JAFIB®

Featured Review

Journal of Atrial Fibrillation

www. jafib.com

Acute Procedural Complications of Cryoballoon Ablation: A Comprehensive Review

Tolga Aksu [1], Kivanc Yalin [2,3], Tumer Erdem Guler [1], Serdar Bozyel [1], Christian-H. Heeger [3], Roland R. Tilz [3]

[1]Department of Cardiology, University of Health Sciences, Kocaeli Derince Training and Research Hospital, Kocaeli, Turkey.
[2]Istanbul University- Cerrahpasa, Faculty of Medicine, Department of Cardiology, Istanbul, Turkey.
[3]University Heart Center Lübeck, Medical Clinic II (Cardiology/Angiology/Intensive Care Medicine), University Hospital Schleswig-Holstein, Lübeck, Germany.

Abstract

Catheter ablation is increasingly performed for treatment of atrial fibrillation (AF). Balloon based procedures have been developed aiming at safer, easier and more effective treatment as compared to point to point ablation. In the present review article, we aimed to discuss acute procedural complications of cryoballoon ablation.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in Europe and U.S [1,2]. Despite promising improvements in the management of patients with AF, this arrhythmia remains one of the leading causes of stroke, heart failure, sudden death, and cardiovascular morbidity [3]. Once the demonstration of that the pulmonary veins (PVs) and also non-PV triggers initiates AF, catheter ablation has developed as gold standard method in selected population of patients for AF treatment [4]. CABANA trial tested whether primary catheter ablation for the elimination of AF was superior to state-of-the-art drug therapy and demonstrated that ablation is a safe and effective therapy for AF and, in some cases, is superior to drug therapy [5]. Pulmonary vein isolation (PVI) is now widely accepted as the cornerstone of AF ablation procedures. Radiofrequency based ablation techniques try to achieve this goal by "point by point" ablation; however, in the last years, the use of novel alternative ablation strategies such as cryoballoon (CB) or laserballoon is growing rapidly [6–8]. As expected, CB ablation is related to a significantly had a shorter procedure time and a non-significantly shorter fluoroscopy time compared with radiofrequency catheter ablation because the single or just a couple bonus applications are adequate for durable and complete lesions [6,7, 9]. Cryoballoon ablation technique as a single shot deviece also provides acceptable success rates in complex AF substrates such as; persistent AF, elderly patients, patients with PV abnormalities and even in patients with heart failure [10-14]. With its relatively short learning curve, use of CB has been increased. And the possible concern about the efficacy and safety of the procedure in relatively low-volume centers may be raising. Good news is that, experience does not influence long-term outcome and peri-procedural complications after cryoballoon ablation of paroxysmal AF patients [15]. In the present article, we try to comprehensively review acute procedural complications associated with CB ablation.

Key Words

Atrial fibrillation, Atrio-oesophageal fistula, Bronchial injury, Catheter ablation, Cryoablation, Cryoballoon, Phrenic nerve injury.

Corresponding Author
Tolga Aksu, MD, Associated Professor of Cardiology,
Department of Cardiology, University of Health Sciences,
Kocaeli Derince Training and Research Hospital, Kocaeli, Turkey.

Definition and classification

By definition, peri-procedural complications and complications occurring within the first 24 hours denote as acute complications. Ablation-related complications can be classified into following 4 groups according to their severity: (1) life-threatening complications; (2) severe complications; (3) moderate or minor complications; and (4) complications with unknown significance [3]. Simply, potentially fatal complications such as esophageal injury, cardiac tamponade, and periprocedural stroke are classified as life-threatening complications. Although the definition of serious complication is unclear, when life-threatening complications are removed, it seems to state the same as the definition of major complication used in previous studies. According to this classification, PV stenosis, persistent phrenic nerve palsy (PNP), vascular complications requiring transfusion or surgical intervention, and other rare complications such as mitral valve damage, cardiac conduction system damage requiring pacemaker implantation, and myocardial infarction are called as severe complications. However, there are some limitations related to this classification method. A moderate or minor complication such as femoral hematoma may convert a major complication during the course of the illnes, when it requires transfusion or surgical intervention. Contrary, most patients with significant PV stenosis and persistent PNP remain asymptomatic or have few symptoms [16,17].

In the rest of the article, acute procedural complications of CB ablation will discuss according to place of occurrence.

Complications related to vascular access site

Peripheral vascular complications are the most common complications of AF ablation regardles of used energy type [18]. The complications consist of bleeding, groin or retroperitoneal hematomas, pseudoaneurysms, arteriovenous fistulas, arterial thromboembolism, and arterial air embolism which are cumulatively reported in about 1-2% of cases [19,20]. Theoratically, the risk of access site bleeding should be more during ablation of AF than other cardiac arrhythmias due to peri-procedural anticoagulation requirement. Fortunately, the study results did not confirm this assumption and periprocedural uninterrupted oral anticoagulation therapy was found to be associated with more effective for preventing thromboembolism without any increase in incidence of bleeding complications [20,21]. Furthermore, under uninterrupted warfarine regimen with a therapeutic INR was associated with lower minor bleeding complications than bridging with heparin or LMWH [22]. During CB application, use of a special calibre delivery sheath (FlexCath Advance® Steerable Sheath, Medtronic Inc.) is needed. The sheath has a wide 12F inner and 15F outer diameters, respectively. This may be accepted as a potentially enhancing factor for the risk of vascular complications. However, larger size of the sheath does not seem to cause a serious problem in that case because the sheath is advanced via venous system. In the relevant literature, the similar vascular complication rates between CB and radiofrequency ablation confirms this reasoning [18,19].

The studies for radiofrequency ablation demonstrated that risk of vascular complications may be increased with female gender, older age, and less experienced operators [24,25]. Although similar factors were studied for CB, only female gender was found related to higher vascular complications [25-27]. Theoretically, a higher proportion of vascular access site complication in women might be associated with more, increased body mass index, more sensitive connective tissue and vascular wall or variable femoral veincourse in this population. In a Russian pilot survey, Mikhaylov et al [25] compared AF ablation results between high- and low-volume AF ablation centres. Surprisingly, a higher proportion of vascular access-site complications occured in high-volume AF ablation centres. As a potential explanation, they speculated that, in the lower-volume AF ablation centres, venous access was performed by well experienced vascular puncture operators whereas the higher-volume centres were mainly academic teaching centres, where preparations for ablation procedures were carried out by younger fellow physicians. Therefore, it should be kept in mind that operator experience is more important than volume of center to predict periferic vascular complications.

Arterial pseudoaneurysms are related to inadvertent punctures of the neighboring femoral artery during puncture of femoral vein. Mugnai et al [28] reported incidence of complications in those patients who underwent CBA for AF and the impact of novel oral anticoagulants on adverse events compared with vitamin K antagonists. The incidence of femoral pseudoaneurysms was 1.3%; 1 patient required surgical repair; 1 patient underwent percutaneous thrombin injection due to a false aneurysm; and the other 3 patients were successfully treated conservatively by compression only. Although there is no data related to CBA, ultrasound guidance during femoral puncture may be suggested to reduce this complications [29].

The great majority of bleeding and hematomas resolve spontaneously and are classified as minor complication. Any bleeding severe enough to require a blood transfusion or hematomas requiring surgical intervention is called as major bleeding and encountered in up to 1.5% of cases [30]. Arteriovenous fistula is a rare complication and should be treated surgically.

Despite various precautions to achieve complete hemostasis in a safe and effective manner, no standard approach or technique is available yet. Device-based invasive vascular closure techniques have significant cost with a risk of device failure and specific vascular complications [31]. Despite, modified figure-of-eight suture for femoral venous hemostasis has been found to be safe and time saving hemostasis method for CB procedures [32], manual compression is the most commonly used technique to achieve access site hemostasis after CB procedure. Protamine reversal of anticoagulation may be an option for veinous hemostasis during manual compression. Gurses et al.[33] studied safety and efficacy of protamine administration for reversal of heparin with manuel compression following CBA. Hospital stay was significantly shorter in patients who were administered protamine. Furthermore, all hematoma, pseudoaneurysm and arteriovenous fistula requiring surgical or interventional repair in the femoral access site were lower in patients who received protamine (1.1 %) than patients who did not (6.3%) ($p = 0.011$). In our clinic we routinely use manual compression without heparine reversal and major hematoma requiring intervention was detected in one case (2.1%)[34].

Complications related to transseptal puncture

AF ablation procedure requires transseptal puncture (TSP). In routine approach, Brockenbrough needles are used with a wide variety of sheaths to access the left atrium (LA). To understand complications related to TSP, it should be kept in mind that interatrial septum (IAS) is bordered by the ostia of the inferior vena cava, superior vena cava, coronary sinus, tricuspid septal leaflet, right atrial appendage and posterior wall folds. Therefore, only 20% of total septal area is suitable to be crossed without exiting the heart [35].

