

Long-term outcome of paroxysmal atrial fibrillation catheter ablation with and without pulmonary vein dormant conduction after adenosine challenge

Tomas Skala^a, Jan Precek^a, Martin Hutyra^a, Ondrej Moravec^a, Zbynek Tudos^b, Jitka Skalova^c, Olga Klementova^c,
Andrea Antonicka^d, Jana Zapletalova^e, Milos Taborsky^a

Objectives. The prognostic significance of adenosine-mediated pulmonary vein (PV) dormant conduction is unclear. We prospectively followed patients with adenosine-mediated PV reconnection with a subsequent repeated ablation until there was no reconnection inducible with patients without reconnection after PV isolation.

Method and Results. Consecutive patients (n=179) with paroxysmal atrial fibrillation (AF) without prior catheter ablation (CA) were enlisted in the study. We used a point-by-point CA and general anesthesia in all patients. Twenty minutes after PV isolation we administered adenosine in a dose sufficient to produce an atrioventricular block. If a dormant conduction was present (n=54) we performed additional ablation until there was no adenosine mediated reconnection inducible. During 36 months of follow-up, all patients were examined for eight 7-day ECG recordings. There was no difference in arrhythmia recurrence rate between patients with and without dormant conduction (29.6 vs. 24.8% at 12 months, $P=0.500$; 31.5 vs. 30.4% at 36 months, $P=1.000$), for any echocardiographic parameter or any parameter of the ablation procedure.

Conclusion. The patients with dormant conduction after adenosine during catheter ablation of paroxysmal atrial fibrillation with complete elimination of the dormant conduction by additional extensive ablation have the same outcome in the long term as patients without a dormant conduction.

Key words: atrial fibrillation, catheter ablation, adenosine, dormant conduction, arrhythmia recurrence

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^aDepartment of Internal Medicine I - Cardiology, University Hospital Olomouc, Czech Republic

^bDepartment of Radiology, University Hospital Olomouc, Czech Republic

^cDepartment of Anesthesiology and Intensive Care Medicine, University Hospital Olomouc, Czech Republic

^dCardiovascular Center, Tomas Bata County Hospital, Zlin, Czech Republic

^eDepartment of Biophysics, Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic

Corresponding author: Jan Precek, e-mail: jan.precek@seznam.cz

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia with significant morbidity and mortality¹. Catheter ablation has been demonstrated to be an effective treatment for AF (ref.^{2,4}). Pulmonary vein (PV) isolation is the cornerstone for non-pharmacological treatment of paroxysmal AF.

PV isolation can be achieved in more than 95% patients in one ablation procedure; however, 30-50% of patients present with arrhythmia recurrence⁵. Despite all progress in technology, a single ablation of paroxysmal AF outcome remains limited to only 70% event-free rate⁶. During a repeated ablation, a reconnection to at least one PV is found very often. Pulmonary vein reconnection with the left atrium is considered to be the main cause of AF recurrence, especially in patients with paroxysmal AF (ref.⁷).

A method capable of distinguishing between an acute reversible injury, which will lead to PV reconnection in the long run and permanent injury that will lead to a non-

conducting scar tissue, would be very helpful. Arentz et al. first described adenosine effects on transient pulmonary vein reconnection by selective activation of the IK_{Ado} inward rectifier current⁸. This contributes to membrane hyperpolarization and restores the excitability threshold. The cells that have suffered irreversible damage will have their membrane depolarized and unexcitable and will not respond to adenosine⁹. A second possible mechanism is the increase of the sympathetic tone due to respective increases in arterial chemoreceptor activity¹⁰.

Using adenosine, the so called dormant conduction (DC) can be revealed in about 25% of PV after initial isolation. The place with a transient reconnection can be mapped and thus we can define an area where the ablation was done insufficiently and where a permanent reconnection can be expected. It is possible to perform additional ablation in such a place and possibly achieve a higher rate of permanent PV isolation with a better ablation outcome⁸.

The studies addressing the use of adenosine are noted to have conflicting outcomes¹¹⁻¹⁷.

METHODS

Patient group

A total of 179 patients indicated to catheter ablation of paroxysmal atrial fibrillation were enlisted in the study. Patients were classified as having paroxysmal AF according to current guidelines¹⁸.

Inclusion criteria were paroxysmal AF, at least 3 episodes of AF in the last 6 months, age > 18 years, sinus rhythm (SR) at the beginning of the ablation and a signed informed consent for the study.

