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Complications of Atrial Fibrillation Cryoablation

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Abstract

Catheter ablation either by using radiofrequency or cryo energy in symptomatic patients with atrial fibrillation (AF) has shown to be effective as compared to anti-arrhythmic drugs. However, all the techniques used during AF ablation are not free of complication. There are several well-known peri-procedural complications in which operators should be informed of the possible risks, cautious during the procedure and able to manage them when occurred. Herein, we aimed to review possible complications of AF cryoablation.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with heart failure, thromboembolic events, hospitalizations and cognitive dysfunction [1]. Guideline-writing authorities recommend catheter ablation as a Class I indication in symptomatic paroxysmal AF to improve AF symptoms in patients who have symptomatic recurrences of AF under antiarrhythmic drug therapy (AAD) and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced centre. Catheter ablation should be considered as first-line therapy to prevent recurrent AF and to improve symptoms in selected patients with symptomatic paroxysmal AF as an alternative to AAD and in persistent or long-standing persistent AF patients refractory to AAD, considering patient choice, benefit, and risk [2]

Radiofrequency ablation (RFA) is the conventional ablation procedure. It causes contiguous, transmural lesions due to heat energy. Major drawbacks of RFA have been "point- to- point" ablation and the resultant longer procedural and fluoroscopy time. Cryoballoon ablation (CBA) is the application of single-shot cryoenergy to pulmonary vein (PV) ostia and has emerged as an alternative to RF energy.

In August 2012, US Food and Drug Administration (FDA) approved the use of second-generation cryoballoon (CB-A) (Arctic Front Advance Cryoablation catheter, Medtronic, MN, USA), an updated version of the first-generation cryoballoon (Arctic Front Cryoablation catheter, Medtronic, MN, USA), which has a more uniform and distal cooling pattern. In May 2015, FDA and CE concurrently approved the use of third- generation CB (CB- ST) (Arctic Front Advance ST Cryoablation catheter, Medtronic, MN, USA). Balloon-tip of the novel CB-ST balloon has been shortened by approximately 40% when compared to CB-A for real-time recording of the PV potentials during freezing in a more reliable way.

There are several advantages of the use of cryoenergy when compared to RF energy during AF ablation. First, a single circular freeze can achieve PV isolation (PVI) rather than the application of many RF lesions. In case of incomplete PVI, bonus freeze cycles may be applied. Second, cryoenergy creates durable lesions preserving the structural architecture of the tissue [3], with less endothelial disruption [4]and accordingly, poses a reduced risk of thrombus formation [3]. It does not require three- dimensional mapping, therefore reduces procedural time and complexity. Furthermore, it allows increased catheter contact and stability, thus minimizes the fluoroscopy time. Overall, CBA is believed to have the potential to reduce the risk of complications compared to RFA. The major drawback of CBA for AF is the possibility of the presence of anatomical variants, such a common ostium or supernumerary PVs, which can make the procedure challenging and affect procedural outcomes [5]. Recently, Heeger et al. [6]. reported a multicenter experience in the role of second-generation CBA for left common PV in which there was a similar acute isolation rate and durability of PVI with the CB compared to RF ablation. Additionally, RFA seems more advantageous in persistent and long-standing persistent AF because of the need for additional ablation regions other than PV-triggers. However, very recent studies in such patient populations represented the feasibility and effectiveness of cryoballoon catheter during roof ablation or left atrial appendage and superior vena cava isolation [7–9].

Major complications of percutaneous catheter ablation for AF include pericardial effusion/tamponade, embolic events, PV stenosis, atrioesophageal fistula (AEF), phrenic nerve palsy (PNP) and vascular access problems. Although vascular complications are known to be the most frequent complication of the procedure, rare and life-threatening complications and their management should also be known by the electrophysiologists.

Fortunately, complication rates have shown a marked decline in time. A single- center study evaluating the complication rates in percutaneous catheter ablation of AF using both RFA and CBA [10]. have reported that complication rates have decreased over the study period from 4.67% in 2008 to 1.55% in 2014. This has been attributed to the technological advances and increased experience of

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the operators and the nursing staff by the investigators. Since the conventional ablation strategy for AF has been RFA, data concerning the complications of CBA is often reported as in comparison with RFA in the literature. In this text, possible complications of AF ablation with cryoballoon technique will be reviewed.

