Published in final edited form as:

Int J Cardiol. 2017 August 01; 240: 234–239. doi:10.1016/j.ijcard.2017.02.152.

Spatial relationship of organized rotational and focal sources in human atrial fibrillation to autonomic ganglionated plexi[☆]

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Abstract

Background—One approach to improve ablation for atrial fibrillation (AF) is to focus on physiological targets including focal or rotational sources or ganglionic plexi (GP). However, the spatial relationship between these potential mechanisms has never been studied. We tested the hypothesis that rotors and focal sources for AF may colocalize with ganglionated plexi (GP).

Methods—We prospectively identified locations of AF rotors and focal sources, and correlated these to GP sites in 97 consecutive patients (age 59.9 ± 11.4 , 73% persistent AF). AF was recorded with 64-pole catheters with activation/phase mapping, and related to anatomic GP sites on electroanatomic maps.

Results—AF sources arose in 96/97 (99%) patients for 2.6 ± 1.4 sources per patient (left atrium: 1.7 ± 0.9 right atrium: 1.1 ± 0.8), each with an area of 2–3 cm². On area analyses, the probability of an AF source randomly overlapping a GP area was 26%. Left atrial sources were seen in 94 (97%) patients, in whom 1 source co-localized with GP in 75 patients (80%; $p < 0.05$). AF sources were more likely to colocalize with left vs right GPs ($p < 0.05$), and colocalization was more likely in patients with higher CHADS₂VASc scores (age > 65, diabetes; $p < 0.05$).

Conclusions—This is the first study to demonstrate that clinically detected AF focal and rotational sources in the left atrium often colocalize with regions of autonomic innervation. Studies should define if the role of AF sources differs by their anatomical location.

[☆]All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2017.02.152>.

Conflicts of interest: Dr. Narayan is co-author of intellectual property owned by the University of California Regents and licensed to Topera Inc. Dr. Narayan held equity in Topera and received honoraria from Medtronic and St. Jude Medical.

Keywords

Atrial fibrillation; Ablation; Rotor; Autonomic nervous system; Ganglionated plexi

1. Introduction

Recent trials have reported that extensive ablation for persistent atrial fibrillation (AF) may not improve outcomes from pulmonary vein isolation (PVI) [1]. One potential approach to improve upon the results from PVI has been to target specific atrial regions harboring rotational or focal sources [2], or regions of autonomic nervous system innervation (ANS) at ganglionic plexi (GP) [3], both of which are localized and may be missed by empiric ablation.

The spatial relationship between localized drivers and ganglionic plexi is unstudied in human AF. Physiologically, intense ANS activity may alter repolarization restitution [4,5], and repolarization alternans [6] and conduction slowing [7,8] may both enable the formation of reentrant and/or focal drivers. Studies relating fractionated atrial activity with GP sites [9] also support localized regions of conduction slowing.

We hypothesized that potential drivers may co-localize with anatomic sites of ganglionated plexus innervation sites in patients with AF. We tested this hypothesis by comparing locations of AF sources on endocardial wide-area mapping to anatomic locations of GP in patients undergoing prospective AF mapping and ablation.

2. Methods

2.1. Study design

We analyzed the relationship of GP to mapped focal and rotational sources in 97 consecutive AF patients referred for ablation who underwent prospective contact mapping. Each patient was 21 years of age with symptomatic AF despite the use of one or more class I or III antiarrhythmic drugs. The population included paroxysmal AF (self-limiting episodes), persistent AF (continuous AF for over one week), and longstanding persistent AF (continuous AF for over one year). This study was approved by the Institutional Committee on Human Research at the enrolling institution.

2.2. Electrophysiology study, FIRM mapping

Electrophysiology (EP) study was performed after discontinuing antiarrhythmic medications for 5 half-lives (>60 days in the case of amiodarone). Catheters were advanced transvenously to the right atrium, coronary sinus and transseptally to the left atrium. A 64-pole basket catheter was advanced through an 8.5 Fr SL1 sheath to map AF sources in both atria. Electroanatomic atrial shells were created to relate basket electrode positions to anatomic regions including the GP and pulmonary veins (Fig. 1).