Exclusion criteria were persistent AF, structural heart disease, moderate-to-severe or severe valve disease or history of a valve disease surgery, chronic use of amiodarone, LV EF <35%, presence of intra-cardiac thrombi as documented by transesophageal echocardiography, uncontrolled thyroid disorders, pregnancy, breast feeding, severe renal dysfunction, inadequate follow-up and inability to provide informed consent.

Procedures before catheter ablation

All patients underwent transesophageal echocardiography and cardiac computed tomography focused on pulmonary veins anatomy within 24 h before ablation. At least 3 days before ablation, antiarrhythmic medication was discontinued in all patients. No patient was on amiodarone during 3 months before ablation. Written informed consent was obtained from all subjects. The study protocol was approved by our institutional ethics committee.

Catheter ablation

Catheter ablation was done under general anesthesia in all patients. Two sheaths were introduced via the femoral vein for intra-cardiac echocardiography probe (AcuNav ultrasound catheter, Siemens Healthineers, USA) and decapolar diagnostic coronary sinus catheter (Inquiry™, St. Jude Medical). Two steerable transseptal sheaths (Agilis™ NxT Steerable Introducer, St. Jude Medical) were introduced via femoral vein. A double transseptal puncture was performed in all patients. After transseptal puncture a 3D electro-anatomical map was performed using Carto3™ (Biosense Webster). A fast anatomical map (FAM) was done consistently in all patients. The anatomical map was merged with a 3D model of left atrium (LA) using CartoMerge™ technology. A point-by-point radiofrequency (RF) wide-antral ablation (Fig. 1) was done in all patients using Navistar™ ablation catheter (Biosense Webster) to achieve isolation of ipsilateral PVs.

Ablation energy was set to 25-30 W in all patients with cool flow of 20 mL/min. Lasso™ catheter (Biosense Webster) was used to validate PV isolation (entry block) in all patients. In case of ongoing AF, prior to the final check for PV isolation, a direct current cardioversion was performed. Extra-pulmonary ablation was not performed unless the typical atrial flutter occurred or was documented before ablation, or a spontaneous procedural atrial tachycardia occurred during ablation. Mapping and ablation of these tachycardias was allowed. There was no

inducibility testing or provocation of extra-pulmonary triggers performed after PV isolation. After PV isolation, we waited for 20 min and then adenosine was applied intravenously to test dormant conduction using a double lasso technique. At least 18 mg of adenosine was used for the test. The dose was considered sufficient if it resulted in the second or third degree atrioventricular block. Additional ablation was performed in case of PVs with conduction recovery after adenosine testing. To determine whether dormant conduction was eliminated after re-ablation, another adenosine testing was performed. Once all PVs with conduction recovery were re-isolated, the procedure was ended.

Follow-up post-ablation

In case of warfarin, oral anticoagulation was uninterrupted prior to the ablation procedure. The ablation was performed if the international normalized ratio at the beginning of the procedure was below 3.0. In case of direct anticoagulants, one dose was skipped before ablation. As per common practice, arrhythmia recurrence was managed using antiarrhythmic medication and cardioversion, if necessary. For the whole 3-years long follow-up (FU), all patients were monitored in the out-patient department of our institution. The follow-up was divided into 2 parts. With respect to a possible comparison of the results with other comparable studies, the first part of FU was ended 12 months after ablation (0-12 months - short-term FU). To evaluate the long-term results of ablation using DC elimination, all patients were followed up for at least 36 months (0-36 months - long-term FU). A 7-day ambulatory ECG monitoring was done repeatedly in all patients every 3 months (3, 6, 9, 12 months after ablation) and then every 6 months until the end of a 3-year long FU (18, 24, 30, 36 months after ablation). The patients were instructed about the need of an early examination in the out-patient department in case of palpitations with an effort to document a possible arrhythmia in the period of time between 7-day ambulatory ECG monitoring. A clinical evaluation in an out-patient department was done in all patients 2-4 weeks after every ambulatory ECG monitoring. Any documented arrhythmia (atrial flutter, atrial tachycardia, atrial fibrillation) lasting more than 30 seconds until the end of the FU was considered an arrhythmia recurrence. Blanking period was not used. The statistical analysis was done at 12th and 36th month after ablation. All patients were divided according to presence or absence of arrhythmia recurrence into two groups.

Statistical analysis

The statistical software IBM SPSS Statistics ver. 22 was used to data analysis. Subgroups of patients with and without arrhythmia recurrence were compared in quantitative parameters using Student's t-test or Mann-Whitney U-test depending on data normality. For qualitative parameters, the subgroups of patients were compared using the chi-square test or Fisher's exact test. Data normality was verified using Shapiro-Wilk test. All tests were done at a level of significance 0.05.

