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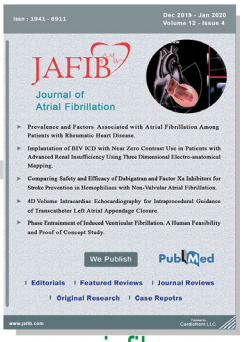

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Hemoptysis After Cryoablation For Atrial Fibrillation

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Abstract

Aim: Cryoballoon is a widely used tool for ablation for atrial fibrillation (AF). There are several complications after cryoablation. This paper assesses the incidence rate and severity of hemoptysis after cryo ablation for AF.

Methods: For current systemic review and meta-analysis, literature has been reviewed from 2008 to 2019 focusing on the incidence of hemoptysis after cryoballoon ablation for atrial fibrillation catheter ablation in PubMed, Cochrane library and EMBASE databases.

Results: This meta-analysis included 3534 patients from 20 studies; of mean age 54.0 ± 10.9 years. All patients had cryoballoon ablation for paroxysmal or persistent AF refractory to treatment and follow up duration for 8.2 ± 5.9 months with mean procedure duration of 153.4± 65.4 minutes. The mean cryoablation duration was 869.4 ± 148 sec with mean temperature of -59.7 ± 5.1°C and a total of 109 patients (3.08%) had hemoptysis which was mild in the majority of cases (76.1%), mild to moderate in 20.2% and severe in only 3.7%. Hemoptysis onset was at 29.0 ± 56.5 day with median of 7 days, range (2 hours to 210 days). In 11 studies hemoptysis occurred early in 51 patients (95% CI for I^2 was 0.0% to 0.0, P =0.95, I^2 was 0.0%), but in 9 studies, hemoptysis occurred late in 58 patients (95% CI for I^2 was 0.0% to 0.0, P =0.96, I^2 was 0.0%).

Conclusions: Mild hemoptysis is experienced by significant number of cryoballoon AF ablation patients and severe type in 3.5 % attributed to significantly lower temperature in inferior pulmonary veins and is more often associated with bigger cryoballoon.

Introduction

Catheter ablation is an effective treatment for atrial fibrillation (AF), and pulmonary vein (PV) isolation is considered the cornerstone of all AF ablation strategies. In recent years, balloon-based ablation has emerged as an encouraging alternative to RF ablation and is equally effective for PV isolation in patients with paroxysmal and persistent AF [(1)]. There are several reasons for this. The acute and long-term safety and efficacy associated with cryoablation appears comparable to that of radiofrequency ablation in patients with both paroxysmal and persistent types of AF. Moreover, cryoablation offers a milder learning curve, shorter ablation duration and overall procedure time and simultaneously avoiding costly electroanatomical mapping technologies. Lastly, with the recent advent of the second-generation cryoballoon, the effectiveness of cryoablation has further improved dramatically [(2)].

It is important to evaluate procedure-related complications described to date, to understand its mechanism and to take steps to minimize their occurrence. Complications of cryoenergy ablation may be due to damage of structures close to the application site, resulting in phrenic nerve (PN) paralysis, gastroparesis, atrioesophageal fistula, or esophageal lesions as collateral cryoablation damage. Until now few authors reported on hemoptysis after cryoballoon ablation but without regular follow-up or a definite etiology. Cryoablation causes vascular injury through multiple factors, including ice formation within the vasculature. The ice during expansion causes the formation of tears, clefts, leakages, and stasis postreperfusion. The interruption of vascular integrity is the reason for intramyocardial hemorrhage as well as for hemoptysis associated with cryoinjury to the lung tissue. A few reports on the effects of freezing have described acute lung injury due to cytokine release in about 35% of animal subjects [(3)].

Key Words

Cryoballoon, Atrial fibrillation, Hemoptysis, Complication, Temperature, Frozen lung.

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Methods

For this current systemic review and meta-analysis, Literature has been reviewed from January 2008 to March 2019 focusing on the incidence of hemoptysis after cryoballoon ablation for AF ablation

in PubMed, Cochrane library and EMBASE databases. Data were analyzed using MedCalc software (MedCalc Software, Mariakerke, Belgium) to perform meta-analysis to provide a numerical estimate of the overall effect of interest from separate but similar studies. Total fixed and random effects were calculated.

Statistical analysis

Data were analyzed using MedCalc software (MedCalc Software, Mariakerke, Belgium). Descriptive statistics were computed for different variables. Qualitative data were presented as number and percentages. Mean ± SD, median, range were calculated for quantitative variables. Meta-analysis was performed to provide a numerical estimate of the overall effect of interest from separate but similar studies. Total fixed and random effects were calculated. To assess heterogeneity, Cochran's Q test and I^2 statistic were calculated, Cochran's Q test with low P-values indicates presence of heterogeneity. I^2 statistic, is the percentage of observed total variation across studies that is due to real heterogeneity rather than chance. The results of the different studies, with 95% CI, and the overall effect (under the fixed and random effects model) with 95% CI are illustrated in a graph called "forest plot" [23].

Continuous variables are expressed as mean ± standard deviation and were compared with the Mann Whitney U-test as appropriate. The significance level was set at $p < 0.05$. The systemic review was conducted according to PRISMA guidelines.

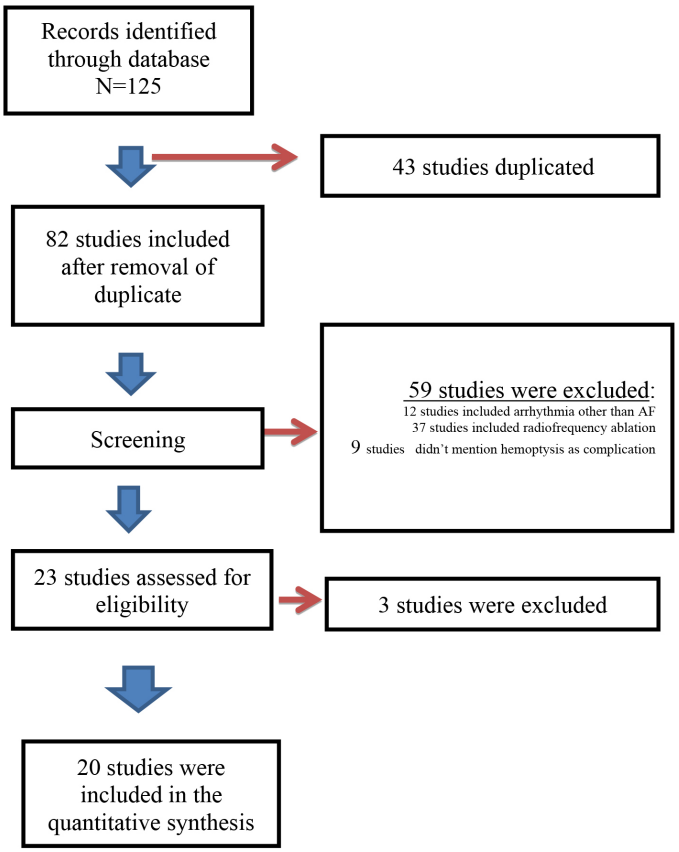


Figure 1: Overview of the manuscripts selected for the systemic review and meta-analysis.

