How to Prevent, Detect and Manage Complications Caused by Cryoballoon Ablation of Atrial Fibrillation

Nitin Kulkarni[1], Wilber Su[2] and Richard Wu[1]

1. University of Texas Southwestern Medical Center, Dallas, TX, USA; 2. Banner University Medical Center, University of Arizona, Phoenix, AZ, USA

Abstract

Atrial fibrillation is the most common cardiac arrhythmia and the prevalence is increasing every year. Patients who fail to maintain sinus rhythm with use of anti-arrhythmic drug therapy are referred for catheter ablation. Cryoballoon (CB) ablation has emerged as an effective and alternative treatment option to traditional point-by-point radiofrequency ablation, but there can be complications. This article reviews the incidence, presentation, risk factors, management and preventative strategies of three major complications associated with CB ablation: phrenic nerve injury, atrial oesophageal fistula and bronchial injury. Although these complications are rare, electrophysiologists should institute measures to identify high-risk patients, implement best-practice techniques to minimise risks and maintain a high index of suspicion to recognise the complications quickly and implement correct treatment strategies.

Keywords

Atrial fibrillation, atrio-oesophageal fistula, bronchial injury, catheter ablation, cryoablation, cryoballoon, dosing, phrenic nerve injury

Atrial fibrillation (AF) is the most common cardiac arrhythmia and the prevalence is increasing every year; it is expected to affect 12 million Americans by the year 2030.[1] A significant portion of patients fail to maintain sinus rhythm with use of anti-arrhythmic drug therapy and are referred for catheter ablation. Ablation is currently indicated for patients with paroxysmal (class I) or persistent (class IIa) AF who are intolerant or refractory to drug therapy.[2] Cryoballoon (CB) ablation has emerged as an effective and alternative treatment option to traditional point-by-point radiofrequency (RF) ablation.[3,4] In addition to the traditional major complications associated with AF ablation – stroke, cardiac tamponade and atrial oesophageal fistula (AEF) – CB ablation is also associated with phrenic nerve and bronchial injury. Knowledge of the close anatomical relationships between the pulmonary veins, the right phrenic nerve, oesophagus and the bronchial tree is critical to understanding why these structures are prone to collateral injury during CB ablation. Additionally, techniques to minimise the cryoablation dose, such as titration of freezing time utilising a time-to-isolation (TTI) strategy, can also help minimise collateral damage and, therefore, complications.

In this article, we review the incidence, presentation, risk factors, management and preventative strategies of three major complications associated with CB ablation: phrenic nerve injury (PNI), AEF and bronchial injury (*Table 1, Table 2*).

Phrenic Nerve Injury

The incidence of PNI with CB ablation has decreased over the years, probably resulting from increased operator experience and improved techniques for early detection. In the STOP-AF trial, a randomised trial comparing drug therapy versus CB ablation utilising the first generation CB (Arctic Front™, Medtronic), the rate of PNI was noted to be 13.5 %.[5] In Freeze AF, a randomised control trial comparing first generation CB ablation versus radiofrequency ablation, 5.8 % of patients in the CB arm were noted to have phrenic nerve palsy and zero patients in the RF arm. In a single centre study of 500 consecutive patients from 2012 to 2015 who underwent CB ablation using the second generation CB, PNI was noted in 7.2 % of patients.[6] In more recently published data utilising contemporary techniques, rates of PNI appear to be lower. In the landmark FIRE AND ICE trial, in which both first and second generation CB (Arctic Front Advance™, Medtronic) were used, 3.2 % of patients experienced PNI.[3]

The anatomical relationship between the phrenic nerves and pulmonary vein anatomy is fundamental to pathogenesis of PNI. The left phrenic nerve courses anteriorly across the left atrial appendage during its descent to the diaphragm.[7] The right phrenic nerve descends parallel along the anterolateral aspect of the superior vena cava, and then courses posteriorly in between the right pulmonary veins and the superior vena cava–right atrial junction. Histological studies have shown that there may be as few as 2.1 mm (±0.4) and 7.8 mm (±1.2) of distance between the right phrenic nerve and the anterior wall of the right superior pulmonary vein and the right inferior pulmonary vein, respectively.[8] This close proximity accounts for why the PNI risk is highest during ablation of the right superior pulmonary vein. However, there are case reports of left PNI during CB ablation of the left superior pulmonary vein.[9] Multiple risk factors have been associated with the development of PNI. The common theme among these risk factors is inadvertent deep seating of the CB, which has been shown to distort pulmonary vein anatomy leading to an even shorter distance between the vein and the phrenic nerve.[10] These risk factors include:

Table 1: Overview of Cryoballoon Complications

Complication	Incidence	Mechanism	Risk Factors
Phrenic nerve injury	3.2–13.5 %[3,5,6]	• Deep seating of CB in RSPV	• Distance between RSPV and right phrenic nerve • Larger ostial vein size • Circular shape pulmonary vein ostium rather than eccentric shape • Greater obtuse angle between RSPV and LA
Atrial oesophageal fistulae	0.016–0.03 %[22,24,29,43]	• Collateral injury of oesophagus during CB ablation • Continued oesophageal injury post ablation due to acid reflux and mechanical trauma	• Low body mass index • General anaesthesia • Low nadir luminal oesophageal temperature • Longer cumulative CB ablation time (multiple and/or longer freeze applications)
Bronchial injury	1.7–3.6 %[49]	• Deep seating of CB in LSPV • Collateral injury of left mainstem bronchus during CB ablation	• Low nadir balloon temperature

CB = cryoballoon; LA = left atrium; LSPV = left superior pulmonary vein; RSPV = right superior pulmonary vein.

