Efficacy and Safety of Ablation-Index Guided Catheter Ablation For Atrial Fibrillation: An Updated Meta-Analysis

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Abstract:

Background: Despite recent advances in catheter ablation for atrial fibrillation (AF), pulmonary vein reconnection (PVR) and AF recurrence remain significantly high. Ablation index (AI) is a new method incorporating contact force, time and power that should optimize procedural outcomes.

We aimed to evaluate the efficacy and safety of AI-guided catheter ablation compared to a non-AI-guided approach.

Methods: A systematic search was performed on MEDLINE (via PubMED), EMBASE, COCHRANE and European Society of Cardiology (ESC) databases (from inception to 1st July 2019). We included only studies that compared AI-guided with non-AI-guided catheter ablation of AF.

Results: Eleven studies reporting on 2306 patients were identified. Median follow up period was 12 months. AI-guided ablation had a significant shorter procedural time (141.0 vs. 152.8 minutes, P=0.01; I_2=90%), ablation time (21.8 vs. 32.0 minutes P<0.00001; I_2=0%), achieved first pass isolation more frequently (OR=0.09, 95%CI 0.04-0.21; 93.4% vs. 62.9%, P<0.001; I_2=58%) and was less frequently associated with acute PVR (OR=0.37, 95%CI 0.18-0.75; 18.0% vs 35.0%; P=0.006; I_2=0%). Importantly, atrial arrhythmia relapse post-blanking was significantly lower in AI compared to non-AI catheter ablation (OR=0.41, 95%CI 0.25-0.66; 11.8% vs. 24.9%, P=0.0003; I^2=35%). Finally, there was no difference in complication rate between AI and non-AI ablation, with the number of cardiac tamponade events in the AI group less being numerically lower (OR=0.69, 95%CI 0.30-1.60, 1.6% vs. 2.5%, P=0.39; I^2=0%).

Conclusions: These data suggest that AI-guided catheter ablation is associated with increased efficacy of AF ablation, while preserving a comparable safety profile to non-AI catheter ablation.

Keywords: ablation index, atrial fibrillation, radiofrequency ablation

Abbreviations: AF = Atrial fibrillation, AI = Ablation index, CF = Contact force, FTI = Force time integral, PVI = Pulmonary vein isolation, PVR = Pulmonary vein reconnection,

Condensed Abstract:

This meta-analysis demonstrated that AI-guided catheter ablation had a shorter total procedural time, achieved first pass isolation more frequently and atrial arrhythmia relapse was significantly lower, with no difference in complication rates, suggesting it is associated with increased efficacy, while preserving a comparable safety profile to non-AI guided catheter ablation.

What's New?

- Ablation index is a commercially available new marker/index that combines contact force, radiofrequency time and radiofrequency power in a non-linear formula in real time.
- It is suggested to allow intra-procedural visualization of radiofrequency current application in a 3-D mapping system, therefore improving outcomes in patients undergoing AF ablation.

- In this meta-analysis we demonstrated that AI-guided catheter ablation had a shorter total procedural time, achieved first pass isolation more frequently and atrial arrhythmia relapse post-blanking was significantly lower, with no difference in complication rates.
- A large randomized controlled trial is required confirm the benefits of AI guided catheter ablation.

Introduction

Pulmonary vein isolation (PVI) is well established as the gold standard for ablation of paroxysmal atrial fibrillation (AF), and has been shown to be non-inferior to extensive ablation in persistent AF.[1-3]

Despite recent advances in technology and ablation methods such as the use of contact force (CF) and force-time integral (FTI), AF recurrence rates remain significantly high for both paroxysmal and persistent AF [4, 5]. Studies have shown that low CF and FTI during AF ablation are associated with a higher incidence of PV reconnection (PVR) and recurrence of AF [6, 7]. CF sensing catheters are now routinely used, but FTI has failed to make a clear impact on AF ablation outcomes [8] and hence alternatives are being developed. Radiofrequency power is still not taken into account by FTI [9]. Furthermore, FTI assumes a linear association between CF and time, which is not the case according to recently published data [10].

AI is a commercially available new marker/index that combines CF, RF time and RF power in a non-linear formula in real time [11-13]. It is suggested to allow intra-procedural visualization of radiofrequency current application in a 3-D mapping system, therefore improving outcomes in patients undergoing AF ablation.

In this meta-analysis, we aim to assess the efficacy and safety profile of AI in patients undergoing catheter ablation for atrial fibrillation compared those having a non-AI procedure.

