Reentry and atrial fibrillation

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The mechanisms of human atrial fibrillation (AF) are poorly understood. Experimental studies have demonstrated that cholinergic AF in the sheep heart is maintained by high-frequency reentrant sources (drivers) that result in a consistent left-to-right frequency gradient. More recently, clinical studies have confirmed the existence of a hierarchical organization in the rate of activation of different regions in the atria of patients with paroxysmal and chronic AF. Although maximal dominant-frequency sites were found to play a crucial role in the maintenance of AF in some patients, whether AF drivers in humans are focal or reentrant and whether changes in driver activity alter spatial frequency gradients are unclear. To test the hypothesis that localized functional reentry maintains AF in humans, we determined the effects of adenosine infusion on local dominant frequency at different sites of both atria. In patients with paroxysmal AF, adenosine infusion increases local dominant frequencies, particularly at the pulmonary vein–left atrial junction region, amplifying a left-to-right frequency gradient. In patients with chronic AF, dominant frequency is significantly higher than in patients with paroxysmal AF in all atrial regions surveyed, with the highest adenosine increase of frequencies outside the pulmonary vein region. Adenosine-induced driver acceleration is strongly suggestive of a reentrant mechanism in both groups of AF patients.

KEYWORDS Adenosine; Inward-rectifying potassium channels; Rotors; Wavebreak; Pulmonary veins-left atrial junction

Atrial fibrillation (AF) is the most common arrhythmia seen in clinical practice.[1] It accounts for approximately one third of hospitalizations for cardiac rhythm disturbances and is associated with an increased long-term risk of stroke, heart failure, and all-cause mortality.[1] AF prevalence continues to increase due to a combination of factors, which include aging of the population, the rising prevalence of chronic heart disease, and the recent increase in survival rates from other cardiovascular diseases.[1,2] As a consequence, AF represents an extremely expensive public health problem, with an estimated overall cost of approximately $15.7 billion in the United States alone.[3] Unfortunately, medications aimed at suppressing AF and maintaining sinus rhythm (rhythm control) or at controlling ventricular rate (rate control) usually are not effective and may cause serious adverse effects.[4] The limitations of pharmacologic treatment have fueled the development of new interventional strategies, including radiofrequency (RF) ablation. Current techniques of RF ablation can achieve a 60%–80% improvement in highly selected patients with medically refractory AF. However, the procedure is not without risk; it is long-lasting, and recurrence rates still are high. Moreover, the results in patients with chronic AF are far from optimal, requiring the creation of extensive atrial lesions and use of repeated procedures to attain a success rate of 50%–60% without antiarrhythmic drugs.[1] Currently, the application of RF is primarily guided by the anatomy and is secondarily assisted by local electrical activity, although considerable variance exists among laboratories with regard to both the ablation procedure methodology and the results.

Arguably, the main explanation for our current disappointing ability to control AF is an incomplete understanding of the mechanism(s) underlying its maintenance, despite many years of research and speculation.[5] Over the past 50 years, the multiple wavelet hypothesis has been the dominant mechanistic model of AF.[6–8] The hypothesis, first postulated by Moe et al,[7] states that AF is the result of randomly propagating multiple electrical wavelets that interact in very complex ways, with local excitation limited by the heterogeneous distribution of refractory periods throughout the atria.[6,7] This concept was challenged by the observation in patients made by Haissaguerre et al[8] that a rapidly firing excitation source located inside or close to one of the pulmonary veins (PVs) could also be responsible for initiating, and in some cases maintaining the arrhythmia, particularly in patients presenting with paroxysmal AF.[8] However, whether the electrophysiologic mechanisms underlying such rapid discharges is enhanced automaticity, triggered activity, or even microreentry is unknown.[9] Optical mapping studies in isolated sheep hearts have suggested that at least some cases of AF can be maintained by high-frequency reentrant sources (rotors), usually located in the posterior left atrium (LA), which result in spatially distrib-

uted frequency gradients.[9–13] According to the so-called *rotor hypothesis,* rapidly succeeding wavefronts emanating from an ectopic focus in a PV may break, when conditions of heterogeneity are appropriate, and initiate two counter-rotating vortices (i.e., rotors).[9] Eventually, only one of the rotors survives and becomes the high frequency engine that maintains AF through fibrillatory conduction to the remainder of the atria.[6,9] Thus, focal triggers at or near a PV may initiate rotors as a consequence of abnormal impulse conduction and wavebreak. A rotor that anchors anywhere in the atria, and generates spiraling waves at an exceedingly high frequency, may become the dominant source that maintains AF.[9–13]

