Chessboard of atrial fibrillation: reentry or focus? Single or multiple source(s)? Neurogenic or myogenic?

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The refractory period may be shortened to one-fifth or one-sixth the normal, although vagus action is a necessary accompaniment of such high-grade shortening. This change makes rapid reexcitation possible and the formation of circuits having diameters of but a few millimetres. Since the refractory phase does not occur simultaneously in all fibers, the circuits must be formed in different and shifting locations.


Atrial fibrillation (AF) is the most prevalent tachyarrhythmia in humans. AF continues to gain increasing prevalence with the aging of the population, reaching 2.3% after 40 yr of age and 10% after 80 yr of age (6). Despite more than a century of research, the mechanisms of initiation and maintenance of AF remain unclear, and the same principle issues have been of research, the mechanisms of initiation and maintenance of age and 10% after 80 yr of age (6). Despite more than a century of research, the mechanisms of initiation and maintenance of AF remain unclear, and the same principle issues have been debated over and over again since the 1870s to the 1900s: Is AF myogenic or neurogenic in nature? 2) Is AF maintained by reentry or by focal activity? 3) Is AF maintained by a single source, or are multiple sources required? and 4) Is there a critical mass of myocardium required to maintain AF?

Initial discovery of fibrillation produced by “faradization” (electrical stimulation) in Ludwig’s laboratory (11) during studies of autonomic control of the heart led to domination of the neurogenic theory of fibrillation. Yet, the subsequent studies of Vulpian (28) and MacWilliam (18) laid to rest the neurogenic theory. They put forward a myogenic theory of fibrillation that remained dominant for over a century. The triumph of this theory was imprinted in the term “fibrillation,” coined by Vulpian. Yet, MacWilliam himself and many to follow have demonstrated that unlike ventricular fibrillation (VF), AF is strongly dependent on the autonomic nervous system: “The movements excited by faradisation in the auricles and ventricles differ very markedly in their relation to the inhibitory influence of the vagus nerve” (18). More recently, numerous studies have shown a prominent role played by the autonomic nervous system in the initiation and maintenance of AF (3, 4, 17, 24, 32). Thus it became generally accepted that AF is not a purely myogenic phenomenon. Future studies will undoubtedly uncover new neurogenic elements of AF. The study of Zou et al. (33) published in this issue of the American Journal of Physiology-Heart and Circulatory Physiology demonstrates one of such neurogenic elements, which appears to play a critical role in the induction and maintenance of AF. The study demonstrates how cholinergic effects may contribute to the maintenance of microreentrant circuit sustaining AF.

In addition to the neurogenic-myogenic debates, focal and reentrant theories of AF have been debated since the early days of arrhythmia research. Seminal work of Garrey (8) and Lewis et al. (15, 16) provided convincing and overwhelming support for the reentrant theory of initiation and maintenance of AF, as it was understood until recently. Garrey and Lewis et al. agreed on the reentrant nature of AF, yet they disagreed on the number of reentrant circuits that are required to maintain AF. Lewis et al. (16) formulated a “mother ring” theory that suggested that a single reentry circuit is sufficient to initiate and to sustain AF. This theory has been further developed into the “mother rotor” hypothesis and supported experimentally by Jalife’s group (19). In contrast, Garrey (8) and subsequently Moe (21) suggested that multiple reentrant sources are required for AF maintenance. Allessie et al. (2) provided compelling experimental evidence in support of a theory of multiple reentrant sources for the initiation and maintenance of AF. Similarly, a focal theory of AF has been reborn from the ashes by the clinical observations of Haissaguerre et al. (10). Thus the research community remains divided as it was in 1940 when Carl Wiggers wrote: “As to the fundamental mechanisms of fibrillation we have plenty of theories, but none is universally accepted. Space is lacking to review the different hypotheses, but we may note in passing that they all center around two ideas, viz., (a) that the impulses arise from centers, or pacemakers, or (b) that the condition is caused by the re-entry of impulses and the formation of circles of excitation. Each of these views, again, has two groups of exponents, viz., (a) those who believe that a single focus, or excitation ring, occurs, and (b) those who favour the idea that multiple foci, or numerous circus rings, are developed” (30). The study of Zou et al. (33) provides an interesting theoretical support to microreentrant theory of AF, showing that strong cholinergic discharges in a small area of atrial myocardium can provide the substrate for a microreentrant circuit as was initially proposed by Garrey (8).

