Adenosine-guided pulmonary vein isolation versus conventional pulmonary vein isolation in patients undergoing atrial fibrillation ablation: an updated meta-analysis

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1

Abstract

Background: Recurrent atrial fibrillation episodes following pulmonary vein isolation (PVI) are frequently due to reconnection of PVs. Adenosine can unmask dormant conduction, leading to additional ablation to improve AF-free survival. We performed a meta-analysis of the literature to assess the role of adenosine testing in patients undergoing atrial fibrillation (AF) ablation.

Methods: PubMed, EMBASE, Cochrane databases were searched through until December 2015 for studies reporting on the role of adenosine guided-PVI versus conventional PVI in AF ablation.

Results: Eleven studies including 4,099 patients undergoing AF ablation were identified to assess the impact of adenosine testing. Mean age of the population was 61±3years: 25% female, 70% with paroxysmal AF. Follow up period of 12.5±5.1 months. A significant benefit was observed in the studies published before 2013 (OR=1.75; 95%CI 1.32-2.33, p<0.001, I^2=11%), retrospective (OR=2.05; 95%CI 1.47-2.86, p<0.001, I^2=0%) and single-centre studies (OR=1.58; 95%CI 1.19-2.10, p=0.002, I^2=30%). However, analysis of studies published since 2013 (OR=1.41; 95% CI 0.87-2.29, p=0.17, I^2=75%) does not support any benefit from an adenosine-guided strategy. Similar findings were observed by pooling prospective case-control (OR=1.39; 95%CI 0.93-2.07, p=0.11, I^2=75%), and prospective randomized controlled studies (OR= 1.62; 95%CI 0.81-3.24, p=0.17, I^2=86%). Part of the observed high heterogeneity can be explained by parameters such as dormant PVs percentage, use of new technology, improvement of center/operator experience, patients' characteristics including gender, age, AF type.

Conclusions: Pooling of contemporary data from high quality prospective case-control & prospective randomized controlled studies fails to show the benefit of

adenosine-guided strategy to improve AF ablation outcomes.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia with significant morbidity and mortality [1]. Catheter ablation has a class I indication for drug-refractory symptomatic AF patients [2,3]. However, AF can recur in a significant proportion of patients requiring either ongoing medical treatment with anti-arrhythmic drugs or repeat ablation procedure [4]. Pulmonary vein isolation (PVI) is the cornerstone of AF catheter ablation and most of the recurrent AF episodes are due to reconnection of PVs [2].

Studies have shown that intra-operative adenosine can potentially unmask dormant pulmonary vein conduction, resulting from failed PVI, and thereby guide further ablation to improve procedural success and AF-free survival [5,6].

A previous meta-analysis [7] of studies published before 2013 aimed to determine the impact of routine adenosine administration on clinical outcomes in patients undergoing PVI. However, it was inconclusive as the available data were sparse and contradictory [6,8,9]. Therefore, we performed an updated systematic review and meta-analysis of the literature to assess the impact of adenosine-guided PVI on the outcome of AF ablation.

Methods

Study selection

We undertook searches on MEDLINE (via PubMED), EMBASE, clinicaltrials.gov and COCHRANE databases (from inception to 1st December 2015) using the following search string: "atrial fibrillation" AND "adenosine" AND "catheter ablation" (Figure 1). Even though we included all potentially eligible entries from inception to 1st December 2015, this updated meta-analysis focused on studies

following that of McLellan et al. [7]. This meta-analysis [7] included studies before 2013, when no randomized controlled or multi-centre studies were available. Importantly, the authors included only 3 studies [10-12] assessing the role of adenosine infusion in AF recurrence post PVI with favorable results for adenosine testing (HR: 1.25 95%CI: 1.12-1.40, p<0.001, I2=0.0%, p=0.784). Further to that, random effects modeling was performed demonstrating a non-significant trend to a reduction in freedom from AF in patients with adenosine/ATP-induced PV reconnection who underwent additional catheter ablation compared with patients without adenosine-induced PV reconnection with a pooled relative risk of 0.91 (95% CI: 0.81–1.03, p=0.145).