RESULTS

Follow-up

All 179 patients completed a 3-year long FU. PV isolation (entry and exit block) was achieved in all patients. A dormant conduction was present in 54 patients (30.2%). Elimination of adenosine mediated reconnection was achieved in all 179 patients. No major complications such as cardiac tamponade, stroke, atrio-esophageal fistula and/or pulmonary vein stenosis were documented in the study sample. 3 patients presented with a large groin hematoma. All of them were treated conservatively without consequences. All 179 patients completed all eight 7-day ambulatory ECG recordings. No patient was lost during the follow-up.

The difference in short-term and long-term outcome in patients with and without dormant conduction

In patients with DC after adenosine, the AF recurrence rate until 12 months after ablation was 29.6%. In patients without DC after adenosine, the AF recurrence rate until 12 months after ablation was 24.8%. The difference was not significant, $P=0.500$. In patients with DC after adenosine, the AF recurrence rate until 36 months after ablation was 31.5%. In patients without DC after adenosine, the AF recurrence rate until 36 months after ablation was 30.4%. The difference was not significant, $P=1.000$. The patients with AF recurrence did not have DC present more often than patients without AF recurrence (Table 1).

Table 1. The difference in short-term and long-term outcome in patients with and without dormant conduction.

		DC -	DC +	P
12 months	AF recurrence -	94 (75.2%)	38 (70.4%)	0.5
	AF recurrence +	31 (24.8%)	16 (29.6%)	
36 months	AF recurrence -	87 (69.6%)	37 (68.5%)	1
	AF recurrence +	38 (30.4%)	17 (31.5%)	

In patients with arrhythmia recurrence at 12 months, a DC was present in 34.0%. In patients without arrhythmia recurrence in 12 months, a DC was present in 28.8%. The difference was not significant, $P=0.500$. In patients with arrhythmia recurrence at 36 months, a DC was present in 30.9%. In patients without arrhythmia recurrence in 36 months, a DC was present in 29.8%. The difference was not significant, $P=1.000$. The presence of DC was not significantly connected with a future AF recurrence (Table 2).

Table 2. The difference in DC absence or presence in patients with and without AF recurrence (at 12 and 36 months).

	12 months			36 months		
	Recurrence +	Recurrence -	P	Recurrence +	Recurrence -	P
DC +	16 (34.0%)	38 (28.8%)	0.5	17 (30.9%)	37 (29.8%)	1
DC -	31 (66.0%)	94 (71.2%)		38 (69.1%)	87 (70.2%)	

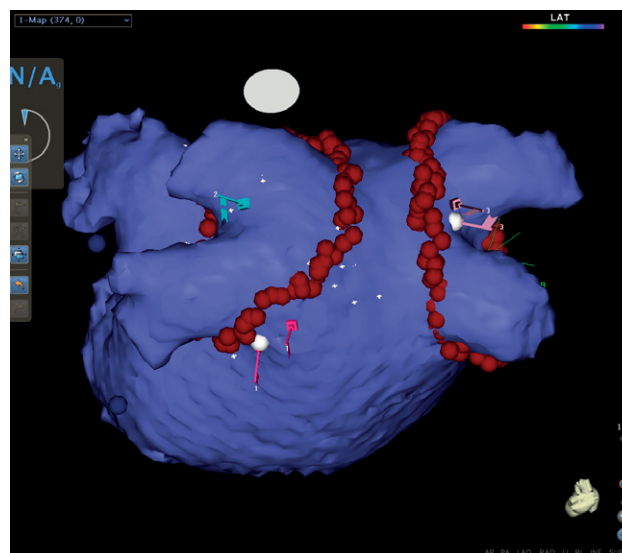


Fig. 1. CARTO3 anatomical model of left atrium. Wide encircling lesions around ostia of ipsilateral pulmonary veins. Red dots = ablated areas.

The difference in time to arrhythmia according to presence or absence of DC in the short-term (12 months) and long-term (36 months) follow-up

In the first 12 months, there was no significant difference in time to AF recurrence between the subgroups according to DC presence or absence (10.39 (95% CI 9.55-11.23) vs. 10.44 (95% CI 9.87-11.01), Log-rank test $P=0.549$).

After the first year, there was no significant difference in time to AF recurrence between the subgroups according to DC presence or absence (27.2 (95% CI 25.7-29.6) vs. 27.8 (95% CI 25.5-30.1), Log-rank test $P=0.889$) (Fig. 2).

The difference in ablation procedure length and fluoroscopy time in patients with and without arrhythmia recurrence

The procedure length, defined as time from groin puncture until sheaths extraction, was not significantly different between patients with and without AF recurrence in the short-term FU (mean length 120 vs. 120 min, Mann-Whitney U test $P=0.241$) as well as in the long-term FU (mean length 120 vs. 120 min, Mann-Whitney U test $P=0.35$).

