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CLINICAL RESEARCH

Transient atriovenous reconnection induced by adenosine after successful pulmonary vein isolation with the cryothermal energy balloon

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Aims Cryothermal energy balloon ablation (CBA), using cryogenic ablative energy, has proven very effective in producing pulmonary vein (PV) isolation in patients with paroxysmal atrial fibrillation (AF). Adenosine testing after PV isolation has demonstrated to be able to unmask incomplete lesion after radiofrequency (RF) ablation. The aim of our study was to assess the rate of transient atriovenous reconnection induced by adenosine after successful PV isolation with the CBA in a group of patients with paroxysmal AF.

Methods and results We prospectively enrolled 39 patients (31 male; age 59 ± 11 years) elected to circumferential PV isolation with CBA for highly symptomatic paroxysmal AF. A total of 149 PVs were evidenced. Adenosine testing after CBA induced a left atrium–PV reconnection only in 7 (4.6%) of PV.

Conclusion Our study showed a low rate of transient PV reconnection after adenosine infusion following successful PV isolation with CBA. However, larger studies will be needed in order to confirm our findings and the prognostic value of adenosine testing after successful PV isolation obtained with CBA.

Keywords Ablation • Atrial fibrillation • Adenosine • Cryoballoon

Introduction

Nowadays, transcatheter ablation using radiofrequency (RF) has become a common technique to attempt curing drug-resistant paroxysmal atrial fibrillation (AF). Since ectopic beats originating from the pulmonary veins (PVs) have been shown to be the main trigger initiating AF,[1,2] electrical isolation of these venous structures has become the goal when performing this procedure. Most AF recurrences after RF catheter ablation are caused by left atrium (LA)–PV reconnections; therefore, absolute demonstration of PV isolation is mandatory for a successful clinical outcome. Recent studies have demonstrated that intravenous injection of adenosine after AF ablation can induce transient reconduction in isolated PVs, due to incomplete lesions.[3,4] Additionally, clinical evidence indicates that elimination of transient reconnection by further ablation might lead to a reduction in the rate of AF recurrences.[5] However, all these observations were done after PV isolation using a focal RF catheter.

The novel cryothermal energy balloon ablation (CBA), using cryogenic ablative energy, has proved to be very effective to produce PV isolation;[6,7] however, no study has yet assessed the rate of transient PV reconduction following adenosine injection after CBA.

In a series of consecutive patients with paroxysmal AF, we assessed the incidence and anatomical features of adenosine-induced transient LA–PV reconnection after successful PV isolation with the CBA.

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Methods

Patients characteristics

We prospectively enrolled 39 patients (31 male; age 59 ± 11 years) elected to circumferential PV isolation with CBA for symptomatic paroxysmal AF. All patients signed an informed consent prior to the procedure. Inclusion criteria were based on the frequent occurrence of recurrent episodes of AF, in spite of treatment with at least two antiarrhythmic drugs. To exclude the presence of thrombi in the left atrial appendage, all patients underwent 2D transoesophageal echocardiography (TEE) the day before the procedure, along with a transthoracic examination (TTE) enabling assessment of LA dimensions, left ventricular and valvular function. Exclusion criteria were the presence of a left atrial thrombus, uncontrolled severe heart failure, or contraindications to general anaesthesia.

Ablation procedure

Before the procedure, detailed information on left atrial anatomy were obtained by 2D TTE, TEE as well as by computed tomography. Ablation was performed under general anaesthesia.

