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Efficacy of ATP-guided pulmonary vein isolation for atrial fibrillation: meta-analysis of evidence from randomized and non-randomized controlled trials.

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Abstract

Aims: This study aims to systematically evaluate the efficacy of ATP guided Pulmonary Vein Isolation (PVI) for the treatment of paroxysmal Atrial Fibrillation (AF) and persistent AF.
Methods: A systematic search was performed on PubMed, EMbase, the Cochrane Library and Medline for Randomized Controlled Trial (RCT) and Non-Randomized Controlled Trials (Non-RCT) of ATP guided PVI treatment efficacy in AF patients until February 2016. RevMan 5.3 was used for meta-analysis.
Results: Finally, 3 RCTs and 9 non-RCTs were included. There was no difference in postoperative freedom from AF for paroxysmal AF patients in 2 non-RCTs; and no difference in postoperative freedom from AF for paroxysmal and persistent AF patients in 4 non-RCTs. The overall meta-analysis results showed that AF recurrence rate was higher in ATP group than that in conventional PVI group ($P<0.05$). Two RCTs showed no difference in postoperative recovery rate of pulmonary vein conduction between the two groups. For 1 year postoperative freedom from AF, 2 RCTs showed no difference between ATP guided and conventional PVI groups. However, 1 year postoperative freedom from AF was significantly higher in ATP guided PVI group than that in conventional PVI group in 4 non-RCTs ($P<0.001$). The overall meta-analysis results also showed that 1 year postoperative freedom from AF was significantly higher in ATP guided PVI group than that in conventional PVI group ($P<0.01$).
Conclusions: ATP is safe and effective in identification of occult conduction in PVI.

Keywords: Atrial fibrillation, ATP, Pulmonary vein isolation, Systematic review, Meta-analysis.

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Introduction

Atrial Fibrillation (AF) is the most common refractory arrhythmias. In Europe and United States AF treatment guidelines [1], catheter ablation treatment was recommended as first-line therapy for refractory AF. Pulmonary vein isolation (PVI) is the most widely used radiofrequency ablation treatment for AF [1]. Controlled clinical trials showed that PVI was more effective for AF patients [2,3] than that of drug therapy. However, the success rate of PVI is limited due to recovery of pulmonary vein conduction and second operation might be required for some patients [4,5].

Adenosine can identify occult pulmonary vein conduction [6]. Adenosine Triphosphate (ATP) is rapidly degraded into adenosine in human body, which can bind with the A1 receptor on atrial cardiomyocytes. This binding results in increased outward potassium currents on atrial cardiomyocytes and cell membrane hyperpolarization of atrial cardiomyocytes. The action potential duration and effective refractory period of atrial cardiomyocytes are shortened with prolonged vulnerability, which facilitates electricity conduction. Therefore, atrial arrhythmia could easily be induced, such as atrial premature beats and atrial fibrillation [7]. Recently, one Randomized Controlled Trial (RCT) showed that adenosine guided PVI was safe and effective [8]. However, two subsequent RCTs [9,10] showed that ATP guided PVI did not significantly improve the AF prognosis compared with that of conventional PVI. Therefore, this study systematically evaluated the efficacy of ATP guided PVI treatment for the paroxysmal and persistent AF in order to provide evidence for future surgical treatment selection.

Methods

Search strategy

A systematic search was performed on PubMed, EMbase, the Cochrane Library and Medline for RCT and Non-Randomized Controlled Trials (non-RCT) of ATP guided PVI treatment efficacy in AF patients until February 2016 using key words of "atrial fibrillation" AND ("adenosine" OR "ATP") and

"pulmonary vein isolation". To reduce publication bias, all references of included studies were identified and reviewed.

Inclusion and exclusion criteria

The inclusion criteria were 1) clinical trials published in English; 2) adult patient with symptomatic or clinical diagnosed AF without surgical intervention; 3) ATP guided PVI as experiment group, conventional PVI as control group. The outcome measurements were 1) postoperative freedom from AF in patients with and without occult conduction; 2) postoperative pulmonary vein conduction recovery rate; 3) 1-year postoperative freedom from AF.

