What Exactly Is Atrial Fibrillation and How Do We Diagnose it?

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The article "Differentiating Between Atrial Flutter and Atrial Fibrillation Using Right Atrial Bipolar Endocardial Signals" published by Isa et al[1] might pose a surprising question for many readers. Is it really that difficult to distinguish between atrial flutter and atrial fibrillation, or is it that electrophysiologists like to complicate the issue?

Strictly speaking, the approach taken in the study could be criticized on the basis of the bias inherent in the selection of the patients, since if patients were selected according to presentation of atrial fibrillation with an "organized electrical pattern" it is not surprising that the variation in the intervals between the electrograms was not indicative of atrial fibrillation in that group. The study also lacks quantification of the incidence of such an organized pattern of atrial fibrillation in the right atrium to allow assessment of the general applicability of the values of sensitivity and specificity calculated based on the study group. However, aside from methodologic questions, which can always be raised, the study addresses an underlying problem that is of major theoretical and practical interest and that can be summarized in the question expressed in the title of this editorial: what exactly is atrial fibrillation and how do we diagnose it?

Surprising as it may seem, there is no simple and accurate electrophysiologic definition of atrial fibrillation. For instance, the definition offered in the August 2006 edition of the American Heart Association/American College of Cardiology/European Society of Cardiology guidelines[2] is limited to a description of the pattern of irregular atrial waveforms in the electrocardiogram (ECG), with a reference to the book published by Bellet[3] in 1971. Atrial fibrillation is also defined in this way in many studies from the electrophysiology literature. It is true that at least the latest guidelines draw attention to the fact that an irregular ventricular rate is not diagnostic of atrial fibrillation and that atrial flutter can generate this irregularity as a result of irregular atrioventricular conduction patterns. But, in continuing to focus on the ECG pattern as the only diagnostic criterion of atrial
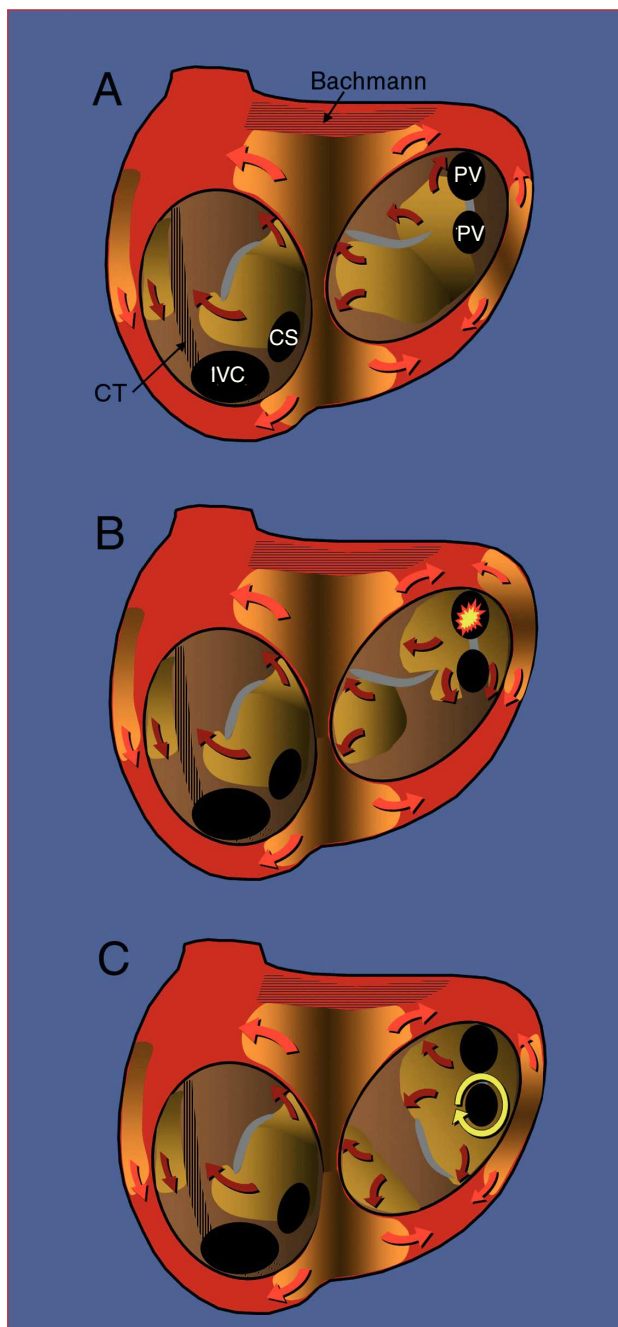
fibrillation, have we not made any progress at all in 35 years? And to what extent do we understand the underlying causes of this irregular ECG pattern?