Total time of ablation was not significantly different between patients with and without AF recurrence in the short-term FU (mean length 32 vs. 33 min, Mann-Whitney U test $P=0.461$) as well as in the long-term FU (mean length 32 vs. 33 min, Mann-Whitney U test $P=0.377$).

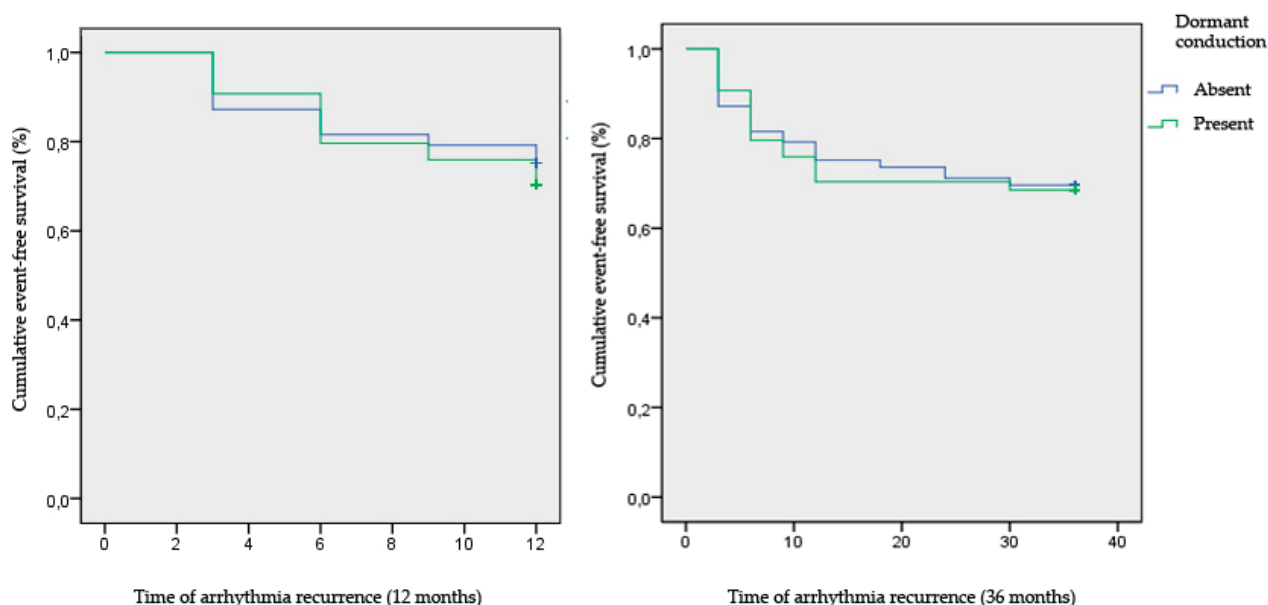


Fig. 2. Kaplan-Meier curve of cumulative event free survival.

The fluoroscopy time was not significantly different between patients with and without AF recurrence in the short-term FU (mean length 5 vs. 5 min, Mann-Whitney U test $P=0.566$) as well as in the long-term FU (mean length 5 vs. 5 min, Mann-Whitney U test $P=0.745$).

The difference in height, width and body-mass index in patients with and without arrhythmia recurrence

No significant difference was found in any of these parameters between patients with and without recurrence in the short-term as well as the long-term follow-up (Table 3).

Height, width – Student's t-test, BMI – Mann-Whitney U test. LA, LAA – Student's t-test, LVEF – Mann-Whitney U test. PLAX=parasternal long axis. LAA=left atrium appendage. LVEF=left ventricle ejection fraction

The difference in echocardiographic parameters performed 1-24 h before ablation in patients with and without arrhythmia recurrence

No significant difference was found in any of these parameters between patients with and without recurrence in a short-term as well as long-term follow-up (Table 3).

The difference in baseline clinical parameters before ablation in patients with and without arrhythmia recurrence

No significant difference was found in any of these parameters between patients with and without recurrence in the short-term as well as long-term follow-up (Table 4).

DISCUSSION

The use of adenosine was first described by Arentz⁸. Thereafter, a number of studies documented the possible use of adenosine to reveal future reconduction from LA to PV due to insufficient PV isolation and the potential

Table 3. The difference in height, width, body-mass index and in echocardiographic parameters performed 1-24 h before ablation in patients with and without arrhythmia recurrence.