Cardiac perforation with or without tamponade is the most common acute procedural life threatening complication of TSP. The main cause is inadvertent penetration of the posterior segments. Less commonly, left atrial lateral wall, left atrial roof or left atrial appendage (LAA) may be damaged due to sudden jumping of needle across the IAS [36]. TSP guided only by fluoroscopy is complicated by tamponade in 0.1–3.2% of cases [37]. ICE or TEE provided direct visualization of the septum may offer a safer TSP, especially in atypical anatomy, a resistant/elastic septum and inexperienced operators [38-40]. As demonstrated in our recently published article, a simple deep inspiration maneuver during TSP may be a reliable and safe method after failed conventional attempts in some of these cases [41]. However, it should be kept in mind that the need for multiple punctures and intraprocedural systemic/ongoing oral anticoagulation may increase the risk or aggravate the consequences of complications. In the presence of hypotension, diaphoresis, sinus tachycardia or asystole, cardiac tamponade should be taken into account, immediately. Although the diagnosis is easily confirmed by transthoracic echocardiography, fluoroscopic reduction in the excursion of cardiac silhouette on fluoroscopy is an early diagnostic sign of cardiac tamponade during the procedure and may be used to detect impending pericardial tamponade before hemodynamic collapse[42]. Once perforation or tamponade is detected, the effect of anticoagulants (heparin or oral anticoagulant) should be reversed by using proper reversal agent such as protamine, four-factor prothrombin complex concentrate rather than fresh frozen plasma, idarucizumab, andexanet alpha or recombinant factor VIIa in addition to fluid administration[43,44]. If tamponade does not resolve with these precautions, the patient should prepare for immediate pericardiocenthesis with autologous transfusion without wasting time. Urgent cardiac surgery should be attempted in case of continuos bleeding[45].

Due to large outer diameter of the FlexCath catheter the rate of iatrogenic atrial septal defect (ASD) may be high up to 38% at 6 months, with a mean size of 5.5 mm[46]. The incidence of iatrogenic ASD has been found significantly higher in CBA compared to double transseptal conventional radiofrequency ablation[47]. Despite hemodinamically significant iatrogenic ASD has been reported previously[48], in the majority of the cases this complication is not clinically relevant and mostly does not cause any adverse events not only in acute period but also during the follow-up.

Transient inferior ST-segment elevation accompanied by profound hypotension and bradycardia has been reported in 0.3% of cases[49]. The most plausible mechanism of this phenomenon is Bezold-Jarisch–like vasovagal responsedue to the mechanical effects of puncture on the vagal network located close to the puncture site. This vagal network usually innervates the right coronary artery and leaves it vulnerable to cholinergic vasospasm [50]. However coronary embolism should be kept in mind as an alternative diagnosis in all cases. If the cause is vagal hyperactivity, it usually resolves spontaneously. In rare situations, dopamine or fast saline drip can resolve the problem without sequelae or other complications [49].

Peripheral or central embolism including silent microemboli, transient ischemic attack and stroke is usually caused by thrombus formation in the space between the needle and the dilator, if proper anticoagulation is not administered prior to or immediately following TSP. Once the TSP system reaches the LA, ACT of at least 300-350 seconds with intravenous heparin should be achieved and maintained until all the catheters are removed from the LA. According to the latest expert consensus statement on catheter and surgical ablation of AF, uninterrupted oral anticoagulation regimen is recommended with VKAs or NOACs in addition to intraprocedural heparin infusion[4].

Air embolism to the systemic circulation is another important complication during TSP. Recurrent catheter exchanges and rapid removal of catheters or dilators, deep sedation and prolonged apnea periods with deep breaths during general anesthesia, and incomplete hemostasis valves are the most commonly reported causes of air embolism[51]. All these causes inadvertent negative pressure in catheter lumen or in the LA and air passage into the left hear chamber. To avoid this devastating complication, usage of a continuous flush through a closed system is mandatory. Also, the wire and dilators should be withdrawn from the catheter gradually. Also, the syringe should be held upright during hand injections. Once the complication is happening, the target should be to prevent further air entry, reduce the volume of the air embolus, and provide haemodynamic support. Administration of high-flow oxygen therapy is usually suggested to accelerate reabsorption of the air and minimize the size of the air bubble[52]. In a recently published article, Cay et al[53] presented a case of massive coronary air embolism and discussed its acute management. Excange of large diameter FlexCath with thinner transseptal sheath, aspiration of the air through coronary artery by an aspiration catheter solved the problem in their case. Then, full patency of the vessel and complete resolution of ST segment elevations was achieved after multiple rapid suctions through the catheter.

Aortic root injury is a rare complication of TSP due to penetration of the anterior segments. Proper usage of fluoroscopy, transesophageal or intracardiac echocardiography is mandatory to avoid inadvertent aortic root needle puncture. Also, contrast injection and pressure recording after the needle has been passed septum may facilitate to recognize aortic puncture before advancing the sheath. In case of aortic puncture with needle, withdrawing of the needle slowly is reported to be safe and effective strategy[54]. If the sheath entered the aorta, the sheath should be pulled back with a wire left in the aorta in the presence of surgical standby. Once ensuring hemodynamic stabilization, the wire may also be pulled back. Careful haemodynamic and echocardiographic observation is mandatory during all these steps. Gerbode defect is a rare congenital anomaly that permits shunting from the left ventricle to the right atrium[55]. Preprocedural evaluation of IAS with echocardiography is important in terms of uncovering existence of this defect because it may cause inadvertent aortic root puncture.

Complications during ablation

Pericardial effusion is a relatively common complication of CB ablation. In a recently published study, mild and moderate pericardial effusion was detected in 78% of patients undergoing CB ablation[56]. Although the incidence of cardiac tamponade has been reported to be higher with radiofrequency energy, the incidence of pericardial effusion were similar in both energy types[57,58]. Acute pericarditis is another pericardial complication of CB ablation and may occurr in up to 4% of patients[56]. The total number of cryoapplications and the total freeze duration were significantly higher in patients with pericarditis compared with those without. In patients demonstrating altering findings such as low blood pressure, tachycardia, and narrowed pulse pressure, a transthoracic echocardiography should be performed without wasting time. Becasue the approach in cardiac tamponade is described in detail in the above section; it is not mentioned again, here.

Although published complication rates of CB2 based-PVI are relatively low and several safety algorithms have been implemented in the protocols the most frequent complication is right-sided phrenic nerve injury (PNI). PNI develops due to the close proximity to the PNs with the PVs. Although the incidence of PNI has decreased over the years due to advanced balloon and improved techniques for early detection, PNI was noted in 3.2%-7% of patients [59,60]. High incidence

Table 1: Complications of CBA.

Complication	Mechanism	Incidence	Management	How to avoid
Vascular Access site: Inguinal bleeding, hematoma, pseudoaneurism, atriovenous fistula, arterial thromboembolism, arterial air embolism	Vascular damage, inadequate hemostasis, inadvertent puncture, inadequate anticoagulation	1-2% More common in women, elderly pts, less experienced operators, high volume centers	Conservative compression, thrombin injection, surgery for pseudoaneurism, Most hematomas resolve spontaneously Surgery for AV fistula	USG guidance during puncture, Protamine reversal, figure of eight suture for hemostasis
Cardiac perforation	During TSP inadvertent posterior segment penetration, LAA, LA lateral wall injury, Aortic root injury	0.1%-3.2%	Heparine reversal, fluids, pericardiocentesis, surgery, if the sheath advanced to aorta surgery is generally needed.	ICE/TEE guidance, Deep inspiration maneuver
Iatrogenic ASD	Thick transseptal sheath	38% at 6 months	Mostly clinical nonrelevant	
Transient ST elevation	Mostly Besold Jarich like reflex, Coronary embolism	0.3%	Coronary angiogram, Dopamine, fast saline drip	Proper anticoagulation, 300-500 ACT, uninterrupted anticoagulation
Air embolism	Recurrent catheter change, rapid catheter removal, deep sedation, deep breathing, incomplete hemostatic valves		Positioning, high pressure O2, hemodynamic support, air aspiration	Proper anticoagulation, 300-500 ACT, uninterrupted anticoagulation, removal of air bubbles from catheter
TIA, Stroke	Mostly due to air embolism	Silent cerebral lesions common, clinical TIA/ Stroke less than %1	Anticoagulation, consider neurology consultation	Proper anticoagulation, 300-500 ACT, uninterrupted anticoagulation, removal of air bubbles from catheter
PNI	Anatomical relationship between right sided veins and right PN Anatomical relationship between LAA and left PN	3.2-7%	Diagnosed by fluoroscopic evaluation 1-3 days 35% recovery 1-3 months 18% recovery 0.018% persistent and symptomatic	Operator hand control CMAP
Bronchial injury hemoptisis	Thermal trauma, Catheter injury	rare	Reverse anticoagulation, mostly recurs	Avoid lower freezing temperature
Gastroparesis, esophageal injury	Periesophageal plexus or esophageal thermal injury		Gastroparesis mostly during inferior sided vein application with large balloon in small LA	Use temperature probe
PV stenosis	Large PV ostia, low freezing temperature	rare	PV angioplasty, surgery	Avoid low freezing temperature
AV block		Very rare	Careful rhythm control	
Cx arterial vasosplasm	During LAA isolation	Very rare	ECG ST elevation	
Achieve catheter breakage	Mechanical	Very rare		

of PNI after CB ablation is related to close anatomical relationship between the PNs and PV anatomy. The right PN descends posteriorly in between the right PVs and the superior vena cava–right atrial junction. Sánchez-Quintana et al [61] studied by gross dissection the courses of the right and left PNs in 6 cadavers and demonstrated that the distance between the right PN and the anterior wall of the right superior PV may be as few as 2.1±0.4 mm whereas the distance with the right inferior PV is higher (7.8 mm±1.2). As an expected result of this close proximity, the risk of PNI is highest during ablation of the right superior PV[62] however, it is not clear why PNI appears to be more common with CB compared with radiofrequency ablation [63]. One suggested mechanism implicates anatomic distortion of the PV orifice/PN relationship, through increasing contact or shortening the relative distance between the ablation site and the PN, even without displacement of the balloon into the PV[64].

