damage was observed in 48% of the general anesthesia group, whereas only 4% of the conscious sedation group had evidence of esophageal injury,[28] probably as a result of enhanced contact during general anesthesia. General anesthesia may also reduce/eliminate esophageal motility/peristalsis, which could increase esophageal damage and eliminate the patients' ability to alert the operator to esophageal injury (by voicing discomfort/pain). These studies highlight the importance of lesion biophysics as a controllable risk factor. Contact force, lesion duration, catheter tip size, wattage, and irrigation flow require optimization on the posterior wall compared with other regions of the LA, although optimal parameters have not been determined. Undoubtedly, improvements in monitoring lesion size and depth will be required to help limit esophageal injury.

We have hypothesized that decreased irrigation flow during radiofrequency application may be more appropriate on the posterior wall to prevent "surface sparing" by excessive cooling. Lower irrigation rates favor transmural lesion creation in a shorter radiofrequency application, which decreases lesion size beyond the atrial wall. Unpublished data from preclinical and clinical studies (G.M. and S.K.) suggest that a lower irrigation flow rate allows decreased total energy delivery without sacrificing efficacy or safety, but further studies are needed to confirm this approach.

Other Procedural Risk Factors

Given the concern for esophageal heating as a mechanism for injury, esophageal temperature monitoring has become commonly used.[29] Some analyses suggest that lesions occurred in patients with an esophageal temperature >41°C, and for every 1°C increase in esophageal temperature, the odds of an esophageal lesion increased by a factor of 1.36, highlighting the importance of real-time esophageal monitoring.[30] Although we perform real-time monitoring of luminal esophageal temperature, it is important to note that there has been some suggestion of harm associated with a temperature probe.[31] A recent study comparing post-AF ablation EGD in 80 patients with and without continuous temperature monitoring using a single-sensor temperature probe revealed a significantly greater incidence of esophageal injury in the temperature probe group (30% versus 2.5%). Multivariable logistic regression analysis revealed the use of an esophageal temperature probe as the only independent predictor for the development of esophageal lesions (odds ratio, 16.7).[32] Some have highlighted that esophageal temperature probes with noninsulated metal thermistors may function as lightning rods, attracting electric current from the ablation catheter and potentiating heat transfer to the esophagus.[33] Others have suggested that use of an esophageal temperature probe with insulated thermocouples resulted in no increase in endoscopically detected esophageal lesions compared with ablations performed without a temperature probe.[34] Different materials are known to have different thermodynamics, which may serve as a heat sink.[35] Whereas high esophageal wall temperatures may predict thermal injury, high-density fast response surveillance is needed. Recently, a near-infrared monitoring probe scanning the complete esophagus at the site of contact with the LA has been introduced.[36] Further research is needed to confirm which, if any, esophageal temperature probe will be useful in preventing esophageal injury.

Notably, visualization of the esophageal course by barium contrast was not able to prevent esophageal ulceration in small randomized studies.[37] Echocardiography can also delineate the course of the esophagus relative to the LA wall, but this has not been shown to prevent injury.

PHARMACOLOGICAL PROPHYLAXIS

Adequately powered clinical trials to establish the efficacy of pharmacological prophylaxis to reduce AEF may never be feasible given the low incidence of AEF. We currently prescribe periprocedural gastric acid suppression agents. Reported practice includes proton pump inhibitors or H_2 blockers starting either before or immediately after the ablation and continuing 1 to 6 weeks after ablation.

CLINICAL PRESENTATION

AEF typically occurs 1 to 6 weeks after the catheter ablation procedure, although earlier and later onsets have been reported.[38,39] The majority of signs and symptoms of AEF are not specific and may include fever, fatigue, malaise, chest discomfort, nausea, vomiting, dysphagia, odynophagia, hematemesis, melena, and dyspnea. A high index of suspicion is recommended in patients with constitutional symptoms after AF ablation, particularly if preceded by sudden-onset chest pain.

A systematic review of observational cases of 53 cases of AEF after ablation procedures for AF characterized the presentation. The patients' mean age was 54±13 years; 73% of cases occurred in men. The mean interval between procedure and presentation

was 20±12 days, ranging from 2 to 60 days. Fever was the most common presenting symptom (n=44), followed by neurological deficits (n=27) and hematemesis (n=19).[3] These findings support the idea that the fistula often serves as a 1-way conduit, allowing bacteria (resulting in sepsis) and air (resulting in stroke) from the esophagus into the bloodstream, as opposed to the other way (blood entering the esophagus). Although immediate periprocedural strokes (noted on the day of or after the procedure) are unlikely to be related to esophageal fistulization, neurological symptoms within the 1- to 6-week window may necessitate esophageal evaluation in the right clinical context. Delay between symptom onset and hospital admission was associated with an increased prevalence of fever and neurological abnormalities.[2]

DIAGNOSIS

Early diagnosis is important because esophageal perforation without communication to the LA is associated with a greater chance of full recovery by urgent intervention.[40]

When the diagnosis of AEF is being entertained, a white blood cell count should be obtained because it is an early and sensitive laboratory marker of an AEF.[41] Blood cultures from patients with sepsis secondary to AEF often grow Gram-positive organisms.