Methods

Study selection

A systematic electronic search was performed on PubMed, EMBASE, Cochrane clinical trials database (from inception to July 2019) with no language limitations,

using the following search string: “atrial fibrillation” AND (“ablation” OR “catheter ablation” OR “radiofrequency ablation”) AND “ablation index”

The population, intervention, comparison and outcome (PICO) approach was used. The population of interest included patients with atrial fibrillation, and the intervention was catheter ablation of AF comprising of pulmonary vein isolation (± additional lesions) using radiofrequency. The comparison of interest was AI-guided ablation vs. non-AI guided ablation. The primary outcome measure was AF or atrial tachycardia recurrence post-blanking. Other outcomes included: PV isolation during first pass, acute PV reconnection, total procedural time, ablation time, fluoroscopy time. Assessed procedural complications were: cardiac tamponade, a composite of all pericardial complications, oesophageal fistula, phrenic nerve palsy, stroke and “other life-threatening complications”, assessed on a study by study basis.

In order to be included, studies needed to provide a minimum of information regarding the patient demographics of the sample of AF patients undergoing catheter ablation, and at least one of the aforementioned outcomes of interest. Observational non-controlled case series required a minimum of 5 patients to be considered eligible.

For the endpoint Relapse after blanking, the minimum mean study follow-up duration was 12 months.

Review articles, editorials and case reports, were not considered eligible for the purpose of this review.

Three independent reviewers (AI, TW and RP) screened all abstracts and titles to identify potentially eligible studies. The full texts of these potentially eligible studies were then evaluated. AI and WL formally evaluated study quality using the Ottawa-Newcastle scale.[13] Agreement between both reviewers was required for decisions regarding inclusion or exclusion of studies. When this was not possible, RP

intervened as the arbiter and had the final decision. Data extraction and presentation for the preparation of this manuscript followed the recommendations of the PRISMA group (Figure 1). 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 and proportion of persistent and paroxysmal AF patients (Table 1 and Table S-1), ablation settings (Table 2), procedural information (Table 3) blanking period, follow-up duration, monitoring of AF relapse and use of anti-arrhythmic drugs (Table 4).

The definitions AF/atrial arrhythmia relapse, blanking period, and methods used for monitoring during follow-up were collected in all studies.

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

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 for binary outcomes, and the mean difference and respective 95%CI were used as a measure of treatment effect for continuous outcomes. Pairwise comparisons were performed all the endpoints.

The number needed to treat (NNT) was estimated for the primary endpoint: number of patients who have to be treated with the active treatment group to prevent a relapse.

In order to assess study-design related factors that could interfere with the results of the meta-analysis, sub-analyses were performed for the primary efficacy endpoint to assess the impact of study design, proportion of patients with paroxysmal AF, type of ablation catheters used, and date when studies were published.

Statistical heterogeneity on each outcome of interest was assessed and quantified using the Cochran Q test and the I^2 statistic, respectively. The I^2 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.

Results

1. Search results

A total of 69 non-duplicate citations were screened of which 50 were excluded following screening of the title and abstract. The remaining 19 results were carefully screened, and after analysis of the full-text, only 11 articles [14-24] were considered appropriate for the purpose of our meta-analysis. The selection process is illustrated in Figure 1 and there was an excellent agreement between investigators on the inclusion of the selected trials.

2. Study Design and Population

The baseline data of patients and the design of the trials are summarized in Table 1 and Supplementary Table S-1. A total of 2306 patients were included, 1046 (45.4%) underwent AI guided ablation and 1260 (54.5%) underwent non-AI (control group). Four of the studies were retrospective and seven were prospective studies. None of

the studies was randomized controlled. The type of AF was recorded for 2096 patients, 1215 (58.0%) of which had paroxysmal AF.

Quality assessment of the included studies was assessed using the Newcastle–Ottawa score, as they were all cohort studies and demonstrated that 3 studies scored 9, [14, 18, 20] 4 studies scored 8, [16, 19, 21, 23, 24] 2 studies scored 6, [17, 22] and 1 study scored 5 [15] (Table S-2). The Delphi criteria were not used, as none of the studies were randomized controlled trials.

Funnel plots were carried out on the comparison for procedural time only, as there were not 10 studies available for any of the other comparisons.

3. AI & Ablation settings

Most studies used lower power levels for the posterior wall (Table 2). However, Hussein et al. , Phlips et al. and Kobori et al. used the same power levels all around the left antrum (30W, 35W & 50W, respectively). Dhillon et al utilized 40W for the anterior wall. Settings for catheter stability varied widely going from 2.5 to 4 mm and from 3 to 15 s. Minimum force was 5 g for most studies, despite presenting variation. Similarly, force over time varied widely, between 25 and 60%, with 25% and 30 % being the most popular settings. Maximum interlesion distance was set as ≤6mm for most studies (6 out of 8 studies). AI targets were lower for the posterior wall, usually set between 380 and 450, and for the anterior wall it ranged between 400 and 600 (Table 2).

