Atrial Fibrillation (AF), the most common sustained tachyarrhythmia, currently affects 1% to 2% of the general population. Age is arguably the strongest determinant of AF occurrence, and the prevalence of AF is increasing as the population ages, projected to increase from ≈7 million today to ≈12 to 16 million predicted for the United States in 2050 (including estimates for paroxysmal and silent AF). There has been a marked progress in our understanding of the basic mechanisms underlying AF for the past 20 years. The management of AF continues to face huge challenges, but advancing knowledge and new technologies have also created unprecedented opportunities, which will undoubtedly revolutionize AF management over the next 20 years.

Recognizing the importance of this area and the rapid pace of knowledge development, the Editorial Board of Circulation Research decided to develop a Compendium on Atrial Fibrillation. The compendium includes 6 state-of-the-art review articles on themes of clinical features and pathophysiology of AF, molecular electrophysiology of AF initiation, maintenance and progression, autonomic nervous system control of AF, genetic factors determining AF occurrence and risk, the use of mathematical modeling to understand and manage AF better, and the mechanisms governing present and future therapy of the arrhythmia. The goal of the present article is to provide a context and unifying vision for the compendium, showing how each of the components relates to each other, to our overall understanding of AF, and to the future of the field.

Historical Perspective on AF Mechanisms

Figure 1 provides a timeline illustrating major milestones of the research into AF mechanisms that has led to our present understanding. An immediate obvious point is the accelerating pace of research. Although this analysis is clearly subjective, the many important discoveries for the past 20 years greatly dwarf the quantity of discoveries in the 75 preceding years. This having been said that it is nevertheless humbling to read how much was accurately inferred by scientists of the early 20th century based on then-available relatively primitive methods, as summarized by Garrey in a classical review article from 1924. Garrey points out that “AF is now recognized as the commonest of all cardiac irregularities,” recognizes the inter-relationships between atrial flutter and AF, and describes experimental evidence to support competing notions that AF is maintained by (1) local ectopic foci (multiple or single with fibrillatory conduction), (2) a single re-entry circuit (in Garrey’s words, a “mother wave”) with fibrillatory conduction, or (3) multiple simultaneous functionally determined re-entry circuits. We continue to debate many of these issues today, seeking their mechanisms and application. Moe et al published the first computer-based mathematical model of AF.

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in 1964, which established the multiple-wavelet concept of AF that became the dominant conceptual framework for over 30 years. In a series of classical articles beginning in 1978, principally in the French literature, Coumel et al. championed the importance of autonomic nervous system involvement in clinical AF. In 1988, Rensma et al. provided evidence that the key factor determining the occurrence of AF or atrial flutter is the wavelength for re-entry, an idea that remains useful for heuristic purposes but fails to reflect key AF determinants in some disease conditions and in response to Na+ channel blocking drugs.

The pace of discovery greatly accelerated after 1995, when Wijffels et al. published the seminal observation that AF begets AF by causing important electrophysiological alterations in the atrium, and Morillo et al. reported that atrial tachycardia leads to an atrial cardiomyopathy with dilated atria, short refractory periods, and sustained AF. These studies introduced the notion of atrial remodeling, which has subsequently become a central concept in AF pathophysiology. The work of Haissaguerre et al. on the role of the pulmonary veins (PVs), first reported in 1997 and then fully exposed in a landmark article in 1998, led to the first really effective approaches to definitive management of AF by ablation of atrial tissue and provided a novel and challenging pathophysiological paradigm in terms of the basis for PV involvement. Around the same time, the ion current mechanisms involved in atrial remodeling were first described in detail, and the first detailed human atrial action potential computer simulation models based on realistic mathematical representations of directly measured ion currents were reported. These models became the basis of a wide range of sophisticated mathematically based analyses of the ionic, structural, and functional determinants of AF. On the basis of pioneering work of Winfree, the Jalife laboratory applied the concepts of spiral waves and rotors to AF, arguing that uninterrupted activity of discrete re-entrant sites plays a central role in AF maintenance.

Although the work of Wijffels et al. and Morillo et al. revealed how the rapid atrial rates induced by AF, once begun, lead to atrial vulnerability and AF promotion, the changes leading to the initial occurrence of AF remained unexplored.