	12 months			36 months			DC -	DC +	P
	Recurrence -	Recurrence +	P	Recurrence -	Recurrence +	P			
Height (cm)	177±10	177±9	0.961	178±10	177±9	0.848	178±10	176±9	0.218
Width (kg)	90±17	88±17	0.324	90±16	89±18	0.589	90±17	90±15	0.844
BMI	28.6±4.4	27.8±4.8	0.364	28.5±4.3	28.1±4.9	0.615	28.2±4.7	28.8±4.1	0.135
LA (PLAX) (mm)	42±6	42±7	0.832	41±6	43±7	0.306	42±7	42±6	0.954
LAA output velocity (cm/s)	74±26	75±32	0.785	74±27	74±30	0.984	75±30	72±22	0.941
LVEF (%)	56.9±5.4	56.0±5.9	0.414	56.9±5.4	56.3±5.9	0.541	56.8±5.9	56.3±4.7	0.358

Table 4. The difference in baseline clinical parameters before ablation in patients with and without arrhythmia recurrence.

	12 months			36 months			DC -	DC +	P
	Recurrence +	Recurrence -	P	Recurrence +	Recurrence -	P			
Arterial hypertension	78 (59.1%)	32 (68.1%)	0.277	73 (58.9%)	37 (67.3%)	0.287	76 (60.8%)	34 (63.0%)	0.868
Diabetes mellitus	9 (6.8%)	7 (14.9%)	0.133	9 (7.3%)	7 (12.7%)	0.262	9 (7.2%)	7 (13.0%)	0.255
Heart failure	7 (5.3%)	1 (2.1%)	0.683	7 (5.6%)	1 (1.8%)	0.438	8 (6.4%)	0 (0.0%)	0.108
Coronary artery disease	6 (4.5%)	0 (0.0%)	0.343	5 (4.0%)	1 (1.8%)	0.668	4 (3.2%)	2 (3.7%)	1
Myocardial infarction	4 (3.0%)	0 (0.0%)	0.574	4 (3.2%)	0 (0.0%)	0.314	3 (2.4%)	1 (1.9%)	1
Hyperlipidemia	41 (31.1%)	17 (36.2%)	0.52	37 (29.8%)	21 (38.2%)	0.271	39 (31.2%)	19 (35.2%)	0.606
Stroke	6 (4.5%)	2 (4.3%)	1	6 (4.8%)	2 (3.6%)	0.201	6 (4.8%)	2 (3.7%)	1
Obstructive sleep apnea	5 (3.8%)	0 (0.0%)	0.328	5 (4.0%)	0 (0.0%)	0.325	5 (4.0%)	0 (0.0%)	0.324

P – Fisher's exact test.

impact of additional ablation on reduction of arrhythmia recurrence^{11,12,17}. Although the older studies were quite optimistic, the newer studies, including meta-analyses, did not show a positive effect of adenosine-guided ablation on arrhythmia-free rate and the former enthusiasm faded away to a significant degree^{13,14,19-21}.

Adenosine leads to revealing DC in 25-53% of patients. The presence of DC is connected with arrhythmia recurrence^{14,15,22}. Adenosine leads in a certain degree to a falsely negative evaluation of a PV as permanently isolated, although after a local edema recedes, a reconnection from PV to LA will emerge.

A waiting time of 20-30 min after ablation is important as it leads more often to the documentation of DC further increasing the efficacy of this method²³. It is not precisely known what is an adequate dose of adenosine that will lead to DC in 100% of PVs that are ablated insufficiently and will reconnect after the procedure^{24,25}.

In the case of DC, additional ablation is performed in the area of temporary PV reconnection. After this additional ablation, another dose of adenosine should be administered, though it is only rarely applied after another sufficiently long waiting time.

A sufficient waiting time and an adequate adenosine dose are just two of several reasons behind the heterogeneity of the results of the studies published so far. The main reason is the huge difference in methodology and in basic hypothesis. The essential difference is in the elementary evaluated question. Answers for the following two questions are usually sought. Is there a difference in clinical outcome if we use adenosine or not? If we use adenosine in all patients, is there a difference in clinical outcome if we perform additional ablation in patients with DC?

Macle et al. (ADVANCE trial) showed that additional ablation leads to an outcome equivalent to no acute reconnection¹⁵. However, Kobori et al. (UNDER-ATP trial) showed that routine adenosine testing does not improve the outcome compared to no testing at all¹⁴.

