Dynamics factors preceding the initiation of atrial fibrillation in humans

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Atrial fibrillation (AF) is the most common arrhythmia in the United States, yet its mechanisms remain unclear.[1] Seminal observations that premature beats from the pulmonary veins (PV) may initiate paroxysms of AF[2] led to the development of PV isolation for that condition. However, ablation is much less effective in persistent AF, largely because its pathophysiology is less well understood.[1] A major contemporary translational challenge is therefore to build upon insights from the animal laboratory to identify mechanisms that separate persistent from paroxysmal AF in humans.

Clinical observations on AF initiation

Focal triggers or tachycardias and the autonomic nervous system

Sympathetic or parasympathetic stimulation[1] may explain the importance of thoracic vein sites as AF triggers[2] and may underlie vagally or adrenergically mediated AF.[3] In dogs, sympathovagal stimulation of PVs shortens action potential duration (APD) to cause early after-depolarizations (EADs) and triggered beats.[4] In support of this mechanism in humans, PV beats that trigger AF are likely focal,[5] AF is less likely to recur if the PV antra are dennervated,[3] and routine PV isolation often causes denervation.[6] Nevertheless, the mechanisms linking autonomic innervation with human AF are incompletely understood.

Atrial flutter is strongly associated with AF

Epidemiological studies show that patients with typical atrial flutter (AFL) often develop AF over time,[7] while in patients with paroxysmal AF, recent data suggest that coexisting AFL indicates substrate that renders PV isolation less effective.[8] These data are consistent with clinical experience that links AF with AFL, particularly with atypical macroreentry.[9]

Mechanistically, AFL could directly initiate AF[9] or facilitate AF by creating its substrate.[10] In dogs, typical AFL requires a short period of AF to cause functional block across the *crista terminalis,* which protects isthmus-dependent reentry.[11] However, answers to the inverse questions are less clear—does macroreentry disorganize to human AF[12] or does microreentry perpetuate ("drive") AF?[13]

Proposed mechanisms for AF

It remains unclear whether human AF results from reentrant or focal processes, whether both coexist, and under what conditions one predominates. Elegant animal studies show that AF is self-facilitating by virtue of remodeling, in which refractory periods shorten and conduction may slow.[14] Although this encourages reentry, by shortening tissue wavelength, it may also promote focal mechanisms, since shortened APD facilitates EAD-triggered activity in canine PVs.[4]

Evidence for multiwavelet reentry in human AF (15)

Intraoperative mapping suggests that human AF represents multiple reentrant wavelets,[16] as quantified by elegant electrophysiologic methods.[17] Elimination of AF by the Maze surgery also supports this mechanism, although it has been suggested that Maze surgery also isolates the PVs and may thus eliminate potential triggers or drivers.[18] Interestingly, human AF shows nonuniform spatial organization that may be consistent between patients.[19,20] If multiwavelet reentry is a predominant mechanism, studies are needed to explain why reentry or wave break are confined to certain locations or why wave break occurs elsewhere. As described below, this organization may reflect dynamic regional spatial or temporal properties of the atria.

Evidence for focal drivers of human AF

An alternative hypothesis is that rapid regular sources sustain human AF by activating too fast for remaining tissue to keep pace (fibrillatory conduction). This mechanism has been shown *in vitro* in sheep[13] and *in vivo* in dogs[21] and could potentially coexist with reentry.

Drivers of human AF have yet to be identified categorically, despite provocative observations. Sahadevan et al[20]

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and Wu et al[22] used intraoperative mapping to reveal sites of rapid regular activation in AF, often near the PVs. However, these sites were not ablated or otherwise perturbed, and so it is uncertain whether they reflect drivers or local tissue properties.

Moreover, termination of paroxysmal AF by PV isolation does not prove that PVs are drivers because PV isolation in any sequence slows AF progressively before termination.[23] Indeed, the PVs may also represent preferred anchors for reentry. Furthermore, using short AF cycle length to identify a driver site is problematic since this may also represent short refractoriness[14] or wave collision.[24] An important study showed that sites of rapid AF, identified spectrally by sequential point mapping in patients with persistent AF, were unrelated to successful ablation.[25]

As a result, it may be important to assess electrogram regularity and rate and to use simultaneous multisite mapping to circumvent some limitations of the spectral analysis of temporally varying AF (Figure 1).[24,26] A regular AF driver should have a high-frequency yet narrow spectral dominant frequency (DF), while surrounding tissue should not.[13,21] We recently used this approach, with simultaneous multisite biatrial mapping,[27] to identify sites from which a radial step down in rate and regularity was seen (centrifugal activation).[28] These criteria have been used to define drivers in animal models[13,21] and, in our series, were seen in half of our patients. Proposed drivers lay near the PVs in patients with paroxysmal AF but elsewhere in those with persistent AF.