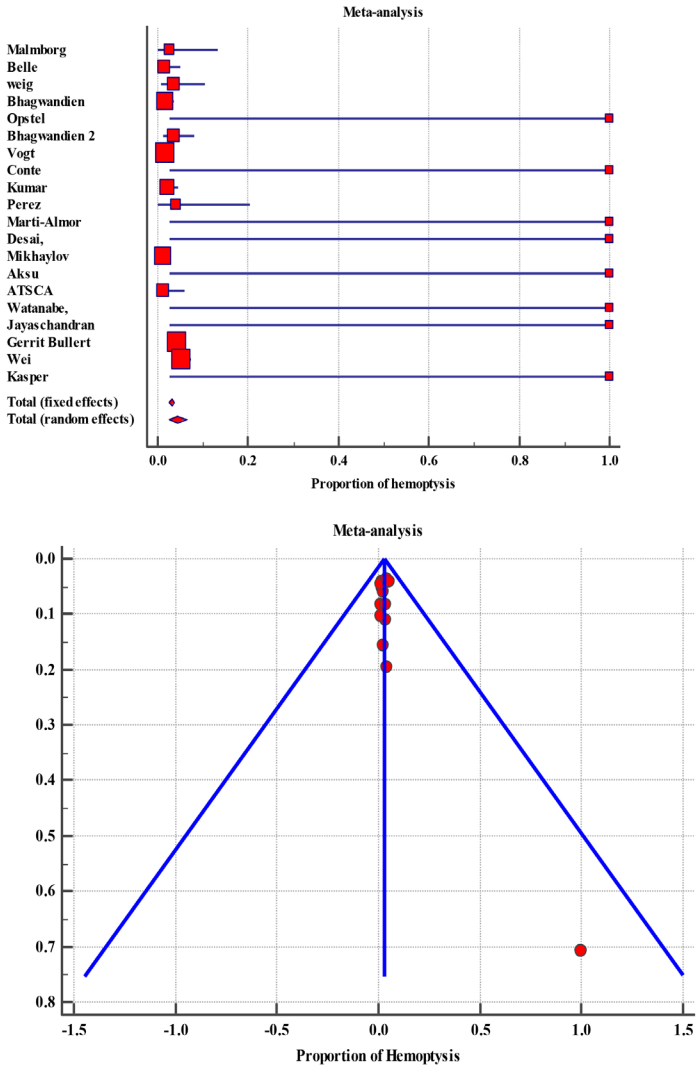


Figure 2: Meta-analysis of proportion and Forest plot for the proportions of hemoptysis incidence

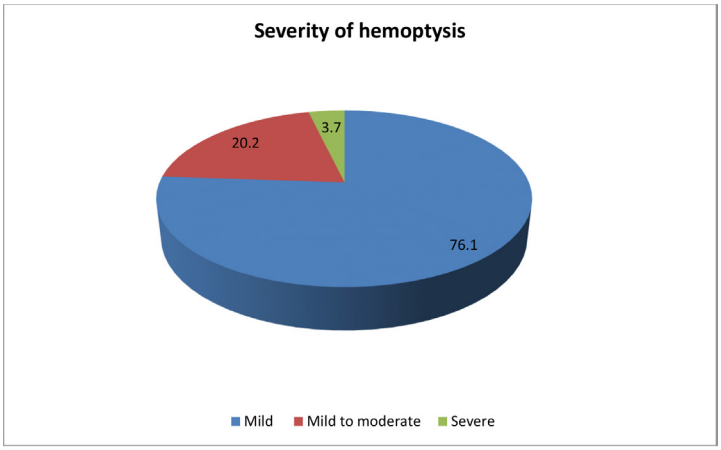
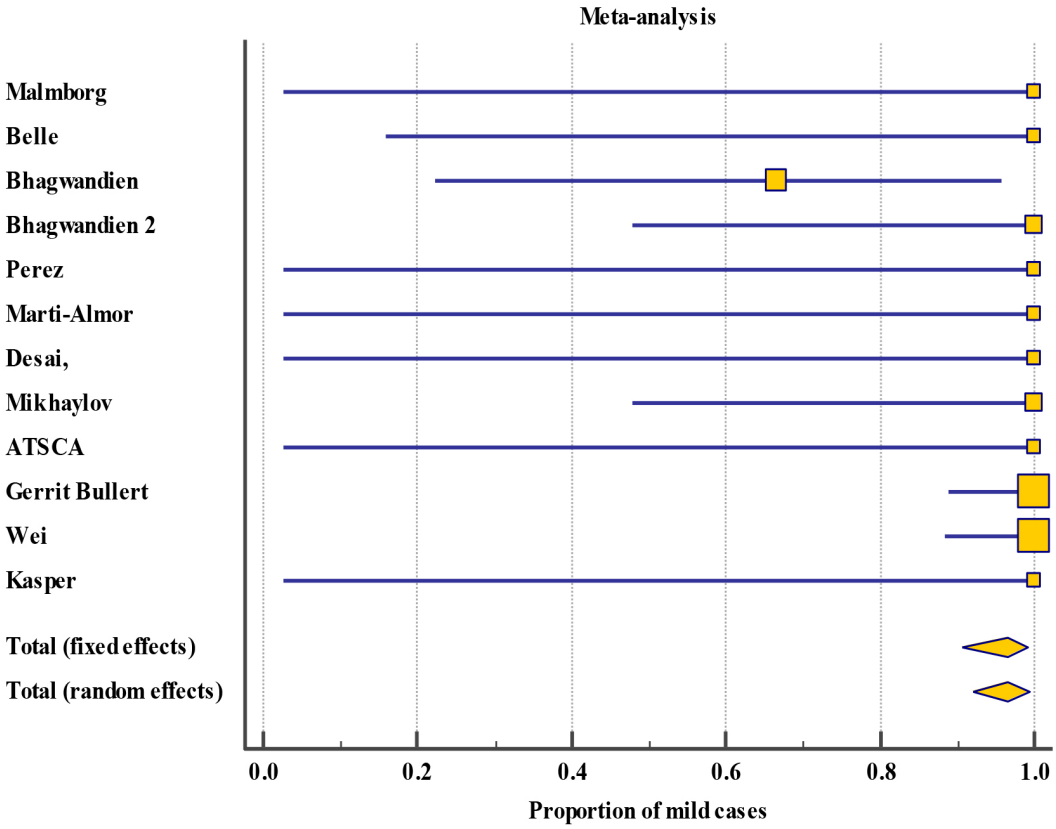


