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Atrial fibrillation: the mother rotor and its rebellious offspring take turns sustaining the family

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Our poor understanding of the mechanisms of atrial fibrillation (AF) is humbling. Although valuable insights have been gained after decades of active research, the simple question of whether it is caused by reentry or focal activity remains unanswered, even if we tried to do so just in relative terms. More than a century ago, Winterberg suggested that AF was the consequence of multiple ectopic foci.¹ Decades later, the idea that a single rapid-firing site could lead to AF was proven by Scherf² and Prinzmetal,³ who showed that focal injection of aconitine (a sodium channel opener) produced rapid regular focal activations at the injection site, but global atrial fibrillatory activation patterns. However, when Moe and Abildskov^{4, 5} proposed the multiple wavelet hypothesis, it became accepted that AF was caused by self-perpetuating activation wavelets that propagated on heterogeneous atrial tissue. Indeed, mapping studies were able to demonstrate such multiple wavelets,⁶ and it became accepted that a minimum of 4–6 wavelets were required to sustain AF.⁷

However, Allesie et al had also previously demonstrated functional reentry in the atrium in the absence of an anatomical substrate,⁸ which supported the idea that reentry –by definition a self-sustainable process– could underlie the mechanisms of perpetuation of AF. How could a periodic phenomenon such as reentry underlie a chaotic and aperiodic one such as AF? Rapidly activating rotors may lead to global fibrillatory activation patterns if drifting,⁹ or if activations stemming from the rotor fail to conduct 1:1 to neighboring tissues. This so-called fibrillatory conduction has been shown to be caused by wavebreak in anatomically-determined locations, such as pectinate muscles.¹⁰ Support for relatively stable rotors as the engine of AF came from a series of works from Jalife's laboratory, showing fast, local periodicity¹¹ and reentry in the left atrium¹² that led to stable left-to-right frequency gradients¹³ during sustained AF. A predilection for left atrial reentry to occur in the neighborhood of the pulmonary veins was also evident: Arora et al¹⁴ showed detailed optical mapping of such local reentry, and Chen's group emphasized the complex underlying histological patterns in this region (including the ligament of Marshall), that could lead to reentry,¹⁵ a concept that had been predicted by Spach decades earlier¹⁶ and that seems to be relevant in ventricular fibrillation as well.¹⁷ In the clinical realm, the concept of focal discharges as a cause of AF got enormous support with Haissaguerre et al's seminal finding that ectopic beats from the pulmonary veins initiated AF.¹⁸ Mechanistically, focal beats triggering AF were shown to arise from electrogenic sodium/calcium exchange in situations of calcium overload.^{19, 20}

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During ongoing AF, however, focal activations have been harder to prove. Indeed, Atienza et al²¹ postulated that frequency acceleration by adenosine administration during AF supported reentry as the primary mechanism of AF maintenance.

In this issue of Heart Rhythm, Yamazaki and colleagues²² report on the effects of several pharmacological interventions in the activation patterns of AF induced by mechanical stretch (stretch-related AF, SRAF). This is a well-established model, previously described by the authors, that leads to sustained AF for hours. The central purpose in this work is to assess the relative relevance of focal activations vs. reentry in the maintenance of AF. Using this model of sustained AF, the authors then attempted to suppress intracellular calcium-derived afterdepolarizations with caffeine or ryanodine and showed that either of these two drugs succeeded at terminating AF (10/13 cases). When on top of the physiological alterations created by stretch, the authors added the combined administration of acetylcholine and isoproterenol, then caffeine or ryanodine failed to terminate AF (1/11 cases). The authors correlate these differential effects with the specific activation patterns of AF, suggesting that without acetylcholine/isoproterenol, AF is maintained by focal activations (which would be suppressed by caffeine or ryanodine), whereas with acetylcholine/isoproterenol, reentry plays an increasingly predominant role, which becomes seemingly exclusive when caffeine or ryanodine are added and focal activations are suppressed. Although the overall interpretation seems rather simple and it is not without important caveats, this is a commendable, rigorous effort to attempt to correlate mapped activation patterns with the underlying physiological conditions leading to AF. Furthermore, the authors complement their results with computer simulations to show how focal discharges interact with rotor core meandering dynamics. While answering some important questions, the paper raises more additional questions that remain unanswered.