Incidence Of Complications During Cryoablation Of AF

The major complication is defined as a complication that results in permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48 hours [11]. The incidence of major complications during cryoablation has been reported to vary between 2.2-7.0% [12],[13]. The most recent study is a single-center prospective registry of 450 consecutive patients undergoing PVI using CB between 2011 and 2015 [12]. Major complications, namely persistent phrenic nerve injury (PNI), episodes of symptomatic pericardial effusion, deep vein thrombosis and arteriovenous fistula, occurred in 10 (2.2%) patients. In 49 (10.8%) patients, at least transient PNI was observed; only 5 persisted beyond the procedure (1.1%). All cases of PNI resolved eventually, with the longest time to the resolution being 48 days. There were no significant predictors of major complications [12]. Another study including 500 consecutive patients who underwent PVI using CB-A technology between June 2012 and February 2015 has reported the incidence of major complications as 2.0% [14]. PNP occurred in 7.2% of patients and was persistent in 2.2% of patients [14]. Therefore, although nearly all resolve eventually at least within the first year following the procedure, the most common complication associated with CBA is PNI/PNP.

Single Center Studies Comparing The Safety Of CB Ablation Vs. RF Ablation

Mugnai et al. [10]. have evaluated the complication rates in 1.233 patients who underwent AF ablation using either RF energy (n= 642) or CB (n= 591), between January 2008- December 2014. Authors have reported the incidence of serious adverse events as 2.9% (36/1.233): specifically, vascular complications requiring intervention or prolonged hospital stay in 14 (1.1%); cardiac tamponade in 13 (1.0%); a thromboembolic event in 4 (0.3%); and atrioesophageal fistula, PV intramural hematoma, retroperitoneal hematoma, pleural hematoma and persisting phrenic nerve palsy all occurred in 1 patient individually (0.1%). No deaths related to the procedure occurred. The complication rate did not significantly differ in the RF and CB groups (respectively, 3.6% vs 2.2%; p=0.1).

Chun et al. [15]. have recently published the differential risk of cardiac tamponade in AF ablation procedures undertaken from May 2010 to July 2015 at a single center. In total, 3.000 AF ablation procedures (RFA: 2.125, CB: 589, laser balloon: 286 patients) were performed. Cardiac tamponade was significantly lower in balloon-based ablation group than in RFA group (0.1 vs. 1.5%, p= 0.001). In addition, the authors have reported an increased complication rate (2.9% vs. 5.4%) beyond cardiac tamponade, which was driven primarily by PNP persistent at patient discharge (15 of 875 [1.7%]; 11 of 589 with CBs [1.9%] vs. 4 of 286 with laser balloon [1.4%]; p= 0.616) in the balloon-based ablation group.

Meta-Analyses Comparing The Safety Of CB Ablation vs. RF Ablation

The most recent meta-analysis [16]. has compared the safety and efficacy of CB and RF ablation for paroxysmal AF. It included a total of 38 eligible studies, 9 prospective randomized or randomized controlled trials (RCTs), and 29 non-RCTs, adding up to 15.496 patients (CB, n= 6218 vs. RF, n= 9278). CB ablation was shown to result in less complications when PNI was excluded [odds ratio (OR) = 0.79; 95% CI, 0.67–0.93; p= 0.004], however, the total complications of CB was higher than RF (OR = 1.37; 95% CI, 1.19–1.57; p < 0.0001)

Another meta-analysis published this year [17]. has included nine observational studies (2.336 patients) assessed the efficacy and safety of the CB-A compared with RF for paroxysmal AF ablation. The total complication rate showed no statistical difference (8.8 vs. 4.4 %, OR 2.01, 95 % CI 0.91- 4.43, p = 0.08). There was no report of PV stenosis or atrioesophageal fistula in the two groups. Almost all cases of PNP occurred in the CB-2 group except one which occurred in the RF group (6.6 vs. 0.1 %, OR 17.35, 95 % CI 6.57 to 45.85, p< 0.00001), whereas pericardial tamponade was seldom manifested in the CB-2 group (0.4 vs. 1.5%, OR 0.32, 95%CI 0.13 to 0.78, p = 0.01)

A meta-analysis [18] has aimed to compare the efficacy and safety of CB vs. RFA in patients with paroxysmal AF. The meta-analysis included a total of 6473 participants from 10 studies (CB, n= 2232 vs. RF, n= 4241). CB ablation was performed with 23–28 mm CB catheters, except for two studies [5], [19]. using only 28 mm CB catheters. The risk of procedure-related complications was found to be similar between patients treated with CB and those with RFA (4.7 vs. 4.3%; RR [95% CI]= 0.92 [0.66–1.28], p= 0.61). CBA has been shown to result in a higher risk of persistent PNP (RR [95% CI]= 13.60 [3.87–47.81], p< 0.01) and a lower risk of cardiac tamponade (RR [95% CI]= 0.48 [0.25–0.89], p= 0.02) compared with RF ablation. Although the risk of persistent PNP was significantly higher among patients receiving CB ablation, in all cases phrenic nerve palsy resolved within 1 year from the ablation procedure. Moreover, there was no significant interaction between the incidence of persistent PNP and the type of CB used