Figure 3: Severity of hemoptysis



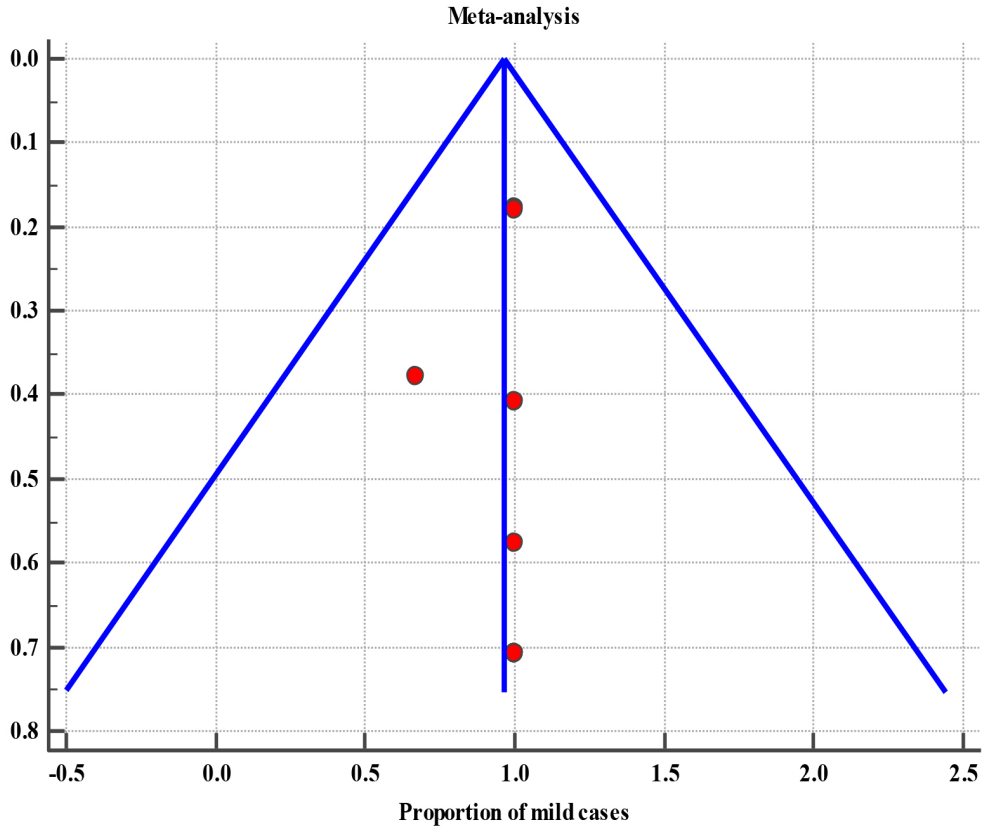
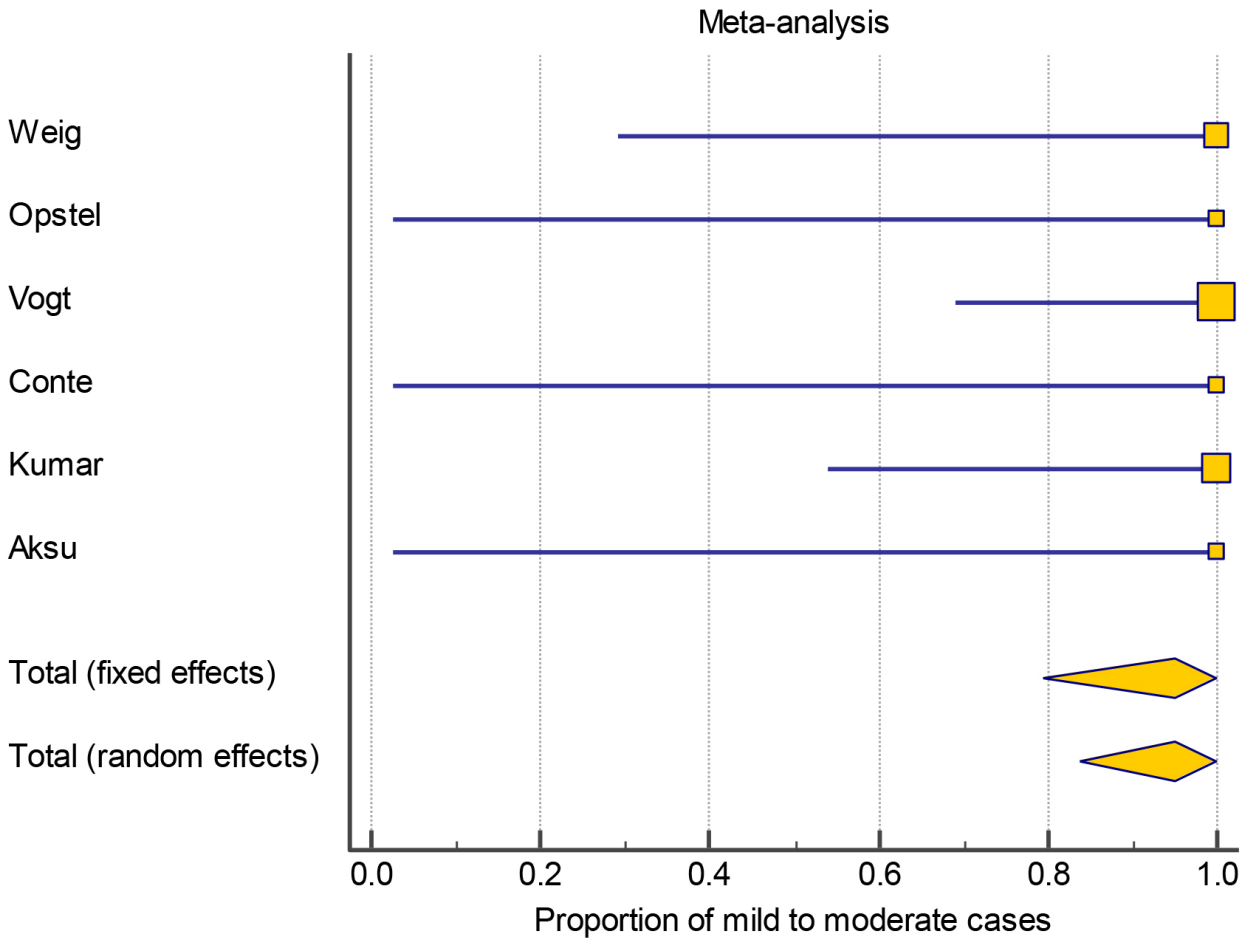