Important caveats relate to the methods of suppression of intracellular calcium-derived afterdepolarizations. The authors chose ryanodine or caffeine. A better drug regime would have included thapsigargin along with ryanodine to completely disable the calcium cycling, which has been shown to suppress focal discharges in AF models.²³ The calcium chelator BAPTA would have also been an uncontroversial eliminator of calcium-induced arrhythmogenesis.²⁴ Additionally, it is unclear whether conclusions drawn from a very specific form of AF (stretch-related) apply to others.

The overall picture remains complex. One conclusion that can be safely drawn from this paper is that AF is an ever-changing phenomenon whose mechanisms vary depending on the underlying physiological conditions. Thus, rotors and focal activations do not seem to have a fixed hierarchy. AF may be sustained by a rotor from which daughter wavelets emanate but propagate in an irregular pattern due to fibrillatory conduction. However, the rotor's stability is subject to continuous threats by focal activations that may arise at any given time by a triggered activity mechanism.^{19, 20} Arguably, the irregularity of fibrillatory conduction would enhance the generation of triggered activity by promoting relative pauses, and focal activations would still owe their existence to their triggering beats and indirectly to the mother rotor. Thus, the mother rotor seems to be a promiscuous source of offspring wavelets, both by direct emanation and by indirect triggering. What this paper illustrates is that AF seems to be a continuous struggle between two related phenomena: 1) the tendency of wavelets to self-organize as rotors, 2) the triggered beats that can invade the rotor and extinguish it, or form a new rotor. Each can lead to one another, and either can predominate depending on the underlying conditions.

Additional questions remain regarding the mechanistic, clinical, prognostic and therapeutic relevance of focal- vs. rotor-driven AF: Are activation patterns merely a reflection of the underlying atrial physiology -as in this paper- applicable to clinical scenarios where AF

develops, for example hypertensive AF vs lone AF? Clinically, do the activation patterns impact the long-term stability of AF? Do they impact the clinical course of AF (paroxysmal or persistent)? Or its thrombogenic potential? Or the susceptibility to different therapies, ablative, antiarrhythmic or substrate-based (i.e. ACE inhibitors)? All electrophysiologists ablating AF have experienced the enormous variability of activation patterns in different patients, as reflected by intracardiac recordings. The current paper illustrates mechanistic variations of AF caused by different underlying physiological conditions, and perhaps suggests that our focus should be not so much on AF itself, but the conditions that generate it.

