Europace (2015) **17**, 1383–1390
doi:10.1093/europace/euu411

Incidence and predictors of dormant conduction after cryoballoon ablation incorporating a 30-min waiting period

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Received 9 October 2014; accepted after revision 30 December 2014; online publish-ahead-of-print 2 May 2015

Aims Electrical reconnection after pulmonary vein (PV) isolation is associated with atrial fibrillation (AF) recurrence. Reconnection may already develop within a 30 min waiting period and may only occur as dormant conduction (DC) revealed by adenosine infusion. This study determines incidence and predictors of DC after cryoballoon ablation incorporating a 30 min waiting period and the effect of treating this 'late' DC on 1 year AF-recurrence.

Methods and results Consecutive patients scheduled for a first ablation were prospectively included. Intravenous adenosine was administered 30 min after PV isolation to unmask DC (adenosine+). Additional applications were performed to abolish DC. Atrial fibrillation recurrence was evaluated after 3, 6, and 12 months with ECG and 24 h Holter recordings. Results were compared with a prior group of consecutive patients that underwent cryoablation without DC testing (adenosine−). The adenosine+ group consisted of 36 patients (78% male, 61 ± 10 years, paroxysmal AF 86%). ***Dormant conduction was found in 42% of patients (15/36) and 14% of PVs (20/143). Multivariate analysis showed that PV isolation during the first freeze independently reduced DC risk (OR = 0.064, $P < 0.01$). After 12 ± 1 months, 11 (83%) of adenosine+ patients had no AF-recurrences, compared with 37 (60%) of adenosine− patients ($n = 62$, 70% male, 59 ± 11 years, 90% paroxysmal AF, $P = 0.02$). Ablation with DC treatment independently reduced the risk of AF-recurrence (OR = 0.26, $P = 0.02$).

Conclusion Incorporating a 30-min waiting period after cryoballoon ablation increases the incidence of DC compared with previous results. Absence of PV isolation during the first freeze is associated with an increased risk of late DC. Treatment of this DC seems to improve outcome.

Keywords Atrial fibrillation • Cryoballoon ablation • Dormant conduction • Adenosine

Introduction

Pulmonary vein isolation for atrial fibrillation (AF) is an established invasive treatment. Cryoballoon ablation is an effective technique with acute procedural success in 92% of selected patients or 95% of targeted PVs.[1] Electrical reconnection after initial isolation is associated with AF recurrence.[2] After cryoablation, reported freedom of AF recurrence at 1 year follow-up ranges from 73% for patients with paroxysmal and 45% of patients with persistent AF.[1] Reconnection may already manifest itself during the initial procedure and its incidence increases when the waiting period after initial isolation is prolonged from 33% after 30 min to 50% after 60 min after radiofrequency ablation.[3,4] Of importance, PV reconnection may only occur as DC transiently revealed by infusion of intravenous adenosine.[5] The incidence of DC after cryoballoon ablation has been reported to range from 4.6 to 8% of all veins when tested immediately after ablation.[6,7] Applying additional cryoablation for DC has been associated with lower AF recurrences during follow-up.[6]

A longer waiting period after initial isolation before administration of adenosine may increase the incidence of DC which can be targeted by ablation.[3,8] However, extensive prolongation of the waiting period is not acceptable for many patients and electrophysiology laboratories. It would therefore be beneficial to identify procedural factors predictive for DC.

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What's new?

- Incorporation of a 30-min waiting period elucidates an increased incidence of dormant conduction (DC) as revealed by adenosine infusion after pulmonary vein (PV) isolation during cryoballoon ablation.
- Treatment of late DC significantly seems to improve sinus rhythm maintenance at 1-year follow-up.
- Late DC can be predicted by absence of PV isolation during the first freeze. Therefore, a 30-min waiting period after cryoballoon ablation may only be necessary when PV isolation is not achieved during the first freeze, thereby obviating the need for a 30 min waiting period in a substantial number of procedures.

The aims of this study were (i) to assess the incidence of late DC after cryoballoon ablation while incorporating a 30-min waiting period before administration of adenosine, (ii) to evaluate the effect of additional ablation to abolish late DC on 1 year AF recurrence, and (iii) to identify potential predictors of late DC.

Methods

Patient population

Consecutive patients with drug-refractory AF eligible for cryoballoon PV isolation were included. All patients underwent a CT-scan prior to ablation to establish LA and PV anatomy according to the institutional protocol. Patients were considered ineligible for cryoablation when they suffered from longstanding persistent AF or when the CT-scan showed a PV diameter of over 26 mm and/or presence of more than three right PVs.

Patients were prospectively included between mid-2008 and August 2012. The control group comprised consecutive patients that were selected for cryoballoon ablation before June 2010 (adenosine− group). Starting from June 2010, the procedure was routinely performed with adenosine infusion and patients were included that underwent cryoballoon ablation with adenosine infusion (adenosine+ group). Clinical data were collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analysed.