Reference lists of all accessed full-text articles were further searched for sources of potentially relevant information. Authors of full-text papers and congress abstracts were also contacted by email to retrieve additional information.

Only longitudinal studies performed in humans were considered for inclusion. The population, intervention, comparison and outcome (PICO) approach was used [13]. The population of interest included AF patients and the intervention was catheter ablation of AF. The comparison was adenosine-guided PVI vs. standard PVI. Relapse of AF or atrial tachycardia following ablation and after a blanking period of no less than 2 to 3 months was the primary outcome assessed.

Minimum study follow-up duration was five months. Both registries and randomized trials were considered eligible for analysis. The methods sections of evaluated studies were reviewed to confirm the suitability and composition of the reported endpoint.

In order to be eligible, studies needed to:

1. Present matched control-groups with the only difference in the treatment strategy being adenosine administration (with or without concomitant isoproterenol infusion)

in one group with ablation if reconnection occurred & no adenosine administration in the control group.

2. Adenosine administration in the active treatment group or in both groups, but further ablation only in the active adenosine-guided strategy group (i.e. as an active-treatment was considered this group where in the event of reconnection following adenosine infusion further ablation was performed. The control group consisted of patients where either no adenosine testing was done, or if it was performed, no further ablation was delivered).

If other differences with regard to treatment were present in the study protocol, namely additional ablation of lines or other triggers in the active treatment group alone, the study was not considered appropriate for inclusion. Full-text articles remaining unpublished more than three years after initial congress abstract presentation were not considered appropriate for inclusion.

Three independent reviewers (NP, RP and KB) screened all abstracts and titles to identify potentially eligible studies. The full text of these potentially eligible studies was then evaluated. Agreement of at least two reviewers was required for decisions regarding inclusion or exclusion of studies. Study quality was formally evaluated using the Delphi Consensus criteria for randomized controlled trials [14] and a modified Newcastle–Ottawa Quality Assessment Scale for Cohort Studies [15] by three reviewers (NP, RP KB) (Table S-1). An agreement, between the three reviewers was mandatory for the final classification of studies.

Data extraction and presentation for the preparation of this manuscript followed the recommendations of the PRISMA group (Figure 1) [16]. The following data were extracted for characterizing each patient sample in the selected studies, whenever available: demographics and sample characterization, AF duration, presence of

structural heart disease, atrial size, left ventricular ejection fraction, adenosine administration, procedural characteristics, follow-up duration, monitoring of AF relapse and use of anti-arrhythmic drugs, and proportion of persistent and paroxysmal AF patients (Table 1). The definitions AF or AF relapse, blanking period, and methods used for monitoring during follow-up were collected in all studies (Tables 2, 3).

Statistical analysis

Data were pooled using random-effects, according to the Mantel-Haenszel model, through Review Manager (RevMan), Version 5.1. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). The odds ratio (OR) and respective 95% confidence intervals (95%CI) were used as a measurement of treatment effect. Pairwise comparisons were performed for the endpoint: AF or atrial tachycardia relapse.

In order to assess study-design related factors that could interfere with the results of the meta-analysis, sensitivity analysis was performed to assess the impact of study design, treatment approaches, proportion of patients with paroxysmal AF, date when studies were published, and ablation energy or technology used for PVI. Sensitivity analysis was only performed for conditions fulfilled by at least 2 studies, and gathering at least 15% of the whole meta-analysis population.

Statistical heterogeneity on each outcome of interest was assessed and quantified using the Cochran Q test and the I2 statistic, respectively. The I2 statistic describes the percentage of total variation across studies due to heterogeneity rather than chance. Values of less than 25%, 25% to 50% and greater than 50% are by convention classified low, moderate, and high degrees of heterogeneity, respectively.

Funnel plot and meta-regression analyses were obtained using Comprehensive Meta-Analysis software (Version 2). Funnel plots were used for evaluating the presence of publication bias and traced for comparisons including more than 10 studies (minimum number for assuring the appropriateness of the method) [17]. A meta-regression (using the Unrestricted ML method) was performed for comparisons involving more than 10 studies for assessing the possible association of modulator variables with the endpoint of AF relapse.

