

University of Szeged
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**Atrial Fibrillation Catheter Ablation Treatment with Novel
Mapping Systems**

PhD Thesis

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LIST OF PAPERS RELATED TO THE SUBJECT OF THE THESIS

- I. The Short and Long-Term Efficacy of Pulmonary Vein Isolation as a Sole Treatment Strategy for Paroxysmal Atrial Fibrillation: A Systematic Review and Meta-Analysis.

Kis Z, Muka T, Franco OH, Brammer WM, De Vries LJ, Kardos A, Szili-Torok T.

Curr. Cardiol Rev. 2017;13(3):199-208.

doi: 10.2174/1573403X13666170117125124. Review.

Q2

- II. Type and rate of atrial fibrillation termination due to rotational activity ablation combined with pulmonary vein isolation.

Kis Z, Theuns DA, Bhagwandien R, Wijchers S, Yap SC, Szili-Torok T.

J Cardiovasc Electrophysiol. 2017 Aug;28(8):862-869. Epub, 2017 Jun 21.

doi: 10.1111/jce.13240.

IF: 2,875 **Q1**

1. Introduction

Atrial fibrillation (AF) is the most common supraventricular tachycardia resulting in reduction of quality of life, functional clinical status and overall survival. Atrial fibrillation prevalence as well as its associated comorbidities are progressively increasing. Therefore, AF has become an important public health issue. Catheter ablation of AF with pulmonary vein isolation (PVI) is an increasingly sophisticated, widely applicable non-pharmacological method as rhythm control in AF management. Multiple fundamental and clinical trials have established PVI as the gold standard catheter ablation method of AF and have shown that this is superior to pharmacological treatment, but its long-term success rate remains suboptimal in patients with persistent AF. The variable long-term arrhythmia free survival data after a technically successful PVI may be related to the technology and to incomplete understanding of the mechanisms of AF. Although, several basic and clinical studies demonstrated that pulmonary vein isolation (PVI) is superior to medical therapy in AF management, the underlying mechanism of PVI efficacy is still not completely clear. There is substantial evidence that apart from the pulmonary veins other parts of the atria may contribute to triggering and maintaining AF through various mechanisms. It is still debated what mechanism should be targeted during AF ablation, and it is still not completely clear how it works when it is successful. If we agree that elimination of AF sources should result in termination of AF comparable to observations in other arrhythmias, then if we could individually define the AF source(s) we should be able to reach more promising results with catheter ablation even in persistent AF patients. One can assume if a driver of AF is eliminated then it should result in termination and/or non-inducibility of the arrhythmia. Recently, the focal impulse and rotor modulation (FIRM) mapping became available, which aims to identify areas of the atria functioning as patient-specific AF driver(s). Targeting these atrial substrates ensures a patient-tailored ablation strategy for AF elimination. Despite this, the clinical outcome data of AF termination after FIRM-guided ablation is still controversial.

2. Objectives

- 2.1 Firstly, we aimed to systematically review and perform a meta-analysis by compiling the results of all relevant studies that have evaluated the short-, mid-, and long-term outcome of PVI as a sole treatment strategy (from the same group of investigators) for a homogenous paroxysmal AF patient population.
- 2.2 Secondly, we evaluated the timing and rate of AF termination using ablation of rotational activity detected by focal impulse and rotor modulation mapping in combination with conventional PVI in persistent AF patients.

3. Materials and methods

3.1. Systematic review and meta-analysis

3.1.1. Data sources and search strategy

This review was conducted in accordance with the PRISMA and MOOSE guidelines. We aimed to identify all published articles discussing the short-, mid- and long-term follow-up data of percutaneous, manually guided PVI-only procedures with radiofrequency or cryoballoon ablation (CBA) for PAF, which derived from the same group of investigators. We searched Embase.com, Ovid Medline, Web-of-science and the Cochrane Central registry of trials from inception until the 14th of December 2015. We included studies that reported outcome data of patients after PAF PVI, with both a short and at least a median/mean follow-up period of >24 months. If success rate outcome data with either on- and off-drug therapy was available, the off-drug data was used. Studies involving surgical AF ablation or AV-nodal ablation, or those using adjunctive, stepwise linear ablation methodology after PVI were also excluded.