One other meta-analysis [20]. included 18 randomized or non-randomized cohorts that directly compared CB to irrigated RF catheter ablation for PVI in patients with AF with a total of 8.668 patients (CB, n= 3.706 vs. RF, n= 4.962). Pericardial effusion associated with PVI was significantly less common in patients who underwent CB (25/3.113; 0.8%) as compared to RF (84/4.004; 2.1%) (OR 0.44; 95% CI 0.28-0.69; p<0.01). There was also a significantly lower incidence of pericardial tamponade in CB ablations (7/1,922; 0.3%) when compared to the RF group (44/3,198; 1.4%) (OR 0.31; 95% CI 0.15-0.64; p<0.01). Conversely, PNP at discharge was exclusively observed after CB procedures (34/2,041 patients; 1.7%; OR 7.40; 95% CI 2.56-21.34; p<0.01). The vast majority of those cases resolved during short-term follow-up. PNP lasting >12 months was exceedingly rare, reported in only 4/1,716 (0.2%) patients in the CB group. Vascular complications (14 studies; 6.463 patients; 1.7% CB vs. 2.0% RF; OR 0.75; 95% CI 0.51-1.11; p=0.15) and major vascular complications (7 studies; 3.264 patients; 1.1% CB vs. 1.3% RF; OR 0.79; 95% CI 0.38-1.62; p=0.52) were not significantly different between groups. The incidence of stroke was exceedingly rare and not significantly different between CB (3/1.422; 0.2%) and RF (8/2.636; 0.3%) ablations (p=0.63). The incidence of pericardial effusions (11 studies; 5.821 patients; 0.8% CB vs. 130 2.1% RF; OR 0.45; 95% CI 0.28-0.75; p<0.01) and pericardial tamponade (7 studies; 5.020 patients; 0.3% CB vs. 1.3% RF; OR 0.30; 95% CI 0.14-0.65; p<0.01) was also lower with CB ablations in the subgroup of paroxysmal AF

Studies Comparing The Safety Of First , Second And Third Generation CB Ablation

Pandya et al. [21] have published a meta-analysis that included a total of ten published studies comparing the safety and efficacy of CBA for AF, with 2310 patients (CB-A: 957, CB: 1237 patients). They have found that PVI using CB-A resulted in a higher incidence of persistent and transient PNP compared to CB [OR=1.64 (95 % CI 1.19, 2.26), p=0.002, and OR= 2.38 (95 % CI 1.46, 3.88), p=0.0005, respectively]. The differences in the rate of pericardial effusion and incidence of access site complications were not statistically significant

On the other hand, a single center study [10] have shown no significant differences in complication rates among groups of CB (n= 145) and CB-A (n= 446). Although numerically higher in CB-A group, the difference between groups regarding the incidence of persistent PNP also did not reach statistical significance (2.5% vs 0%, p= 0.06), probably due to the low number of events, similar to a previous study [22].

A few studies comparing outcomes of CBA using CB-A and CB-ST balloon have reported similar complication rates between groups. Furnkranz et al. [23]. have evaluated 472 consecutive patients who underwent CB-PVI for AF (CB-ST: 49 patients, CB-A: 423 patients). There was no difference regarding the rate of transient (CB-A: 5.2% vs. CB-ST: 2.0%, p> 0.05) PNP, persistent PNP (CB-A: 1.9% vs. CB-ST: 2.0%, p> 0.05) or access-site complications (CB-A: 2.1% vs. CB-ST: 2.0%, p> 0.05) among groups. Mugnai et al. [24] have evaluated a total of 600 consecutive patients (100 CB-ST and 500 CB-A ablations). In the overall study population, major complications occurred in 12 of 600 patients (2.0 %). Most common complications were peripheral vascular complications requiring intervention or prolonged hospital stay (8 patients, 1.3 % per procedure), followed with transient ischemic attacks (TIA), pericardial effusion requiring intervention, retroperitoneal hematoma and symptomatic PNP persisting at final follow-up all occurred in one patient individually (0.2 % per procedure). No significant differences in major complications were observed between the two groups. Aryana et al. [25]. have also reported a similar incidence of PNP and procedure-related adverse events between the 2 groups

Possible Complication During Cryoablation For AF

A) Energy- Dependent Complication

Energy-dependent complications of CBA for AF include pericardial effusion/ tamponade, PV stenosis, AEF and thromboembolic complications. Cryoenergy is known to reduce this category of complications (See “Introduction”).

