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Getting to the Core of AF Irregularity: Are We There Yet?

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Editorial comment

“When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades; when the pulse is slender (smaller than feeble, but still perceptible, thin like a silk thread), then the impulse of life is small.”

Huang Ti Nei Ching Su Wen, circa 2000 B.C.¹

This observation, along with other astute works on atrial fibrillation (AF), formed the early foundations for the classical bedside description of an irregularly irregular pulse for AF and chaotic f-waves on the ECG. Despite the passage of time, the mechanistic underpinnings for this ancient disease remain hotly debated, although with increasing clarity of late. Early computer models suggested that “global” disordered mechanisms may sustain AF, in the form of multiple chaotic, waves that bifurcated, collided, extinguished, and meandered within the atria.² In parallel, Mines,³ Sir Thomas Lewis,⁴ and others proposed an alternative “driver” hypothesis: that AF is caused by stable localized circus movement or repetitive focal sources such that disorganization is an epiphenomenon rather than the mechanism that actually sustains AF. This dichotomy is of central clinical importance—in the first, therapy should strive to constrain disorganized activity while ignoring organized regions; in the second, therapy should target organized drivers while ignoring disorganized ‘bystander’ activity.

The “global disorganization” model is supported by studies in early computer models² and in small atrial regions⁵ showing completely nonrepeating AF patterns, but also seminal intraoperative mapping studies by Cox, Schuessler, Boineau *et al.*⁶—although these actually revealed consistent circuits for which the Maze procedure was developed. In fact, studies showing completely disordered activity are difficult to reconcile with insightful observations from biatrial mapping in AF patients. Such studies show that human AF can be eliminated by ablating localized tachycardias at pulmonary veins⁷ and other critical sites in either atrium,^{8–10} that even persistent AF may terminate early during an ablation procedure⁹ before electrical compartmentalization has been achieved, and that AF patients may exhibit localized regions of high dominant frequency or rapid rate^{11,12} and stable gradients in rate

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and organization over time.^{13,14} These observations are in fact more consistent with elegant animal models in which AF is caused by drivers, in the form of localized electrical spiral waves (rotors) in optical studies by Jalife¹⁵ and others in sheep and canine¹⁶ atria, or repetitive focal sources in detailed contact mapping in canine models of AF by Ryu *et al.*¹⁷ and others.

The CONFIRM trial¹⁸ recently directly demonstrated drivers in human AF, in the form of a small number of stable rotors or focal sources often remote from the PVs in either atrium, by combining contact electrodes in a wide field of view with novel computational algorithms (“contact panoramic mapping”) to reveal sources in 97% of patients.¹⁹ Brief ablation at sources, that were stable for hours during mapping, was able to acutely terminate AF, render AF noninducible before PV isolation^{18,20} and greatly improve freedom from AF compared to conventional ablation alone.¹⁸ Several other groups have now demonstrated stable rotors in human AF^{20–23} using contact (but not noncontact²⁴) methods. A major remaining challenge, however, is the need to rapidly detect rotors and focal sources that may lie at widespread locations in both atria often outside the PVs.

In this issue of the *Journal*, Lee and colleagues²⁵ present an important contribution that furthers our ability to reliably identify activation rates during AF in either atrium, for the potential detection of AF drivers. The authors’ rationale is that measuring AF cycle length (CL) manually is the gold standard, yet is both difficult and time consuming. Applying their well-characterized Waldo-sterile pericarditis model of AF in 6 dogs, the authors developed a cycle length variability detection (CLVD) algorithm to quantify beat-to-beat AF CL variation for 6 AF episodes, each measured at 400 unipolar electrograms (200–210 bipolar pairs; >20,000 cycles). CLVD operates first by subtracting the median ventricular complex on each channel, followed by Botteron–Smith signal conditioning. After applying an adaptive peak detection method to detect successive AF activations, CLVD iteratively rejects CL instances falling outside a 95% tolerance window centered on the mean CL until no cycles are rejected. Mean and standard deviation of this CL series were compared to manual CL measured by 2 investigators and to spectral dominant frequency (DF). The authors found a high correlation between CLVD and manual estimates (correlation coefficient for CL = 0.96, for CL SD = 0.89). Spectral DF also estimated AF CL accurately compared to manual CL, although the well-described spectral organization index (OI) correlated poorly with CL standard deviation (correlation coefficient –0.59). The authors concluded that CLVD was more accurate than DF in detecting varying degrees of AEG CL regularity, and that both reflected manual estimates of AF CL.

The authors should be congratulated on this contribution to assist in the rapid quantification of AF rate, that extends clinical studies^{11,12,26} and basic science reports¹⁵ that regions of high spectral dominant frequency may indicate AF drivers. As with any interesting study, of course, this work raises issues that are very pertinent to future human testing of CLVD. The first relates to the accuracy of manual CL measurements, in this study and in general. The study used unipolar and bipolar electrograms to mirror clinical recordings of AF. Unlike studies using optical action potentials, such signals are surrogates that must be considered when interpreting spectral DF²⁷ to avoid obfuscating AF CL estimates.²⁸ Lee *et al.* used a 50-millisecond blanking period to estimate local repolarization time before assigning activation. However, clinical studies show that AF electrograms may exhibit variable large amplitude artifacts, reflecting the spatiotemporal integral of asynchronous far-field fibrillatory activations on any given electrode, that obscure true local activation.²⁹ Accordingly, some studies have used direct measures of monophasic action potential duration to provide beat-to-beat (restitution)³⁰ and regional repolarization information to improve AF rate estimates.³¹ Although these caveats mostly apply to complex electrograms²⁹ that were not observed by the authors, such signals are common in human

AF. This makes future clinical testing of CLVD in relation to spectral DF of particular importance. In addition, while the authors compared spectral OI to AF CL, the indices are not exactly analogous since spectral OI quantifies variations in signal morphology, amplitude and CL sequence as well as CL variability.²⁷ Thus, spectral OI may be more sensitive for a rapid, regular, organized site while, theoretically, low CL SD may indicate regularity even if signal shapes or amplitudes vary considerably. This again makes future clinical comparisons of CLVD against spectral DF of particular interest in clinical AF whose signals may exhibit morphologic, amplitude, and other variations.

In conclusion, we commend the authors on an important contribution to the field, that may help identify drivers that sustain AF in a particular case, for the ultimate goal of targeted ablation. Lee *et al.* provide a thorough and detailed analysis of a promising time-domain algorithm to accurately identify regional AF rates and rate gradients. It is now important to determine the accuracy of CLVD for identifying AF drivers in humans. This study advances still further the concept that the key to treating AF is not the mapping of irregularity, but of “regularity within irregularity.”

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