Atrioesophageal Fistula

Clinical Presentation, Procedural Characteristics, Diagnostic Investigations, and Treatment Outcomes

See Editorial by Crystal and Shurrab

BACKGROUND: Percutaneous or surgical ablation are increasingly used worldwide in the management of atrial fibrillation. The development of atrioesophageal fistula (AEF) is among the most serious and lethal complications of atrial fibrillation ablation. We sought to characterize the clinical presentation, procedural characteristics, diagnostic investigations, and treatment outcomes of all reported cases of AEF.

METHODS AND RESULTS: Electronic searches were conducted in PubMed and Embase for English scientific literature articles. Out of 628 references, 120 cases of AEF were identified using various ablation modalities. Clinical presentation occurred between 0 and 60 days postablation (median 21 days). Fever (73%), neurological (72%), gastrointestinal (41%), and cardiac (40%) symptoms were the commonest presentations. Computed tomography of the chest was the commonest mode of diagnosis (68%), although 7 cases required repeat testing. Overall mortality was 55%, with significantly reduced mortality in patients undergoing surgical repair (33%) compared with endoscopic treatment (65%) and conservative management (97%) (adjusted odds ratio, 24.9; $P<0.01$, compared with surgery). Multivariable predictors of mortality include presentation with neurological symptoms (adjusted odds ratio, 16.0; $P<0.001$) and gastrointestinal bleed (adjusted odds ratio, 4.2; $P=0.047$).

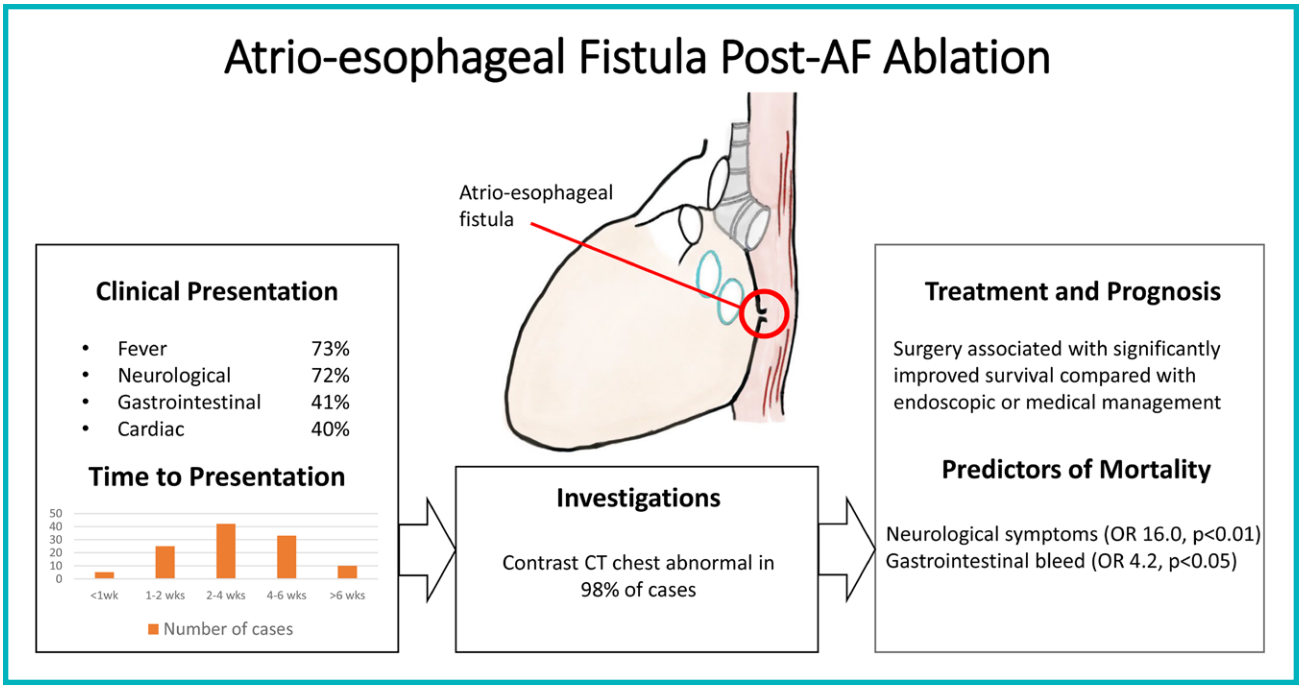
CONCLUSIONS: AEF complicating atrial fibrillation ablation is associated with a high mortality. Clinicians should have a high suspicion for the development of AEF in patients presenting with infective, neurological, gastrointestinal, or cardiac symptoms within 2 months of an atrial fibrillation ablation. Investigation by contrast computed tomography of the chest with consideration of repeat testing can lead to prompt diagnosis. Surgical intervention is associated with improved survival rates.

Hui-Chen Han, MBBS, BMedSc*
Francis J. Ha, BMedSc*
Prashanthan Sanders, MBBS, PhD
Ryan Spencer, MBBS
Andrew W. Teh, MBBS, PhD
David O'Donnell, MBBS
Omar Farouque, MBBS, PhD
Han S. Lim, MBBS, PhD

*Drs Han and Ha are joint first authors.

Correspondence to: Han S. Lim, Department of Cardiology, Austin Hospital, Level 5N, 145 Studley Rd, Heidelberg 3084, Victoria, Australia. E-mail hanlimdr@gmail.com

Key Words: atrial fibrillation ■ esophageal fistula ■ safety ■ survival rate ■ treatment outcome



WHAT IS KNOWN?

- Ablation procedures for atrial fibrillation is rapidly increasing with >50 000 procedures being performed annually in the United States.
- Atrioesophageal fistula is one of the most serious complications of atrial fibrillation ablation and can be rapidly fatal.

WHAT THE STUDY ADDS?

- Fever, neurological, gastrointestinal, and cardiac symptoms are the most common clinical presentations for atrioesophageal fistula.
- Atrioesophageal fistula can present ≤2 months post-atrial fibrillation ablation.
- Contrast-enhanced computed tomography of the chest is the diagnostic modality of choice.
- Surgical intervention is superior to endoscopic intervention and conservative management.

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder in clinical practice worldwide. The estimated prevalence of individuals with AF globally was 33.5 million in 2010, and the estimated incidence was close to 5 million new AF cases per year, with the highest incidence rates estimated in North America.[1,2] Catheter ablation is increasingly being used to treat patients with AF worldwide.[3,4] From the Nationwide Inpatient Sample in the United States, the number of catheter ablation procedures for AF increased from 3367 in the year 2000 to 12 006 in the year 2010.[5] Currently, ≈50 000 catheter ablation procedures for AF occur annually in the United States.[6] A significant association has been demonstrated between adverse outcomes related to AF ablation and operator and hospital volume.[5]

The periprocedural complication rate for percutaneous AF ablation is estimated at 5%.[7] Atrioesophageal fistula (AEF) is one of the most serious complications of AF ablation. While estimated at 0.03% to 0.08%,[8,9] the incidence may be underestimated because of under-reporting or misdiagnosis. Furthermore, it is rapidly fatal without intervention.[10] Since the first published case in 2001,[11] numerous case reports and case series have reported this dire complication in surgical and percutaneous approaches and in various ablation techniques, including radiofrequency, cryoballoon, and high-intensity focused ultrasound (HIFU).[10,12–14] There is a need to improve safety measures in AF ablation and increase awareness in the management of its associated serious complications. This review aims to systematically evaluate all cases of AEF reported in the literature to date, focusing on patient and procedural characteristics, the clinical presentation, diagnostic workup, treatment received, and survival outcome.