Atrial fibrillation has always been considered a reflection of the fragmentation of atrial activation into multiple wavelets of varying width and spread. In the 1950s, it was suggested that there was a focal origin for this activation during atrial fibrillation, implying that the fragmentation of activation would be due to the inability of the atrial myocardium to conduct regularly at very high frequencies[4] (Figure 1). Impulse conduction would encounter refractory and anisotropic regions that would produce functional blocks with a variable spatial distribution, leading to fragmentation of activation into multiple fronts or waves. This is known as fibrillatory conduction. This hypothesis of the focal origin of atrial fibrillation was soon sidelined by the hypothesis of sustained reentry of multiple wavelets proposed by Moe et al[5] and confirmed in 1985 by Allessie et al[6] using advanced atrial endocardial mapping. According to this hypothesis, atrial fibrillation is a chaotic reentry (complexly determined) with multiple simultaneously active wavefronts (Figure 1) that can be sustained indefinitely as long as the preparation or the fibrillating organ is sufficiently large, the refractory period is short and variable (dispersion of refractoriness), and the conduction velocity is slow. Allessie et al found that the coexistence of at least 6 activation fronts was necessary in order for atrial fibrillation to be sustained indefinitely. During mapping of atrial fibrillation, they occasionally observed new activation fronts that indicated the presence of foci,[6,7] but these apparent anomalies were explained as the result of 3-dimensional reentry.[8]

Studies of atrial activation during atrial fibrillation in humans have revealed a notable complexity, making it difficult to arrive at a simple definition using endocardial recordings. Already in 1978, Wells et al[9] published a study in patients with atrial fibrillation following heart surgery in which isolated atrial electrograms were recorded over periods of up to 15 minutes via electrodes sutured in an unspecified region of the "atrial epicardium." The intervals between the atrial potentials ranged from highly organized, with well-defined isoelectric intervals between the complexes (1/3 of all cases), to completely disorganized recordings in which it was impossible to define individual complexes (continuous fragmented activity). However, in all cases, analysis of a large number of complexes over

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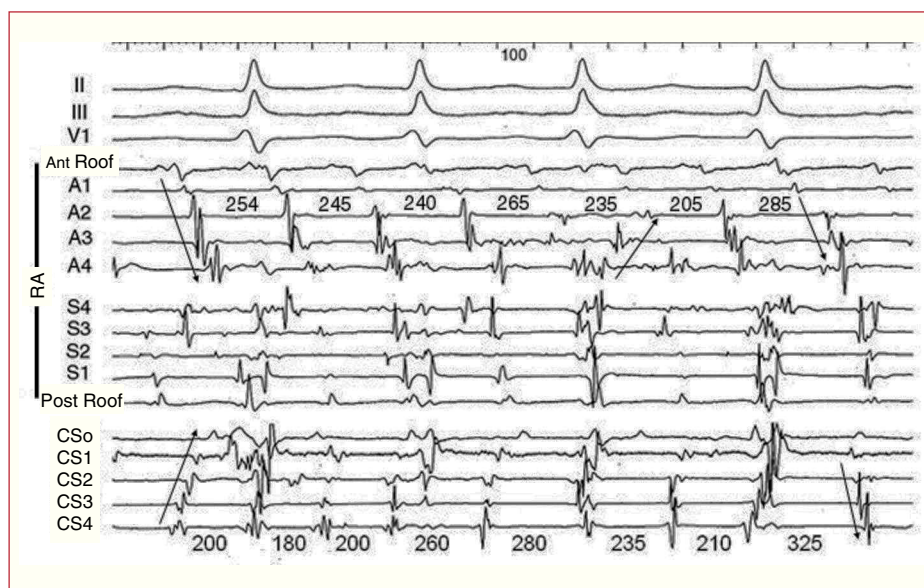Ctra. de Toledo, km. 12,5. 28905 Getafe. Madrid. España.

