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Editorial

The fibrillating atrial myocardium. What can the detection of wave breaks tell us?

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See article by Chen et al. [14] (pages 220–232) in this issue.

Ventricular and atrial fibrillation have fascinated clinical cardiologists and cardiac scientists since the beginning of the last century [1,2]. They are important determinants of cardiac mortality and morbidity, and their biophysical mechanisms share close similarities with spatio-temporal instabilities occurring in other excitable media, such as chemical and biological non-cardiac excitation–diffusion systems [3,4].

Normal cardiac electrical excitation requires propagation from a pacemaker site and extinguishes after recovery to the resting state to be reexcited only by a new pacemaker pulse. However, even the normal myocardium fibrillates relatively easily if electrically stimulated by an appropriate protocol. In diseased states, tachycardia and fibrillation may arise from a local site hosting a pathological substrate (e.g. regional ischemia) and/or be perpetuated by a more general change in the electrophysiological properties of the tissue (e.g. general shortening of the refractory period). The observation in the experimental laboratory of the sudden transition of a regularly beating heart to fibrillatory activity of cardiac muscle had already stimulated important experiments early last century. Another series of key experiments by Dr. Gordon Moe and his collaborators started in 1959 [5]. By selecting the appropriate tools, these investigators could distinguish between two types of experimentally induced atrial fibrillation (AF). In a first case, local application of aconitine [6] would produce a type of AF that terminated upon mechanical isolation of the source (aconitine deposit) that initiated rapid focal excitation. In the second case, AF was induced by vagal stimulation and created AF, which was self-sustained. In this case, re-entry, requiring a critical mass of tissue for the circulating excitations to persist, was most likely responsible for maintenance of the arrhythmia. In 1964, based on a simulation study, Moe and Abildskov formulated the classical 'multiple-wavelet' hypothesis to explain the mechanisms of self-maintenance [7]. According to this hypothesis circulating excitation waves would break into daughter waves at sites of gradients in refractoriness, while other waves would extinguish by collision with anatomical or functional boundaries (refractory tissue). In such a highly unstable system, the disorder would maintain itself, if the rate of formation of new wave breaks would equal or exceed the rate of wave extinction. By contrast, in AF induced by rapid focal activation, the turbulent rapid activation would lead to multiple local circulating waves with rare or no full re-entries – a state which has been termed *fibrillatory conduction* (see Allessie et al. [8]).

On a first glance, the experimental conditions to produce such extreme forms of AF may seem rather far from the clinical reality. However, it has become increasingly evident over the past years, that (1) human atrial fibrillation occurs in various, diverse forms, and that (2) some of these forms may at least partially share similarities with experimental models [9]. Also, clinical AF is rarely stable in its appearance and reaction to therapy but may evolve from a paroxysmal form, where functional re-entry is likely to dominate, to a permanent form and even a chronic form, where altered microstructure may be a crucial factor explaining the resistance to antiarrhythmic drugs and electrotherapy. If this alteration in structure is confined to specific areas of the atria, e.g. the region around or below the pulmonary veins, a 'focal' model of AF with accompanying fibrillatory conduction will be appropriate for the description of the basic electrophysiological events. Other clinical forms may better correspond to an intermediate stage, where unstable, circulating excitation waves are found during each cycle, sharing a common, anatomically-defined pathway segment, e.g. the Bachmann's bundle. Most importantly, the biological medium determining the

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electrophysiological behavior of these different forms is not stable in time but undergoes remodeling [9]. This remodeling is perpetuated by the arrhythmia itself ('AF begets AF' [10]) and involves short term changes in ion channel expression and longer term changes in micro-structure [9–11]. The importance of the different models and the methods able to distinguish among the different forms is evident. While the purely functional re-entry is expected to react to drugs prolonging refractoriness and/or abolishing conduction at sites of unidirectional block and current-to-load mismatch, the evolution to structurally defined re-entry will make AF less responsive to drugs either affecting the tail or the head of the propagating wave fronts. If the structural changes are heterogeneous and most prominent at specific locations, surgical and ablation techniques may be appropriate. Also drugs slowing or preventing the remodeling process may become important.