The best diagnostic modalities are CT or magnetic resonance imaging of the esophagus.[14] Figure 3 depicts CT diagnosis of an AEF. Although a barium swallow may detect a fistula, its sensitivity is low. If an AEF is suspected, endoscopy should be avoided because insufflation of the esophagus with air may result in a large air embolus producing stroke or death. In a systematic review of 53 documented cases of AEF, CT of the chest was the modality that made the diagnosis in more than half (n=27).[3] CT angiography of the chest can show the connection between the esophagus and LA with extravasation of contrast from the LA into the esophagus via a fistulous tract, but more often evidence of contrast or air extravasation from the esophagus is found.

It is important to realize that once esophageal perforation is suspected, EGD is no longer a safe imaging modality because insufflations may open a 1-way valve to the atrium and cause catastrophic neurological injury and death.

MANAGEMENT

Once the diagnosis of AEF is made, early surgical repair is essential because the mortality rate is 100% without treatment.[42] Various surgical approaches are available for the repair of AEF. Both endoscopic stenting of the esophagus and primary esophageal repair and placing a biological barrier between the esophageal and atrial repair have been reported.

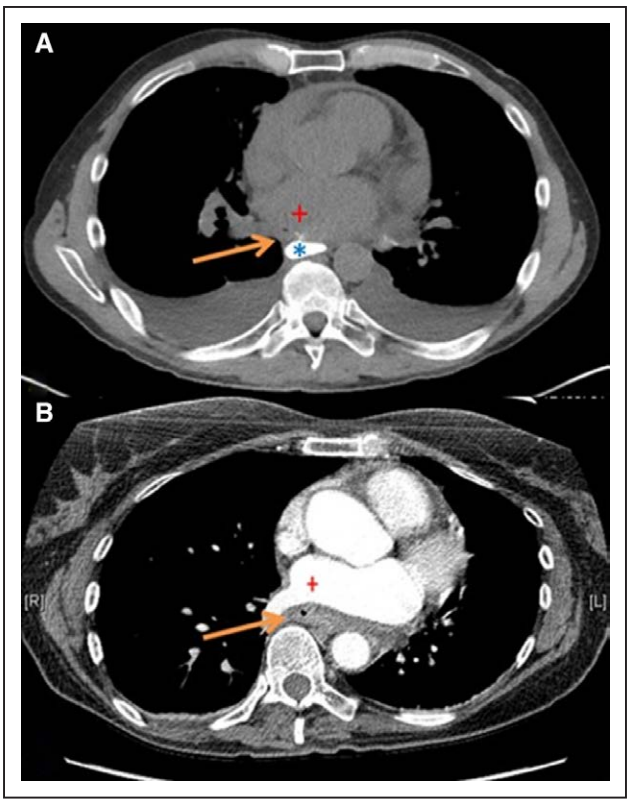

Figure 3. Imaging of esophageal-pericardial fistula. **A**, A 55-year-old man with gastric reflux presents 3 weeks after catheter ablation of atrial fibrillation (AF) with odynophagia and chest pain. The patient had no gastrointestinal bleeding, neurological deficits, or infectious symptoms. An axial image from a computed tomographic (CT) scan with oral contrast revealed pleural/pericardial effusions and extravasation of contrast and air from the esophagus (*) to the pericardial space abutting the left atrium (+). **B**, A 72-year-old woman with no medical history other than paroxysmal AF presents with odynophagia and chest pain 4 weeks after ablation. Axial CT imaging showed air in the pericardium. Both patients underwent emergent repair of esophageal perforation with an intercostal muscle flap and a pericardial patch repair of the left atrium. Both patients recovered without neurological complication.

A retrospective cohort analysis of 29 patients with AEF showed that 100% of patients who underwent esophageal stenting died, whereas 41% who underwent surgical repair died. Patients who did not receive primary esophageal repair were more likely to experience postoperative complications, including mediastinitis, need for percutaneous endoscopic gastrostomy feeds, esophageal stent, or death. Technically, interposing tissue between the repaired esophagus and the LA appears to result in fewer postoperative complications.[43] A separate study reviewed 9 patients, 5 who received stents and 4 who underwent surgical repair of fistula. All 5 patients receiving stents died within 1

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week of the procedure of cerebral embolism, septic shock, or respiratory failure. On the other hand, the 4 patients who received surgical repair were alive at a median follow-up of 2.1 years.[44]

Because these are observational studies, the role of selection bias is unclear in the finding that primary surgical repair is the optimal treatment. In fact, in 1 reported case, the patient was conservatively managed with repeated endoscopic snaring of the esophageal mucosa, accompanied by antibiotic therapies, which eventually led to improvement in the patient's condition without any evidence of symptom recurrence.[45]

In cases in which esophageal perforation but not fistulization into the LA has occurred, esophageal fixated covered stents, broad antibiotic coverage, and repeat endoscopy may be a therapeutic option, but it can be difficult to exclude fistula formation definitively, and fistula may develop over time despite treatment.