Figure 4: Meta-analysis and Forest plot for the proportions of mild hemoptysis



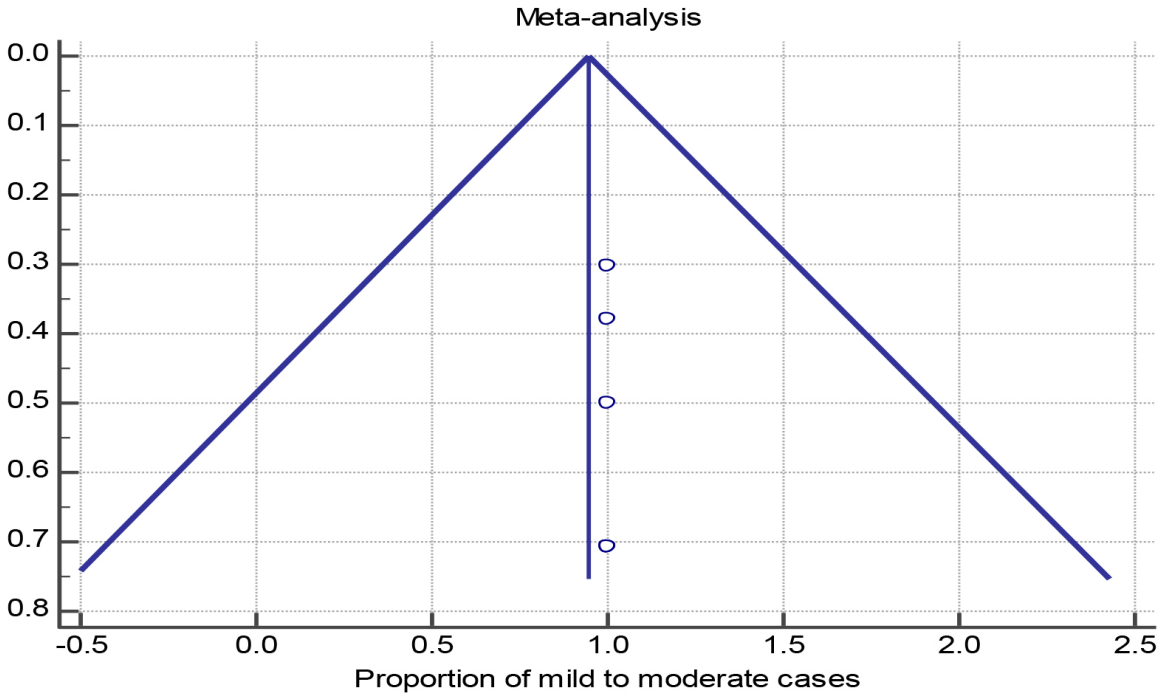


Figure 5: Meta-analysis and Forest plot for the proportions of mild to moderate hemoptysis