Posterior LA–PV junction and the substrate for AF maintenance

Several studies performed in humans analyzed the electrophysiologic characteristics of the PVs and the LA junction and other atrial regions and demonstrated distinctive electrophysiologic properties in the PVs of patients with AF.[14–21] These studies showed the following. (1) Distal PVs have shorter refractory periods than do the proximal PVs, the atrial junction, and the LA appendage.[15,20,21] (2) The likelihood of AF induction is higher with distal PV extrastimulation.[21] (3) Directional conduction delay is present within the PV, with more frequent and greater likelihood of intermittent conduction block patterns to the LA,[20,21] most likely due to tissue expansion and source to sink mismatch. (4) The PVs possess both anisotropic conduction and repolarization heterogeneity, with evidence of reentry in response to extrastimulus testing.[17,21] Thus, the significant differences in the electrophysiologic properties in the PVs and PV–LA junction provide a fertile substrate for reentry within or around the PVs. However, these data do not provide direct evidence that reentry is the mechanism that maintains AF.

The thoracic veins and especially the PVs contain discrete myocytes fascicles that are electrically connected to the atria. In some cases, such fascicles spontaneously generate electrical impulses.[8,14,15] Several electrophysiologic mechanisms may explain the origin of such activity: abnormal impulse formation (automaticity), abnormal focal activity (afterdepolarizations), or abnormal impulse propagation (reentry). Experiments have demonstrated a high incidence of spontaneous rhythms, enhanced automaticity, and occurrence of early and delayed afterdepolarizations in the PVs, particularly in response to atrial distension, rapid atrial pacing, or congestive heart failure.[14] Moreover, the PVs and the posterior LA wall provide the electrophysiologic milieu capable of sustaining reentry.[15–17,21] The specific action potential configuration of the PV cells, with slower upstroke phase 0 and slower duration, leads to a shorter refractory period and a slower conduction velocity.[19] The architecture of the PVs and the LA junction provide preferential zones for reentry. The complex geometric arrangement of cardiac fibers around the veins with changing myocardial fiber orientation and the poorly coupled cardiac tissue overlying vascular smooth muscle seem to be an ideal substrate for unidirectional conduction block and for initiation of wavebreaks and sustained reentry.[16] Optical mapping studies in animal hearts have consistently demonstrated that AF is maintained by functional microreentry, in most cases localized to the posterior LA wall and the PV–LA junction.[9–13,18] Ionic differences in the channel distribution between the atria, responsible for the shorter action potential duration and effective refractory period in the LA, also favor reentry and may help to explain the preferential anchoring of rotors to the posterior wall and PV–LA junction.[19]

Role of the PVs and posterior wall in AF maintenance

The vast majority of atrial premature beats that initiate frequent paroxysms of AF originate in the PVs.[8] However, with the exception of some cases of rapid focal discharges with distal-to-proximal activation of the PV representing the true focally driven AF, the main role of these extrasystolic beats and rapid rhythms is triggering AF.[20] The results of PV isolation performed during ongoing AF have provided novel insights that underscore the important role of not only the PVs but also the LA junction. The focal ablation approach to eliminate AF triggers that initially was used is effective in less than 50% of patients because other nontargeted locations/veins may act as triggers.[22] This led to the development of the segmental ostial ablation technique, which aimed to electrically isolate the PVs.[23] After sequential PV isolation, progressive prolongation of the AF cycle length was obtained, culminating in AF termination in a significant proportion of patients with paroxysmal AF.[23] These results provided conclusive evidence for the direct participation of PV activity in the maintenance of AF. However, a randomized study showed that a more extensive ablation, which included the LA–PV junction area and the posterior wall, was more effective in preventing recurrences than was pure electrical PV isolation.[24] Several findings support the critical role of the posterior wall in AF maintenance. First, despite the high prevalence of dissociated spontaneous rhythms following PV electrical isolation, sustained PV tachycardias spontaneously occur or can be induced in only 2%–6% of patients. Thus, there seems to be a dynamic interplay between the LA and PVs during AF, with PV tachycardia depending on input from the LA.[25] Second, AF termination during PV isolation frequently occurs prior to complete electrical isolation of the vein is obtained. Elimination of the substrate needed for a reentrant circuit to be sustained is the most likely explanation for this finding. Finally, ablation of sites of short cycle length activity in the posterior LA leads to termination of the arrhythmia both in experiments and in humans.[26,27] Thus, these data point to reentry involving both the PVs and the LA junction as the most likely mechanism sustaining AF in some cases of paroxysmal AF, but more conclusive evidence is needed.