Heterogeneity-adjusted trial sequential analysis was applied to the meta-analysis to reduce the risk of random error due to repetitive testing of accumulating data [18]. The optimal information size with adaptation of monitoring boundaries, and the cumulative Z-statistics after each trial were assessed. This was based on an α significance level of 5% and a β of 20% (80% power), an expected decrease in AF relapse of 30%, and adjusted to the level of heterogeneity and relapse rate in the control group.

Results

1. Search results

A total of 153 entries were retrieved for analysis of titles and abstracts. Of these, 100 were excluded as they were either duplicates or deemed unsuitable for the purpose of the meta-analysis (editorials, letters, reviews or case-reports). The remaining 53 results were carefully screened, and after analysis of their full-text, only 10 full-text papers [5,6,8-12,19-21] were considered appropriate for the purpose of our meta-analysis. Manual searches also provided one last entry, an observational study recently presented at a major cardiovascular meeting [22] . The selection process is

illustrated in Figure 1. There was an excellent agreement between investigators on the inclusion of the selected trials.

2. Study Design and Population

Baseline data and the design of selected trials are summarized in Tables 1-3. A total of 4,099 patients (2,037 with adenosine followed by further ablation and 2,062 controls) undergoing AF ablation were found to assess the impact of adenosine testing. Three studies were prospective randomized controlled [6,9,21]. Seven studies were prospective case-control [5,6,8,20-22], of those four were single-centre observational studies [5,8,20,22] and three were prospective multi-centre randomized controlled studies [6,9,21]. Quality assessment of the included studies is shown in S-Table 1 in the Supplementary material. Three randomized-controlled studies had ≥6 Delphi criteria [6,9,21]. Of the cohort studies, there was one [11] that had ≥7 and four [5,8,19,20] which had ≥6 Newcastle–Ottawa score.

Trial Sequential Analyses showed that assuming an α=0.05 and β=0.80, this meta-analysis was powered to show a 30% reduction in AF relapse (or the inverse: 42% higher chances of remaining free from atrial arrhythmia relapse) using the adenosine-guided strategy, both when combining all studies (500 individuals would be required based on 64.4% freedom of atrial arrhythmia relapse in the control group and a heterogeneity, I2=67%), or when combining studies published only after 2013 (654 individuals would be required based on 65.8% freedom from atrial arrhythmia relapse and a heterogeneity, I2=76%).

Procedural data

In all studies the ablation procedure involved PVI and 7 of those studies used standard radiofrequency catheter ablation [6,8-12,21]. Other studies used RF through Stereotaxis® [22], one used the PVAC® catheter [19], one used the 1st generation cryoballoon–Arctic Front® [20] and another study used the 2nd generation cryoballoon–Arctic Front Advance® [5]. Macle et al [6] and Kobori et al [9] were the only studies using contact force (CF) sensing technology in a percentage of 1.9% and 2.5% respectively. Overall, 4 studies [6,11,19,21] included patients with a repeat ablation procedure (Tables 2 and 3).

Across the studies, adenosine infusion was applied ranging from a minimum dose of 6mg to a maximum dose of 36mg in [5,6,8,19-22], while 4 studies [9-12] used ATP during an intravenous isoproterenol infusion. The administration of adenosine/ATP was performed in no less than 20 minutes after PVI. However this time was not specified in all of the studies and a cut-off of 30 minutes, the median value in the included studies, was used for sensitivity analysis purpose as shown in Table 4. Differences in adenosine/ATP administration protocol are presented in Tables 1 and S-2. The overall percentage (%) of patients with pulmonary vein reconnection following adenosine in the active treatment arm (adenosine) was 37%, (S-Table 3).

3. Safety

In most of the studies common ablation procedure complications were reported such as access site haematoma, pericardial tamponade, AV fistula, transient phrenic nerve paralysis. Adenosine testing proved to be safe and no significant complications related to adenosine were reported (Figure 3 and S-Table 4). Transient hypotension and facial flushing (13%) were documented in one of the studies [5].