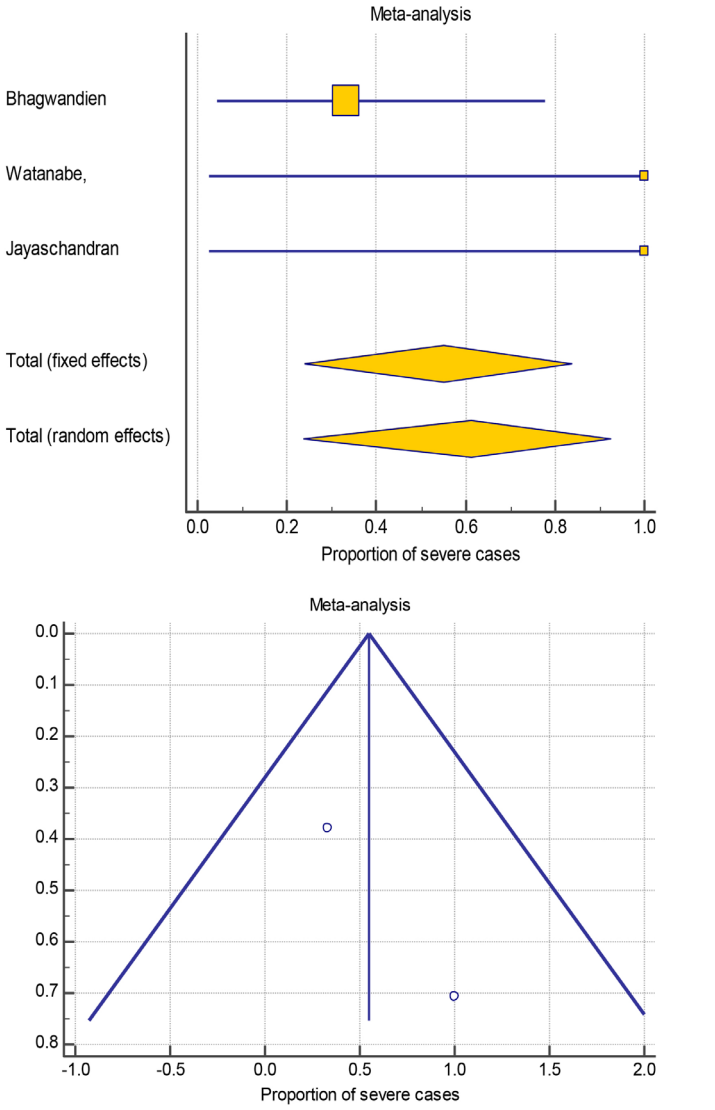


Figure 6: Meta-analysis and Forest plot for the proportions of severe hemoptysis

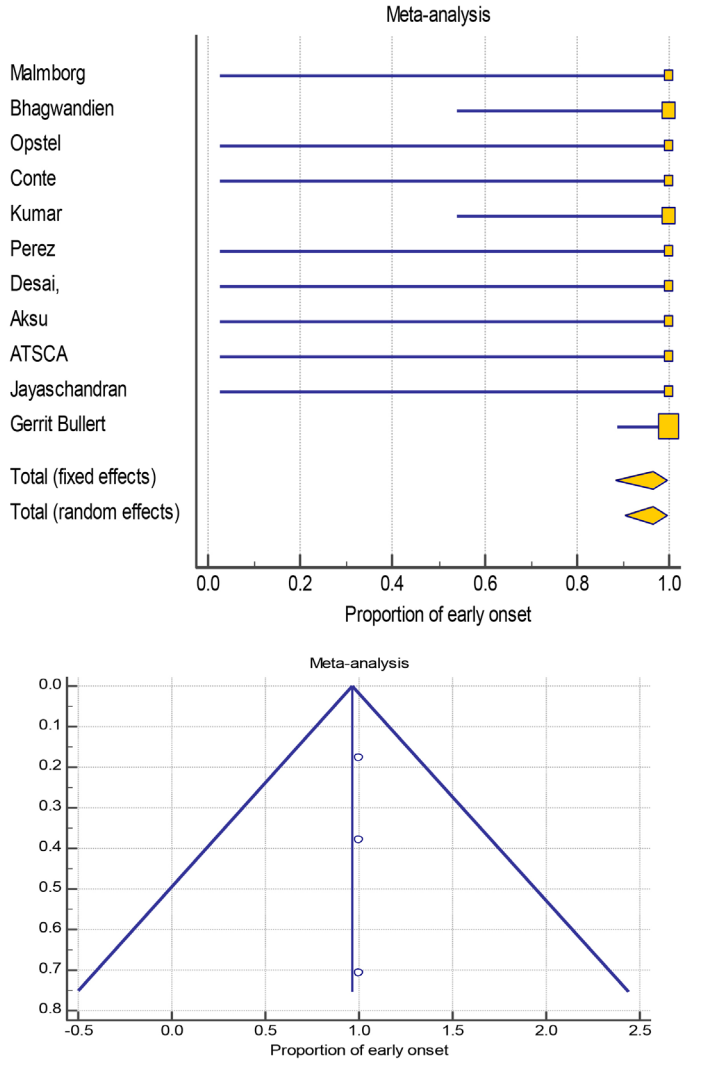


Figure 7: Meta-analyses and Forest plot for the proportions of early onset hemoptysis

Study selection criteria

Total of 125 studies were included through database and 43 studies were excluded as duplicate or irrelevant references. Further, a total of 59 studies were excluded by screening, and 3 more study by eligibility, so the final number of the studies included in the quantitative synthesis were 21 studies as shown in Figure 1 and 11. Of the 20 studies that were included in the meta-analysis, 8 studies were prospective while 2 were retrospective. The other 8 studies were case studies, with last 2 being surveys.

Study population

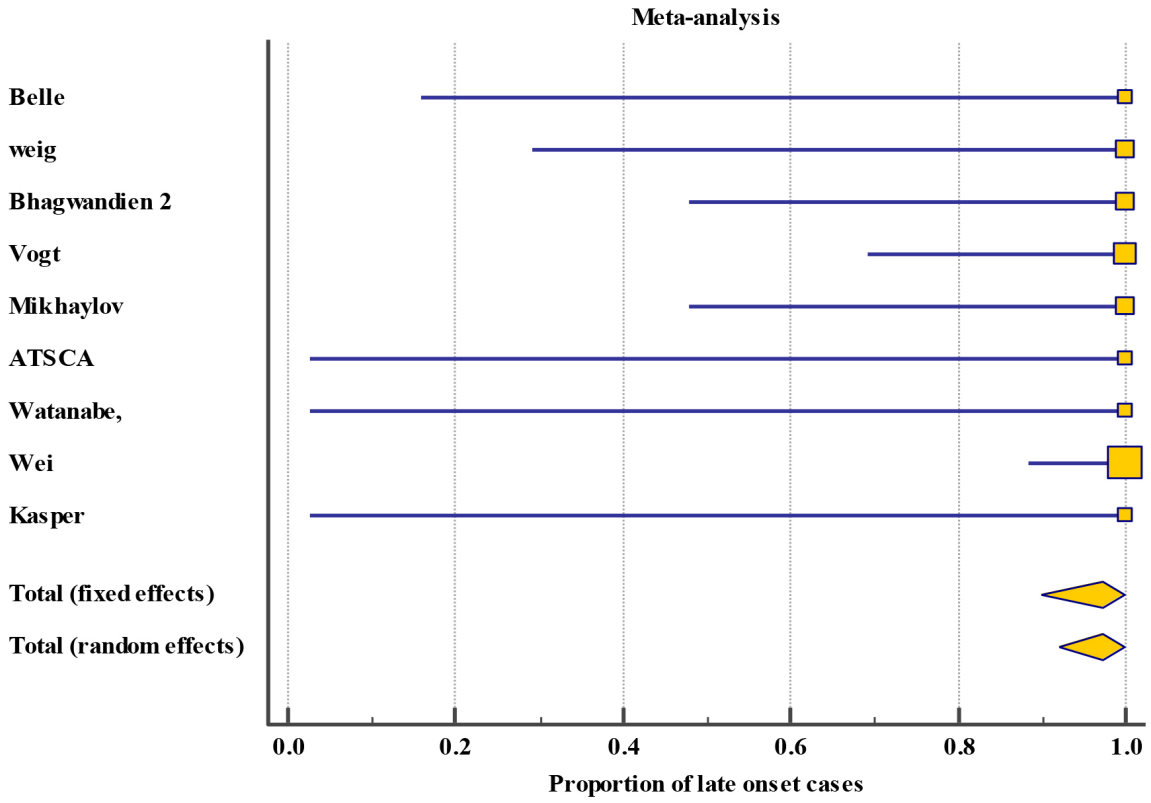
From 20 studies, a total of 3,534 patients of mean age 54.0 ± 10.9 years had balloon cryoablation for paroxysmal or persistent AF with follow up duration for 8.2 ± 5.9 month. The mean procedure duration was 153.4 ± 65.4 minutes, mean cryoballoon ablation duration was 869.4 ± 148 seconds and mean temperature was -59.7 ± 5.1 °C.

Incidence and severity of hemoptysis

Out of 3,534 patients included in the study; 109 patients 3.08% developed hemoptysis (95% CI for I^2 was 69.3 to 86.5, P < 0.001, I^2 was 79.7%) as shown in Figure 2. Hemoptysis was mild in the majority of cases i.e. 77%, and mild to moderate in 19.5% and severe in only 3.5% as shown in Figure 3.

