Atrial fibrillation: from cells to computers

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Atrial fibrillation is one of the commonest arrhythmias encountered in clinical practice. The incidence of this arrhythmia increases with age and it is responsible for substantial morbidity, mortality \cite{1}. Numerous studies have been performed to elucidate the cellular and molecular events associated with this rhythm. Our conceptual framework for understanding this rhythm disturbance is based on the pioneering work of Gordon Moe \cite{2}. Atrial fibrillation is thought to be due to repetitive activation of the atria by multiple reentrant wavelets. Subsequent experimental work confirmed the key elements of the hypothesis of Moe \cite{1}. The exact origin and the behavior of such wavelets is a source of intense ongoing investigation utilizing experimental and computational approaches.

1. Cellular electrophysiological changes due to AF

The cellular ionic changes that allow repetitive activation of the atria at such high rates have been the focus of several studies. Several investigators have demonstrated that the ERP of the atrium shortens even after a brief duration of atrial fibrillation. The demonstration of the phenomenon of ‘electrical remodeling’ provided the impetus for some detailed studies of atrial electrophysiology \cite{3}. Single cell recordings from human atrial myocytes (from explanted hearts during orthotopic cardiac transplantation and excised atrial appendages) have been studied in great detail to determine the ionic currents that regulate the atrial action potential. Electrical remodeling is a dynamic phenomenon and reflects rapid physiological changes in the electrical behavior of atrial cells \cite{3,4}. Ionic currents that regulate the atrial action potential have been studied in this setting to determine the mechanisms that are responsible for the shortening of the atrial ERP. Changes in inward and outward membrane currents have been characterized in both human and animal studies of atrial fibrillation \cite{4,5}. Findings from these studies include: (i) shortening of the ERP \cite{3,6,7}, (ii) shortening of the action potential duration (APD) \cite{8}, (iii) decreased shortening of ERP and APD with increasing frequency of stimulation (rate adaptation), (iv) increased dispersion of cellular refractoriness. Ionic current changes that have been reported include: (i) reduction in $I_{\text{CaL}}$ \cite{8,9}, (ii) reduction in $I_{\text{Na}}$ \cite{10}, (iii) reduction in $I_{\text{K}}$ \cite{8,9}, and (iv) very little change in the inward rectifier K current (see Nattel \cite{5} for a detailed review).

2. The present study

Workman and colleagues \cite{11} have characterized cellular electrophysiological data from isolated human atrial myocytes obtained from patients with chronic atrial fibrillation and compared it to data from patients in sinus rhythm. The data on normal myocytes adds to the data from ‘control’ arms of similar studies. The study aims to determine the relative contribution of changes in inward and outward ionic currents to single cell electrophysiological properties. Using standard voltage protocols and pharmacological interventions, the contributions of $I_{\text{CaL}}, I_{\text{K}}, I_{\text{KUS}}$ and $I_{\text{f0}}$ to electrophysiological alterations were studied. There are several important findings reported by the authors: (i) Fast-rate induced depolarization and APD-shortening was attenuated in AF, (ii) atrial ERP was shortened and its rate adaptation was attenuated in myocytes from patients with AF, (iii) $I_{\text{CaL}}$ was reduced at physiological rates in atrial cells from patients with AF, (iv) changes in $I_{\text{CaL}}$ and $I_{\text{f0}}$ are insufficient to completely explain the ERP and MDP adaptations observed in myocytes from patients with AF. An impressive finding of...
the study is the ability to pace the cells so rapidly under whole cell clamp conditions without loss of stability. A potential limitation, however, is that the whole cell technique dialyzes the cytoplasm and disturbs physiological intracellular signaling. The perforated patch method has been suggested as a technique for better preservation of normal intracellular signaling. An unavoidable limitation of the study is the inability to assess how atrial fibrillation affected regional electrophysiological heterogeneity, such as dispersion of refractoriness, throughout the atrium. Since all the cells were obtained from the RA appendage, it is possible that the effects of AF on rate adaptation and other properties may be different in other regions. This is relevant to the observation that LA activations are typically more rapid than right atrial activations during AF, suggesting that the engine of AF may be typically located in the LA [12]. It would have been interesting to compare LA appendage myocytes to RA appendage myocytes. Obviously, the role of PV sites and other ‘focal’ sites that trigger AF are very important and relevant, although beyond the scope of this study. The data using 4-AP need to be interpreted with caution. The effects of this pharmacological intervention cannot be completely ascribed to \( I_{to} \) block. The effect of the drug on other inward and outward currents needs to be considered. It is interesting that APD restitution was flattened by chronic AF (at least in the RA appendage), suggesting that either APD restitution steepness [13] might be less important in maintenance of AF than other effects, such as wavelength shortening, anatomical/electrophysiological heterogeneity, and/or left atrial changes.

