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Hemoptysis as a side effect of cryoballoon pulmonary vein isolation in atrial fibrillation: a retrospective case-control study

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Abstract

Purpose Hemoptysis and pulmonary hemorrhage are rarely described as complications of cryoballoon ablation for pulmonary vein isolation (CB PVI). This study evaluated a large cohort to determine the frequency and risk factors for manifestation of these complications and assess the clinical relevance of hemoptysis after CB PVI.

Methods Seven hundred fifteen consecutive patients (351 female) from a single-center database were evaluated to identify those who developed hemoptysis after CB PVI.

Results A total of 31 patients with hemoptysis (4.3%; 2 female, age 60.5 ± 11.5 years) were matched with a control group ($n = 31$). Hemoptysis developed within 72 h after CB PVI. Cases versus controls had significantly lower ablation temperatures in the right inferior pulmonary vein (PV) (− 56.2 ± 26.6 vs − 49.1 ± 13.2 °C; $p = 0.004$) and left inferior PV (− 56.4 ± 11.9 vs − 47.2 ± 7.6 °C; $p = 0.001$). A trend to lower temperatures not reaching the level of significance was also found for the superior PV. All other procedural parameters were not significantly different between cases and controls. Although pre-procedural hemoglobin levels were comparable, post-procedural hemoglobin was lower in cases versus controls (12.9 ± 1.6 vs 13.7 ± 1.5 g/dL; $p < 0.05$). Twenty-six patients presenting with hemoptysis underwent chest CT scan, which showed perivenous infiltration at either the right ($n = 23$) or left inferior PV ($n = 2$) or no infiltrate ($n = 1$). No negative long-term effects were reported after 3, 6, and 12 months' follow-up.

Conclusions Post-procedural hemoptysis after CB PVI is a relatively frequent finding and was associated with low freezing temperatures and pulmonary tissue infiltration predominantly located at the right inferior PV. Hemoptysis resolved without long-term sequelae.

Keywords Cryoballoon ablation · Atrial fibrillation · Hemoptysis · Pulmonary hemorrhage · Complications

1 Introduction

Pulmonary vein isolation (PVI) is recommended as a first-line treatment option for patients with paroxysmal atrial fibrillation (pxAF) based on Class I evidence [1]. Radiofrequency current has long been the standard energy source for PVI [2], but cryoballoon (CB) PVI is now considered equally successful [3].

CB ablation has recently been shown to be effective for persistent AF [4]. Given that the number of this type of procedure is increasing, it is important to evaluate procedure-related complications described to date and take steps to minimize their occurrence [5, 6]. One such complication is hemoptysis, with or without pulmonary hemorrhage [7]. Data is limited to case reports and small case series on hemoptysis after CB PVI, but available data suggest that lower peri-procedural temperatures are associated with perivenous tissue defects. However, this remains speculative given the paucity of data [7–13]. This study was designed to make a detailed evaluation of hemoptysis and pulmonary hemorrhage in a larger cohort and determine factors associated with this complication to facilitate its avoidance in the future.

2 Methods

2.1 Patients

Electronic records for all patients ($n = 715$) who underwent CB PVI for drug-refractory pxAF in our heart center between 2005 and 2014 were evaluated. Patients with hemoptysis

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(defined as coughing up blood or blood-stained mucus from the respiratory tract) were identified and matched one-to-one by means of individual matching by age, gender, and body mass index with a control group who did not have any complications. In detail, the controls were picked one to one from the entire cohort. The first criterion was age. Because there were several controls in each case of the same age, individuals with the same body mass index could be selected from these controls. After this was done, there were several controls in each case of the same age and BMI left, so it was even possible to assign controls of the same gender. All patients had an indication for CB PVI in accordance with the relevant guidelines and provided signed informed consent prior to CB PVI. The study was approved by the ethics committee of the Ruhr-Universität Bochum, Sitz Bad Oeynhausen.