Figure 4 shows that a total of 12 studies revealed mild hemoptysis in 83 patients (95% CI for I^2 was 0.0 to 55.8 %, P =0.50, I^2 was 0.0%). Figure 5 shows that a total of 6 studies demonstrated mild to moderate hemoptysis in 22 patients (95% CI for I^2 was 0.0 to 0.0 %, P =0.97, I^2 was 0.0%). Figure 6 shows that 4 studies demonstrated severe hemoptysis in 4 patients (95% CI for I^2 was 0.0 to 97.7%, P =0.227, I^2 was 32.4%).

Moreover, on doing detailed analysis further, bigger cryoballoon was



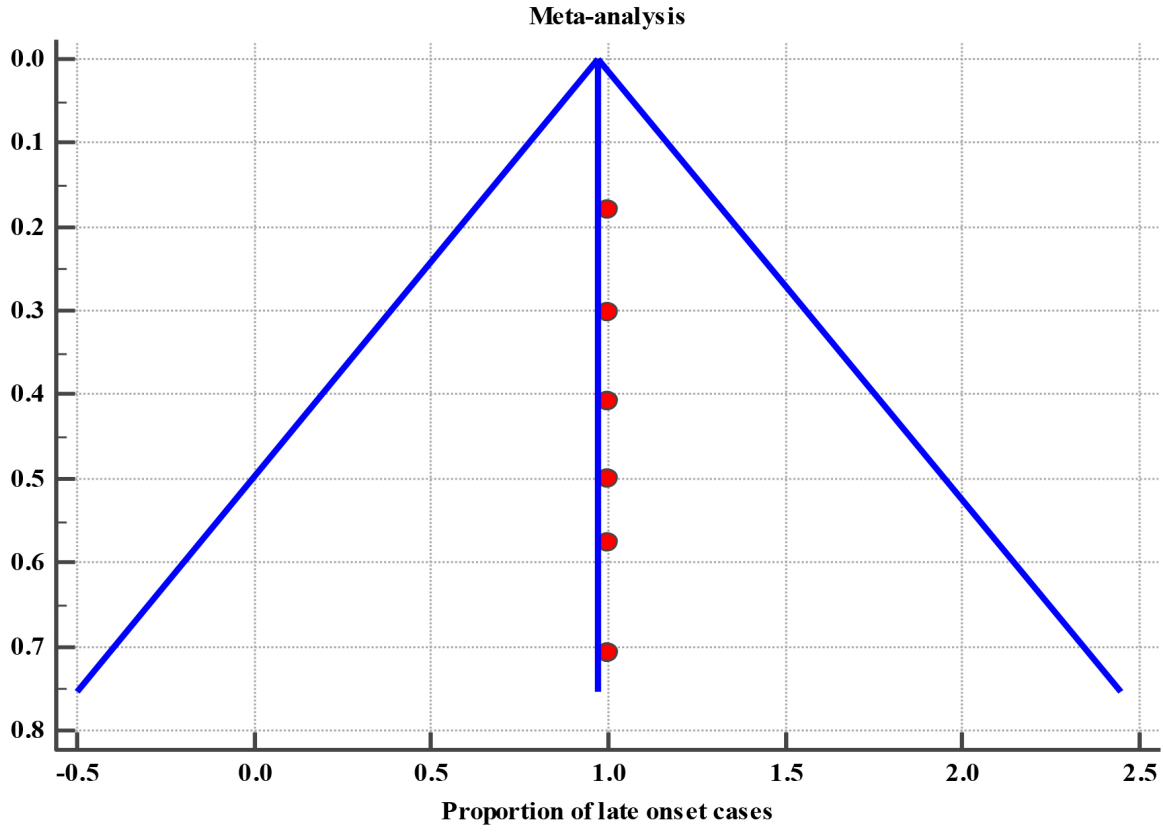


Figure 8: Meta-analysis and Forest plot for the proportions of late onset hemoptysis

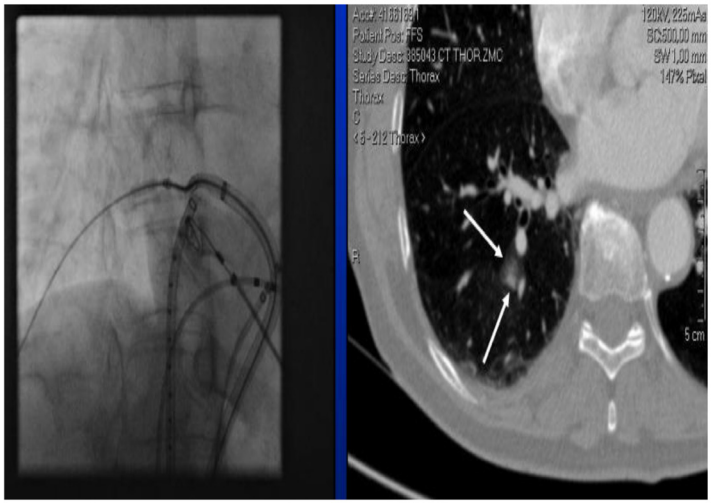


Figure 9: a)The deep position of the guide wire in the Right inferior pulmonary vein during intra procedural fluoroscopy. b) ground glass opacification seen on computed tomography scan.

Potential mechanism of hemoptysis:
• **Extremely low nadir temperatures (–60°C or lower):** lower nadir temperature during CB application (–66°C vs –45°C) showed increased bronchial mucosal oedema, erythema and inflammation in post-ablation bronchoscopy.
• **Deep seating of the CB:** collateral thermal injury of the bronchial tree
•**PV stenosis and obstruction**: induce lung circulatory stagnation and pulmonary artery dysfunction. this stagnation causes ischemia of the lung. this ischemia leads to overgrowth and abnormal development of the bronchial artery, which eventually dominates the ischemic lung and causes congestion in the lung because blood cannot flow to the left atrium. Finally, this rapidly developed fragile artery induces hemoptysis