Although the left PN courses anteriorly across the LAA and is far from the left PVs, there are published cases of left PNI during CB ablation of the left superior PV[65,66]. The risk may be higher during isolation of the LAA by using CB[67]. Despite this general acceptance, the incidence and prognosis of left-sided PNI during CB ablation was recently evaluated by recording the amplitude of the compound motor action potentials during the CB ablation. Premature termination of the freezing was required to avoid PNP in 1.8% of patients [68].

Following pre-operative computed tomography findings have been associated with the development of PNI: (1) shorter distance between the right superior PV and right PN; (2) larger PV dimensions; (3) Larger external angle between the right superior PV and right anterolateral wall of the LA; and (4) smaller eccentricity index (ratio of maximum over minimum ostial diameter). In a recently published study, the prevalence of right common ostium and temperature drop velocity from basal to - 20 °C were found as predictors of PNI in the multivariate analysis[69].

Additionally, type of CB has also an impact on possibility of PNI. Comparison of first and second generation of CB ablation showed significantly larger number of reversible and persistent PNI with the second-generation CB[70, 71].

The CB ablation protocol may influence the incidence of PNI. Rottner and coworkers studied to to assess the impact of different ablation protocols on the incidence and characteristics of procedural complications. Time-to effect protocol was found to be safe and effective. The observed difference in the occurrence of procedural complications between the ablation protocols is mainly driven by the higher incidence of PNI in bonus freeze and no-Bonus freeze arm.

However, distinctive risk factors for the occurrence of procedural complications could not identified, lower number and shorter length of the applied freeze-cycles in the 'time-to-effect' protocol could possibly explain the low incidence of PNI[72].

The diagnosis of PNI is usually made with evidence of diaphragmatic elevation at the chest X-ray or a paradox diaphragmatic movement in the fluoroscopy in a patient demonstrating complaints such as dyspnea, cough, or hiccups. To diagnose during CB ablation, anciently, the PN function was evaluated by direct visulation of diaphragmatic motion on fluoroscopy; however, it is the least optimal method as it exposes the patient and operator to additional radiation and may delay the diagnosis ([Figure 1], Movie 1-2). As a second method, the PN function may be evaluated by manual palpation of the patient's abdomen to monitor the excursion of the right hemidiaphragm during high amplitude pacing from the superior vena cava (Movie 3). Weakening of the diaphragmatic motion can indicate PNI. This method is easily applicable but the subjectivity associated with the measurement and respiratory variations in the diaphragmatic contraction strength can be mistaken as PNI. To provide earlier warning of PNI, novel techniques utilizing diaphragmatic compound motor action potential (CMAP) has been recently developped[73, 74]. During ablation of the right-sided PVs, CMAP recordings were obtained using two leads: a standard surface right arm ECG electrode positioned 5 cm above the xiphoid and a left arm ECG electrode positioned 16 cm along the right costal margin. The PN is paced continuously with high-output during CB application. A decrease in CMAP amplitude by 35% from baseline may predict and prevent PNI[73].

Link For Movie 1

Link For Movie 2

Link For Movie 3

Once the suspicion of PNI is determined by one of the methods described above, immediate termination of cryoenergy is the cornerstone of the prevention. If the PN function returns immediately, another CB application may attempt with condition more antral position of the balloon to be confirmed. Otherwise, ablation should be continued with radiofrequency energy. Prognosis of PNI after CBA has been investigated in a large YETI registry[74]. a total of 13693 patients received CB2 or CB3 based-PVI in 23 EP centers. A total of 596 (4.4%) of patients experienced PNI during treatment of the right superior (84%) right inferior (15%) right middle (0.3%) (and left superior (0.3%) pulmonary veins. After 1-3 months 18% of patients showed persistent PNI including 13% of patients complaining of dyspnea. After 6-12 months of follow-up including fluoroscopic evaluation PNI was persistent in 1.8% of patients while dyspnea was reported by 1.7% patients. Only 0.08% of the overall population of 13693 patients showed permanent and symptomatic PNI.

Bronchial injury is a less defined but potentially serious complication of CB ablation. While the most obvious finding is haemoptysis, cough or dyspnea may be the only complaint[75-77]. Persistent cough was reported as high as 17% in the STOP-AF Trial, and hemoptysis has been reported in 1% of cases in the cryoballoon STOP-AF Post Approval Study[75,76]. Unfortunately, the exact cause of this complication is uncertain. Although collateral thermal injury of the bronchial tree is the most widely accepted mechanism of haemoptysis, it might be related to pulmonary infarct, pulmonary haemorrhage or PV stenosis[77-79]. Also, direct damage to the tissue surrounding the PN or deeper inside the lung could be caused by catheterizing it with the guide wire or by distal inflation of the balloon. High-resolution computed tomography of the chest should be used to diagnose [Figure 2]. There is no well accepted treatment option for these cases. Although some groups suggest

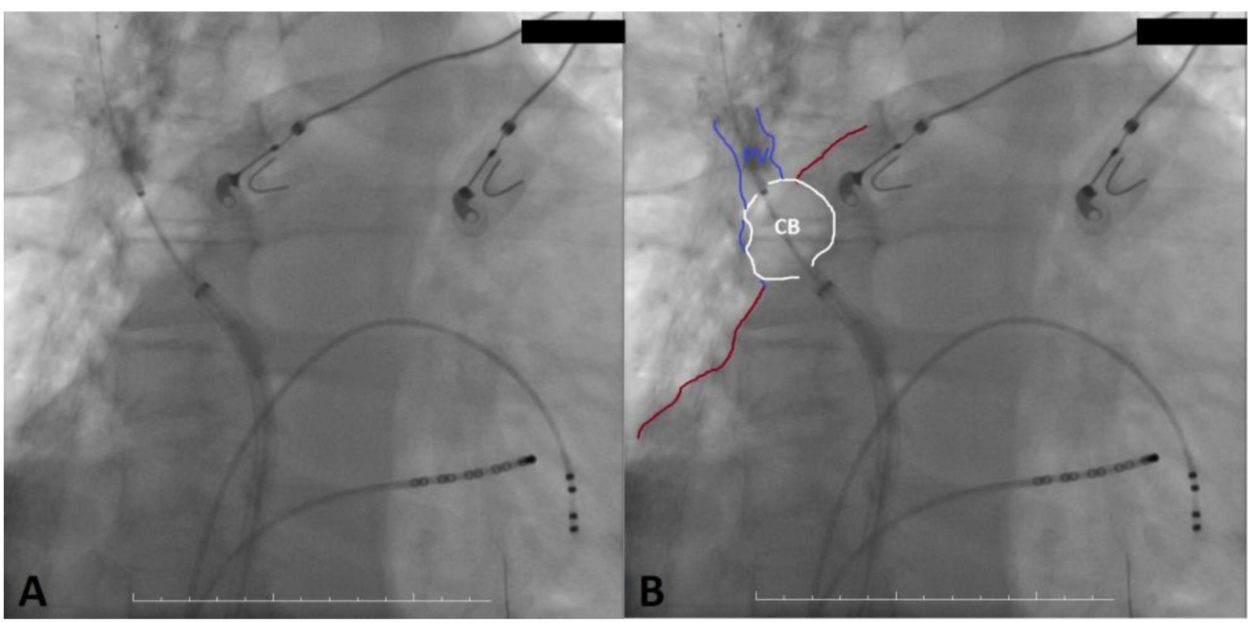

Figure 1: Deep settlement of cryoballoon catheter is seen on fluroscopy. To facilitate demonstration of catheter position and shape borders of cryoballoon, the right superior pulmonary vein, and the left atrium was drawn with White, blue, and red lines, respectively (B).