Complex fractionated atrial electrograms (CFAEs) may also be mechanistically important to human AF.[29] In intraoperative unipolar mapping studies, fractionation identified sites of slow conduction.[16] It has recently been proposed that CFAE during human sinus rhythm results from vagal stimulation[30] and that CFAE during AF in dogs reflects autonomic stimulation.[31] Nevertheless, because CFAE may also reflect wavelet collision, far-field signals or noise (Figure 1), the role of CFAE sites in human AF remains unclear. We found no relationship between CFAE and sites of centrifugal step down in rate and organization in our series of patients.[28]

Validating proposed drivers of human AF

A major clinical challenge is to prove that any proposed driver sustains AF. Naturally, terminating AF by ablation at this site would provide compelling evidence. However, elimination of one source may allow the emergence of alternate perpetuating mechanisms. Indeed, this may explain why termination of persistent AF typically requires ablation of sequential AF sources.[32] Quantifying fibrillatory conduction (i.e., step down in rate and organization) may also validate that a candidate site perpetuates AF. In sheep, the radial increase in cycle length from a driver is 33 ms/cm

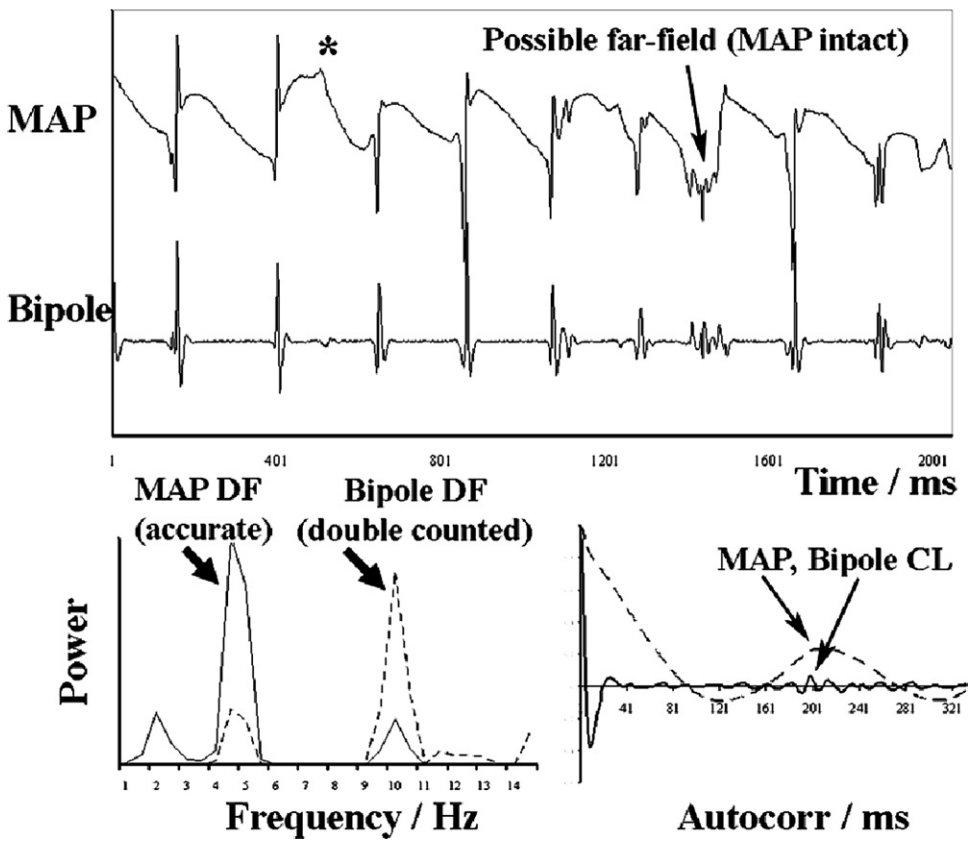

Figure 1 Fractionated electrograms may indicate wavelet collision or far-field signals, as validated from monophasic action potentials. This far-field signal or noise may cause overestimation of the spectral DF (*bottom left*), which is avoided using time domain autocorrelation (reproduced from reference 24 with permission).