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Human Atrial Fibrillation: insights from computational electrophysiological models

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Abstract

Computational electrophysiology has proven useful to investigate the mechanisms of cardiac arrhythmias at various spatial scales, from isolated myocytes to the whole heart. Here we review how mathematical modeling has aided our understanding of human atrial myocyte electrophysiology to study the contribution of structural and electrical remodeling to human atrial fibrillation. We suggest potential new avenues of investigation and model development.

Models of the human atrial cardiomyocyte

It is well established that computational electrophysiology allows for an integrated understanding of cardiac (patho)physiological processes that may complement and inform experimental work with new testable predictions. In recent years, mathematical models of heart cell electrophysiology have become increasingly complicated and biophysically detailed due to increased availability of experimental data. Increased complexity is justified, for example, by the need to capture the subcellular nature of ion channel gating or compartmentation of signaling proteins. Specialized models for atrial and ventricular cells of several species have been made available, as well as for Purkinje, atrio-ventricular, and sino-atrial node cells, characterized by specific amalgams of ion channel expression and function. Limited availability of human samples for experiments has made perhaps even more crucial the development of human electrophysiological models.

The Courtemanche et al. (1998) and Nygren et al. (1998) models have been the first attempts to establish a quantitative framework for elucidating the ionic mechanisms of human atrial myocyte electrophysiology and atrial fibrillation (AF) (Courtemanche et al. 1999). These models focused primarily on the description of transmembrane ion channels generating the atrial action potential (AP), whereas little emphasis was placed on intracellular Ca^{2+} dynamics. The Nygren and Courtemanche models have vastly different properties, especially in their rate-dependent behavior, due to marked differences in Ca^{2+} handling (Cherry et al. 2008). Maleckar et al. (2009) refined the K^+ current description in the Nygren model, based on newly available data, to improve the representation of repolarization processes and reproduce AP rate-dependence. However, because of limited appropriate experimental data the formulation of Ca^{2+} handling was not improved.

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Recently, Koivumaki et al. (2011) extended the Nygren model to describe the heterogeneous subcellular Ca^{2+} dynamics of human atrial cells accounting for a delay between peripheral and central sarcoplasmic reticulum (SR) Ca^{2+} release, which is expected in cells lacking t-tubules. However, atrial myocytes from human tissue exhibit an extensive t-tubular network (Richards et al. 2011), like atrial myocytes from large mammals (Dibb et al. 2009; Lenaerts et al. 2009). The role of Ca^{2+} in chronic AF (cAF), where indeed remodeling of the t-tubular network may occur, was not investigated.

Understanding AF requires an integrated quantitative understanding of ionic currents and Ca^{2+} transport in healthy and remodeled human atrium. We have recently developed a new human atrial model (Fig. 1A) that provides an accurate representation of electrophysiology and Ca^{2+} homeostasis in human atrial myocytes in sinus rhythm and chronic AF conditions ((Grandi et al. 2011), Fig. 1B–E), built upon recent Ca^{2+} handling data at physiological temperature in atrial myocytes from patients in sinus rhythm and with cAF.

While all models have been shown to replicate many fundamental aspects of atrial electrophysiology, the latter two have highlighted the strong impact of Ca^{2+} and Na^{+} dynamics on the AP and its rate-dependent characteristics.

Remodeling in human AF

AF is characterized by severe structural, electrical and contractile remodeling that is believed to contribute to the arrhythmogenic substrate and favor AF maintenance (see (Grandi et al. 2012) and key molecular/ionic bases of AF-induced remodeling in Fig. 1A). We (Grandi et al. 2011) and others (Courtemanche et al. 1999; Zhang et al. 2005) have accounted for the marked reduction in I_{CaL} (Christ et al. 2004; Grandi et al. 2011; Van Wagoner et al. 1999; Voigt et al. 2009), I_{to} and I_{Kur} densities (Caballero et al. 2010), as well as I_{K1} enhancement (Van Wagoner et al. 1997) in cAF *vs.* sinus rhythm. For the first time, the reported enhancement in I_{Ks} (Caballero et al. 2010) and late I_{Na} (Sossalla et al. 2010) were incorporated in our cAF model (Grandi et al. 2011). cAF-induced alterations result in shortening of AP duration (APD, Fig. 1B, *inset*) and effective refractory period (ERP), and loss of rate-adaptation of both atrial repolarization (Fig. 1C *vs.* 1B, see below for proposed mechanism) and refractoriness compared to sinus rhythm, in agreement with experimental data (Van Wagoner et al. 1999; Workman et al. 2001).

