



## Review on “High-Density Mapping of Atrial Fibrillation in Humans: Relationship Between High-Frequency Activation and Electrogram Fractionation”

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Catheter ablation has rapidly gained acceptance as a mainstay of therapy for many symptomatic patients with atrial fibrillation since the original publication by the Bordeaux group.<sup>1</sup> Early on it became apparent that in most patients with paroxysmal AF, the arrhythmia was initiated by focal firing in the pulmonary veins. Ablation focused on elimination of such triggers and was largely limited to patients who would stay in sinus rhythm long enough to allow successful mapping within the pulmonary veins. As this was time consuming and was associated with high risk of developing pulmonary vein stenosis, ablation lesions were moved further and further away from the sources of focal firing with co-development of Circumferential Pulmonary Vein Ablation (CPVA)<sup>2</sup> aiming to encompass pulmonary vein ostia with circular lesions without verification of conduction block and Segmental Pulmonary Vein Isolation<sup>3</sup> evolving into Pulmonary Vein Antrum Isolation<sup>4</sup> with the targeted area similar to that in CPVA but with requisite documentation of entry and / or exit block of conduction. While successful in the majority of patients with paroxysmal AF, these approach-

es were lacking in patients with persistent and permanent AF. A concurrent approach addressing the fibrillatory substrate was developed and proved to be a successful standalone alternative to lesions encircling the pulmonary veins at one center.<sup>5</sup> This approach had the advantage of better tailoring the lesion set to the individual patient and potentially limiting energy delivery and associated risks. Addressing fibrillatory conduction as an adjunct to ablating triggers had since become incorporated into the lesion set targeting persistent and permanent atrial fibrillation in a stepwise approach popularized by the Bordeaux group.<sup>6</sup> At the same time better tools have enabled clinicians to probe deeper into the complex interaction of the mechanisms initiating and maintaining atrial fibrillation. So in experimental models of atrial fibrillation “drivers” or areas of microentry were seen surrounded by areas of fibrillatory conduction.<sup>7-9</sup> Research has pointed to the possibility of the “drivers” or “triggers” to be in close proximity to areas of atrial myocardium innervated by autonomic ganglionated plexi with areas of fibrillatory conduction 1-2 cm remote from these.<sup>10</sup> Relation-

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ship between areas of high dominant frequency and atrial tachyarrhythmias that follow AF ablation has been demonstrated<sup>11</sup> suggesting that such arrhythmias may actually drive AF prior to de-fragmentation.

In their paper published last month,<sup>12</sup> Drs Stiles and Brooks describe high-density bi-atrial mapping during atrial fibrillation prior to ablation to identify areas of presumed drivers and fibrillatory conduction. The investigators collected around 500 points in each of the 20 patients during atrial fibrillation using a PentaRay (Biosense Webster, Diamond Bar, CA, USA) catheter and NavX software (St. Jude Medical, St. Paul, MN, USA). Each point was screened manually to eliminate points with unacceptable signal-to-noise ratio. Eight second recordings were used. Points were stratified into one of 4 right atrial or 8 left atrial areas. The authors then processed the collected signals to arrive at three-dimensional maps of dominant frequencies (DF) and complex fractionated atrial electrograms (CFAE). CFAE were mapped using integral “CFE-mean” included as part of the NavX distribution with a refractory period set at 30ms, peak-to-peak sensitivity set to 0.1 mV and signal duration set at 10 ms. Points with a CFE-mean value of 40 – 250 ms were included in the analysis. DF analysis occurred offline using Coperniqs software (Medicalgorithmics, Austin, TX, USA) which allowed the investigators to analyze only those points exhibiting high degree of signal regularity. They confirmed prior findings of frequency gradients between the left and the right atria and found that signal frequency was higher in patients with persistent AF. Median CFE-mean and median DF correlated with AF cycle length. Clusters of points with the shortest CFE-mean and highest DF were spatially compared. Patients with paroxysmal AF had higher DF around the pulmonary veins, left atrial appendage and the roof, whereas those with persistent AF had a more uniform distribution of DF throughout the left atrium. Areas of highest fractionation clustered around the left atrial roof, posterior, inferior and anterior walls and the septum in all patients. Median distance between DF and CFAE clusters was 5 mm with 80% of DF clusters within 10 mm of CFAE clusters.

This is an important contribution to the literature on the mechanisms of atrial fibrillation highlight-

ing frequency distribution differences between paroxysmal and chronic AF, where patients with persistent AF have a more uniform distribution of the areas with high DF and faster global AF cycle lengths. These differences may be responsible for the difference in ablation success rates between AF subtypes. The investigators demonstrated a close spatial relationship between areas of high DF and surrounding areas of high fractionation, suggesting that the two are indeed related and as was seen in experimental optical mapping studies, fibrillatory activity represented by CFAE surrounds more organized “drivers” with high DF. Such local frequency gradients were further supported by limited activation mapping. No conclusions could be drawn on whether or not ablation of the high DF sites could help improve outcomes since DF analysis occurred offline and DF mapping was not used to guide ablation. There is emerging evidence that ablation guided using DF<sup>13</sup> or CFAE<sup>14</sup> mapping may result in higher success rates, but the question of whether CFAE or DF is a more important ablation target remains to be answered. While development of tools which will allow rapid high density activation mapping to better delineate the relationship between DF and CFAE and hopefully fine-tune the ablation strategy is ongoing, ablation targeting anatomical substrate of the pulmonary veins with tailored adjunctive de-fragmentation will likely remain at the core of invasive treatment for AF.