Another important consideration is the size of tissue needed to sustain AF. After the initial observations of MacWilliam related to VF (18), Garrey experimentally determined that a certain minimal size of atrial tissue is required for the induction and maintenance of AF (7). This hypothesis, known as the “critical mass of fibrillation” theory, remained commonly accepted for nearly a century for both AF and VF. The theoretical basis of the critical mass theory was developed using the concept of wavelength (14), which is the product of the refractory period and the conduction velocity of an impulse. Allessie et al. (1) presented compelling evidence in support of a “leading circle” hypothesis, which is based on the wavelength theory. They showed that the reentrant circuit cannot be shorter than the wavelength (22). Yet again, recently, several groups challenged that and showed what seemed impossible: fibrillation in the mouse heart (9, 27, 29). These data seemed to challenge the critical mass hypothesis. However, one could argue that there is no conflict between these findings and the critical mass hypothesis. The wavelength of the atrial myocardium can change significantly in response to pharmacological intervention, autonomic effects, structural remodelling, and genetic manipulations in mouse models. Thus the existence of
microreentry reflects the fact that cholinergic effects include dramatic shortening of wavelength as was shown by Lewis et al. and Garrey. The study of Zou et al. provides further insight into the importance of cholinergic modulation of wavelength and critical mass theory.

Experimental validation of the competing theories remains challenging due to limited spatiotemporal resolution of the experimental technologies and the profound complexity of atrial myocardium. Zou et al. constructed, elegant in its simplicity, a chessboard-like model of the atria, which contains regions rich in cholinergic receptors intermingled with myocardium void of them. They showed that specific anatomic details of cholinergic heterogeneity are not essential for creating the substrate for microreentry circuits. The model predicts the coexistence of several scales of reentrant patterns that dwell on a heterogeneous substrate in their model: either single dominant rotors or multiple unstable rotor-based reentry can underlie persistent fibrillatory activity in their atrial model. Their model shows that treatment with a high mean concentration of acetylcholine sets the stage for single primary rotors anchored in low-acetylcholine concentration zones, which maintains AF. Surrounding cholinergic rich areas stabilize the leading source of AF. At lower mean concentrations of acetylcholine, extensive spiral waves meander and precluded the emergence of single stable rotors.

These observations provide a clear explanation for several experimental findings in cholinergic AF. Sharifov et al. (26) showed that in most cases of AF onset, a single leading and stable source of excitation was established after the second to third beats. Sustained cholinergic AF associated with a single stable reentrant source was also observed in the isolated canine right atrium (25). Early studies have shown that acetylcholine-mediated reentry can be three dimensional, revealing simultaneously focal and reentrant activation patterns, respectively, on epicardial and endocardial surfaces of the isolated canine right atrium (31). The transition from macroreentrant to microreentrant patterns has been observed in a similar preparation, in which AF was induced by electric stimulation in the presence of incremental concentrations of acetylcholine resulting in drastic shortening of atrial refractoriness and a decreasing reentrant circuit beyond the mapping system’s spatial resolution. Stable microreentrant sources as a mechanism of electrically induced cholinergic AF were also documented in an optical mapping study of the isolated sheep heart (19).

The spatial resolution of existing mapping systems is often insufficient to distinguish microreentry from focal activity in the heterogeneous three-dimensional structure of the atria.

Theoretically, the diameter of the microreentrant circuit induced in the atria during cholinergic stimulation can be <1 mm (23). Thus it is still unclear whether focal activity, which was observed in the human (10) and animal models (25, 26), is in fact due to microreentry. New imaging modalities are needed to assess spatial anatomic heterogeneity with temporal complexity of the microreentrant pattern. This controversy is likely to drive experimental research in the near future. This work, however, will require the development of novel imaging modalities that will provide high-resolution three-dimensional mapping of electrical activity in the three-dimensional mammalian atria, with a spatial resolution that enables accurate quantitation of the changes in wave propagation parameters produced by the cholinergic input and causing reentry initiation. New optical coherence tomography (12, 13) in combination with second harmonic-based transmembrane voltage sensing (20) may provide such a future technology.