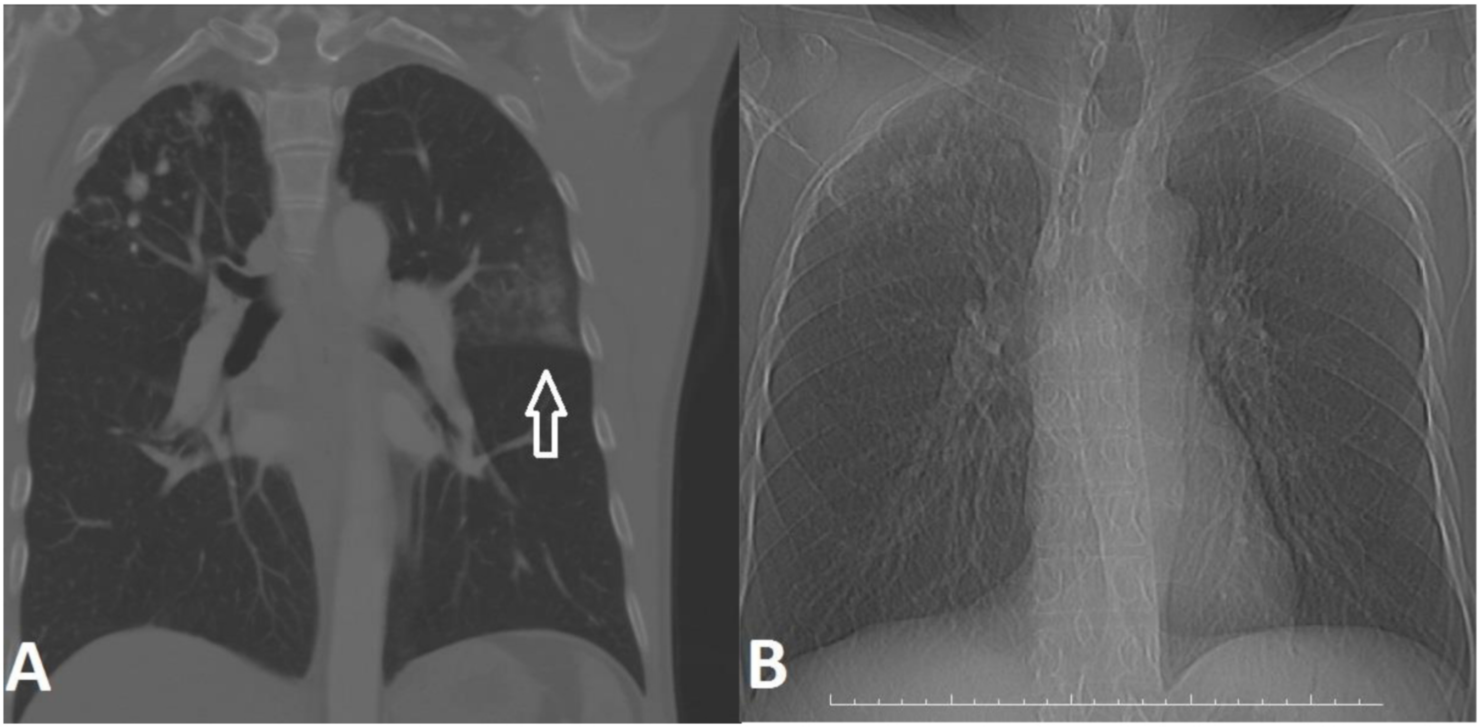

Figure 2: A The computed tomography scan of the chest demonstrates the consolidation in the left lower lobe at the superior boundary suggestive of a pulmonary haemorrhage. B Complete resolution of pulmonary haemorrhage is seen in control computed tomography 1 month later.

reversal of anticoagulation and urgent bronchoscopy, haemoptysis usually resolves spontaneously and does not reoccur after restarting anticoagulation theraphy[78-81].

Atrioesophageal fistula due to direct esophageal injury has been reported as anecdotal case reports after CB ablation[82,83]. Thus, knowledge about the clinical findings and the clinical course of the disease is derived from ablation studies using radiofrequency energy. It usually occurs within 1-4 weeks following ablation procedure with non-specific signs and symptoms such as fever, fatigue, malaise, chest discomfort, nausea, vomiting, dysphagia, odynophagia, hematemesis, melena, and dyspnea. Because the current article is dedicated to inform about acute complications of CB ablation, atrioesophageal fistula will not discuss in detail. But, in patients presenting with infection findings without a clear focus, retrosternal pain, and cerebrovascular findings, the diagnosis should be considered. The esophageal effects of CB have been studied by different groups by using endoscopy. Lower freezing temparature and lower average minimal luminal esophageal temperature was found related to higher esophageal effects and gastrointestinal complaints[84-89].

Although efficacy real-time luminal esophageal temperature monitoring by placing a temperature probe into the esophagus has not been investigated for CB ablation, the data from radiofrequency ablation suggests that it may be successful to detect a decrease in luminal esophageal temperature. There is no other well defined prevention strategy for this complication.

Gastroparesis is a relatively common but little known complications of CB ablation. The most possible mechanism of gastroparesis related with AF ablation is collateral periesophageal vagal nevre injury. Gastroparesis has been reported mostly occurring during CBA in inferior PVs with relatively larger balloon in small LA[90].

The diagnosis should be considered in the present of following symptoms: epigastric discomfort, abdominal pain, heartburn, bloating, nausea, or vomiting during the procedure. As it demonstrated in our report, all symptomatic patients may be evaluated by fluoroscopy for an air-filled stomach or air fluid level in the fundus of an enlarged fluid-filled stomach [Figure 3][90]. The patients showing these scopical findings should evaluated by gastric emptying scintigraphy (GES) to confirm the diagnosis. Although the FIRE AND ICE trial reported no instance of gastroparesis, the ratio of patients reporting symptoms that are shared with gastroparesis (abdominal pain, diabetic gastroparesis, epigastric discomfort, gastritis, impaired gastric emptying, nausea, and vomiting) was 3.2% for CB ablation and 2.1% radiofrequency ablation, respectively [91]. However, in our study gastroparesis was higher with CB ablation. Fortunately, gastroparesis had a good prognosis and resolving in all patients who received CB ablation [90].

Pulmonary vein stenosis (PVS) is a well defined and serious complication of point by point radiofrequency ablation. Evolving of ablation from osteal and segmental to wide area circumferential caused a decrease in the incidence of PVS from 20%-%30 to approximately 1%[92-95]. The incidence of PVS by CB ablation is approximately 3.1% after cryoablation with the first generation balloon[96]. The diagnosis should be considered in the patients demonstrating symptoms such

Figure 3: Fluoroscopy demonstrates the stomach which is completely full of air.

as cough, dyspnea, chest pain, and hemoptysis. The severity of PV stenosis is generally defined as mild (<50%), moderate (50–70%) or severe (>70%), according to the percentage reduction of the luminal diameter and it determines the severity of the clinical presentation[97].

In recently published studies, a larger PV ostium, lower minimum freezing temperature, and an increased number of applications per vein during CB ablation were found as independent predictors of PVS[98,99]. Although cardiac computed tomography and magnetic resonance imaging are well defined imaging modalities to diagnose, acute edema and dissection-like changes on intravascular ultrasonography might be used for early diagnosis during the procedure[100]. Although there is no an effective treatment strategy, percutaneous balloon angioplasty alone or in conjuction with stent implantation might be a potential alternative in the acute setting. However, high restenosis rish should be kept in mind in long-term follow-up[101].

Peripheral or central embolism is one of the most devastating complications of CB ablation. Theoratically, cryoenergy should be related to lower incidence of thrombus formation because it causes lower platelet and fibrin activation by preserving the endothelial layer during ablation[102,103] whereas recent studies reported similar levels of platelet activity and coagulation activation by cryoenergy and radiofrequency energy[102]. Besides symptomatic cerebral events such as transient ischemic attack or stroke, AF ablation also carries a risk of silent cerebral embolic lesions. By using pre and post-procedural cerebral magnetic resonance imaging, different groups demonstrated that new embolic lesions might be detected in up to 10% of cases after radiofrequency ablation[104,105]. A similar finding was recently demonstrated for CB ablation by using real-time transcranial doppler monitoring[106]. To reduce the incidence of asymptomatic cerebral embolism during cryoablation, the removal of air bubbles from CB in heparinized saline water with extracorporeal balloon inflation before utilization was suggested by Tokuda et al[107].

Despite high rate of silent cerebral embolic lesions, the incidence of TIA or stroke has been reported lower than 1%[108]. To decrease thromboembolic complications of ablation, uninterrupted anticoagulation strategy should be preferred compared with bridging strategies using heparin or enoxaparin regardles of used anticoagulant agent[109,110]. To reveal the presence of thrombus formation in the LAA, routine usage of transesophageal echocardiography is recommended by some authors. Although the incidence of LAA thrombus before AF ablation is low (0.6% to 2%) in patients using uniterrupted anticoagulation or bridging with low-molecular-weight heparin, it should be kept in mind that it is not 0%[111,112]. In a recently published study, dual-source cardiac-computed tomography was succesfully used to exclude thrombus formation. As a main advantage of this new modality, it may deliver additional anatomic details of PVs and LA anatomy with an acceptable radiation exposure[113]. The diagnosis of acute brain lesion can be detected by high-resolution diffusion-weighted magnetic resonance imaging [Figure 4]. Once the diagnosis is confirmed, treatment of the disease should be maintained under the supervision of a neurologist.

Transient ST-segment elevation during cryoballoon application due to coronary slow flow during CB application was firstly reported

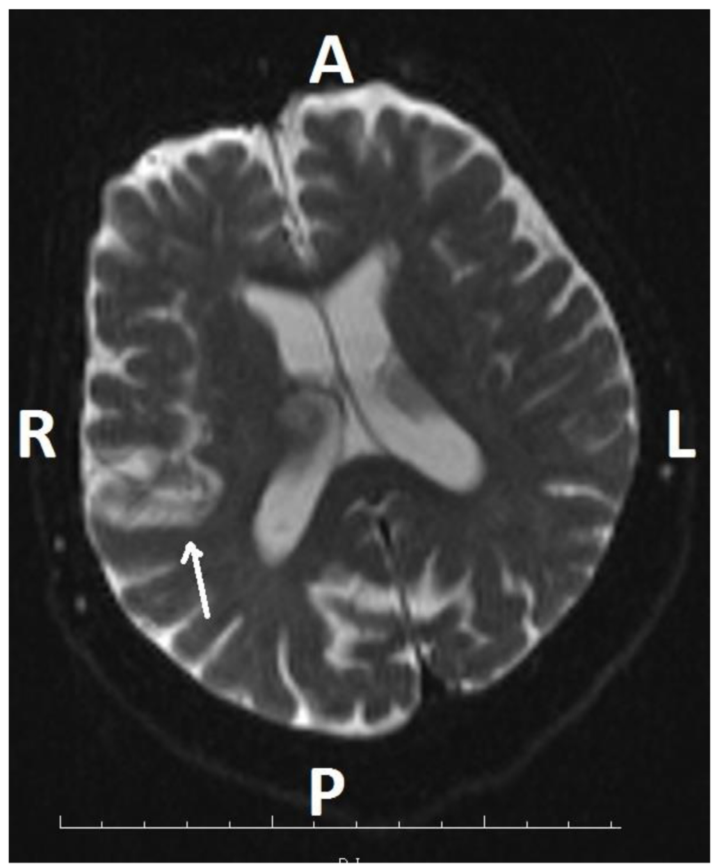

Figure 4: Acute cortical infarcts within the left parietal lobe is seen on diffusion weighted cranial magnetic resonance imaging.

by our group[114]. During the first freezing attempt in the left superior PV, at 188 seconds and -48°C, an ST-segment elevation was observed in the V1 and V6 leads, without any complaint. Coronary artery angiography was performed less than 5 minutes after balloon deflation and revealed coronary slow flow without any significant flow-limiting lesion, coronary vasospasm, thromboembolus, or air embolus. The ST-segment elevation started to decrease within 3 minutes and returned to baseline in 14 minutes, without any intervention.