References

1. Winterberg H. Studien über herzflimmern. I. Über die wirkung des N. vagus und accelerans auf das Flimmern des Herzens. *Pflügers Arch* 1907;117:223–256.
2. Scherf D, Terranova R. Mechanism of auricular flutter and fibrillation. *Am J Physiol* 1949;159:137–142. [PubMed: 15391089]
3. Prinzmetal M, Corday E, et al. Mechanism of the auricular arrhythmias. *Circulation* 1950;1:241–245. [PubMed: 15403029]
4. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. *Am Heart J* 1959;58:59–70. [PubMed: 13661062]
5. Moe GK, Rheinboldt WC, Abildskov JA. A Computer Model of Atrial Fibrillation. *Am Heart J* 1964;67:200–220. [PubMed: 14118488]
6. Allesie, MA.; Lammers, WJEP.; Bonke, FIM.; Hollen, J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes, DP.; Jalife, J., editors. *Cardiac Electrophysiology and Arrhythmias*. Orlando, Florida: Grune and Stratton, Inc; 1985. p. 265-275.
7. Jalife J, Berenfeld O, Mansour M. Mother rotors and fibrillatory conduction: a mechanism of atrial fibrillation. *Cardiovasc Res* 2002;54:204–216. [PubMed: 12062327]
8. Allesie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. *Circ Res* 1973;33:54–62. [PubMed: 4765700]
9. Gray RA, Jalife J, Panfilov AV, Baxter WT, Cabo C, Davidenko JM, Pertsov AM. Mechanisms of cardiac fibrillation. *Science* 1995;270:1222–1223. author reply 1224–1225. [PubMed: 7502055]
10. Berenfeld O, Zaitsev AV, Mironov SF, Pertsov AM, Jalife J. Frequency-dependent breakdown of wave propagation into fibrillatory conduction across the pectinate muscle network in the isolated sheep right atrium. *Circ Res* 2002;90:1173–1180. [PubMed: 12065320]
11. Skanes AC, Mandapati R, Berenfeld O, Davidenko JM, Jalife J. Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart. *Circulation* 1998;98:1236–1248. [PubMed: 9743516]
12. Mandapati R, Skanes A, Chen J, Berenfeld O, Jalife J. Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. *Circulation* 2000;101:194–199. [PubMed: 10637208]
13. Mansour M, Mandapati R, Berenfeld O, Chen J, Samie FH, Jalife J. Left-to-right gradient of atrial frequencies during acute atrial fibrillation in the isolated sheep heart. *Circulation* 2001;103:2631–2636. [PubMed: 11382735]
14. Arora R, Verheule S, Scott L, et al. E. Arrhythmogenic substrate of the pulmonary veins assessed by high-resolution optical mapping. *Circulation* 2003;107:1816–1821. [PubMed: 12665495]
15. Chou CC, Nihei M, Zhou S, et al. Intracellular calcium dynamics and anisotropic reentry in isolated canine pulmonary veins and left atrium. *Circulation* 2005;111:2889–2897. [PubMed: 15927973]
16. Spach MS, Miller WT 3rd, Dolber PC, Kootsey JM, Sommer JR, Mosher CE Jr. The functional role of structural complexities in the propagation of depolarization in the atrium of the dog. *Cardiac conduction disturbances due to discontinuities of effective axial resistivity*. *Circ Res* 1982;50:175–191. [PubMed: 7055853]
17. Valderrabano M, Lee MH, Ohara T, et al. Dynamics of intramural and transmural reentry during ventricular fibrillation in isolated swine ventricles. *Circ Res* 2001;88:839–848. [PubMed: 11325877]
18. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;339:659–666. [PubMed: 9725923]

19. Burashnikov A, Antzelevitch C. Reinduction of atrial fibrillation immediately after termination of the arrhythmia is mediated by late phase 3 early afterdepolarization-induced triggered activity. *Circulation* 2003;107:2355–2360. [PubMed: 12695296]
20. Patterson E, Lazzara R, Szabo B, et al. Sodium-calcium exchange initiated by the Ca^{2+} transient: an arrhythmia trigger within pulmonary veins. *J Am Coll Cardiol* 2006;47:1196–1206. [PubMed: 16545652]
21. Atienza F, Almendral J, Moreno J, et al. Activation of inward rectifier potassium channels accelerates atrial fibrillation in humans: evidence for a reentrant mechanism. *Circulation* 2006;114:2434–2442. [PubMed: 17101853]
22. Yamazaki M, Vaquero LM, Hou, et al. Mechanisms of Stretch Induced Atrial Fibrillation in the Presence and the Absence of Adreno-Cholinergic Stimulation: Interplay between Rotors and Focal Discharges. *Heart Rhythm*. 2009 In press.
23. Chou CC, Nguyen BL, Tan AY, et al. Intracellular calcium dynamics and acetylcholine-induced triggered activity in the pulmonary veins of dogs with pacing-induced heart failure. *Heart Rhythm* 2008;5:1170–1177. [PubMed: 18554987]
24. Warren M, Zaitsev AV. Evidence against the role of intracellular calcium dynamics in ventricular fibrillation. *Circ Res* 2008;102:e103. [PubMed: 18467634]