Figure 1. Schematic representation of the 3 mechanisms described for atrial fibrillation. The endocardial surface is shown through the mitral and tricuspid valves, revealing the openings of the inferior vena cava (IVC), the coronary sinus (CS), and the left pulmonary veins (PV). The surfaces colored in orange represent the activation fronts and the arrows indicate the direction in which the wavefront is propagated, with a lighter leading edge and a darker refractory wake. The grey areas represent lines of functional block. The hatched regions represent anisotropic fiber bundles: the crista terminalis (CT) in the right atrium and Bachmann's bundle in the left. A) Activation through multiple wavelets, with no localized point of origin, maintained by the dynamics of the activation fronts themselves. B) Focal mechanism in which irregular (fibrillatory) activation has its origin in a high frequency automatic focus (yellow star) in a pulmonary vein. C) Rotor anchored in the region of the left inferior pulmonary vein that drives activation and also produces fibrillatory conduction.

time revealed variation in the intervals between individual complexes of up to 100 ms with changes from highly organized electrograms to a disorganized pattern and vice versa. This contrasted with the exquisite organization and regularity of the recordings obtained by the same group during episodes of atrial flutter in the same clinical context.[10] Similar observations were made by Konings et al[11] using high-density activation mapping of the anterior right atrium performed during atrial fibrillation induced during heart surgery. Those authors observed relatively uniform activation at this site, with 1 or 2 activation fronts in 72% of the patients, although there was a variation in the interval between cycles of greater than 40 ms. The presence of multiple activation fronts (waves) could only be demonstrated in 28% of cases, while the majority of the patterns indicated passive activation that was more or less irregular and originated in some point outside the atrium. One limitation of that study was the short analysis time of 12 seconds (actually very similar to that used in the study of Iza et al[1]). A longer period of recording would probably increase the possibility of detecting greater variation in the local intervals.[9] The organization of activation in the anterior right ventricle is favored by the conduction barrier represented by the crista terminalis[12-14] and the openings of the vena cava and tricuspid valve, meaning that this region is probably quite unrepresentative of the general mechanism of atrial fibrillation. The organization of electrical activity in the right atrium can be extreme in cases of atrial fibrillation with defective interatrial conduction.[15]
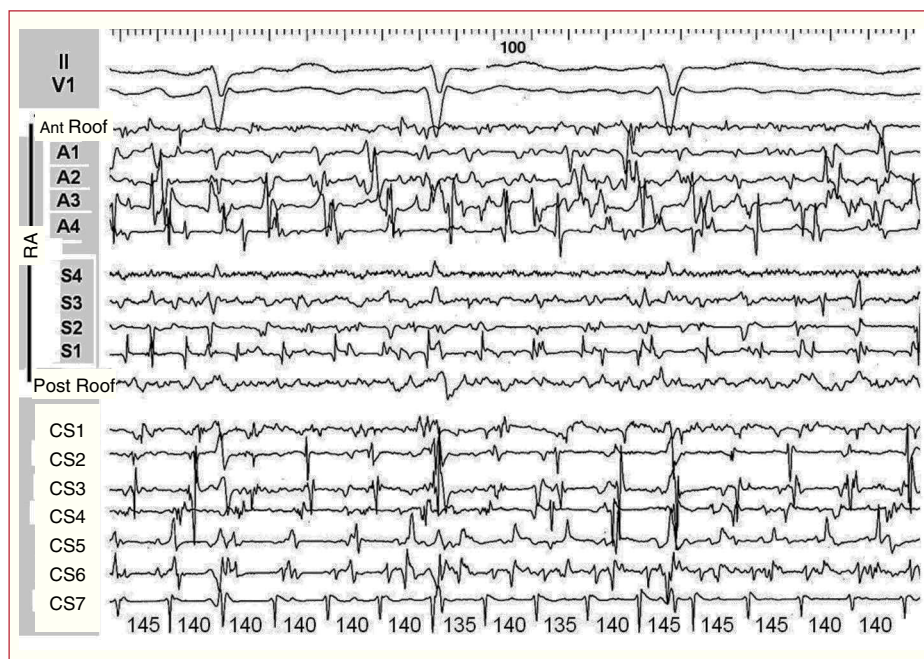
The recent resurgence of the focal hypothesis of atrial fibrillation is now well known through the work of Haïssaguerre et al,[16] which has been confirmed by other authors,[17] demonstrating induction of atrial fibrillation following rapid discharges from the pulmonary veins and, less frequently, from other venous and atrial structures.[18] But this observation is complemented by others related not to the onset but rather to the maintenance of atrial fibrillation. In 1992, Schuessler et al[19] demonstrated in dogs that localized reentry could provoke irregular (fibrillatory) activation of the atria that was indistinguishable from atrial fibrillation unless very detailed mapping of the origin of the activation was performed. Later, the group led by Jalife demonstrated using optical mapping in sheep that a stable rotor could sustain atrial fibrillation[20] (Figure 1). These rotors were mainly located in the left atrium, while the right atrium tended to be passively and irregularly activated through the appearance of lines or regions in which high frequency activation was blocked. Local ablation of the anchor point of the rotor can prevent induction of atrial fibrillation in some experimental models[21]; however, other models of functional reentry in the atrium have confirmed that rotors can migrate from one zone to another in both atria,[22] making the proposed "focal" ablation of these anchor points highly debatable.

