Comprehensive Review of Pulmonary Hemoptysis After Cryoballoon Ablation of Atrial Fibrillation: A Serious Problem Needs Special Care

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Abstract

To review the literature and published data for pulmonary hemorrhage and hemoptysis after cryo-balloon ablation of atrial fibrillation. PubMed, Embase, Medline, Scopus, Web of Science, and Cochrane Library were searched for published articles and case reports. Our review and search have no restrictions on regions but were limited to human case reports and case series and articles published in English language. We also manually reviewed the publications reference lists to identify other relevant studies. The data was set until first of March 2020 with total of 93 cases out of 2064 with hemoptysis after CBA. From 9 studies a total of 2051 patients with mean age of 57.9±4.3 years had CBA for AF. These studies reported 80 cases with hemoptysis with incidence of 3.9%. The mean follow-up duration ranged from 1 to 12 months. Published cases showed onset of hemoptysis within the first day (47.5%) up to 7 (47.5%) days after CBA. Only 5 cases with massive hemoptysis have been reported during the procedure and 80% of reported cases presented with mild hemoptysis. Mean number of applications for CBA was 2.3±0.9 and mean duration of application was 235.9±57.8 seconds. Recently a concern has been raised about pulmonary complications post CBA. The long-term sequelae of CBA to the lungs are, thus far, unexplored. This review highlights that hemoptysis post CBA is not uncommon and can be avoided by careful selection of patients with careful manipulation during isolation of LSPV and RIPV with optimized freezing temperature will decrease hemoptysis incidence in the near future. The Positive aspect is that most of patients present with mild form of hemoptysis but with the fact that this complication has delayed occurrence.

Keywords: Pulmonary Hemoptysis; Cryo-balloon; Ablation; Atrial Fibrillation; Lung Injury; Pulmonary Veins Isolation; PVI; Cryo-balloon Complications

Introduction

Randomized trials showed superiority of AF ablation in comparison to antiarrhythmic drugs (AADs) in terms of improving the quality of life in AF patients. It is recommended that catheter ablation is more effective therapy than AADs for restoring and maintaining sinus rhythm (SR) in patients with symptomatic paroxysmal AF (PAF) and persistent AF (PerAF) [1].

Currently AF ablation is one of the most commonly performed procedures in electrophysiology. The cornerstone of paroxysmal AF ablation is the elimination of triggers by pulmonary vein isolation (PVI). But it is further noted that additional AF substrates modification are needed for ablation of persistent AF on top of PVI. Nowadays, radiofrequency ablation (RFA) navigated by 3D electro-anatomical mapping systems and cryo-balloon innovation are similar in terms of the efficacy and safety of the pulmonary vein isolation (PVI) approach [2]. The FIRE AND ICE trial, a large, randomized, controlled study, showed that CBA is not inferior to RFA with respect to efficacy and overall safety [3]. After the introduction of the second-generation cryo-balloon (CB-2), it has been proved that CBA is a rapid, effective, and safe strategy [4]. However, cryo-balloon ablation still has some week points, including an inability to perform ablation of atrial roof, complex fractionated atrial electrograms (CFAEs) and non-pulmonary veins (PVs) triggers [5]. Although the number of pulmonary veins CBA procedures is increased, there is growing interest in evaluating procedure-related complications described and take steps to minimize their incidence.

Methods

PubMed, Embase, Medline, Scopus, Web of Science, and Cochrane Library were searched for published articles and case reports. We included guidelines, metaanalysis, case reports and case series, the search key words were as follows: (“Catheter Ablation” OR “Cryo-balloon” OR “Cryo-ablation”), (“Hemoptysis” OR “hemoptysis after ablation” OR “pulmonary hemorrhage” AND “Atrial Fibrillation” “Complication of cryo-balloon ablation”). Our review and search have no restrictions on regions but were limited to human case reports and case series and articles published in English language. We also manually reviewed the publications reference lists to identify other relevant studies.
Complications of Cryo-balloon Ablation

The cornerstone of cryoablation is based on eliminating energy and heat absorption from the tissue in contact, by freezing, thus destroying the structure of the cellular membranes resulting in cell death with maintenance of the underlying tissue construction. Pressurized cryo-refrigerant (nitrous oxide [N2O]) is delivered to reach tissue temperatures of around -80°C. Successful CBA depends on freezing rate, duration and the lowest temperature reached. Cryo-mapping which is creating completely reversible lesion can be done by freezing tissue to a temperature of around -30°C. This maneuver allows the operator to expect the effect of a permanent lesion before it is actually produced. Permanent lesions can be done by freezing tissue to temperatures as low as possible up to -80°C for a minimum duration of 4 minutes to induce the maximum cell death [6].

In addition to classic complications post AF ablation as stroke/ transient ischemic attack, hemoptoma at the puncture site, and femoral arteriovenous fistula, pericardial effusion and tamponade, PV stenosis and atrio-esophageal fistula, CBA is also can be complicated with phrenic nerve and bronchial injury [7].