Frequency mapping, adenosine, and sources that maintain AF

Time-domain analysis of atrial activation is extremely difficult to interpret, but frequency mapping allows a simpler analysis of AF activity and enables localization of sites of rapid and periodic activity that likely are closely linked to sources that maintain AF. Experimental studies using frequency-domain analysis have demonstrated that cholinergic AF is maintained by high-frequency reentrant sources (drivers), which results in spatially distributed frequency gradients throughout the atria.[9–13,18] More recently, clinical studies have confirmed the existence of a hierarchical organization in the rate of activation of different regions in the atria of patients with paroxysmal and chronic AF.[28–31] Moreover, retrospective analysis demonstrated that ablation of the highest frequency sites coincided with slowing and termination of the arrhythmia in a significant proportion of patients with paroxysmal AF.[30] Although these maximal dominant-frequency sites were found to play a crucial role in the maintenance of AF in some patients,[30] whether AF drivers in humans are focal or reentrant remains was unclear. To test the hypothesis that localized functional reentry maintains AF in humans, we determined the effects of adenosine infusion on local activation frequency at different sites of the fibrillating atria.[31] By increasing potassium conductance through activation of specific inward rectifier channels, adenosine shortens action potential duration and refractoriness and inhibits spontaneous pacemaker discharge as well as early and delayed depolarizations.[32,33] As expected from a reentrant mechanism of AF maintenance, adenosine infusion increased frequency primarily at sites that activate at the highest rate at baseline. In patients with paroxysmal AF, adenosine infusion increased local dominant frequency, particularly at the PV–LA region, amplifying a left-to-right frequency gradient. In patients with chronic AF, dominant frequencies were significantly higher than in patients with paroxysmal AF in all atrial regions surveyed, with the highest adenosine increase of frequencies outside the PV region. Thus, adenosine-induced acceleration of activation frequency points toward reentry as the mechanism of AF maintenance in the patients surveyed and all but rules out an automatic or triggered mechanism.[31–33] The results support the idea that AF in humans is maintained by high-frequency reentrant sources that can be accelerated by intravenous administration of adenosine.[31]

Why reentry and not early afterdepolarizations?

At first glance, use of adenosine to rule out automatic or triggered mechanisms seems inconsistent with recent results showing that calcium overload conditions present after termination of vagally mediated AF contribute to the development of late phase 3 early afterdepolarization (EAD)-induced triggered activity.[34] Similarly, affirmation that the sustained AF acceleration observed upon intravenous administration of adenosine strongly supports the idea that AF in humans is maintained by high-frequency reentrant sources seems to be in conflict with a report showing that, in the presence of acetylcholine, tachycardia pause triggers rapid firing within the PV sleeve through an EAD mechanism.[35] The proposed explanation for EAD generation lies in the fact that rapid activation during AF or tachycardia leads to intracellular calcium overload mediated through sodium accumulation and Na/Ca exchange.[34,35] If AF were to suddenly stop and a long pause ensued, the already increased sarcoplasmic reticulum calcium loading would result in greatly enhanced contractility upon excitation in subsequent beats, as well as increased calcium extrusion through the exchanger in the reverse mode.[34] Under these conditions, it would be expected that, in the presence of acetylcholine-induced shortening of the action potential, the electrogenic inward current generated by the exchanger would result in EADs and triggered activity. Yet it is important to note that in the two studies cited, an absolute requirement for the generation of triggered activity was the presence of a long pause after termination of rapid excitation,[34,35] which is a condition that is never present in the adenosine test for a reentrant mechanism in human AF, as proposed recently by Atienza et al.[31]