Pericardial Effusion And Tamponade

Pericardial effusion can manifest itself from acute pericardial tamponade to asymptomatic effusion. A study has compared the incidence of pericardial effusion in a total of 133 consecutive patients undergoing ablation for paroxysmal AF (87 by RFA vs. 46 patients by CB-A) and no significant difference in the incidence of pericardial effusion between the cryoballoon and the RF groups were detected (11 vs. 16%) [26]. However, the incidence of cardiac tamponade has been reported to be higher following RFA [15]. A longer procedural time, coronary artery disease and arterial hypertension were found to be independent predictors of pericardial effusion during AF ablation [26]. Ablation technology (RFA), ablation strategy (PVI plus) and the number of procedures per patient were reported as predictors of cardiac tamponade [15]. Mugnai et al. [10]. have reported that 2 cases of cardiac tamponades occurred during PVI, respectively during freezes in the LSPV and in the RSPV, and the third one did occur 3 h after the ablation procedure. However, it may also occur following transseptal puncture.

How to manage it?

All patients should undergo routine transthoracic echocardiography prior to, after a transseptal puncture and at the end of ablation to assess the pericardial space. Furthermore, in case of suspicion (low blood pressure, tachycardia, narrowed pulse pressure), it should be repeated. Pericardial effusion usually resolves spontaneously, however immediate recognition and intervention is of vital importance in tamponade, since it may threaten life. The procedures should immediately be stopped and the drainage should be achieved by a percutaneous pericardial puncture in case of tamponade.

How to prevent it?

Successful one- shot transseptal puncture is essential for minimizing pericardial effusion/ tamponade. Safety of transseptal puncture lies in the recognition of the right atrial anatomy and in particular of the fossa ovalis. Some have reinforced the use of intracardiac echocardiography (ICE) or transesophageal echocardiography (TEE) in those procedures in which right atrial anatomy is unusual or in which fossa ovalis is difficult to engage [27]. However, TEE requires deep sedation or general anesthesia and ICE is associated with increased costs and needs a precise expertise. Furthermore, optimal anticoagulation management should be adopted before and after PVI [11].

-PULMONARY VEIN STENOSIS

Pulmonary vein stenosis is the constriction or narrowing of the PV ostium due to thermal injury to the vessel wall. This condition can restrict blood flow from the lungs into the heart. This had been a more common complication of RFA compared to cryoablation. In STOP-AF trial, CB therapy was associated with a 3.1% incidence of PV stenosis [28].

PV stenosis is often clinically silent. Symptoms may include a cough, dyspnea, chest pain, hemoptysis and recurrent respiratory infections. The severity of the clinical presentation depends on the severity of the stenosis and the number of PVs involved [29]. 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.

How to manage it?

Pulmonary vein stenosis should be suspected in every patient presenting with one the above clinical symptoms after an AF catheter ablation. Cardiac computed tomography (CT) and magnetic resonance imaging (MRI) are diagnostic tools to make the definite diagnosis. Echocardiography might be useful to assess PV flows. Radionuclide ventilation/perfusion imaging may also serve as a screening tool in symptomatic patients and help to clarify the hemodynamic significance of PV stenosis [30].

Optimal treatment for PV stenosis is still unknown. Balloon angioplasty alone or in association with stent implantation seems to be efficacious in the acute setting but is also associated with restenosis in 30–50% of the patients.

How to prevent it?

Pulmonary vein stenosis may be minimized by not positioning the cryoablation catheter within the tubular portion of the pulmonary vein. The balloon should not be inflated while the catheter is positioned inside the pulmonary vein. The balloon should always be inflated in the atrium and then positioned at the pulmonary vein ostia.

-ATRIOESOPHAGEAL FISTULA

An atrioesophageal fistula is a rare but fatal complication of the procedure. Despite the higher frequency with the use of RFA, it has been reported as case reports following cryoablation of AF [31–34]. Although its incidence has been reported to be approximately 0.01–0.2% [35], it has high mortality rates, up to 63% [36]–[37].

Very low temperatures (below -60°C), long freezing cycles and sharp temperature descent during first 30 seconds of the procedure are thought result in ulcer and fistula formation, respectively [38]. Heat is thought to affect esophageal endothelial cells directly or indirectly via damaging anterior esophageal arteries causing ischemia and ulceration of the mucosal layers [39]. In addition, pre-existing esophagitis due to gastroesophageal reflux is believed to exacerbate the esophageal injury by interfering with the repair mechanisms after esophageal injury [40]. Left atrial enlargement, persistent AF leading to left atrial enlargement and extensive ablation of the posterior wall have been proposed to be risk factors of AEF [30]–. Though unclear in underlying mechanism, general anesthesia has also been suggested to be a risk factor for AEF due to decreased esophageal peristalsis and swallowing during anesthesia and frequent use of orogastric/nasogastric tubes during the procedure [43].

How to manage it?