It has been shown that hemoptysis (coughing up blood or blood-stained mucus from the respiratory tract) can occur due to a pulmonary vein stenosis, as a long-term complication of PVI using radiofrequency [8]. Incidence of PV stenosis after CB has steadily decreased over time. STOP AF study reported a PV stenosis in 10 patients with rate of 3.1% using the first-generation CB [9]. A more recent trial, The STOP AF PAS, included 344 patients for pulmonary vein isolation (PVI) using the CB2 to assess long-term safety and efficacy of the CBA in patients with drug-refractory symptomatic pAF. Hemoptysis was seen in 3 patients 0.9% and PV stenosis was seen in 2 (0.6%) patients. These 2 cases had severe asymptomatic left superior PV stenosis >75% [10].

Characteristics and results of included patients

Of the 230 articles screened, 107 were selected for detailed review and 22 were finally retained for analysis: 13 case report between 2011 and 2019; and 9 studies reporting hemoptysis after cryo-ablation between 2008 and 2019 (Figure 1). There were 6 retrospective studies and 3 perspective studies included. Cryo-ablation of pulmonary vein was performed with both first and second generation cryo-balloons.

From 9 studies a total of 2051 patients with mean age of 57.9±4.3 years had CBA for atrial fibrillation. These studies reported 80 cases with hemoptysis and incidence of 3.9%. The mean follow-up duration ranged from 1 to 12 months. Tables 1 and 2 show the procedural and clinical characteristics of included cases. From the reported cases only one patient with massive hemoptysis and delayed presentation 1 month after cryo-ablation has been reported [11]. Although our observations showed that there is high incidence of hemoptysis in patients who have 28 mm CBA, but it is difficult judge this results as most of studies are retrospective and there are no head to head comparison studies.

Most of reported patients showed onset of hemoptysis within first day (47.5%) up to 7 (47.5%) days after CBA. Only 5 cases with massive hemoptysis have been reported during the procedure. Eighty percent of reported cases presented with mild hemoptysis (Figure 2). All studied populations have been used both vitamin K dependent oral anticoagulants and different types of direct oral anticoagulants. Our observation in this review showed that LSPV and RIPV (42.5% versus 35%) were the most culprit veins in reported patients (Figure 3).

Analysis of Mechanisms Lead to Hemoptysis

Bronchial injury as a cause of hemoptysis post CBA has been reported to be 1.7–3.6% [7,12]. Persistent cough which might be a sign for bronchial injury was reported as high as 17% in the STOP-AF Trial.
Various mechanisms have been proposed to explain the etiology of hemoptysis following cryoablation specially with deep seating of CB inside PVs [23]. Collateral injury of left mainstem bronchus during CBA due to barotrauma [14]. Although the risk of hemoptysis is increased with low nadir balloon temperature [12,16,18,21,24-26], a clear cut-off degree could not be defined [25].

Direct mechanical trauma causing damage to the tissue surrounding the pulmonary vein or deeper inside the lung could be caused by guide wire, catheters or by distal inflation of the CB [19,17], in this situation bleeding would be expected to occur immediately and is usually severe.

A possible mechanism for hemoptysis might be PV stenosis which causes vascular damage in the pulmonary capillary due to a pressure rise in absence of collateral circulation [15,20,22,27]. High cooling area near the tip of the second-generation balloon could explain reported cases with PV stenosis after CBA [28]. However, RFA is not away from this serious complication [29]. The Fire and Ice Trial reported no cases with PV stenosis [3]. Stop af Pas study recognized asymptomatic PV stenosis in <1% of its population. This reduction in PV stenosis over time is related to increased operator experience resulting in more appropriate positioning of CBA and a reduction in the number and duration of applications [10]. These results almost downgrading PV stenosis as a true cause for hemoptysis after CBA.

Close proximity of PVs to bronchial tree special LSPV and longer duration of ablation both have been reported to predict bronchial injury after cryo-ablation [13,30, and 31]. Animal studies done by Aryana A, et al. (2016) reported not the prolonged duration was possible culprit, but lower nadir temperature during CBA (~66°C vs –45°C) [32]. Bronchial mucosal edema, erythema and inflammation were reported in post-ablation bronchoscopy with these low temperatures. The mechanism for this appears to be direct collateral injury [32]. Cryoablation induced bronchial injury can manifest as life-threatening and catastrophic hemoptysis due to formation of atrial bronchial fistula with delayed presentation [11].

In a limited prospective observational study with real-time bronchoscopy was performed during CBA under general anesthesia, Ice formation was seen in the left mainstem bronchus at 50 seconds in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33]. The ice mass continued to grow in 7 of 10 patients (70%) with normal left atrial size without rapid decrease in balloon temperature [33].

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Coagulopathies, anticoagulation before CBA and intra-procedural ACTs were unlikely to be potential causes of hemoptysis. Furthermore, PV diameters did not play a role in the development of hemoptysis in comparison to control groups [25].