- the distance between the right superior pulmonary vein and right phrenic nerve as assessed on pre-operative imaging;[11]
- larger ostial vein size;[12,13]
- a more circular shape pulmonary vein ostium rather than eccentric shaped ostium;[12] and
- an obtuse angle between the right superior pulmonary vein and left atrium (i.e. minimal angulation of the vein and left atrium).[13]
  A vein with a large, circular-shaped ostium with an obtuse take off can inadvertently lead to a more deeply seated CB, and thus higher rates of PNI. Care should be taken to avoid deep seating of the CB by noting the position of the balloon relative to the cardiac silhouette – a greater portion of the CB lying outside the cardiac shadow has been associated with higher rates of PNI.[14]

Multiple methods for phrenic nerve monitoring during CB ablation have been published.[15–19] It is imperative that the patient not be under any paralytics during this portion of CB ablation. All methods use a pacing catheter to capture the phrenic nerve cranial to the site of CB ablation. Although any catheter can be used, our institution uses a deflectable multipolar catheter placed at the right brachiocephalic vein and superior vena cava junction paced at a cycle length between 1 and 2 seconds at twice the capture threshold. It is important to maintain stable catheter position since loss of capture can be mistaken as PNI during CB ablation.

During phrenic pacing, various techniques have been described to assess for impending PNI. These can be classified as a qualitative or quantitative methods. The most common qualitative method used is palpation of diaphragmatic excursion at the costal margin, with either diminishment in strength or loss of excursion considered of concern for PNI. Visualisation of diaphragmatic excursion with either fluoroscopy or intracardiac echocardiography has also been described.[16] The most well described quantitative method for assessment of PNI is the monitoring of diaphragmatic compound motor action potential (CMAP), in which diminishment in signal amplitude of CMAP considered of concern for PNI. The diaphragmatic CMAP can be recorded using a modified surface lead I[17] or a quadrapolar catheter in the hepatic vein.[18] Another objective method for phrenic nerve monitoring is the use of venous pressure waveform monitoring, in which a venous sheath is attached to a pressure transducer;[19] in this case, reduction in pressure signal amplitude is considered of concern for PNI. Although there are no prospective

Table 2: Strategies to Prevent Collateral Damage

Phrenic nerve injury
- Intra-procedural monitoring for phrenic nerve injury during phrenic nerve pacing
  - Palpation of diaphragmatic excursion at the costal margin
  - Visualisation of diaphragmatic excursion with fluoroscopy or intracardiac echocardiography
  - Monitoring of diaphragmatic compound motor action potential
  - Venous pressure waveform monitoring
- Avoid deep seating of CB in RSPV during ablation
  - Avoid positioning of CB outside cardiac silhouette on fluoroscopy
  - Utilisation of proximal seal technique

Atrial oesophageal fistulae
- Monitoring of luminal oesophageal temperature
- Avoid excessive CB ablation dose by monitoring TTI and adjusting dose accordingly
- Use of proton pump inhibitors post-procedure

Bronchial injury
- Avoid low nadir balloon temperature
- Avoid deep seating of CB in LSPV with use of proximal seal technique

CB = cryoballoon; LSPV = left superior pulmonary vein; RSPV = right superior pulmonary vein; TTI = time to isolation.

randomised control trials comparing the effectiveness of strategies, most experts agree that at least two methods should be used for phrenic nerve monitoring.[15]

If PNI is suspected, an immediate balloon deflation, rather than merely stopping refrigerant flow to the balloon, is the recommended course of action.[20] If PNI persists at the end of the case, the diagnosis is confirmed by the visualisation of an elevated hemidiaphragm on inhalation/exhalation chest X-ray. The overall prognosis for this condition is good – a majority of the patients have phrenic nerve recovery within 1 year. In a post-approval study of patients enrolled in the STOP-AF trial, fewer than 1 % of patients had persistent PNI after 12 months.[21]

The use of a 'proximal seal technique' to increase the distance between the phrenic nerve and the CB may reduce the likelihood of PNI.[22] Proximal seal is achieved by first injecting the contrast during the occlusion (*Figure 1A*). If good occlusion is observed, one should not immediately initiate ablation, but slowly relax the sheath or withdraw the catheter and allow the CB to retract until contrast leaks around the true pulmonary vein ostium (*Figure 1B*). Often, a

Figure 1: Proximal Seal Technique
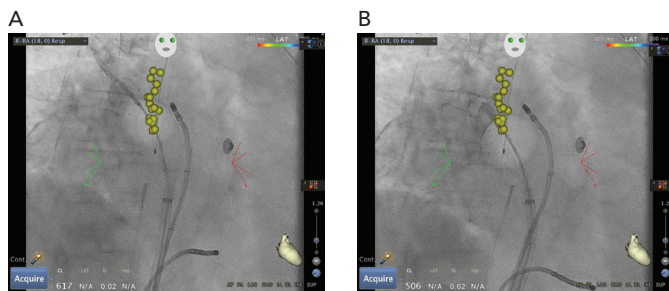
(A) After inflation of cryoballoon, contrast injected into the right superior pulmonary vein (RSPV) demonstrates location of the balloon is inside the pulmonary vein distal to the ostium. The anticipated fluoroscopic course of the phrenic nerve (PN) is annotated by yellow dots using a 3D mapping system and was identified by pacing from the superior vena cava to localise sites of PN. Cryoablation at this location increases risk of PN injury. (B) The cryoballoon is pulled back until contrast leak is observed in order to identify the pulmonary vein ostium. Minimal pressure is reapplied to the balloon to obtain occlusion of the RSPV ostium prior to ablation. Cryoablation can also be initiated just prior to re-advancing the balloon to full inflation in order to position the balloon more proximal in the PV antrum. This method increases the distance to the PN (course annotated with yellow dots) and lessens the risk of PN injury when used in combination with PN pacing and monitoring of PN function.