2.2 Periprocedural management

Twenty-four hours prior to the ablation procedure, age, height, and weight were documented, and ECG, chest X-ray, routine blood examination, and transthoracic (TTE) and transesophagal echocardiography (to exclude left atrial thrombi) were performed. In M-mode TTE, the left atrial (LA) diameter in a parasternal long-axis view and the ejection fraction (Simpson's method) were measured. Antiarrhythmic drugs, except for amiodarone, were discontinued at least three half-lives before the ablation procedure. Vitamin K antagonists (VKAs) were continued with a target international normalized ratio (INR) of 2.5 (range 2.0–3.0 was acceptable). Direct oral anticoagulants (DOACs) were discontinued one half-life before ablation. All patients underwent TTE within 2 h of CB PVI to assess for pericardial effusion (PE) and had ECG monitoring for at least 36 h. Anticoagulation with VKA, DOAC or, if necessary, intermittent use of heparin, was restarted within 2 h after CB PVI. For a 3-month period after ablation, antiarrhythmic drugs were prescribed at the operator's discretion.

2.3 Ablation procedure

The CB ablation procedure was performed as described previously [14, 15] without use of intracardiac echocardiography (ICE). Fentanyl and propofol were used for conscious sedation and analgesia, adjusted based on individual patient requirements. Stimulation of the phrenic nerve was performed with a quadripolar catheter (Dynamic XTTM Boston Scientific, Marlborough, MA, USA) placed in the superior vena cava. A steerable sheath (Flexcath, Medtronic, Minneapolis, MN, USA) was used for trans-septal access and guidance of the CB. A 28-mm CB (Arctic Front Advance, Medtronic, Minneapolis, MN, USA) was the first choice in all procedures independent of PV diameters; a 23-mm CB was chosen in cases of insufficient occlusion or unsuccessful attempts to isolate a PV. For PV mapping before and after ablation, a circumferential multipolar mapping catheter (AchieveTM Mapping Catheter, Medtronic, Minneapolis, MN, USA) was introduced, followed by PV angiography (NIH closed-end four side holes, Cordis Corporation, Miami Lakes, FL, USA). Starting early in 2013, PV angiography was skipped and replaced by intracardiac echocardiography. After balloon inflation and placement, the effectiveness of PV occlusion was controlled by contrast injection followed by angiographic verification in the early freezing period. Freezing time was either 2 × 180 or 2 × 240 s. The previously described "hockey stick" and "pull-down" techniques were applied to achieve complete occlusion, if required [16]. In case of pull-down maneuver at 120 s, freezing time was prolonged for another 180 s, up to 240 s. Phrenic nerve function was checked in both groups by constant palpation of abdomen for diaphragmatic contractions during ablation of the right superior PV under phrenic nerve stimulation. After freezing, PVs were re-evaluated 20 min after ablation, confirming the persistence of pulmonary vein isolation (PVI). Activated clotting time (ACT) was evaluated before trans-septal puncture and every 20 min thereafter. Heparin 10,000 U was administered before trans-septal access and additional heparin applications were performed depending on ACT, with a target value of > 350 s.

2.4 Data collection

The following parameters were collected for both groups: age, height, weight, timing of ablation, latest hemoglobin (Hb) level, INR, PTT and thrombocytes within 24 h before ablation, lowest Hb level over the 72 h after ablation, heparin used (IU) and maximum ACT during ablation, angiographic size of the PV ostia, balloon size, summarized time of ablation freezes per PV, lowest temperature achieved per vein, and balloon size. Radiological examinations were evaluated with respect to signs of bleeding.

2.5 Follow-up

All patients stayed in hospital for at least 36 h after the procedure. Thereafter, they were routinely scheduled for follow-up including a clinical visit and ambulatory 7-day Holter monitoring at 3, 6, and 12 months after CB PVI. AF episodes lasting longer than 30 s were counted as recurrence. In case of external follow-up, data were collected from the patients' cardiologists or other physicians with particular focus on impairment potentially related to lung injury.