Ablation procedure

The ablation procedure was performed under conscious sedation and i.v. analgesia. Oral anti-coagulation was continued to maintain an International Normalized Ratio (INR) between 2.0 and 3.0. After venous access, 5000–7500 IU heparin was administered, depending on the pre-procedural INR. An activated clotting time was maintained between 300 and 400 s. A quadripolar reference catheter was placed in the coronary sinus. Under fluoroscopic and intracardiac echocardiography guidance, a transseptal puncture and venography were performed, and the cryoballoon (Arctic Front, Medtronic, Minneapolis, MN, USA) was placed at the ostia of the PVs. The circular mapping catheter (Achieve, Medtronic, Minneapolis, MN, USA) was placed inside the PVs through the lumen of the cryoballoon catheter and used to continuously document PV potentials. The first 26 ablation procedures performed in the adenosine− group used a separate cryoballoon and circular mapping catheter (Lasso 2515 catheter, Biosense Webster, Daimond Bar, CA, USA), which needed to be exchanged through the single transseptal sheath under fluoroscopic guidance after each cryo-application to evaluate whether PV isolation was achieved. In order to prevent phrenic nerve palsy, the phrenic nerve was paced from the superior caval vein during cryoballoon applications at the right-sided veins. Ablation was immediately stopped in case of reduced phrenic nerve capture. Ablation was performed at least two times 5 min for each vein until PV isolation. Ablation was not routinely terminated if PV isolation was not obtained during the application. Entrance block was confirmed by verification of the signals during sinus rhythm and during pacing from the reference catheter. Exit block was tested by bipolar pacing from all electrode pairs of the circular mapping catheter. Pulmonary vein isolation was re-checked 30 min after isolation of all PVs to evaluate whether early reconnection occurred. In case of early reconnection, one or more additional applications with the cryoballoon were performed until re-isolation. In the adenosine− group, acute success was defined as electrical isolation of all PVs at least 30 min after ablation and the procedure was terminated.

Dormant PV conduction (adenosine+ group only)

Because we postulated that a 30-min waiting period may increase the incidence of spontaneous PV reconnection and the incidence of DC, we incorporated a 30 min waiting period after PV isolation before DC was assessed using a bolus of adenosine. The adenosine dose was initiated at 6 or 12 mg and increased up to 30 mg until at least one atrial beat with AV-block was observed. ***Dormant conduction was defined as the reappearance of a PV potential for at least two consecutive atrial beats. In case of DC, additional cryoenergy applications were performed with the cryoballoon and after 30 min waiting, PV isolation and DC was rechecked. In case PV reconnection occurred or if DC was still present, additional applications were applied with a conventional device (FreezorMAX, Medtronic, Minneapolis, MN, USA) once more. To limit procedure time, DC treatment was performed with a maximum of two separate attempts (*Figure 1*).

Clinical follow-up

Patients were followed up at 3, 6, and 12 months after ablation according to the institutional clinical care track (MISSION! AF). All anti-arrhythmic drugs (AADs), except for amiodarone, were discontinued 3 days before ablation and restarted immediately after the procedure until at least 3 months follow-up. This policy is current clinical practice in our institution and is partly supported by the results of the 5A trial, although there is no evidence that this improves long-term success of the procedure.[9,10] If no AF recurrences occurred in the month before the first follow-up, AADs were discontinued. Heart rhythm was documented with ECG and 24 h Holter recordings. Atrial fibrillation recurrence was defined as any recording of any atrial arrhythmia, including atrial flutter, on ECG or any atrial arrhythmia >30 s on 24 h Holter registration after a blanking period of 3 months. Patients were requested to obtain an ECG recording if symptoms occurred that ***could be related to an arrhythmia.

Statistical analysis

Data were analysed using SPSS (version 20.0, SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean ± standard deviation. Baseline characteristics between groups were compared with an unpaired Student's *t*-test. Potential predictors of 12 month outcome were evaluated with univariate and multivariate logistic regression analyses including important confounding factors (type of AF, AF duration, and LA diameter at baseline) together with the type of procedure (with or without evaluation and treatment of DC). Prediction of DC occurrence was evaluated with logistic regression analysis. Variables with a *P*-value of <0.1 in