large right superior pulmonary vein may have a deep engagement with the CB and the initial occlusion without balloon deformation may appear ostial; however, the CB may be a few centimetres deeper than intended. Only apply the minimal amount of pressure to regain occlusion before ablation. This will also likely reduce the risk of collateral injury and ablate in the true antrum of the pulmonary vein. Multicentre experience of CB ablation using the proximal seal method combined with time-to-isolation dosing has reduced the incidence of PNI to 0.34 % when performed with monitoring of phrenic nerve function.[23]

Atrial Oesophageal Fistulae

AEF is a deadly complication of CB ablation; the mortality rate is well over 80 %.[24] Patients with AEF may present with something relatively benign, like odynophagia, or more serious clinical conditions, such as gastrointestinal bleeding, endocarditis, severe sepsis or cerebrovascular accident.[25–27] Stroke, secondary to air or food embolism, is the most common clinical presentation among patients with AEF.[24] Given the variety of clinical presentations, a high index of suspicion after recent AF ablation is needed to make a diagnosis.

The pathogenesis of AEF is related to the close proximity of the oesophagus to the posterior wall of the left atrium. However, the precise mechanism is unclear. A proposed hypothesis is that oesophageal injury during AF ablation is the triggering event, with progressive inflammation and injury resulting from swallowing and gastric reflux, leading to continued oesophageal injury, perforation, and fistulae formation.[28] The theory of oesophageal injury leading to AEF, rather than left atrial perforation, is consistent with the delayed time course of the disease. Patients appear to present approximately 19 days after ablation, with some patients presenting as early as 6 days and as late as 59 days.[29]

Fortunately, the incidence of AEF is quiet low. In a survey of 405 physicians from 2013 to 2014 who had performed a total of 191,215 AF ablations, 31 cases of AEF were reported – a rate of 0.016 %.[29] An older physician survey notes a slightly higher rate of AEF. In a survey of 585 physicians from 2004 to 2005 who had performed 20,425 AF ablations, six cases of AEF were reported – a rate of 0.03 %.[24] Of note, these rates of AEF are largely with RF ablation. The risk of AEF formation with CB

ablation is unknown but much lower, and an AEF after CB ablation is a case-reportable event.[30–33] Some authors estimate that although the risk of AEF with RF ablation is between 1:400 and 1:1000, the risk with CB ablation is 1:10,000.[22]

Despite the low incidence, given the high mortality associated with this condition, strategies to identify high-risk patients and techniques to avoid this complication are warranted. Although much of the research has been in patients who have undergone RF ablation, some of the results can be extrapolated to the CB ablation patient. In a study of 104 patients who underwent RF ablation followed by upper endoscopy within 48 hours, 9.6 % of patients were found to have asymptomatic oesophageal injury. On multiple regression analysis, the only risk factor that was significant for oesophageal injury was low body mass index.[34] Another risk factor appears to be the use of general anaesthesia. In a study of 50 patients undergoing RF ablation in which patients were randomised to general anaesthesia versus conscious sedation, the rate of oesophageal injury as assessed by capsule endoscopy was 48 % in the general anaesthesia arm and only 4 % in the conscious sedation arm.[35] The authors attributed this finding to reduced motility and peristalsis during general anaesthesia, exposing the same oesophageal tissue to RF energy.

The most common intra-procedural strategy to minimise oesophageal injury is the use of luminal oesophageal temperature (LET) monitoring, with cessation of ablation when oesophageal temperature becomes too low. However, there is no consensus of what nadir oesophageal temperature should be used as a safety cut-off. In a study of 32 patients who underwent CB ablation with the second generation catheter utilising two 240 seconds applications for each vein, the authors noted that a minimal LET of ≤12°C was associated with higher rates of oesophageal injury as assessed by postoperative upper endoscopy.[36] In a more recently published study with a larger study cohort (92 patients), the same authors found that a higher cut-off of 15°C further reduced oesophageal injury.[37] Another study utilising deflectable and non-deflectable temperature probes and a single 3-minute freeze with the second generation CB found a similar temperature cut-off (12.8°C) to decrease risk of oesophageal injury.[38] However, one study found an even lower temperature cut-off of 10°C utilising the second generation CB and two 240 s freezes.[39] It is worth noting that in all these studies, the oesophageal lesions were healing on follow-up endoscopy, and no patients developed AEF. It is thought these oesophageal ulcers or injuries are precursors to AEF. Although further studies may help to help establish a safety cut-off LET, it is important to emphasise that oesophageal ulceration or AEF may occur without a measured drop in LET.[40] We can only say that when the oesophageal temperature is low, oesophageal ulceration or injury is more likely to occur. However, when the measured oesophageal temperature is not low, it does not exclude the possibility of AEF formation.

Interestingly, the left inferior pulmonary vein appears to be the most common culprit in AEF formation after CB ablation. In a recently published case control study in which the authors obtained 11 AEF cases from the Manufacturer and User Facility Device Experience database, 10 of the cases of AEF involved the left pulmonary veins, and eight of the 10 involved the left inferior pulmonary vein.[41] The left inferior pulmonary vein often requires more posteriorly directed forces to achieve isolation. These posteriorly directed forces shorten the left atrium-to-oesophagus distance, which has been found to be a risk factor in the development of oesophageal injury.[42] Given these findings,

proceduralists should practice extra precaution when ablating the left inferior pulmonary vein.