A 6 F pigtail catheter was positioned in the aortic root via a left femoral approach, to monitor arterial pressure and to assess the position of the aorta. A 6 F quadripolar catheter was inserted in the right jugular vein and advanced to the coronary sinus (CS). A single transseptal puncture was then performed under fluoroscopic guidance, using the right femoral venous approach. After gaining left atrial access, a 70 UI/kg heparin iv bolus was given. A selective angiogram in each PV in order to delineate the ostium was then performed. Immediately after, a 0.032″ 260 cm long guide-wire (Emerald, Cordis, Johnson & Johnson, Diamond Bar, CA, USA) was advanced in the left superior PV (LSPV) and a steerable 15 F over-the-wire sheath (FlexCath, Cryocath, Montreal, Quebec, Canada) was positioned in the LA. A circular mapping catheter (Lasso, Biosense Webster, Inc., Diamond Bar, CA, USA) was then advanced in each PV ostium to obtain baseline electrical information. After withdrawing the mapping catheter, a 28 mm double-walled cryoballoon (Arctic Front, Cryocath) was advanced over the wire up to the LA, inflated and positioned in the PV ostium of each vein. Optimal vessel occlusion was considered to have been achieved when selective contrast injection showed total contrast retention with no flow to the atrium. For each vein, cryoablation consisted of a minimum of two applications lasting 5 min each. Whenever possible, we tried to engage with the guide-wire two different branches of the same vein and to orient the balloon differently, in the attempt of covering a wider ostial surface. However, if successful occlusion could only be obtained in one branch, both applications were delivered by leaving the guide-wire in the same branch. Usually, the LSPV was treated first, followed by the left inferior (LIPV), right superior (RSPV) and right inferior (RIPV). In order to avoid phrenic nerve palsy, a complication observed during RSPV isolation with CBA, a quadripolar catheter was inserted in the superior vena cava and diaphragmatic stimulation was achieved by pacing the ipsilateral phrenic nerve with a 1000 ms cycle and a 12 mA pulse output. The reason of pacing at such a slow rate was to prevent catheter displacement in the early phases of application due to diaphragmatic contraction. During the whole procedure, activated clotting time was maintained over 300 s by supplementing heparin infusion, as required.

Assessment of pulmonary vein isolation

We recorded PV activity before and after CBA. Effective PV isolation was considered to have been obtained when all PV potentials were abolished or dissociated from atrial activity, and bidirectional block was documented. Entry block was demonstrated by the absence of PV activity while pacing in the distal CS. Exit block was verified by pacing from each bipolar pair of the mapping catheter in the PV at 10 mA and 2 ms pulse width.

Pharmacological testing

Fifteen minutes after PV isolation, we performed an injection of 20 mg of intravenous adenosine during isoproterenol infusion (1–3 μg/min) with the circular mapping catheter maintained in the proximal PV ostium. After each injection, the intracardiac electrograms and the surface ECG were monitored for 2 min. If there was a documentation of transient LA–PV reconnection, a second injection of adenosine was given to confirm the findings. Further attempts of CBA were first made with the goal to eliminate incomplete lesions. If the latter persisted after further adenosine testing, a focal ablation catheter was used to target the earliest activation site identified on the circular multipolar catheter.

Follow-up

All patients underwent physical examination and 24 h Holter recordings at 1, 3 and 6 months after the procedure and when arrhythmic symptoms occurred. We considered a post-ablation blanking period of 2 months.

Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical variables are expressed as percentages.

Results

Mean total procedure time was 173 ± 23 min. Mean total fluoroscopy time was 45 ± 8 min. Mean left atrial size was 42.5 ± 2.7 mm. Mean duration of AF before procedure was 3.5 years. Structural heart disease (coronary artery disease) was present in four patients. During all procedures, patients were in sinus rhythm and no one developed atrial fibrillation at any stage. A total number of 149 PV were targeted. Three left-sided common ostia were found. Thanks to the steerability of both the FlexCath (Cryocath) and the Lasso (Biosense Webster, Inc.), it was possible to map all PV ostia. Potentials were present in all PV ostia before ablation. Successful occlusion could be obtained in 139 (93%) PV. In eight PVs, we performed more than two CBA applications as optimal occlusion could not be reached with the first two. After a mean of 2.1 (range 2–4) CBA applications, PV isolation (*Figure 1*) could be demonstrated in 146 (98%) PVs. Bidirectional block was present in all these veins at first testing after ablation. Additional lesions with a focal ablation catheter were needed to isolate one LIPV and one RIPV in the same patient. At the end of the procedure, all 149 (100%) veins were isolated.

