

# New insights into the molecular basis of atrial fibrillation: mechanistic and therapeutic implications

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**This editorial refers to a collection of nine reviews and nine original articles that are part of this special issue on atrial fibrillation, guest edited by Dobromir Dobrev and Stanley Nattel.**

Atrial fibrillation (AF), the most common sustained arrhythmia, is associated with substantial cardiovascular morbidity and mortality, with stroke being the most critical complication.<sup>1</sup> Present drugs used for AF therapy have major limitations, including incomplete efficacy and risks of life-threatening proarrhythmic events and bleeding complications.<sup>1,2</sup> Non-pharmacological ablation procedures are efficient and relatively safe, but the very large size of the patient population allows ablation treatment of only a small number of patients. Therefore, drug therapy remains the mainstay of AF treatment. Maintenance of sinus rhythm (rhythm control) appears preferable, but studies to date have failed to demonstrate tangible advantages of rhythm control. The failure to show benefits in mortality and stroke incidence motivates attempts to identify new therapeutic targets relating to basic mechanisms underlying arrhythmia susceptibility. A better mechanistic understanding of the molecular basis of AF may allow for the development of safer and more effective treatment approaches.

The mechanisms underlying AF susceptibility are multiple and incompletely understood. The two major determinants of AF maintenance are reentry and ectopic impulse formation (ectopic activity).<sup>3</sup> Reentry induction requires an appropriate arrhythmogenic substrate and a trigger that initiates reentry within the substrate. The likelihood of reentry is determined by the tissue properties of conduction and refractoriness, with slow conduction and short refractoriness making persistence of reentry more likely. Ectopic activity is governed by factors controlling the occurrence of afterdepolarizations, primarily Ca<sup>2+</sup> handling abnormalities that can cause early and delayed afterdepolarizations. The changes in atrial structure and function that result from heart disease, and indeed AF itself, constitute atrial remodelling and are key elements of the AF substrate.<sup>3,4</sup> Atrial remodelling

has the potential to increase the likelihood of reentry and/or ectopic activity. In addition, genetic factors establish electrophysiological substrates that determine individual vulnerability to AF occurrence and maintenance. Recognizing the clinical relevance of AF, unmet therapeutic needs, and rapid advances in basic research technology, *Cardiovascular Research* initiated a Review Focus Issue dealing with important topics related to the enormous advances in understanding the molecular basis of AF that have occurred over the past few years. This issue contains important work—both review and original articles—addressing the role of genetic background, microRNA, atrial fibroblasts, key ion channels, and the spatiotemporal organization and dynamics of tissue conduction in arrhythmia development and the potential therapeutic implications.

The first few articles address the role of genetic factors in AF pathophysiology. Disease-causing mutations have provided stimulating insights into AF pathophysiology. Mahida *et al.*<sup>5</sup> review the role of single-gene mutations in AF pathophysiology, highlighting the potential of monogenic forms to provide important paradigmatic insights into AF mechanisms. This is supported by the original paper by Olesen *et al.*<sup>6</sup> that shows that mutations in the sodium channel  $\beta$ -subunit SCN3B are associated with early-onset lone AF, supporting the notion that decreased sodium current enhances AF susceptibility. Genome-wide association studies (GWASs) are providing breakthroughs in understanding a wide range of diseases. Sinner *et al.*<sup>7</sup> review the basic principles of high-throughput genetic analyses and GWASs, reviewing the rapidly evolving evidence in AF that has provided important new insights into genetic predisposition and raised challenging pathophysiological questions.

MicroRNAs are part of an integrated system controlling development, physiology, and disease-related remodelling processes. There is recent and increasing evidence of a key role of microRNAs in AF. Wang *et al.*<sup>8</sup> critically evaluate the evidence for a role of microRNAs in cardiac excitability and arrhythmias, providing a comprehensive overview of the available experimental data on the participation of microRNAs in generating the AF substrate. The authors discuss the potential of these new regulators as novel therapeutic targets for AF.

