Atrial fibrillation: Insights from animal models, computational modeling, and clinical studies

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Summary

Atrial fibrillation (AF) is the most common human arrhythmia, affecting millions of patients worldwide. A combination of risk factors and comorbidities results in complex atrial remodeling, which increases AF vulnerability and persistence. Insights from animal models, clinical studies, and computational modeling have advanced the understanding of the mechanisms and pathophysiology of AF. Areas of heterogeneous pathological remodeling, as well as altered electrophysiological properties, serve as a substrate for AF drivers and spontaneous activations. The complex and individualized presentation of this arrhythmia suggests that mechanisms-based personalized approaches will likely be needed to overcome current challenges in AF management. In this paper, we review the insights on the mechanisms of AF obtained from animal models and clinical studies and how computational models integrate this knowledge to advance AF clinical management. We also assess the challenges that need to be overcome to implement these mechanistic models in clinical practice.

Keywords: Atrial fibrillation; Reentrant drivers; Arrhythmia mechanisms; Personalized computational modeling; Pulmonary vein isolation

Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia, affecting more than 43 million people worldwide.1 AF is associated with significant morbidity and mortality, posing substantial burden to patients and the health care system. Common therapies for AF include anti-arrhythmic drug therapy and radiofrequency or cryoballoon ablation.2 Despite significant advances in AF detection, management, and understanding of this arrhythmia, AF treatment remains suboptimal, partly due to gaps in knowledge on the mechanisms and pathophysiology of this rhythm.3–5 A combination of risk factors and comorbidities were also found to contribute to complex atrial remodeling, increasing vulnerability to AF and AF persistence. Altered electrophysiological (EP) properties, and areas of heterogeneous pathological structural remodeling serve to promote triggers of spontaneous activations as well as serve as the substrate for reentrant drivers.6–8 The autonomic nervous system plays an important role in the predisposition to AF.6 A combination of the mechanisms of AF, which combine triggers and substrate influences, have been shown to be on a spectrum of organization, from highly disorganized to globally organized fibrillatory conduction. The complex and individualized presentation of this arrhythmia suggests that deep understanding of the mechanisms and mechanisms-based personalized approaches to AF management and treatment will likely be crucial to improve and overcome the current AF burden on the healthcare system and the society at large. Over the past decade, personalized computational models of AF have been increasingly used to investigate AF mechanisms, provide risk prediction, and explore and define the personalized approaches to therapy.9 These models allow for realistic personalized simulations and full control over parameters, facilitating the investigation of disorder.1

Abbreviations: AF, atrial fibrillation; AP, action potential; PAF, paroxysmal AF; perAF, persistent AF; PV, pulmonary vein; RF, radio-frequency; PVI, pulmonary vein isolation; FIRM, Focal Impulse and Rotor Modulation; CONFIRM, CONventional ablation with or without Focal Impulse and Rotor Modulation; ECG, electrocardiographic imaging; 3D, three-dimensional; CT, computed tomography; MRI, magnetic resonance imaging; EP, electrophysiological; ERP, effective refractory period; CV, conduction velocity; LGE, late gadolinium enhancement; LA, left atrium; DECAAF, Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation; EAT, epicardial adipose tissue; DT, diffusion tensor; PLA, posterior LA; APD, AP duration; CE, contrast-enhanced; EAM, electroanatomic mapping; OPTIMA, Optimal Target Identification via Modelling of Arrhythmogenesis

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the multifaceted interactions between AF substrates, drivers, and triggers. Accordingly, this brief review focuses on the mechanisms of AF obtained from animal models and clinical studies and how computational models integrate this knowledge to advance AF clinical management.

Mechanisms of atrial fibrillation derived from animal studies – two schools of thought
Based on experimental results from animal studies, two schools of thought consolidated the initial understanding of the mechanisms of AF. The first proposes self-sustained disorganized activity consisting of multiple wavelets, while the second reports the presence of AF drivers, which then shed multiple new “daughter” wavelets.

Multiple wavelets
In a seminal study on AF mechanisms in 1964, Moe et al. developed a computational model of AF describing impulse propagation in a nonuniform two-dimensional system. The variables in their model were derived from animal experiments and the results suggested that AF was sustained by multiple wavelets propagating randomly through atrial tissue; 23–40 random wavelets were necessary to sustain AF in the model. This hypothesis was later supported by Allessie et al. who demonstrated that AF could be self-sustained in the acetylcholine-infused canine atrial animal model, although only four to six simultaneous wavelets were needed to sustain AF.