METHODS

Literature Search

We conducted a literature search of PubMed and Embase on January 1, 2017, using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15] PubMed search terms were ("atrioesophageal fistula") OR ("atrial-esophageal fistula") OR ("esophageal fistula" AND "catheter ablation") OR ("esophageal fistula" AND

"radiofrequency ablation"). Embase search terms were ("catheter ablation" OR "radiofrequency ablation") AND ("esophagus fistula"). Both searches included the spellings of "esophagus" and "oesophagus". Titles and abstracts were screened for relevance by 2 reviewers (Dr Han and F.J. Ha), and bibliographies of all included publications were screened to identify further references. Eighty-five articles met our inclusion criteria. Details of the search algorithm are shown in Figure 1. A list of all included studies is presented in Table I in the Data Supplement.

Inclusion Criteria

Study characteristics deemed eligible for inclusion were the following: (1) patient underwent surgical or percutaneous ablation for AF, (2) documented development of AEF after procedure, and (3) published in English language. For the purposes of the study, cases of pericardio-esophageal fistula, an atypical form or potential precursor to AEF, were also included in the study. Eligible studies included case reports, case series, and prospective studies if the study characteristics fulfilled the above criteria.

Exclusion Criteria

We excluded studies in languages other than English and those published only in abstract form.

Data Extraction

Details of our data extraction are shown in the Data Supplement.

Statistical Analysis

Continuous data are presented as medians with ranges. Categorical data are presented with absolute numbers and percentages. Categorical variables were compared using Pearson's χ^2 test, while continuous variables were compared using 1-way analysis of variance. Statistical significance was established at $P<0.05$. All data were analyzed using Stata MP 15.0 (Stata Corp LP, College Station, TX).

Statistical analysis is described in detail in the Data Supplement.

RESULTS

A total of 112 cases of AEF and 8 cases of pericardio-esophageal fistula from 85 articles were identified and included in our analysis. A comprehensive list of the cases is available in Table I in the Data Supplement.

Patient Demographics

Of the 119 patients where age and sex were available, the median age was 59 years (range, 27–85 years; Figure I in the Data Supplement), and the majority of patients were male (73%; Table 1). Where reported, patients underwent ablation for both paroxysmal (48%, 35/73) and persistent AF (52%, 38/73). Presence of comorbid conditions was reported in 31 patients, most commonly hypertension (16) and coronary artery disease (8).

Procedural Characteristics

Table 2 details the procedural characteristics which were reported, including mode of ablation, procedure time, ablation time, and use of gastrointestinal protection methods.

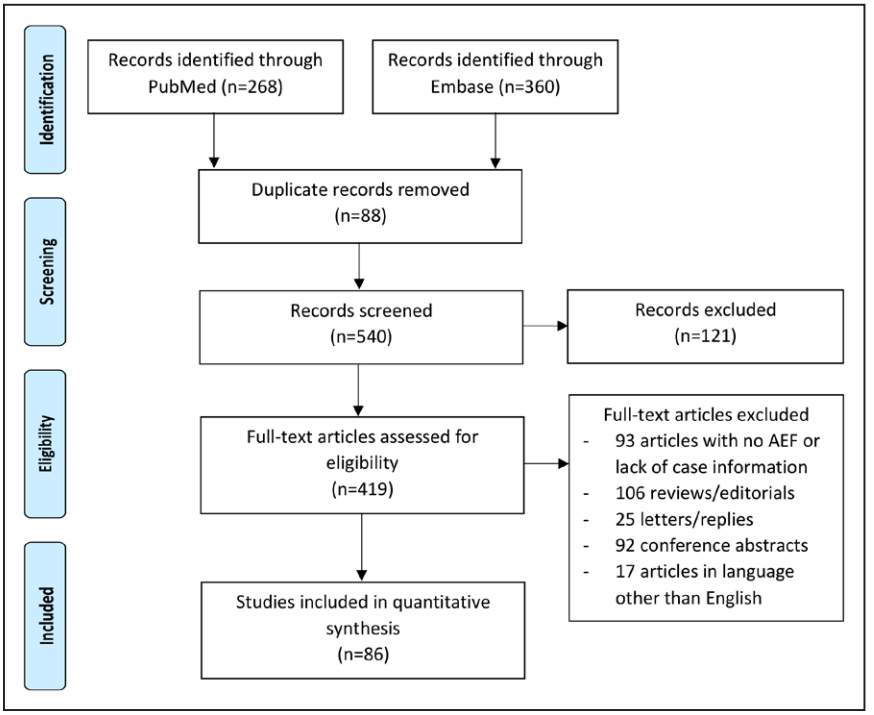


Figure 1. Search algorithm. AEF indicates atrioesophageal fistula.

Table 1. Patient Demographics

	Patient Demographics (N=120)
Age, median (range)	59 y (27–85)
Sex	
Male	87 (73%)
Female	32 (27%)
Not specified	1
Comorbidities (reported in 31 patients)	
Hypertension	16
Coronary artery disease	8
Valvular heart disease	5
Obstructive sleep apnea	3
Diabetes mellitus	3
Previous stroke	2
Chronic kidney disease	1
Chronic obstructive pulmonary disease	1
Congestive cardiac failure	2
Other	10
Nil	5
Not specified	89
Atrial fibrillation duration	
Paroxysmal	35 (48%)
Persistent	38 (52%)
Not specified	47

Percutaneous Radiofrequency Ablation

Of the 92 cases undergoing percutaneous radiofrequency ablation (RFA), total ablation time, maximum temperature settings, and maximum applied power ranged from 25 to 81 minutes (median 48.5 minutes), 33°C to 60°C (median 47°C), and 18 to 100 Watts (median 30 Watts), respectively, although this was infrequently reported. Power settings of 60, 70, 100 W were reported in 3 cases in 2004 using 8-mm-tip catheters,[16,17] while power settings of 18 W were reported with a multielectrode irrigated tip catheter (see Table 2).[18] Excluding the above cases, maximum applied power ranged between 25 and 45 Watts (n=27, median 30 Watts). Cases of AEF have also been reported using contact force catheters, with maximum power settings of 25 Watts on the posterior left atrial wall.[19]

Esophageal Protection Methods

Esophageal protection methods used in the cases are detailed in Table I in the Data Supplement and further details regarding esophageal temperature monitoring in Table II in the Data Supplement.

