The study by Jadidi et al.1 described the locations of areas of continuously fractionated atrial electrograms during atrial fibrillation (AF) using high-resolution endocardial mapping in 9 patients with paroxysmal AF and 9 patients with persistent AF. This study then correlated these areas with the locations of fractionated atrial potentials during sinus rhythm and coronary sinus (CS) pacing in the same patients. Their premise was that fractionation resulted from conduction abnormalities (conduction slowing/block, pivot points, asynchronous activation, and wave collision).2,3 They postulated that areas exhibiting fractionation during all 3 rhythms (AF, sinus rhythm, and CS pacing) may differentiate fixed atrial/anatomic substrate (structural remodeling) from wave collision or functional slow conduction. They were hopeful that a better understanding of these patterns would help identify which of the areas of fractionation were optimal targets for ablation.

The study was carefully designed and executed, as expected from one of the premier AF laboratories in the world. Some of the findings were expected. The left atrial area was greater, the global left atrial bipolar voltage during AF was lower, and the area of continuously fractionated electrograms was greater (although not as a percentage of the overall area) in patients with persistent AF than in patients with paroxysmal AF.

Perhaps most important were the findings that were not expected under the premise that fractionated electrograms were exclusively due to conduction abnormalities. First, the continuously fractionated areas during AF (CFE mean, <80 milliseconds) did not exhibit lower voltage than the surrounding areas during AF, nor did those sites exhibit low voltage (<1 mV) during sinus rhythm or CS pacing. The voltage during AF was actually higher in the fractionated areas than in the surrounding areas. There was a surprising inverse relationship between the mean bipolar voltage in AF and the mean interval between electrogram components (CFE mean, Figure 5).

Second, there was little or no correlation between the locations of continuously fractionated electrograms during AF (CFE mean, <80 milliseconds), the locations of fractionated electrograms during sinus rhythm (≥4 deflections), and/or the locations of fractionated electrograms during CS pacing (≥4 deflections). Most of the left atrial sites exhibiting continuous fractionation during AF “appear entirely normal in sinus rhythm.” Third, the areas of fractionated electrograms during sinus rhythm and CS pacing had normal voltage (>1 mV). And, finally, mentioned only in the discussion, was the observation that “pulmonary vein isolation during the ablation of persistent AF results in an altered distribution and a significant reduction in left atrial preablation fractionation.”

Given the limitation that the mapping data were obtained sequentially (19 electrograms at a time), rather than simultaneously, the authors interpreted the normal voltage and lack of overlap in locations of fractionation during AF, sinus rhythm, and CS pacing to indicate that electrogram fractionation in this group of patients was due to functional conduction disturbances and depended on both direction and rate of activation and was infrequently related to scarring. Curiously, the authors never suggested that focal activity (focal firing and rotors), highly dependent on autonomic activity, could be responsible for some of the fractionated electrograms, even though they have previously postulated such mechanisms.4–7 The limitations of sequential mapping prohibited mapping of activation in areas of fractionated electrograms. Consequently, focal firing and rotors could not be recognized by the characteristic activation patterns. Also, the authors’ stated observation that sites of continuously fractionated electrograms play a more important role in the maintenance of AF may have impeded the detection of focal firing. Focal firing is generally associated with repetitive, pause-dependent short bursts of activity producing fractionated electrograms with short periods of an organized electrogram.8,9 The mechanism is likely triggered activity associated with early afterdepolarizations, and is heavily dependent on both parasympathetic stimulation (shortening action potential duration) and sympathetic stimulation (calcium loading).8–10 Areas of autonomic ganglionated plexus (GP) activity also manifest shorter refractory periods, favoring the formation of rotors and multiple wavelets that may generate fractionated electrograms.

Fractionated electrograms during AF with brief periods of organized potentials (intermittently fractionated electrograms), characteristic of focal firing, are found at far more sites than continuous fractionation, especially in patients with paroxysmal AF.11 Intermittently fractionated electrograms probably were not included in the algorithm used by the authors (CFE mean, <80 milliseconds). They are located typically in areas surrounding the autonomic GP, both in animal models12,13 and in patients with AF.14–17 Activating the GP by high-frequency stimulation (20 Hz, 10-millisecond
pulse firing (complex ectopy) in the adjacent pulmonary vein and the region surrounding the GP, often initiating AF in patients starting in sinus rhythm.\textsuperscript{18–21} Similarly, stimulation of the GP by heat during radiofrequency ablation abruptly shortens the fibrillatory cycle length in the adjacent pulmonary vein.\textsuperscript{3} Interruption of autonomic nerves from the GP may explain the frequent termination of pulmonary vein firing by wide pulmonary vein isolation (rather than persistence of firing in isolated pulmonary veins).

To test the hypothesis that autonomic factors, and GP activity, might be responsible for fractionated electrograms during AF, Lin et al\textsuperscript{12} and Lu et al\textsuperscript{13} created a canine model of AF by applying a high concentration of acetylcholine (100 mmol/L) to the right atrial appendage. Acetylcholine produced firing in the appendage, and also produced firing in the right superior pulmonary vein and region surrounding the anterior right GP (which receives afferent activation from the appendage and innervates the right superior pulmonary vein). In the region between the GP and the appendage, the degree of fractionation (measured as the dominant frequency) was greatest close to the GP, and decreased progressively as sites closer to the appendage, suggesting that fractionation outside the appendage was driven by the GP. Sequential ablation of 4 fat pads, each containing a GP (located far from the appendage), without injuring the atrial myocardium, produced progressive slowing and organization of electrograms in the atria (and in the appendage), followed by the elimination of firing in the appendage and termination of AF.\textsuperscript{22} This response is similar to the progressive slowing and electrogram organization observed during the stepwise ablation for persistent AF, previously introduced by the authors of the present study.\textsuperscript{23} The fractionated electrogram ablation sites most frequently associated with termination of AF are located in the same regions as the GP, supporting the possible role of inadvertent GP ablation in electrogram organization in these patients.