Contact AF mapping (Focal Impulse and Rotor Mapping, FIRM) has been described elsewhere [3,10]. Briefly, AF signals are recorded using basket catheters, then first mapped using algorithms to determine activation sequences from unipolar AF electrograms. When

deflections are monophasic or non-complex, mapping can identify rotational activations as reported [11] and illustrated in Fig. 1. Conversely, when AF electrograms exhibit multiple deflections, classical dV/dt rules may result in marking deflections within repolarization (far-field) [2]. FIRM assigns activation based on physiological data such as action potential duration restitution [12] to account for altered refractoriness with AF cycle length. Maps of AF activation sequence are generated, supported by phase analyses, from which organized regions are identified to target ablation.

Rotational spiral waves were defined as a phase singularity radiating spiral waves to drive disorganization. Rotors were considered sources if stable (within one electrode) in minutes of recordings. Focal impulses showed centrifugal activation from an origin, again stable over minutes. Rotational and focal regions were considered AF sources and targeted for ablation if they were sustained in spatial regions of $<2-3 \text{ cm}^2$ (precession) in maps.

2.3. Determination of ganglionic plexus (GP) sites

Identification of sites of GP location in the human atria is challenging. The first two approaches assign GP locations at sites where high frequency stimulation or endocardial ablation elicits a vagal response, although both may not identify GP sites in any given patient [3,13,15,17]. The third approach is to identify GP sites by sites of electrogram fractionation, although this is non-specific and identifies large regions of the atria and the definition of fractionated electrograms is variable [3,5]. A fourth approach, used in this study, is to identify GP sites by their stereotypical locations in autopsy and animal studies [3,10,15]. Emerging approaches, which are undergoing validation, include MIBG imaging or other functional scanning.

We defined GP sites anatomically on deidentified electroanatomic shells of the left atrium. The left superior GP is superior and posterior to the left superior PVs, starting 1 cm outside the ostium of the left superior PV between the superior aspect of the PV antrum and the posterior left atrial wall. The left inferior GP is inferior to the left inferior PV, approximately 2 cm from the ostium of the left inferior PV from below the left inferior PV toward the right inferior PV for an average length of 2 cm. The right anterior GP is 1 cm from the ostium of the right superior PV toward the superoanterior left atrial wall down a vertical line anterior to the ostia of the right PVs. The inferior right GP is identified 2 cm inferiorly from the ostium of the right inferior PV, extending to the left inferior PV over an average length of 2 cm (Fig. 2).

Electroanatomic shells of the left atrium (LA) were studied by four blinded observers to determine if at least 50% of the mapped area of left atrial focal and rotational sites (i.e. $>1 \text{ cm}^2$), facilitated by retrospective review of the ablation lesions actually applied on the electroanatomic shell, overlapped with anatomically defined GP sites (superior/inferior left GPs: SLGP, ILGP; or anterior/inferior right GPs: ARGP, IRGP). Disagreement of at most two raters was allowed. The Fleiss kappa score was 0.59 (<0.001), suggesting moderate agreement between raters. Right atrial rotors and focal sources typically comprise [3, 10] a third of sources, but were not correlated to GP whose locations are less well-defined in right atria.

2.4. Ablation

Long-term outcome was not a primary endpoint of this study, because patients were enrolled in different ablation protocols. Radiofrequency energy was delivered via an irrigated catheter (Thermocool, Biosense-Webster) at 25–35 W or in early heart failure patients, via an 8 mm tip catheter (Blazer, Boston Scientific) at 40–50 W, target 52 °C. All patients in this report had AF mapping prior to any ablation. FIRM-guided ablation for each source, when performed, was delivered by applying radiofrequency lesions for 15–30 s at any given site before moving the catheter to the next site to cover the precession areas (typically 1–2 cm²) of each source, prior to any other ablation. Conventional ablation comprised wide area circumferential ablation (WACA) of left and right PV pairs, with verification of PV isolation.