Breakage of the achieve circular mapping catheter in a the right PV was recently reported by Makimoto et al[115]. As a main cause of this unique complication, authors accused the wedged position of the catheter in PV, although they had felt no grating or resistance during catheter advencement. The circular part of catheter was remained and followed-up in the right PV without any complaint.

Canpolat et al[116] recently published a case with vasospasm at the proximal segment of the circumflex artery after CB application in the LAA due to close relationship between the LAA and the the circumflex artery. After administration of intracoronary nitrate, vasospasm was rapidly relieved.

Atrioventricular block is a rare complication of CB ablation[117,118]. Atrioventricular node ischemia is hypothesized as the most probable mechanism because coronary angiography performed 30 min after atrioventricular block demonstrated a patent atrioventricular node artery originating from the right coronary artery. In the case of Fedida et al, a short distance between the RIPV ostium and aortic annulus at proximity of the AV node region showed by CT-scan reconstruction could explain mechanical AV bock during manipulation of the 28 mm cryoballoon catheter. This could be due to mechanical bump of the IAS and crux cordis, but also to left sided pathway of the AV-node. Data for comparison with CT-scan reconstruction are needed to confirm this hypothesis.

Conclusion

Cryoablation has become a commonly used tool for the management of AF due to require less experience than radiofrequency ablation without affecting effectivity. However, it can lead to some significant and even fatal acute complications. Although the ratio of these complications are rare, operators should know how to detect and manage the complications, quickly.

References

1. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 2006; 27: 949–953.
2. Colilla S, Crow A, PetkunW, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. Am J Cardiol 2013; 112: 1142–1147.
3. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016; 18: 1609-1678.
4. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Cosedis Nielsen J, Curtis AB, Davies DW, Day JD, d'Avila A, Natasja de Groot NMS, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017; 14: e275-e444.
5. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, Flaker GC, Pokushalov E, Romanov A, Bunch TJ, Noelker G, Ardashev A, Revishvili A, Wilber DJ, Cappato R, Kuck KH, Hindricks G, Davies DW, Kowey PR, Naccarelli GV, Reiffel JA, Piccini JP, Silverstein AP, Al-Khalidi HR, Lee KL; CABANA Investigators. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. JAMA. 2019 Apr 2;321(13):1261-1274
6. Kuck KH, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP, Tondo C; FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med 2016; 374: 2235–2245.
7. Luik A, Radzewitz A, Kieser M, Walter M, Bramlage P, Hörmann P, Schmidt K, Horn N, Brinkmeier-Theofanopoulou M, Kunzmann K, Riexinger T, Schymik G, Merkel M, Schmitt C. Cryoballoon versus open irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation: the prospective, randomized, controlled, noninferiority FreezeAF Study. Circulation 2015; 132: 1311–1319.
8. Reynolds MR, Zheng Q, Doros G. Laser balloon ablation for AF: A systematic review and meta-analysis. J Cardiovasc Electrophysiol 2018 Jul 17. [Epub ahead of print]
9. Ma H, Sun D, Luan H, Feng W, Zhou Y, Wu J, He C, Sun C. Efficacy and safety of cryoballoon ablation versus radiofrequency catheter ablation in atrial fibrillation: an updated meta-analysis. Postepy Kardiol Interwencyjnej 2017; 13: 240-249.
10. Guler TE, Aksu T, Yalin K, Golcuk SE, Mutluer FO, Bozyel S. Combined Cryoballoon and Radiofrequency Ablation Versus Radiofrequency Ablation Alone for Long-Standing Persistent Atrial Fibrillation. Am J Med Sci 2017; 354: 586-596.
11. Yalin K, Abdin A, Lyan E, Sawan N, Liosis S, Elsner C, Jobs A, Brüggemann B, Koester J, Eitel I, Eitel C, Tilz RR. Safety and efficacy of persistent atrial fibrillation ablation using the second-generation cryoballoon. Clin Res Cardiol. 2018 Jul;107(7):570-577
12. Abdin A, Yalin K, Lyan E, Sawan N, Liosis S, Meyer-Saraei R, Elsner C, Lange SA, Heeger CH, Eitel C, Eitel I, Tilz RR. Safety and efficacy of cryoballoon ablation for the treatment of atrial fibrillation in elderly patients. Clin Res Cardiol 2018 Sep 5.
13. Yalin K, Lyan E, Abdin A, Heeger CH, Vogler J, Liosis S, Eitel I, Meyer-Saraei R, Elsner C, Eitel C, Tilz RR. Second-generation cryoballoon for pulmonary vein isolation in patients with pulmonary vein abnormality: Safety, efficacy and lessons from re-ablation procedures. Int J Cardiol 2018 Jul 9. pii: S0167-5273(18)32846-

8.