Atrioesophageal fistula typically develops within 1-4 weeks following catheter ablation. The signs and symptoms are non-specific and include fever, fatigue, malaise, chest discomfort, nausea, vomiting, dysphagia, odynophagia, hematemesis, melena, and dyspnea. Diagnosis should be kept in mind particularly in patients with the typical triad of infection without a clear focus, retrosternal pain, and stroke or TIA. Early recognition is important, as patients often develop endocarditis with septic emboli leading to neurological manifestations such as altered mental status, seizures, and coma within hours of symptom onset [44].

White blood cell count is an early and sensitive laboratory marker of an AEF [44]. Chest CT should be performed emergently. The test can be considered diagnostic if intravenous contrast enters the esophagus or mediastinum from the left atrium. Transthoracic echocardiography may demonstrate air in the left heart, pericardium or the presence of a pericardial effusion.

Esophageal instrumentation with endoscopy or TEE is not recommended as they theoretically may worsen the situation by increasing fistula size and also increase the risk of air embolism secondary to increased esophageal pressure with instrumentation and insufflation.

Available therapeutic options for AEF include surgical repair of the fistula (combined left atrial and esophageal repair) via thoracotomy [45], esophageal stenting [46] and conservative management with aggressive chest tube drainage and treatment of sepsis. Of these three approaches, conservative treatment of esophageal fistula remains controversial, as it requires frequent radiologic assessments and is associated with very high mortality rate. Data on stenting versus surgical treatment of AEF are conflicting and at the present, there is no consensus on the most effective treatment strategy for AEF. In addition, associated mediastinitis should also be treated. A multidisciplinary approach including cardiothoracic surgeons, infectious diseases specialists, neurologists and critical care physicians should be adopted.

How to prevent it?

Proton pump inhibitors should be initiated prophylactically prior to ablation [40].. Real-time luminal esophageal temperature monitoring by placing a temperature probe in the esophagus at the level of the ablation catheter may be beneficial to detect increases in luminal esophageal temperature and may alert the operator. Although its efficacy has been investigated for RFA, there are no studies evaluating the use of real-time esophageal temperature monitoring for cryoablation. However, several studies have reported incident AEF despite the lack of rising in esophageal temperature in the probes due to mismatch of the esophageal diameter relative to that of the probe [47]., the phenomenon of thermal latency and difference between luminal and mural temperature in the esophagus [48]. And what is worse, Nguyen et al. [49]. have highlighted esophageal temperature probes may function as “lightning rods”, attracting electrical current from the ablation catheter and potentiating heat transfer to the esophagus. Further research is necessary to confirm the safety of the esophageal temperature probes.

Another strategy for prevention of AEF is the mechanical deflection of the esophagus by using a TEE probe placed within the esophagus or endotracheal stylet within a thoracic chest tube [50],[51]. Feasibility of this method has been evaluated in patients undergoing RF ablation [50].,[51], however, there are no studies for CBA. Instrumentation of the pericardial space and introduction of a balloon catheter between the LA and esophagus has been suggested as an alternative approach to moving the esophagus away from the LA to reduce heat transfer to the esophagus during RFA [52].,[53].. However, it adds significant complexity to the procedure.

-THROMBOEMBOLIC COMPLICATIONS

Patients with AF undergoing catheter ablation have an increased risk for thromboembolic complications during, immediately following, and for days to months after procedure independent from pre-procedural thromboembolism risk [54].Despite the lower risk in cryoablation compared to RFA, CBA may also result in endothelial disruption and subsequent clot formation leading to thromboembolic complications. Maintaining optimal levels of anticoagulation and taking measures to prevent clot formation on sheaths and catheters (such as maintaining a constant heparinized flush through all long sheaths with access to the left atrium) are essential [11].

B) Procedure - Related Complications

Procedure-related complications include embolic (thromboembolism and air embolism) and vascular complications. These are related to the invasive nature of the procedure (sheaths, guidewires, manipulation) and the perioperative changes in anticoagulation, therefore it is unlikely that changes in AF ablation technology will completely eliminate these complications. Operator experience and optimization of periprocedural management might be the only way to reduce these inherent procedure-related complications.

-THROMBOEMBOLIC COMPLICATIONS

Thromboembolic complications include silent microemboli, transient ischemic attack (TIA) or stroke. Silent microemboli are asymptomatic white matter lesions detectable by cranial MRI and have been observed in around 10% of patients treated with RF and cryoballoon ablation [55]. Their clinical significance is unknown. The incidence of TIA/ stroke has been reported to be <1% [55].