3.1.2. Statistical Analysis

The inverse variance weighted method was used to combine success rates to produce a pooled success rate using random-effects models to allow for between study heterogeneity. Additionally, we reported the results using fixed effect models. Fixed-effects models were also used to pool rates of the same study. All tests were two-tailed and p-values of 0.05 or less were considered significant. STATA release 12 (Stata Corp, College Station, Texas) was used for all statistical analyses.

3.2. Prospective study conducting FIRM- guided ablation with PVI for atrial fibrillation

This single-center, prospective study enrolled thirty-eight consecutive patients with symptomatic persistent AF despite pharmacologic therapy and/or prior ablation undergoing a combined conventional PVI and FIRM-guided ablation between March 2015 and April 2016. Atrial fibrillation was recorded using wide field of view basket catheters. The system then analysed the AF cycles at each electrode over successive timepoints. The resulting computational phase map depicts the putative propagation of electrical activity of AF. The AF propagation maps are then projected onto a two-dimensional grid. The two-dimensional grid portrays the right atrium opened through the tricuspid annulus vertically, while representing the left atrium opened horizontally through the mitral valve. The location of the rotors and focal sources could be identified by their electrode coordinates based on three-dimensional (3D) electroanatomic map. If FIRM-mapping revealed rotational activity (RoAc), then a FIRM-guided ablation was executed first in the right then in the left atrium. Subsequently, conventional PVI-only was performed. In FIRM-guided ablation the RF applications were applied directly to centre of the RoAc bounded by ≈ 2 electrodes distance in each axis for around 300 s in each side.

The pre-specified primary efficacy endpoint was the rate and timing of AF elimination during the combined RoAc and PVI ablation procedure. Secondary endpoint was safety, defined as incidence of peri-procedural complication(s).

3.2.1. Statistical analysis

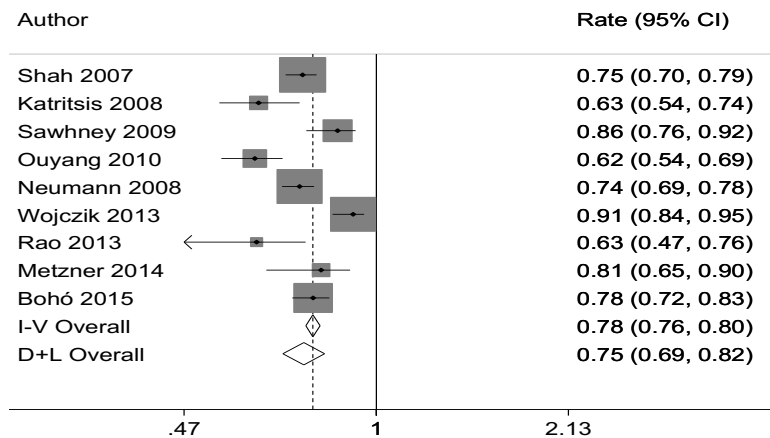
Normality of distribution was assessed using with the Shapiro-Wilks test. Continuous variables are presented as mean \pm standard deviation (SD), if normally distributed, otherwise by median and corresponding 25th and 75th percentile. Data were compared by the ANOVA or Mann-Whitney U test, as appropriate. Categorical variables are expressed as number and percentage (%) and compared with Fisher's exact test.