Perturbations in intracellular Ca^{2+} handling (Fig. 1A) are important players in AF-induced atrial remodeling. $\text{Na}^{+}/\text{Ca}^{2+}$ exchange (NCX) is upregulated in cAF, (El-Armouche et al. 2006; Grandi et al. 2011; Neef et al. 2010; Voigt et al. 2009), whereas SR Ca^{2+} pump (SERCA) expression is decreased, causing slower Ca^{2+} transient decay *vs.* sinus rhythm (El-Armouche et al. 2006; Grandi et al. 2011; Voigt et al. 2009). SR Ca^{2+} leak is increased in AF, due to enhanced ryanodine receptor (RyR) activity (Neef et al. 2010; Voigt et al. 2009). Intracellular Ca^{2+} transient amplitude is diminished (Fig. 1D, *inset*), mostly due to reduced Ca^{2+} influx via I_{CaL} . The positive dependency of Ca^{2+} transient amplitude on pacing frequency is markedly attenuated in our cAF model compared to sinus rhythm (Fig. 1E *vs.* Fig. 1D).

Ca^{2+} abnormalities (and enhanced Ca^{2+} loading expected at high atrial rates during AF) are in turn likely to influence atrial electrophysiology, via effects on Ca^{2+} -dependent currents, as I_{NCX} , I_{Ks} , I_{ClCa} . It has been proposed that Ca^{2+} -activated K^{+} (SK2) channels play a role in AF, although the functional impact of these channels is still controversial (Nagy et al. 2009), as knockout of SK2 channels causes AP prolongation and AF in mouse (Li et al. 2009). Incorporation into our model may well be warranted once more data on SK2 channel density, gating, and Ca^{2+} -sensitivity are available. Stretch-activated Cl^{-} channels may also be involved in AF (e.g., secondary to structural remodeling).

Rate-dependent APD adaptation

Typically, the human atrial APD shortens when paced at faster rates (Fig. 1B), but the mechanisms underlying this rate-dependent APD adaptation are not fully understood. Our human atrial myocyte model (and (Koivumaki et al. 2011)) predicted this is due to the increase of $[Na^+]_i$ at fast pacing rates, which causes outward (repolarizing) shifts in Na^+/K^+ pump (NKA) and NCX currents that shorten the APD. An effect of $[Na^+]_i$ accumulation to shorten APD has been shown previously in guinea pig (Faber and Rudy 2000), canine (Decker et al. 2009) and human (Grandi et al. 2010; Iyer et al. 2004) ventricle. Notably, we confirmed experimentally in human atrial myocytes the prediction of our model that acute block of (outward) I_{NKA} causes AP prolongation, followed by APD shortening as I_{NKA} increases secondary to $[Na^+]_i$ increase, supporting the involvement of $[Na^+]_i$ in APD and rate-dependent APD adaptation in human atrial cells (Grandi et al. 2011). The diminished Ca^{2+} transients and shorter APs in the remodeled human atrial myocyte cause less Ca^{2+} extrusion and less Na^+ entry via Na^+/Ca^{2+} exchange, and the blunted positive inotropy limits predicted Na^+ accumulation, thus causing smaller outward shifts in NCX and NKA and contributing to the predicted (and measured) impairment of APD rate-adaptation in cAF (Fig. 1C).

Cell Signaling Pathways

The (mal)adaptive alterations associated with human chronic AF may be accounted for, or complicated by, activation and/or crosstalk between cellular signaling pathways (Fig. 2).

Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII)

CaMKII phosphorylates several key Ca^{2+} handling and regulatory proteins (Maier and Bers 2007), myofilament proteins, and various sarcolemmal ion channels (Bers and Grandi 2009) (Fig. 2). CaMKII is more expressed and more phosphorylated in human cAF (Neef et al. 2010; Tessier et al. 1999), and may be responsible for the reported increase in RyR activity (Neef et al. 2010). Conversely, a blunted effect of CaMKII inhibition on I_{CaL} in human cAF has been reported (Neef et al. 2010). Reduced inhibition of SERCA by hyperphosphorylated phospholamban (El-Armouche et al. 2006) in cAF could help maintaining a normal SR Ca^{2+} load despite increased RyR activity. CaMKII acutely enhances I_{to} in human atrial myocytes (Tessier et al. 1999), and this may reduce Ca^{2+} influx and minimize Ca^{2+} overload during AF by shortening the AP. On the other hand, a larger I_{to} is expected to accentuate the AP early repolarization, thus increasing the driving force for I_{CaL} . The effects of I_{to} changes on Ca^{2+} influx are potentially complex and modeling may help identifying the net impact of these two opposite mechanisms. Increased CaMKII activity may also explain the AF-induced increase in late Na^+ current (Sossalla et al. 2010).

Autonomic regulation

Both sympathetic and vagal activation have been shown capable of producing proarrhythmic changes in atrial APD and refractoriness and contributing to induction and/or perpetuation of AF.

