Indian Pacing and Electrophysiology Journal 18 (2018) 203–207

Contents lists available at ScienceDirect

Indian Pacing and Electrophysiology Journal

journal homepage: www.elsevier.com/locate/IPEJ

Repeat ablation for paroxysmal atrial fibrillation – Does adenosine play a role in predicting pulmonary vein reconnection patterns?

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ARTICLE INFO

Article history:
Received 17 May 2018
Received in revised form
5 September 2018
Accepted 27 September 2018
Available online 2 October 2018

Keywords:
Atrial fibrillation
RF ablation
Pulmonary vein isolation
Adenosine
Recurrence of atrial fibrillation

ABSTRACT

Background: Pulmonary vein (PV) reconduction after PV isolation (PVI) unmasked by adenosine is associated with a higher risk for paroxysmal atrial fibrillation (PAF) recurrence. It is unknown if the reconnected PVs after adenosine testing and immediate re-ablation can predict reconnection and reconnection patterns of PVs at repeat procedures. We assessed reconnection of PVs with and without dormant-conduction (DC) during the first and the repeat procedure.

Methods: We included 67 patients undergoing PVI for PAF and a second procedure for PAF recurrence. DC during adenosine administration at first procedure was seen in 31 patients (46%). 264 PVs were tested with adenosine; DC was found in 48 PVs (18%) and re-ablated during first procedure. During the second procedure, all PVs where checked for reconnection.

Results: Fifty-eight patients (87%) showed PV reconnection during the second procedure. Reconnection was found in 152/264 PVs (58%). Of 216 PVs without reconnection during adenosine testing at the first ablation, 116 PVs (53.7%) showed reconnection at the repeat procedure. Overall, 14.9% of patients showed the same PV reconnection pattern in the first and second procedure, expected statistical probability of encountering the same reconnection pattern was only 6.6%($p = 0.012$).

Conclusions: In repeat procedures PVs showed significantly more often the same reconnection pattern as during first procedure than statistically expected. More than 50% of initial isolated PVs without reconnection during adenosine testing showed a reconnection during repeat ablation. Techniques to detect susceptibility for PV re-connection like prolonged waiting-period should be applied. Elimination of DC should be expanded from segmental to circumferential re-isolation or vaster RF application.

1. Introduction

Pulmonary vein isolation (PVI) is an established treatment option for patients with paroxysmal atrial fibrillation (PAF) with a success rate of approximately 70–75% [1–4]. Nevertheless, approximately 30% of patients require a second ablation for AF recurrence which is mainly due to PV reconnection. Achieving permanent PVI is associated with an increased rate of arrhythmia-free survival.

Several trials report that Adenosine administration following PVI can unmask dormant PV conduction and predict the durability of PVI [5–7]. Adenosine hyperpolarizes PVs via a purinergic A1 receptor, activating the outward potassium current, and leading to restoration of tissue excitability, along with reversible, thermally mediated membrane depolarization. In dormant PVs, the degree of depolarization is smaller than in nondormant PVs, and therefore adenosine provokes reconnection [7,8]. If the application of additional radiofrequency (RF) ablation to sites of transient reconnection improves the rate of arrhythmia-free survival is discussed controversially [5,9].

A recently published meta-analysis shows that adenosine unmasked dormant PV conduction after PVI is associated with a higher risk for recurrence of PAF [10]. Some studies conclude that the risk for AF recurrence is higher even if dormant conduction is abolished by additional RF application [11]. *A possible explanation might be that reconnected PVs are more likely to have a more extensive muscular PV-left atrium connection and therefore have a*

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Peer review under responsibility of Indian Heart Rhythm Society.

https://doi.org/10.1016/j.ipej.2018.09.002

higher chance of regaining excitability and conduction in the long term. Another explanation might be that reconnection during adenosine testing is a surrogate for an incomplete transmural circumferential PVI due to anatomical challenges and potentially created edema. [11–13] It remains unclear whether PVs that show reconnection during adenosine testing with additional ablation are the ones that show reconnection at a repeat procedure for AF recurrence. We assessed the difference in reconnection rates between PVs with and without dormant conduction at the first procedure and if PV reconnection sites are predictable by the initial adenosine testing.

2. Methods

2.1. Patient characteristics

A total of 67 patients who underwent PVI for PAF as well as a second procedure for PAF recurrence between June 2013 and April 2015 were retrospectively analysed. All patients had sinus rhythm at the beginning of the index procedure. Patients' characteristics and comorbidities are shown in Table 1. The mean age was 60.9 (±10.8) years and n = 39 (58.2%) patients were male. The mean history of AF was 23 months (±21.3 months), mean LA size was 42.8 mm (±5.6 mm), and LA area was 21.6 cm^2 (±4.5 cm^2).