3. Acute procedural outcomes

Procedural time was available in 10 studies. AI guided ablation had a statistically significant shorter procedural time (141.0 minutes vs. 152.8 minutes, P=0.01) with

high heterogeneity across studies (I^2=90%, P<0.001). Funnel-plots suggested potential publication bias regarding this endpoint with most of the study results outside the specified 95%CI in the plot (Figure 2). In addition, AI-guided ablation had a significantly shorter ablation time (21.8 minutes vs. 32.0 minutes, P<0.00001; very low heterogeneity, I^2=0%) (Figure S-1) and fluoroscopy time (10.2 minutes vs. 12.0 minutes, P=0.009; I^2=75%) compared to non-AI guided ablation (Figure S-2).

Procedures performed using AI-guided radiofrequency ablation had a higher rate of first pass PVI (OR=0.09, 95%CI 0.04-0.21; 93.4% vs. 62.9%, P<0.001; high heterogeneity, I^2=58%) (Figure 3). Importantly, acute PVR was less likely to occur in the AI (OR=0.37, 95%CI 0.18-0.75; 18.0% vs. 35.0%; P=0.006, very low heterogeneity, I=0%) (Figure S-3).

In all but one of the studies, ablation procedure complications were reported. These included pericardial tamponade, pericardial effusion (not requiring drainage), arteriovenous fistula, phrenic nerve palsy and retroperitoneal haematoma. Cardiac tamponade as the most common complication was reported in 7 patients undergoing AI-guided catheter ablation compared to 17 in the non-AI studies (1.6% vs. 2.4%, P=0.39) (Figure S-4), while pericardial complications (including both pericardial tamponade and pericardial effusion not requiring drainage) were reported in 8 patients undergoing AI-guided catheter ablation compared to 21 in the non-AI studies (1.5% vs. 2.5%, P=0.28) (Figure S-5). Of note there were no atrio-oesophageal fistulas, strokes or deaths reported in either group.

4. Freedom from AF/AT relapse post-blanking

Recurrence of indexed arrhythmia was evaluated by clinical assessment, ECG or Holter. Follow up duration was available in 6 of the studies (blanking period 3

months). The overall median follow-up was 12 months, while the interquartile range was 12.0-16.5 months. The minimum median follow-up was 12 months, while the maximum median follow-up was 24 months.

Analysis of available data from 6 studies showed that AI-guided catheter ablation is characterized by significantly less AF recurrence compared to non-AI ablation studies (OR=0.41, 95%CI 0.25-0.66; 11.8% vs. 24.9%; p=0.0003; moderate heterogeneity, I^2=35%) (Figure 4). The number of patients who had to be treated (NNT) with the AI-guided strategy to prevent one relapse (compared to control) was 7.6.

Sub-analyses for this primary endpoint based on different scenarios are shown in the supplementary material (Table S-3). For most of the assessed sub-analyses, except for retrospective studies or studies published only as an abstract [24], the AI-guided approach was associated with a significant reduction in atrial arrhythmia relapse [24]. Multi-centre studies and those where the SmartTouch SF catheter was used displayed higher levels of heterogeneity.

Discussion

Our results suggest that AI-guided catheter ablation is associated with lower incidence of AF recurrence, with a safety profile comparable to non-AI catheter ablation.

We also found that AI-guided catheter ablation is associated with a significant reduction in procedural, fluoroscopy, and ablation time. Furthermore, PV isolation after single encirclement was more frequent in the AI-guided radiofrequency ablation group, while acute PV reconnection was more frequently observed in non-AI-guided ablation. High heterogeneity observed for procedure duration, fluoroscopy duration and first-pass isolation can be explained by different work-flows used in different centers, differences in operator skill, speed and need for screening. The variability in

the performance of operators and centres performing radiofrequency ablation has been previously discussed.[25]

With regards to safety, the incidence of events was low in both treatment groups, and this systematic review was not powered to show significant differences between groups. Also, not enough data were available to compare the incidence of complications across studies depending on AI settings. However, the rate of pericardial complications was numerically lower (nearly half) in the AI-guided approach. Importantly there were no aorto-oesophageal fistulas reported in any of the patients who underwent AI-guided ablation, and this was despite the use of high power in the backwall (power $\geq$ 35W) in 2 the studies.

No randomized-controlled trials were identified, with evidence for the use of AI comes from observational and non-randomized studies. However, these low to moderate quality data suggests a clear efficacy benefit and comparable safety.