A key question is the relationship between GP ablation and ablation of complex fractionated atrial electrograms (CFAEs). In a recent study by Nakagawa et al.,\textsuperscript{24} 33 patients (21 with paroxysmal AF and 12 with persistent AF) with sustained AF, inducible without isoproterenol, underwent ablation of the 5 major left atrial GP (including the ligament of Marshall) before pulmonary vein antrum isolation and linear lesions (if required). A map of the left atrium was obtained during AF to measure the left atrial area exhibiting fractionated electrograms (including intermittently fractionated electrograms). Ablation of the 5 major left atrial GP, targeting only sites exhibiting a “vagal response” (AV block during AF) to high-frequency stimulation,\textsuperscript{20} used a median of only 23 radiofrequency applications and covered a relatively small fraction of the area of fractionated electrograms. After GP ablation, sustained AF was reinduced in only 19 (58\%) of 33 patients. A repeat map during “AF” in 16 of the 19 patients showed widely organized electrograms, with a decrease in the area of fractionation from a median of 27.9 cm\textsuperscript{2} to only 1.8 cm\textsuperscript{2}. These results suggest that reducing GP activity markedly reduces CFAE in paroxysmal and persistent AF. Similarly, of the studies exploring CFAE ablation, the greatest success has been associated with the clustering of radiofrequency applications in the regions of the GP.\textsuperscript{14,25}

The authors found the areas of fractionation during sinus rhythm and CS pacing overlapped by only $\approx 30\%$, and believed the activation maps revealed that local wave collision could explain 71\% and “dysynchronous” activation around a zone of slow conduction could explain another 24\% of the fractionated electrograms during sinus rhythm and CS pacing. Recent experimental studies in our laboratory using isopotential right atrial mapping during sinus rhythm and pacing-induced AF showed that the area of fractionated electrograms in sinus rhythm and in AF varied over the respiratory cycle and increased during 3 hours of pacing-induced AF (Y. Fan, B.J. Scherlag, Y. Liu, H. Cai, L. Yu, E. Hepler, T. Sharma, V. Varna, S. Male, G. Fu, S.S. Po, unpublished data). The respiratory cycle changes and the increase in area of fractionation during sinus rhythm by 3 hours of pacing-induced AF were prevented by GP ablation, consistent with the known respiratory cycle of GP activity\textsuperscript{26} and the increase in GP activity during pacing-induced AF.\textsuperscript{27} We also found that the areas of fractionated electrograms during sinus rhythm and AF overlapped, similar to the findings of “AF nests” by Pachon et al.,\textsuperscript{28,29} and Arruda and Natale.\textsuperscript{30}

Two recent studies by the authors\textsuperscript{31} and Habel et al\textsuperscript{32} examined the effects of pharmacological cholinergic and adrenergic blockade (atropine and a $\beta$-blocker) on electrogram fractionation in patients with paroxysmal and persistent AF. The results were far less dramatic than the effects of GP ablation.\textsuperscript{12,24} In a few patients, AF terminated with the administration of $\beta$-blocker alone\textsuperscript{32} or the combination\textsuperscript{31} and could not be reinduced. In most patients,\textsuperscript{32} especially with paroxysmal AF,\textsuperscript{31} electrogram fractionation was attenuated to some degree. There was no significant effect on electrogram fractionation observed during persistent AF in 1 study,\textsuperscript{31} and in a smaller subset, areas of fractionation increased.\textsuperscript{32} The authors\textsuperscript{31} found an increase in atrial cycle length (recorded in the left atrial appendage) in the patients with a decrease in the number of electrograms defined as CFAE, and attributed the decrease in fractionation sites to the decrease in rate (fewer conduction abnormalities). However, the combination of atropine and a $\beta$-blocker, by lengthening action potential duration and refractory periods and reducing calcium loading, would be expected to reduce the occurrence of focal firing and rotors and lengthen the wavelength in reentrant wavelets, any of which might lengthen the cycle length recorded in the atrial appendage. The greater effects of these agents on fractionation in patients with paroxysmal AF\textsuperscript{31} may be explained by a greater preponderance of focal firing in patients with paroxysmal AF. The varied response emphasizes the multiple mechanisms that probably play a role in electrogram fractionation. More important, the fewer effects on suppression of fractionation by atropine and a $\beta$-blocker, compared with GP ablation,\textsuperscript{12,24} suggest the importance of other neurotransmitters in the GP.\textsuperscript{32–34} Other neurotransmitters may also explain the ability of low-level stimulation of the vagal nerves to suppress GP activity and fractionated electrograms.\textsuperscript{35}

We agree with the authors\textsuperscript{1} and with Lockwood and Nademanee\textsuperscript{25} that a greater understanding of the different patterns of fractionated electrograms could lead to more
individualized and effective approaches to AF ablation therapy. The search is complicated by the multiple mechanisms, and it is important to realize that any particular method used to study fractionated electrograms could overemphasize the role of a particular mechanism. Mechanisms notwithstanding, it would appear that we have not, as yet, been able to differentiate those CFAEs that are “bystanders” and those that are critical targets for AF ablation.

**Disclosures**

None.

**References**


**KEY WORDS:** Editorials ■ atrial fibrillation ■ fractionated electrograms ■ electrophysiology ■ autonomic nervous system
Nature of Electrogram Fractionation During Atrial Fibrillation
Warren M. Jackman and Benjamin J. Scherlag

Circ Arrhythm Electrophysiol. 2012;5:5-7
doi: 10.1161/CIRCEP.111.969279

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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