2.2. PVI and adenosine testing

After written, informed consent was obtained from each patient, the electrophysiological study was performed under conscious sedation with a combination of propofol, midazolam and fentanyl. Vascular access was achieved via puncture of the femoral vein and insertion of two 8F sheaths and one 11.7F (Agilis, St Jude Medical, Minneapolis, USA) sheath. A multipolar, steerable diagnostic catheter was placed into the coronary sinus. Patients received singular transseptal puncture with double access to the left atrium, using a steerable 11.7F sheath. After transseptal puncture, a weight-adapted heparin bolus was given, followed by continuous heparin administration. The target activated clotting time (ACT) was between 280 s, for patients taking direct oral anticoagulants, and 300 s, for patients taking vitamin K antagonists (VKA). Thereafter 3D Mapping of the left atrium was performed with a steerable, multipolar circular catheter using the CARTO™ (Biosense Webster, Diamond Bar, CA, USA) or NaVX™ system (St Jude Medical, Minneapolis, USA). The circular mapping catheter was placed in the PV ostia to target electrical isolation.

All patients underwent antral circumferential PVI via RF application through an 8F irrigated-tip catheter. A Stockert RF generator (Stockert, GmBH, Germany) was used in all patients. Ablation technique was a continuous dragging of the catheter. Catheter stability setting for automated lesion tagging using Automark™ (NaVX) or Visitag™ (Carto) was a 2 mm surface distance limit for at least 8 s. Contact force catheters were not used. PVI was confirmed after elimination of all PV potentials followed by a 20 min waiting period. If PVs were not isolated after encircling both ipsilateral veins, additional segmental PVI was performed.

After confirmed PVI, intravenous adenosine was rapidly administered, with at least 9 mg separately for each vein since no contraindication for adenosine like bronchospastic disorders or allergies to adenosine were present in this cohort. Adenosine dose was increased if neither third-degree atrioventricular (AV) block nor sinus arrest occurred. If PVs showed DC on the circular mapping catheter, additional segmental re-ablation was applied at the earliest PV activation time on the level of the circumferential lesion in order to achieve complete PVI without DC after repeated adenosine testing.

2.3. Repeat ablation for PAF recurrence

A 7-day Holter recording and diagnostic cut-off of AF for 30 s were used to diagnose AF recurrence. After a blanking period of three months, a second procedure was performed. As part of the second procedure, all PVs were checked with a circular mapping catheter to determine reconnection. Re-isolation of the reconnected PVs was performed. At the end of the procedure, adenosine testing was performed as described above to confirm complete electrical PV disconnection.

2.4. Statistics

Continuous variables are presented as mean ± standard deviation or median. Categorical data are expressed as frequencies and percentages. Univariate comparisons were performed using T-test (continuous variables) and the X [2] test. The expected statistical probability of encountering the same reconnection pattern in the second procedure compared to the DC pattern during first procedure was calculated using a probability calculation with two options (reconnected vs. not-reconnected) in patients with four PVs (4^2) resulting in 16 possible reconnection patterns and 8 possible reconnection patterns in patients with three PVs, due to common ostia (3^2). This calculation resulted in a statistical probability of 6.6% for encountering the same reconnection pattern at random. A *P*-value of <0.05 was considered statistically significant. All analyses were performed using SPSS for Mac version 20.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Index adenosine testing

At the first procedure, a total of 264 PVs were tested with adenosine. Patients had 3.9 ± pulmonary veins and 4 patients had a common left PV ostium. Adenosine testing revealed transient reconnection of at least one pulmonary vein in 31 of 67 patients (46%). DC was recorded on the circular mapping catheter in 48/264 tested PVs (18%). If PVs showed DC, additional segmental ablation was applied at the earliest PV activation time on the level of the circumferential lesion to achieve complete PV disconnection without DC under recurrent adenosine testing. Transient AV block with spontaneous recovery was detected during Adenosine testing in all PVs. No adverse events occurred due to adenosine testing. Mean RF time for the index procedure was 41.5 min (±16.8 min).

Table 1
Baseline characteristics of patients.