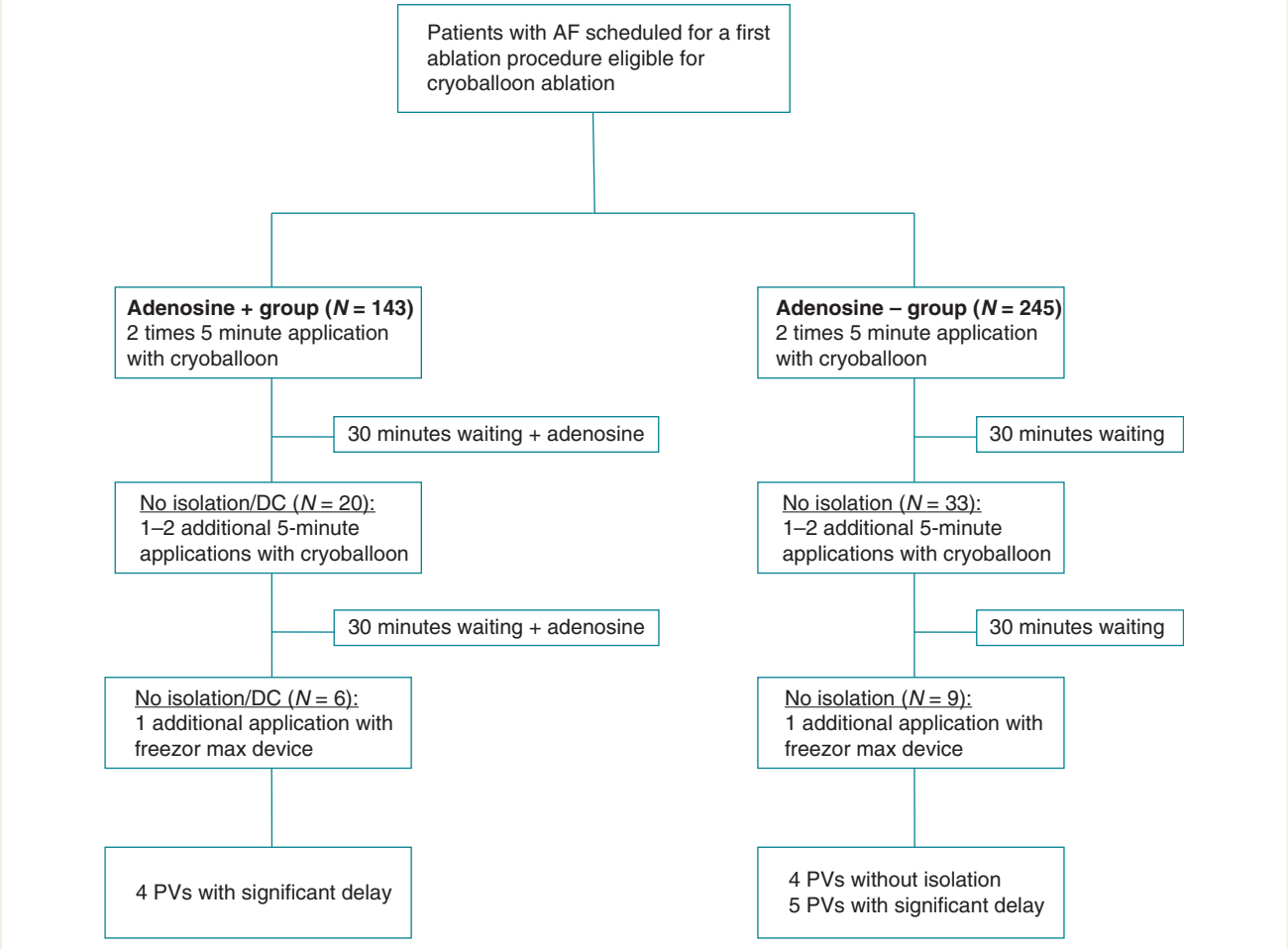

Figure 1 Flowchart cryoballoon ablation procedure, *N*, number of veins not isolated.

univariate analysis were included for further evaluation in a multivariate model, using stepwise forward regression. However, although the independent variables 'isolation during the first freeze' and 'time to isolation' were both significantly related to DC in univariate analysis, collinearity between these two variables was too high to include both in the multivariate analysis. We therefore decided to select 'isolation during the first freeze' for the multivariate analysis as 'time to isolation' does not indicate a specific cut-off value that would be useful for clinical practice. A *P*-value of <0.05 was considered statistically significant.

Results

Patient characteristics

Thirty-six patients (78% male, age 61 ± 10, 86% paroxysmal AF) underwent cryoballoon ablation with DC evaluation and treatment (adenosine+ group) and 62 patients (70% male, 59 ± 11 years, 90% paroxysmal AF) underwent cryoballoon ablation only (adenosine− group).

Baseline characteristics of the patients were comparable between both groups (*Table 1*). Mean number of used AADs had a tendency to be higher in the control group, although this was not significant.

Procedural parameters and outcome

For the adenosine+ group, time to isolation was 55 ± 28 s (s) on average and 75 ± 30 s for the LSPV, 57 ± 35 s for the LIPV, 38 ± 19 s for the RSPV, and 51 ± 29 s for the RIPV (*Table 2*). For the adenosine− group, time to isolation was 65 ± 49 s (s) on average and 66 ± 30 s for the LSPV, 63 ± 43 s for the LIPV, 54 ± 55 s for the RSPV, and 78 ± 68 s for the RIPV. The differences in time to isolation between both groups were not statistically significant. A PV signal was not registered on the Achieve catheter during ablation in 7 PVs in the adenosine+ group and 17 PVs in the adenosine− group.

In the adenosine+ group, DC was found in 42% of patients (15/36) and 14% of the PVs (20/143, *Table 3*). One patient had a single left PV with a common ostium without DC. During the first freeze, 75% of PVs (107/143) were isolated (*Figure 1*). After the 30-min waiting period and first identification of DC, additional applications with the cryoballoon were performed in 20 PVs. After another 30 min waiting period and adenosine infusion, six PVs still showed DC and received supplementary applications with the FreezorMax device. At the end of the procedure, 97.2% of veins were completely isolated. Four veins (2.8%) showed significant conduction delay with adenosine, since complete abolishment of DC could not be achieved.