The incidence of AEF is also related to the freezing time or cryoablation dose. The initial clinical trials used traditional 240 seconds freeze–thaw–freeze (two cycles per pulmonary vein at the same location) ablation for the first generation balloon. When the same protocol was used for the second generation CB, the highest incidence of AEF (7/30,000 reported cases) was observed.[43] After reducing the standard dosing to 180 seconds, which was based on consensus user experience, AEF is now rarely observed (1/120,000 reported cases) when using two conventional applications per pulmonary vein.[43] However, multiple consecutive applications, longer cumulative CB ablation time and higher 'dosing' for a single pulmonary vein are still considered incremental risk factors for collateral injury, including AEF.[40]

Some studies suggest adjusting CB ablation dose based on the time-to-isolation (TTI) of the pulmonary vein may reduce collateral injury or AEF. Observing the physiology of pulmonary vein isolation using an intraluminal circular mapping catheter (Achieve™, Medtronic) positioned between the left atrium and proximal pulmonary vein during CB ablation may be the most important factor in determining the permanence of pulmonary vein isolation. To better observe the pulmonary vein electrogram of interest, the circular Achieve™ can be positioned in the ostium of the pulmonary vein or prolapsed in front of the inflated CB to assess TTI. Predictors of permanent pulmonary vein isolation are a TTI of less than 30 to 60 seconds. If a rapid TTI is seen with less than 30 seconds, the total ablation time may be reduced to 150 seconds.[22]

Experimental canine data have shown that permanent pulmonary vein isolation can be reproduced with a TTI of 20 seconds, with the total ablation time of only 80 seconds.[44] Conversely, a long TTI of greater than 90 seconds with an additional 180-second freeze is generally not able to permanently isolate the vein, even though initial acute isolation was seen. Longer CB application time beyond 180 seconds will create a deeper lesion and increase the risk of collateral injury or AEF, but not improve pulmonary vein isolation efficacy. Therefore, we do not recommend increasing ablation time when acute isolation does not occur with the first CB application. If TTI does not occur within 90 seconds, we recommend stopping the application and repositioning the CB catheter to modify tissue contact, confirm pulmonary vein occlusion before freezing and aim for TTI < 60 seconds to achieve permanent pulmonary vein isolation.[22,44] Reducing application time during a repeat freeze to 150 seconds or less may be warranted due to faster temperature decline on the repeat freeze, which may also avoid deep tissue injury. Repeated ablation more than twice at the identical location or same CB catheter position should be avoided to prevent collateral injury.

Although there are no clinical data to support the use of proton pump inhibitors (PPIs) after AF ablation, most physicians prescribe a short course of these medications to reduce AEF risk.[45] Additionally, in the studies entailing endoscopic evaluations after CB ablation, most practitioners prescribed PPIs, and all patients with oesophageal injury were noted to have healing or healed lesions on follow-up.[36–38] It is a routine practice in our institution to prescribe 4 weeks of PPI since there are only minimal side effects of a short course of PPI, and we believe that the benefits outweigh the risks.

Figure 2: Cardiac Computed Tomography Scan
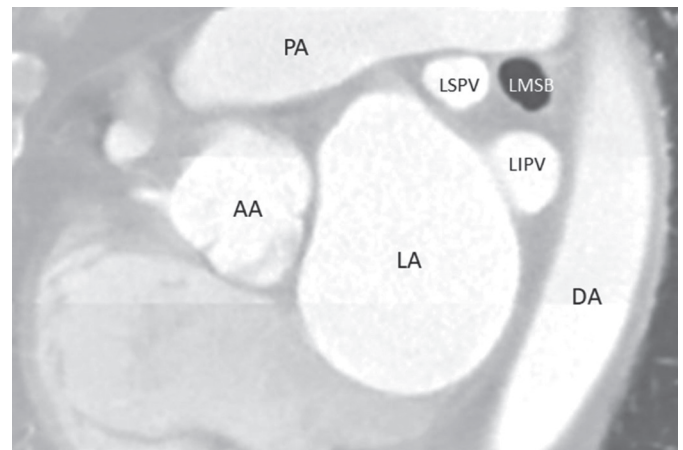
Intravenous iodinated contrast in sagittal view demonstrating the close proximity of the left superior pulmonary vein and the left main stem bronchus, a structure susceptible to collateral damage during cryoballoon ablation. AA = ascending aorta; DA = descending aorta; LA = left atrium; LIPV = left inferior pulmonary vein; LMSB = left main stem bronchus; LSPV = left superior pulmonary vein; PA = pulmonary artery.