14. Heeger CH, Abdin A, Mathew S, Reissmann B, Yalin K, Liosis S, Fink T, Proietti R, Eitel C, Vogler J, Lemeš C, Maurer T, Rillig A, Meyer-Saraei R, Graf T, Wohlmuth P, Goldmann B, Ouyang F, Kuck KH, Metzner A, Tilz RR. Efficacy and Safety of Cryoballoon Ablation in Patients With Heart Failure and Reduced Left Ventricular Ejection Fraction - A Multicenter Study. Circ J. 2019 Jul 25;83(8):1653-1659
15. Landolina M, Arena G, Iacopino S, Verlato R, Pieragnoli P, Curnis A, Lunati M, Rauhe W, Senatore G, Sciarra L, Molon G, Agricola PMG, Padeletti L, Tondo C. Center experience does not influence long-term outcome and peri-procedural complications after cryoballoon ablation of paroxysmal atrial fibrillation: Data on 860 patients from the real-world multicenter observational project. Int J Cardiol. 2018 Dec 1;272:130-136.
16. Saitoh Y, Irfan G, Ciconte G, Mugnai G, Sieira J, Di Giovanni G, Baltogiannis G, Conte G, Hünük B, Ströker E, Velagić V, Overeinder I, De Asmundis C, Chierchia GB, Brugada P. Persistence of Phrenic Nerve Palsy Following 28-mm Cryoballoon Ablation: A Four-Year Single Center Experience. Pacing Clin Electrophysiol 2015; 38: 807-814.
17. Edriss H, Denega T, Test V, Nugent K. Pulmonary vein stenosis complicating radiofrequency catheter ablation for atrial fibrillation: A literature review. Respir Med 2016; 117: 215-222.
18. Voskoboinik A, Moskovitch JT, Harel N, Sanders P, Kistler PM, Kalman JM. Revisiting pulmonary vein isolation alone for persistent atrial fibrillation: A systematic review and meta-analysis. Heart Rhythm 2017; 14: 661-667.
19. Cardoso R, Mendirichaga R, Fernandes G, Healy C, Lambrakos LK, Viles-Gonzalez JF, Goldberger JJ, Mitrani RD. Cryoballoon versus Radiofrequency Catheter Ablation in Atrial Fibrillation: A Meta-Analysis. J Cardiovasc Electrophysiol. 2016; 27: 1151-1159.
20. Di Biase L, Burkhardt JD, Santangeli P, Mohanty P, Sanchez JE, Horton R, Gallinghouse GJ, Themistoclakis S, Rossillo A, Lakkireddy D, Reddy M, Hao S, Hongo R, Beheiry S, Zagrodzky J, Rong B, Mohanty S, Elayi CS, Forleo G, Pelargonio G, Narducci ML, Dello Russo A, Casella M, Fassini G, Tondo C, Schweikert RA, Natale A. Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation(COMPARE) randomized trial. Circulation 2014; 129: 2638-2644.
21. Zhao Y, Yang Y, Tang X, et al. New oral anticoagulants compared to warfarin for perioperative anticoagulation in patients undergoing atrial fibrillation catheter ablation: a meta-analysis of continuous or interrupted new oral anticoagulants during ablation compared to interrupted or continuous warfarin. J Interv Card Electrophysiol 2017; 48: 267–282.
22. 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.
23. Baman TS, Jongnarangsin K, Chugh A, Suwanagool A, Guiot A, Madenci A, Walsh S, Ilg KJ, Gupta SK, Latchamsetty R, Bagwe S, Myles JD, Crawford T, Good E, Bogun F, Pelosi F Jr, Morady F, Oral H. Prevalence and predictors of complications of radiofrequency catheter ablation for atrial fibrillation. J Cardiovasc Electrophysiol 2011; 22: 626–631.
24. Spragg DD, Dalal D, Cheema A, Scherr D, Chilukuri K, Cheng A, Henrikson CA, Marine JE, Berger RD, Dong J, Calkins H. Complications of catheter ablation for atrial fibrillation: incidence and predictors. J Cardiovasc Electrophysiol 2008; 19: 627–631.
25. Mikhaylov EN, Lebedev DS, Pokushalov EA, Davtyan KV, Ivanitskii EA, Nechepurenko AA, Kosonogov AY, Kolunin GV, Morozov IA, Termosesov SA, Maykov EB, Khomutinin DN, Eremin SA, Mayorov IM, Romanov AB, Shabanov VV, Shatakhtsyan V, Tsivkovskii V, Revishvili ASh, Shlyakhto EV. Outcomes of Cryoballoon Ablation in High- and Low-Volume Atrial Fibrillation Ablation Centres: A Russian Pilot Survey. Biomed Res Int 2015;2015:591603. Epub 2015 Nov 12.
26. Moran D, De Regibus V, de Asmundis C, Takarada K, Mugnai G, Ströker E, Aryana A, Iacopino S, Ruggiero D, Coutiño-Moreno HE, Choudhury R, Abugattas JP, Hacioglu E, Paparella G, Brugada P, Chierchia GB. Second generation cryoballoon ablation for atrial fibrillation in young adults: midterm outcome in patients under 40 years of age. Europace 2018; 20: 295-300.
27. Abugattas JP, Iacopino S, Moran D, De Regibus V, Takarada K, Mugnai G, Ströker E, Coutiño-Moreno HE, Choudhury R, Storti C, De Greef Y, Paparella G, Brugada P, de Asmundis C, Chierchia GB. Efficacy and safety of the second generation cryoballoon ablation for the treatment of paroxysmal atrial fibrillation in patients over 75 years: a comparison with a younger cohort. Europace 2017; 19: 1798-1803.
28. Mugnai G, de Asmundis C, Iacopino S, Stroker E, Longobardi M, De Regibus V, Coutino-Moreno HE, Takarada K, Choudhury R, Abugattas de Torres JP, Storti C, Brugada P, Chierchia GB. Comparison of the Incidences of Complications After Second-Generation CryoballoonAblation of Atrial Fibrillation Using Vitamin K Antagonists Versus Novel Oral Anticoagulants. Am J Cardiol 2017; 120: 223-229.
29. Kalish J, Eslami M, Gillespie D, Schermerhorn M, Rybin D, Doros G, Farber A; Vascular Study Group of New England. Routine use of ultrasound guidance in femoral arterial access for peripheral vascular intervention decreases groin hematoma rates. J Vasc Surg 2015; 61: 1231-1238.
30. Okishige K, Nakamura T, Aoyagi H, Kawaguchi N, Yamashita M, Kurabayashi M, Suzuki H, Asano M, Shimura T, Yamauchi Y, Sasano T, Hirao K. Comparative study of hemorrhagic and ischemic complications among anticoagulants in patients undergoing cryoballoon ablation for atrial fibrillation. J Cardiol 2017; 69: 11-15.
31. Mahadevan VS, Jimeno S, Benson LN, McLaughlin PR, Horlick EM. Pre-closure of femoral venous access sites used for large-sized sheath insertion with the Perclose device in adults undergoing cardiac inter- vention. Heart. 2008;94:571-572.
32. Yorgun H, Canpolat U, Ates AH, Oksul M, Sener YZ, Akkaya F, Aytemir K. Comparison of standard vs modified "figure-of-eight" suture to achieve femoral venous hemostasis after cryoballoon based atrial fibrillation ablation. Pacing Clin Electrophysiol. 2019 Sep;42(9):1175-1182
33. Gurses KM, Kocyigit D, Yalcin MU, Evranos B, Yorgun H, Sahiner ML, Kaya EB, Oto MA, Ozer N, Aytemir K. Safety and efficacy outcomes of protamine administration for heparin reversal followingcryoballoon-based pulmonary vein isolation. J Interv Card Electrophysiol 2015; 43: 161-167.
34. Aksu T, Baysal E, Guler TE, Golcuk SE, Erden İ, Ozcan KS. Predictors of atrial fibrillation recurrence after cryoballoon ablation. J Blood Med. 2015 Jun 29;6:211-7.
35. Klimek-Piotrowska W, Hołda MK, Koziej M, Piątek K, Hołda J. Anatomy of the true interatrial septum for transseptal access to the left atrium. Ann Anat 2016; 205: 60-64.
36. O'Brien B, Zafar H, De Freitas S, Sharif F. Transseptal puncture - Review of anatomy, techniques, complications and challenges. Int J Cardiol 2017; 233: 12-22.
37. De Ponti R, Cappato R, Curnis A, Della Bella P, Padeletti L, Raviele A, Santini M, Salerno-Uriarte JA. Trans-septal catheterization in the electrophysiology

laboratory: data from a multicenter survey spanning 12 years. J Am Coll Cardiol 2006; 47: 1037-1042.
38. Bayrak F, Chierchia GB, Namdar M, Yazaki Y, Sarkozy A, de Asmundis C, Muller-Burri SA, Rao J, Ricciardi D, Sorgente A, Brugada P. Added value of transoesophageal echocardiography during transseptal puncture performed by inexperienced operators. Europace 2012; 14: 661-665.
39. Saliba W, Thomas J. Intracardiac echocardiography during catheter ablation of atrial fibrillation. Europace 2008 Nov;10 Suppl 3:iii42-7.
40. Erden İ, Erden EÇ, Golcuk E, Aksu T, Yalin K, Güler TE, Özcan KS, Turan B. Impact of transesophageal echocardiography during transseptal puncture on atrial fibrillation ablation. J Arrhythm 2016; 32: 170-175.
41. Aksu T, Guler TE, Yalin K, Golcuk SE, Ozcan KS, Guler N. A Novel Deep Inspiration Maneuver for Difficult Transseptal Puncture. Am J Cardiol 2017; 119: 428-433. [PMID: 27884419 doi: 10.1016/j.amjcard.2016.10.023].
42. Fisher JD, Krumerman AK. Tamponade detection: did you look at the heart borders (redux)? Pacing Clin Electrophysiol 2011; 34: 8.
43. Holbrook A, Schulman S, Witt DM, andvik PO, Fish J, Kovacs MJ, Svensson PJ, Veenstra DL, Crowther M, Guyatt GH. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141: e152S-e184S.
44. Ruff CT, Giugliano RP, Antman EM. Management of Bleeding With Non-Vitamin K Antagonist Oral Anticoagulants in the Era of Specific Reversal Agents. Circulation 2016;134:248-61.
45. Mujović N, Marinković M, Marković N, Kocijančić A, Kovačević V, Simić D, Ristić A, Stanković G, Miličić B, Putnik S, Vujisić-Tešić B, Potpara TS. Management and Outcome of Periprocedural Cardiac Perforation and Tamponade with Radiofrequency Catheter Ablation of Cardiac Arrhythmias: A Single Medium-Volume Center Experience. Adv Ther 2016; 33: 1782-1796.
46. Chan NY, Choy CC, Lau CL, Lo YK, Chu PS, Yuen HC, Mok NS, Tsui PT, Lau ST. Persistent iatrogenic atrial septal defect after pulmonary vein isolation by cryoballoon: an under-recognized complication. Europace 2011; 13: 1406-1410.
47. Mugnai G, Sieira J, Ciconte G, Hervas MS, Irfan G, Saitoh Y, Hünük B, Ströker E, Velagic V, Wauters K, Tondo C, Molon G, De Asmundis C, Brugada P, Chierchia GB. One year incidence of atrial septal defect after PV isolation: a comparison between conventional radiofrequency and cryoballoon ablation. Pacing Clin Electrophysiol 2015; 38: 1049-1057.
48. Eshcol J, Wimmer AP. Hemodynamically significant iatrogenic atrial septal defects after cryoballoon ablation. HeartRhythm Case Rep. 2018 Oct 9;5(1):17-21.
49. Tang RB, Dong JZ, Long DY, Yu RH, Liu XP, Cheng YL, Sang CH, Ning M, Jiang CX, Avula UM, Bai R, Liu N, Ruan YF, Du X, Ma CS. Incidence and clinical characteristics of transient ST-T elevation during transseptal catheterization for atrial fibrillation ablation. Europace 2015; 17: 579-83.
50. Arita T, Kubota S, Okamoto K, Kuma F, Nakasuga K, Koga H, Ito H, Maruyama T, Kaji Y, Harada M. Bezold– Jarisch-like reflex during Brockenbrough's procedure for radiofrequency catheter ablation of focal left atrial fibrillation: report of two cases. J Interv Card Electrophysiol 2003; 8: 195-202.
51. Kuwahara T, Takahashi A, Takahashi Y, Kobori A, Miyazaki S, Takei A, Fujii A, Kusa S, Yagishita A, Okubo K, Fujino T, Nozato T, Hikita H, Sato A, Aonuma K. Clinical characteristics of massive air embolism complicating left atrial ablation of atrial fibrillation: lessons from five cases. Europace 2012; 14: 204–208.
52. Malik N, Claus PL, Illman JE, Kligerman SJ, Moynagh MR, Levin DL, Woodrum DA, Arani A, Arunachalam SP, Araoz PA. Air embolism: diagnosis and management. Future Cardiol 2017; 13: 365-378.
53. Cay S, Ozeke O, Ozcan F, Topaloglu S, Aras D. Coronary Air Embolism during Cryoablation of Atrial Fibrillation: A Catastrophic Complication and Its Management. J Atr Fibrillation 2017; 10: 1728.
54. Wasmer K, Zellerhoff S, Köbe J, Mönnig G, Pott C, Dechering DG, Lange PS, Frommeyer G, Eckardt L. Incidence and management of inadvertent puncture and sheath placement in the aorta during attempted transseptal puncture. Europace 2017; 19: 447-457.
55. Gerbode F, Hultgren H, Melrose D, Osborn J. Syndrome of left ventricular-right atrial shunt; successful surgical repair of defect in five cases, with observation of bradycardia on closure. Ann Surg. 1958; 148: 433-446.
56. Mugnai G, de Asmundis C, Iacopino S, Ströker E, Longobardi M, Negro MC, De Regibus V, Coutino-Moreno HE, Takarada K, Choudhury R, de Torres JPA, Storti C, Brugada P, Chierchia GB. Acute pericarditis following second-generation cryoballoon ablation for atrial fibrillation. J Interv Card Electrophysiol 2018; 51: 279-284.
57. Chierchia GB, Capulzini L, Droogmans S, Sorgente A, Sarkozy A, Müller-Burri A, Paparella G, de Asmundis C, Yazaki Y, Kerkhove D, Van Camp G, Brugada P. Pericardial effusion in atrial fibrillation ablation: a comparison between cryoballoon and radiofrequency pulmonary vein isolation. Europace 2010; 12: 337–341.
58. Chun KRJ, Perrotta L, Bordignon S, Khalil J, Dugo D, Konstantinou A, Fürnkranz A, Schmidt B. Complications in Catheter Ablation of Atrial Fibrillation in 3,000 Consecutive Procedures: Balloon Versus Radiofrequency Current Ablation. JACC Clin Electrophysiol 2017; 3: 154-161.
59. Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP, Tondo C; FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med 2016; 374: 2235–2245.
60. Aksu T, Golcuk SE, Guler TE, Yalin K, Erden I. Prediction of mid-term outcome after cryo-balloon ablation of atrial fibrillation using post-procedure high-sensitivity troponin level. Cardiovasc J Afr 2015; 26: 165-170.
61. Sanchez-Quintana D, Cabrera JA, Climent V, Climent V, Farré J, Weiglein A, Ho SY. How close are the phrenic nerves to cardiac structures? Implications for cardiac interventionalists. J Cardiovasc Electrophysiol 2005; 16: 309–13.
62. Neumann T, Vogt J, Schumacher B, Dorszewski A, Kuniss M, Neuser H, Kurzidim K, Berkowitsch A, Koller M, Heintze J, Scholz U, Wetzel U, Schneider MA, Horstkotte D, Hamm CW, Pitschner HF. Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. J Am Coll Cardiol 2008; 52: 273-278.
63. Ma H, Sun D, Luan H, Feng W, Zhou Y, Wu J, He C, Sun C. Efficacy and safety of cryoballoon ablation versus radiofrequency catheter ablation in atrial fibrillation: an updated meta-analysis. Postepy Kardiol Interwencyjnej 2017; 13: 240-249.
64. Okumura Y, Henz BD, Bunch TJ, Dalegrave C, Johnson SB, Packer DL. Distortion of right superior pulmonary vein anatomy by balloon catheters as a contributor to phrenic nerve injury. J Cardiovasc Electrophysiol 2009; 20: 1151–1157.
65. Andrie RP, Schrickel JW, Nickenig G, Lickfett L. Left phrenic nerve injury during cryoballoon ablation of the left superior pulmonary vein. Pacing Clin Electrophysiol 2012;35:e334–6.
66. Hermida JS, Traullé S, Kubala M. Left phrenic nerve injury after cryoballoon ablation of the pulmonary veins. Europace 2013; 15: 514.
67. Yorgun H, Canpolat U, Kocyigit D, Çöteli C, Evranos B, Aytemir K. Left atrial appendage isolation in addition to pulmonary vein isolation in persistent atrial fibrillation: one-year clinical outcome after cryoballoon-based ablation. Europace. 2017 May 1;19(5):758-768.
68. Okishige K, Aoyagi H, Nishimura T, Shigeta T, Keida T, Yamauchi Y, Sasano T, Hirao K. Left phrenic nerve injury during electrical isolation of left-sided pulmonary veins with the second-generation cryoballoon. Pacing Clin