In cases of percutaneous RFA, the use of esophageal protection methods was reported for 31 cases. Seven cases reported esophageal temperature moni-

Table 2. Procedural Characteristics

	Procedural Characteristics
Percutaneous RF ablation	N=92
Anesthesia	
Sedation	11
General anesthesia	19
Not specified	62
Approach	
PVI	84
Presumed	50
Documented	34
Circumferential+linear ablation	8
Circumferential+linear ablation+CFAE	1
Procedural time, min (n=3)	65 (65–340)
Total ablation time, min (n=8)	48.5 (25–81)
Maximum set temperature, °C (n=14)	47 (33–60)
Maximum set power, Watts (n=32)	30 (18–100)*
Esophageal temperature monitoring	22
Maximum esophageal temperature, °C (n=14)	39 (36.4–44)
Prophylactic PPI or H2RA	24
Percutaneous cryoballoon ablation	N=12
Procedural time	NR
Ablation time, min (n=5)	48 (28–65)
Lowest temperature, °C (n=10)	–60 (–75 to –40)
Esophageal temperature monitoring	2
Esophageal temperature reported for 1 case	<20°C
Prophylactic PPI or H2RA	2
High-intensity focused ultrasound	N=2
HIFU only	1
HIFU+touch up RF	1
Ablation time, min (n=1–HIFU only)	10
Maximum set power, Watts (n=2)	42.5 (40–45)
Esophageal temperature monitoring	1 (HIFU+RF)
Max esophageal temperature, °C	39.1
Surgical procedure	N=14
Approach	
Maze	1
RF (including RF maze, PVI, PVI+linear, linear only)	11
Combined maze+cryoablation	1
Combined surgical maze+RF	1
Concurrent valve surgery	5
Procedure time, min (n=4)	167.5 (160–212)

(*Continued*)

Table 2. Continued

	Procedural Characteristics
Ablation time, min (n=4)	13.4 (9.75–22.5)
GI protection	NR

Values provided are either number of cases or median value (range) unless otherwise stated. CABG indicates coronary artery bypass graft; CFAE, complex fractionated atrial electrograms; GI, gastrointestinal; HIFU, high-intensity focused ultrasound; H2RA, H2-receptor antagonist; NR, not recorded; PPI, proton pump inhibitor; PVI, pulmonary vein isolation; and RF, radiofrequency.

*Includes 3 cases reported in 2004 using an 8-mm-tip catheter and power settings of 60, 70, and 100 Watts and 2 cases using power settings of 18 Watts with nMARQ (Biosense Webster, Irwindale, CA) catheter. Excluding these cases, median power was 30 Watts (range 25–45 Watts).

toring alone, 9 cases used prophylactic proton pump inhibitor or H2-receptor antagonist post-ablation, and 15 cases implemented both esophageal temperature monitoring and prophylactic antacid use. Seven cases reported measures to assess esophageal position during ablation, including intracardiac echocardiogram, radiopaque temperature probe (TP), and gastric tube insertion with barium contrast. Three cases reported adjusting TP position during ablation.

Cryoballoon and Other Ablation Approaches

Twelve cases of AEF were described in patients undergoing cryoballoon ablation. Lowest temperature used varied between –75°C and –40°C (median –60°C). Two cases involved esophageal temperature monitoring, with TP repositioning during the procedure and measures to assess esophageal position (intracardiac echocardiogram in one case and radiopaque TP in another).

One case used HIFU ablation only, while another used HIFU with touch-up RFA. Power settings were 45 and 40 Watts, respectively. Esophageal temperature monitoring using a radiopaque TP with intraprocedural TP repositioning was used for the case involving HIFU plus RFA.

Surgical Ablation

Of the 14 cases undergoing surgical ablation, isolated surgical ablation was reported in 9 (64%) cases, while ablation in combination with valve surgery was reported in 5 (38%) cases. Twelve (86%) surgical cases involved the use of RFA.

Clinical Presentation

The median time from ablation procedure to clinical presentation of AEF, either to a primary care physician or hospital, was 21 days (range, 0–60 days; Figure 2). The most common period for presentation was 2 to 4 weeks after procedure (42%; Figure 2 inset). At clinical presentation, fever (73%) and neurological symptoms (72%) were the most common findings, while 41% of patients had gastrointestinal symptoms (Table III in the Data Supplement and Figure 3).

Diagnostic Evaluation and Other Tests

Table 3 details the specific findings of imaging modalities used in the diagnosis of AEF. The most common

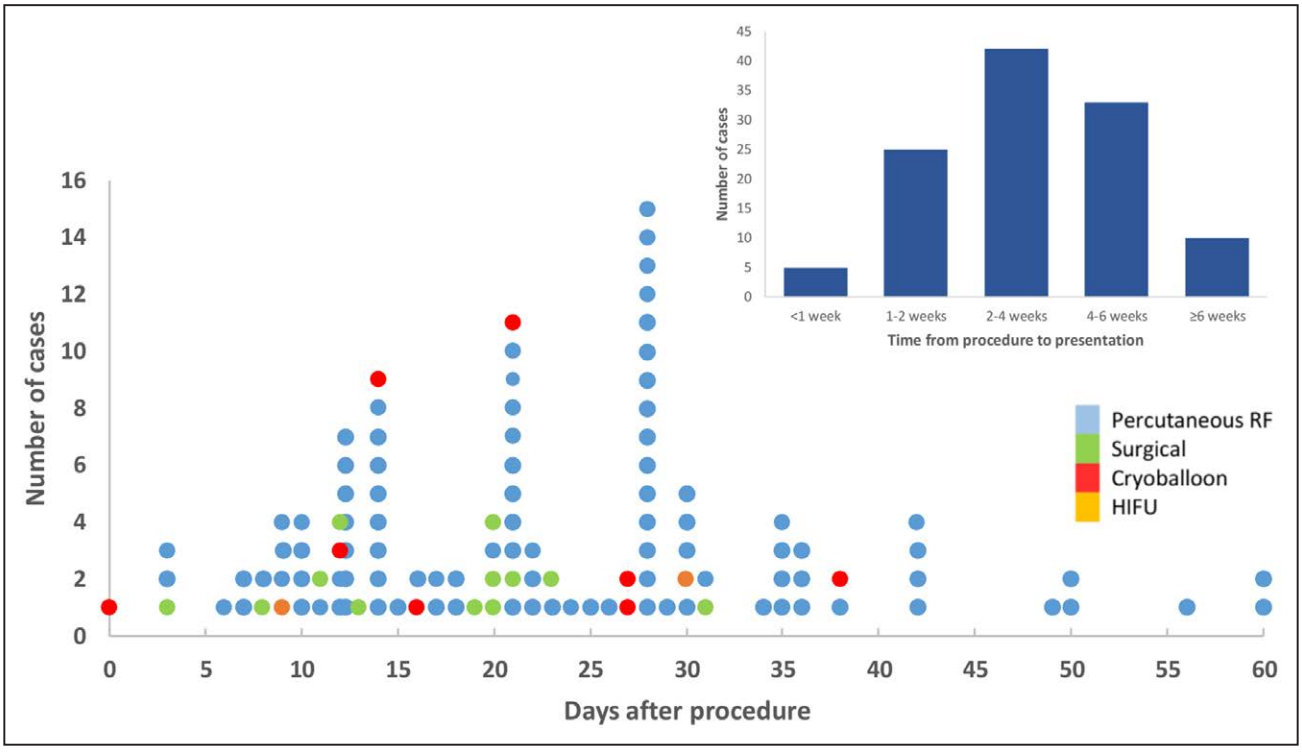


Figure 2. Time to clinical presentation.
HIFU indicates high-intensity focused ultrasound; and RF, radiofrequency.