2.5. Statistical analysis

Continuous data are represented as mean $\pm$ standard deviation (SD) or median and interquartile range (IQR) as appropriate. The presence of hypertension (HTN), diabetes mellitus (DM), obstructive sleep apnea (OSA), congestive heart failure (CHF); body mass index (BMI) and laboratory values (brain natriuretic peptide (BNP), magnesium, glomerular filtration rate) were identified from each patient's electronic medical record. Normality was evaluated using the Kolmogorov-Smirnov test. Comparisons between two groups were made with Student's *t*-tests and summarized with means and standard deviations for independent samples if normally distributed (e.g. age, left atrial diameter), or if not normally distributed, with the Mann-Whitney *U* test and summarized with medians and quartiles. Nominal values were expressed as *n* (%) and compared with chi-square tests (e.g. hypertension, AF type, diabetes mellitus, obstructive sleep apnea) or the Fisher exact test when expected cell frequency was <5 (e.g. gender). The GP site area was estimated from the need to apply numerous lesions (dozens) [4] with a 3.5 mm tip catheter. Assuming 20% overlap of lesions and a circular catheter tip, the GP location has a total potential area of 3.072 cm². The probability of an AF source area (2–3 cm²) or a GP site (area 3 cm²) overlapping by chance in the left atria with areas of 80–138 cm² on MRI studies [3,13] is <25% with a 1 cm² resolution. Thus, we used 25% as a conservative estimate of random association. Binominal test was used to assess statistical significance of rotors co-localizing to GP sites. Multi-rater agreement was assessed using Fleiss' Kappa score. A probability of <0.05 was considered statistically significant throughout all analyses.

3. Results

AF focal or rotational sources were detected in 96/97 (99%) patients, for 2.6 ± 1.4 sources per patient (LA 1.7 ± 0.9 , RA 1.1 ± 0.8). Of all patients, 94 patients had LA sources and 63 had RA sources (of 77 patients in whom RA was mapped). Fig. 1 illustrates rotational sources in the left and right atria, where a rotational pattern can be traced in this patient from electrograms (without the need for phase analysis) and where ablation terminated AF. The Supplemental Table summarizes patient characteristics.

3.1. Relationship of AF focal sources and rotors to ganglionic plexi

Overall, 75 patients (80%) had at least one source that co-localized to a GP ($p < 0.05$). Fig. 2B shows examples of left atrial rotational sites colocalizing to the SLGP.

Left atrial sources ($n = 167$) were more likely to overlay left than right GP sites ($p < 0.05$). Overall, 26% of left atrial sources overlapped with the SLGP, 20% with the ILGP, 8% with the ARGP and 11% with the IRGP as demonstrated in Fig. 2C. Further examples of patients with left atrial sources (indicated by lesions) at ARGP and ILGP sites, and cases in which AF source regions did not colocalize with GP sites are demonstrated in Fig. 3.

3.2. Relationship of GP co-localization on acute impact of AF rotor ablation

Overall, 47% of all patients had a localized source at the SLGP site, 34% at ILGP, 14% at ARGP and 19% at IRGP sites. In 27 patients ($n = 24/50$ undergoing FIRM ablation and $n = 3/47$ of patients with PVI only), localized ablation lesions at an identified AF source region terminated AF to sinus rhythm or atrial tachycardia (Fig. 4A). In patients with acute AF termination, there was no apparent lateralization of AF sources to specific GP sites (Fig. 4B). This was true for patients with local termination of persistent AF or paroxysmal AF by ablation at rotational or focal sources (prior to PVI).

