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A decade of complex fractionated electrograms catheter-based ablation for atrial fibrillation: Literature analysis, meta-analysis and systematic review

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ABSTRACT

Background: It has been a decade since the complex fractionated atrial electrograms (CFAEs) were first established following the publication of Nademanee's standards. However, the status and focus of CFAE research are unclear, as is the efficacy of additional CFAE ablation in atrial fibrillation (AF). This literature review and meta-analysis were designed to determine the status of CFAE research and the efficacy and complications of CFAE ablation alone, pulmonary vein isolation (PVI) alone and PVI plus CFAE ablation in AF.

Methods: With the assistance from reference librarians and investigators trained in systematic review, we conducted a literature search of MEDLINE (via PubMed), Embase, the Cochrane Library, ScienceDirect, Wiley Blackwell and Web of Knowledge, using "complex fractionated atrial electrograms" for MeSH and keyword search.

Results: The literature on CFAEs increased from 2007, mainly focusing on mapping studies, with mechanism studies increasing significantly from 2012. Fifteen trials with 1525 patients were qualified for our meta-analysis. Success rates were as follows. Overall ($P < 0.001$): CFAE ablation alone, 23.5–26.2%; PVI, 64.7%; PVI plus CFAE ablation, 67.0%. Single ablation: PVI, 60.4%; PVI plus CFAEs, 68.8% (OR 1.53, 95% CI 1.07–2.20, $P = 0.02$). Re-ablation: PVI, 69.0%; PVI plus CFAEs, 77.2% (OR 1.54, 95% CI 1.06–2.24, $P = 0.02$). Paroxysmal AF: PVI, 76.7%; PVI plus CFAEs, 79.1% (OR 1.20, 95% CI 0.79–1.81, $P = 0.39$). Persistent or permanent AF: PVI, 47.9%; PVI plus CFAEs, 58.7% (OR = 1.59, 95% CI 1.13–2.24, $P = 0.008$). Complication rates: PVI, 2.6%; PVI plus CFAEs, 3.4% (OR 1.22, 95% CI 0.58–2.57, $P = 0.61$).

Conclusions: In the literature, CFAE mapping studies preceded mechanism studies. CFAE ablation alone is insufficient for the treatment of AF. Additional CFAE ablation after adequate PVI or PVI plus linear ablation improves the outcome of single ablation and re-ablation without increasing complications, especially in persistent or permanent AF. There are insufficient data to support a similar improvement in paroxysmal AF or inducible AF after PVI for paroxysmal AF.

1. Introduction

Radiofrequency catheter ablation (RFCA) procedures for atrial fibrillation (AF) are well established in the management of symptomatic, drug-refractory AF. Pulmonary vein isolation (PVI) alone, as the cornerstone of RFCA, is typically sufficient to treat patients with paroxysmal AF, though it is less than optimal for persistent AF [1,2]. Additional ablation targeting complex fractionated atrial electrograms (CFAEs) as the AF substrate may be necessary in patients with persistent AF [3–5]. The CFAEs are defined as a fractioned atrial electrograms comprising two or more deflections with continuous baseline activity or an atrial electrograms with cycle length (CL) ≤ 120 ms [6]. CFAEs are unlikely to be rapid drivers; they may represent other phenomena that facilitate

Abbreviations: AF, atrial fibrillation; PAF, paroxysmal AF; NPAF, non-paroxysmal AF; Radiofrequency catheter ablation, RFCA; PVI, pulmonary vein isolation; CPVI, circumferential pulmonary vein isolation; PVAI, pulmonary vein antrum isolation; PVI, pulmonary vein isolation, including CPVI and PVAI; CFAEs, complex fractionated atrial electrograms; PVs, pulmonary veins; SVC, superior vena cava; RCT, randomized control trials; MCT, matched controlled trial; DF, dominant frequency; GP, ganglionated plexi; AFL, atrial flutter; AT, atrial tachycardia; LA, left atrium or left atrial diameter; CS, coronary sinus; LVEF, left ventricular ejection fraction; NR, no report; AADs, anti-arrhythmic drugs; INR, international normalized ratio; FI, fractionated interval; CL, cycle length.

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AF, such as zones of slow conduction, pivot points, or wave-breaks [7,8]. Continuous fractionation or rapid, regular "rotor-like" electrograms, both locally and at distant atrial sites, are due to a wider activation of the cardiac neural network [9]. Some researchers have reported that targeting ganglionated plexi (GP) eliminated these areas of continuous fractionation, both locally and at distant sites [9,10]. Thus far, the effect of CFAE ablation on prognosis is unclear. The aim of this study was to determine the effects of PVI (both circumferential PVI [CPVI] and pulmonary vein antrum isolation [PVAI]) alone, CFAE ablation alone and PVI plus CFAE ablation (or CFAEs plus PVI) on the prognosis of different types of AF.

2. Material and methods

2.1. Study selection

We classified AF according to a recent consensus statement as follows: paroxysmal AF–recurrent AF that terminates spontaneously within 7 days; persistent AF–AF that is sustained beyond 7 days or lasts less than 7 days but necessitates pharmacologic or electrical cardioversion. Included within the category of persistent AF is "longstanding persistent AF", which is defined as continuous AF of more than 1 year duration [11].