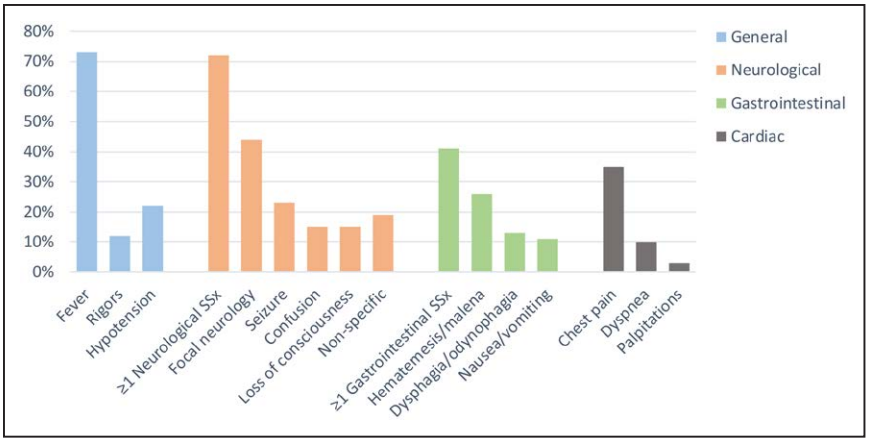


Figure 3. Clinical presentation. SSx indicates signs or symptoms.

modality for diagnosing AEF was computed tomography (CT) of the chest (68%), see Table IV in the Data Supplement.

Confirmation of Diagnosis

CT chest abnormalities were present in 95 of 97 (98%) cases. Where reported, the majority of CT scans (n=74) were performed with contrast, while 5 patients had AEF diagnosed on noncontrast CT, with findings of free air in either the left atrium or pericardium. Notably, in 7 of these cases (7%), the initial CT was reported as normal, suggesting progression of the AEF over time. In these cases, a repeat CT 4 to 12 days later (median 5 days) was required to demonstrate the abnormal findings. Initially, normal CT findings occurred with both contrast and noncontrast scans.

Cardiac magnetic resonance imaging reported abnormalities in 2 cases.

Esophagogastroduodenoscopy was attempted in 36 patients. Of the 36 patients undergoing esophagogastroduodenoscopy, 10 (28%) experienced clinical deterioration either during or shortly after the procedure. In 2 cases, the procedure resulted in immediate clinical deterioration and death. Endoscopic abnormalities were documented for 32 of 35 (91%) patients who completed the procedure. In one case, an initial esophagogastroduodenoscopy was reported as normal but a second esophagogastroduodenoscopy performed 1 day later revealed a fistulous tract.

Esophagram demonstrated contrast extravasation in 12 of 14 (86%) patients.

Echocardiography and Other Investigations

Transthoracic echocardiogram and transesophageal echocardiogram (TEE) were abnormal in 14 of 32 (44%) and 15 of 24 (63%) cases of AEF. One patient undergoing TEE developed drowsiness, aphasia, and hemiparesis a few hours post-procedure.

CT brain and magnetic resonance imaging of the brain were abnormal in 36 of 46 (78%) and 19 of 21 (90%) patients who underwent the tests, respectively. In one patient where the magnetic resonance imaging brain was reported normal, a repeat CT brain 2 weeks later demonstrated multiple intracerebral air emboli.

Electrocardiographic manifestations of AEF (Table V in the Data Supplement) can vary between nonspecific changes, to ST elevation, or cardiac arrest in the absence of ST elevation. In this series, 8 patients had ECGs, which reportedly fulfilled ST-segment–elevation myocardial infarction criteria. Five patients underwent invasive coronary angiography, with one case receiving coronary stenting and the others demonstrating no focal coronary lesions.

Pathology tests were reported infrequently and are presented in Table V in the Data Supplement. Of note, blood culture results were available for 27 patients. In 23 of these patients, ≥1 *Streptococcus* species were isolated, and 26 patients had at least one Gram-positive cocci grown in their blood culture (Table VI in the Data Supplement). Organisms reported included bacteria found in the oral cavity, such as viridans streptococci, including *S. mitis, S. oralis, S. sanguinis, S. salivarius, S. anginosus* (15 cases specified), and *Mycoplasma salivarium*, or gastrointestinal tract such as *Enterococcus* and *Candida albicans*.

The key warning signs and investigations in the diagnosis of AEF are listed in Table 4.

Treatments and Outcomes

Treatment for AEF included surgery (70 cases), endoscopic treatment (20), or noninterventional measures (30) as shown in Table 5. Noninterventional treatment included cases where patients died prior to planned intervention or cases which were diagnosed at autopsy. Baseline characteristics for the 3 treatment arms showed no significant difference in terms of age, sex, duration of AF, and ablation approach. There was a significantly higher proportion of patients with gas-

Table 3. Diagnostic Evaluation Findings

	Diagnostic Evaluation Findings		
	Reported Abnormalities	Abnormal, %	Normal or Nonspecific Changes, %
CT chest (n=97)		95 (98)*	2 (2)
	Free air (LA, mediastinum, or pericardium)	53	
	LA changes (diverticulum, thrombus, wall abnormality)	7	
	Mediastinal inflammation	1	
	Esophageal perforation (contrast extravasation)	5	
	Other esophageal changes only (thickening, ulcer)	3	
	AEF tract	11	
	AEF confirmed†	15	
MRI chest (n=2)		2 (100)	0 (0)
	Infected thrombus	1	
	Diagnosed AEF (not further specified)	1	
Endoscopy‡ (n=35)		32 (91)§	3 (9)
	Esophageal erythema or ulcer	9	
	Thrombus or active bleeding	5	
	Perforation	5	
	AEF or left atrial tissue protrusion	13	
Esophagram (n=14)		12 (86)	2 (14)
	Esophageal leak	12	
TTE (n=34)		15 (44)	19 (56)
	Echogenic material in or around LA	3	
	Pericardial effusion	5	
	Gas bubbles in the LA pneumopericardium	4	
	Pneumopericardium	1	
	Wall motion abnormalities	2	
TEE (n=24)‖		15 (63)	9 (38)
	Findings consistent with endocarditis or echogenic material present in the LA	14	
	Pericardial effusion	1	
CT brain (n=46)		36 (78)¶	10 (22)
	Focal infarcts	3	
	Multi-territory infarcts (including air emboli) Pneumocephalus or intravascular air	20	
	Pneumocephalus or intravascular air	8	
	Hemorrhagic infarct	2	
	Diffuse cerebral edema	2	
	Not reported	1	
MRI brain (n=21)		19 (90)	2 (10)
	Focal infarcts	2	
	Multi-territory infarcts (including air emboli) Pneumocephalus or intravascular air	15	
	Punctate lesions in the brain	1	
	Pneumocephalus or intravascular air	1	

AEF indicates atrioesophageal fistula; CT, computed tomography; LA, left atrium; MRI, magnetic resonance imaging; TEE, transesophageal echocardiogram; and TTE, transthoracic echocardiogram.

*Seven cases required repeat imaging to detect abnormal findings.

†In 2 case series (total 12 patients) and 3 case reports, CT chest confirmed the presence of AEF, but abnormalities were not specifically commented on.

‡Two cases were abandoned during procedure (not included in table).

§Three cases required repeat endoscopy to demonstrate AEF.

‖Intraoperative TEE showing air in the left ventricle was reported in 2 patients (not presented in table).

¶Two cases required repeat imaging to detect abnormal findings.

trointestinal bleed and a trend toward increased time to clinical presentation and presence of neurological symptoms in the conservative treatment group (Table VII in the Data Supplement).