Activated clotting time >300 s and high-flow perfusion of the transseptal sheath are mandatory to reduce thromboembolic complications during AF catheter ablation. Furthermore, a continuation of oral anticoagulation at a therapeutic international normalized ratio at the time of ablation is recommended in patients under warfarin treatment compared with bridging strategies using heparin or enoxaparin [56]. Anticoagulation with NOACs is an alternative to warfarin [57]–[59]. No adverse effects have been reported in cohorts treated with uninterrupted NOAC therapy undergoing catheter ablation [58]–[60]. The RE-CIRCUIT study has been completed and published recently, which compared uninterrupted dabigatran vs. uninterrupted warfarin in patients undergoing AF catheter ablation. A total of 704 patients were randomized to these two anticoagulation strategies. The incidence of major bleeding events during and up to 8 weeks post-ablation among the 635 patients who underwent AF ablation was significantly lower with dabigatran than with warfarin [(1.6% vs 6.9%); absolute risk difference [RD] 25.3%, RR reduction 77%]. No strokes or other thromboembolic events occurred in the dabigatran arm compared with one TIA in the warfarin arm [61]. Ongoing studies compare uninterrupted VKA with NOAC therapy in AF patients undergoing ablation [e.g. AXAFA – AFNET 5 (Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation Catheter Ablation: Comparison to vitamin K antagonist therapy; NCT02227550) [2].

HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of AF is also reported some recommendations regarding peri-procedural strategies to prevent thromboembolic complications [54]. It is now evident that a strategy of performing AF ablation safely on patients receiving uninterrupted anticoagulation based on previous clinical trials. Performing TEE in patients with AF before catheter ablation depends on the clinical experience of operators. While some operators perform TEE in all patients presenting for AF ablation regardless of presenting rhythm and anticoagulation status, others perform TEE in patients with a CHA2DS2-VASc score of ≥2. Unfractionated heparin should also be administered prior to or immediately after a transseptal puncture during AF catheter ablation procedure and the dose is titrated to maintain an ACT of at least 300 seconds. Systemic anticoagulation with warfarin (time in therapeutic range (TTR) should be 65-70% on warfarin) or a NOAC is recommended for at least 2 months post-catheter ablation of AF. Discontinuation of systemic anticoagulation after 2 months post-ablation should be based on the CHA2DS2-VASc score.

-VASCULAR COMPLICATIONS

Vascular access site complications are the most common complications of AF ablation and include groin hematoma, retroperitoneal bleeding, femoral pseudoaneurysm or femoral arteriovenous fistula. Large-calibre [outer diameter of 15 French (Fr)] delivery sheath and maintained anticoagulation during the procedure may increase the risk of vascular complications. Furthermore, the additional 6Fr pigtail catheter in the aortic root in order to monitor arterial pressure and also to assess the radiological position of the aorta during transseptal puncture may contribute to femoral pseudoaneurysm formation [10].

Hematomas generally resolve spontaneously. Femoral pseudoaneurysms may be successfully treated conservatively by compression only, by percutaneous thrombin injection or by surgical repair. Arteriovenous fistulas are treated surgically without significant sequelae.

Operator experience is the main factor considering the incidence of vascular complications. Another critical point is the insurance of optimal hemostasis. Standard manual compression has already been used as an effective technique for access site hemostasis after AF ablation in most centers. However, it may lead to rebleeding, thrombosis or embolism. Besides, manual compression is time-consuming and exhausting for the qualified medical staff. Reversal of heparin-mediated anticoagulation by protamine sulfate prior to sheath removal has been shown to be useful for prevention of vascular access complications in patients undergoing CB ablation for AF (1.1 vs. 6.3%, p= 0.011) [62]. In an effort to reduce patient discomfort and other complications, application of "figure- of- eight" suture following removal of the sheath has been reported to be a safe and efficacious technique to achieve an immediate hemostasis in a cohort of patients undergoing CBA compared to conventional manual compression[63].

C) Device - Dependent Complication

-PHRENIC NERVE INJURY/ PALSY

Phrenic nerve injury (PNI) develops due to the close proximity to the right phrenic nerve with the right-sided PVs. The right phrenic nerve courses rightward and anterior to the right PVs, particularly closer to the RSPV (1.5–2.5 mm) than the RIPV (10–15.5 mm) [64]. PNI has emerged as the most common clinically significant complication of CBA of AF. Through a study conducted on animal models, Andrade et al.[65]. demonstrated that PNP and injury induced by CBA were axonal in nature and characterized by Wallerian degeneration, with potential for recovery. In addition, functional resumption of PNP was closely related to the degree of axon injury.