2.6 Statistical analysis

All statistical analyses were performed using SPSS-IBM software, version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous data are presented as mean ± SD. Categorical

variables were compared using the chi-square test. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test whether a single univariate sample differs significantly from a normal distribution. Comparisons of continuous data were performed with a Student's *t* test. The Mann-Whitney *U* test was used to compare differences between two independent groups when the dependent variable was either ordinal or continuous, but not normally distributed.

A forward selection of the age, height, weight, BMI, the maximum ACT during ablation, angiographic size of the PV ostium, the summered time of ablation freezes per PV, and the nadir temperature was done to identify predictive variables for pulmonary tissue infiltration in patients developing hemoptysis. Subsequently, a multivariate logistic regression analysis was performed.

Two-sided p value < 0.05 was considered statistically significant.

3 Results

3.1 Patient characteristics

The characteristics of the two groups and pre-procedural laboratory findings are outlined in Table 1. The matching process was effective because baseline characteristics did not differ significantly between cases and controls.

3.2 Hemoptysis and imaging

Hemoptysis occurred within 72 h post intervention in 31 patients (4.3% of the total sample); hemoptysis was more common in men ($n = 29$) than in women ($n = 2$). Radiology was used to diagnose hemoptysis in all cases (chest CT scan in 26 cases, MRI in 1 patient, and two-plane chest X-ray only in 4 patients). In 23 pts who underwent a CT scan, perivenous hematoma/infiltrate was identified at the opening area of the right inferior pulmonary vein (RIPV) (Fig. 1), 2 patients had infiltrate identified at the opening area of the LIPV, and 1 had costophrenic angle effusion on the right but no hemorrhage. There were no abnormalities on three of the four chest X-rays and the MRI, but one chest X-ray showed costrophrenic angle effusions and no hemorrhage.

3.3 Relation to procedural parameters

The ablation temperature was lower in all 4 veins in cases versus controls, but this only reach statistical significance for our RIPV ($p = 0.004$) and the left inferior pulmonary vein (LIPV) ($p = 0.001$). Although a strong trend was found for lower temperatures in the case group, there were no statistically significant between-group differences in ablation temperatures for the left superior pulmonary vein (LSPV) and right superior pulmonary vein (RSPV) in a *t* test comparison (Table 2). When focusing on ablation temperatures at PVs adjacent to abnormal radiological findings, lowest temperatures were − 37 to − 75 °C (mean − 57 °C) at the RIPV and − 37 to − 75 °C (mean − 61 °C) at the LIPV. However, clear cut-off values could not be defined, particularly for veins adjacent to radiological findings, where a temperature of − 50 °C was not reached in 6 of 23 RIPV.

PV diameters did not differ significantly between cases and controls (Table 3), and application times per PV were comparable (Table 4). The 23-mm balloon was used significantly more often in cases, especially for isolation of the LIPV ($p = 0.04$) (Table 5). Retrospective evaluation of all angiographies revealed no balloon placement inside the PV.

Maximum ACT during the procedure was similar in cases and controls (411 ± 102 s and 406 ± 121 s, respectively; $p = 0.628$). Furthermore, comparable amounts of unfractionated heparin were administered during the procedure to maintain therapeutic ACT levels (14,080 ± 3384 vs 14,161 ± 3726 IU, respectively; $p = 0.929$).

Table 1 Baseline characteristics in cases and controls

	Cases ($n = 31$)	Controls ($n = 31$)	*P* value
Age, years	60.5 ± 11.5	60.5 ± 11.5	1.0
Males, *n* (%)	29 (93.5)	29 (93.5)	1.0
BMI, kg/m^2	26.2 ± 2.9	27.0 ± 4.0	0.395[a]
INR[†]	1.6 ± 0.6	1.4 ± 0.6	0.302[a]
PTT, s[b]	32 ± 7	29 ± 6	0.082[a]
Thrombocytes, thousands/μL[b]	238 ± 47	215 ± 50	0.08[a]
Hb, g/dL[b]	14.8 ± 1.1	14.7 ± 1.3	0.687[a]