3. Intra-atrial and inter-atrial heterogeneity in action potential characteristics

Several studies have shown that atrial action potential shapes are pleomorphic and are ‘sculpted’ by relative differences in the strength of inward and outward currents (at any given point in time the membrane potential reflects the net balance between inward and outward currents). Even normal atrial myocytes have different action potential shapes, analogous to ventricular myocytes. Nattel and colleagues demonstrated three types of action potential morphologies in human atrial myocytes [14]. They characterized cells as Type I, Type II and Type III based on the relative ratios of \( I_K \) and \( I_{to} \). Cells with only \( I_{to} \) showed a triangular action potential waveform. LeGrand and co-workers observed two types of AP morphologies in atrial cells in their study [15]. Thus normal atrial myocardium is likely to have cells with differing ERP and APD rate adaptation properties. Cells with different repolarization characteristics (due to differences in ionic currents) may respond with dramatic differences in APD and ERP when exposed to interventions that augment outward currents, for example adenosine or vagal stimulation. Intuitively ‘all or none’ repolarization response (abrupt shortening of the APD) could be observed in cells with a prominent \( I_{to} \) analogous to cells in the epicardial regions of the ventricle [16]. Thus, small differences in refractoriness (between cells with slightly different repolarization characteristics) may set the stage for reentry within the atrium. Once atrial fibrillation starts ‘electrical remodeling’ perhaps perpetuates the process. Cells from patients with chronic AF (after a period of remodeling), not surprisingly, show significant differences in APD morphologies between individual cells. Further, the etiology/underlying disease that resulted in AF seems to have different ionic changes (heart failure vs. pacing-induced AF) [17].

4. What are the implications of such studies?

The obvious importance of such studies is identification of potential ionic current targets for drug therapy to prevent atrial fibrillation and help maintain sinus rhythm. In addition to this, data along these lines are valuable for refining mathematical models of atrial action potentials. A continuing challenge in modern electrophysiology is the integration of knowledge gained in cellular and molecular studies to improve our understanding of arrhythmias in the whole organ. An important aspect of such integrative research is mathematical modeling of cardiac arrhythmias. Such models allow us to understand how cellular characteristics of individual cells/ionic currents contribute to the behavior of excitatory electrical waves in the atria as a whole.

Mathematical modeling of atrial activation is now being attempted in ‘anatomically accurate’ mathematical models which incorporate key anatomical structures such as the crista terminalis and the pectinate bundles. Recently, Harrild and Henriquez have used a complex model of the atrium (taking into account anatomic structures) and assigned different conduction velocities to each region to study atrial activation in three dimensions [18]. Future studies that incorporate functional differences between different regions of the atria will undoubtedly provide a framework to improve our understanding of atrial arrhythmias. For instance, areas of the atrium that display marked anisotropy related to structural characteristics have been shown to play an important role in the behavior of reentrant waves in animal experiments and mathematical models. ‘Anchoring’ of reentrant spiral waves to anatomic ‘obstacles’ has been shown to create a flutter like activation pattern resulting in conversion of fibrillation to flutter in combined mapping and modeling studies [19].

5. Future questions

Recently, focal triggers of atrial fibrillation have received a lot of attention and in a subset of patients these triggers can be ablated using catheter techniques to provide some meaningful clinical benefit [20]. We still do not understand the cellular behavior of ‘triggers’ of atrial fibrillation. Further, the exact reason why fibrillation persists in some settings and is self limiting in others is
also poorly understood. Clearly triggers have to be incorporated into pathophysiological paradigms of atrial fibrillation. The normal atrium, perhaps due to physiological heterogeneity, has the potential to fibrillate. Triggers of AF in this setting are likely to result in brief paroxysms of fibrillation. If such triggers are frequent enough, AF may sustain due to electrical remodeling analogous to the pacing model of AF. In a diseased atrium, triggers may very well result in prolonged episodes of AF due to accentuated heterogeneities in electrical function (and ultrastructural changes such as fibrosis). Remodeling during AF in this setting is likely to set the stage for permanent AF (Fig. 1). These questions are likely to be answered by a combination of approaches (cellular, molecular, mapping, human and mathematical modeling) to improve our understanding of the complex pathophysiological mechanisms of this common arrhythmia. An opportunity now exists to build stronger bridges from cells to computers!

References