The incidence has been reported to be substantially higher in patients undergoing CBA [66]. when compared to RFA (11.2% vs. 0.48%) [67]. In a review [68]. that analyzed 23 articles using CBA for PVI, PNP incidence was 6.38% (86/1349 procedures) and 4.73% of patients had persistent PNP after the procedure. Among these, 0.37% of patients had persistent PNP lasting over 1 year [68].. PNP occurred in a much higher proportion of procedures that used the 23- mm CB compared with the 28- mm CB (12.37 vs 3.53%; p = 0.0001). A higher risk of PNP during CBA with CB- A has been reported [69]. Casado-Arroyo et al.[22]. reported that CB-A was more likely to cause PNP compared to CB ablation due to its larger cooling surface area and deeper damage foci. Compared to CB, CB- A has resulted in an approximate doubling of acute (from 12.6% to 19.5%) and persistent (from 5.4% to 7.3% [beyond discharge from the index procedure]) PNI [22],[70].Regression analysis identified 23-mm balloon use (16.3% vs. 5.2%, OR 2.94, p=0.011) and increased age (62.8± 7.7 vs. 58.7± 0.12 years, OR 1.058, p=0.014) as independent significant predictors of PNI in a recent study including 450 consecutive patients undergoing cryoablation [12]. 23-mm balloon as a predictor of PNI has also been reported in previous studies [13],[71],[72]. An increased risk of PNI is likely when the balloon is positioned distal toward the vein, which occurs more frequently with the 23-mm balloon compared with the 28-mm balloon given its smaller size. Another hypothesis has been that the 28-mm balloon represents later cases in which the operator has gained experience.

Recently, various studies have compared the incidence of PNP between CB- A and CB- ST groups. Patients having undergone CB-A ablation experienced 36 PNPs (7.2 %) (5% transient and 2.2% persistent) and in the CB-ST patient group, there were six transient PNPs (6 %; p=0.6) and one persistent PNP (1 %; p = 0.7) which completely recovered within 1 month [24].. Another study reported lower incidence due to the application of preventive measures and the rates did not differ between groups (CB- A: 1.9%; CB- ST: 2.0%, p> 0.05) [23].

Phrenic nerve palsy is usually associated with dyspnea, cough, or hiccups; diagnosis is usually made with evidence of diaphragmatic elevation at the chest X-ray.

How to prevent it?

Phrenic nerve injury may be minimized by positioning the catheter as antral as possible and vigilantly monitoring the right hemidiaphragm contractions by pace-mapping during cryotherapy delivery. Pace-mapping is performed by pacing at a high output in the areas of presumable contact with phrenic nerves (usually right superior pulmonary vein, superior vena cava, and the roof of the left atrial appendage). Intermittent fluoroscopy is another practical method. Physicians should stop ablation immediately if evidence of phrenic nerve impairment is observed. However, intermittent fluoroscopy exposes the patient to an extra dose of radiation during the procedure. The palpation of the diaphragmatic excursion is a reliable method, but it requires an extra staff member to monitor the diaphragm. Furthermore, relying only on diaphragmatic contractions may result in long-lasting PN injury beyond 1 year [10],[73].

Electromyography of diaphragmatic contractions and auditory cardiotocograph can be used to monitor the phrenic nerve during cryoablation procedures. A diaphragmatic compound motor action potential (CMAP) can be recorded by two standard surface electrodes positioned across the diaphragm: one 5 cm above the xiphoid and the second along the right costal margin [74]. CMAP can also be measured by intravascular recording from the subdiaphragmatic hepatic vein [75]. The reduction in the amplitude of the CMAP precedes diaphragmatic paralysis and it may aid in early detection of phrenic nerve injury [75],[76].. A study of CMAP monitoring during CB-A ablation has reported a 24.5% incidence of CMAP changes that prompted early termination of ablation but only a 1.5% incidence of persistent PN injury with recovery [77]. A more recent case series of CMAP monitoring has found that 13.6% of subjects had CMAP-defined acute PNI leading to termination of cryoablation, and none developed persistent injury [78].

Regarding ablation technique, the exclusive use of the large 28-mm CB-A and shortening the delivery time to 180 s and avoiding "bonus" ablation after isolation is achieved may prevent PNI[79].. Combination of the use of a large 28-mm balloon, "single- shot" 3-min freezes with no "bonus" freezes, active balloon deflation, and CMAP monitoring has been reported to result in a persistent PNI incidence of 3%, with all patients recovering during follow-up [80].. Active and rapid deflation of the cryoballoon at the first sign of PNI [10],[71],[81], and terminating cryothermy ablation if there is a particularly rapid decrease in temperature to <- 38°C within the first 40 s [82]. are additional reported techniques. Another technique includes manipulation of the CB-A to avoid displacing the catheter into the RSPV by carefully disengaging the cryoballoon until a trivial leak around the balloon is visible before initiating freezing which then expands the balloon slightly to determine the freezing zone as near to the ostia-left atrium (LA) junction as possible.

Another approach for monitoring and diagnosing PNP is to use ICE during CBA of the right PVs. This monitoring technique has the advantage of continuous direct diaphragmatic visualization without the use of fluoroscopy, hence significantly minimizing radiation to both the patient and the operator. In addition, this technique does not require extra staff to monitor the diaphragm using manual palpation [83].