The next series of papers provides evidence for a crucial role of  $\text{Ca}^{2+}$  handling abnormalities in AF pathogenesis. As elegantly summarized by Greiser *et al.*,<sup>9</sup> impaired  $\text{Ca}^{2+}$  handling can precede AF development, potentially contributing to arrhythmia initiation, but can also result from AF itself, thereby contributing to arrhythmia maintenance. AF has been traditionally considered a reentrant arrhythmia, but increasing evidence points to a role for  $\text{Ca}^{2+}$ -related triggered activity. Recent molecular work suggests a primary role for abnormal  $\text{Ca}^{2+}$  handling by the ryanodine receptor as a final common pathway. The original paper by Zhang *et al.*<sup>10</sup> validates previous work in genetically modified mice,<sup>11,12</sup> clearly showing that increased diastolic sarcoplasmic reticulum  $\text{Ca}^{2+}$  leak through mutated ryanodine receptors (RyR2-P2328S) enhances susceptibility to pacing-induced AF in the absence of repolarization abnormalities. Finally, Dobrev *et al.*<sup>13</sup> summarize and review in detail evolving concepts about the role of ryanodine receptor function and dysfunction in AF development.

Another group of articles provides new insights into the molecular determinants of atrial structural remodelling. Increasing evidence points to key importance of fibrosis in AF, as both a cause and a therapeutic target.<sup>14</sup> Yue *et al.*<sup>15</sup> review the distinguishing characteristics of atrial fibroblasts, in particular the molecular determinants of their electrical function and how these properties contribute to fibrosis and arrhythmogenesis. Tsai *et al.* report an elegant original study, following up on an earlier observation that rapidly activating cardiomyocytes secrete substances that promote fibroblast activation,<sup>16</sup> by demonstrating that the cardiomyocyte-derived factors are angiotensin II and reactive oxygen species that act via enhanced TGF- $\beta$ 1 production.<sup>17</sup> The molecular mechanisms of atrial structural changes caused by stretch and their signal transduction pathways are addressed in a comprehensive review by De Jong *et al.*<sup>18</sup> The complex structural changes described by these articles likely contribute to the progressive endo-epicardial electrical dissociation of atrial muscle bundles occurring with long-lasting AF in a goat model, as described in an original paper by Eckstein *et al.*<sup>19</sup>

The next three articles deal with the role of neuroanatomic factors and spatiotemporal disorganization in AF. Nishida *et al.*<sup>20</sup> investigate the role of pulmonary veins vs. autonomic ganglia in different experimental substrates of canine AF. The authors show that pulmonary veins play a minor role in experimental AF due to heart failure (HF) or atrial tachycardia remodelling, whereas autonomic ganglia are important in AF related to atrial tachycardia remodelling (but not HF) by virtue of left atrial autonomic hyperinnervation. In another original paper, Lu *et al.*<sup>21</sup> identify distinct restitution properties in vagally mediated AF and AF induced by short-term (6 h) atrial tachycardia remodelling, implicating restitution kinetics in AF pathophysiology. Finally, Jalife elegantly reviews and critically discusses our current understanding of the theory of AF dynamics.<sup>22</sup> He suggests that future research should focus on the development and validation of new numerical and humanized animal models to better understand mechanisms underlying AF.

The final group of papers deals with new approaches to AF treatment. Ultra-rapid delayed rectifier channels are a unique set of ion channels that provide interesting opportunities for atrial-selective antiarrhythmic drug development. The review article by Ravens and Wettwer<sup>23</sup> provides a state-of-the-art update of the many new developments with the goal of understanding their physiology and pathophysiology and discuss their potential as atrial-selective anti-AF targets. In a pig model, Pandit *et al.*<sup>24</sup> demonstrate that the

atrial-selective ultra-rapid delayed rectifier channel is an ineffective antiarrhythmic drug target in cholinergic AF, whereas manipulating  $\text{Na}^{+}$  current 'availability' might represent a viable antiarrhythmic strategy. By integrating the structural biology of drug-ion channel interactions with electrophysiology and optical mapping, Noujaim *et al.*<sup>25</sup> identified the structural determinants of the inhibitory interaction of chloroquine and quinidine with the Kir2.1 subunit of IK1, potentially explaining the different antifibrillatory efficacy of these drugs at the whole-heart level. This approach might be a useful molecular strategy for developing structurally based ion channel-interacting drugs in the future. In the final original work, Mayyas *et al.*<sup>26</sup> show that dietary  $\omega$ -3 fatty acids reduce atrial inflammation and iNOS and ET-1 expression and attenuate AF inducibility following cardiac surgery by modulating autonomic tone, providing insight into the reported efficacy of  $\omega$ -3 fatty acids in preventing post-operative AF in some studies.

In summary, a number of outstanding experts have contributed to the realization of this Review Focus Issue. Our understanding of the molecular pathophysiology of AF is still limited but is improving very rapidly as evidenced by this collection of articles. Hopefully, these advances will ultimately lead to improved clinical management of AF.

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