There is a difference between these trials in several other principal parameters. In the ADVANCE trial, only pa-

tients with paroxysmal AF were enlisted in the study with additional LA ablation at 3% and cavo-tricuspid isthmus (CTI) ablation in 17%. In the UNDER-ATP trial, 22.7% of patients with persistent and 10.1% with long-standing persistent AF were included. Additional extensive LA ablation was performed in 30% of patients and a CTI ablation in more than 70%. In the ADVANCE trial, the dose of adenosine was titrated to achieve atrioventricular (AV) block and it was applied 20 min after PV isolation. During this waiting time, a spontaneous reconnection was documented in 27% of patients. After adenosine, DC was found in 53% of patients. In the UNDER-ATP trial, the dose of adenosine was selected based on patient's weight and it was not necessarily sufficient to result in AV block and document DC. A waiting time was markedly longer with a median of 57 min. A spontaneous reconnection occurred in 42% of patients. This allowed them to precisely focus on areas with insufficient ablation and thus, after adenosine, DC manifested only in 28%.

In our study, at least 18 mg of adenosine was applied to assess DC in every single PV. The dose was increased when necessary until at least one blocked P wave occurred. We have applied adenosine 20 min after isolation of the last PV. In the case of a spontaneous reconnection during the waiting time, additional ablation was performed to achieve isolation again, and the waiting time was restarted. Additional ablation was performed in all patients until no DC was apparent. We have to admit that the waiting time could have been longer, further revealing areas of DC, however, a 20-min long period of waiting time was also used in the ADVANCE study. Nonetheless, a longer waiting time initially and/or before each adenosine test would not be most probably accepted in real life due to a major prolongation of the ablation procedure.

In another two trials, Ghanbari and Efremidis demonstrated that further ablation of unmasked DC does not improve outcome^{13,19}. This further strengthened a reserved view on the adenosine-guided approach to AF ablation. Nevertheless, as in the UNDER-ATP trial, the study design was different compared to the ADVANCE trial. In the

meta-analysis by Papageorgiou et al., when all types of trials were evaluated together, a better outcome of adenosine compared to no adenosine strategy was apparent with a 40% decrease in the recurrence of AF in adenosine-guided strategy. However, pooling of data from RCTs only, there was no evidence of adenosine-guided approach on better event-free survival after catheter ablation²¹.

Currently, it is difficult to show clear evidence of the superiority of the adenosine-guided approach. Nevertheless, the ADVICE trial and meta-analyses are in agreement that if we find DC after adenosine and we do not treat that area with additional ablation, these patients will have the worst outcome of the whole patient group^{15,25}.

The aim of our study was to show, on a maximum possible homogenous patient group that elimination of a specific subgroup of patients with documented DC by additional ablation has a clear clinical outcome and that adenosine-guided strategy makes sense. We evaluated only patients with paroxysmal AF, without prior ablation, without a history of amiodarone and without additional ablation in either atria with the exception of patients with a previous documentation of typical atrial flutter. We consistently used a single technology approach in all patients. We showed that if you treat the areas with DC after adenosine with additional ablation until abolition of DC, the outcome of this subgroup equalizes with patients without a documented DC. This favorable outcome lasts not only for one year, as shown before, but for a long period of time. The long FU is one of the strengths of our study since it is uncommon in these trials. According to a recent meta-analysis of trials evaluating the impact of adenosine-guided strategy on AF ablation outcome, the FU was 6-17 months long with a majority of trials following the patients up for one year²⁴.

Our findings are in contradiction with the results of a systematic review by Wang et al. According to their analysis of 18 studies, 3,038 patients received adenosine and freedom from AF in those with dormant PV reconnection was significantly lower (62.9%) compared to patients without PV reconnection (67.2%) (RR 0.87; 95% CI: 0.78-0.98). They concluded that adenosine administration produced superior outcomes than no adenosine administration; however, adenosine reconnection was still associated with a greater likelihood of AF recurrence than patients with no adenosine reconnection, despite further ablation²⁶. Our results are different. By a thorough and repeated ablation in the areas with a documented DC we were able to achieve a similar outcome for patients with and without DC.

So far, the most used parameter predicting the outcome of catheter ablation is LA diameter²⁷. We found no difference between patients with and without AF recurrence in this parameter. A possible reason might be that in patients with a paroxysmal form of AF the most important thing to do is to isolate PVs as best as possible.

We can speculate that with new technologies such as Contact-Force, Force-Time-Power integral, diamond-tip catheters, etc. the percentage of permanently isolated PVs will be much higher, thus decreasing the role of adenosine²⁸.

The more permanently ablated areas we will produce, the less useful the methods identifying these areas will become. Nevertheless, until we all have an available technology that will allow us to achieve isolation of all PVs in all patients, we will have to identify patients with insufficiently performed ablation. Adenosine allows us to identify these patients. We can treat these poorly ablated areas with additional ablation and, as we have shown in our cohort of patients, patients treated in this way do not have worse outcome than other patients.