4. Result

4.1. Overall efficacy of catheter ablation

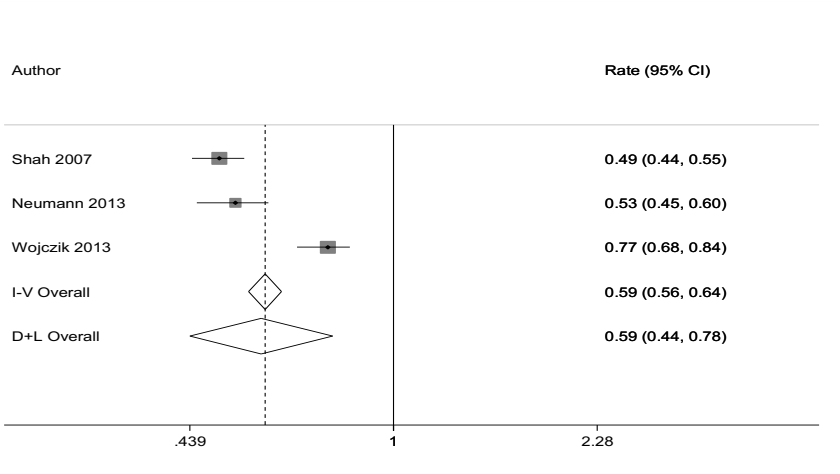
Outcome data concerning the freedom from AF after PVI for PAF were available in all studies. The pooled 12-month and 62-month success rate for 9 observational studies reporting outcome for PAF PVI-only procedure was 78% (95% CI 0.76% to 0.855%, Fig. 1.) and 59% (95% CI 0.56% to 0.64%, Fig 2.) respectively. Stratified analysis by type of ablation procedure (radiofrequency ablation or cryoballoon ablation) did not reveal any significant difference.

Figure 1.: 12-month success rate of pulmonary vein isolation



Assessment of heterogeneity, $X^2=57.3$, $I^2=86.0\%$; $P < 0.001$.

Figure 2.: 62-month success rate of pulmonary vein isolation



Assessment of heterogeneity, $X^2=36.1$, $I^2=94.5\%$; $P < 0.001$.

4.2. Prospective study conducting FIRM- guided ablation with PVI for atrial fibrillation

4.2.1. Timing of AF termination

Two distinctive types of the AF termination were defined. The “abrupt termination” of AF presented during PVI RF delivery. It was tended to be more present among patients without RoAc (P = 0.051) (Fig.3) The “late-onset termination” of AF occurring between 3 minutes and 24 hours following RoAc activity ablation was significantly more prevalent in patients with right-sided RoAc. (P = 0.049). (Fig.4.) The mean time of “late-onset termination” was 13.8 ± 4 minutes after RoAc ablation.

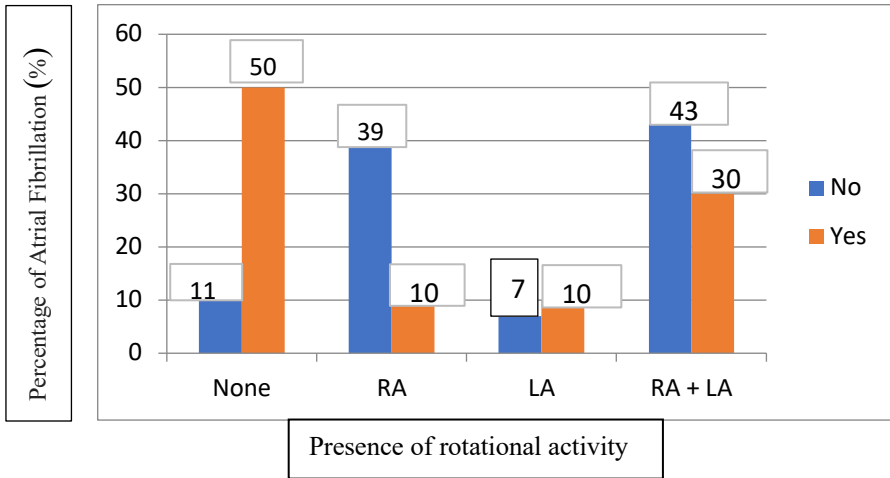
4.2.2. Rate of AF termination

The overall termination of AF after combined RoAc ablation with PVI was observed in 22 out of 38 patients (58%). Atrial fibrillation terminated abruptly during PVI RF delivery in 10 out of 38 pts (26%). Late-onset termination was observed in 12 (32%) patients after RoAc ablation (ranging between 3 minutes and 24 hours).