Values are mean ± standard deviation, or number of patients (%)

BMI body mass index, *Hb* hemoglobin, *INR* international normalized ratio, *PTT* partial thromboplastin time

[a] Student's *t* test

[b] Value within 24 h before cryoballoon pulmonary vein isolation

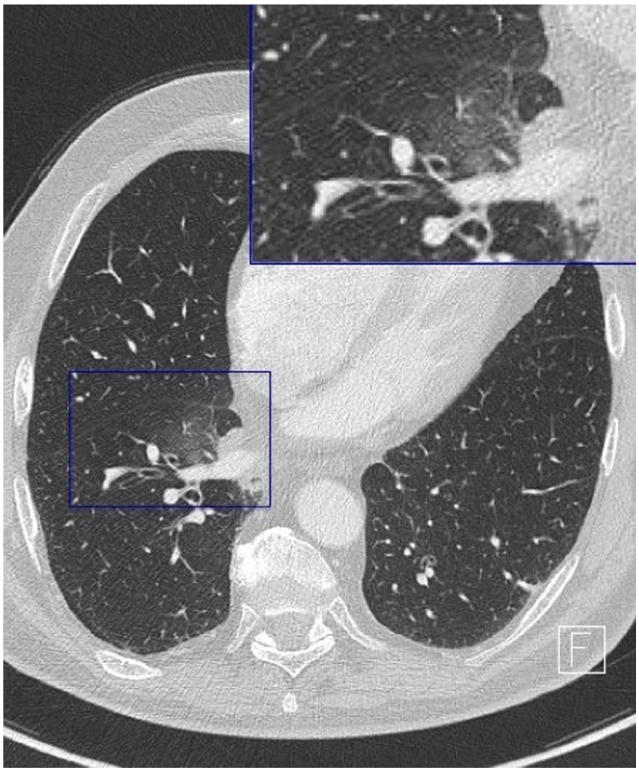

Fig. 1 Computed tomography depicting opacification due to perivenous hemorrhage around the right inferior pulmonary vein in a 77-year-old male patient

In a forward selection of the age, height, weight, BMI, the maximum ACT during ablation, angiographic size of the PV ostium, the summered time of ablation freezes per PV, and the nadir temperature, only the lowest temperatures could be identified as predictive variables. A multivariate subsequent logistic regression analyses demonstrated an increase of likeliness to belong to the case group with a decrease in temperature solely in the RIPV ($p = 0.049$).

Table 2 Nadir temperatures (°C)

	Cases ($n = 31$)	Controls ($n = 31$)	*P* value
LSPV	− 53.6 ± 9.7	− 49.1 ± 8.8	0.067[b]
LIPV	− 56.4 ± 11.9	− 47.2 ± 7.6	0.001[a]
RSPV	− 53.7 ± 7.7	− 49.9 ± 8.1	0.062[a]
RIPV	− 56.2 ± 26.6	− 49.1 ± 13.2	0.004[b]

Values are mean ± standard deviation

LIPV left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *PV* pulmonary vein, *RIPV* right inferior pulmonary vein, *RSPV* right superior pulmonary vein

[a] Student's *t* test

[b] Mann-Whitney *U* test

Table 3 Pulmonary vein diameters (mm)

	Cases ($n = 31$)	Controls (n = 31)	*P* value
LSPV	19.7 ± 2.8	21.0 ± 3.3	0.112[a]
LIPV	17.7 ± 3.4	17.0 ± 2.0	0.388[a]
RSPV	20.3 ± 2.6	19.5 ± 2.0	0.236[a]
RIPV	18.4 ± 2.8	19.2 ± 4.3	0.411[a]

Values are mean ± standard deviation

LIPV left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *PV* pulmonary vein, *RIPV* right inferior pulmonary vein, *RSPV* right superior pulmonary vein

[a] Student's *t* test

3.4 Laboratory findings

Hb measured within 24 h prior to CB PVI was similar in cases and controls ($p = 0.687$), but the lowest Hb recorded in the 72 h after the procedure was significantly lower in cases versus controls ($p = 0.046$).