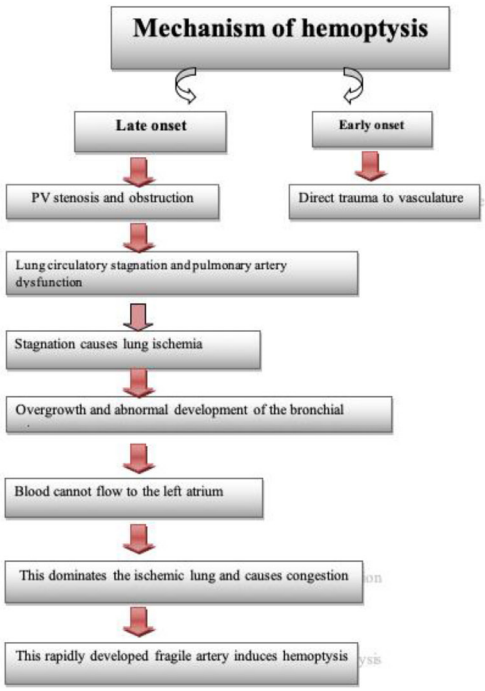


Figure 10: The potential mechanism for hemoptysis

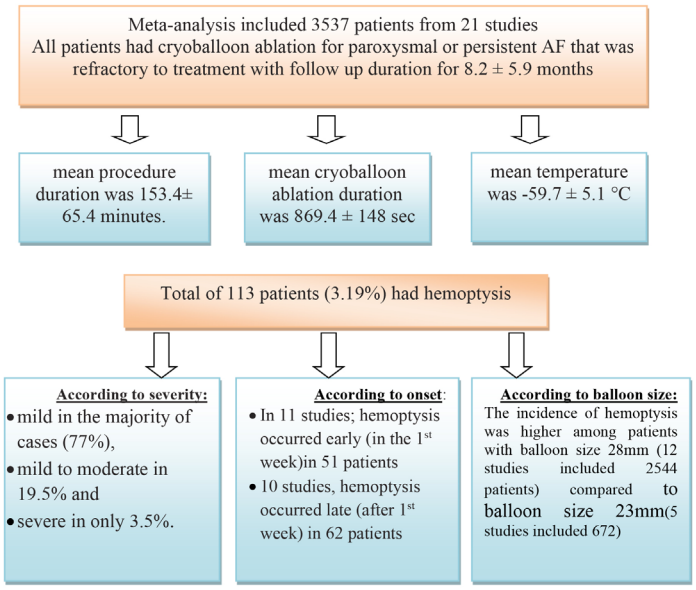


Figure 11: Central illustration for hemoptysis after cryoballoon ablation for atrial fibrillation.

associated higher incidence of hemoptysis as seen in supplementary file.

Onset of hemoptysis

The onset of hemoptysis was at the day 29.0 ± 56.5 after cryoablation with median of 7 days, and range of 2 hours to 210 days. Considering the median of 7 days, the hemoptysis onset was classified into

1) early onset: starting in the 1st week and

2) late onset: starting after 1st week.

As per Figure 7, a total of 11 studies revealed hemoptysis occurred in 51 patients within the 1st week of procedure (95% CI for I^2 was 0.0 to 0.0%, P =0.95, I^2 was 0.0%). However, Figure 8 shows that 9 studies with 58 patients developed late hemoptysis (after 1 week of procedure) (95% CI for I^2 was 0.0 to 0.0%, P =0.96, I^2 was 0.0%).

Discussion

Hemoptysis has been reported sporadically by different authors following cryoablation of AF with varying incidence. The present paper emphasizes the association between hemoptysis and cryoballoon ablation of AF which is attributable to significantly lower temperature in inferior PVs. Transient interruption of vascular integrity, perhaps within the pulmonary capillary system due to cryoinjury, has been postulated as the reason for hemoptysis. Very low freezing temperature (which always is associated with good isolation) is the etiology for hemorrhagic infarction and the hemoptysis [9,17]. A possible mechanism might be that a complete isolation with very low freezing temperatures causes cryo-injury to the adjacent tissues and vasculature as summarized in Figure 10. Based on the evidence till date, both the clinical symptoms and findings appear to be self-limiting, with gradual resolution over time [10-14]. No evidence has shown that these cases are associated with catastrophic complications, such as the formation of a fistula [3]. Bronchial erosion can also be detected during bronchoscopy [15-16]. Moreover, an argument against direct trauma is the fact that in some cases it took several hours to days for the hemoptysis to become clinically overt. When causing

a vascular rupture through instrumentation, bleeding would be expected to occur immediately and is usually severe. PV ablation might cause vascular damage in the pulmonary capillary tissue caused by a pressure rise when no collateral circulation is present. Meanwhile, it might be wise to limit the number of occlusions, or to shorten the occlusion time to a minimal duration [9]. But mechanisms leading to complications have not been studied in details and the underlying mechanism, onset and severity were different in clinical trials as we can see from previous experience [18-21]. Below are several important studies who reported hemoptysis after cryoballoon ablation of AF.

Weig et al investigated 82 patients with paroxysmal AF who underwent single big cryoballoon technique for PV isolation and were followed up for 5 months. In 3 patients with a minimum temperature of −56°C and −59°C at a rather small left inferior and right inferior PV, respectively, a CT documented frozen lung complication, leading to coughing and hemoptysis for a maximum of one week. This complication forced them to stop post interventional anticoagulation [7].

In a series of 359 cryoballoon ablations, Bhagwandien et al [8] discovered clinically important hemoptysis requiring readmission in 2 patients. In the first patient the guiding wire was very distal in one of the veins and exceptional low freezing temperatures (-55° c) were recorded in the left inferior PV. Four additional patients complained of hemoptysis at the 3-month follow-up visit, which resolved after temporary cessation of anticoagulation. The authors concluded that hemoptysis can occur after cryoballoon ablation when a stringent anticoagulation regimen is adhered to, and when occlusion is associated with very low freezing temperatures. The authors further observed that PV isolation using a cryoballoon on 142 patients with AF was associated with hemoptysis in 4% of the patients. [9]

Vogt et al conducted a prospective observational study involved 605 consecutively enrolled patients with symptomatic paroxysmal AF (n = 579) or persistent AF. After 24 months. Hemoptysis with hematoma or edema around PVs was observed in 10 cases, all of which healed within 10 days. Patients remained free of hemoptysis during the follow-up period. [10]

Recently, Wei et al observed that 30 patients developed hemoptysis after second generation cryoballoon ablation, and it was compared with a matched control group. PV isolation was performed with 28-mm balloon using single 3-minute freeze technique. A shorter distance between left superior PV (LSPV) and left main bronchus (LMB) was associated with hemoptysis, whereas no significant difference in the distance between right superior PV (RSPV) and right main bronchus (RMB) was found between groups. LMB-LSPV distance as an independent predictor of hemoptysis (odd ratio 2.676; 95% CI 1.121–4.843, P < 0.001). A cutoff value ≤ 9.5 mm predicted hemoptysis after cryoballoon ablation with 93.8% sensitivity and 75.0% specificity [22].