Clinical implications of adenosine acceleration of atrial activation frequency

Because ablation at the highest-frequency sites is associated with paroxysmal AF termination and because adenosine is expected to shorten the refractory period and accelerate reentry, we used adenosine infusion during ongoing AF to highlight sites driving paroxysmal AF that could be targeted for ablation. Our study shows that a baseline dominance of the LA is further enhanced by the adenosine infusion and can potentially point to the location of the source.[31] Our preliminary results using high-density, real-time, dominant-frequency mapping confirm the ability of adenosine to highlight sites driving paroxysmal AF that could be targeted for ablation. In fact, adenosine-guided ablation of high-frequency drivers resulted in AF termination in a significant proportion of patients with paroxysmal AF. Thus, identification of reentrant drivers by adenosine infusion may be a useful strategy for guiding AF ablation.[31]

Conclusion

In contrast to other cardiac arrhythmias for which safe and highly effective nonpharmacologic therapies have been developed, AF continues to be a challenge to treatment. The high efficacy of ablation in treating most arrhythmias has been based upon a fundamental understanding of the electrophysiologic mechanisms and anatomic substrates underlying these arrhythmias.[5] However, in the case of AF, the exact electrophysiologic mechanism and anatomic substrate remain elusive, despite an extensive body of animal and human research. The anatomic ablation approach currently used in most electrophysiology laboratories has evolved because of the failure to identify the substrate of AF maintenance. A better understanding of the fundamental mech-

anisms underlying AF probably will lead to safer and more effective mechanism-based therapeutic strategies (either pharmacologic or invasive). The approach described here, which is based on adenosine-assisted identification of AF-maintaining sources, is a promising step in the right direction.

References

1. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). Circulation 2006;114:e257–e354.

2. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). Am J Cardiol 1994;74:236–241.

3. Le Heuzey JY, Paziaud O, Piot O, et al. Cost of care distribution in atrial fibrillation patients: the COCAF study. Am Heart J 2004;147:121–126.

4. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825–1833.

5. Sung RJ, Lauer MR. Atrial fibrillation: can we cure it if we can't explain it? J Cardiovasc Electrophysiol 2005;16:505–507.

6. Atienza F. The atrial fibrillation substrate: pulmonary veins, posterior wall or both. Rev Esp Cardiol 2006;59:643–646.

7. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharges. Am Heart J 1959;58:59–70.

8. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659–666.

9. Jalife J, Berenfeld O, Mansour M. Mother rotors and fibrillatory conduction: a mechanism of atrial fibrillation. Cardiovasc Res 2002;54:204–216.

10. 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.

11. Mandapati R, Skanes AC, 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.

12. Berenfeld O, Mandapati R, Dixit S, Skanes AC, Chen J, Mansour M, Jalife J. Spatially distributed dominant excitation frequencies reveal hidden organization in atrial fibrillation in the Langendorff-perfused sheep heart. J Cardiovasc Electrophysiol 2000;11:869–879.

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.

14. Chen YJ, Chen SA, Chang MS, Linb CI. Arrhythmogenic activity of cardiac muscle in pulmonary veins of the dog: implication for the genesis of atrial fibrillation. Cardiovasc Res 2000;48:265–273.

15. Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, Yu WC, Hsu TL, Ding YA, Chang MS. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins. Electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. Circulation 1999;100:1879–1886.

16. Hocini M, Ho SY, Kawara T, Linnenbank AC, Potse M, Shah D, Jais P, Janse MJ, Haissaguerre M, De Bakker JM. Electrical conduction in canine pulmonary veins: electrophysiological and anatomic correlation. Circulation 2002;105:2442–2448.

17. Arora R, Verheule S, Scott L, Navarrete A, Katari V, Wilson E, Vaz D, Olgin JE. Arrhythmogenic substrate of the pulmonary veins assessed by high-resolution optical mapping. Circulation 2003;107:1816–1821.

18. Kalifa J, Tanaka K, Zaitsev AV, Warren M, Vaidyanathan R, Auerbach D, Pandit S, Vikstrom KL, Ploutz-Snyder R, Talkachou A, Atienza F, Guiraudon G, Jalife J, Berenfeld O. 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;113:626–633.

