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Anti-arrhythmic strategies for atrial fibrillation
The role of computational modeling in discovery, development, and optimization

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ABSTRACT

Atrial fibrillation (AF), the most common cardiac arrhythmia, is associated with increased risk of cerebrovascular stroke, and with several other pathologies, including heart failure. Current therapies for AF are targeted at reducing risk of stroke (anticoagulation) and tachycardia-induced cardiomyopathy (rate or rhythm control). Rate control, typically achieved by atrioventricular nodal blocking drugs, is often insufficient to alleviate symptoms. Rhythm control approaches include antiarrhythmic drugs, electrical cardioversion, and ablation strategies. Here, we offer several examples of how computational modeling can provide a quantitative framework for integrating multiscale data to: (a) gain insight into multiscale mechanisms of AF; (b) identify and test pharmacological and electrical therapy and interventions; and (c) support clinical decisions. We review how modeling approaches have evolved and contributed to the research pipeline and preclinical development and discuss future directions and challenges in the field.

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1. Introduction

Atrial fibrillation (**AF**) is the most prevalent cardiac arrhythmia, occurring in 1–2% of the general population — projected to increase to 4% by 2050 (Andrade et al., 2014). Because age is the most powerful predictor of AF risk, the impact of AF is furthermore estimated to increase dramatically in coming decades, as Westernized populations continue to age. AF markedly increases risk for cerebrovascular stroke and thrombo-embolic events, impairs quality of life and exercise capacity, and often coexists with other pathologies, such as heart failure (**HF**) and left ventricular dysfunction, causing increased morbidity and mortality. AF has significant economic impact: at least 1% of the healthcare budget of the United States and European countries is currently spent on AF management, and annual related costs are estimated at $6.65

Abbreviations: AF, atrial fibrillation; AP, action potential; APD, action potential duration; ARB, angiotensin receptor blocker; cAF, chronic AF; CaMKII, Ca/calmodulin dependent protein kinase II; CV, conduction velocity; DAD, delayed afterdepolarization; DF, dominant frequency; EAD, early afterdepolarization; ECG, electrocardiogram; ERP, effective refractory period; I_f, hyperpolarization-activated cyclic nucleotide-gated 'funny' current; I_{K1}, inward-rectifier K current; $I_{K,Ach}$, acetylcholine-dependent K current; $I_{K,Ca}$, small-conductance Ca-activated K current; I_{KATP}, ATP-sensitive K current; I_{Kr}, rapidly activating delayed rectifier K current; I_{Ks}, slowly activating delayed rectifier K current; I_{Kur}, ultra-rapid delayed rectifier K current; I_{Na}, Na current; I_{NaL}, late Na current; I_{to}, transient outward K current; K_{2P}, 2-pore domain K channel; LA, left atrium; MRI, magnetic resonance imaging; nSR, normal sinus rhythm; pAF, paroxysmal AF; PKC, protein kinase C; PKCε, PKC type-ε; PV, pulmonary vein; RAAS, Renin–Angiotensin–Aldosterone System; RMP, resting membrane potential; ROS, reactive oxygen species; RyR, ryanodine receptor; SK, small-conductance calcium-activated K (channel); SR, sarcoplasmic reticulum.

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billion in 2001 and €13.5 billion, respectively (Coyne et al., 2006; Fuster et al., 2006). These are largely attributed to hospitalization and acute care, whereas outpatient treatment and pharmacotherapy account for about one-third of the economic burden (Coyne et al., 2006).

In the majority of patients, there appears to be an inexorable progression from sporadic paroxysmal AF (**pAF**) to persistent or chronic (**cAF**) forms, associated with arrhythmia-induced changes of atrial electrophysiological properties, mechanical function, and atrial ultrastructure that may perpetuate the arrhythmia. For AF to be initiated and maintained, both triggers for its onset and a substrate for its maintenance are required. We refer the readers to recent thorough reviews for detailed descriptions of the mechanisms underlying AF (Wakili et al., 2011; Heijman et al., 2014; Guillem et al., 2016). These involve both increased ectopic firing of atrial cells and impulse reentry through atrial tissue (Fig. 1). At the cellular level, focal ectopic/triggered activity is likely caused by early and delayed afterdepolarizations (**EAD**s and **DAD**s) or enhanced automaticity. At the tissue level, afterdepolarization-prone regions have to overcome the surrounding stable tissue to produce ectopic activity. Focal ectopic activity can maintain AF as a driver or act on vulnerable reentrant substrates. Reentry is promoted by shorter action potential (**AP**) duration (**APD**) and effective refractory period (**ERP**), and APD alternans. At the tissue level, it is favored by slow conduction velocity (**CV**) and heterogeneous conduction, spatially heterogeneous APD, and abbreviated refractoriness. Fibrotic regions may additionally serve as architectural anchors which stabilize AF reentry rotors. Virtually all of these mechanisms are modulated by the autonomic nervous system, which has a profound influence on the occurrence of AF (Dimmer et al., 1998; Bettoni & Zimmermann, 2002). Indeed, simultaneous sympathovagal discharges commonly precede arrhythmias, and both sympathetic and vagal activation has been shown capable of producing proarrhythmic atrial myocyte APD changes and predispose to Ca-dependent triggered activity (Fig. 1).