Electrophysiol 2017; 40: 1426-1431.

69. Abugattas JP, de Asmundis C, Iacopino S, Salghetti F, Takarada K, Coutiño HE, Ströker E, De Regibus V, de Greef Y, Brugada P, Sieira J, Chierchia GB. Phrenic nerve injury during right inferior pulmonary vein ablation with the second-generation cryoballoon: clinical, procedural, and anatomical characteristics. Europace. 2017 Nov 22.
70. Furnkranz A, Bordignon S, Schmidt B, Gunawardene M, Schulte-Hahn B, Urban V, Bode F, Nowak B, Chun JK. Improved procedural efficacy of pulmonary vein isolation using the novel second-generation cryoballoon. J Cardiovasc Electrophysiol 2013; 24: 492-497.
71. Giovanni GD, Wauters K, Chierchia GB, Sieira J, Levinstein M, Conte G, DE Asmundis C, Baltogiannis G, Saitoh Y, Ciconte G, Julia J, Mugnai G, Irfan G, Brugada P. One-year follow-up after single procedure Cryoballoon ablation: a comparison between the firstand second generation balloon. J Cardiovasc Electrophysiol 2014; 25: 834-839.
72. Rottner L, Fink T, Heeger CH, Schlüter M, Goldmann B, Lemes C, Maurer T, Reißmann B, Rexha E, Riedl J, Santoro F, Wohlmuth P, Mathew S, Sohns C, Ouyang F, Kuck KH, Metzner A. Is less more? Impact of different ablation protocols on periprocedural complications in second-generation cryoballoon based pulmonary vein isolation. Europace. 2018 Sep 1;20(9):1459-1467.
73. Lakhani M, Saiful F, Parikh V, Goyal N, Bekheit S, Kowalski M. Recordings of diaphragmatic electromyograms during cryoballoon ablation for atrial fibrillation accurately predict phrenic nerve injury. Heart Rhythm 2014; 11: 369–374.
74. Heeger CH, Pott A, Sohn C, Rilling A, Metzner A, Kuniss M, et al. Phrenic Nerve Injury During Pulmonary Vein Isolation Using the Second-Generation Cryoballoon: Characteristics and Follow-up – First Results of the Worldwide YETI registry. ESC 2019
75. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, Lehmann JW, Ruskin; STOP AF Cryoablation Investigators. 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: 1713–1723.
76. Knight BP, Novak PG, Sangrigoli R, Champagne J, Dubuc M, Adler SW, Svinarich T, Essebag V, Jain SK, John RM, Mansour M. Second generation cryoballoon ablation in paroxysmal atrial fibrillation patients: 12 month safety and efficacy from the STOP-AF post approval study. P001-38. Heart Rhythm 2016; 13: S111.
77. van Opstal JM, Timmermans C, Blaauw Y, Pison L. Bronchial erosion and hemoptysis after pulmonary vein isolation by cryoballoon ablation. Heart Rhythm 2011; 8: 1459. [PMID: 20601153 DOI: 10.1016/j.hrthm.2010.06.024].
78. Bhagwandien R, Belle YV, deGroot N, Jordaens L. Hemoptysis after pulmonary vein isolation with a cryoballoon: an analysis of the potential etiology. J Cardiovasc Electrophysiol 2011; 22: 1067–9.
79. Aksu T, Ebru Golcuk S, Yalin K. Haemoptysis and pulmonary haemorrhage associated with cryoballoon ablation. Europace 2015; 17: 1240.
80. Kasper Ł, Gross-Sondej I, Machalica B, Soja J, Pawlik W, Sładek K. Hemoptysis and lung disease as a manifestation of pulmonary vein stenosis after cryoballooncatheter ablation for atrial fibrillation. Pol Arch Med Wewn 2016; 126: 94-96.
81. Aryana A, Bowers MR, Hayatdavoudi SM, Zhang Y, Afify A, D'Avila A, O'Neill PG. Impact of Pulmonary Vein Cryoballoon Ablation on Bronchial Injury. J Cardiovasc Electrophysiol 2016; 27: 861-867.
82. Stockigt F, Schrickel JW, Andrie' R, Lickfett L. Atrioesophageal fistula after cryoballoon pulmonary vein isolation. J Cardiovasc Electrophysiol 2012; 23: 1254-1257.
83. 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.
84. Ahmed H, Neuzil P, d'Avila A, Cha YM, Laragy M, Mares K, Brugge WR, Forcione DG, Ruskin JN, Packer DL, Reddy VY. The esophageal effects of cryoenergy during cryoablation for atrial fibrillation. Heart Rhythm 2009; 6: 962-969.
85. 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.
86. Guiot A, Savoure A, Godin B, Anselme F. Collateral nervous damages after cryoballoon pulmonary vein isolation. J Cardiovasc Electrophysiol 2012; 23: 346-351.
87. Metzner A, Burchard A, Wohlmuth P, Rausch P, Bardyszewski A, Gienapp C, Tilz RR, Rillig A, Mathew S, Deiss S, Makimoto H, Ouyang F, Kuck KH, Wissner E. Increased incidence of esophageal thermal lesions using the second-generation 28-mm cryoballoon. Circ Arrhythm Electrophysiol 2013; 6: 769-775.
88. Kuwahara T, Takahashi A, Takahashi Y, Kobori A, Miyazaki S, Takei A, Fujino T, Okubo K, Takagi K, Fujii A, Takigawa M, Watari Y, Hikita H, Sato A, Aonuma K. Clinical characteristics and management of periesophageal vagal nerve injury complicating left atrial ablation of atrial fibrillation: lessons from eleven cases. J Cardiovasc Electrophysiol 2013; 24: 847-851.
89. Fürnkranz A, Bordignon S, Schmidt B, Böhmig M, Böhmer MC, Bode F, Schulte-Hahn B, Nowak B, Dignaß AU, Chun JK. Luminal esophageal temperature predicts esophageal lesions after secondgeneration cryoballoon pulmonary vein isolation. Heart Rhythm 2013; 10: 789-793.
90. Aksu T, Golcuk S, Guler TE, Yalin K, Erden I. Gastroparesis as a Complication of Atrial Fibrillation Ablation. Am J Cardiol 2015; 116: 92-97.
91. Kuck KH, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP, Tondo C; FIRE AND ICE Investigators. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. N Engl J Med 2016; 374: 2235-2245.
92. Arentz T, Jander N, von Rosenthal J, Blum T, Fürmaier R, Görnandt L, Josef Neumann F, Kalusche D. Incidence of pulmonary vein stenosis 2 years after radiofrequency catheter ablation of refractory atrial fibrillation. Eur Heart J 2003; 24: 963-969.
93. Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, Yu WC, Hsu TL, Ding YA, Chang MS. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. Circulation 1999; 100: 1879-1886.
94. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Packer D, Skanes A. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation 2005; 111: 1100-1105.
95. 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.
96. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, Lehmann JW, Ruskin JN; STOP AF Cryoablation Investigators. 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: 1713-1723.
97. Holmes DR Jr, Monahan KH, Packer D. Pulmonary vein stenosis complicating ablation for atrial fibrillation: clinical spectrum and interventional considerations. JACC Cardiovasc Interv 2009; 2: 267–276.
98. Coutiño HE, Takarada K, Sieira J, Abugattas JP, Salghetti F, De Regibus V, Ströker E, Brugada P, Iacopino S, de Asmundis C, Chierchia GB. Anatomical and procedural predictors of pulmonary vein stenosis in the setting of second-