Further to selecting and defining appropriate experimental models for various forms of AF, the basic scientist is faced with the problem of analyzing fibrillating, seemingly disordered, electrical activity at high spatio-temporal resolution. Several kinds of information may be important in experimental analysis. The first concerns the local change in transmembrane potential. For analysis of propagation, the time of the maximal steepness of the upstroke of the transmembrane potential is usually (and arbitrarily) taken as the local activation time. It is reflected in the unipolar extracellular electrogram as the steepest portion of the intrinsic deflection [12]. As long as the information can be limited to the analysis of propagation alone without emphasis on local details, such as the exact definition of sites of unidirectional block with respect to the underlying micro-structure or the exact size of areas of functional block, the use of *extracellular* electrodes is certainly the method of choice. Direct multisite optical measurement of *transmembrane or intracellular* potential, involving the recording of the fluorescence change of dyes sensitive to membrane potential, was originally introduced into cardiac science by Dillon and Morad [13] and has ever since found a wide application in the analysis of arrhythmia mechanisms. In the setting of atrial and ventricular fibrillation, it allows recording of a signal proportional to the whole transmembrane action potential. Therefore, not only depolarization but also repolarization can be analyzed. As shown by Chen et al. [14] in this issue of *Cardiovascular Research*, the optical mapping technique also enables a more accurate spatio-temporal definition of the inner cores of the excitation waves during AF, the so-called wave breaks or *phase singularities*. This work has been carried out in the outstanding laboratory of Dr. Jalife that has contributed essentially to our understanding of the mechanism of fibrillating myocardium [15,16]. The term *phase singularity* denotes a fascinating behavior of circulating cardiac excitation waves (see e.g. Fast and Kléber for review [17]). If a cardiac wave turns around a functional or anatomical obstacle, the wavefront assumes a convex shape. The convex curvature is associated with a mismatch between the source producing local excitatory circuit current in the head of the propagating wave and the load excited by this same current. As a consequence, propagation velocity decreases with an increase in convexity of the wavefront, i.e. a decrease in curvature radius. At a critical value of curvature (in the inner core of a rotor or a spiral wave) the wave suddenly breaks. At this inner site, there is a location in time and space where the depolarizing tissue zone or 'phase' in the wavefront head (e.g. characterized by flow of Na^+ inward current), the already excited (refractory) phase and the non-exited, resting phase merge into a single location, the *phase-singularity*. It is obvious that experimental determination of the locations of phase singularities will provide, at the temporal resolution of the optical mapping system, important information about the dynamic behavior of wavelets in AF. Thus, it provides an elegant approach to test the original hypothesis of Dr. Gordon Moe in a given experimental setting [7]. Using this original approach, Chen et al. show that atrial fibrillation in arterially-perfused hearts of normal sheep, exposed to acetylcholine, consists of a large number of wavelets of small dimensions and short duration. Mapping relatively large areas (3×5 cm in the right atrium, 3×3 cm in the left atrium), Chen et al. show that the majority of wavelets have a very short life span, insufficient to produce full reentry. In the majority of cases, waves encountering locally refractory tissue break up into two phase-singularities that rotate in opposite direction ('figure of eight re-entry'). Full re-entrant circuits are rarely seen and necessitate a large separation of the phase-singularities (8 mm in average). Moreover, the rate of wavelets leaving a given area is in most cases smaller than the rate of entering wavelets, suggesting that the relative large mapping area comprises fibrillatory conduction in most cases, but full re-entry in only about 10% of the recordings. Relative to the total number of phase singularities observed, only 2% of the circulating wavelets lead to full reentrant circuits. As a further interesting finding, it is shown that the spatial organization of phase singularities is not random, suggesting the involvement of the atrial micro-structure in the formation of new (non-reentrant) wavelets. As a main conclusion, Chen et al. suggest that, even in vagally-induced AF, fibrillatory conduction is the major mechanism explaining excitation of large parts of the atria. On the basis of earlier work, maintenance of AF was suggested to be due to one or a few stationary sources confined to left atrium in this model [18]. As extensively discussed by Chen et al., these results are in partial conflict with earlier results by Allessie et al. who observed at least three rotating waves per atrium during sustained AF [8]. Although it is possible that these discrepancies are due to species-related differences, both the studies by Allessie et al. and by Chen et al. provide a ***common message***. It appears that fibrillatory conduction in acute, vagally-induced AF, can explain the excitation patterns in a large

part of the atria, either in the presence of a few (but not 'multiple') unstable, fully-reentrant waves or with one or more stationary sources maintaining AF.

The fascinating visualization of phase singularities or wave breaks from local recordings of transmembrane action potentials may revive a classical discussion related to the interpretation of extracellular or transmembrane potential recordings with respect to the underlying behavior of ionic channels. In a normally propagating planar wavefront, the flow of ionic current through specific protein channels can be related to a given phase of the transmembrane action potential. This correlation, which requires sophisticated computer simulation for quantification [19], is very important for the understanding of the effects of drugs or genetic alterations on the action potential and associated arrhythmias. During the phase of normal depolarization, the maximal flow of inward Na^+ current can be associated with the late phase of the action potential upstroke. However, if conduction becomes discontinuous – as in AF – due to functional or structural obstacles, the association of an action potential upstroke with the underlying excitation process is not straightforward. If discontinuities result in current-to-load mismatch, action potential upstrokes may become bi- or triphasic and the instant of local ionic activation does not coincide with the steep portion of the upstroke. Moreover the upstrokes may become very long in duration and spatial extension while the underlying ionic excitation phase is short [20]. In the case of a discontinuity leading to partial or full collisions of excitation waves, the upstroke of the action potential may be short and steep, while the amount of activated I_{Na} is considerably smaller than in steady-state [21]. Moreover, local electrograms from sites that are functionally inexcitable during a given phase of an arrhythmia may show an electrotonic reaction mimicking a wave caused by local activation of ion channels. In other words, it seems difficult to establish a straightforward correlation between the phasic changes in transmembrane potential and underlying ionic events, especially during fibrillation in anatomically heterogeneous tissue. This difficulty has limited the accuracy of determination of local activation times in ischemic hearts showing tachycardia and fibrillation, particularly at sites close to the core or the inner site of block (or 'leading circle') of a reentrant wave [22]. Since the construction of phase singularity maps is based on the cyclic changes of transmembrane potentials as well, it seems justified to reactivate this discussion in the context of the analysis of AF by phase singularities. An elegant way to correlate the potential changes with flow of depolarizing current was suggested by the late Dr. Frank Witkowski who developed a method to estimate local ionic current flow from the spatial derivatives ('Laplacian') of the electrical field [23]. Another possibility would be to compare the fluctuations in transmembrane potential with recordings of 'ionic waves', e.g. with a spatio-temporal analysis of the early increase in intracellular free Na^+ or Ca^{++} during fibrillation. Further experiments are required to clarify these points. One may argue that knowledge of the oscillation-like behavior of membrane potential is sufficient to define electrical propagation per se during defibrillation. However, if the interest is focused on the effect of drugs in AF, simultaneous knowledge of the underlying state of ion channels would provide additional relevant information.