Baseline characteristic	Measurement
Age (years)	60.9 ± 10.8
Male	n = 39 (58.2%)
Atrial fibrillation (AF) duration (months)	23 ± 21.3
Left atrial size (mm)	42.8 ± 5.6
Left atrial area (cm^2)	21.6 ± 4.5
Ejection fraction (%)	60 ± 2 .9
Hypertension	n = 35 (52.24%)
Diabetes mellitus	n = 5 (7.46%)
CAD	n = 4 (5.97%)
Radiofrequency duration first procedure (minutes)	41.5 ± 16.8
Radiofrequency duration second procedure (minutes)	24.2 ± 12.9
Time to AF recurrence (months)	4.4 ± 2.3

CAD: Coronary artery disease.

Table 2
Summary of reconnection patterns.

		Reconnection at index adenosine testing		Reconnection at re-ablation	
Number of patients	67	46% (n = 31/67)		87% (n = 58/67)	
Number of pulmonary veins	264	18% (n = 48/264)		58% (n = 152/264)	
PV reconnections		**LSPV:** 31% (n = 15)	**RSPV:** 27% (n = 13%)	**LSPV:** 22% (n = 33)	**RSPV:** 28% (n = 43)
		LIPV: 19% (n = 9)	**RIPV:** 23% (n = 11)	**LIPV:** 20% (n = 31)	**RIPV:** 30% (n = 45)

PV: Pumonary vein; LSPV: Left superior pulmonary vein; LIPV: Left inferior pulmonary vein, RSPV: Right superior pulmonary vein, RIPV: Right inferior pulmonary vein.

3.2. PAF recurrence and repeat procedure

All 67 patients showed symptomatic PAF recurrence and underwent a repeat procedure 7.8 months ± 5.4 months after the initial ablation. PV reconnection was found in 58 patients (87%) and 152/264 PVs (58%).

During adenosine testing in the first ablation, 216/264 PVs had shown no DC ("adenosine-negative"). A reconnection at the beginning of the repeat procedure was shown in 116 of these 216 PVs (53.7%). A summary of reconnection rates and patterns is shown in Table 2.

The same PV reconnection pattern in the first and repeat procedure was found in 14.9% of all patients (n = 10). The expected statistical probability of encountering the same reconnection pattern was only 6.6% and, therefore, reached significance in the exact binomial testing with $P = 0.012$ (Table 3).

In the repeat procedure, 9 patients showed no PV reconnection, indicating non-PV–triggered atrial fibrillation. After confirming that all PVs were isolated, burst stimulation via the coronary sinus catheter was performed. AF was induced in five patients and a modified stepwise approach as described in earlier publications was performed [14]. In 2 patients, typical atrial flutter was induced and ablation of the cavo-tricuspid isthmus performed. In one patient, roof-dependent atypical atrial flutter was induced and terminated by a roof line and in another patient, perimitral atypical atrial flutter was successfully treated with an anterior line. Mean RF time of the second procedure was 24.5 min ± 12.9 min.

4. Discussion

To the best of our knowledge, this is the first study to evaluate the role of adenosine testing at PVI with respect to PV reconnection and patterns during a repeat procedure for PAF recurrence.

In addition to an impaired quality of life, recurrence of AF after RF ablation is associated with a higher rate of morbidity [2,15]. Therefore, there is considerable interest and focus on improving the treatment outcomes for patients with PAF after ablation. To meet this challenge, new techniques such as enhanced irrigated-tip catheters with contacted force, the third-generation cryoballoon or other single-shot devices, and enhanced 3D mapping and ablation algorithms with enhanced lesion assessment such as the Carto Ablation Index™ (Biosense Webster, Diamond Bar, CA, USA) have become available or are currently in development. An extended waiting period after PVI plus testing with adenosine for dormant conduction could improve rates of arrhythmia-free survival, but may not lead to an increases success rate above 75–80% after the completion of one procedure [5].

4.1. Information due to PV reconnection

Our data demonstrate that reconnected PVs during adenosine testing in the first procedure are significantly more often the reconnected ones after a recurrence of AF. This knowledge gleaned from the first adenosine testing delivers additional information that should lead to an adjustment of further ablation. Strategies to eliminate dormant conduction might be expanded if dormant conduction in PVs is found while testing with adenosine. Possible strategies include an extension from segmental re-isolation to a broader, second circumferential re-isolation or, at least, use of a vaster RF application in areas of dormant reconnection. Data from Steven et al., showed that pacing along the PVI line to ensure unexcitability of the ablated tissue improves single-procedure success in patients with AF [16]. If dormant conduction is found, this strategy could be enacted to ensure that a sufficient ablation circle is performed. Furthermore, a more extensive waiting period for the adenosine-positive veins in the first procedure could be an option for improving outcomes.