Further research by the Allessie’s team revealed that these multiple wavelets might be the result of a discontinuous propagation between epicardial and endocardial atrial layers, as evidenced by simultaneous endo-epi mapping of ex vivo hearts. A dissociation between endo- and epicardial atrial layers has been reported in AF patients, suggesting that sites of epicardial breakthrough (Fig. 1a) facilitate multiple wavelet reentry. In other words, fibrillation waves appearing on the epicardium before activation of its surroundings originate from the endocardium and are responsible for sustaining AF.

AF driver (“mother rotor”)
A number of studies have suggested that AF may not be random and may exhibit a level of periodicity. With the advances in mapping technology, specifically the combination of optical mapping and frequency domain analysis, the electrical activity of AF was further characterized, and new insights were obtained supporting a potentially different mechanism of AF in animal models. The “mother rotor” hypothesis surmised that AF is driven by reentrant drivers – high-frequency sources that rotate around a phase singularity (or core) (Fig. 1b). Once a rotor is formed, the myocardium near its core cannot sustain conduction of the action potential (AP) in a one-to-one fashion (due to the short cycle length) and the high-frequency wavefronts stemming from the rotor core may fragment further when they encounter anatomical or functional obstacles. Therefore, according to the “mother rotor” hypothesis, wavebreaks are the hallmark of AF maintenance as they lead to further rotor initiation and fibrillatory waves. Optical mapping and computational simulation studies of the atria have revealed rapid rotors activating atrial tissue at high-frequency and driving the fibrillatory conduction with a degree of spatiotemporal organization during the apparent chaos.

Breakthrough clinical advancements in our understanding of AF

Pulmonary veins as focal sources of AF
Results from animal studies have offered insights on the characteristics of AF, but the understanding and treatment of this arrhythmia in humans unfolded after a number of breakthrough clinical studies. The three clinical types of AF are paroxysmal AF (PAF; episodes of arrhythmia that terminate spontaneously or with intervention within seven days of onset), persistent AF (perAF; continuous episodes that are not self-terminating and are sustained for more than seven days), and long-standing perAF (continuous episodes that last more than one year). In the late 90’s, Haissaguerre et al. discovered that PAF was initiated by focal sources originating in the pulmonary veins (PVs; Fig. 2). Electrical recordings preceding the onset of AF revealed that 94% of the focal sources were located in the PVs, and radiofrequency (RF) ablation encircling the PVs (i.e., pulmonary vein isolation, PVI) terminated AF. This landmark study led to PVI ablation becoming the cornerstone of clinical therapy for AF.

Discovery of reentrant drivers sustaining human AF
Another pivotal advancement in the understanding of human AF was the demonstration that reentrant drivers (together with focal impulses) were the sustaining mechanisms of AF in humans (Fig. 2) and that catheter ablation of these drivers terminated the arrhythmia. The first report of rotors driving human AF came from the Focal Impulse and Rotor Modulation (FIRM) case study, which was soon followed by the prospective, multicenter clinical trial CONFIRM (CONventional ablation with or without Focal Impulse and Rotor Modulation). In the CONFIRM trial, persistent rotors (spiral waves) as well as focal beats (centrifugal activation from an origin) were identified using electrogram recordings from a 64-pole basket catheter. Ablation of these localized sources terminated or substantially organized (>10% slowing) AF in all patients.
Furthermore, FIRM-guided ablations (targeting stable rotors and focal impulses) combined with PVI resulted in freedom from AF in more than 80% of patients—after one year from the procedure—in contrast to 45% of patients who were treated with conventional ablations. A follow up study showed that FIRM-guided ablations prevented early and late arrhythmia recurrence for more than three years (compared to one year for PVI-only). A follow up study showed that FIRM-guided ablations prevented early and late arrhythmia recurrence for more than three years (compared to one year for PVI-only). However, further studies have not been able to demonstrate the efficacy of reentrant driver ablation using FIRM, which could potentially be attributed to the low resolution of the basket catheter. Similarly, studies using electrocardiographic imaging (ECGI) data also identified rotors to be the driver of AF in PAF and perAF patients. ECGI consists of a noninvasive three-dimensional (3D) mapping technique used to reconstruct the electrical activity of the epicardium based on electrocardiogram (ECG) signal and an imaging modality, such as computed tomography (CT). Using this technique, Haissaguerre et al. recorded atrial EP activity in more than one hundred perAF and long-standing perAF patients and identified more than four thousand drivers; around 80% of them were rotors and the rest, focal breakthroughs. They found that the time
of continuous AF duration and the number of driver regions were positively correlated and that driver ablation alone terminated fibrillation, but the termination rate strongly declined when the period of continuous AF was greater than 6 months. This suggests that, at least in the early months, reentries and focal sources are responsible for AF maintenance and personalized targeted ablation can terminate AF.