The average amount of adenosine administered was 17 ± 5 mg for each vein.

Minimal temperatures for the individual PVs were comparable between both groups. The procedure was performed with a 23 mL (mm) balloon ($n = 8$ for the adenosine+ group and $n = 28$ for the adenosine− group) or an 28 mm balloon (=26 for the adenosine+ group and $n = 36$ for the adenosine− group). Cardioversion was performed in approximately one-third of patients ($P = 0.44$). Cryo-application time had a tendency to be shorter in the adenosine− group compared with the adenosine+ group (51 ± 11 vs. 57 ± 21 min, respectively, $P = 0.06$). Mean fluoroscopy time was significantly longer in the adenosine− group (34 ± 10 and 24 ± 11 min, respectively, $P < 0.01$, *Table 2*).

Table 1 Baseline characteristics

	Adenosine+ ($n = 36$)	Adenosine− ($n = 62$)	*P*-value
Age (years, ± SD)	61 ± 10	59 ± 11	0.43
Male (%)	78	70	0.39
BMI (± SD)	27 ± 3.7	27 ± 4.0	0.87
Paroxysmal AF (%)	86	90	0.50
Duration AF (months, ± SD)	64 ± 60	58 ± 53	0.60
Atrial flutter (%)	28	29	0.92
Number of AADs (± SD)	1.7 ± 0.7	2.0 ± 0.7	0.07
Left atrial diameter (mm, ± SD)	42 ± 6.7	42 ± 5.6	0.74
Hypertension (%)	50	52	0.84
Structural heart disease (%)	25	15	0.21

AAD, anti-arrhythmic drug; AF, atrial fibrillation; SD, standard deviation.

Prediction of DC

Univariate analysis showed two predictor of DC: PV isolation during the first freeze ($P < 0.01$), time to isolation ($P < 0.01$), and a trend for minimum balloon temperature ($P = 0.058$). After multivariate analysis, using PV isolation during the first freeze and not time to isolation, only PV isolation during the first freeze was found to independently reduce the risk of DC (OR = 0.06, $P < 0.01$, *Figure 2*).

Twelve-month outcome

In the adenosine+ group, 83% of patients had no AF/AT recurrences on AADs and 64% of patients off AADs after a single procedure and a mean follow-up of 12 ± 1 months. In the adenosine− group, 60% of patients were without recurrences while taking AADs and 47% of patients without AADs after a mean follow-up of 11 ± 1 months. The number of patients with AF recurrences in the adenosine+ group was significantly lower than in the adenosine− group ($P = 0.02$).

When corrected for confounders, including age, BMI, gender, AF type, AF duration, LA diameter, hypertension, cardioversion, and balloon size, using multivariate analysis, ablation with additional DC evaluation and treatment was still found to independently reduce the risk of AF recurrence at follow-up (OR = 0.29, 95% CI 0.09–0.75, $P = 0.01$, *Figure 3*). Paroxysmal instead of persistent AF had a tendency to independently reduce the risk of AF recurrence during follow-up (OR = 0.26, 95% CI 0.07–1.04, $P = 0.06$).

A subanalysis including only patients with paroxysmal AF from the adenosine+ group showed a lower incidence of AF recurrence (23%) after 12-month follow-up.

Complications

Transient phrenic nerve injury was observed in 9% of patients ($n = 9$). In all but one patient, the phrenic nerve palsy completely resolved during hospitalization. This patient did not experience any symptoms, although the palsy only partially resolved. Groin

Table 2 Procedural characteristics

	Adenosine+ ($n = 36$)	Adenosine− ($n = 62$)	*P*-value
Fluoroscopy time (min, ± SD)	24 ± 11	34 ± 10	**<0.01**
Cryo time (min, ± SD)	57 ± 21	51 ± 11	0.06
Minimal temperature			
Left superior PV (°C, ± SD)	−51 ± 8	−49 ± 9	0.50
Left inferior PV (°C, ± SD)	−48 ± 8	−48 ± 11	0.89
Right superior PV (°C, ± SD)	−54 ± 6	−49 ± 15	0.12
Right inferior PV (°C, ± SD)	−49 ± 8	−48 ± 12	0.63
Time to isolation			
Left superior PV (s, ± SD)	75 ± 30	66 ± 30	0.40
Left inferior PV (s, ± SD)	57 ± 35	63 ± 43	0.63
Right superior PV (s, ± SD)	38 ± 19	54 ± 55	0.18
Right inferior PV (s, ± SD)	51 ± 29	78 ± 68	0.13
Cardioversion (%)	36	29	0.44

Bold *P*-values indicate significance ($P < 0.05$).
PV, pulmonary vein; SD, standard deviation.

haematoma occurred in 4% of patients ($n = 4$). Overall, complications did not lead to repeat hospitalization or death.