Exclusion criteria were 1) duplicate publications; 2) articles with incomplete results; 3) dissertations or reviews; 4) patients with ATP or antiarrhythmic drug intolerance, bronchial asthma, severe ischemic angina, persistent tachycardia, renal insufficiency, heart failure, left ventricular ejection fraction<40%, left atrial diameter>55 mm, acute myocardial infarction in the past 6 months, or severe heart valve disease.

Data substraction and evaluations

Two independent investigators were entrusted to screen the articles, extract information and evaluate study quality. The disagreement was resolved by discussion or a third investigator was involved. The following information was extracted: 1) general information, such as study name, authors' name, publication date and trial site; 2) study general characteristics, such as the number of cases; 3) outcome measurements, such as treatment successful rate. The study quality was evaluated using Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [11] as following: 1) randomization method; 2) allocation concealment; 3) blinding for the patients as well as among the investigators; 4) assessment of the blinding implementation; 5) data integrity; 6) reporting integrity; and 7) other bias. All studies were evaluated as "Yes", "No", "unclear (N/A)" for the above criteria. Detailed randomization methods were described in the quality evaluation table.

Statistical analysis

RevMan 5.3 was used for meta-analysis. Quantitative data was expressed as Relative Risk (RR) and 95% Confidence Interval (CI). The Chi square test was used for study heterogeneity evaluation. If no heterogeneity was detected ($P>0.1$, $I^2<50\%$), fixed effects model was used; otherwise ($P \leq 0.1$, $I^2 \geq 50\%$), the heterogeneity factors were explored using subgroup analysis. If there was only statistical heterogeneity or method heterogeneity between the two study groups, random effect model was used. If the heterogeneity was significant ($I^2 \geq 75\%$) or data source could not be identified, descriptive analysis was used. A P value less than 0.05 was considered as statistically significant.

Results

Characteristics of literature search and included studies

There were 3596 articles identified, and 758 remained after reviewing the titles and abstracts. After removing illegible studies, 11 studies were finally included [8-10,12-19]. The flowchart of screening process was shown in Figure 1.

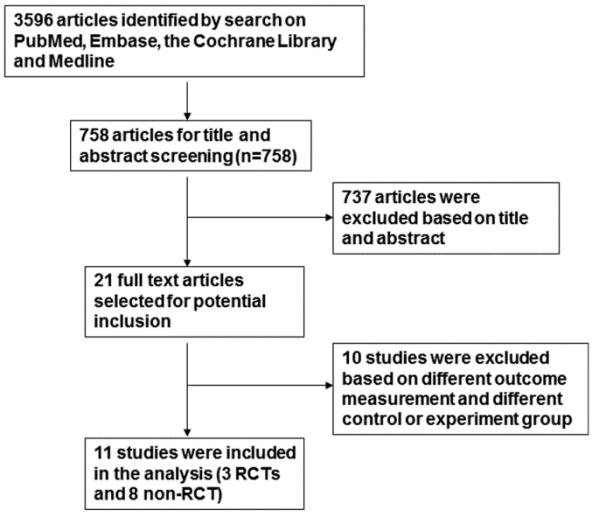

Figure 1. *Flow chart of literature screening process and results.*

The basic characteristics of the included studies and quality assessment

The basic characteristics of the included studies were shown in Table 1. The included studies were prospective RCTs, cohort studies and case control studies. Surgical procedures were ATP guided PVI and conventional PVI. AF types included paroxysmal AF and persistent AF. There were no differences in age between the groups, and follow up time ranged from 3 months to 1 year. The methodological quality evaluation results were shown in Table 2. Random number table or computer generated random numbers were used in 3 RCTs. However, the concealment grouping was not mentioned. Because that the treatment method was surgery, the blind method was not used.