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**Nonstandard Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>PV</td>
<td>pulmonary vein</td>
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**Milestones in AF research**

- 1920
- 1950
- 1978
- 1988
- 1995
- 2014

**Figure 1.** A schematic representation of the history of atrial fibrillation (AF) research, leading to our present understanding of clinically relevant mechanisms. ANS indicates autonomic nervous system; AP, action potential; EP, electrophysiology; PV, pulmonary vein; and SNPs, single nucleotide polymorphisms.
In 1999, Li et al.\textsuperscript{26} studied the substrate for AF occurrence associated with congestive heart failure, one of the most important clinical causes.\textsuperscript{1} To their surprise, the re-entrant wavelength was unaltered, challenging the widely accepted role of wavelength in determining AF occurrence; rather, there was important atrial fibrosis associated with marked local conduction abnormalities.\textsuperscript{26} This study established atrial fibrosis as a potentially important pathophysiological contributor to AF. Another potential important determinant of AF is autonomic tone. Schauerte et al.\textsuperscript{27} applied Coumel’s concepts of autonomic control of AF by pioneering a detailed series of studies on the cardiac autonomic nervous system as a central player in AF and target for ablation procedures.

An important biochemical motif in AF was revealed in 2001, when the potential importance of oxidative stress was noted.\textsuperscript{28,29} Although initial studies pointed to significant protection from AF with antioxidant interventions as simple as vitamin C,\textsuperscript{29} subsequent animal work suggested a more complicated picture.\textsuperscript{30} A recent randomized, double-blind, clinical trial demonstrated the ability of a combination of antioxidant drugs to prevent postoperative AF.\textsuperscript{31} The complexity of the mechanisms connecting oxidative stress to AF, and the associated therapeutic challenges, was outlined in a recent editorial.\textsuperscript{32}

Although a genetic locus for familial AF was first described in 1997,\textsuperscript{33} the culprit gene remains to be identified and sequenced. In 2003, Chen et al.\textsuperscript{34} pinpointed the first gene responsible for familial AF, involving a gain-of-function mutation in KCNQ1, which encodes the \( \alpha \) subunit of the slow delayed-rectifier K\textsuperscript{+} channel. This discovery ushered in an era of rapid progress in defining the genetic determinants of AF. A range of monogenic causes was subsequently identified, primarily involving ion channel subunit mutations, leading to faster atrial repolarization and greater risk of re-entry. The next major contribution in this field was the publication by Gudbjartsson et al.\textsuperscript{35} of the first genome-wide

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**Figure 2.** Atrial fibrillation (AF) mechanisms and contributions of various areas discussed by articles in the compendium. Each article is referenced and represented by a distinct color. Various AF mechanisms are illustrated diagrammatically in the boxes. The ultimate goal of understanding AF mechanisms is to develop new therapeutic approaches, which are depicted in detail in Figure 3. 2D indicates 2-dimensional; AP, action potential; APD, AP duration; DAD, delayed afterdepolarizations; EAD, early afterdepolarizations; and PV, pulmonary vein.
association study in AF. Unlike candidate gene approaches and analyses of high penetrance rare mutations, genome-wide association studies allow for the identification of less powerful but much more prevalent genetic risk determinants in the population, without a priori assumptions about pathophysiology. Consequently, they provide clues to novel mechanistic determinants. The study of Gudbjartsson identified an important AF determining locus in chromosomal location 4q25, situated far away from any known gene. The closest candidate gene is Pitx2, with important roles in cardiac development, notably including that of the PVs. One of the emerging challenges emanating from genome-wide association studies, which have now identified a substantial number of AF-related gene variants, is to determine the mechanistic basis of the observed associations, none of which have yet been established unequivocally.

Another important advancement was the establishment of the basis for atrial ectopic beat formation. Whereas, historically, the focus of understanding AF was on re-entrant mechanisms, which are readily reproduced in animal models; the role of presumed PV triggers and the observation of frequent atrial ectopic firing in patients with AF suggested an important contribution of spontaneous atrial impulse formation that is not readily reproduced in animal models. In 2004, Hove-Madsen et al reported that right atrial cardiomyocytes from patients with AF display more spontaneous sarcoplasmic reticulum Ca\textsuperscript{2+} releases and Ca\textsuperscript{2+} waves than cells from sinus rhythm patients. Several subsequent studies confirmed the important potentially arrhythmogenic Ca\textsuperscript{2+}-handling abnormalities in atrial cells from patients with AF. Virtually all of the patients studied had long-standing persistent AF, with extensive AF-induced remodeling and presumably little role for spontaneous ectopy in the face of rapid activation by continuously propagating complex atrial re-entry. However, Voigt et al recently studied atrial cardiomyocytes from patients with paroxysmal AF, confirming a susceptibility to triggered activity caused by spontaneous Ca\textsuperscript{2+} releases because of discrete Ca\textsuperscript{2+}-handling disturbances.