Adverse events

Transient phrenic nerve palsy was observed in three patients when delivering energy in the RSPV. Diaphragmatic contraction completely recovered before the end of the procedure. One patient was excluded from the study because of occurrence of pericardial tamponade due to the transseptal puncture.

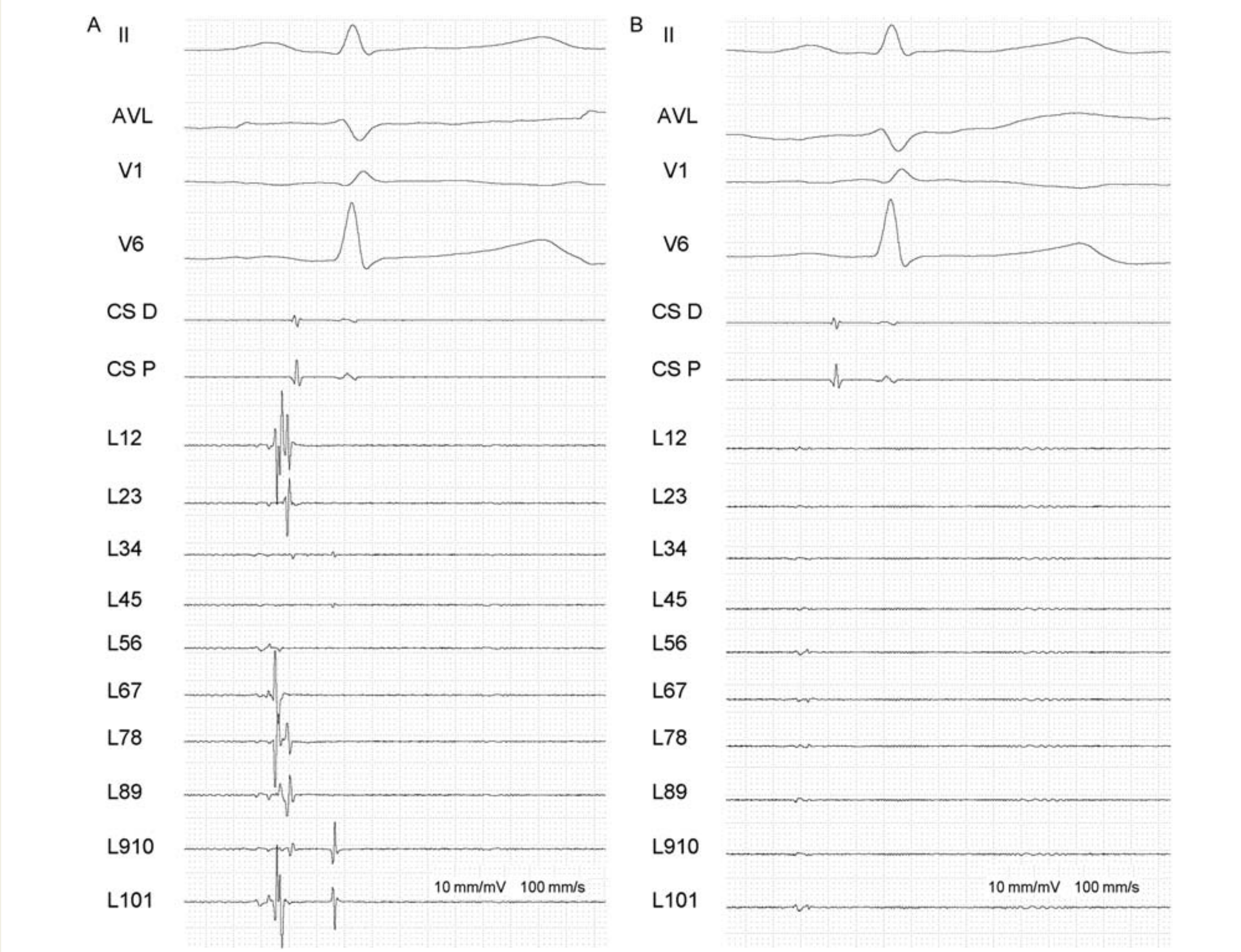

Figure 1 Successful isolation of right superior pulmonar vein antrum after cryothermal energy balloon ablation in a 53-year-old man with paroxysmal atrial fibrillation. In both panels, from top to bottom, surface II, aVL, V1 and V6 leads electrocardiogram are displayed together with the recordings of the distal and proximal coronary sinus (CS D and CS P) and of the Lasso catheter (L1-2 to L10-1) outside the right superior pulmonar vein ostium. The tracings were recorded before (*A*) and after (*B*) pulmonary vein isolation with cryothermal energy balloon ablation. Before ablation, the Lasso catheter records discrete pulmonary vein potentials from bipolar electrodes (L1-2 to L 10-1). Following cryothermal energy balloon ablation, no pulmonary vein potentials were recorded.

Pharmacological testing

During adenosine testing, transient PV reconnection (*Figure 2*) was observed in seven (4.6%) PVs in five (13%) patients (*Table 1*). Successful PV occlusion had been documented in five of these seven PVs during ablation. Four out of seven reconnected veins were right inferior. Mean duration of adenosine induced LA–PV reconnection was 9 $\pm$ 4 s.

Ablation of pulmonary vein exhibiting adenosine induced reconnection

Further applications of CBA resulted in disappearance of adenosine induced PV reconduction in five veins after testing (*Table 1*). Isolation of the other two veins required the use of a focal catheter after unsuccessful CBA (*Figure 3*).

Follow-up

Clinical examination, baseline ECG and 24 h ECG Holter registrations were performed at 1, 3 and 6 months after the procedure.

At a follow-up of 6 months, 9 patients (23%) experienced symptomatic arrhythmic recurrence. In all these individuals, AF episodes were recorded. Of the nine patients, two had experienced LA–PV reconnection during adenosine testing. During the first month, five patients had palpitations and AF was recorded at Holter monitoring. After this period, these patients did not experience any other symptomatic arrhythmic recurrence with documented absence of AF episodes at the 3- and 6-month Holter recordings. One patient had arrhythmic recurrences up to 2 months after the procedure. The other three patients continued to complain of AF-related symptoms at 6-month follow-up.

Discussion

Complete PV isolation has proved to be essential for long-term success following AF ablation. Adenosine injection can unmask transient LA–PV conduction after successful PV isolation.[3]