Discussion

This study evaluated the incidence and predictors of DC 30 min after cryoballoon ablation in patients with AF and the effect of treating this 'late' DC on the incidence of AF recurrences during follow-up.

The most important findings are (i) if a 30-min waiting period after the last ablation is incorporated, incidence of DC during adenosine infusion after cryoballoon ablation is increased compared with previous studies, (ii) treatment of this late DC with addition ablation increases efficacy of cryoballoon ablation, and (iii) late DC can be predicted by absence of PV isolation during the first freeze. Therefore, a 30-min waiting period after cryoballoon ablation may only be necessary when PV isolation is not achieved during the first freeze, thereby obviating the need for a 30-min waiting period in a substantial number of procedures. In this study, all PVs were isolated during the first freeze in 33% of procedures.

Incidence of DC

Pulmonary vein reconnection is the underlying mechanism of a large part of AF recurrences after ablation and identification of incompletely ablated PV connections with depolarized but still viable atrial myocytes is important.[11,12] Incorporation of a waiting period after PVI was identified as an important tool to identify PV reconnection and to reduce AF recurrences by treating this reconnection with additional applications.[2] The value of employing adenosine after PVI was described by Matsuo *et al.*,[13] who showed that performing additional RF applications after identification of DC was found to reduce AF recurrences to 20% after a mean follow-up period of 20 months when compared with patients treated with RF ablation only (40% AF recurrences). Recently, the results of the ADVICE trial were presented at the Scientific Sessions of the Heart Rhythm Society, in which patients were randomized to no ablation or ablation of DC. Dormant conduction was present in 21% of veins and treatment of DC led to a 13% absolute increase in 1 year outcome of PVI. The effect of both adenosine infusion and incorporating a 30-min waiting period after PVI to identify PV reconnection in patients with paroxysmal AF has been evaluated as well.[3] Both techniques were found to reveal a significant amount of early PV reconnection with the waiting period showing the highest efficacy (19.8 vs. 14.6% of all veins). Combining the two may result in a complementary effect aiming at reduction of AF recurrences. A study performed by Ninomiya *et al.*[14] evaluated the effect of adenosine infusion during radiofrequency AF ablation after a waiting time of at least 30 min. Twenty of 81 PVs (25%) were found to have DC; DC of 12 PVs (60%) was detected after a mean waiting period of 66 ± 55 min and an additional eight PVs (40%) showed DC after adenosine infusion. The effect on the incidence of AF recurrences was not evaluated, however.

Chiercha *et al.*[7] assessed the incidence of DC with 20 mg adenosine and a 15 min waiting period after PVI was achieved with cryoballoon ablation. In this study, only 4.6% of PVs showed DC. Van Belle *et al.*[6] found a higher incidence of DC with 24 mg adenosine after cryoballoon ablation (8% of PVs) without incorporation of a waiting time after PVI. In our study, the incidence of DC after cryoballoon ablation was even higher with 14% of PVs showing DC after a 30-min waiting period and with an average of 17 mg adenosine. Since other procedural characteristics were comparable between the studies, the 30 min waiting period that was applied in our study

Table 3 Localization and incidence of DC

	LSPV	LIPV	RSPV	RIPV	Total
Total number of veins	36	35	36	36	143
Number of veins with DC	7	7	4	2	20
% of veins with DC	19	20	11	6	14
Number of veins with acute isolation	34	34	34	35	137

DC, dormant conduction; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

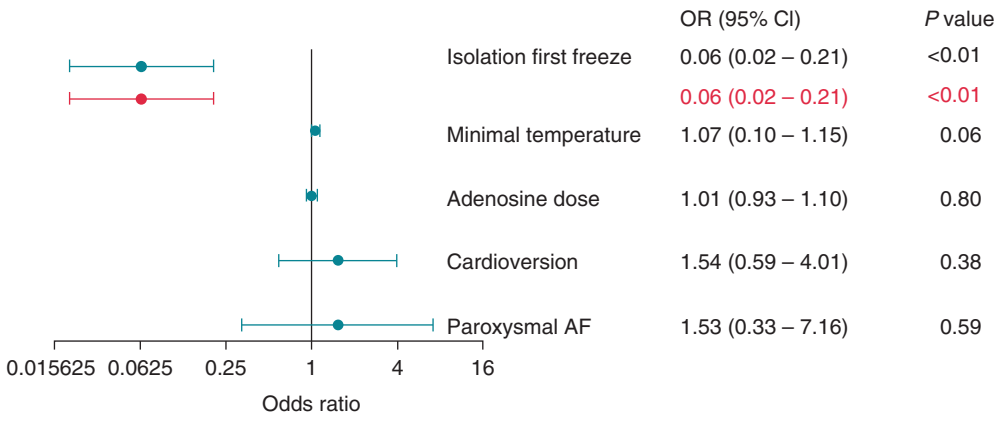

Figure 2 Univariate and multivariate prediction of DC (AF, atrial fibrillation; OR, odds ratio, turquoise line represents univariate analysis, red line represents multivariate analysis).