**Discovery of fibrosis in patients with AF**

Another important advancement in the understanding of AF mechanisms was the discovery of fibrotic remodeling in the atria of AF patients. After histological analysis of autopsy specimens, Platonov et al. demonstrated that AF patients presented two to three times more fibrosis than patients without history of AF. Their results also showed a significant correlation between fibrosis and AF severity, where patients with longstanding perAF exhibited more fibrosis than PAF patients. Furthermore, delayed-enhancement magnetic resonance imaging (MRI) studies revealed that every patient with AF presented some degree of fibrotic remodeling, even the ones with lone AF. Both clinical MRI and histological studies of explanted human atria have revealed a significant amount of fibrosis in the left and right atrium in patients with AF. All these findings suggest that fibrosis is highly correlated with AF and likely plays a significant role in the maintenance of the arrhythmia. The individual levels of fibrosis (total amount, as well as specific distribution) in AF patients together with the different mechanisms of AF maintenance (illustrated in Fig. 2) lead unique fibrillatory conduction patterns during AF.

Fibrotic tissue is characterized by altered EP properties, resulting in increased effective refractory period (ERP) and decreased conduction velocity (CV). This pathological remodeling leads to arrhythmogenic conduction blocks that serve as a substrate for AF. These conduction blocks were studied in *ex vivo* human atria where fibrotically insulated myobundles showed CV anisotropy up to 10:1, leading to microreentry. *Ex vivo* studies of the diseased human atria demonstrated a significant difference between endocardial and epicardial activation during pacing and sustained AF caused by the complex atrial microstructure (local myofiber orientations, wall thickness variation, and fibrosis distribution). Furthermore, experimental results from high-resolution 3D functional and structural imaging of explanted human atria revealed that AF driver regions have significant amount of fibrosis in the left and right atrium in patients with AF. All these findings suggest that fibrosis is highly correlated with AF and likely plays a significant role in the maintenance of the arrhythmia. The individual levels of fibrosis (total amount, as well as specific distribution) in AF patients together with the different mechanisms of AF maintenance (illustrated in Fig. 2) lead unique fibrillatory conduction patterns during AF.

**Fig. 2: Mechanisms of AF maintenance: ectopic foci on PVs, rotors, and wavelets.** Representation of AF maintenance near a PV by an ectopic focus on the vein (I), a rotor (II), or multiple wavelets (III). Representation of rotor maintenance in conjunction with other mechanisms: rotor formation as a result of wavebreaks near an ectopic focus (IV), intramural rotors resulting in endocardial or epicardial breakthroughs (V), and drifting rotors (trajectory illustrated in blue) causing multiple epicardial wavelets (From [22]). While insight about how rotational activity sustains AF has been derived from animal studies, ectopic foci as drivers of AF were first recorded in human studies.
exhibit distinct structural differences when compared to nondriver regions. For example, Zhao et al. found that AF drivers were located in areas of increased fibrosis density (20–30%), as well as normalized wall thickness between 20 and 30%, which may be used to identify arrhythmogenic regions driving AF. Of notice, there are many similarities in the mechanisms of AF maintenance in both ex vivo and in vivo human atria, allowing for a direct comparison between them.