Overall mortality in patients with AEF was 55% (Table 5). Mortality was higher in those who had non-interventional management (97%) compared with endoscopic management (65%), which was in turn significantly higher than those undergoing surgery (33%). Multivariable analysis confirmed that those undergoing noninterventional (adjusted odds ratio,

Table 4. Warning Signs and Key Investigations for AEF

Warning Signs for AEF
Presentation within 60 days of AF ablation*
Infective symptoms occur in >70%—fever, rigors
Neurological symptoms occur in >70%—focal neurology, seizures, loss of consciousness
Gastrointestinal symptoms—upper GI bleed, dysphagia/odynophagia
Cardiac—ST elevation MI with no obstructive coronary lesions, cardiac arrest
Blood culture positive for organisms from the oral cavity
Key Investigations
CT chest with contrast would be the most useful first-line test in suspected AEF
Esophagram provides an additional diagnostic modality for AEF
Endoscopy may result in rapid clinical deterioration
Consider repeat investigation in patients with clinical suspicion

AEF indicates atrioesophageal fistula; AF, atrial fibrillation; CT, computed tomography; GI, gastrointestinal; and MI, myocardial infarction.

*AEF developing >60 days post-AF ablation have not been reported in the literature.

Table 5. Treatment and Clinical Outcomes

	Survived	Deceased	*P* Value
Surgical,* n=70	46 (67)	23 (33)	
Pericardial/atrial repair only: 8†	2	3	
Esophageal surgery only: 9	7	2	
Pericardial/atrial and esophageal repair: 10†	7	2	
Pericardial and esophageal repair and muscle or pericardial flap: 22†	15	5	
Pericardial drainage only±fistula repair: 5	5	0	
Not specified: 16‡	6	9	
Endoscopic intervention alone, n=20	7 (35)	13 (65)	0.02
Stenting: 19	6	13	
Snare: 1	1	0	
Noninterventional management§, n=30	1 (3)	29 (97)	<0.001‖
Total outcomes,¶ %	54 (45)	65 (55)	

*Patients undergoing surgical intervention may have also had an endoscopic procedure.

†Aggregated reporting in one case series did not allow for further breakdown of outcomes.

‡One case which had nonspecified surgery did not report mortality outcome.

§Also involves cases where patient passed away prior to initiation of planned intervention.

‖Significant difference compared with endoscopic stenting alone (*P*=0.005).

¶Data are available for 119 cases.

24.9; 95% confidence interval [CI], 3.10–201; *P*<0.01) and endoscopic (adjusted odds ratio, 7.14; 95% CI, 1.74–29.3; *P*<0.01) management had a significantly higher mortality compared with those undergoing surgery (Table 6).

Univariable predictors of increased mortality in the overall cohort included presentation with loss of consciousness, seizure, ≥1 neurological symptom, and gastrointestinal bleed (Table VIII in the Data Supplement).

Table 6. Multivariable Predictors of Mortality

	Adjusted Odds Ratio	95% CI	*P* Value
Age	1.00	0.96–1.05	0.90
Female sex	2.91	0.65–13.1	0.16
≥1 neurological symptom	16.0	3.37–75.7	<0.001
GI bleed	4.22	1.02–17.5	0.047
Chest pain	1.01	0.32–3.18	0.98
Treatment			
Surgery	Reference		
Stent	7.14	1.74–29.3	<0.01
Noninterventional treatment	24.9	3.10–201	<0.01

CI indicates confidence interval; and GI, gastrointestinal.

Chest pain as a presenting symptom conferred favorable outcome on univariable analysis but was not significant on multivariable analysis. On multivariable analysis, independent predictors of mortality were presentation with neurological symptoms (adjusted odds ratio, 16.0; 95% CI, 3.37–75.7; *P*<0.001) and gastrointestinal bleed (adjusted odds ratio, 4.22; 95% CI, 1.02–17.5; *P*=0.047; Table 6). Within the group undergoing surgery, the presence of any neurological symptoms (adjusted odds ratio, 11.2; 95% CI, 3.32–37.8; *P*<0.001) or gastrointestinal bleed (adjusted odds ratio, 5.96; 95% CI, 1.78–20.0; *P*<0.01) was associated with a higher mortality (Table IX in the Data Supplement).

Of the 54 patients who survived, 9 (17%) were noted to have made a complete recovery, 19 (35%) were reported to have minimal deficits or made significant improvements, 10 (19%) had ongoing significant deficits or were still in the early stages of recovery, and 16 (30%) had unreported functional status (Table X in the Data Supplement).

DISCUSSION

Main Findings

This comprehensive review of all cases of AEF after AF ablation published to date demonstrates the following key findings:

1. AEF was reported to occur with various ablation modalities, including RFA, cryoablation, HIFU, surgical ablation (radiofrequency and cryoablation), and can occur despite current esophageal protection methods.
2. The most common time to presentation of AEF is 2 to 4 weeks post-procedure but can occur up to 2 months post-ablation.
3. Fever and neurological symptoms are the most common clinical presentations.
4. CT chest (with contrast) is the diagnostic modality of choice; however, repeat testing may be required for eventual diagnosis. In contrast, urgent endoscopy in these patients may result in clinical deterioration.
5. Mortality is extremely high with conservative management (odds ratio, 24.9), and prompt surgical intervention offers the best chance of survival.
6. Multivariable predictors of mortality include presentation with neurological symptoms and gastrointestinal bleed.

Patient Demographics and Procedural Characteristics

In this review, the reported baseline patient demographics were varied but in keeping with patients from

previous series of AF ablation in regard to age, sex, and type of AF.[20] Notably, there was significant underreporting of both patient and procedural characteristics in the published literature, which did not allow for significant trends to be identified.

Percutaneous RFA was the most common procedure reported, although this likely reflects higher volumes of this procedural approach.

Preventative Measures for AEF

In patients undergoing percutaneous RFA for AF, use of general anesthesia, ablation time, temperature and power settings, and ablation over the posterior wall[21] are hypothesized as potential contributors to the development of AEF. There was limited reporting of procedural characteristics in the studies. However, of note, even maximum power settings of 25 Watts in the posterior wall with the use of contact force catheters[19] can still be associated with AEF. Furthermore, only 9 out of the 92 cases of percutaneous RFA (10%) documented additional linear ablation or use of CFAE, indicating that even the standard approach with pulmonary vein isolation is not immune to the development of AEF.

Advancements in ablation technology, including the use of phased RF energy[22] and use of remote magnetic navigation,[23] may offer improvements in preventing esophageal injury, although further experience is required. Additionally, the absence of recognized AEF in remote magnetic navigation cases may suggest that the mechanism of AEF formation is related to time-dependent heating of the esophagus.[9]

Suggested preventative measures for AEF include esophageal temperature monitoring protocols,[24] esophageal cooling,[25] posterior displacement of the esophagus with the TEE probe,[26] and prophylactic proton pump inhibitor use.[27] The effectiveness of these esophageal protection strategies remains uncertain,[28] and the occurrence of AEF in cases adopting these strategies demonstrate that AEF prevention cannot be guaranteed. Additionally, there is a suggestion that use of luminal esophageal temperature monitoring probe may contribute to thermal effects on the esophagus during AF ablation.[22] Further investigation of measures to prevent AEF is warranted, although clinical vigilance in the postoperative period will remain an important strategy.

Clinical Presentation of AEF

The time from procedure to clinical presentation of AEF is highly varied. Although we found a median time of 21 days, this ranged from the evening of the procedure (0 days) in 1 case and up to 60 days in another 2 cases. Clinical suspicion of AEF should persist for at least the first 2 months post-AF ablation in the context of relevant signs and symptoms.