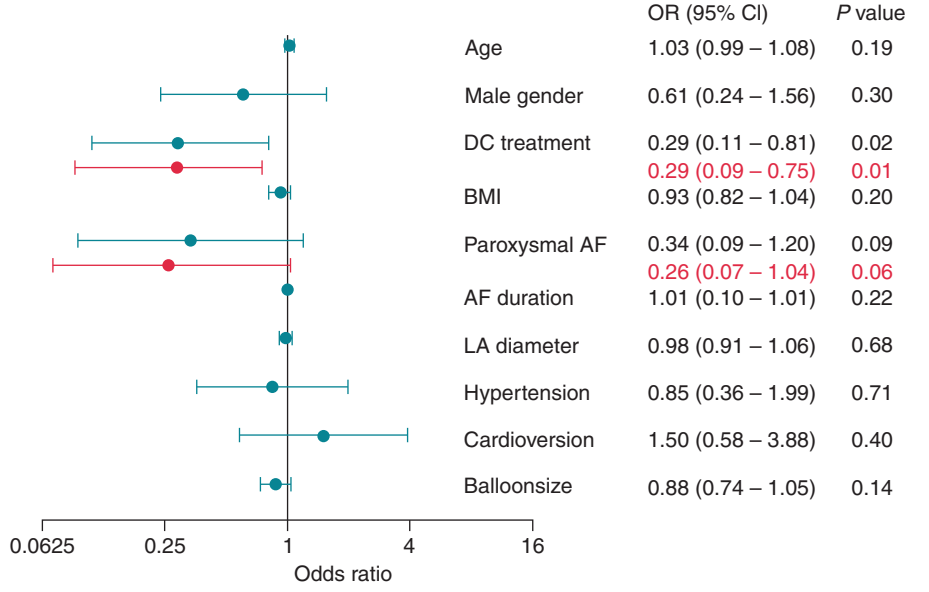

Figure 3 Univariate and multivariate prediction of AF recurrence (AF, atrial fibrillation; LA, left atrium; OR, odds ratio, turquoise line represents univariate analysis, red line represents multivariate analysis).

may have led to an increase in DC incidence. Interestingly, however, the incidence of DC 30 min after ablation in our study was not increased compared with infusion of adenosine immediately after RF ablation.[3] This may be explained by the more homogeneous lesions created by the cryoballoon compared with point-by-point RF ablation, in which catheter contact and lesion efficacy may vary between different ablation points thereby potentially increasing the incidence of DC.

Predictors of DC

To our knowledge, no other study reported on factors that can predict the presence of DC after AF ablation. As mentioned before, identification of other predictors, besides prolongation of the waiting time, to identify DC is very important in order avoid prolonged waiting times whenever possible.

In this study, isolation of a PV during the first freeze was found to independently reduce the incidence of DC. It has been suggested that poor contact between an ablation catheter and the myocardium may cause tissue oedema and thereby incomplete ablation lesions.[15] In addition, a recent study on lesion formation on MRI after ablation with RF energy showed that patients with AF recurrences during follow-up had more oedema immediately after ablation and less necrosis 3 months after ablation, indicating the presence of more reversible tissue injury.[16] In line with this, it may be hypothesized that poor tissue contact with the cryoballoon may have caused both absence of isolation during the first freeze and DC due to tissue oedema in our study.

Effect of treating DC on 12 month outcome

The efficacy of cryoballoon ablation described in the literature shows large variations, depending on multiple factors including number of patients with persistent AF, frequency of rhythm monitoring, applied criteria for AF recurrence, and follow-up period.

The effective treatment of the higher incidence of DC described in this study did not seem to result in better outcome compared with the outcome described by van Belle *et al.*, since the efficacy of both procedures appears comparable.[6] Van Belle *et al.* also reported a longer follow-up period compared with our study (17 ± 5 vs. 12 ± 1 months). On the other hand, failure of ablation in the study by Van Belle *et al.* was defined as recurrence of AF only, while we included recurrence of other types of atrial arrhythmia as well. In addition, we included patients with either paroxysmal or persistent AF, while Van Belle *et al.* only included patients with paroxysmal AF.

Therefore, we performed a subanalysis including only patients with paroxysmal AF from the adenosine+ group which showed a lower incidence of AF recurrence (23%) during follow-up compared with Van Belle *et al.* (32%). These results suggest that incorporation of a waiting period after PVI before adenosine administration may reduce the amount of AF recurrences. The difference between success with and without usage of AADs was relatively high. Two patients of the control group used a low dose of AADs for symptomatic premature atrial complexes and two patients of the adenosine group for premature ventricular complexes or a combination of PVCs and PACs. The ablation procedure may have been successful in these patients without the use of AADs.

Procedural characteristics

The cryoablation duration showed a tendency to be prolonged in the adenosine group ($P = 0.06$), which can be explained by the additional cryo-applications for treatment of DC. Mean fluoroscopy time was significantly longer in the control group compared with the adenosine group ($P < 0.01$, *Table 2*). This is probably due to the fact that the first procedures in this group were performed using a separate

circular mapping catheter, which needed to be exchanged through the single transseptal sheath. When comparing patients of both groups ablated with the mapping catheter integrated in the cryoballoon catheter, fluoroscopy times were no longer significantly different (28 ± 6.9 min for the control group vs. 24 ± 11 min for the adenosine group, $P = 0.12$).