## References

1. Haissaguerre, M., P. Jais, D.C. Shah, A. Takahashi, M. Hocini, G. Quiniou, S. Garrigue, A. Le Mouroux, P. Le Metayer, and J. Clementy, Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*, 1998. 339(10): p. 659-66.
2. Pappone, C., G. Oreto, F. Lamberti, G. Vicedomini, M.L. Loricchio, S. Shpun, M. Rillo, M.P. Calabro, A. Conversano, S.A. Ben-Haim, R. Cappato, and S. Chierchia, Catheter ablation of paroxysmal atrial fibrillation using a 3D mapping system. *Circulation*, 1999. 100(11): p. 1203-8.
3. Haissaguerre, M., D.C. Shah, P. Jais, M. Hocini, T. Yamane, I.I. Deisenhofer, S. Garrigue, and J. Clementy, Mapping-guided ablation of pulmonary veins to cure atrial fibrillation. *Am J Cardiol*, 2000. 86(9 Suppl 1): p. K9-K19.
4. Marrouche, N.F., D.O. Martin, O. Wazni, A.M. Gillinov, A. Klein, M. Bhargava, E. Saad, D. Bash, H. Yamada, W. Jaber, R. Schweikert, P. Tchou, A. Abdul-Karim, W. Saliba, and A. Natale, Phased-array intracardiac echocardiography monitoring during pulmonary vein isolation in patients with atrial fibrillation: im-

- pact on outcome and complications. *Circulation*, 2003. 107(21): p. 2710-6.
5. Nademane, K., J. McKenzie, E. Kosar, M. Schwab, B. Sunsa-neewitayakul, T. Vasavakul, C. Khunnawat, and T. Ngarmukos, A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol*, 2004. 43(11): p. 2044-53.
6. Haissaguerre, M., P. Sanders, M. Hocini, Y. Takahashi, M. Rotter, F. Sacher, T. Rostock, L.F. Hsu, P. Bordachar, S. Reuter, R. Roudaut, J. Clementy, and P. Jais, Catheter ablation of long-lasting persistent atrial fibrillation: critical structures for termination. *J Cardiovasc Electrophysiol*, 2005. 16(11): p. 1125-37.
7. Skanes, A.C., R. Mandapati, O. Berenfeld, J.M. Davidenko, and J. Jalife, Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart. *Circulation*, 1998. 98(12): p. 1236-48.
8. Morillo, C.A., G.J. Klein, D.L. Jones, and C.M. Guiraudon, Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. *Circulation*, 1995. 91(5): p. 1588-95.
9. Kalifa, J., K. Tanaka, A.V. Zaitsev, M. Warren, R. Vaidyanathan, D. Auerbach, S. Pandit, K.L. Vikstrom, R. Ploutz-Snyder, A. Talkachou, F. Atonza, G. Guiraudon, J. Jalife, and O. Berenfeld, Mechanisms of wave fractionation at boundaries of high-frequency excitation in the posterior left atrium of the isolated sheep heart during atrial fibrillation. *Circulation*, 2006. 113(5): p. 626-33.
10. Zhou, J., B.J. Scherlag, J. Edwards, W.M. Jackman, R. Lazzara, and S.S. Po, Gradients of atrial refractoriness and inducibility of atrial fibrillation due to stimulation of ganglionated plexi. *J Cardiovasc Electrophysiol*, 2007. 18(1): p. 83-90.
11. Yoshida, K., A. Chugh, M. Ulfarsson, E. Good, M. Kuhne, T. Crawford, J.F. Sarrazin, N. Chalfoun, D. Wells, W. Boonyapisit, S. Veerareddy, S. Billakanty, W.S. Wong, K. Jongnarangsin, F. Pelosi, Jr., F. Bogun, F. Morady, and H. Oral, Relationship between the spectral characteristics of atrial fibrillation and atrial tachycardias that occur after catheter ablation of atrial fibrillation. *Heart Rhythm*, 2009. 6(1): p. 11-7.
12. Stiles, M.K., A.G. Brooks, P. Kuklik, B. John, H. Dimitri, D.H. Lau, L. Wilson, S. Dhar, R.L. Roberts-Thomson, L. Mackenzie, G.D. Young, and P. Sanders, High-density mapping of atrial fibrillation in humans: relationship between high-frequency activation and electrogram fractionation. *J Cardiovasc Electrophysiol*, 2008. 19(12): p. 1245-53.
13. Atonza, F., J. Almendral, J. Jalife, S. Zlochiver, R. Ploutz-Snyder, E.G. Torrecilla, A. Arenal, J. Kalifa, F. Fernandez-Aviles, and O. Berenfeld, Real-time dominant frequency mapping and ablation of dominant frequency sites in atrial fibrillation with left-to-right frequency gradients predicts long-term maintenance of sinus rhythm. *Heart Rhythm*, 2009. 6(1): p. 33-40.
14. Verma, A., P. Novak, L. Macle, B. Whaley, M. Beardsall, Z. Wulffhart, and Y. Khaykin, A prospective, multicenter evaluation of ablating complex fractionated electrograms (CFEs) during atrial fibrillation (AF) identified by an automated mapping algorithm: acute effects on AF and efficacy as an adjuvant strategy. *Heart Rhythm*, 2008. 5(2): p. 198-205.