3.5 Clinical outcome

No other complications or side effects were documented in either group. In particular, there were no further bleeding complications apart from hemoptysis and/or lung hemorrhage. Long-term follow-up did not identify any negative long-term effects as a result of lung hemorrhage, and no medical treatment for lung problems was necessary after hospital discharge. An early recurrence of atrial tachyarrhythmia within 3 months after ablation was observed in 8 cases and 12 controls ($p = 0.42$). During long-term follow-up, one patient died from prostatic cancer and one patient was lost to follow-up in the case group. Of the remaining 29 cases, 8 (27.6%) experienced recurrence of atrial tachyarrhythmias in a 12-month follow-up excluding a 3-month blanking period. In the control group, three patients were lost to follow-up. Of the remaining 28 control pts, 12 (42.9%) had atrial tachyarrhythmia recurrence respectively ($p = 0.27$ vs cases).

Table 4 Summary application time per pulmonary vein

	Cases ($n = 31$)	Controls ($n = 31$)	*P* value
LSPV	824.5 ± 304.0	761.9 ± 265.7	0.39[a]
LIPV	726.4 ± 248.0	798.9 ± 333.3	0.48[b]
RSPV	712.0 ± 317.5	810.3 ± 242.9	0.080[b]
RIPV	703.9 ± 319.4	773.9 ± 218.5	0.064[b]

Values are mean ± standard deviation

LIPV left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *PV* pulmonary vein, *RIPV* right inferior pulmonary vein, *RSPV* right superior pulmonary vein

[a] Student's *t* test

[b] Mann-Whitney *U* test

Table 5 Balloon size (mm)

	Cases (n = 31)	Controls (*n* = 31)	*P* value
LSPV (23 mm)	15 (50%)	9 (29%)	$p = 0.12^a$
LIPV (23 mm)	21 (70%)	13 (42%)	$p = 0.04^a$
RSPV (23 mm)	13 (43%)	10 (32%)	$p = 0.43^a$
RIPV (23 mm)	20 (67%)	14 (45%)	$p = 0.12^a$

Values are mean ± standard deviation

LIPV left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *PV* pulmonary vein, *RIPV* right inferior pulmonary vein, *RSPV* right superior pulmonary vein

[a] Fisher's exact test (two-sided)

4 Discussion

To the best of our knowledge, this is the largest study evaluating hemoptysis as a complication of CB PVI. The rate of hemoptysis in our population was 4.3%, with no negative medium-term effects. Although patients with hemoptysis had lower mean nadir temperatures during CB freezing impulses in the lower pulmonary veins than those from a matched control group, a clear cut-off value as a potential lower temperature limit for future procedures could not be defined.

Hemoptysis after CB PVI was first reported by Bhagwandien et al. [10]. One of the affected patients had known bronchiectasis while the other had no history of respiratory tract or pulmonary disease. Very low temperatures (down to − 76 °C) were recorded in one PV in one patient, and a guide wire had been advanced far into one pulmonary venous branch. In addition, angiography of the LIPV indicated that the balloon appeared to be oval-shaped, which is an indicator for placement of the balloon inside the PV. In the other patient, low temperatures had been registered during freezing of all PVs (− 62 to − 74 °C). In addition to those two cases, they described four additional cases of short-term hemoptysis after discharge, adding up to a rate of almost 1.7%. Aryiana A et al. [12] confirmed the potential for creating mucosal injury with low temperatures (− 66 ± 6 °C) in a porcine model. However, they also found bronchus irritation at adequate temperatures (− 46 ± 3 °C) in some animals. Several subsequent reports described an association between low temperatures and the occurrence of hemoptysis [9, 11], and a relationship between low temperatures and pathological bronchoscopic findings was demonstrated [9, 11, 13]. However, some authors have reported hemoptysis in patients where lowest temperatures were at or above − 50 °C [7, 17].