Patients with suspected AEF require rapid evaluation and treatment. Given the lack of specific findings, a high index of suspicion is required to make a diagnosis. An upper endoscopy is absolutely contraindicated given the risk of massive air embolism after air insufflation during endoscopy.[27,45] Either computed tomography (CT) or magnetic resonance imaging (MRI) of the chest is needed to make the diagnosis when air is found in the mediastinum, pericardium or left atrium.[26,27] While oesophageal stenting is a therapeutic option, surgery offers the best chance of survival.[26,46–48]

In addition to AEF, CB ablation has been associated with various upper gastrointestinal dysmotility syndromes, including gastroesophageal reflux and gastroparesis.[49] The hypothesised mechanism is injury to the parasympathetic nerve inputs that overly the oesophagus during ablation. The exact incidence of these injuries is unknown because symptoms may be subclinical and practitioners may not have the necessary index of suspicion to make the diagnosis. In small observational studies, the incidence of gastroparesis in patients undergoing CB ablation was approximately 9–17 %.[50–52] In one study of 66 consecutive patients undergoing CB ablation, all six patients were asymptomatic and the diagnosis was made on post-procedure upper endoscopy as part of the study protocol.[51] A larger study of 144 patients who underwent upper endoscopy as per study protocol found 18 patients with gastric hypomotility, all of whom were asymptomatic.[52] Lastly, in a study of 58 patients undergoing CB ablation, the six patients who reported gastrointestinal symptoms intra-procedure had prospective evaluation to make the diagnosis and all six patients had symptomatic recovery within 2 months.[50] Further large-scale studies are warranted to identify the true incidence, develop strategies to minimise collateral risk and examine the long-term prognosis of these injuries.

Bronchial Injury

Bronchial erosion and injury is becoming recognised as another serious complication of CB ablation. Although the exact incidence is not known, small single-centre studies have reported rates of 1.7 % and 3.6 %.[53] Patients can present with a cough and production of blood tinged sputum[54,55] or frank haemoptysis.[56–58] Onset of symptoms can be variable. Patients may become symptomatic during the procedure[58] on postoperative Day 1[54,55,57] or even a day later.[56,57,59]

Although the exact mechanism of injury is not known, case reports suggest that these injuries result from extremely low nadir temperatures (–60°C or lower) and deep seating of the CB[54,56] leading to collateral thermal injury of the bronchial tree. Radiological studies have shown the close proximity of the bronchial system to the pulmonary veins, making this structure prone to injury during CB ablation (*Figure 2*).[60,61] A recently published case series of CB ablation patients who underwent real-time bronchoscopy found ice formation in the left main stem bronchus in 70 % of patients during ablation of the left superior pulmonary vein (average nadir CB temperature of –48.5°C).[62] These findings of thermal injury have been replicated in pig studies, where lower nadir temperature during CB application (–66°C vs –45°C) showed increased bronchial mucosal oedema, erythema and inflammation in post-ablation bronchoscopy.[63]

No definitive recommendations exist for the management of bronchial injury. Protocol at our institution for suspected bronchial injury entails anticoagulation reversal with protamine, urgent bronchoscopy and, at times CT of the chest to evaluate for consolidation suggestive of pulmonary haemorrhage. Bronchoscopy findings can range from mucosal petechiae,[54] bronchial wall erosion[56] to haematoma formation.[55] Lastly, cough suppressants may play a role in the management of bronchial injury.[55] Although the prognosis is not precisely known given limited data, on the basis of case reports it appears that most patients do well on follow-up.[54–57] However, rare catastrophic cases of atriobronchial fistula have been reported.[59,64]

Conclusion

Cryoballoon ablation has become a widely accepted tool for the management of atrial fibrillation. However, cryoballoon ablation can lead to collateral extra-cardiac damage, which can lead to catastrophic complications: phrenic nerve injury, atrial oesophageal fistula and bronchial injury. Although these complications are rare, electrophysiologists should institute measures to identify high-risk patients, implement best-practice techniques to minimise risks and maintain a high index of suspicion to recognise the complications quickly and implement correct treatment strategies. ∎

Clinical Perspectives

- Cryoballoon catheter ablation to achieve pulmonary vein isolation has emerged as a major technique for the treatment of atrial fibrillation.
- Atrio-oesophageal fistula, bronchial injury and phrenic nerve injury are rare but serious complications associated with cryoballoon ablation.
- Knowledge of techniques for cryoballoon catheter positioning, methods for monitoring collateral tissue injury and dosing of cryoablation time may reduce the three major complications.