The postoperative freedom from AF

The postoperative freedom from AF in patients with and without occult conduction was analysed after ATP guided PVI. There were 6 non-RCTs [12-17] and one RCT [8] that reported the postoperative freedom from AF after ATP guided PVI for occult and non-occult conduction AF patients. Therefore, subgroup analysis was used based on study type and whether patients were with paroxysmal AF. Random effects model meta-analysis was conducted. As shown in Figure 2, two non-RCTs [12,13] showed that there were no significant differences in postoperative freedom from AF between occult and non-occult conduction AF patients with paroxysmal AF (RR=0.86,

95% CI (0.59, 1.26), P=0.43). Four non-RCTs [14-17] showed that there were no significant differences in postoperative freedom from AF between occult and non-occult conduction AF patients with persistent and paroxysmal AF between the two groups (RR=0.93, 95% CI (0.80, 1.08), P=0.34). However, one RCT [8] showed that the postoperative AF recurrence rate of ATP guided PVI was higher in occult conduction group compared with that in non-occult conduction group (RR=0.76, 95% CI (0.59, 0.98), P=0.04). The overall result showed that the postoperative AF recurrence rate of ATP guided PVI group was higher compared with that of conventional PVI group (RR=0.88, 95% CI (0.79, 0.99), P=0.03), indicating that ATP is effective in identification of occult conduction.

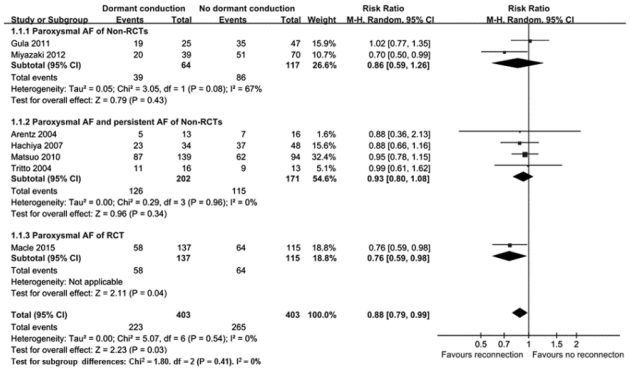

Figure 2. *The postoperative freedom from AF of ATP guided PVI in occult conduction and non-occult conduction patients.*

Postoperative recovery rate of pulmonary vein conduction

The effect of ATP guided PVI and conventional PVI on postoperative recovery rate of pulmonary vein conduction was evaluated. Two RCTs reported the postoperative recovery rate of pulmonary vein conduction and it showed that there was no significant difference between ATP guided and conventional PVI groups (RR=0.64, 95% CI (0.21, 1.91), P=0.42) (Figure 3). This result indicates that ATP has no obvious effect on pulmonary vein conduction recovery.

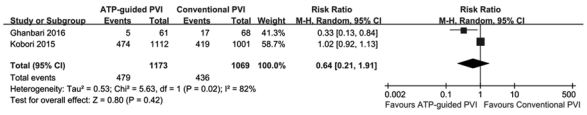

Figure 3. *The postoperative recovery rate of pulmonary vein conduction for ATP guided and conventional PVI groups.*

The 1-year postoperative freedom from AF

To determine the efficacy of ATP guided PVI and conventional PVI, AF patients were followed up for 1 year and 1-year postoperative freedom from AF was observed. Two RCTs [9,10] showed that there was no significant difference in 1 year postoperative freedom from AF between ATP guided and conventional PVI groups (RR=1.04, 95% CI (1.00, 1.09), P=0.27) (Figure 4). Four non-RCTs [15,18-20] showed that postoperative freedom from AF was higher in ATP guided PVI group than that in conventional PVI group (RR=1.22, 95% CI (1.11, 1.35), P<0.0001). The overall meta-analysis results demonstrated that ATP guided PVI group had higher postoperative freedom from AF than conventional PVI group (RR=1.12, 95% CI (1.02, 1.22), P=0.01). This data suggests that ATP guided PVI has better efficacy than conventional PVI.