4.2.2. Follow-up

The one-year single-procedure success rate was 69,1% (13/21). Figure 5. demonstrates the outcome flowchart at each time interval. At 1-year follow-up freedom from AF/AT was detected in 4 out of 10 patients (25%) within the “abruptly” terminated group, while in 7/12 (58,3%) patients in the “late-onset terminated” group and in 5/16 (31,25%) patients in the “none terminating” group. Neither termination of AF to SR itself nor the termination type predicted the arrhythmia free survival at 1-year follow-up.

Figure 3.: Abrupt termination of atrial fibrillation tended to be more present in patients without identifiable rotational activity n=10 (p=0, 051)



(* RA: right atrium, + LA: left atrium, ‡RA+LA: right + left atrium, # None: pts without rotational activity)

Figure 4.: Late-onset termination of atrial fibrillation was more prevalent in patients with right-sided rotational activity n=12 (P= 0,049)

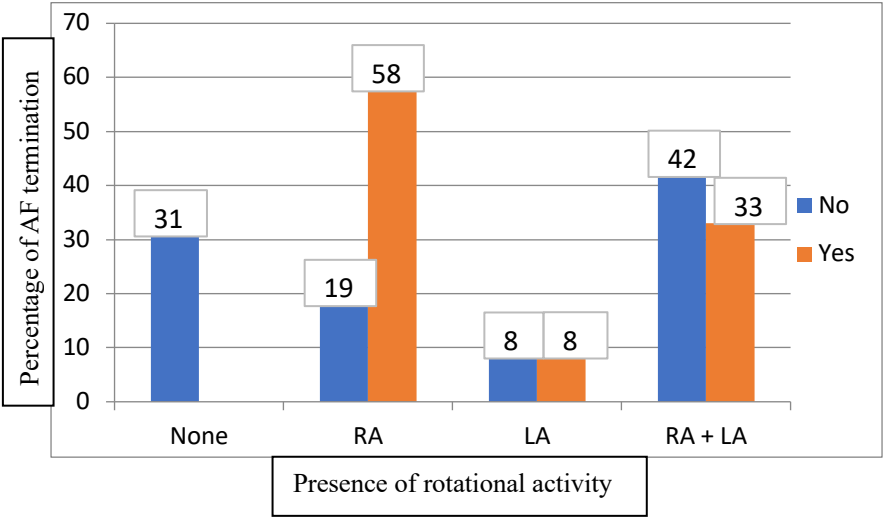
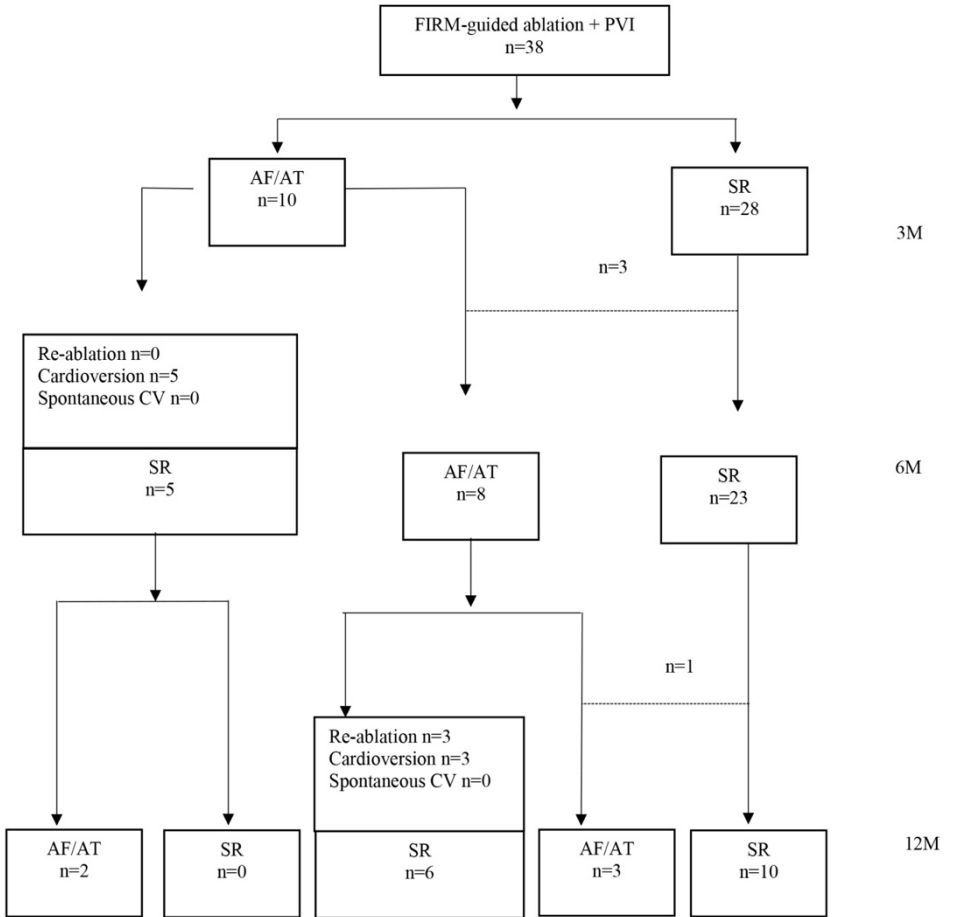