The previous reports are all consistent with the findings of our systematic analysis in a large cohort of patients. We found a clear relationship between temperature and the occurrence of hemoptysis in the inferior PVs. However, because we were able to localize the site of injury using CT or MRI in a relevant proportion of patients (81% of all patients, 93% of those undergoing CT or MRI), we could also clearly demonstrate that injuries are not necessarily linked to temperatures below − 50 °C during freezing in the adjacent PV. This is clinically relevant because discontinuation of the application at − 50 °C might not prevent injury of pulmonary tissue.

Interestingly, perivenous infiltrations predominantly affected the RIPV and rarely the LIPV, and the superior PVs were never involved. This could be a result of significantly lower temperatures in the inferior veins compared with the control group. Although comparison of temperatures between the groups did not reach the level of significance in the superior PVs, a strong trend was found towards lower temperatures also in the case group. This does not seem to have the potential to result in infiltrations visible in imaging techniques applied.

In our analysis, cases and controls were similar in terms of baseline Hb and coagulation parameters (Table 1). This suggests that coagulopathies and pre-procedural intense anticoagulation are unlikely to be potential causes of hemoptysis. In addition, intra-procedural ACTs were not significantly different between the patient groups, meaning that this is also unlikely to have contributed to the occurrence of hemoptysis. Furthermore, PV diameters and summed application time probably did not play a role in the development of hemoptysis because these were also similar between groups. In our patients, the 23-mm balloon was used more frequently in the LIPV and there was also a trend towards increased use in the RIPV. Given that lower temperatures are reached with smaller balloons, this is a possible explanation for the different distribution of nadir temperatures between the groups. Although veins were of comparable average diameters and smaller balloons were in use more frequently in cases, retrospective evaluation of all angiographies revealed no balloon placement inside the PV.

Although Hb was comparable between patient groups at baseline, post-procedural values were significantly lower in cases versus controls, most likely due to blood loss secondary to hemoptysis in the cases.

The overall rate of hemoptysis in our cohort (4.3%) is quite high compared with most recent randomized trials [18, 19]. However, Verma et al. recently reported ice formation inside pulmonary bronchi visualized by real-time bronchoscopy in 70% of their patients undergoing CBA [17]. Not all ice formations will lead to bleeding, and minor bleeding may not result in hemoptysis. However, continuous clinical monitoring over at least 36 h in our study cohort may have resulted in a higher detection rate compared with other trials. Although there was a trend towards less arrhythmia recurrence in patients who did versus did not develop hemoptysis (cases versus controls), outcomes were not significantly different between the two groups.

5 Limitations

This was a retrospective single-center evaluation, and patients have not been specifically assessed to identify the occurrence of hemoptysis. In addition, in-hospital monitoring was limited. Therefore, it is possible that the real prevalence of hemoptysis is higher than reported in this study due to underreporting. Finally, the single-center nature of the study meant that the number of cases was limited. A lack of power may have contributed to lack of statistical significance for some between-group comparisons.

Esophagus temperature monitoring has not been performed. Therefore, no data on esophagus temperatures can be provided. Due to potential time delay between occurrence, reporting, and documentation of hemoptysis, no valuable data on the exact time of occurrence of hemoptysis can be provided. No other complications than hemoptysis have been documented in either group of our matched pair analysis. However, complications other than hemoptysis have not been evaluated in the entire population in this study. Temperature data evaluation in this study was limited to the case and the control group. Therefore, we are unable to provide a ROC analysis on the entire population.

6 Conclusion

Post-procedural hemoptysis appears to be relatively frequent in patients undergoing cryoballoon ablation but did not have any negative impact on medium-term prognosis. An association between lower freezing temperatures and the occurrence of hemoptysis can be demonstrated, but there are not yet any clear cut-off safety values.

Compliance with ethical standards

The study was approved by the ethics committee of the Ruhr-Universität Bochum, Sitz Bad Oeynhausen.

Conflicts of interest The authors declare that they have no conflicts of interest.

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