To identify and retrieve all potentially relevant studies reporting the procedure, outcome or success rate of PVI, PVI combined with CFAE ablation and CFAE ablation alone in AF, we conducted a literature search with the assistance of librarians and investigators trained in systematic review procedures in MEDLINE (via PubMed), Embase, the Cochrane Library, ScienceDirect, Wiley Blackwell and Web of Knowledge. MEDLINE was searched for abstracts first, using the Medical Subject Heading "atrial fibrillation" and PubMed was searched for "complex fractionated electrograms". The Embase search used a similar strategy. The Cochrane Library, ScienceDirect, Wiley Blackwell and Web of Knowledge were searched for abstracts using the keywords "complex fractionated electrograms". A manual check of the reference lists of all accepted studies and of recent reviews and meta-analyses was performed to supplement the above searches and ensure optimal and complete literature retrieval. After deleting duplicated abstracts, we obtained 399 references, which we used to determine the status and focus of CFAEs studies (Fig. 1).

Randomized controlled trials (RCTs) and matched controlled trials (MCTs) were included in our meta-analysis. Mapping studies, mechanism studies, reviews, meeting reports, comments, case reports, abstracts only, meta-analyses, systematic reviews, articles not in English and other clinical abstracts were excluded (Fig. 2). Non-surgical studies involving ablation were included. The search was conducted on January 1, 2014. Study quality was assessed using a modified version of the quality assessment criteria for MCTs [12]. Data were collected on paper extraction forms by one investigator and independently verified by a second investigator. Discrepancies were reviewed by the two investigators and, when necessary, by the entire group. Most discrepancies in data extraction involved the assigning of ablation techniques. When the technique was unclear or when the investigators could not agree on a particular data variable, the authors of the study were contacted for clarification.

2.2. Statistical analysis

Review Manager 5 was used to synthesize the data. Differences in categorical outcomes among ablation groups were reported as odds ratio (OR) with 95% confidence interval (95% CI) using a fixed or random effect model. Differences in adverse events associated with the procedure among groups were reported as ORs with 95% CIs using a fixed effect model. The presence of heterogeneity between trials was assessed by the chi-squared (χ^2) statistic and the extent of inconsistency was assessed using the I^2 statistic. Heterogeneity was considered significant if the P value was less than 0.1. Publication bias was evaluated using funnel plots. All tests were two-tailed with a P value of less than 0.05 as the level of statistical significance.

3. Results

3.1. Search and analysis of literature

We searched several databases and obtained 915 references, all of which we imported into Medical Citation Manager 3.0 (Jin Ye Tian Sheng Corporation, China); after deleting duplicated references, we identified 399 unique references (Fig. 1). The literature on CFAEs increased from 2007, mainly focused first on mapping studies and then on mechanism studies, which increased significantly from 2012 (Fig. 2). Fifteen publications were identified that met our meta-analysis inclusion criteria. The basic characteristics of these 15 studies are presented in Table 1. The included studies were published in 2004–2012 and comprised 10 single-center and five multicenter studies, 10 RCTs and five MCTs. The size of the enrolled patient population ranged from 35 to 119. Five and six studies reported outcome data solely for paroxysmal AF or persistent AF, respectively.

3.2. Patient characteristics

The 15 studies included a total of 1525 patients. The mean age of the patients ranged from 52 to 62 years (Table 1). All studies were predominantly of male subjects (1127/1525, 73.9%), with the proportion of males ranging from 63% to 88%. Mean left atrium (LA) diameter was 34–49 mm and mean left ventricular ejection fraction (LVEF) was 45–66%. The percentage of enrolled patients with hypertension was 42.0% (487/1159), though four studies did not report this information. The percentage of patients with other cardiac conditions was 30%; these included coronary disease, valvular disease, history of cardiac surgery, hyperthyroidism, heart failure, structural heart disease and congenital heart disease. Three studies did not report this information. Only one study estimated the $CHADS_2$ score. Three studies (Andrade 13]; Chen [14]; Verma [15]) reported the number of patients with a history of stroke, which was 3.4% (11/317). According to their inclusion criteria, most of the studies focused on symptomatic and drug-refractory AF or high-burden AF. The details of the studies' inclusions were symptomatic and refractory AF or high burden AF, including paroxysmal, persistent and permanent AF. The exclusion criteria included AF secondary to reversible cause; left atrial thrombus; previous ablation; inadequate anticoagulation; LA > 55 mm; pregnant; coronary artery bypass graft surgery within 12 months; LVEF < 35%; valvular disease; prosthetic heart valves; myocardial infarction, cardiac surgery or stroke within 3 months; congenital heart disease; allergy to contrast media; contraindication to warfarin; age < 18 years; and hyperthyroidism. The mean duration of follow-up was 8–23 months. Methods of follow-up included 24 h, 48 h or 7 day Holter monitoring, transtelephonic monitoring, implanted devices, event recorder, external loop recorder and symptomatic 12-lead electrocardiography (ECG). Six studies defined the primary end point as no atrial tachycardia (AT) or AF lasting > 30 s [13–17] and three studies defined the primary end point as no AT or AF lasting > 1 min [18–20] according to the Holter monitoring, symptomatic ECG or event recording. The other studies defined the primary end point as no recurrence of AF, AT or atrial flutter (AFL) [21–26]. One study did not define a primary end point [27].

3.3. Catheter ablation

The mapping systems used in these studies were the NavX and CARTO systems. Seven studies used NavX only and two CARTO only; five studies used both NavX and CARTO. One study did not report which mapping system was used. CFAEs were defined according to Nademanee's standard. The definition of CFAEs was simplified as