Returning to the diagnosis of atrial fibrillation, we find that endocardial recordings in patients with irregular

Figure 2. Electrocardiogram (ECG) and endocardial recordings in atrial fibrillation – 1. Moving from top to bottom, the figure shows leads II, III, and V_1, which record low voltage disorganized atrial waves, followed by bipolar recordings from the right atrium (RA) that cover the anterior wall from the roof (Ant Roof) to the most inferior portion (A4) centimeter by centimeter, and the septal wall from the most inferior portion (S4) to the most superior (Post Roof), centimeter by centimeter. The lower part of the figure shows the recordings in the coronary sinus from the ostium (CSo) to the distal coronary sinus (CS4), centimeter by centimeter. The numbers indicate the intervals between the complexes. The arrows indicate changes in the direction of activation. It can be seen that although there are wide isoelectric intervals between the complexes, the intervals and sequences change continually.

Figure 3. Electrocardiogram (ECG) and endocardial recordings in atrial fibrillation – 2. In the upper part of the figure, leads II and V_1 show disorganized atrial activity. All of the recordings from the right atrium (RA) and coronary sinus (CS) display complete disorganization, with multiple deflections and a nonexistent baseline at numerous points. The only exception is in the most distal CS (CS7) recordings, which display perfectly regular complexes at very high frequency (140-ms cycle, equivalent to 430/min), consistent with regular, highly localized reentrant activity (rotor) in the left atrium as a driver of activation.

atrial activation and a changeable configuration in the ECG can exhibit highly variable patterns. It is easy to record electrograms from multiple points in the right atrium with multielectrode catheters, but the activity of the left atrium is usually only recorded from the coronary sinus. In some cases relatively organized activity is recorded in both the right atrium and the coronary sinus, but with continuously changing sequences (Figure 2); however, in other cases with highly fragmented activity throughout the right atrium and in the recordings from the coronary sinus, a highly regular and very rapid activity can be recorded in a highly localized point, perhaps indicating the presence of a microreentrant circuit (rotor) with fibrillatory conduction to both atria (Figure 3).

Antiarrhythmia drugs would tend to increase the organization of the atrial fibrillation, either by prolonging the refractory period or by widening the radius of the pivot point for the reentrant wavefront,[23] with a reduction in the number of small rotors. The drugs can also increase the block at the crista terminals,[24] an effect that would accentuate even further the organization of activation. In fact, the appearance of flutter in patients with atrial

fibrillation treated with antiarrhythmic drugs is no more than a consequence of this organization of reentry.

What can we use then to establish a differential diagnosis between atrial fibrillation and flutter, to allow us to obtain an automatic diagnosis? When using individual electrograms, the answer lies in the recording time. If sufficiently long recordings are used, lasting at least 30 seconds, it is very rare not to observe a variation of ≥50 ms between the atrial fibrillation potentials, while in atrial flutter the reverse is true. The use of a long detection period is perfectly possible in this situation, since these arrhythmias are rarely life threatening; in addition, it would avoid unnecessary and potentially arrhythmogenic interventions in episodes of self-limiting tachycardia. Sufficient time for recording and examination is also central to differential diagnosis of atrial flutter and atrial fibrillation, where transitions between one arrhythmia and the other are also possible and the use of various recording points over an extended period will sooner or later reveal the irregularity and changes in sequence associated with atrial fibrillation. Similarly, detailed analysis of the pattern of atrial waveforms in the ECG allows recognition of their irregularity and changing morphology during atrial fibrillation in cases where their relative organization suggests a possible diagnosis of atrial flutter.

Finally, how do we refer to a rhythm that generates organized activity in one atrium and disorganized activity in the other? Should we develop terms like "localized flutter with fibrillatory conduction" or "atrial fibrillation with a localized source?" There are no answers to these questions, and the analysis of each case will have to carry with it a descriptive definition of the mechanism observed. If fibrillatory conduction is an indicator of diffuse defects in atrial conduction, the distinction between this and multiple reentry would be of little practical use, because both would indicate profound electrophysiologic dysfunction. For the time being, only the perfect organization of activation in both atria that characterizes atrial flutter[25] opens the way for treatment by cardioversion using programmed pacing and/or curative treatment by catheter ablation of an isthmus critically located in the circuit.