Current therapies for AF are targeted at treating the faulty heartbeat and reducing risk of tachycardia-induced cardiomyopathy (rate or rhythm control) and/or stroke (anticoagulation). Rhythm control is the preferred treatment approach for the majority of patients with pAF or cAF (Camm et al., 2012; Ball et al., 2013; January et al., 2014). Rate control, typically achieved by atrioventricular nodal blocking drugs, such as β-blockers, L-type calcium channel blockers, or digoxin, is often insufficient to alleviate symptoms. Rhythm control is attempted with antiarrhythmic drugs, electrical cardioversion, and ablation strategies. Drug treatment of AF is limited by low efficacy and the side effects of currently available antiarrhythmic agents, which often increase the propensity for life-threatening ventricular arrhythmias. Section 2 documents the ongoing search for new agents against AF with more favorable benefit-to-harm relation, which has led to the development of atrial-selective antiarrhythmic drugs. In Section 3, we focus on non-pharmacological interventions to limit AF, e.g., ablation techniques, which have been substantially developed in the past decade and proven successful to reduce the symptomatic burden associated with the arrhythmia. Throughout the article, we discuss how atrial modeling and simulation have enhanced our mechanistic understanding of AF, and contributed to the development of therapeutic strategies.

Many commonly used human atrial myocyte models (Courtemanche et al., 1998; Nygren et al., 1998; Maleckar et al., 2009; Grandi et al., 2011; Koivumäki et al., 2011), their main properties and their evolution, have been recently reviewed and compared elsewhere (Heijman et al., 2016b). These models show important differences in AP morphology and rate dependence, which affect reentrant behaviors in multicellular simulations (Cherry et al., 2008; Wilhelms et al., 2012). Notably, a study adopting population-based simulations to study inter-subject variability has shown remarkable similarities in the mechanisms identified using three widely used different human atrial AP models (Sanchez et al., 2014), and also provided a new approach to analyzing differences among various models and identifying which model might be best suited for certain questions.

More recent models, such as the Grandi and Koivumäki models, have focused more in depth on the simulation of atrial Ca handling, and emphasized the importance of Ca and Na homeostasis for atrial electrophysiological properties (Grandi et al., 2011; Koivumäki et al., 2011). The Koivumäki model also provided a spatial representation of Ca handling, with centripetal Ca diffusion between transverse cytosolic and SR compartments (Koivumäki et al., 2011). Heijman and colleagues developed the first human atrial cardiomyocyte model with both transverse and longitudinal Ca compartmentation (Voigt et al., 2014), coupled with the Grandi et al. electrophysiological model (Grandi et al., 2011). The latter allows simulating the consequences of sympathetic and vagal (as in the

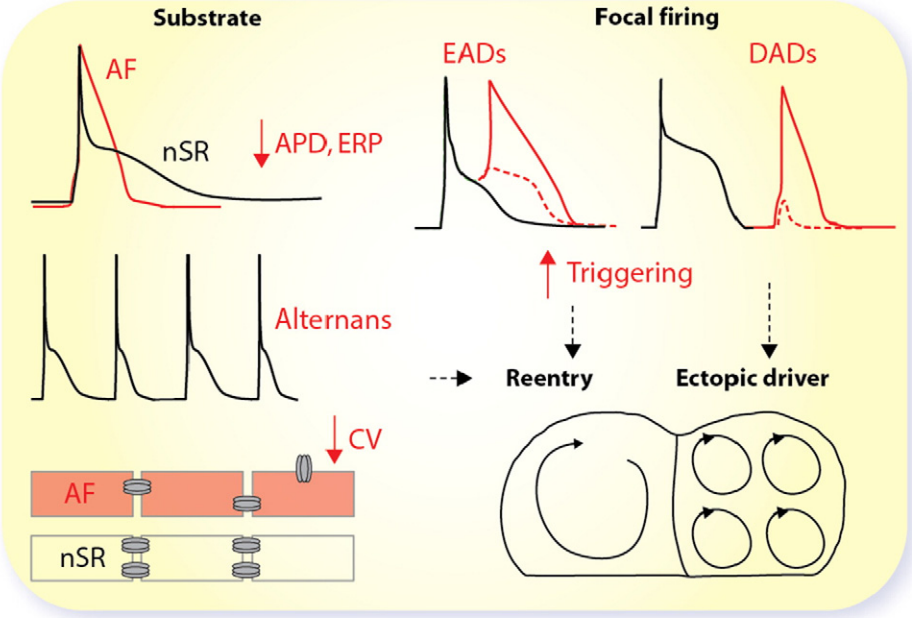

Fig. 1. Arrhythmia Mechanisms in AF. AF remodeling causes abbreviated APD and ERP, alternans, decreased CV (e.g., due to connexin downregulation or lateralization, and/or fibrosis), all contributing to a reentrant substrate. Focal firing via enhanced automaticity or triggered activity due to early or delayed afterdepolarizations causes local ectopic activity, which can act as an AF-maintaining ectopic driver, or can trigger AF-maintaining re-entry in a vulnerable substrate.