As a whole, the study by Chen et al. is an important and interesting step towards the understanding of the mechanisms underlying the various forms of atrial fibrillation.

References

[1] Garrey WE. Auricular fibrillation. Physiol Rev 1924;4:215–250.
[2] Lewis T. The mechanism and graphic registration of the heart beat, London: Shaws & Sons, 1920.
[3] Winfree AT. Spiral waves of chemical activity. Science 1972;175:634–636.
[4] Lechleiter J, Girard S, Peralta E, Clapham D. Spiral calcium wave propagation and annihilation in Xenopus laevis oocytes. Science 1991;252:123–126.
[5] Moe G, Abildskov J. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. Am Heart J 1959;58:59–70.
[6] Scherf D. Studies on auricular tachycardiac studied by aconitine administration. Proc Soc Exp Biol Med 1947;64:233–239.
[7] Moe G, Reinboldt W, Abildskov J. A computer model of atrial fibrillation. Am Heart J 1964;67:200–220.
[8] Allessie MA, Lammers WJEP, Bonke FIM, Hollen J. Experimental evaluation of Moe's multiple wavelet hypotheis of atrial fibrillation. In: Zipes DP, Jalife J, editors, Cardiac arrhythmias, New York: Grune & Stratton, 1985, pp. 265–276.
[9] Allessie M, Boyden P, Camm J, Kléber A, Lab M, Legato M, Rosen M, Schwartz P, Spooner P, Van Wagoner D, Waldo A. Prevention of atrial fibrillation. Circulation 2000: in press.
[10] Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92:1954–1968.
[11] Thijssen VL, Ausma J, Liu GS, Allessie MA, van Eys GJ, Borgers M. Structural changes of atrial myocardium during chronic atrial fibrillation. Cardiovasc Pathol 2000;9:17–28.
[12] Hoffman BF, Cranefield PF. Electrophysiology of the heart, New York: McGraw-Hill, 1960.
[13] Dillon S, Morad M. A new laser scanning system for measuring action potential propagation in the heart. Science 1981;214:453–456.
[14] Chen J, Mandapati R, Berenfeld O, Skanes A, Gray RA, Jalife J. Dynamics of wavelets and their role in atrial fibrillation in the isolated sheep heart. Cardiovasc Res 2000;48:220–232.
[15] Jalife J. Ventricular fibrillation: mechanisms of initiation and maintenance. [In process citation]. Annu Rev Physiol 2000;62:25–50.
[16] Jalife J. Spatial and temporal organization in ventricular fibrillation. Trends Cardiovasc Med 1999;9:119–127.
[17] Fast VG, Kléber AG. Role of wavefront curvature in propagation of cardiac impulse. Cardiovasc Res 1997;33:258–271.
[18] 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.
[19] Shaw RM, Rudy Y. Ionic mechanisms of propagation in cardiac tissue. Roles of the sodium and L-type calcium currents during reduced excitability and decreased gap junction coupling. Circ Res 1997;81:727–741.
[20] Fast VG, Kléber AG. Cardiac tissue geometry as a determinant of

unidirectional conduction block: assessment of microscopic excitation spread by optical mapping in patterned cell cultures and in a computer model. Cardiovasc Res 1995;29:697–707.
[21] Spach MS, Kootsey JM. Relating the sodium current and conductance to the shape of transmembrane and extracellular potentials by simulation: effects of propagation boundaries. IEEE Trans Biomed Eng 1985;32:743–755.
[22] Janse MJ, Van Capelle FJL, Morsink H, Kléber AG, Wilms-Schopman FJG, Cardinal R, Naumann d'Alnoncourt C, Durrer D. Flow of 'injury' current and patterns of excitation during early ventricular arrhythmias in acute regional myocardial ischemia in isolated porcine and canine hearts. Evidence for two different arrhythmogenic mechanisms. Circ Res 1980;47:151–165.
[23] Witkowski FX, Kavanagh KM, Penkoske PA, Plonsey R. In vivo estimation of cardiac transmembrane current. Circ Res 1993;72:424–439.