REFERENCES

1. Isa R, Villacastín J, Moreno J, Pérez-Castellano N, Salinas J, Doblado M, et al. Diferenciación entre aleteo y fibrilación auricular en los electrogramas bipolares de aurícula derecha. Rev Esp Cardiol. 2007;60:104-9.
2. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC: guía de práctica clínica 2006 para el manejo de pacientes con fibrilación auricular. Versión resumida. Rev Esp Cardiol. 2006;59:1329e1-64.
3. Bellet S. Clinical disorders of the heart beat. 3rd ed. Philadelphia: Lea & Febiger; 1971.
4. Scherf D. The atrial arrhythmias. N Engl J Med. 1955;252:928-33.
5. Moe GK, Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. Am Heart J. 1964;67:200-20.
6. Allessie 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. New York: Grune & Stratton; 1985. p. 265-75.
7. Holm M, Johansson R, Brandt J, Lührs C, Olsson SB. Epicardial right atrial free wall mapping in chronic atrial afibrillation. Documentation of repetitive activation with a focal spread: a hitherto unrecognised phenomenon in man. Eur Heart J. 1997;18:290-310.
8. Gray RA, Pertsov AM, Jalife J. Incomplete reentry and epicardial breakthrough patterns during atrial fibrillation in the sheep heart. Circulation. 1996;94:2649-61.
9. Wells JL, Karp RB, Kouchoukus NT, JacLean WAH, James TN, Waldo AL. Characterization of atrial fibrillation in man: studies following open heart surgery. PACE. 1978;1:426-38.
10. Wells JL, MacLean WA, James TN, Waldo AL. Characterization of atrial flutter. Studies in man after open heart surgery using fixed atrial electrodes. Circulation. 1979;60:665-73.
11. Konnings KTS, Kirchhof CJHJ, Smeets JLRM, Wellens HJJ, Penn OC, Allessie MA. High density mapping of electrically induced atrial fibrillation in humans. Circulation. 1994;89:1665-80.
12. Shumacher B, Jung W, Schmidt H, Fischenbeck C, Lewalter T, Hagendorff A, et al. Transverse conduction capabilities of the crista terminalis in patients with atrial flutter and atrial fibrillation. J Am Coll Cardiol. 1999;34:363-73.
13. Arenal A, Almendral J, Alday JM, Villacastin J, Ormaetxe JM, Sande JL, et al. Rate-dependent conduction block of the crista terminalis in patients with typical atrial flutter: influence on evaluation of cavotricuspid isthmus conduction block. Circulation. 1999;99:2771-9.
14. Cosío FG. The right atrium as an anatomic set-up for re-entry: electrophysiology goes back to anatomy. Heart. 2002;88:325-7.
15. Ndrepepa G, Zrenner B, Schreieck J, Karch MR, Shceider MAE, Chomig A, et al. Left atrial fibrillation with regular right atrial activation and a single left-to-right electrical interatrial connection: multisite mapping of dissimilar atrial rhythms. J Cardiovasc Electrophys. 2000;11:587-92.
16. Haïssaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quimiou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339:659-66.
17. Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, Yu W-C, et al. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. Circulation. 1999;100:1879-86.
18. Lin WS, Tai CT, Hsieh MH, Tsai CF, Lin YK, Tsao HM, et al. Catheter ablation of paroxysmal atrial fibrillation initiated by non-pulmonary vein ectopy. Circulation. 2003;107:3176-83.
19. Schuessler RB, Grayson TM, Bromberg BI, Cox JL, JP Boineau. Cholinergically mediated tachyarrhythmias induced by a single extrastimulus in the isolated canine right atrium. Circ Res. 1992;71:1254-67.
20. 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;101:194-9.
21. 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;91:1588-95.
22. Allessie MA, Lammers WJEP, Bonke IM, Hollen J. Intra-atrial reentry as a mechanism for atrial flutter induced by acetylcholine and rapid pacing in the dog. Circulation. 1984;70:123-35.
23. Danse PW, Garratt CJ, Allessie MA. Flecainide widens the excitable gap at pivot points of premature turning wavefronts in rabbit ventricular myocardium. J Cardiovasc Electrophys. 2001;12: 1010-7.
24. Tai CT, Chen SA, Chen YJ, Yu WC, Hsieh MH, Chen CC, et al. Conduction properties of the crista terminalis in patients with typical atrial flutter: basis for a line of block in the reentrant circuit. J Cardiovasc Electrophysiol. 1998;9 :811-9.
25. García Cosío F, Pastor A, Núñez A, Magalhaes AP, Awamleh P. Flúter auricular: perspectiva clínica actual. Rev Esp Cardiol. 2006;59:816-31.