Clinicians should also recognize the wide presentations of AEF. Over 70% of patients with AEF developed infective symptoms. AEF should be excluded in patients developing fever, rigors even in the absence of fever,[29] or blood cultures which are positive for organisms from the oral cavity after an AF ablation.

Diagnosis of AEF in patients with neurological changes is made more difficult because of the inherent thromboembolic stroke risk of patients in AF.[30] The periprocedural risk for stroke or transient ischemic attack post-AF ablation procedure is ≈1%,[31] and may be exacerbated by a prothrombotic response.[32] However, the presence of neurological deficits post-AF ablation should also raise suspicions about the development of an AEF.

Patients who experience upper gastrointestinal bleeding or odynophagia/dysphagia post-AF ablation should receive prompt workup to exclude the presence of AEF. In patients with upper gastrointestinal bleeding, this is particularly important because of the high mortality associated with this presentation.

Patients presenting with cardiac symptoms had a trend toward lower mortality (43%) compared with the overall mortality. We hypothesize that these patients with cardiac symptoms were brought to the attention of the cardiologist or cardiac surgeon performing the procedure earlier on who may have been more aware of the potential for AEF, leading to an earlier diagnosis.

The varying nature of clinical presentations of AEF can potentially lead to a delay in diagnosis. Predominant symptoms of fever, neurological changes, or gastrointestinal changes may result in patients being initially treated by various medical specialties other than cardiology. Awareness of the variable clinical presentations of AEF post-AF ablation is paramount not only for cardiologists and cardiothoracic surgeons performing these procedures, but also the wider medical community, such as emergency and family physicians. The early diagnosis of this condition may allow for interventions prior to the patient developing significant circulatory compromise or long-term neurological sequelae.

Diagnostic Evaluation of AEF

Prompt radiological diagnosis is critical in patients presenting with the above constellation of symptoms.

In cases where CT chest or CT angiogram information was reported, 95 out of 97 (98%) cases demonstrated abnormalities. In 7 of these cases (7%), an initial CT was reportedly normal and a repeat CT performed 4 to 12 days later was needed to establish the diagnosis, indicating the importance of repeat imaging in cases with high clinical suspicion. Based on the above findings, we suggest CT chest with contrast should be the

initial investigation in all patients with suspected AEF, with consideration of repeat CT depending on clinical suspicion.

In the 14 reported cases where esophagram was performed, abnormalities were demonstrated in 12 (86%) cases. Additionally, in 1 of these cases, contrast extravasation was seen on esophagram despite an initially normal CT, with subsequent CT scans being abnormal but nondiagnostic.[33]

The role of endoscopy in the diagnosis of AEF remains uncertain. Routine endoscopy,[34] capsule endoscopy,[35] and endoscopy with endoscopic sonography[36] post-AF ablation have been investigated. Studies have demonstrated reversible mucosal changes in the esophagus post-AF ablation[34,35] and reversible peri-esophageal changes evident on endoscopic sonography.[36] Similar esophageal thermal injury has also been demonstrated in patients undergoing cryoballoon ablation for AF.[37] However, once an AEF is suspected on clinical grounds, endoscopy should be avoided because of the potential for air embolization during esophageal insufflation. In 2 cases, endoscopy resulted in immediate clinical deterioration and death.[38,39] In the setting of an acute gastrointestinal bleed, this can be a challenging management issue. Although gastrointestinal bleeding can occur with anticoagulation use in AF in the absence of AEF, study data suggest that the incidence is ≈1% per year.[40] Thus, where a patient has acute upper gastrointestinal bleeding within 2 months of an AF ablation, AEF should be strongly considered.

Either transthoracic echocardiogram or TEE may identify features suggestive of AEF. However, cardiac imaging in AEF may be normal (56% for transthoracic echocardiogram and 38% for TEE), and TEE in a patient with AEF may also lead to clinical deterioration.[41] Echocardiographic imaging should not be a first-line investigation in cases of suspected AEF because of the significant number of false-negative scans reported in the literature.

Patients developing ST-segment–elevation myocardial infarction post-AF ablation should receive prompt evaluation and treatment for coronary artery disease. In those patients who have atypical angiographic findings in the setting of a recent AF ablation,[42] a possible diagnosis of AEF should be considered.

Treatment and Outcomes

Overall mortality in AEF was 55%, which is lower than what has been previously reported.[43] Additionally, mortality in patients undergoing some form of intervention (surgery or endoscopic management) was also lower than in previous reports.[28]

Neurological symptoms and the presence of gastrointestinal bleed were independent predictors of increased mortality in patients with AEF. Prompt diagnosis and treatment of AEF prior to the development of these symptoms may result in improved survival outcomes in cases of AEF.

Management options described for AEF include conservative approaches such as intravenous antibiotics, endoscopic esophageal stenting, and surgical intervention. From the reported literature, only 1 patient not receiving intervention survived but had significant neurological deficits.[41] Additionally, some patients died prior to the institution of any intervention.

Esophageal stenting that was offered in patients who were deemed unfit for surgical intervention improved survival when compared with noninterventional management. Surgical intervention should, however, be considered as the gold standard of therapy in all patients experiencing AEF, although the mortality in this group remains high at 33%.

Study Limitations

This is the largest systematic review of published cases of AEF after ablation to date. We provide a comprehensive insight into the heterogeneous clinical presentation, the diagnostic modalities, and their relevant abnormal findings and the need for early detection and surgery to increase survival.

However, reported information regarding clinical presentation, diagnostic evaluation, and treatment is dependent on both the reporting bias of the case authors and publication bias. Inherent in this are potential cases of missed diagnosis. Reporting bias also significantly affects our ability to comment on whether patient comorbid conditions and procedural characteristics affect the risk of developing AEF post-AF ablation. The prevalence of certain clinical presentation features may be underestimated because of reporting differences of the various case reports.

The time to clinical presentation of patients with AEF is somewhat skewed by the variable time frames specified in the case reports (eg, specific number of days versus time periods of weeks or months). Additionally, we were unable to assess the role of cardiac magnetic resonance imaging because of the low number of cases reported using this imaging modality. Finally, there is an inherent selection bias in the patient treatment from reported cases, whereby only the more stable and neurologically intact patients may be offered interventional strategies.

Conclusions

AEF is a rare complication of AF ablation but is associated with a high mortality. A diagnosis of AEF should be considered in all patients presenting with infective, neurological, cardiac, or gastrointestinal symptoms within 2 months of an AF ablation procedure. Investigation by

CT chest with consideration of repeat testing can lead to prompt diagnosis. Surgical intervention is associated with improved survival rates compared with conservative management in this serious condition.

AFFILIATIONS

From the Austin Health, Melbourne, Victoria, Australia (H.-C.H., F.J.H., R.S., A.W.T., D.O., O.F., H.S.L.); University of Melbourne, Victoria, Australia (H.-C.H., A.W.T., O.F., H.S.L.); Centre for Heart Rhythm Disorders (CHRD), South Australia Health and Medical Research Institute (SAHMRI), University of Adelaide and Royal Adelaide Hospital (P.S.); and Northern Health, Melbourne, Victoria, Australia (H.S.L.).