4. Efficacy Outcomes and Sensitivity Analyses

The overall median follow-up was 12 months, while the interquartile range was 6.8 months. The minimum median follow-up was 5.7 months, while the maximum median follow-up was 22 months. Studies with <3 months of follow-up were excluded from the analysis.

The patients followed-up with clinical assessment, ECG and Holter monitoring which varied from 1-7 days. Importantly, there was no study documenting the use of loop recorder as recommended in the previous AF ablation guidelines (Table 2) [23].

The pooling of studies published since 2013 shows that the use of adenosine does not influence the success of AF ablation (OR=1.41; 95%CI 0.87-2.29, p=0.17, I2=75%). Similar findings were observed by pooling prospective case-control (OR=1.39; 95%CI 0.93-2.07, p=0.11, I2=75%), and prospective randomized controlled studies (OR= 1.62; 95%CI 0.81-3.24, p=0.17, I2=86%). Importantly, these non-significant differences were observed in the setting of high heterogeneity (Table 4, Figure 2).

On the contrary, a significant benefit was observed in the studies published before 2013 (OR=1.75; 95%CI 1.32-2.33, p<0.001, I2=11%), when no randomized controlled studies or multi-centre studies were available. Among all included studies, results in favor of the adenosine-guided strategy were only found in retrospective (OR=2.05; 95%CI 1.47-2.86, p<0.001, I2=0%), single-centre (OR=1.58; 95%CI 1.19-2.10, p=0.002, I2=30%), and observational/non-randomized studies (OR:1.63; 95%CI: 1.18-2.25, p=0.003, I2=37%).

Assessment of high quality data, on pooling the multi-centre, prospective case-control and prospective randomized controlled studies, confirmed that the differences were not statistically significant across studies. Examining randomized controlled trials alone showed that there was no significant difference in the freedom from AF

between the adenosine and the control groups (OR=1.62; 95%CI 0.81-3.24, p=0.17). This was also true for the results of prospective (case-control and randomized controlled) (OR=1.39; 95%CI 0.93-2.07, p=0.11) and multi-centre studies (OR=1.81; 95%CI 0.67-4.90, p=0.25), when these were examined separately. Taking into consideration that: i) studies with variable ablation strategies introduce a significant challenge in evaluating the sole effect of adenosine targeted ablation, ii) heterogenous technology was used across the included studies and iii) the timing of adenosine infusion post PVI, we performed additional analyses. As shown in Table 4, the use of Stereotaxis, 1st generation cryoballoon, 2nd generation cryoballoon and CF-sensing catheters did not have a significant effect on AF recurrence between the adenosine and non-adenosine groups. This could possibly be the result of existing small studies, catheter ablation technology or underpowering. We also assessed the effect of timing of adenosine administration on AF relapse post PVI, which remained ambiguous. More specifically we found that there was a lower AF recurrence in the adenosine compared with the non-adenosine group for studies with a waiting time of <30min (OR=2.96; 95%CI 1.96-4.47, p<0.001, I2=0%). However there was no difference between the 2 groups for studies with waiting time >30min (OR=1.42; 95%CI 0.65-3.09, p=0.38, I2=59%). Finally we found that checking for bidirectional block may be worth to examine in patients undergoing adenosine challenge. This derives from an observed trend towards lower rates of AF recurrence in the adenosine group when testing of bidirectional block was performed (OR=1.49; 95%CI 1.01-2.20, p=0.05, I2=64%). The results of other sensitivity analyses are presented in Table 4.

5. Meta-regression

The assessment of potential moderator variables through meta-regression is shown in S-Table 5 and Figure 4a-e.

Studies showing a benefit of the adenosine-guided strategy had a lower % of female patients, lower mean age, higher percentage of paroxysmal AF, a higher % of PV reconnection following adenosine, and used no CF-sensing catheters (Figure 4a-e), even though the usage of CF-sensing catheters was restricted to two entries (Macle et al [6] and Kobori et al [9], 1.9% and 2.5% respectively).