Adenosine is undoubtedly able to show areas of future reconnection in some patients. And if we do not use it routinely and correctly, we will doom these patients to arrhythmia recurrence with non-negligible medical and economic consequences.

Study limitations

Our work is prospective but not randomized. Due to clear evidence for an unfavorable outcome of patients with DC and no further ablation, we considered it unethical to incorporate such a subgroup.

A potential limitation is the fact that after repeated adenosine administrations after additional ablation we did not repeat another 20-min long period of waiting time.

CONCLUSION

The patients with apparent dormant conduction after adenosine during catheter ablation of paroxysmal atrial fibrillation with complete elimination of the dormant conduction by additional extensive ablation have the same outcome in the long term as the patients without a dormant conduction.

Author contributions: TS: study design, performing CA, complete patient FU, data analysis, data interpretation, manuscript writing and literature search; JP: study design, data analysis, data interpretation; ZT: acquiring CT; MH: data analysis, data interpretation; OM: data collection; performing CA, patient FU; JS, OK: general anesthesia; AA: data collection; JZ: statistical analysis; MT: final approval of the manuscript.

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REFERENCES

1. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Moroux AL, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;339:659-66.
2. Brooks AG, Stiles MK, Laborde J, Lau DH, Kuklik P, Shipp NJ, Hsu LF, Sanders P. Outcomes of long-standing persistent atrial fibrillation ablation: A systematic review. *Heart Rhythm* 2010;7:835-46.
3. Jais P, Haissaguerre M, Shah DC, Chouairi S, Gencel L, Hocini ML, Clementy J. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. *Circulation* 1997;35:572-6.
4. Cappato R, Calkins H, Chen SA, Davies W, Lesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the methods, efficacy and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;3(1):32-8. doi: 10.1161/CIRCEP.109.859116