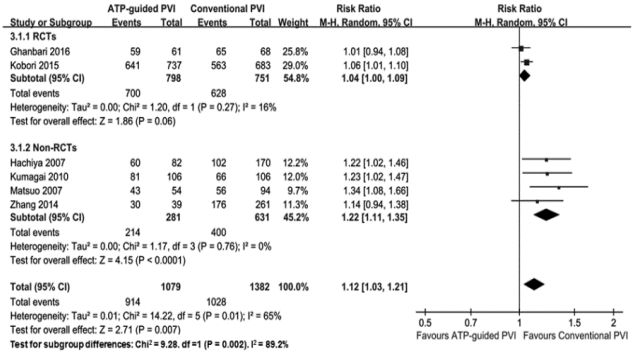

Figure 4. *The 1-year postoperative freedom from AF of ATP guided and conventional PVI groups.*

Table 1. *General characteristics of included studies.*

Article	Study type	Compared groups	AF Type	Age	N	Follow-Up	Freedom from AF
Macle [8]	Prospective randomized controlled trial	Dormant conduction	Paroxysmal AF	58.4 ± 9.7	137	368 ± 43 d	58
		No dormant conduction		58.9 ± 10.9	115		64
Ghanbari [9]	Prospective randomized controlled trial	ATP given	Paroxysmal AF	59.7 ± 8.7	61	278.6 ± 211.9 d	59
		ATP not given		58.9 ± 10.7	68		65
Kobori [10]	Prospective randomized controlled trial	ATP given	Paroxysmal AF +Persistent AF	58.6 ± 8.6	737	330-450 d for 12 m	641
		ATP not given		68.5 ± 8.8	683		563
Gula [12]	Prospective cohort	Adenosine transient reconnection	Paroxysmal AF	56.7 ± 9.2	25	12 m	19

		No Adenosine transient reconnection			47		35
Miyazaki [13]	Prospective cohort	ATP reconnection	Paroxysmal AF	56.7 ± 9.2	39	12 m	20
		No ATP reconnection		61.4 ± 11.2	70		51
Arentz [14]	Prospective cohort	Adenosine-induced reconnection	Paroxysmal AF +Persistent AF	54 ± 10	13	12 m	5
		No adenosine reconnection			16		7
Hachiya [15]	Retrospective cohort	ATP reconnection	Paroxysmal AF +Persistent AF	56 ± 9	34	6.1 ± 3.3	23
		No ATP reconnection			48		37
		ATP not given		54 ± 9	170		102
Matsuo [16]	Retrospective cohort	ATP dormant PV conduction	Paroxysmal AF +Persistent AF	54.3 ± 9.6	139	29.7 ± 13.0	87
		No ATP dormant PV conduction		54.2 ± 10.9	94		62
Tritto [17]	Prospective cohort	Adenosine-induced reconnection	Paroxysmal AF +Persistent AF	55 ± 8	16	6.3 ± 2.4	11
		No adenosine reconnection			13		9
Kumagai [18]	Retrospective cohort	ATP given	Paroxysmal AF +Persistent AF	58 ± 11	106	16 ± 5.2	81
		ATP not given		59 ± 10	106	16 ± 6.9	66
Matsuo [19]	Retrospective cohort	ATP given	Paroxysmal AF +Persistent AF	53.9 ± 9.1	54	19.9 ± 6	43
		ATP not given		52.7 ± 10.1	94		56
Zhang [20]	Retrospective cohort	ATP given	Paroxysmal AF	57.4 ± 6.3	39	6 m	30
		ATP not given			261		176

Note: AF: Atrial Fibrillation.

Table 2. *The methodology quality evaluation.*

Included studies	Randomization method	Concealment	Blind method		Data integrity	Selective reporting of results	Other bias
			Patients and investigators	Evaluators			
Macle [8]	Computer generated random numbers	N/A	No	No	Yes	Yes	N/A
Kobori [10]	Random number table	N/A	No	No	Yes	Yes	N/A
Ghanbari [9]	Random number table	N/A	No	No	Yes	Yes	N/A

Note: N/A indicates unclear.