β -adrenergic stimulation (Fig. 2) increases human atrial I_{CaL} (Christ et al. 2004; Van Wagoner et al. 1999) and I_{Kur} (Li et al. 1996), which are predicted to result in no net effect on atrial APD (Grandi et al. 2011), consistent with experiments (Workman 2010). The increased I_{CaL} elevates the AP plateau and, along with enhanced phospholamban phosphorylation, increases $[Ca^{2+}]_i$ and favors afterdepolarizations (Workman 2010). Chronic AF potentiates the effect of β -adrenergic stimulation to increase human atrial I_{CaL} (Christ et al. 2004; Van Wagoner et al. 1999), although basal I_{CaL} is markedly reduced in cAF, possibly due to increased phosphatase activity (Christ et al. 2004).

Vagal stimulation activates the muscarinic-receptor activated K^+ channel I_{KACH} , which shortens APD (Koumi et al. 1994) and ERP, thus promoting reentry. Our model demonstrated an acetylcholine dose-dependent reduction in human atrial APD, consistent with previous modeling studies (Maleckar et al. 2008), and Ca^{2+} transient amplitude (Grandi et al. 2011). Chronic AF appears to induce constitutively active I_{KACH} in human atrium, but attenuates the acetylcholine-mediated increase in atrial I_{KACH} (Dobrev et al. 2005).

Inflammation and oxidative stress

Increased myocardial oxidative stress (Mihm et al. 2001; Van Wagoner 2008) and inflammation (Van Wagoner 2008) have been associated with AF, and might be involved in AF pathogenesis. Several ion channels (Zima and Blatter 2006) (Fig. 2), myofilament proteins (Mihm et al. 2001), and protein kinases (e.g., CaMKII (Howe et al. 2004)) and phosphatases are subject to redox modulation. S-nitrosylation of the L-type Ca^{2+} channel alpha subunit is increased in AF, and exogenously applied glutathione partially restores the AF-related I_{CaL} reduction (Carnes et al. 2007), suggesting that oxidative stress may play a role in I_{CaL} downregulation. Oxidation increases RyR open probability and may contribute to AF-associated RyR hyperactivity. K^+ channels (e.g., I_{to} and I_{KATP}) are also sensitive to redox states. Kv1.5 current is inhibited by S-nitrosylation (Nunez et al. 2006), which may contribute to I_{Kur} suppression in AF. Redox-dependent modulation of I_{Na} has also been reported (Fearon and Brown 2004) and may account for the increased late component in cAF (both directly and via CaMKII activation).

Crosstalk and/or synergy between β -adrenergic and acetylcholine or CaMKII pathways, or the effects of oxidative stress (and oxidation vs. nitrosylation) deserve further investigation and would be important extensions for future modeling studies, as done in ventricular models (Soltis and Saucerman 2010),(Heijman et al. 2011). In fact, while the effects on targets in Figure 2 have been shown, a direct causal link to AF remodeling has not yet been established. In addition, Ca^{2+} loading and subsequently altered Ca^{2+} signaling may be involved in AF-associated remodeling of ion-channel expression and/or function (Makary et al. 2011; Qi et al. 2008). The incorporation of such processes would be a challenging next step to take in modeling AF.

Multiscale simulations

Animal and clinical studies have suggested that AF is a reentrant arrhythmia sustained by reentrant circuits propagating in a remodeled atrial tissue substrate (Jalife 2011). Rapid ectopic activity (possibly generated in the pulmonary veins) may also contribute to AF maintenance. These mechanisms are thoroughly reviewed in a recent article by (Wakili et al. 2011). Thus, understanding the mechanisms underlying initiation of reentry requires the integration of multiscale data (at ionic channel, cellular, tissue and whole atria levels) into multidimensional computational frameworks.

Numerous studies have used tissue-level simulations to determine the mechanisms that help maintain, or terminate, the small reentrant sources (rotors) during AF. A recent paper analyzed systematically the relative importance of ionic currents and transporters in modulating excitability, refractoriness and rotor dynamics in the human atrium (Sanchez et al. 2011). The study highlighted the fundamental role of NKA in modulating APD, APD restitution, ERP, and reentrant dominant frequency (DF) both in sinus rhythm and AF. The importance of I_{K1} , which was previously indicated as crucial in stabilizing rotors during cAF (Pandit et al. 2005), was confirmed. Also, I_{Na} was shown to alter atrial rotor dynamics by affecting conduction velocity and ERP. Specific blockade of I_{Kur} or I_{to} can also terminate rotor activity (Pandit et al. 2005), although the impact of these currents may be limited due to their downregulation in cAF (Sanchez et al. 2011). Emphasis has also been placed

recently on the effects of structural remodeling (e.g., dilation, fibrosis) associated with AF (Krogh-Madsen et al. 2012). Ashihara et al. (2012) have also coupled fibroblasts to atrial myocytes in human atrial tissue simulations and predicted reduced APDs, conduction velocity and excitability, as previously shown (MacCannell et al. 2007). They concluded that fibroblast proliferation in atria might cause complex fractionated atrial electrograms, which are normally the target of catheter ablation, during persistent AF.