DISCLOSURES

Dr Lim reports having received research funding from St Jude Medical and is supported by the Neil Hamilton Farley Early Career Fellowship from the National Health and Medical Research Council of Australia. Dr Sanders reports having served on the advisory board of Biosense-Webster, Medtronic, St Jude Medical, Sanofi-Aventis and Merck, Sharpe and Dohme. Dr Sanders reports having received lecture fees from Biosense-Webster, Medtronic, St Jude Medical, Boston Scientific, Merck, Sharpe and Dohme, Biotronik and Sanofi-Aventis. Dr Sanders reports having received research funding from Medtronic, St Jude Medical, Boston Scientific, Biotronik and Sorin. The other authors report no conflicts.

FOOTNOTES

Received April 5, 2017; accepted September 7, 2017.

The Data Supplement is available at http://circep.ahajournals.org/lookup/suppl/doi:10.1161/CIRCEP.117.005579/-/DC1.

Circ Arrhythm Electrophysiol is available at http://circep.ahajournals.org.

REFERENCES

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129:837–847. doi: 10.1161/CIRCULATIONAHA.113.005119.
2. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119–125. doi: 10.1161/CIRCULATIONAHA.105.595140.
3. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2010;3:32–38. doi: 10.1161/CIRCEP.109.859116.
4. Piccini JP, Sinner MF, Greiner MA, Hammill BG, Fontes JD, Daubert JP, Ellinor PT, Hernandez AF, Walkey AJ, Heckbert SR, Benjamin EJ, Curtis LH. Outcomes of Medicare beneficiaries undergoing catheter ablation for atrial fibrillation. *Circulation*. 2012;126:2200–2207. doi: 10.1161/CIRCULATIONAHA.112.109330.
5. Deshmukh A, Patel NJ, Pant S, Shah N, Chothani A, Mehta K, Grover P, Singh V, Vallurupalli S, Savani GT, Badheka A, Tuliani T, Dabhadkar K, Dibu G, Reddy YM, Sewani A, Kowalski M, Mitrani R, Paydak H, Viles-Gonzalez JF. In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures. *Circulation*. 2013;128:2104–2112. doi: 10.1161/CIRCULATIONAHA.113.003862.
6. Freeman JV, Wang Y, Akar J, Desai N, Krumholz H. National trends in atrial fibrillation hospitalization, readmission, and mortality for medicare beneficiaries, 1999-2013. *Circulation*. 2017;135:1227–1239. doi: 10.1161/CIRCULATIONAHA.116.022388.
7. Shah RU, Freeman JV, Shilane D, Wang PJ, Go AS, Hlatky MA. Procedural complications, rehospitalizations, and repeat procedures after catheter ablation for atrial fibrillation. *J Am Coll Cardiol*. 2012;59:143–149. doi: 10.1016/j.jacc.2011.08.068.
8. Gupta A, Perera T, Ganesan A, Sullivan T, Lau DH, Roberts-Thomson KC, Brooks AG, Sanders P. Complications of catheter ablation of atrial fibrillation: a systematic review. *Circ Arrhythm Electrophysiol*. 2013;6:1082–1088. doi: 10.1161/CIRCEP.113.000768.
9. Nair KK, Shurrab M, Skanes A, Danon A, Birnie D, Morillo C, Chauhan V, Mangat I, Ayala-Paredes F, Champagne J, Nault I, Tang A, Verma A, Lashevsky I, Singh SM, Crystal E. The prevalence and risk factors for atrioesophageal fistula after percutaneous radiofrequency catheter ablation for atrial fibrillation: the Canadian experience. *J Interv Card Electrophysiol*. 2014;39:139–144. doi: 10.1007/s10840-013-9853-z.
10. Neven K, Schmidt B, Metzner A, Otomo K, Nuyens D, De Potter T, Chun KR, Ouyang F, Kuck KH. Fatal end of a safety algorithm for pulmonary vein isolation with use of high-intensity focused ultrasound. *Circ Arrhythm Electrophysiol*. 2010;3:260–265. doi: 10.1161/CIRCEP.109.922930.
11. Gillinov AM, Pettersson G, Rice TW. Esophageal injury during radiofrequency ablation for atrial fibrillation. *J Thorac Cardiovasc Surg*. 2001;122:1239–1240. doi: 10.1067/mtc.2001.118041.
12. Sonmez B, Demirsoy E, Yagan N, Unal M, Arbatli H, Sener D, Baran T, Ilkova F. A fatal complication due to radiofrequency ablation for atrial fibrillation: atrio-esophageal fistula. *Ann Thorac Surg*. 2003;76:281–283.
13. Stöckigt F, Schrickel JW, Andrié R, Lickfett L. Atrioesophageal fistula after cryoballoon pulmonary vein isolation. *J Cardiovasc Electrophysiol*. 2012;23:1254–1257. doi: 10.1111/j.1540-8167.2012.02324.x.
14. Borchert B, Lawrenz T, Hansky B, Stellbrink C. Lethal atrioesophageal fistula after pulmonary vein isolation using high-intensity focused ultrasound (HIFU). *Heart Rhythm*. 2008;5:145–148. doi: 10.1016/j.hrthm.2007.08.023.
15. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097. doi: 10.1371/journal.pmed.1000097.
16. Pappone C, Oral H, Santinelli V, Vicedomini G, Lang CC, Manguso F, Torracca L, Benussi S, Alfieri O, Hong R, Lau W, Hirata K, Shikuma N, Hall B, Morady F. Atrio-esophageal fistula as a complication of percutaneous transcatheter ablation of atrial fibrillation. *Circulation*. 2004;109:2724–2726. doi: 10.1161/01.CIR.0000131866.44650.46.
17. Scanavacca MI, D'ávila A, Parga J, Sosa E. Left atrial-esophageal fistula following radiofrequency catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2004;15:960–962. doi: 10.1046/j.1540-8167.2004.04083.x.
18. Vurma M, Dang L, Brunner-La Rocca HP, Sütsch G, Attenhofer-Jost CH, Duru F, Scharf C. Safety and efficacy of the nMARQ catheter for paroxysmal and persistent atrial fibrillation. *Europace*. 2016;18:1164–1169. doi: 10.1093/europace/euw048.
19. Gitenay E, O' Hara GE, Sarrazin JF, Nault I, Philippon F, Sadron Blaye-Felice M, Laaouaj J, Champagne J. Contact-force catheters: efficacy versus safety? Case report of 2 atrioesophageal fistulae. *J Cardiovasc Electrophysiol*. 2016;27:1483–1487. doi: 10.1111/jce.13079.
20. Dagres N, Hindricks G, Kottkamp H, Sommer P, Gaspar T, Bode K, Arya A, Husser D, Rallidis LS, Kremastinos DT, Piorkowski C. Complications of atrial fibrillation ablation in a high-volume center in 1,000 procedures: still cause for concern? *J Cardiovasc Electrophysiol*. 2009;20:1014–1019. doi: 10.1111/j.1540-8167.2009.01493.x.
21. Nair GM, Nery PB, Redpath CJ, Lam BK, Birnie DH. Atrioesophageal fistula in the era of atrial fibrillation ablation: a review. *Can J Cardiol*. 2014;30:388–395. doi: 10.1016/j.cjca.2013.12.012.
22. Deneke T, Bünz K, Bastian A, Päsler M, Anders H, Lehmann R, Meuser W, de Groot JR, Horlitz M, Haberkorn R, Mügge A, Shin DI. Utility of esophageal temperature monitoring during pulmonary vein isolation for atrial fibrillation using duty-cycled phased radiofrequency ablation.