4.2. Waiting period and durability of PVI

In our study, 53.7% of PVs that remained isolated during adenosine testing showed a reconnection in the repeat procedure. Our data demonstrate that PVs that remain isolated during adenosine testing are not necessarily isolated in the repeat procedure. A possible explanation is that inflammation created at the circumferential RF lesions leads to maturation and immigration of immune cells that influence healing processes, leading to gap formations in circular ablation lines over time, and limiting the negative predictive value of adenosine testing.

Adenosine, nevertheless, can help identify those PVs with reversible membrane depolarization likely to recover over a shorter timeframe [12,17]. PVs can still regain excitability after a certain period of time occurring non dormant after adenosine admission. As a consequence, a certain "waiting-period" remains important

Table 3
Results of reconnection patterns and calculated statistical probability.

$$\frac{Number\ of\ PVs * \frac{1}{possible\ reconnection\ patterns}}{Number\ of\ PVs}$$

Expected probability of "same reconnection pattern" (Vein-by-vein patterns with common Ostia) $\frac{63 * \frac{1}{16} * 4 * \frac{1}{8}}{67} = 0.066$

Expected probability	Calculated number of the same reconnection pattern	95% confidence interval	*P*-value
6.6%	14.9%	0.073–0.258	0.012

PV: Pulmonary vein.

after PVI.

In particular, time appears to be an important factor with respect to long-term durability of PVI. Studies have shown that lengthening the waiting time up to 60 min can reveal acute PV reconnection in 90% of patients [18]. In a canine model, approximately 80% of PVs that showed no PVI reconnection after testing with adenosine showed dormant conduction after an additional waiting period of 90 min [8].

It remains unclear whether the long-term aim in patients with PAF is a durable PVI, or if complete periprocedural PVI is merely a surrogate for modulation of a certain amount of ostial tissue needed to change PV conduction in such a way that supraventricular extrasystoles either cannot cause AF or so that a substantial LA–PV conduction is achieved [19].

Furthermore, it remains unclear if, in patients without recurrence of PAF, all PVs remain isolated over the long term. Recent studies have shown that, even in patients with no recurrence of AF, not all PVs remained isolated after RF ablation. Jiang et al. showed that 91% of patients without recurrence of AF showed PV reconnection [20]. Data from Miyazaki et al. showed that the incidence and characteristics of PV reconnections after a second-generation cryoballon ablation were similar between patients with and without clinical AF recurrences [21].

4.3. Limitations

One limitation of this study is its retrospective design. In addition, the limitations of adenosine testing should be addressed. Due to changes in respiration patterns, wall contact between the spiral catheter and ostial tissue could be inadequate, resulting in the missing of transient reconnection of PVs. Moreover, the use of propofol and opioids could lead to an underestimation of local PV triggers; since these drugs also affect depolarization during adenosine testing, resulting in an underestimation of dormant conduction.

After PVI, each vein was tested separately with adenosine. If reconnection occurred, additional segmental ablation was performed. Therefore, any possible simultaneous temporary reconnection during adenosine testing of the ipsilateral veins could not be detected. Those possible reconnections could be affected by the additional ablation (especially ablation between the veins) resulting in an additional isolation of the ipsilateral vein. Furthermore, exact reconnection sites of PV during Adenosine testing in the first ablation and during the second procedure where not assessed. Therefore, it remains unclear if the reconnection site was exactly the same.

We used multipolar spiralcatheters with an electrode spacing of 8 mm and 12 electrodes (LASSO® 2515 NAV eco, Biosense Webster, Diamond Bar, CA, USA) and 5 mm and 14 electrodes, respectively (Orbiter™ PV, Bard Electrophysiology, Lowell, MA, USA). Recent studies have shown that mapping catheters with smaller spacing and smaller electrodes can show reconnection that remain concealed by using “conventional” multipolar spiralcatheters [22,23].

5. Conclusion

Our data demonstrate that PVs exhibiting no re-excitability after adenosine administration during the first PVI procedure are still susceptible to regaining excitability after a certain period of time. Therefore, additional techniques to detect susceptibility for PV reconnection should be applied, such as enacting a longer waiting-period. In repeat procedures, PVs significantly more often showed the same reconnection patterns seen during first-procedure adenosine testing than statistically expected. As a result, strategies to eliminate dormant conduction should be expanded from segmental to circumferential re-isolation, or at least to a vaster RF application in reconnected areas.

Disclosures

None.

Conflicts of interest

None specific to this topic.

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