5. Wilber DJ, Pappone C, Neuzil P, De Paola A, Thermocool AF Trial investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010;303:333-40.
6. Kuck KH, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun K, FIRE and ICE investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med* 2016 9;374:2235-45.
7. Khan AR, Khan S, Sheikh MA, Khuder S, Grubb B, Moukarbel GV. Catheter ablation and antiarrhythmic drug therapy as first-or second-line therapy in the management of atrial fibrillation: systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* 2014;7:853-60.
8. Arentz T, Macle L, Kalusche D, Hocini M, Jais P, Shah D, Haissaguerre M. "Dormant" pulmonary vein conduction revealed by adenosine after ostial radiofrequency catheter ablation. *J Cardiovasc Electrophysiol* 2004;15:1041-7.
9. Datino T, Macle L, Qi XY, Maguy A, Comtois P, Chartier D, Guerra P G, Arenal A, Fernandez-Aviles F, Nattel S. Mechanisms by which adenosine restores conduction in dormant canine pulmonary veins. *Circulation* 2010;121:963-72.
10. Biaggioni I, Killian TJ, Mosqueda-Garcia R, Robertson RM, Robertson D. Adenosine increases sympathetic nerve traffic in humans. *Circulation* 1991;83:1668-75.
11. Hachiya H, Hirao K, Takahashi A, Nagata Y, Suzuki K, Maeda S, Sasaki T, Kawabata M, Isobe M, Iesaka Y. Clinical implications of reconnection between the left atrium and isolated pulmonary veins provoked by adenosine triphosphate after extensive encircling pulmonary vein isolation. *J Cardiovasc Electrophysiol* 2007;18:392-8.
12. Andrade JG, Pollak SJ, Monir G, Khairy P, Dubuc M, Roy D, Talajic M, Deyell M, Bennett M, Dyrda K, Rivard L, Thibault B, Guerra PG, Nattel S, Macle L. Pulmonary vein isolation using a pace-capture-guided versus anadenosine-guided approach: effect on dormant conduction and long-term freedom from recurrent atrial fibrillation — a prospective study. *Circ Arrhythm Electrophysiol* 2013;6:1103-8.
13. Ghanbari H, Jani R, Hussain-Amin A, Al-Assad W, Huether E, Ansari S, Jongnarangsin K, Crawford T, Latchamsetty R, Bogun F, Morady F, Oral H, Chugh A. Role of adenosine after antral pulmonary vein isolation of paroxysmal atrial fibrillation: A randomized controlled trial. *Heart Rhythm* 2016;13:407-15.
14. Kobori A, Shizuta S, Inoue K, Kaitani K, Morimoto T, Nakazawa Y, UNDER-ATP trial. Adenosine triphosphate-guided pulmonary vein isolation for atrial fibrillation: The unmasking dormant electrical reconnection by adenosine triphosphate (UNDER-ATP) trial. *Eur Heart J* 2015;36:3276-87.
15. Macle L, Khairy P, Weerasooriya R, Novak P, Verma A, Willems S, ADVICE trial investigators. Adenosine-guided pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: An international, multicentre, randomised superiority trial. *Lancet* 2015;386:672-9.
16. Matsuo S, Yamane T, Date T, Inada K, Kanzaki Y, Tokuda M, Shibayama K, Miyazaki S, Miyazaki H, Sugimoto K, Mochizuki S. Reduction of AF recurrence after pulmonary vein isolation by eliminating ATP-induced transient venous re-conduction. *J Cardiovasc Electrophysiol* 2007;18:704-8.
17. Van Belle YLE, Janse PA, de Groot NS, Anné W, Theuns DAMJ, Jordaens LJ. Adenosine testing after cryoballoon pulmonary vein isolation improves long-term clinical outcome. *Neth Heart J* 2012;20:447-55.
18. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar J G, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot NMS, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace* 2018;20:157-208. doi: 10.1093/europace/eux275
19. Efremidis M, Letsas KP, Lioni L, Vlachos K, Georgopoulos S, Saplaouras A, Geladari E, Giannopoulos G, Liu T, Deftereos S, Sideris A. Adenosine-guided pulmonary vein antral isolation for paroxysmal atrial fibrillation: A randomized study. *J Interv Card Electrophysiol* 2016;27:1288-92.
20. McLellan AJ, Kumar S, Smith C, Morton JB, Kalman JM, Kistler PM. The role of adenosine following pulmonary vein isolation in patients undergoing catheter ablation for atrial fibrillation: a systematic review. *J Cardiovasc Electrophysiol* 2013;24:742-51.
21. Papageorgiou N, Providência R, Srinivasan N, Bronis K, Costa F M, Cavaco D, Adragao P, Tousoulis D, Hunter RJ, Schilling RJ, Segal OR, Chow A, Rowland E, Lowe M, Lambiase PD. Adenosine-guided pulmonary vein isolation versus conventional pulmonary vein isolation in patients undergoing atrial fibrillation ablation: An updated meta-analysis. *Int J Cardiol* 2017;227:151-60.
22. Ouyang F, Bansch D, Ernst S, Schaumann A, Hachiya H, Chen M, Chun J, Falk P, Khanedani A, Antz M, Kuck KH. Complete isolation of left atrium surrounding the pulmonary veins: New insights from the double-lasso technique in paroxysmal atrial fibrillation. *Circulation* 2004;110:2090-6.
23. Compier MG, DeRiva M, Dyrda K, Zeppenfeld K, Schalij MJ, Trines SA. Incidence and predictors of dormant conduction after cryoballoon ablation incorporating a 30-min waiting period. *Europace* 2015;17:1383-90.
24. Luni FK, Khan AR, Singh H, Riaz H, Malik SA, Khawaja O, Farid T, Cummings J, Taleb M. Identification and Ablation of Dormant Conduction in Atrial Fibrillation Using Adenosine. *Am J Med Sci* 2018;355:27-36.
25. McLellan AJ, Kumar S, Smith C, Ling LH, Prabhu S, Kalman JM, Kistler PM. The role of adenosine challenge in catheter ablation for atrial fibrillation: A systematic review and meta-analysis. *Int J Cardiol* 2017;236:253-61.
26. Wang N, Phan S, Kanagaratnam A, Kumar N, Phan K. Adenosine Testing After Atrial Fibrillation Ablation: Systematic Review and Meta-Analysis. *Heart Lung Circ* 2018;27:601-10.
27. Matsuo S, Lellouche N, Wright M, Bevilacqua M, Knecht S, Nault I, Lim KT, Arantes L, O'Neil MD, Platonov PG, Carlson J, Sacher F, Hocini M, Jais P, Haissaguerre M. Clinical predictors of termination and clinical outcome of catheter ablation for persistent atrial fibrillation. *J Am Coll Cardiol* 2009;54:788-95.
28. Marijon E, Faza S, Narayanan K, Guy-Moyat B, Bouzeman A, Providencia R, Treguer F, Combes N, Bortone A, Boveda S, Combes S, Albenque JP. Real-time contact force sensing for pulmonary vein isolation in the setting of paroxysmal atrial fibrillation: procedural and 1-year results. *J Cardiovasc Electrophysiol* 2014;25:130-7.