Given the evidence linking fibrosis to AF, fibrosis has become an important clinical predictor of success and AF recurrence post-catheter ablation. Clinically, late gadolinium enhancement (LGE) MRI scans are used to quantify atrial fibrosis, which corresponds to hyper enhanced voxels in the image (Fig. 3a). This has been validated by LA wall biopsies from healthy and AF patients, which confirmed that regions of LGE MRI enhancement correspond to fibrotic tissue (Fig. 3b). Using LGE MRI to quantify pre-ablation fibrosis in the left atrium (LA), four different stages of structural remodeling were defined: Utah I (≤5% LA wall enhancement), Utah II (>5% to ≤20%), Utah III (>20% to ≤35%), or Utah IV (>35%). Accordingly, patients with extensive enhancement (i.e., fibrosis) pre-ablation have a higher probability of AF recurrence post PVI ablation compared to those with moderate or minimal enhancement. The same trend was observed in the landmark DECAAF (Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation) clinical trial, which revealed that AF recurrence post ablation is positively related to the baseline atrial fibrosis prior to ablation as well as the amount of residual fibrosis (remaining fibrotic areas that were not altered by ablation scar). These findings suggest that ablation of targets associated with the presence of fibrosis in addition to PVI is likely to reduce AF recurrence rates caused by non-PV triggers. However, what part of the distributed fibrosis in the atria that needs to be ablated remains unknown.

Computational models of AF uniting insights from animal models and clinical studies

Computational models of the whole atria allow for multilevel integration of multiple datasets, empowering the investigation of AF mechanisms, risk prediction, and personalized therapy. The motivation behind the development of these in silico mechanistic models comes from their ability to recreate healthy and diseased states of the atria by fine tuning of multiple parameters, which is simply not possible clinically or experimentally. Several whole-atria models have been developed to better understand the mechanisms of AF, each with varying degrees of complexity. While these models were initially developed from pathophysiological properties of the animal atria, the focus has recently shifted towards human AF models.

General principles

Whole-atria computational models that simulate atrial EP consist fundamentally of AP propagation in a network of cells, which is usually done in a bottom-up approach from cell to organ level (Fig. 4). Equations describing channel gating kinetics and ionic currents are integrated into a membrane framework based on the formalism introduced by Hodgkin and Huxley. A cell-level model recreating the atrial myocyte AP dynamics is coupled with other cells to create an electrically coupled tissue (tissue level). A simplified or realistic atrial geometry (organ level) integrates information about fiber orientation, wall thickness, and other structural features in a 3D shape that simulates atrial electrophysiology and arrhythmias.

Insights from computational modeling of AF in animal-model atria

Whole-atria models based on the animal heart offer the advantage of integrating data from histology as well as high-resolution imaging and electrical or optical...
mapping – something not easily attainable in in vivo human studies. While there is not a well-established correlation between the pathophysiology of the animal and human AF, these animal-based models have shed light on some important mechanisms of AF. Numerous atrial models have been developed using realistic geometry from the sheep, rabbit, pig, and canine atria. These models presented morphologically realistic atria, including anatomical structures such as fiber orientation, orifices of veins and valves, as well as
muscle structures like the crista terminalis and pectinate muscles. The Auckland group developed a remarkable whole-atria model based on high-resolution imaging of the sheep heart.47,48,52 For the first time, realistic myofiber architecture obtained from diffusion tensor (DT) MRI was incorporated into a computational model of the atria. Their model was used to explore the role of atrial myofiber architecture during normal and abnormal electrical activation, and their results suggest that the myofiber arrangement in the posterior LA (PLA) increases vulnerability to AF maintenance. Their structure tensor approach was also applied to canine atrial models to investigate the role of PVs in AF.53 Furthermore, a study using optical mapping, histology, and computer simulations of the sheep atria have investigated the role of fibrosis in AF, and the results indicate that patchy fibrosis in the PLA may be an arrhythmogenic substrate for rotors and intramural reentry.54

Other in silico modeling studies have demonstrated that intrinsic differences in AP duration (APD) in various atrial regions predispose these areas to AF reentry. Similarly, local variations of atrial wall thickness have also been shown to create conditions for reentry generation in computational models.55 In conclusion, these animal-based whole-atria models have exemplified their capability to simulate AF under different scenarios and provided insightful information on the mechanisms sustaining atrial arrhythmias.