An exciting advance has been provided by the development of advanced imaging tools for the identification of mechanistic contributors to AF in man. On the basis of growing evidence for the importance of atrial fibrosis in AF, the Marrouche laboratory developed late gadolinium enhancement MRI methods to image and quantify atrial connective tissue. Subsequent results support the potential value of this technology in understanding the structural basis of AF and guiding management. Until recently, precise arrhythmia mapping in humans was limited to intraoperative contact-electrode methods. However, the Rudy laboratory labored patiently and doggedly to apply body surface mapping and inverse-problem solutions to deduce intracardiac electric events based on voltage changes on the surface of the body. This work finally culminated in the ability to map detailed arrhythmia mechanisms noninvasively, revealing

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**Figure 3.** Diagnostic and therapeutic modalities and their relationship with the principal contributors to atrial fibrillation (AF) mechanisms shown in detail in Figure 2. CFAE indicates complex fractionated atrial electrogram; GP, ganglionated plexus; LGE, late gadolinium enhancement; PV, pulmonary vein; and RyR2, ryanodine receptor type-2.
the underlying basis of atrial arrhythmogenesis in man. More recently, Narayan et al. developed and applied basket electrode-catheter technology and advanced analytical methods to study AF mechanisms in the electrophysiology laboratory, using the information to guide ablation therapy with apparently substantial increases in success rates.

Overview of the AF Compendium

The subjects of the articles in the compendium were chosen to provide a detailed perspective on key aspects of the translational pathophysiology of AF, with authors selected based on recognized leadership in their subject areas. Figure 2 illustrates the inter-relationships among the articles in the compendium, highlighting particularly the 5 articles dealing primarily with mechanisms, each of which is represented by a discrete color. AF mechanisms and their determinants are shown schematically in the boxes in Figure 2. Focal firing occurs mainly in PVS, via enhanced automaticity or triggered activity because of early or delayed afterdepolarizations. Reduced action potential duration and tissue fibrosis are thought to be important AF-maintaining substrates that promote re-entry. Local ectopic activity can act as an AF-maintaining ectopic driver, or can trigger AF-maintaining re-entry in a vulnerable substrate. Andrade et al. review the detailed epidemiological aspects of AF and associated risk factors and discuss their link to underlying mechanisms. Heijman et al. explain how complex changes in cellular and molecular electrophysiology contribute to the occurrence of focal firing via ion current and Ca²⁺-handling abnormalities and produce a re-entrant substrate via electric remodeling. They also review the relationship between cellular and molecular electrophysiological determinants and the progression of structural remodeling. Chen et al. discuss important features of the cardiac autonomnic innervation, including anatomy, molecular biochemistry, and function, along with their relationship with the AF substrate. They emphasize the role of both intrinsic and extrinsic autonomic neural regulation of the heart, note the importance of simultaneous sympathovagal discharge, review the notion of autonomic remodeling, and introduce therapeutic interventions targeting the autonomic nervous system.

Tucker and Ellinor describe advances and challenges in understanding the genetic determinants of AF, illustrating how gene variants may alter ion channel, structural, and anatomic components to induce AF. Trayanova reviews the evolution of mathematical modeling and computer simulation approaches, such as atrial cell action potential models, 2-dimensional (2D) and 3D tissue models, and recent developments in the reproduction of realistic atrial tissue geometries. This article relates closely to all the others in the compendium because mathematical modeling approaches are used to test ideas about mechanisms arising from all levels and types of biological research quantitatively. Of course, the ultimate goal of mechanistic discovery is not the satisfaction of curiosity but the improvement of disease management. Advances in AF treatment, many of them emanating from improved mechanistic understanding (Figure 3), are the subject of the article by Woods and Olgin. They provide an overview of current and future AF therapies, including pharmacological, biological, and ablation approaches, along with novel treatment-guiding diagnostic modalities, such as late gadolinium enhancement MRI and noninvasive arrhythmia mechanism mapping. Included are interventions targeting the autonomic nervous system (ganglionated plexus ablation, renal sympathetic denervation, and low-level vagal nerve stimulation), cellular electrophysiological determinants (atrial selective ion channel blockers, ryanodine receptor stabilizers, gap junction enhancers, and upstream therapy), genetic characteristics and risk factors (personalized therapy based on gene profiling and tissue characterization with MRI, as well as upstream therapy), and targeted ablation procedures (PV isolation, focal source and rotor ablation, noninvasive ECG imaging to guide ablation, and MAZE surgery). Mathematical methods play a key integrating role in understanding the inter-relationships among mechanistic targets and their potential therapeutic consequences.

The Future

It is our conviction that the future of AF management will be determined by the application of new scientific insights into the underlying mechanistic determinants. The extensive work reviewed in this compendium highlights the dramatic advances achieved in understanding AF pathophysiology over the past 20 years, which suggests that mechanism-based therapeutic breakthroughs are just around the corner, and provides hope that medical textbooks presenting the management of AF will be radically different in 20 years.

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None.

References


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Kunihiro Nishida and Stanley Nattel

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