Clinical implications

Since incomplete PV isolation is a risk factor for AF recurrence, identification, and treatment of DC may increase success of ablation. Failure to isolate a PV during the first freeze was found to be an independent predictor for the presence of DC. Since inadequate occlusion of the PV and poor contact between the catheter and PV tissue might cause oedema, operators should carefully check whether the PV is completely occluded with the cryoballoon before ablation and terminate ablation when isolation is not reached after a reasonable amount of time to prevent formation of oedema leading to incomplete lesions.

Evaluation of DC during cryoballoon ablation seems a useful tool to improve durable PV isolation, especially for PVs that are more difficult to isolate, thereby reducing AF recurrences during follow-up.

Limitations

During follow-up, ECGs and 24 h Holter recordings were only obtained every 3 months or if a patient experienced complaints possibly related to AF recurrence. Although this is according to guideline recommendations, AF recurrences that could have occurred during in-between periods may have been missed.[17] Although the HRS/EHRA/ECAS Expert Consensus Statement requires the application of event recorders in the presence of symptoms, event recorders were not applied in this study.[18] Alternatively, we made any effort to stimulate patients to obtain an ECG recording if symptoms occurred that could be related to an arrhythmia. However, this limited registration of heart rhythm during follow-up may have led to underestimation of the incidence of AF recurrence and thereby to an overestimation of success rates. In patients with AF recurrences, no systematic electrophysiological evaluation was performed to investigate the relation between treated DC during the first procedure and PV reconnection during follow-up.

This study was non-randomized, observational, and single centre. The group sizes were relatively small, especially the adenosine group. Due to statistical collinearity, we could not include both 'time to isolation' and 'isolation during the first freeze' in the multivariate model for the prediction of DC. We selected 'isolation during the first freeze' as it is a dichotomous parameter and may therefore be more useful to assess the risk of developing DC and to decide whether it would be necessary to test for DC after a 30-min waiting period. As we did not test DC directly after ablation, we cannot definitely conclude that incorporating a 30-min waiting period after ablation increased the incidence of DC.

Besides this, a new cryoballoon catheter (Arctic Front Advance, Medtronic, Minneapolis, MN, USA) was developed to reduce AF recurrences. The improved cooling seems to result in higher rates of permanent PV isolation and a lower rate of AF recurrences during follow-up.[19,20] However, several papers have recently reported on a higher incidence of phrenic nerve and oesophageal complications during ablation with this balloon.[21,23] Single 3 min freezes per vein are now considered to prevent these complications, which may once more lead to an increase in DC incidence.[24] Therefore, testing for and treatment of DC in cryoballoon ablation may remain valuable with the second-generation cryoballoon. A randomized controlled trial based on a pre-specified sample size is therefore necessary to evaluate the additional value of DC identification and treatment with the new cryoballoon.

Conclusions

Incorporating a 30-min waiting period after cryoablation increases the incidence of DC compared with previous studies. Treatment of this late DC with additional ablation may increase efficacy of cryoballoon ablation. Late DC can be predicted by the absence of PV isolation during the first freeze. Therefore, a 30 min waiting period after cryoballoon ablation may only be necessary when PV isolation is not achieved during the first freeze. This predictor may therefore be a useful tool for optimizing cryoballoon ablation, aiming at both reduction of procedure times and AF recurrences.

Conflict of interest: The Department of Cardiology of Leiden University Medical Center received unrestricted research grants from Medtronic, Biotronik, Boston Scientific, Lantheus medical imaging, St. Jude Medical, Edwards Life sciences & GE Healthcare.