19. Li D, Zhang L, Kneller J, Nattel J. Potential ionic mechanism for repolarization differences between canine right and left atrium. Circ Res 2001;88:1168–1175.

20. Jais P, Haïssaguerre M, Shah DC, Chouairi S, Gencel L, Hocini M, Clementy J. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. Circulation 1997;95:572–576.

21. Kumagai K, Ogama M, Noguchi H, Yasuda T, Nakashima H, Saku K. Electrophysiologic properties of pulmonary veins assessed using a multielectrode basket catheter. J Am Coll Cardiol 2004;43:2281–2289.

22. Marchlinski FE, Callans D, Dixit S, Gerstenfeld EP, Rho R, Ren JF, Zado E. Efficacy and safety of targeted focal ablation versus PV isolation assisted by magnetic electroanatomic mapping. J Cardiovasc Electrophysiol 2003;14:358–365.

23. Haïssaguerre M, Sanders P, Hocini M, Hsu LF, Shah DC, Scavée C, Takahashi Y, Rotter M, Pasquie JL, Garrigue S, Clementy J, Jais P. Changes in atrial fibrillation cycle length and inducibility during catheter ablation and their relation to outcome. Circulation 2004;109:3007–3013.

24. Oral H, Scharf C, Chugh A, Hall B, Cheung P, Good E, Veerareddy S, Pelosi F Jr, Morady F. Catheter ablation for paroxysmal atrial fibrillation: segmental pulmonary vein ostial ablation versus left atrial ablation. Circulation 2003;108:2355–2360.

25. Oral H, Ozaydin M, Tada H, Chugh A, Scharf C, Hassan S, Lai S, Greenstein R, Pelosi F Jr, Knight BP, Strickberger SA, Morady F. Mechanistic significance of intermittent pulmonary vein tachycardia in patients with atrial fibrillation. J Cardiovasc Electrophysiol 2002;13:645–650.

26. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing: structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation 1995;91:1588–1595.

27. Todd DM, Skanes AC, Guiraudon G, Guiraudon C, Krahn AD, Yee R, Klein GJ. Role of the posterior left atrium and pulmonary veins in human lone atrial fibrillation: electrophysiological and pathological data from patients undergoing atrial fibrillation surgery. Circulation 2003;108:3108–3114.

28. Lazar S, Dixit S, Marchlinski FE, Callans DJ, Gerstenfeld EP. Presence of Left-to-Right atrial frequency gradient in paroxysmal but not persistent atrial fibrillation in humans. Circulation 2004;110:3181–3186.

29. Sahadevan J, Ryu K, Peltz L, Khrestian CM, Stewart RW, Markowitz AH, Waldo AL. Epicardial mapping of chronic atrial fibrillation in patients. Circulation 2004;110:3293–3299.

30. Sanders P, Berenfeld O, Hocini M, Jaïs P, Vaidyanathan R, Hsu LF, Garrigue S, Takahashi Y, Rotter M, Sacher F, Scavée C, Ploutz-Snyder R, Jalife J, Haïssaguerre M. Spectral analysis identifies sites of high frequency activity maintaining atrial fibrillation in humans. Circulation 2005;112:789–797.

31. Atienza F, Almendral J, Moreno J, Vaidyanathan R, Talkachou A, Kalifa J, Arenal A, Villacastin JP, Torrecilla EG, Sanchez A, Ploutz-Snyder R, Jalife J, Berenfeld O. Activation of inward rectifier potassium channels accelerates atrial fibrillation in humans: evidence for a reentrant mechanism. Circulation 2006;114:2434–2442.

32. Kabell G, Buchanan LV, Gibson JK, Belardinelli L. Effects of adenosine on atrial refractoriness and arrhythmias. Cardiovasc Res 1994;28:1385–1389.

33. Belardinelli L, Shryock JC, Song Y, Wang D, Srinivas M. Ionic basis of the electrophysiological actions of adenosine on cardiomyocytes. FASEB J 1995;9:359–365.

34. 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.

35. Patterson E, Lazzara R, Szabo B, Liu H, Tang D, Li YH, Scherlag BJ, Po SS. Sodium-calcium exchange initiated by the Ca^{2+} transient: an arrhythmia trigger within pulmonary veins. J Am Coll Cardiol 2006;47:1196–1206.