3.3. Association of organized sources, GP and demographic variables

There was an association between sources colocalizing at GP sites and a higher number of left atrial sources ($p < 0.001$). Patients with increasing age ($p = 0.041$) and diabetes mellitus (0.039) also had a higher likelihood of an AF source region co-localizing to a GP site, whereas patients with lower ejection fractions were more likely to have AF sources remote from GPs ($p = 0.005$). Hypertensive patients had a trend ($p = 0.061$) for rotors to lie at a GP site. There was no clear relationship to remaining CHADS2VASc factors (heart failure, vascular disease), and the predominantly male population precluded assessment of gender. We did not observe a relationship between source co-localization at GPs and type of AF or left atrial size (both, $p > 0.10$).

4. Discussion

To the best of our knowledge, this is the first study on the spatial relationship between two potential localized mechanisms for human AF: autonomic ganglionic plexi and organized focal and rotational source regions. Prospectively mapped AF sources frequently colocalized to GP sites in the left atrium, particularly in patients with advanced age, diabetes mellitus and hypertension, and this was less frequent in patients with reduced ejection fraction. The spatial relationship was stronger for left than right GP. Nevertheless, a significant number of AF sources were distant from GP sites, and source regions where ablation terminated AF showed no specific propensity to GP colocalization. These data motivate further studies to define how GP activity may modulate repolarization, conduction and potential driver mechanisms for AF, and if therapy at these sites may modulate long-term elimination of AF.

4.1. Ganglionated plexi as AF-sustaining substrates

There is evidence from basic and clinical studies that the autonomic nervous system plays an important role in the pathophysiology of AF. The intrinsic cardiac ANS, in particular, formed by interconnected clusters of epicardial autonomic GP, is critical for both the initiation and maintenance of AF [14,15]. Under intense GP activity, an increase in parasympathetic tone shortens action potential duration in PV versus atrial myocardium, which may initiate reentry in AF [5], while the rise of sympathetic tone increases calcium loading that may initiate early after-depolarizations and trigger firing from PVs [9]. In addition, autonomic neural activity increases with rapid atrial pacing [15], whereas GP ablation reverses AF-mediated effects on atrial remodeling [16], suggesting additional autonomic effect on AF substrate. While the recent surgical AFACT study was negative [17], several studies show that GP-targeted endocardial ablation may improve the results of PVI [15,18]. It is also possible that GP anatomic locations and sizes vary between patients. These studies need to be reconciled.

The relationship between GP sites (and the ANS in general), rotational and focal sources has not previously been studied in human AF. Potential mechanisms linking the ANS with localized AF reentry or focal activity include rate-related alterations in repolarization [5] or conduction [4], but their contribution to clinical AF and ablation outcomes is unclear. Our results suggest such a relationship, although its precise physiological nature remains to be defined. One may discount this relationship since many AF source regions were not colocalized to GP sites. Conversely, most AF source regions are in the left atrium [19], and it is possible that sources near the GPs could be dominant over those in other locations. Studies should define the functional importance of AF drivers in different atrial locations.

4.2. Focal and rotational drivers for human AF

Mechanistic uncertainty continues on the contribution of rotational and focal drivers to human AF. This study brings a novel dimension to this debate. In optical mapping studies of human AF, Hansen et al. [20] showed that AF was maintained by stable endocardial rotational drivers, where localized endocardial ablation terminated AF. Preliminary studies show concordance between AF sources mapped simultaneously by FIRM and optical mapping in human atria [21]. Promising results have been reported by ablating such sites at multiple centers [22–26], although AF-driver ablation outcomes are disappointing at some centers [27–29]. It is unresolved if conflicting results reflect patient selection, methodology or inter-center variations in the results of any approach to AF ablation [30]. AF rotational and focal drivers from ECG imaging [31] and surgical [32], studies of the epicardium may be unstable yet return to the same spatial locations, which may potentially be explained by data from human optical imaging in which AF sources are stable on the endocardium yet transient and unstable on the epicardium [20]. Comparative mapping studies are required to address these discrepancies.