References

1. Andrade JG, Khairy P, Guerra PG, Deyell MW, Rivard L, Macle L *et al.* Efficacy and safety of cryoballoon ablation for atrial fibrillation: a systematic review of published studies. *Heart Rhythm* 2011;**8**:1444–51.
2. Anter E, Contreras-Valdes FM, Shvilkin A, Tschabrunn CM, Josephson ME. Acute pulmonary vein reconnection is a predictor of atrial fibrillation recurrence following pulmonary vein isolation. *J Interv Card Electrophysiol* 2014;**39**:225–32.
3. Jiang CY, Jiang RH, Matsuo S, Liu Q, Fan YQ, Zhang ZW *et al.* Early detection of pulmonary vein reconnection after isolation in patients with paroxysmal atrial fibrillation: a comparison of ATP-induction and reassessment at 30 minutes postisolation. *J Cardiovasc Electrophysiol* 2009;**20**:1382–7.
4. Cheema A, Dong J, Dalal D, Marine JE, Henrikson CA, Spragg D *et al.* Incidence and time course of early recovery of pulmonary vein conduction after catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2007;**18**:387–91.
5. Arentz T, Macle L, Kalusche D, Hocini M, Jais P, Shah D *et al.* "Dormant" pulmonary vein conduction revealed by adenosine after ostial radiofrequency catheter ablation. *J Cardiovasc Electrophysiol* 2004;**15**:1041–7.
6. Van Belle YL, Janse PA, de Groot NM, Anne W, Theuns DA, Jordaens LJ. Adenosine testing after cryoballoon pulmonary vein isolation improves long-term clinical outcome. *Neth Heart J* 2012;**20**:447–55.
7. Chierchia GB, Yazaki Y, Sorgente A, Capulzini L, de Asmundis C, Sarkozy A *et al.* Transient atriovenous reconnection induced by adenosine after successful pulmonary vein isolation with the cryothermal energy balloon. *Europace* 2009;**11**:1606–11.
8. Datino T, Macle L, Qi XY, Maguy A, Comtois P, Chartier D *et al.* Mechanisms by which adenosine restores conduction in dormant canine pulmonary veins. *Circulation* 2010;**121**:963–72.
9. Roux JF, Zado E, Callans DJ, Garcia F, Lin D, Marchlinski FE *et al.* Antiarrhythmics after ablation of atrial fibrillation (5A study). *Circulation* 2009;**120**:1036–40.
10. Darkner S, Chen X, Hansen J, Pehrson S, Johannessen A, Nielsen JB *et al.* Recurrence of arrhythmia following short-term oral AMIOdarone after CATheter ablation for atrial fibrillation: a double-blind, randomized, placebo-controlled study (AMIO-CAT trial). *Eur Heart J* 2014;**35**:3356–64.
11. Verma A, Kilicaslan F, Pisano E, Marrouche NF, Fanelli R, Brachmann J *et al.* Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. *Circulation* 2005;**112**:627–35.
12. Kaitani K, Kurotobi T, Kobori A, Okajima K, Yao T, Nakazawa Y *et al.* Late re-conduction sites in the second session after pulmonary vein isolation using adenosine provocation for atrial fibrillation. *Europace* 2014;**16**:521–7.
13. Matsuo S, Yamane T, Date T, Hioki M, Ito K, Narui R *et al.* Comparison of the clinical outcome after pulmonary vein isolation based on the appearance of adenosine-induced dormant pulmonary vein conduction. *Am Heart J* 2010;**160**:337–45.

14. Ninomiya Y, Iriki Y, Ishida S, Oketani N, Matsushita T, Ichiki H *et al.* Usefulness of the adenosine triphosphate with a sufficient observation period for detecting reconduction after pulmonary vein isolation. *Pacing Clin Electrophysiol* 2009;**32**: 1307–12.
15. Neuzil P, Reddy VY, Kautzner J, Petru J, Wichterle D, Shah D *et al.* Electrical reconnection after pulmonary vein isolation is contingent on contact force during initial treatment: results from the EFFICAS I study. *Circ Arrhythm Electrophysiol* 2013;**6**: 327–33.
16. Arujuna A, Karim R, Caulfield D, Knowles B, Rhode K, Schaeffter T *et al.* Acute pulmonary vein isolation is achieved by a combination of reversible and irreversible atrial injury after catheter ablation: evidence from magnetic resonance imaging. *Circ Arrhythm Electrophysiol* 2012;**5**:691–700.
17. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S *et al.* Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 2010;**12**:1360–420.
18. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH *et al.* 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation – developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;**14**:1385–413.
19. Furnkranz A, Bordignon S, Schmidt B, Gunawardene M, Schulte-Hahn B, Urban V *et al.* Improved procedural efficacy of pulmonary vein isolation using the novel second-generation cryoballoon. *J Cardiovasc Electrophysiol* 2013;**24**:492–7.
20. Straube F, Dorwarth U, Vogt J, Kuniss M, Kuck KH, Tebbenjohanns J *et al.* Differences of two cryoballoon generations: insights from the prospective multicentre, multinational FREEZE Cohort Substudy. *Europace* 2014;**16**:1434–42.
21. Casado-Arroyo R, Chierchia GB, Conte G, Levinstein M, Sieira J, Rodriguez-Manero M *et al.* Phrenic nerve paralysis during cryoballoon ablation for atrial fibrillation: a comparison between the first- and second-generation balloon. *Heart Rhythm* 2013;**10**:1318–24.
22. Metzner A, Burchard A, Wohlmuth P, Rausch P, Bardyszewski A, Gienapp C *et al.* Increased incidence of esophageal thermal lesions using the second-generation 28-mm cryoballoon. *Circ Arrhythm Electrophysiol* 2013;**6**:769–75.
23. Fürnkranz A, Bordignon S, Schmidt B, Perrotta L, Dugo D, De Lazzari M *et al.* Incidence and characteristics of phrenic nerve palsy following pulmonary vein isolation with the second-generation as compared with the first-generation cryoballoon in 360 consecutive patients. *Europace* 2015;**17**:574–8.
24. Chierchia GB, di Giovanni G, Sieira-Moret J, de Asmundis C, Conte G, Rodriguez-Manero M *et al.* Initial experience of three-minute freeze cycles using the second-generation cryoballoon ablation: acute and short-term procedural outcomes. *J Interv Card Electrophysiol* 2014;**39**:145–51.