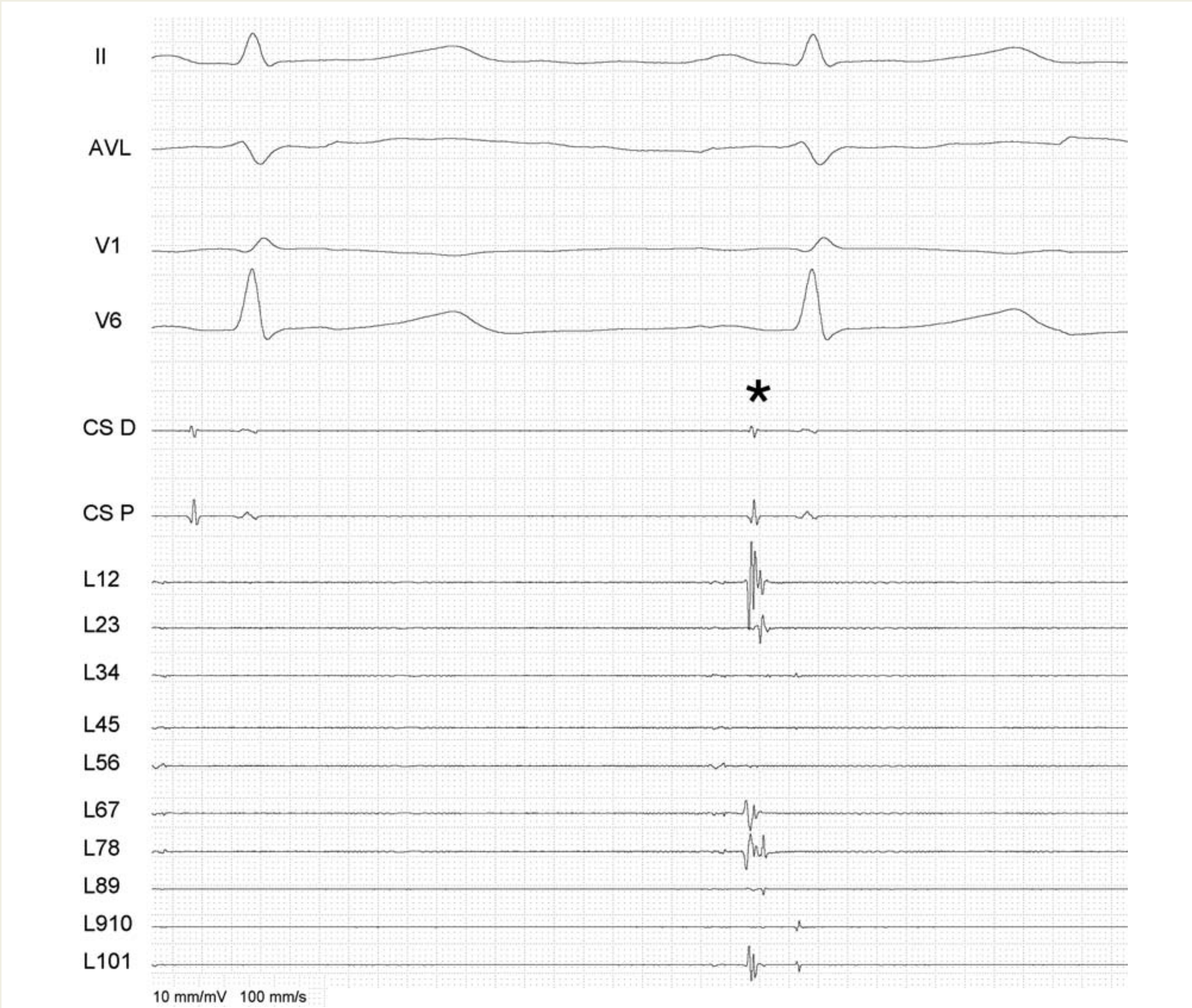

Figure 2 Transient left atrium–pulmonary vein reconnection after adenosine testing in the same patient shown in *Figure 1*. Display of the surface and intracavitary signals as in *Figure 1*. The beat in which reconnection is observed is marked by an asterisk.

Table 1 Detailed description of pulmonary vein reconnection after adenosine infusion

	Involved PV	Anatomical location of adenosine-induced PV reconnection	Modality of isolation of adenosine-reconnected PV
1	RIPV	Inferior	One cryoballoon application
2	RIPV	Inferior	One cryoballoon application
3	RIPV	Inferior	One cryoballoon application attempt + two focal applications
4	RIPV	Inferior	One cryoballoon application
5	LSPV	Interpulmonary carina	One cryoballoon application
6	LIPV	Interpulmonary carina	One cryoballoon application
7	LIPV	Inferior	One cryoballoon application + one focal application

Although the reason for this phenomenon remains uncertain, the most accredited mechanism seems to be that adenosine activates the outward potassium current via purinergic A1-receptors. This produces hyperpolarization of the cell membrane and shortening of the action potential that may cause electronic conduction.[3] However, regardless of the underlying