generation cryoballoon ablation. J Cardiovasc Med (Hagerstown) 2018; 19: 290-296.

99. Narui R, Tokuda M, Matsushima M, Isogai R, Tokutake K, Yokoyama K, Hioki M, Ito K, Tanigawa SI, Yamashita S, Inada K, Shibayama K, Matsuo S, Miyanaga S, Sugimoto K, Yoshimura M, Yamane T. Incidence and Factors Associated With the Occurrence of Pulmonary Vein Narrowing After Cryoballoon Ablation. Circ Arrhythm Electrophysiol 2017 Jun;10(6). pii: e004588.
100. Baran J, Lewandowski P, Smarż K, Sikorska A, Zaborska B, Kułakowski P. Acute Hemodynamic and Tissue Effects of Cryoballoon Ablation on Pulmonary Vessels: The IVUS-Cryo Study. J Am Heart Assoc 2017 Jun 25; 6(6). pii: e005988.
101. Fender EA, Widmer RJ, Hodge DO, Packer DL, Holmes DR Jr. Assessment and Management of Pulmonary Vein Occlusion After Atrial Fibrillation Ablation. JACC Cardiovasc Interv 2018; 11: 1633-1639.
102. Tse HF, Kwong YL, Lau CP. Transvenous cryoablation reduces platelet activation during pulmonary vein ablation compared with radiofrequency energy in patients with atrial fibrillation. J Cardiovasc Electrophysiol 2005; 16: 1064–1070.
103. Khairy P, Chauvet P, Lehmann J, Lambert J, Macle L, Tanguay JF, Sirois MG, Santoianni D, Dubuc M. Lower incidence of thrombus formation with cryoenergy versus radiofrequency catheter ablation. Circulation 2003; 107: 2045–2050.
104. Lickfett L, Hackenbroch M, Lewalter T, Selbach S, Schwab JO, Yang A, Balta O, Schrickel J, Bitzen A, Lüderitz B, Sommer T. Cerebral diffusion-weighted magnetic resonance imaging: a tool to monitor the thrombogenicity of left atrial catheter ablation. J Cardiovasc Electrophysiol 2006; 17: 1–7.
105. Gaita F, Caponi D, Pianelli M, Scaglione M, Toso E, Cesarani F, Boffano C, Gandini G, Valentini MC, De Ponti R, Halimi F, Leclercq JF. Radiofrequency catheter ablation of atrial fibrillation: a cause of silent thromboembolism? Magnetic resonance imaging assessment of cerebral thromboembolism in patients undergoing ablation of atrial fibrillation. Circulation 2010; 122: 1667–1673.
106. Miyazaki S, Watanabe T, Kajiyama T, Iwasawa J, Ichijo S, Nakamura H, Taniguchi H, Hirao K, Iesaka Y. Thromboembolic Risks of the Procedural Process in Second-Generation Cryoballoon Ablation Procedures: Analysis From Real-Time Transcranial Doppler Monitoring. Circ Arrhythm Electrophysiol. 2017 Dec;10(12). pii: e005612.
107. Tokuda M, Matsuo S, Kato M, Sato H, Oseto H, Okajima E, Ikewaki H, Isogai R, Tokutake K, Yokoyama K, Narui R, Tanigawa SI, Yamashita S, Inada K, Yoshimura M, Yamane T. Effect of air removal with extracorporeal balloon inflation on incidence of asymptomatic cerebral embolism during cryoballoon ablation of atrial fibrillation. Heart Rhythm 2017; 14: 1291-1296.
108. Mugnai G, Irfan G, de Asmundis C, Ciconte G, Saitoh Y, Hunuk B, Velagic V, Stroker E, Rossi P, Capulzini L, Brugada P, Chierchia GB. Complications in the setting of percutaneous atrial fibrillation ablation using radiofrequency and cryoballoon techniques: A single-center study in a large cohort of patients. Int J Cardiol 2015; 196: 42-49.
109. Di Biase L, Burkhardt JD, Santangeli P, Mohanty P, Sanchez JE, Horton R, Gallinghouse GJ, Themistoclakis S, Rossillo A, Lakkireddy D, Reddy M, Hao S, Hongo R, Beheiry S, Zagrodzky J, Rong B, Mohanty S, Elayi CS, Forleo G, Pelargonio G, Narducci ML, Dello Russo A, Casella M, Fassini G, Tondo C, Schweikert RA, Natale A. Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) randomized trial. Circulation 2014; 129: 2638–2644.
110. Tscholl V, Lsharaf AK, Lin T, Bellmann B, Nagel P, Lenz K, Landmesser U, Roser M, Rillig A. Apixaban, rivaroxaban, and dabigatran use in patients undergoing catheter ablation for atrial fibrillation using the second-generation cryoballoon. Clin Cardiol 2017; 40: 1095-1099.
111. Calvo N, Mont L, Vidal B, Nadal M, Montserrat S, Andreu D, Tamborero D, Pare C, Azqueta M, Berruezo A, Brugada J, Sitges M. Usefulness of transoesophageal echocardiography before circumferential pulmonary vein ablation in patients with atrial fibrillation: is it really mandatory? Europace 2011; 13: 486-491.
112. McCready JW, Nunn L, Lambiase PD, Ahsan SY, Segal OR, Rowland E, Lowe MD, Chow AW. Incidence of left atrial thrombus prior to atrial fibrillation ablation: is pre-procedural transoesophageal echocardiography mandatory? Europace 2010; 12: 927-932.
113. Kottmaier M, Jilek C, Berglar S, Reents T, Bourier F, Semmler V, Telishevska M, Koch-Büttner K, Lengauer S, Kornmayer M, Rousseva E, Brooks S, Hadamitzky M, Kolb C, Hessling G, Deisenhofer I. Exclusion of left atrial thrombus by dual-source cardiac computed tomography prior to catheter ablation for atrial fibrillation. Clin Res Cardiol. 2018 Jul 26.
114. Güler TE, Aksu T, Özcan KS, Bozyel S. Transient ST-segment elevation due to coronary slow flow during cryoballoon application. Turk Kardiyol Dern Ars 2018; 46: 396-400.
115. Makimoto H, Kelm M, Shin DI, Blockhaus C. Breakage of a Circular Catheter Wedged in a Right Pulmonary Vein during Cryoballoon Pulmonary Vein Isolation. Intern Med 2017; 56: 1057-1059.
116. Canpolat U, Kivrak A, Hazirolan T, Aytemir K. Coronary Vasospasm After Isolation of Left Atrial Appendage Using a Second-Generation Cryoballoon. JACC Clin Electrophysiol 2017; 3: 417-419.
117. Fonseca WP, Pisani CF, Lara S, Scanavacca M. Transient complete atrioventricular block during catheter balloon cryoablation of atrialfibrillation: a case report. Europace 2017; 19: 1943.
118. Fedida J, Badenco N, Gandjbakhch E, Waintraub X, Hidden-Lucet F, Duthoit G. Reversible mechanical atrioventricular block during cryoablation for paroxysmal atrial fibrillation with a 28 mm balloon. HeartRhythm Case Rep September 28, 2018.