Patient education on symptoms associated with severe esophageal thermal injury (prolonged thoracic pain, pain during swallowing, fever attacks) is important for early detection of esophageal perforation. These symptoms should be communicated directly to a physician with knowledge about the diagnosis and management of AEF.

A proposed workup of patients with suspected perforating esophageal thermal complications after AF ablation is outlined in Figure 4.

PROGNOSIS

AEF is associated with a very high morbidity that includes air embolism and sepsis and a mortality rate that is staggeringly high. Among patients with esophageal perforation related to AF ablation, a significantly greater proportion of those who died or had severe neurological injury ultimately received a diagnosis of AEF (94% versus 36%; P=0.002).[5] No association was found between timing of symptom onset and mortality.[3] Little information is available on the prognosis of nonfistulizing, perforating esophageal injury. Of the 4 reported cases in a global survey, 3 patients survived after esophageal stenting, and 1 patient died of sepsis after surgical repair.[2]

NOVEL STRATEGIES OF PREVENTION

Because of the rare nature of AEF, it is difficult to evaluate and validate novel strategies of prevention. At present, no strategy has garnered widespread acceptance or use.

Cooling esophageal protection systems are being developed to prevent thermal damage during ablation. Some include a temperature-controlled fluid-circulating system (EPSac [esophageal protective system], RossHart Technologies Inc).[46] Its safety and efficacy remain to be demonstrated in patients undergoing AF ablation. Other studies with alternative systems have demonstrated human feasibility of an esophageal cooling method using a cooled water-irrigated intraesophageal balloon.[47]

Mechanical techniques to move the esophagus away from the tip of the ablation catheter have been devised with the hope of preventing thermal injury to the esophagus. Mechanical esophageal displacement with the transesophageal echocardiography transducer during catheter radiofrequency ablation of AF has been shown to prevent a rise in esophageal intraluminal temperature.[48] However, transesophageal echocardiography is decreasingly used, and the risk of esophageal trauma from the probe has not been sufficiently evaluated.

Another group used an endotracheal stylet within a thoracic chest tube to deflect the esophagus in 20 patients undergoing AF ablation. The stylet/chest tube remained in the esophagus to allow for sustained deviation during ablation.[49] Postprocedural endoscopy

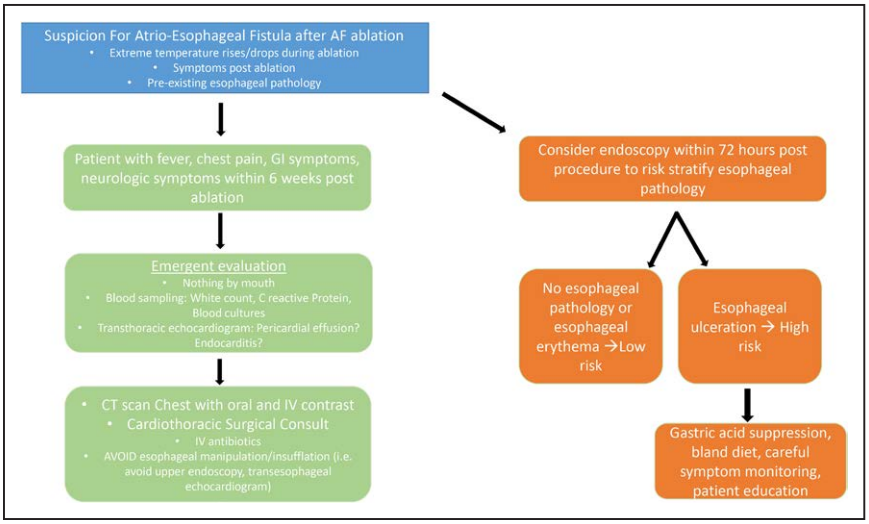

Figure 4. Proposed workup of patients with suspected perforating esophageal thermal complications after atrial fibrillation (AF) ablation.
CT indicates computed tomography; GI, gastrointestinal; and IV, intravenous.

demonstrated ulceration in 1 patient (5%) and evidence of trauma from esophageal instrumentation without clinical consequence in 12 patients (63%). The ratio of risk to benefit requires further evaluation.

CONCLUSIONS

AEF formation is a rare consequence of AF ablation and seems to begin with severe damage to the esophagus that results in ulceration. Despite recognition of this complication >10 years ago, cases still are being reported, and the safety and efficacy of procedural techniques for minimizing incidence remain undefined. Early detection by CT scan with oral and intravenous contrast is essential, and aggressive intervention with skilled cardiac and thoracic surgeons may improve chances of stroke-free survival. Postablation endoscopy documenting esophageal thermal ulcer may identify patients at higher risk for AEF formation.

DISCLOSURES

None.

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FOOTNOTE

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