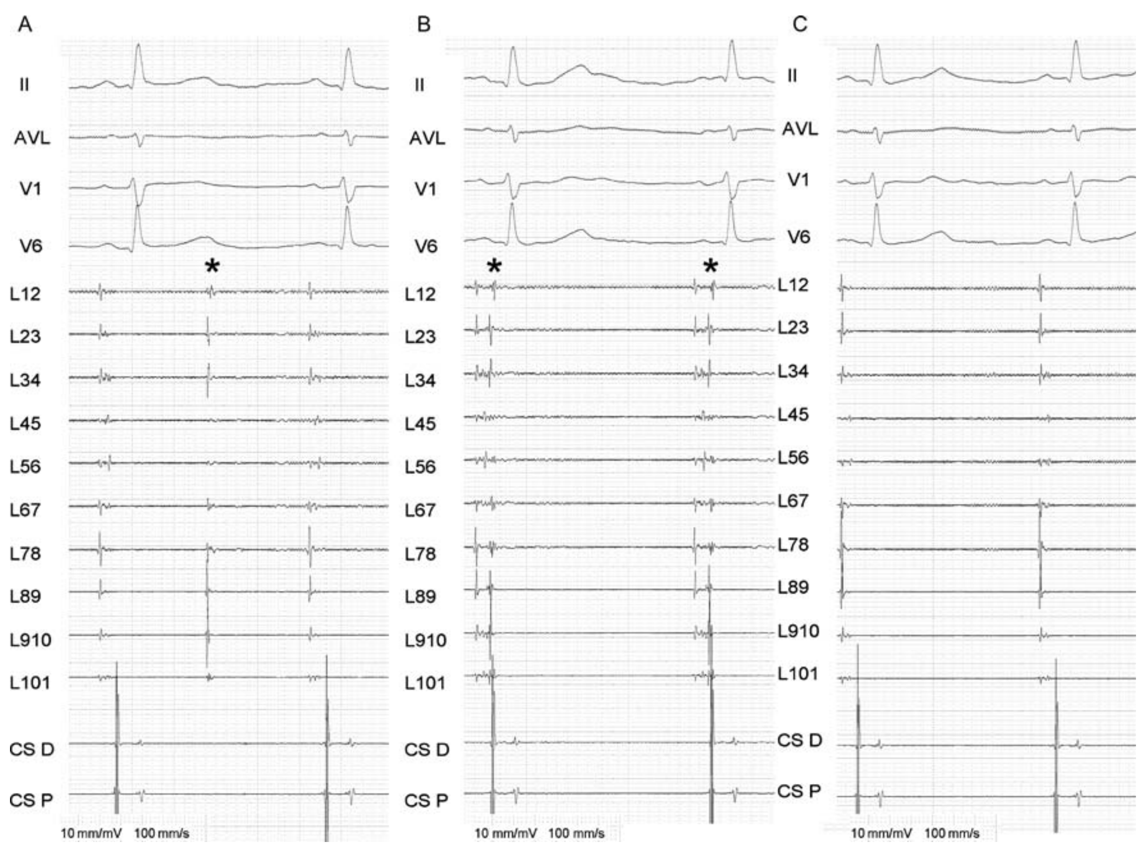

Figure 3 Demonstration of RIPV isolation after transient adenosine-induced reconnection in a 47-year-old man with paroxysmal atrial fibrillation. In all three panels, from top to bottom, Display of the surface and intracavitary signals as in *Figure 1*. (*A*) Dissociation of right inferior pulmonary vein potentials (marked by an asterisk) after cryothermal energy balloon ablation. (*B*) Adenosine-induced transient reconnection of right inferior pulmonary vein potentials (marked by asterisks). (*C*) right inferior pulmonary vein isolation after focal applications.

mechanism, intravenous adenosine injection has shown to provoke transient atriovenous reconnection in a substantial number of veins following successful PV isolation using RF.[3–5] Arentz *et al.*[3] were the first to demonstrate that adenosine could unmask incomplete lesions following PV isolation. They reported transient reappearance of atriovenous conduction in roughly 25% of the veins. However, only the superior veins were tested in each patient in order to limit the mapping time in the LA. In a study conducted on 29 patients, Tritto *et al.*[4] confirmed the previous findings by reporting a rate of 35% of reconducting veins during adenosine administration. This time, the left inferior veins were also analysed.