Discussion

PVI is only suitable for 85% to 90% of the paroxysmal AF with 35% to 45% second operation rate [2,21]. The most common reason for recurrent AF is the restoration of electrical conduction between the atrium and the pulmonary vein [20,22]. And, ATP can detect the occult pulmonary vein conduction [20,23]. A few non-RCTs [20,22] and one meta-analysis [23] have reported that ATP guided PVI may reduce the atrial arrhythmia recurrence for AF patients. One RCT [8] also showed that ATP could detect occult pulmonary vein conduction and subsequent re-dissection vein catheter ablation could improve the prognosis of AF.

The 6 non-RCTs [12-17] and one RCT [8] included in this study analysed the postoperative freedom from AF after ATP guided PVI in AF patients with occult and non-occult conduction. Two non-RCTs [12,13] showed that there were no

significant differences in postoperative freedom from AF between occult and non-occult conduction groups for paroxysmal AF patients. Four non-RCTs [14-17] showed that there were no significant differences in postoperative freedom from AF between occult and non-occult conduction groups for paroxysmal and persistent AF patients. However, one RCT [8] showed that the postoperative AF recurrence rate of ATP guided PVI was higher in occult conduction group compared with that in non-occult conduction group. The overall meta-analysis result showed that the AF recurrence rate was higher in ATP guided PVI group compared with that of conventional PVI group. Our result was inconsistent with the meta-analysis results of non-RCTs. This inconsistence may result from the inclusion of RCTs, which is of fewer biases, more mature techniques and more reliable results. Therefore, this study suggests that ATP is effective for identification of occult pulmonary vein conduction and can improve the AF prognosis.

However, a subsequent large RCT [10] questioned the ATP detection technique. The 2113 patients were randomly assigned to ATP group and control group, and there was no significant difference of postoperative AF recurrence rate between the two groups after the 1-year follow-up [10]. This was in line with Ghanbari's [9] research on ATP's detection of occult pulmonary vein conduction. Because of the different results among RCTs and non-RCTs, subgroup analysis was used in this study. Two RCT [9,10] showed there was no significant difference in postoperative AF recurrence rate between ATP guided PVI group and conventional PVI group, while 3 non-RCTs [15,18,19] showed the AF prognosis was better in ATP group compared with that in conventional PVI group. Overall, the AF prognosis was better in ATP group compared with that in conventional PVI group with high heterogeneity (I^2=71%). The heterogeneity may result from the different study design of RCTs and non-RCTs. The 3 non-RCTs [15,18,19] were all retrospective studies with selection bias for patients as well as for operators. ATP guided PVIs might all have been performed by more experienced operators. Another non-RCT [20] showed that there was no difference between the two groups, however, the atrial arrhythmia recurrence rate was significantly lower in ATP group receiving the second operation, compared with that of control group. In addition, the two recent RCTs [9,10] may have better surgical techniques and may reduce the selection bias in non-RCTs. Last but not least, the observation time of spontaneous recovery of pulmonary vein conduction, which is essential in identification of acute pulmonary vein conduction, is longer in RCTs. During the 1-year follow-up, the AF record is also inaccurate in that the follow-up is based on self-reported symptoms or 24 h ambulatory monitoring or phone call.

One RCT [8] showed that ATP detection of occult conduction might be routinely used for PVI with high safety and efficacy. However, its low postoperative AF recurrence rate was resulted from the second operation with no direct comparison with patients without ATP guided PVI. Two RCTs [9,10] showed no significant difference between the two groups for postoperative atrial arrhythmia recurrence rate.

This study is limited in the small number of RCTs and the bias in non-RCTs. Further RCTs with less selection bias and more objective follow-ups are needed. Our results showed that the AF prognosis was better in ATP guided PVI group. Therefore, overall, ATP is safe and effective in identification of occult conduction in PVI, however, whether ATP guided PVI could improve the AF prognosis requires further assessment.

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None

Conflict of Interest

The authors declare no conflict of interests.

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