4.3. Limitations

The study design relied upon expert consensus to identify GP sites, yet this may remain the gold standard until methods such as nuclear imaging can objectively identify GP sites. Subjects were enrolled and organized sources were identified prospectively, whereas GP

sites were identified retrospectively. However, the study results may be unchanged if GP sites were identified prospectively since GP ablation was not performed. Comparative ablation targets should be addressed in future studies. The ‘by chance’ probability of overlap is an estimate. To our knowledge there are little data comparing the anatomic size of GPs in patients with normal sized versus larger atria. It is possible that the nerve cells, fibrous and connective tissue comprising GPs ‘stretch’ as the atria remodel. However, it is also possible that GP stretch is limited by their structure. Further investigations on GP size are warranted. AF rotational and focal sources were identified by one technique (FIRM), and future studies should examine locations by alternative mapping techniques. It is possible that patients at recurrent AF after prior ablation may have had some AF sources previously ablated. Nevertheless, all had recurrent drug-refractory AF, and we were only able to study sources present during AF mapped at the index procedure. Finally, the cohort predominantly consists of men, although several studies have validated the findings of AF mapping and autonomic interventions in women.

5. Conclusions

Organized left atrial focal and rotational sites for human AF often colocalize with GP regions, suggesting a potential physiological basis for organized AF patterns and arrhythmia maintenance. Specific patient subsets were particularly likely to have rotational sources near GP locations, including patients with diabetes mellitus, reduced systolic function, or older age. Nevertheless, a substantial minority of sources lay remote from GP in the left atria and in the right atria, where innervation is less well defined. These data may serve as a foundation for future studies to define the functional determinants of AF sources to further refine therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank Kathleen Mills for her assistance in research coordination and Kenneth Hopper, RCVT for help in acquisition of electroanatomic mapping images.

Dr. Narayan is supported for this work by NIH grants (HL70529, HL83359, HL103800).

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Fig. 1. Mapping of AF sources by FIRM and activation mapping from contact basket catheters. A. ECG (blue) and unipolar intracardiac signals (black) from a 64-pole basket catheter with atrial activations marked by classic activation rules (maximum negative dV/dt, red lines). B. Isochronal activation map constructed from corresponding [1–5] activation markings from the electrograms, illustrating a left atrial rotational region. C. Electroanatomic shell demonstrating ablation lesions at the left atrial rotational site that terminated persistent AF with localized ablation. A right atrial source was also ablated, demonstrated on the electroanatomic map. D. Fluoroscopic image of the 64-pole basket catheter in the left atrium in this patient.

Fig. 2. Anatomical relationship between mapped left atrial AF rotor sites and anatomic GP sites. A. Reported locations of superior left (SL), inferior left (IL), anterior right (AR), inferior right (IR) ganglionic plexi on the left atrium. B. Left atrial rotational sources (arrows) with definite agreement overlapping the SLGP in (i) a 43-year-old man with paroxysmal AF and (ii) a 60-year-old man with paroxysmal AF without any prior ablation history. C. Bar graphs show agreement of rotors at anatomical GP sites. Of the 167 total LA sources identified, there was definite agreement for 45 sources overlapping SLGP, 33 at ILGP, 14 at ARGP and 18 at IRGP.

Fig. 3.

Examples of AF rotors that did and did not co-localize with ganglionic plexi. A. Biatrial shells in a 74-year-old man with persistent AF who underwent source ablation (FIRM) in addition to PVI. An anterior left atrial rotational source (black arrow) corresponds to the ARGP site. B. Longstanding persistent AF in a 67-year-old man with a source co-localizing to the ILGP. C. Rotors at non-GP sites (i) at the left atrial roof and lateral right atrium, and (ii) in posterior left and lateral right atrium.

Fig. 4.

A. 33-year-old man with persistent AF who had termination (red line) into CTI-dependent atrial flutter following ablation of the left atrial rotational source at an SLGP site by definite agreement. B. Distribution of sources among GP sites on a per-patient basis. There was no difference in this distribution, regardless of whether AF terminated during ablation procedure or not.