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation* 2015;**131**:e29–322. DOI: 10.1161/CIR.0000000000000157; PMID: 25520374.
2. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2011;**130**:e199–267. DOI: 10.1161/CIR.0000000000000040; PMID: 24682347.
3. Kuck KH, Brugada J, Fürnkranz A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med* 2016;**374**:2235–45. DOI: 10.1056/NEJMoa1602014; PMID: 27042964.
4. Luik A, Radzewitz A, Kieser M, et al. Cryoballoon versus open irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation: the prospective, randomized, controlled, noninferiority FreezeAF Study. *Circulation* 2015;**132**:1311–9. DOI: 10.1161/CIRCULATIONAHA.115.016871; PMID: 26283655
5. Packer DL, Kowal MD, Wheelan MD, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol* 2013;**61**:1713–23. DOI: 10.1016/j.jacc.2012.11.064; PMID: 23500312.
6. Mugnai G, Asmundis C, Ciconte G, et al. Incidence and characteristics of complications in the setting of second-generation cryoballoon ablation: a large single-center study of 500 consecutive patients. *Heart Rhythm* 2015;**12**:1476–82. DOI: 10.1016/j.hrthm.2015.04.001; PMID: 25847477.
7. Sanchez-Quintana D, Ho SY, Climent V, et al. Anatomic evaluation of the left phrenic nerve relevant to epicardial and endocardial catheter ablation: implications for phrenic nerve injury. *Heart Rhythm* 2009;**6**:764–8. DOI: 10.1016/j.hrthm.2009.02.029; PMID: 19427272.
8. Sanchez-Quintana D, Cabrera JA, Climent V, et al. How close are the phrenic nerves to cardiac structures? Implications for cardiac interventionalists. *J Cardiovasc Electrophysiol* 2005;**16**:309–13. DOI: 10.1046/j.1540-8167.2005.40759.x; PMID: 15817092.
9. Andrie RP, Schrickel JW, Nickenig G, et al. Left phrenic nerve injury during cryoballoon ablation of the left superior pulmonary vein. *Pacing Clin Electrophysiol* 2012;**35**:e334–6. DOI: 10.1111/j.1540-8159.2012.03470.x; PMID: 22845556.
10. Okumura Y, Henz BD, Bunch TJ, et al. Distortion of right superior pulmonary vein anatomy by balloon catheters as a contributor to phrenic nerve injury. *J Cardiovasc Electrophysiol* 2009;**20**:1151–7. DOI: 10.1111/j.1540-8167.2009.01495.x; PMID: 19500230.
11. Wang YJ, Liu L, Zhang MC, et al. Imaging of pericardiophrenic bundles using multislice spiral computed tomography for phrenic nerve anatomy. *J Cardiovasc Electrophysiol* 2016;**27**:961–71. DOI: 10.1111/jce.13003; PMID: 27138066.
12. Ang R, Hunter RJ, Baker V, et al. Pulmonary vein measurements on pre-procedural CT/MR imaging can predict difficult pulmonary vein isolation and phrenic nerve injury during cryoballoon ablation for paroxysmal atrial fibrillation. *Int J Cardiol* 2015;**195**:253–8. DOI: 10.1016/j.ijcard.2015.05.089; PMID: 26048388.
13. Stroker E, Asmundis C, Saitoh Y, et al. Anatomic predictors of phrenic nerve injury in the setting of pulmonary vein isolation using the 28-mm second-generation cryoballoon. *Heart Rhythm* 2016;**13**:342–51. DOI: 10.1016/j.hrthm.2015.10.017; PMID: 26573972.
14. Saitoh Y, Stroker E, Irfan G, et al. Fluoroscopic position of the second-generation cryoballoon during ablation in the right superior pulmonary vein as a predictor of phrenic nerve injury. *Europace* 2016;**18**:1179–86. DOI: 10.1093/europace/euv362; PMID: 26614521.
15. Kowalski M, Ellenbogen KA, Koneru JN. Prevention of phrenic nerve injury during interventional electrophysiologic procedures. *Heart Rhythm* 2014;**11**:1839–44. DOI: 10.1016/j.hrthm.2014.06.019; PMID: 24952147.
16. Lakhani M, Saiful F, Bekheit S, et al. Use of intracardiac echocardiography for early detection of phrenic nerve injury during cryoballoon pulmonary vein isolation. *J Cardiovasc Electrophysiol* 2012;**23**:874–6. DOI: 10.1111/j.1540-8167.2012.02302.x; PMID: 22494116.
17. Lakhani M, Saiful F, Bekheit S, et al. Recordings of diaphragmatic electromyograms during cryoballoon ablation for atrial fibrillation accurately predict phrenic nerve injury. *Heart Rhythm* 2014;**11**:369–74. DOI: 10.1016/j.hrthm.2013.11.015; PMID: 24252287.
18. Franceschi F, Koutbi L, Mancini J, et al. Novel electromyographic monitoring technique for prevention of right phrenic nerve palsy during cryoballoon ablation. *Circ Arrhythm Electrophysiol* 2013;**6**:1109–14. DOI: 10.1161/CIRCEP.113.000517; PMID: 24114777.
19. Ghosh J, Singarayar S, Kabunga P, et al. Subclavian vein pacing and venous pressure waveform measurement for phrenic nerve monitoring during cryoballoon ablation of atrial fibrillation. *Europace* 2015;**17**:884–90. DOI: 10.1093/europace/euu341; PMID: 25488959.
20. Ghosh J, Sepahpour A, Chan KH, et al. Immediate balloon deflation for prevention of persistent phrenic nerve palsy during pulmonary vein isolation by balloon cryoablation. *Heart Rhythm* 2013;**10**:646–52. DOI: 10.1016/j.hrthm.2013.01.011; PMID: 23333737.
21. Knight BP, Novak P, Sangrigoli R, et al. Second generation cryoballoon ablation in paroxysmal atrial fibrillation patients: 12 month safetyand efficacy from the STOP-AF post approval study. P001-38. *Heart Rhythm* 2016;**13**:S111.
22. Su W, Kowal R, Kowalski M, et al. Best practice guide for cryoballoon ablation in atrial fibrillation: the compilation experience of more than 3000 procedures. *Heart Rhythm* 2015;**12**:1658–66. DOI: 10.1016/j.hrthm.2015.03.021; PMID: 25778428.
23. Ahmad Z, Thomas Svinarich J, Williams A, Su W. Multi-center experience in reduction of phrenic nerve injury with second generation cryoballoon ablation using the proximal seal method. Circulation 2016;134(Suppl 1): A16417.
24. Ghia KK, Chugh A, Good E, et al. A nationwide survey on the prevalence of atrioesophageal fistula after left atrial radiofrequency catheter ablation. *J Interv Card Electrophysiol* 2009;**24**:33–6. DOI: 10.1007/s10840-008-9307-1; PMID: 18836822.
25. Sorgente A, Chierchia GB, Asmundis C, et al. Complications of atrial fibrillation ablation: when prevention is better than cure. *Europace* 2011;**13**:1526–32. DOI: 10.1093/europace/eur209; PMID: 21784748.
26. Chavez P, Messerli FH, Dominguez AC, et al. Atrioesophageal fistula following ablation procedures for atrial fibrillation: systematic review of case reports. *Open Heart* 2015;**2**:e000257. DOI: 10.1136/openhrt-2015-000257; PMID: 26380098.
27. Dagres N, Kottkamp H, Piorkowski C, et al. Rapid detection and successful treatment of esophageal perforation after radiofrequency ablation of atrial fibrillation: lessons from five cases. *J Cardiovasc Electrophysiol* 2006;**17**:1213–5. DOI: 10.1111/j.1540-8167.2006.00611.x; PMID: 16987382.
28. Grubina R, Cha Y, Bell MR, et al. Pneumopericardium following radiofrequency ablation for atrial fibrillation: insights into the natural history of atrial esophageal fistula formation. *J Cardiovasc Electrophysiol* 2010;**21**:1046–9. DOI: 10.1111/j.1540-8167.2010.01740.x; PMID: 20233269.
29. Barbhaiya CR, Kumar S, John RM, et al. Global survey of esophageal and gastric injury in atrial fibrillation ablation: incidence, time to presentation, and outcomes. *J Am Coll Cardiol* 2015;**65**:1377–8. DOI: 10.1016/j.jacc.2014.12.053; PMID: 25835452.
30. Kawasaki R, Gauri A, Elmouchi D, et al. Atrioesophageal fistula complicating cryoballoon pulmonary vein isolation for paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2014;**25**:787–92. DOI: 10.1111/jce.12426; PMID: 24703427.
31. Stockigt F, Schrickel JW, Andrie R, et al. Atrioesophageal fistula after cryoballoon pulmonary vein isolation. *J Cardiovasc Electrophysiol* 2012;**23**:1254–7. DOI: 10.1111/j.1540-8167.2012.02324.x; PMID: 22486804.
32. Lim HW, Cogert GA, Cameron CS, et al. Atrioesophageal fistula during cryoballoon ablation for atrial fibrillation. *J Cardiovasc Electrophysiol* 2014;**25**:208–13. DOI: 10.1111/jce.12313; PMID: 24172231.
33. Vilades Medel D, Marti-Almor J, Serrano JM, et al. Atrioesophageal fistula secondary to pulmonary vein cryo-ablation. *Eur Heart J Cardiovasc Imaging* 2014;**15**:116. DOI: 10.1093/ehjci/jet143; PMID: 23925470.
34. Yamasaki H, Tada H, Sekiguchi Y, et al. Prevalence and characteristics of asymptomatic excessive transmural injury after radiofrequency catheter ablation of atrial fibrillation. *Heart Rhythm* 2011;**8**:826–32. DOI: 0.1016/j.hrthm.2011.01.045; PMID: 21315839.
35. Di Biase L, Saenz LC, Burkhardt DJ, et al. 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**:108–12. DOI: 10.1161/CIRCEP.108.815266; PMID: 19808454.