While a homogeneous 2-D tissue geometry is often chosen to avoid confounding interpretation of the underlying mechanisms due to added complexities of structural and electrophysiological heterogeneities (Pandit et al. 2005; Sanchez et al. 2011), atrial anatomical properties and heterogeneity may play a role in maintaining reentry (Kuo and Trayanova 2006) and should be considered. Human atria are characterized by significant regional electrophysiological differences (Wang et al. 1993), due to intrinsic variations in the ionic currents through the atria (Caballero et al. 2010; Voigt et al. 2010; Wang et al. 1993). We (Grandi et al. 2011) and others (Nygren et al. 1998) accounted for variability in AP morphology within and between atria. Clinical electroanatomic mapping showed localized sites of high-frequency activity during AF in humans (Sanders et al. 2005). In most experiments DF left-to-right gradients are observed (Jalife 2011), and electrical isolation of the pulmonary vein from the left atrium is an effective strategy for preventing AF in many patients with paroxysmal AF (Medi et al. 2010). We simulated left-to-right gradients in repolarizing currents, and showed that the APD left-to-right gradient observed in sinus rhythm cells was reduced in cAF (Grandi et al. 2011), supporting the hypothesis that continuous fibrillatory activity may induce substantial remodeling and increase the likelihood of the appearance of new sources in either atrium (Sanders et al. 2005).

3-D human atria models have been developed (Harrild and Henriquez 2000; Jacquemet et al. 2006; Seemann et al. 2006) but somewhat limited by the lack of a complete set of experimental human data at the various scales. Recently, Aslanidi et al. (2011) developed a multiscale computational framework combining an integrated human atrial anatomical model with heterogeneous AP models for various cell types (Fig. 3) and coupled with a human torso model simulating body surface ECGs. This may constitute a useful platform that takes into account both spatial heterogeneity and anisotropy to study propagation in the normal and fibrillating atria and address some of the aforementioned issues. We hope that more recent and biophysically detailed models that include accurate descriptions of Ca^{2+} handling (Grandi et al. 2011; Koivumaki et al. 2011) will be incorporated in this rich platform.

Therapeutics

Computational models have proven useful in understanding and developing novel antiarrhythmic drug therapy for AF. Modeling has been used to investigate the electrophysiological effects (Tsujimae et al. 2007) and mechanisms of AF termination (Comtois et al. 2008) by available drugs. Recently, this approach has been taken a step forward to determine the relationship between drug dynamic properties and atrial-selectivity (vs. ventricles), AF-selectivity (vs. sinus rhythm), and AF-termination effectiveness (Aguilar-Shardonofsky et al. 2012), and suggested the use of simulations in developing therapeutic agents with optimized pharmacodynamic properties for AF treatment.

Conclusions

It is now clear that cardiac electrophysiology, Ca^{2+} (and Na^{+}) dynamics are intimately associated with respect to atrial arrhythmias. Integrating our present understanding of how they interact with cellular signaling networks may help linking mechanistically maladaptive

atrial remodeling and AF. Incorporation of these detailed models into a multiscale computational framework accounting for atrial structural and electrophysiological heterogeneity will have important predictive value in understanding complex aspects of AF initiation and/or maintenance and aiding future therapeutic strategies.

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Figure 1. **A)** Schematic representation of the electrophysiological and Ca^{2+} handling processes formulated in human atrial myocyte models. Alterations associated to AF are highlighted. Simulated APs (**B** and **C**) and Ca^{2+} transients (**D** and **E**) at various pacing rates in sinus rhythm and cAF respectively [Modified from (Grandi et al. 2011)]. Sinus rhythm (black) and cAF (blue) APs and Ca^{2+} transients at 1-Hz pacing frequency are shown in *insets* for comparison. AC: adenylate cyclase, ATP: adenosine triphosphate, β -AR: β -adrenergic receptor, CaM: calmodulin, cAMP: cyclic adenosine monophosphate, G: guanine nucleotide-binding protein, PKA: protein kinase A, PLB: phospholamban, PLM: phospholemman, PMCA: plasmalemmal Ca^{2+} pump, PPase: protein phosphatase.

Figure 2. Schematic representation of adrenergic (blue), CaMKII (red) and oxidative (green) signaling (all enhanced in cAF) and effects on targets. CFTR: cystic fibrosis transmembrane conductance regulator.

Figure 3. Heterogeneous model of the human atria [From (Aslanidi et al. 2011) with permission]. **A)** AP profiles in the right atrium, left atrium, pectinate muscle and crista terminalis cells. **B)** Spontaneous APs in the SAN. **C)** 3-D anatomical model of the human atria showing the main conductive bundles.