The studies included used a variety of AI settings, and these settings were available in 5 of the 6 studies that demonstrated a reduction in AF recurrence compared to those who underwent non-AI guided ablation. The most commonly used energy was 35W to the anterior and roof segments, and 30W to the posterior and inferior segments. The most commonly used AI target was 500-550 for the anterior segment, 400-450 for the roof, posterior and inferior segments. Importantly, Philps et al demonstrated that high power, short duration lesions using up to 50 W with AI targets of 550 on the anterior wall and 400 on the posterior wall can be effective in achieving PVI safely and efficiently [18].

Up until recently conventional ablation methods mainly involved the use of CF, but the availability of CF-sensing catheters has not translated to the expected improved outcomes. This is partly due to lesion creation not only being dependent on contact,

but also the delivery of power and duration.[6, 7] Hence focus subsequently moved to FTI, which combines force & time. However, FTI also has significant drawbacks. FTI assumes a linear association between CF and time, but in reality the relationship between these factors is far more complex. Furthermore FTI does not account for power delivery.[8-10] Ablation index potentially overcomes the limitations of CF and FTI by incorporating power, CF and time in a weighted formula in order to predict lesion quality, and has been shown to reliably predict lesion depth in an animal model.[25]

Hussein et al [14] showed that AI-guided ablation is associated with significant improvements in the incidence of acute PVR and atrial arrhythmia recurrence compared to non-AI guided ablation. This is potentially due to better quality lesions as suggested by a greater drop in impedance. AI cannot only achieve low rates of PVR, but can also help to shorten the time to achieve acute PVI with a high rate of first-pass isolation. Data suggest that an optimal AI-targeted PVI is generally feasible and could improve acute outcomes in patients with AF [14, 18, 21].

Dhillon et al demonstrated that AI is not only effective, but also reproducible, when a pre-specified protocol is followed respecting strict criteria for contiguity and quality lesion, resulting in high and comparable rate of acute PV isolation among different operators using different catheters, AI settings and fluoroscopy times [21, 26].

Although the safety of AI has not been widely evaluated, PV ablation guided by AI appears to have a low complication rate, and leads to a higher single-procedure arrhythmia-free survival at 12 months [15, 16, 18].

A recent meta-analysis of PVI prior to the use of the AI in 1774 patients with paroxysmal AF demonstrated success rates of 78% after 12 months, which is slightly lower than we observed for paroxysmal AF patients (>90% freedom from atrial

arrhythmia relapse at 12 months).[27] Success rates are lower in patients with persistent AF, with a meta-analysis of 18657 patients reporting a success rate of only 43% following a single procedure.[28] Our study had a mixed population of paroxysmal and persistent AF and no study included only persistent AF patients, and hence we are not able to provide a precise figure on this. However, Hussein et al. have reported this to be close to 80% at 12 months.[14]

Limitations

Our meta-analysis has limitations that should be acknowledged including the following: a) the available studies are not randomized controlled trials and as such are not high quality b) high heterogeneity among included studies for some of the endpoints like procedural and fluoroscopy duration. However, this probably reflects differences in the ablation approach and usage of screening by the different operators as explained above), c) small sample size of studies, d) different AI values for different sites of the atrium, e) follow-up was not consistent across studies, with 7-day Holter not always used; furthermore, the ILR was not used in any of the studies, and hence these may have underestimated the relapse rate; also, comparison of arrhythmia burden with both strategies would be of interest, f) data concerning the ablation settings used in control groups, such as the interlesion distance and catheter stability, was not always available, therefore the observed improvements potentially related to improvements in all these factors, and not just AI.

Conclusions

Low to moderate quality of evidence from non-randomized data suggests that AI-guided catheter ablation is associated with a significantly lower incidence of AF

recurrence, while it has comparable safety profile to non-AI catheter ablation. Also, the AI-guided approach was significantly associated with lower procedure times (total, screening & ablation), more frequent first pass isolation and lower rate of acute PV reconnection. A large randomized controlled trial is required confirm the benefits of AI guided catheter ablation.

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Figure legends

Figure 1. Flowchart diagram illustrating study selection methodology.

Figure 2. Forest plot comparing the total procedural time in minutes in ablation-index guided ablation vs. non-ablation index guided ablation (control), and the corresponding funnel plot.

Figure 3. Forest plot comparing the rate of first pass pulmonary vein isolation in ablation-index guided ablation vs. non-ablation index guided ablation (control).

Figure 4. Forest plot comparing the effect of ablation-index guided ablation vs. non-ablation index guided ablation (control) on freedom from atrial fibrillation (AF) and atrial tachycardia (AT) post blanking period in patients undergoing AF ablation.