Discussion

The present meta-analysis shows that an adenosine-guided strategy for PVI is not associated with lower incidence of AF recurrence compared to a conventional strategy when robust prospective randomized controlled studies are analysed separately. A significant benefit was only observed in the studies published before 2013 [7] but these were retrospective, single-centre and observational/non-randomized providing low quality evidence of the role of adenosine.

It is well established that catheter ablation is an effective treatment for AF, however the recurrence rate following an apparently successful PVI remains high [24-26]. Pulmonary vein reconnection occurs when acute tissue injury, oedema, and inflammation resolve [6]. It is speculated that adenosine can identify pulmonary veins with "dormant" conduction. Although the exact mechanism of adenosine-induced reconnection is not fully elucidated, two possible mechanisms have been suggested: activation of the outward potassium current via the purinergic A1-receptor results in hyperpolarization of the cell membrane and shortening of the action potential/refractory period, thus accommodating electrotonic conduction or restoration

of excitability [27]. A second possible, mechanism is the increase of the sympathetic tone due to respective increases in arterial chemoreceptor activity [28].

However, the impact of detecting dormant pulmonary vein conduction on midterm outcomes is still debatable [9,22]. Interestingly, it is thought that the use of additional RF applications can reduce PV reconnection during follow-up [6,8].

It is noteworthy that adenosine was not superior to non-adenosine testing when we excluded studies with concomitant use of isoproterenol following adenosine infusion (Table 4 and S-2). Therefore, this could raise a question as to whether isoproterenol could be a confounding factor. Previous studies have not demonstrated significant increase in PV reconnection with a combination of isoproterenol and adenosine compared with adenosine alone [29]. However, it is unclear whether isoproterenol could boost the effect of adenosine. Moreover, we found that ATP is more potent compared to adenosine. The mechanism of the electrophysiologic action of ATP and adenosine is not identical. ATP acts (i) via adenosine, the product of ATP's rapid degradation by ecto-enzymes, and via cardiac vagal reflex [30]. In man, limited historical data suggested a vagal component in the mechanism of ATP [31].

We have found a high degree of heterogeneity across the results of included studies in this meta-analysis. This was less obvious for those studies published before 2013 (that support the use of adenosine), studies not using CF-sensing catheters, non-randomized, single-centre and retrospective studies, which are the same studies which gave positive results in favor of the adenosine-guided approach. On the other hand, more recent studies, using new technologies (i.e. newer versions of mapping systems, contact force, cryoablation) and with a prospective design show high heterogeneity and do not confirm these initial encouraging studies. Undoubtedly a publication bias cannot be excluded.

Although, we attempted to detect possible causes for heterogeneity among studies, there is not a simple explanation. Some of those identified on meta-regression, include younger age and lower prevalence of female gender patients. Experimental data suggest that here is an age-related reduction in adenosine A(1) and A(2A) receptor expression [32].

With regards to gender, women are more sensitive to adenosine side effects as observed in patients undergoing myocardial perfusion imaging [33]. In addition, specific cardiac K+ channels contribute to adenosine mediated coronary arteriolar relaxation in men, but not in women [34]. Therefore, there may be a gender-related effect on dormant PVs, however this has not been fully evaluated. Overall, a possible association with age and gender cannot be excluded.

On the other hand, studies with a higher percentage of paroxysmal AF and with higher percentage of dormant vein conduction demonstrated a benefit of this strategy. A possible interpretation may simply be that PV isolation is critical to prevent paroxysmal AF and initial studies lacked the ability to achieve durable transmural lesions as well as including persistent AF patients with non-PV drivers [1,35]. The percentage of dormant vein conduction is higher in older studies, which may also explain why more positive results of adenosine testing were observed in the past.

Importantly, the use of contact force data is very limited with only 2 studies [6,9] reporting CF-sensing catheters. These catheters have been associated with better outcomes at midterm when compared to non-contact force sensing technology [36]. Our results were in agreement as shown in Table 4. However, we are unable to draw safe conclusions in the context of limited data, with these catheters being used in a minority of studies and patients. The mechanism may be a lower PV reconnection rate. This could explain some differences, as lower PV reconnection rates with

adenosine, will likely associate with a lower benefit (lower effect size) following their identification and further ablation. The same principle would apply to newer technology for AF ablation in studies published after 2013, which is thought to lead to a more durable PVI, and hence could explain why the benefit of adenosine could not be illustrated while grouping those studies together. Indeed, there was a higher percentage of PV reconnection following adenosine, using non CF-sensing catheters. Our data were appropriately powered to show a 30% reduction in AF relapse as we included more than 650 patients after 2013.