Conclusion

Physicians must keep hemoptysis in mind with other complications during and after Cryoballoon ablation for AF. It has maximum incidence during and up to few days after procedure and is independent of other complications like phrenic nerve paralysis, gastroparesis. Dexterity of PV location does not influence the incidence. A high degree of suspicion is necessary to avoid misleading diagnostic procedures and to allow proper and prompt management.

References

1. Schmidt B, Neuzil P, Luik A, et al. Laser balloon or wide-area circumferential irrigated radiofrequency ablation for persistent atrial fibrillation: a multicenter prospective randomized study. Circ Arrhythm Electrophysiol 2017;10:pii:e005767.
2. Aryana A, Bowers MR, O'Neill PG. Outcomes Of Cryoballoon Ablation Of Atrial Fibrillation: A Comprehensive Review. J Atr Fibrillation. 2015;8(2):1231. Published 2015 Aug 31.
3. Blackwell TS , Debelak JP , Venkatakrishnan A , et al . Acute lung injury after hepatic cryoablation: correlation with NF-kappa B activation and cytokine production. Surgery . 1999 ; 126 (3): 518 - 526 .
4. Chen S, Schmidt B, Bordignon S, Bologna F, Nagase T, Perrotta L and Julian K. Practical Techniques in Cryoballoon Ablation: How to Isolate Inferior Pulmonary Veins Arrhythmia & Electrophysiology Review 2018;7(1):11–7.
5. Malmborg Helena, Lönnerholm Stefan, Blomström-Lundqvist Carina. Acute and clinical effects of cryoballoon pulmonary vein isolation in patients with symptomatic paroxysmal and persistent atrial fibrillation. Europace. 2008 Nov;10 (11):1277–80.
6. Van Belle Y, Janse P, Theuns D, et al. (2008) One year follow-up after cryoballoon isolation of the pulmonary veins in patients with paroxysmal atrial fibrillation. Europace Nov; 10(11): 1271–
7. Weig, H. J., Weretka, S., Parade, U. et al (2010) Cryo-specific complications using the single big cryoballoon technique for pulmonary vein isolation in patients with paroxysmal atrial fibrillation. European Heart Journal Conference: European Society of Cardiology, ESC Congress 2010 Conference Publication: (var.pagings) 556
8. Bhagwandien Rohit, Van Belle Yves, de Groot Natasja, Jordaens Luc. Hemoptysis after pulmonary vein isolation with a cryoballoon: an analysis of the potential etiology. J. Cardiovasc. Electrophysiol. 2011 Sep;22 (9):1067–9.
9. Bhagwandien, R., Knops, P., VAN, Belle Y., Szili-Torok, Tet al. Haemoptysis after pulmonary vein isolation with a cryoballoon: An increased risk is associated with extreme low freezing temperatures. European Heart Journal Conference: European Society of Cardiology, ESC Congress 2011 Conference Publication: (var.pagings) 801-802.
10. J. Vogt, J. Heintze, K.J. Gutleben, B. Muntean, D. Horstkotte, G. Nölker Long-term outcomes after cryoballoon pulmonary vein isolation J Am Coll Cardiol, 61 (2013), pp. 1707-1712
11. Conte G., Chierchia G.B., Casado-Arroyo R., Ilsen B., Brugada P. Pulmonary vein intramural hematoma as a complication of cryoballoon ablation of paroxysmal atrial fibrillation. J. Cardiovasc. Electrophysiol. 2013;24:830–831
12. Kumar Narendra, Timmermans Carl, Das Marco, Dassen Willem, Philippens Suzanne, Maessen Jos, Crijns Harry J. Hemoptysis after cryoablation for atrial fibrillation: truth or just a myth? Chest. 2014 Nov;146 (5):e173–5.
13. Pérez-castellano N, Fernández-cavazos R, Moreno J. The COR trial : A randomized study with continuous rhythm monitoring to compare the ef fi cacy of cryoenergy and radiofrequency for pulmonary vein isolation. Hear Rhythm. 2014;11(1):8-14.
14. Martí-Almor Julio, Jauregui-Abularach Miguel E, Benito Begoña, Vallès Ermengol, Bazan Victor, Sánchez-Font Albert, Vollmer Ivan, Altaba Carmen, Guijo Miguel A, Hervas Manel, Bruguera-Cortada Jordi. Pulmonary hemorrhage after cryoballoon ablation for pulmonary vein isolation in the treatment of atrial fibrillation. Chest. 2014 Jan;145 (1):156–7

15. Desai AK, Osahan DS, Undavia MB, Nair GB. Bronchial injury post-cryoablation for atrial fibrillation. Ann Am Thorac Soc. 2015; 12:1103–1104.
16. Evgeny N. Mikhaylov, Dmitry S. Lebedev, Evgeny A. Pokushalov, et al., "Outcomes of Cryoballoon Ablation in High- and Low-Volume Atrial Fibrillation Ablation Centres: A Russian Pilot Survey," BioMed Research International, vol. 2015, Article ID 591603, 8 pages, 2015. https://doi.org/10.1155/2015/591603.
17. Aksu T, Golcuk SE, Yalin K. Haemoptysis and pulmonary haemorrhage associated with cryoballoon ablation. Published on behalf of ESC 2015:1-2.
18. Kumar N, Dinh T, Phan K, et al. Adenosine testing after second-generation cryoballoon ablation (ATSCA) study improves clinical success rate for atrial fibrillation. 2015:871-876. doi:10.1093/europace/euu352
19. Watanabe K, Nitta J, Sato A, Goya M. Hemoptysis after fi ve months of cryoballoon ablation : What is the relationship ? Hear Rhythm Case Reports. 2017;3(7):357-359. doi:10.1016/j.hrcr.2017.05.010
20. Bullert K, Gutleben K, Horstkotte D, et al. Hemoptysis as a side effect of cryoballoon pulmonary vein isolation in atrial fibrillation : a retrospective case-control study. Journal of Interventional Cardiac Electrophysiology 2018. /doi.org/10.1007/s10840-018-0468-2
21. 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 cryoballoon catheter ablation for atrial fibrillation. Pol Arch Med Wewn. 2016;126:94-96.
22. Wei H-Q, Guo X-G, Zhou G-B, et al. Predictors of hemoptysis in the setting of pulmonary vein isolation using the second-generation cryoballoon. J Cardiovasc Electrophysiol. 2018;29:958–965.
23. Julian P T Higgins, Simon G Thompson, Jonathan J Deeks, Douglas G Altman. Measuring inconsistency in meta-analyses, BMJ volume 327 6 September 2003 bmj.com.