Elimination of adenosine-induced PV reconduction with further ablation might be associated to better long-term success. In a large cohort of patients undergoing segmental ostial isolation, Matsuo *et al.*[5] compared the clinical outcome between a group undergoing standard procedure and another with additional elimination of transient PV reconduction. The authors observed a significantly better outcome in terms of AF recurrence in the group in which incomplete lesions had been abolished. In fact, with a mean follow-up of 20 months, up to 80% of patients were AF free in this group compared with 60% in the group of individuals who had not been tested. Similar results were observed by Hachiya *et al.*[8] using extensive encircling PV isolation, and 73 vs. 60% of patients did not experience AF recurrence in the group in which transient PV reconduction had been eliminated.

To our knowledge, our study is the first to evaluate the incidence of LA–PV transient reconnection after adenosine injection following successful PV isolation obtained with CBA. We observed a low rate of adenosine-induced transient PV reconnection: this phenomenon occurred in only 7 (4.6%) of 149 veins. Transient reconnection often occurred in the inferior aspect of the lower veins, especially of the right inferior ones. This is not surprising as these regions can sometimes be difficult to target using CBA technology resulting in more superficial contact.

Transient PV reconnection induced by adenosine might occur less frequently after PV isolation obtained with CBA in comparison to RF. This might be explained by the fact that CBA might achieve more homogeneous lesions than traditional RF point by point circumferential PV isolation. This technology might offer better catheter stability in particular left atrial structures, such as the left atrial appendage–LSPV ridge, if compared with a focal RF catheter.[9] In fact when using cryoenergy, the balloon adheres to the atrial wall when reaching lower temperatures. This might result in better catheter–tissue contact and lead to more transmural lesions in these critical anatomical regions.

However, although previously published studies[7,10–12] confirm our findings reporting a high rate of acute PV isolation with CBA, the AF recurrence rate after ablation with this technology still remains relatively high, being observed in between 14 and 40% of individuals.[13] The reason for the mismatch between a low rate of adenosine-induced LA–PV reconnection and a higher recurrence rate of AF during long-term follow-up following CBA is unclear. A certain percentage of recurrence might be attributed to late PV reconnection and to non-PV foci[14,15] that might trigger AF. Also, future studies analysing the effect of the cryoenergy lesion on the ability of Adenosine to unmask LA–PV reconnection might help in giving a possible explanation to this discrepancy.

Limitations

The clinical value of adenosine injection after acute PV isolation after CBA has to be defined. Our study was limited to the description of the incidence of transient LA–PV reconnection and its anatomical features. No comparison in terms of clinical outcome between adenosine test-positive and -negative veins was performed, as all PV incomplete lesions were targeted until complete abolishment. Additionally, the fact of not having combined longitudinal and circumferential mapping of the PV might also in part have contributed to underestimate the incidence of LA–PV conduction recurrence in our report. In fact, as previously evidenced,[4] endocardial PV activation during adenosine-induced atriovenous conduction is limited to the distal portion of PV. In our study, the circular mapping catheter was placed in the proximal portion of the ostium. Furthermore, no patient in our series exhibited abnormal anatomical features, such as extremely large common ostia or adjunctive veins with uncommon ostial position, which might have rendered PV isolation very difficult with CBA. Our study also bares the limit of a single-centre study with a relatively small population and with a follow-up of only 6 months. Larger studies with longer follow-up will be needed in order to confirm our findings and the prognostic value of adenosine testing after successful PV isolation obtained with CBA.

Conclusion

Transient PV reconnection induced by adenosine injection occurs in a very low number of veins following successful PV isolation obtained with CBA. This event occurs predominantly in the inferior veins. However, the mismatch between the low rate of LA–PV reconnection induced by adenosine and the relatively high percentage of AF recurrence following CBA is unclear. Furthermore, the prognostic value on clinical outcome of adenosine testing after ablation with this technique has yet to be determined in larger studies with longer follow-up.

Conflict of interest: none declared.

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