It is worth mentioning the use of concurrent isoproterenol infusion in some studies as this could be an additional confounding factor. This may have interfered with the biologic action of adenosine to unmask dormant PV conduction, or led to additional extra-PV trigger/substrate ablation.

We also grouped studies that used both adenosine and ATP given their close biologic association, and so far no studies have demonstrated a different response to these agents with regards to the unmasking of dormant PV conduction.

Finally, there is also the unaccountable effect of centre and operator experience, as AF catheter ablation is a relatively new procedure, and contemporary results as well as operator-skills most likely improved over the period of the analysis.

The small sample size in most studies with large confidence intervals in results could be another factor to account for the heterogeneity observed among studies. However, sensitivity analysis of studies with bigger samples does not attenuate this problem.

Finally, there was a lower percentage of female patients, lower mean and higher percentage of paroxysmal AF in the those studies showing a benefit of the adenosine-guided strategy.

Limitations

This meta-analysis presents several limitations that should be highlighted. The high heterogeneity in the different study protocol parameters mentioned before, which makes data interpretation non linear. Information about single-shot ablation techniques is still sparse (<15% of the study population), which does not allow a properly powered and non-biased sensitivity analyses to address that matter. Even though preliminary data suggest an association of using CF-sensing catheters with lower benefit from the adenosine-guided strategy, only a very minor percentage of patients were treated with this technology and thus results are not conclusive. Some studies did not specify whether other atrial tachycardias were included in the definition of recurrent atrial fibrillation [6,8,9,19,20,22], but we aimed to compensate for this by means of sensitivity analysis.

Conclusions

Contemporary data suggest that there is no benefit from an adenosine-guided strategy in patients undergoing AF catheter ablation. The benefit observed in the early studies could have been the result of less evolved technology, lower operator-experience leading to a higher rate of dormant vein conduction. In addition, a selection bias of studies with positive results, and a predominance of single-centre retrospective low-quality data may have also contributed to the previously observed benefit.

Our findings question the role of adenosine testing in AF catheter ablation and highlight the need for more high quality data, employing large multicenter randomized controlled trials, with adequate power in order to resolve this issue. Ideally, a study should include more than 650 individuals in order to have the adequate power to show a 30% reduction in AF relapse and it should incorporate

contemporary AF ablation technology (single-shot ablation devices and a high % of

CF-sensing catheters).

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Legends to figures

Figure 1. Flowchart diagram illustrating study selection methodology.

Figure 2. Forest plots comparing the effect adenosine-guided strategy versus non-adenosine testing on freedom from AF in patients undergoing AF ablation. CI indicates confidence interval.

Figure 3. Forest plots comparing the number of complications observed with adenosine and non-adenosine guided strategy.

Figure 4. Meta-regression plots demonstrating a benefit of the adenosine-guided strategy related to % of female patients, mean age, % of paroxysmal AF, % of PV reconnection and % use of CF-sensing catheters.

S-Figure 1. Funnel-plot: Freedom from atrial fibrillation.

Tables

Table 1. Selected Studies for the meta-analysis: Baseline Information

Table 2. Selected Studies for the meta-analysis: Adenosine administration and Follow-Up.

Table 3. Selected Studies for the Systematic Review: Procedure Information.

Table 4. Sensitivity analyses on freedom from AF.

S-Table 1. Assessment of studies according to Delphi or Newcastle-Ottawa scale criteria included in the meta-analysis.

S-Table 2. Drugs given to check for dormant vein conduction, extra-pulmonary vein triggers, and type of arrhythmia used for defining relapse.

S-Table 3. Peri-procedural complications (Adenosine-guided strategy vs Controls).

S-Table 4. Meta-regression results.

S-Table 5. Number of pulmonary veins.