J Cardiovasc Electrophysiol. 2011;22:255–261. doi: 10.1111/j.1540-8167.2010.01916.x.
23. Danon A, Shurrab M, Nair KM, Latcu DG, Arruda MS, Chen X, Szili-Torok T, Rossvol O, Wissner EE, Lashevsky I, Crystal E. Atrial fibrillation ablation using remote magnetic navigation and the risk of atrial-esophageal fistula: international multicenter experience. *J Interv Card Electrophysiol*. 2015;43:169–174. doi: 10.1007/s10840-015-0003-7.
24. Leite LR, Santos SN, Maia H, Henz BD, Giuseppin F, Oliverira A, Zanatta AR, Peres AK, Novakoski C, Barreto JR, Vassalo F, d'Avila A, Singh SM. Luminal esophageal temperature monitoring with a deflectable esophageal temperature probe and intracardiac echocardiography may reduce esophageal injury during atrial fibrillation ablation procedures: results of a pilot study. *Circ Arrhythm Electrophysiol*. 2011;4:149–156. doi: 10.1161/CIRCEP.110.960328.
25. Kuwahara T, Takahashi A, Okubo K, Takagi K, Yamao K, Nakashima E, Kawaguchi N, Takigawa M, Watari Y, Sugiyama T, Handa K, Kimura S, Hikita H, Sato A, Aonuma K. Oesophageal cooling with ice water does not reduce the incidence of oesophageal lesions complicating catheter ablation of atrial fibrillation: randomized controlled study. *Europace*. 2014;16:834–839. doi: 10.1093/europace/eut368.
26. Chugh A, Rubenstein J, Good E, Ebinger M, Jongnarangsin K, Fortino J, Bogun F, Pelosi F Jr, Oral H, Nostrant T, Morady F. Mechanical displacement of the esophagus in patients undergoing left atrial ablation of atrial fibrillation. *Heart Rhythm*. 2009;6:319–322. doi: 10.1016/j.hrthm.2008.12.010.
27. Zellerhoff S, Lenze F, Eckardt L. Prophylactic proton pump inhibition after atrial fibrillation ablation: is there any evidence? *Europace*. 2011;13:1219–1221. doi: 10.1093/europace/eur139.
28. Singh SM, d'Avila A, Singh SK, Stelzer P, Saad EB, Skanes A, Aryana A, Chinitz JS, Kulina R, Miller MA, Reddy VY. Clinical outcomes after repair of left atrial esophageal fistulas occurring after atrial fibrillation ablation procedures. *Heart Rhythm*. 2013;10:1591–1597. doi: 10.1016/j.hrthm.2013.08.012.
29. Kawasaki R, Gauri A, Elmouchi D, Duggal M, Bhan A. Atrioesophageal fistula complicating cryoballoon pulmonary vein isolation for paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 2014;25:787–792. doi: 10.1111/jce.12426.
30. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.
31. Di Biase L, Burkhardt JD, Mohanty P, Sanchez J, Horton R, Gallinghouse GJ, Lakkireddy D, Verma A, Khaykin Y, Hongo R, Hao S, Beheiry S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Santangeli P, Wang P, Al-Ahmad A, Patel D, Themistoclakis S, Bonso A, Rossillo A, Corrado A, Raviele A, Cummings JE, Schweikert RA, Lewis WR, Natale A. Periprocedural stroke and management of major bleeding complications in patients undergoing catheter ablation of atrial fibrillation: the impact of periprocedural therapeutic international normalized ratio. *Circulation*. 2010;121:2550–2556. doi: 10.1161/CIRCULATIONAHA.109.921320.
32. Lim HS, Schultz C, Dang J, Alasady M, Lau DH, Brooks AG, Wong CX, Roberts-Thomson KC, Young GD, Worthley MI, Sanders P, Willoughby SR. Time course of inflammation, myocardial injury, and prothrombotic response after radiofrequency catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2014;7:83–89. doi: 10.1161/CIRCEP.113.000876.
33. Grubina R, Cha YM, Bell MR, Sinak LJ, Asirvatham SJ. Pneumopericardium following radiofrequency ablation for atrial fibrillation: insights into the natural history of atrial esophageal fistula formation. *J Cardiovasc Electrophysiol*. 2010;21:1046–1049. doi: 10.1111/j.1540-8167.2010.01740.x.
34. Knopp H, Halm U, Lamberts R, Knigge I, Zachäus M, Sommer P, Richter S, Bollmann A, Hindricks G, Husser D. Incidental and ablation-induced findings during upper gastrointestinal endoscopy in patients after ablation of atrial fibrillation: a retrospective study of 425 patients. *Heart Rhythm*. 2014;11:574–578. doi: 10.1016/j.hrthm.2014.01.010.
35. Di Biase L, Saenz LC, Burkhardt DJ, Vacca M, Elayi CS, Barrett CD, Horton R, Bai R, Siu A, Fahmy TS, Patel D, Armaganijan L, Wu CT, Kai S, Ching CK, Phillips K, Schweikert RA, Cummings JE, Arruda M, Saliba WI, Dodig M, Natale A. Esophageal capsule endoscopy after radiofrequency catheter ablation for atrial fibrillation: documented higher risk of luminal esophageal damage with general anesthesia as compared with conscious sedation. *Circ Arrhythm Electrophysiol*. 2009;2:108–112. doi: 10.1161/CIRCEP.108.815266.
36. Zellerhoff S, Ullerich H, Lenze F, Meister T, Wasmer K, Mönnig G, Köbe J, Milberg P, Bittner A, Domschke W, Breithardt G, Eckardt L. Damage to the esophagus after atrial fibrillation ablation: Just the tip of the iceberg? High prevalence of mediastinal changes diagnosed by endosonography. *Circ Arrhythm Electrophysiol*. 2010;3:155–159. doi: 10.1161/CIRCEP.109.915918.
37. Fürnkranz A, Chun KR, Metzner A, Nuyens D, Schmidt B, Burchard A, Tilz R, Ouyang F, Kuck KH. Esophageal endoscopy results after pulmonary vein isolation using the single big cryoballoon technique. *J Cardiovasc Electrophysiol*. 2010;21:869–874. doi: 10.1111/j.1540-8167.2010.01739.x.
38. Doll N, Borger MA, Fabricius A, Stephan S, Gummert J, Mohr FW, Hauss J, Kottkamp H, Hindricks G. Esophageal perforation during left atrial radiofrequency ablation: Is the risk too high? *J Thorac Cardiovasc Surg*. 2003;125:836–842. doi: 10.1067/mtc.2003.165.
39. Khan MY, Siddiqui WJ, Iyer PS, Dirweesh A, Karabulut N. Left atrial to esophageal fistula: a case report and literature review. *Am J Case Rep*. 2016;17:814–818.
40. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RELY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151. doi: 10.1056/NEJMoa0905561.
41. O'Kane D, Pusalkar A, Topping W, Spooner O, Roantree E. An avoidable cause of cardioembolic stroke. *Acute Med*. 2014;13:126–128.
42. Aryana A, Arthur A, O'Neill PG, D'Avila A. Catastrophic manifestations of air embolism in a patient with atrioesophageal fistula following minimally invasive surgical ablation of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2013;24:933–934. doi: 10.1111/jce.12117.
43. Finsterer J, Stöllberger C, Pulgram T. Neurological manifestations of atrioesophageal fistulas from left atrial ablation. *Eur J Neurol*. 2011;18:1212–1219. doi: 10.1111/j.1468-1331.2011.03375.x.