Insights and treatment strategies from personalized computational models of AF
Computational modeling of human AF could be used for mechanistic understanding, risk prediction, and personalized therapy through the multilevel integration of multiple datasets. Unlike clinical or experimental
studies, in silico simulations allow critical parameters of AF to be leveraged in a systematic and controlled way, allowing for the study of the relative contribution of each variable. Furthermore, whole-atria models developed from patient-specific features allow for the identification of arrhythmogenic regions and the development of individualized treatment strategies in a prospective fashion. State-of-the-art models combine bi-atrial structural and functional data obtained from ex vivo or in vivo human hearts. Structural data refers to atrial geometry, fibrosis distribution, wall thickness, and myofiber orientation, and it is usually obtained from imaging such as LGE MRI or contrast-enhanced (CE) MRI. Functional data refers to EP properties of the atria that can be measured from electrical or optical mapping, revealing AF driver patterns and locations, variations in local CV and repolarization.

One of the first steps in creating a whole-atria model of human AF is to determine which atrial cell model to implement. Five (of many) biophysical cell models of the human atria (the Courtemanche et al., the Nygren et al., the Maleckar et al., the Koivumaki et al., and the Grandi et al. models) have been reviewed by Wilhelms et al. each with its own calcium transients, restitution properties, AP morphology, and reentrant circuits. Their diversity may reflect the inherent heterogeneity in human atrial myocytes and even local variation in atrial EP properties. Because clinical EP recordings require invasive procedures and sophisticated calibration approaches, modeling inter and intraindividual EP heterogeneity is very challenging, which may limit the assessment of AF trigger mechanisms. Thus, patient-specific AF models are limited in their characterization of electrical remodeling and usually rely on these established atrial cell models to characterize EP properties. Qiu et al. provide additional information on the mechanisms of electrical remodeling in AF.

Another important step in developing a computational model of AF is the reconstruction of the structural features of the atria. Clinically derived whole-atria models usually employ imaging or electroanatomic mapping (EAM) data to recreate patient-specific atrial geometry. Imaging modalities such as CT and LGE MRI are commonly used in many computational studies because, compared to EAM, they allow for a more detailed reconstruction of the anatomy, in addition to being non-invasive. LGE MRI further allows the detection of fibrosis in the atrial wall, which is modeled with altered EP properties, although this remains to be experimentally validated. Various ways of modeling fibrosis have been investigated and the methodology of choice may have large effects on AF dynamics. Studies demonstrated that the location of AF reentrant drivers is dictated by the distribution of atrial fibrosis, with AF induced and sustained only in atrial models above a certain level of fibrosis. Furthermore, computational models also revealed that AF reentrant drivers persisted in fibrotic boundary zones characterized by high fibrosis density and entropy regardless of the pacing location.

However, the relatively low resolution of in vivo LGE MRI scans result in the segmentation of atrial fibrosis from LGE MRI as well as the delineation of the thin atrial wall and interatrial conduction being fraught with uncertainty and is an area of intense research. The need to incorporate myofiber orientation in the personalized computational models has precipitated the development of approaches to assign patient-specific fiber orientations based on mapping from human DT MRI atrial fiber atlases and rule-based methods. Ex vivo studies provide additional information with submillimeter high-resolution data and histological analysis. Fedorov and co-workers developed a 3D atria computational model based on histologically validated CE MRI and panoramic optical mapping at submillimeter resolution, which allowed for integration of detailed atrial anatomy as well as functional data (regional APD, CV, and rate-dependent behaviors). Their results indicate that atrial structural fingerprints – consisting of a specific combination of intermediate wall thickness, intermediate fibrosis, and twisted myofiber orientation – can be used to identify AF drivers. Finally, studies have also used other imaging modalities such as CT for personalized ablation targeting. EAM-based studies for targeting AF substrate have been previously reviewed by Sim et al.