Figure 5.: Arrhythmia outcome flowchart showing arrhythmia-free survival at 3, 6, 12-month time interval



3M: 3-month arrhythmia free survival FU – 73.68% (28/38)

6M: 6-month arrhythmia free survival FU – 63.88% (23/36)

12M: 12-month arrhythmia free survival FU – 76.1% (16/21)

5. Summary of new findings

5.1. Systematic review and meta-analysis

1) We reviewed 13 articles (including 1774 patients), which assessed the short-mid and long-term outcome of PVI as sole treatment strategy for a homogenous paroxysmal AF patient population. We performed a meta-analysis by compiling the results of these studies.

2) Pooled analysis showed that 12-and 62-month success rates with a single catheter ablation was 78% (95% CI 0.76% to 0.88%) and 59% (95% CI 0,56% to 0,64%) respectively.

3) The results did not differ by the type of ablation method.

4) A progressive and significant decline in freedom from AF between 1,3 and 5-years after a successful pulmonary vein isolation was detected.

5) While AF recurrence was most frequent within the first 12-months after catheter ablation, a surprisingly high rate of late AF recurrence was observed, which seems unlikely to be correlated to pulmonary vein reconnections.

5.2. Prospective study conducting FIRM- guided ablation with PVI for atrial fibrillation

1) FIRM-mapping offers a novel and feasible technique for identification of RoAc sustaining human AF.

2) Furthermore, this technique provides a patient-tailored, mechanistically focused method for catheter ablation of AF.

3) The major finding of our study is a moderate rate (58%) of persistent AF termination with two distinctive timing pattern following FIRM-guided ablation combined with PVI.

4) The “late-onset termination” of AF is significantly more prevalent in patients during right-sided RoAc ablation.

5) The “abrupt termination” of AF is tended to be more present among patients during PVI. Termination does not depend on whether AF is induced or ongoing at the beginning of the procedure.

6. Acknowledgements

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