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Spatiotemporal and Spectral Characteristics of AF Waves Through Atrial Walls and Remodeling

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The forms in which atrial fibrillation (AF) may initiate, sustain and develop under the variety of the atrial substrate conditions and remodeling factors are not fully understood yet. 1 A combination of optical mapping and spectral methods to identify the dominant frequency (DF) of local excitation during acute cholinergic AF in the isolated sheep heart have demonstrated that high-frequency sources in the posterior wall of the left atrium drive the fibrillatory activity throughout both atria. 2 Additional studies applying spectral analysis methods in a similar model of sustained AF and numerical simulations have demonstrated that the fibrillatory activity is most pronounced in the periphery of areas of high frequency sources and is related to beat-by-beat variations in conduction velocity and directionality secondary to fast stable or meandering rotors. 3,4 Clinically, it has been demonstrated that paroxysmal AF in patients is initiated by focal triggers usually localized to one of the pulmonary veins (PVs) 5 and can be cured by a catheter-based ablation procedure. 6 Nevertheless, in persistent AF patients it has been suggested that multiple random wavelets of activation coexist to create a chaotic cardiac rhythm, 7 and therapy is more challenging. 8 Subsequent studies have analyzed the spectral content of electrogram recordings during AF in humans, often noting the different spatial distribution of DFs between paroxysmal and persistent AF patients. 9–11 In patients with paroxysmal AF, the high DF (HDF) sites are often localized to the posterior LA near the ostia of the PVs. 12,13 In contrast, patients with permanent AF demonstrate HDF sites that are more often localized to either atrium rather than to the posterior left atrium-PV junction. 12,13 Further use of the spectral analysis demonstrates that the response of the arrhythmia to adenosine is consistent with the mechanistic hypothesis that reentry in those HDF sites maintains human AF, and that reentrant drivers have different locations in paroxysmal compared with persistent AF patients. 14

Thus, the addition of frequency domain measures to those of time and space should help elucidate on the mechanism of AF in the broad range of chronic conditions that are responsible for remodeling the atria, either electrically or structurally. In this issue of *HeartRhythm*, Everett et al 15 present new data and analyses of atrial waves on the endocardial and epicardial surfaces in 5 different types of fibrillation in anesthetized dogs: normal (control), congestive heart failure (CHF), rapid atrial pacing (RAP), mitral regurgitation (MR), and dogs infused with methylcholine (METH) to simulate

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parasympathetic AF. Using extensive endocardial non-contact mapping in the left atrium (LA) and various epicardial multi-electrodes recordings in the LA and right atrium (RA), Everett et al classify a variety of activation patterns during the AF and determine the distributions of DF and the organization index (OI) of the local wave activity. The general finding is that the degree of similarity between the endocardium and epicardium in activation patterns, DFs and OIs, depend on the AF model leading to the conclusion that models exhibiting primarily structural remodeling, i.e., the MR and CHF models, have more transmural similarities and stability of HDF than the RAP model, which is considered to be primarily electrically remodeled. While the results by Everett et al are consistent with some studies characterizing transmural activation properties, they differ from studies on remodeling of the AF. Katsouras et al¹⁶ recently compared frequency and spatiotemporal patterns of activation during AF in the setting of tachy-pacing remodeling and vagal stimulation of dogs under an equivalent atrial refractory period condition. While Everett et al report in their present study that the DFs in the METH model of AF are lower than those for the rapid atrial pacing, both endocardially and epicardially, Katsouras et al found the opposite in their canine models of AF. Obviously, the different conditioning of the atria in these two studies may have played a role in the DFs difference as Katsouras et al note that their tachy-paced remodeling may be considered mild, while their vagal-stimulation can be considered physiologically aggressive.¹⁶ In another study of AF in isolated hearts from sheep representing CHF conditions, Tanaka et al¹⁷ found the frequencies to be lower than in control, in contrast with the present findings by Everett et al. In addition, Tanaka et al also describe an increased variability in beat-to-beat activity in the posterior LA wall of the isolated CHF sheep heart, in apparent contrast to the increased stability of activity in the CHF versus control dog AF models by Everett et al.¹⁵

An important finding by Everett et al is that in all AF models studied, except the RAP one, the highest DF was found mostly on the endocardial surface where focal and reentrant activities also seem to have been found most often.¹⁵ Together with a recent study in the goats suggesting that perpetuation of AF is not dominated by the epicardial and subepicardial layers,¹⁸ this finding is consistent with fast intramural drivers and transmural conduction blocks as a possible AF mechanism. Mandapati et al found that epicardial reentrant activity in isolated sheep hearts during cholinergic AF averages at about 14 Hz with a miniscule core size of about 3 mm across.¹⁹ and together with simulations presented by Tanaka et al,¹⁷ they support the idea that the thin atrial wall can accommodate intramural reentry with endocardial and epicardial breakthrough patterns of propagation.

Considering all of the above studies, one can conclude that the precise relationship between the atrial substrate, the progression of its remodeling and the ensuing frequency and regularity of activation during AF is still not fully resolved. Spectral analysis with its quantifiable measures should enhance mechanistic insight of AF most when it is correlated with both spatiotemporal patterns of propagation and the atrial substrate. Better understanding of this correlation is arguably worth pursuing as clinical evidence shows that a significant reduction in DFs in all chambers with a loss of the left-to-right atrial gradient following ablation is associated with a higher probability of long-term sinus rhythm maintenance in both paroxysmal and persistent AF patients.^{12,13}

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