36. Furnkranz A, Bordignon S, Schmidt B, et al. Luminal esophageal temperature predicts esophageal lesions after second-generation cryoballoon pulmonary vein isolation. *Heart Rhythm* 2013;**10**:789–93. DOI: 10.1016/j.hrthm.2013.02.021; PMID: 23428962.

37. Furnkranz A, Bordignon S, Bohmig M, et al. Reduced incidence of esophageal lesions by luminal esophageal temperature-guided second-generation cryoballoon ablation. *Heart Rhythm* 2015;**12**:268–74. DOI: 10.1016/j.hrthm.2014.10.033; PMID: 25446159.

38. Miyazaki S, Nakamura H, Taniguchi H, et al. Esophagus-related complications during second-generation cryoballoon ablation—insight from simultaneous esophageal temperature monitoring from 2 esophageal probes. *J Cardiovasc Electrophysiol* 2016;**27**:1038–44. DOI: 10.1111/jce.13015 ; PMID: 27221011.

39. Metzner A, Burchard A, Wohlmuth P, et al. Increased incidence of esophageal thermal lesions using the second-generation 28-mm cryoballoon. *Circ Arrhythm Electrophysiol* 2013;**6**:769–75. DOI: 10.1161/CIRCEP.113.000228; PMID: 23748208.

40. Ahmed H, Neuzil P, d'Avila A, et al. The esophageal effects of cryoenergy during cryoablation for atrial fibrillation. *Heart Rhythm* 2009;**6**:962–9. DOI: 10.1016/j.hrthm.2009.03.051; PMID: 19560085.

41. John RM, Kapur S, Ellenbogen KA, et al. Atrioesophageal fistula formation with cryoballoon ablation is most commonly related to the left inferior pulmonary vein. *Heart Rhythm* 2017;**14**:184–9. DOI: 10.1016/j.hrthm.2016.10.018; PMID: 27769853.

42. Martinek M, Meyer C, Hassanein S, et al. Identification of a high-risk population for esophageal injury during radiofrequency catheter ablation of atrial fibrillation: procedural and anatomical considerations. *Heart Rhythm* 2010;**7**:1224–30. DOI: 10.1016/j.hrthm.2010.02.027; PMID: 20188859.

43. Williams AA, Al-Zubaidi M, Su W. Abstract 16411: Incidence of atrial-esophageal fistula in cryoballoon ablation for atrial fibrillation is dose dependent. *Circulation* 2016;**134**:A16411.

44. Su WK, Grassl E, Williams A, et al. Time-to-effect based cryoballoon dosing to achieve permanent pulmonary vein isolation – the first chronic study in canine model. Circulation 2006;134(Suppl 1):A20102.

45. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. *Heart Rhythm* 2012;**9**:632–96.

46. Mohanty S, Santangeli P, Mohanty P, et al. Outcomes of atrioesophageal fistula following catheter ablation of atrial fibrillation treated with surgical repair versus esophageal stenting. *J Cardiovasc Electrophysiol* 2014;**25**:579–84. DOI: 10.1111/jce.12386; PMID: 25013875.

47. Zhou B, Cen XJ, Qian LY, et al. Treatment strategy for treating atrial-esophageal fistula: esophageal stenting or surgical repair? A case report and literature review. *Medicine* 2016;**95**:e5134. DOI: 10.1097/MD.0000000000005134; PMID: 27787367.

48. Singh SM, d'Avila A, Singh SK, et al. Clinical outcomes after repair of left atrial esophageal fistulas occurring after atrial fibrillation ablation procedures. *Heart Rhythm* 2013;**10**:1591–7. DOI: 10.1016/j.hrthm.2013.08.012; PMID: 23954269.

49. Garg L, Garg J, Gupta N, et al. Gastrointestinal complications associated with catheter ablation for atrial fibrillation. *Int J Cardiol* 2016;**224**: 424–30. DOI: 10.1016/j.ijcard.2016.09.069; PMID: 27690340.

50. Aksu T, Golcuk S, Guler TE, et al. Gastroparesis as a complication of atrial fibrillation ablation. *Am J Cardiol* 2015;**116**:92–7. DOI: 10.1016/j.amjcard.2015.03.045; PMID: 25933733.

51. Guiot A, Savoure A, Godin B, et al. Collateral nervous damages after cryoballoon pulmonary vein isolation. *J Cardiovasc Electrophysiol* 2012;**23**:346–51. DOI: 10.1111/j.1540-8167.2011.02219.x; PMID: 22081875.

52. Miyazaki S, Nakamura H, Taniguchi H, et al. Gastric hypomotility after second-generation cryoballoon ablation-Unrecognized silent nerve injury after cryoballoon ablation. *Heart Rhythm* 2017;**14**:670–7. DOI: 10.1016/j.hrthm.2017.01.028; PMID: 28434448.

53. Kumar N, Timmermans C, Pison L, et al. Hemoptysis: deja vu for cryoballoon use for pulmonary vein isolation for atrial fibrillation ablation. *Chest* 2014;**145**:1435. DOI: 10.1378/chest.14-0236; PMID: 24889450.

54. Marti-Almor J, Jauregui-Abularach ME, Benito B, et al. Pulmonary hemorrhage after cryoballoon ablation for pulmonary vein isolation in the treatment of atrial fibrillation. *Chest* 2014;**145**: 156–7. DOI: 10.1378/chest.13-0761; PMID: 24394827.

55. Desai AK, Osahan DS, Undavia MB, et al. Bronchial injury post-cryoablation for atrial fibrillation. *Ann Am Thorac Soc* 2015;**12**:1103–4. DOI: 10.1513/AnnalsATS.201503-135LE; PMID: 26203613.

56. van Opstal JM, Timmermans C, Blaauw Y, et al. Bronchial erosion and hemoptysis after pulmonary vein isolation by cryoballoon ablation. *Heart Rhythm* 2011;**8**:1459. DOI: 10.1016/j.hrthm.2010.06.024; PMID: 20601153.

57. Bhagwandien R, Belle YV, deGroot N, et al. Hemoptysis after pulmonary vein isolation with a cryoballoon: an analysis of the potential etiology. *J Cardiovasc Electrophysiol* 2011;**22**:1067–9. DOI: 10.1111/j.1540-8167.2011.02031.x; PMID: 21352395.

58. Aksu T, Ebru Golcuk S, Yalin K. Haemoptysis and pulmonary haemorrhage associated with cryoballoon ablation. *Europace* 2015;**17**:1240. DOI: 10.1093/europace/euu407; PMID: 25712979

59. Cuoco F, Wharton MJ, Gold MR. Delayed formation of an atrial bronchial fistula following cryoballoon ablation for atrial fibrillation. P001-150. *Heart Rhythm* 2016.

60. Wu MH, Wongcharoen W, Tsao HM, et al. Close relationship between the bronchi and pulmonary veins: implications for the prevention of atriobronchial fistula after atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2007;**18**:1056–9. DOI: 10.1111/j.1540-8167.2007.00915.x; PMID: 17666059.

61. Li YG, Yang M, Li Y, et al. Spatial relationship between left atrial roof or superior pulmonary veins and bronchi or pulmonary arteries by dual-source computed tomography: implication for preventing injury of bronchi and pulmonary arteries during atrial fibrillation ablation. *Europace* 2011;**13**: 809–14. DOI: 10.1093/europace/eur034; PMID: 21345923.

62. Verma N, Gillespie CT, Argento AC, et al. Bronchial effects of cryoballoon ablation for atrial fibrillation. *Heart Rhythm* 2017; **14**:12–6. DOI: 10.1016/j.hrthm.2016.10.012; PMID: 28007093.

63. Aryana A, Bowers MR, Hayatdavoudi SM, et al. Impact of pulmonary vein cryoballoon ablation on bronchial injury. *J Cardiovasc Electrophysiol* 2016;**27**:861–7. DOI: 10.1111/jce.12983; PMID: 27062526.

64. Doshi RN, Cesario DA, Shivkumar K. Atriobronchial fistula formation as a devastating complication of left atrial catheter ablation for atrial fibrillation. [Abstract] *Heart Rhythm* 2006.