At last but not the least, the ability to predict patients are at risk for PNI using preprocedural imaging has been investigated in several studies. Although direct visualization of the PN with multidetector computed tomography (MDCT) can be difficult [84]., a few studies [80].,[85].,[86]. have evaluated the predictive role of the distance between RSPV ostium and PN vascular bundle detected by MDCT on PNI development. In addition, another study has reported that ostial vein area and external RSPV-LA angle measurement had high predictive value for determining PNI at the RSPV in 41 patients undergoing PVI using 28- mm CB [87].

-COLLATERAL NERVE DAMAGE

Gastroparesis is one of the major complications that may occur due to collateral nerve damages during cryoablation due to the close proximity of nerves innervating the pyloric sphincter and stomach to the posterior LA wall and PVs [88]. It is defined as a syndrome characterized by delayed gastric emptying in the absence of any structural lesions in the stomach and usually manifests with nausea and vomiting. The incidence of asymptomatic gastroparesis following CBA at 24 hr documented with esophagogastroduodenoscopy has been reported to be 9% [89]. In another study by Furnkranz et al., 2 of 38 patients experienced symptomatic gastroparesis after cryoballoon ablation for AF, which healed in 1 week after conservative therapy [90].

D) Complications During Cryoablation Of Non-PV Triggers

Cryoablation of non-PV triggers include cryoenergy application to superior vena cava (SVC) and left atrial appendage (LAA).

Potential complications of SVCI using cryoenergy include pericardial tamponade, pneumothorax, venous stenosis, superior vena cava syndrome and right phrenic nerve palsy. Previously, the incidence of right PNI has been reported to vary between 0.17-2.1% [91],[92]. A meta-analysis which included 3 RCTs with a total population of 526 subjects has investigated the outcomes following empiric SVCI in AF ablation [93].. There were a total of 12 serious events in the study population (2.2 %). Two PNI (2/237 = 0.8 %) were seen in the PVI + SVCI arm; one of them was transient while the other had a partial recovery at the end of follow-up. A more recent study by Xu et al. [94]. has reported only vascular access complication in their study evaluating the role of SVC ablation in 102 patients with long-standing persistent AF ablation.

Careful observation of the diaphragm motion on fluoroscopy during isolation of the RSPV or SVC during spontaneous breathing or pacing of the right-sided PN and CMAP monitoring are useful for preventing right-sided PNP [95],[96].

Spasm of the left circumflex artery, left-sided PNP, and changes in mechanical functions of the LAA are specific complications for the cryoablation of the LAA [9]. The incidence of left-sided PNP has been reported to be 1% [9]. Spasm of the left circumflex artery is relatively more common than PNP (4%) [9], it is asymptomatic and has been demonstrated to resolve following intracoronary nitrate administration. The left-sided PN should be paced from the LAA using circular mapping catheter throughout the freezing cycle as like pacing of the right-sided PN and PN capture is assessed by intermittent fluoroscopy and/or tactile feedback obtained from the patient's abdomen [9].

Impact of LAAI on LAA mechanics is complex. A study has reported a significant decrease in LAA flow rates without thrombus formation (mean LAA flow rates: 0.52± 0.19 m/s at baseline vs. 0.46± 0.15 at the 12th- month follow-up, p< 0.001) on 12th month follow-up TEE in patients undergoing LAA ablation in addition to PVI [9] and the only stroke case occurred at 5 months in a patient who discontinued oral anticoagulant for 10 days. Another study evaluating the impact of LAAI on LAA mechanical functions, which included 50 patients undergoing LAAI for the treatment of atrial tachyarrhythmias [97], has shown that during a median follow-up of 6.5 months, stroke occurred in 2 patients on OAC and TIA in one without OAC in the LAAI group. In the remaining 47 patients, LAA thrombus was identified on transesophageal echocardiography in 10 (21%) patients (OAC=9; no OAC=1). Another study showed that in 7/71 (10%) patients with previous LAAI who presented for a subsequent procedure, LAA thrombus formation was detected by pre-procedural TEE [98]. However, in BELIEF trial, although an impaired contractile pattern in LAA was observed in 35 (56.5%) patients, no thrombus was detected on TEE and no stroke or transient ischemic attack was reported [99].. Therefore, this ablation strategy may theoretically be associated with an increased risk of thrombus formation within the LAA and thromboembolic events despite optimal anticoagulation. Subsequent percutaneous LAA closure may be a solution in these patients.

Conclusions

Cryoballoon ablation for atrial fibrillation is a safe and effective strategy when compared to the conventional ablation strategy, RFCA, particularly when energy-dependent complications are taken into account. Phrenic nerve injury is significantly more common in CBA, however, this risk can be minimized and be comparable to RFA if preventive measures are taken. Rare but fatal complications of the procedure, such as atrioesophageal fistula and cardiac tamponade, should be immediately diagnosed and managed appropriately to avoid mortality.

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