The unique and perhaps most exciting aspect of personalized models of AF is the ability to simulate, test, and plan different ablation strategies prospectively, and even predict a patient’s risk of AF recurrence. Following the seminal work of Haisaguerre et al. that led to PVI ablation becoming the cornerstone of clinical therapy for AF, several computational models were developed to test the effectiveness of various PVI ablation strategies. Using CT-based atrial models, Hwang et al. compared the outcome of different ablation strategies and concluded that the most effective one was PVI with posterior box isolation and anterior line ablation. This hypothesis was evaluated in a prospective clinical trial with 108 perAF patients that were randomly selected to receive either standard-of-care ablation or in silico guided ablation. However, the proposed in silico ablation consisted of more extensive lesion sets. This study demonstrated the ability of computational models to guide AF ablation therapy, but it failed to achieve significant improvement compared to standard-of-care, denoting the need for further work. Furthermore, the discovery of fibrosis as a substrate for AF reentrant drivers led to the exploration of personalized in silico ablation strategies targeting fibrotic regions in clinically derived AF models. In these studies, ablations targeting AF drivers restored sinus rhythm in the models. Boyle et al. pioneered a prospective ablation study for patients with perAF and fibrosis on LGE MRI driven entirely by personalized simulations. In this study termed OPTIMA (OPTimal Target Identification
via Modelling of Arrhythmogenesis), ten perAF patients were enrolled and the individual atrial models were reconstructed from LGE MRI scans. From the simulations, the locations of reentrant drivers sustaining AF pre (and possibly post) ablation were determined and the optimal ablation strategy designed (Fig. 5). The proposed ablation targets were used to steer patient treatment, eliminating not only the clinically manifested AF but also any potential emergent AF drivers. While successful, the efficacy of this study will need to be further assessed in a larger cohort. Azzolin et al. used different combinations of imaging (LGE and CT) and mapping (EAM) data from 29 perAF patients to create patient-specific atrial models that were used to determine personalized ablation targets. The results from this study showed that PVI had the lowest acute success rate and that personalized fibrosis-targeted ablation resulted in success rates as high as 90.9%, although it required EAM data for model construction. Lastly, the results from these mechanistic models may also be used to prevent AF recurrence, where the features of a patient’s LGE MRI scan and personalized simulations are used to predict the patient’s risk of AF recurrence.

**Outstanding questions**

AF continues to be a major burden on patients and the healthcare system, and improved management approaches are urgently needed. A deep understanding of the AF mechanisms from animal and clinical studies

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**Fig. 5: Personalized Computational Modeling of the Atria for Ablation Guidance: The OPTIMA approach.** (a) Patient-derived atrial geometry and fibrosis distribution on the left and right atria (left). Activation map after rapid pacing and virtual PVI ablation (middle). Certain areas were activated before (black) or after (gray) the 800 ms time range. Two reentries (pink arrows) were identified near the RAA. OPTIMA ablation strategy showing ablation targets (red circles) and lesion lines (red line) connecting the targets to a non-conductive boundary (right). Anatomical structures: left atrial appendage (LAA), left superior pulmonary vein (LSPV), left inferior pulmonary vein (LIPV), right superior pulmonary vein (RSPV), right inferior pulmonary vein (RIPV), superior vena cava (SVC), inferior vena cava (IVC), right atrial appendage (RAA), tricuspid valve (TCV), and mitral valve (MV). (b) Steps undertaken to identify OPTIMA ablation targets. An initial set of lesions is determined after analysis of the rapid pacing in the model. Virtual ablations are performed targeting the reentrant drivers and the rapid pacing protocol is repeated to determine whether new (emergent) reentries arise in the post-ablation substrate. This is repeated until there are no emergent reentries induced in the model. The final OPTIMA ablation targets are then exported to the clinical electroanatomic navigation system (CARTO) for clinical ablation [Modified with permission from58].

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in combination with mechanistic computational models of AF offer opportunities to advance AF management, including the development of personalized targeted ablation strategies and prediction of AF recurrence. Continuing advances in computational methodologies, as well as clinical imaging modalities may foster new opportunities for personalized in silico AF models. However, several questions remain. First, as clear from this review, the mechanisms of AF are not yet fully understood and the relationship between AF progression and altered EP properties needs to be addressed. Also, given the technological limitations, the extent of personalization regarding atrial wall thickness, myocardial architecture, and fibrosis. Lastly, clinical trials evidencing the benefits of using computational models will be pivotal to propel their routine application in clinic.

Search strategy and selection criteria

Data for this review were identified by searches of PubMed, MEDLINE, and additional references from relevant publications using the search terms “atrial fibrillation,” “computational model,” and “mechanisms” contained in the title or abstract. We focused on articles published between 2012 and 2022.

Contributors

Carolyna Yamamoto was responsible for literature search, drafting the manuscript, and making the figures. Natalia Trayanova was responsible for some of the writing and provided critical revisions of the manuscript. All authors read and approved the final version of the manuscript.

Declaration of interests

None.

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