**Strategies for Prevention and Management of Pulmonary and Bronchial Damage After CBA of AF**

No definitive recommendations exist for the prevention and management of bronchial injury after CBA. There is potential time

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**Table 2: Percentage of different balloon size, onset of hemoptysis and oral anticoagulants.**

<table>
<thead>
<tr>
<th>Case reports</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 15 cases</td>
<td>Total 2051 patients (Cases 80)</td>
</tr>
<tr>
<td><strong>Balloon size</strong></td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td>28 mm</td>
<td>7 (46.7%)</td>
</tr>
<tr>
<td>23 mm</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td><strong>Onset of hemoptysis (% of reported cases)</strong></td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>0 (2.5%)</td>
</tr>
<tr>
<td>Intraprocedural</td>
<td>5 (33.3%)</td>
</tr>
<tr>
<td>After procedure within 24 hours</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>After procedure within first week</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>After one week</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>After one month</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td><strong>Anticoagulation before cryoablation</strong></td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>DOAC</td>
<td>7 (46.7%)</td>
</tr>
</tbody>
</table>

DOAC = Direct Oral Anticoagulants.
delay between occurrence, reporting, and documentation of hemoptysis after CBA. This is the reason why patients are often wrongly diagnosed, and physicians miss a link between lung disease and hemoptysis and a previous history of AF ablation.

Combination of imaging modalities (Bronchoscopy, CT, MRI) can provide valuable data on the exact cause of hemoptysis [20]. However computed tomography (CT) can be very useful in diagnosing the procedure complications, especially in the subacute and delayed phases post ablation. Patients who are suspected to have PV stenosis, TEE including Doppler measurements, V/Q lung scan and MRI or CT imaging may be used [35].

Patient selection may be important, those with dilated atria or superiorly directed pulmonary veins are likely to have higher risk of ice formation due to close anatomical proximity and relationship between the pulmonary veins and the bronchial tree particularly LSPV [33]. Understanding this relationship explain why bronchial tree is prone to collateral injury during CB ablation. Additionally, a skillful maneuver that might reduce cryoablation injury, such as step wise titration of freezing time and avoid low nadir balloon temperature, will lead to better outcomes [7]. Anyhow, careful manipulation of the guide wire and limitation of the number and duration of occlusions seems to be prudent advice with this potential complication in mind. Proposed algorithm in Figure 4 for prevention of hemoptysis post CBA for AF.

Our observation in this review showed that LSPV and RIPV (42.5% versus 35%) were the most culprit veins in reported patients with hemoptysis because of the close proximity of the left to left main bronchus (LMB) and difficult manipulation to adjust CB in the latter leading to deep seated location inside RIPV. Left main bronchus (LMB) to LSPV distance was an independent predictor of hemoptysis after CB ablation. A cutoff value ≤ 9.5 mm for LMB-LSPV distance had 93.8% sensitivity and 75.0% specificity, with a 68.3% positive predictive value and 95.2% negative predictive value [13]. Operators should be aware of coughing during cryo-application or during the thawing phase might be a predictor for bronchial injury [30].

It is important to educate the patients about delayed onset of hemoptysis after CBA so that an early diagnosis and intervention can be made. Conservative management with close follow up is usually satisfactory in most of the cases. Critical patients where transfer to CT is unsafe, intubation and flexible bronchoscopy is the diagnostic and therapeutic procedure of choice and can be performed at the bedside, if available [37]. Although the prognosis is not precisely known given limited data, on the basis of few studies and case reports it appears that most patients do well on follow- up [13,25]. Development of PV stenosis with cryoablation should be suspected with delayed hemoptysis and chronic pulmonary symptoms after CBA. In severe PV stenosis and or occlusion, dilatation of PV using balloon catheter or surgery might be needed. However, in rare catastrophic cases of atrio-bronchial fistula, surgical exploration via a left lateral thoracotomy is the emergency procedure of choice if other methods failed. Proposed algorithm in Figure 5 for Management of hemoptysis post CBA for AF.

Figure 5: Proposed algorithm for management of hemoptysis post CBA for AF.

**Conclusion**

Recently a concern has been raised about pulmonary complications during and after CBA. The long-term sequelae of CBA to the airways are, thus far, unexplored. This review highlights that hemoptysis post CBA is not uncommon and needs further investigation and innovations to identify potential bronchial injury during ablation. Careful selection of patients with careful manipulation during isolation of LSPV and RIPV with optimized freezing temperature will decrease hemoptysis incidence in the near future. The Positive aspect is that most of patients present with mild form of hemoptysis but with the fact that this complication has delayed occurrence. This also focus on the importance of alternative approaches or energy sources for ablation for AF.

**Declarations of Interest**

None.

**Consent of Publication**

The paper is not under consideration elsewhere and its content has not been published before. The manuscript has been read and approved by all named authors.

**Conflict of Interest**

The authors declare that there is no conflict of interests regarding the publication of this paper.
Competing Interests
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