Atrial Fibrillation Pathophysiology
Implications for Management

Yu-ki Iwasaki, MD, PhD*; Kunihiro Nishida, MD, PhD*; Takeshi Kato, MD, PhD; Stanley Nattel, MD

Abstract—Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is an important contributor to population morbidity and mortality. An arrhythmia that is particularly common in the elderly, AF is growing in prevalence with the aging of the population. Our understanding of the basic mechanisms that govern AF occurrence and persistence has been increasing rapidly. This article reviews the basic pathophysiology of AF over a broad range of levels, touching on the tissue mechanisms that maintain the arrhythmia, the relationship between clinical presentation and basic mechanisms, ion channel and transporter abnormalities that lead to ectopic impulse formation, basic models and tissue determinants of reentry, the nature and roles of electric and structural remodeling, autonomic neural components, anatomic factors, interactions between atrial and ventricular functional consequences of AF, and the basic determinants of atrial thromboembolism. We then review the potential implications of the basic pathophysiology of the arrhythmia for its management. We first discuss consequences for improved rhythm control pharmacotherapy; targeting underlying conditions, new atrium-selective drug targets, new targets for focal ectopic source suppression, and upstream therapy aiming to prevent remodeling. We then review the implications of basic mechanistic considerations for rate control therapy, AF ablation, and the prevention of thromboembolic events. We conclude with some thoughts about the future of translational research related to AF mechanisms. (Circulation. 2011; 124:2264-2274.)

Key Words: antiarrhythmia agents • arrhythmia • calcium • electrophysiology • reentry

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is becoming progressively more prevalent with population aging.1 Enormous advances in the understanding of AF pathophysiology have occurred over the past 20 years.2,3 The present article, part of a thematic series in Circulation on AF, provides a broad overview of AF pathophysiology and the potential implications for AF management. In addition, it furnishes background information on basic mechanisms relevant to other articles in the series dealing with AF epidemiology and genetics, stroke prevention, rate control therapy, sinus rhythm maintenance pharmacotherapy, management in structural heart disease, and catheter ablation. For more comprehensive treatment of specific mechanisms, the reader is referred to detailed review articles.2–5

Tissue Mechanisms and Clinical Presentation
AF can be maintained by reentry and/or rapid focal ectopic firing (Figure 1).2 The mechanism maintaining AF is often called the driver. The irregular atrial discharge typical of AF may result from an irregular atrial response to a rapidly discharging regularly firing driver resulting from either local ectopic firing (Figure 1A) or a single localized reentry circuit (Figure 1B). Alternatively, fibrillatory activity may be caused directly by multiple functional reentry circuits varying in time and space (Figure 1C).

The various clinical forms of AF and their presumed mechanistic relationships are shown in Figure 1D. AF often initially presents in a paroxysmal form, defined by self-termination within 7 days. Persistent AF requires termination by pharmacological or direct-current electric cardioversion. In permanent AF, restoration to sinus rhythm is impossible or judged to be inadvisable. Paroxysmal AF usually involves a driver in the cardiac muscle sleeve around ≥1 pulmonary veins (PVs) caused by rapid focal activity or local reentry.6 It is believed that in many cases the natural history of AF involves evolution from paroxysmal to persistent to permanent forms through the influence of atrial remodeling caused by the arrhythmia itself and/or progression of underlying heart disease.7,8 AF-related electric remodeling, resulting from altered expression and/or function of cardiac ion channels, favors the development of functional reentry substrates,7 which are reversible on AF termination (reverse remodeling) and contribute to persistent AF. As atrial disease progresses to irreversible structural changes, AF becomes permanent.7,9 Whereas 90% of paroxysmal AF is driven by PV sources and responds well to PV-directed ablation procedures, as AF progresses, atrial substrates become more complicated and
require more complex ablation procedures. The distinction between paroxysmal and persistent AF can be difficult. Although most recent-onset AF spontaneously terminates within 24 to 48 hours, physicians often decide to terminate AF earlier by pharmacological or electric conversion. Because it is unknown in such cases whether AF would have converted spontaneously, accurate classification is, strictly speaking, impossible. This uncertainty can potentially affect the reliability of clinical trial data.

**Basic Arrhythmia Mechanisms**

**Basic Mechanisms Underlying Ectopic Firing**

Normal atrial cell action potentials (APs) remain at the resting potential after repolarization (Figure 2). The resting potential is maintained by high resting $K^+$ permeability through the inward rectifier $K^+$ current ($I_{K1}$). Although normal human atrial cells manifest pacemaker current ($I_f$), it is overwhelmed by much larger $I_{K1}$, and no manifest automaticity occurs. Enhanced automaticity is caused by changes in this balance resulting from decreased $I_{K1}$ and/or enhanced $I_f$.

Early afterdepolarizations involve abnormal secondary cell membrane depolarizations during repolarization phases. The main factor causing early afterdepolarization is AP duration (APD) prolongation, allowing L-type Ca$^{2+}$ current ($I_{CaL}$) to recover from inactivation, leading to depolarizing inward movement of Ca$^{2+}$ ions. Early afterdepolarizations caused by atrial APD prolongation underlie the increased prevalence of AF in congenital long-QT syndrome patients.

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**AF Mechanisms**

**Relationship to Clinical Forms**

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**Potential Mechanisms of Ectopic Firing**

**A** Enhanced automaticity

Diastolic depolarization
- Decreased $I_{K1}$
- Enhanced $I_f$

Enhanced automaticity

**B** EADs

Atrial APD prolongation
- Loss of $K^+$ channel function
- Congenital (LQTS)
- Acquired

Ca$^{2+}$ overload / RyR dysfunction
- Abnormal SR Ca$^{2+}$ release (RyR)

**C** DADs

At $0$ mV

Ca$^{2+}$ overload / RyR dysfunction
- Abnormal SR Ca$^{2+}$ release (RyR)

$I_f$ through NCK

DAD
Delayed afterdepolarizations (DADs) are caused by abnormal diastolic release of Ca\(^{2+}\) from sarcoplasmic reticulum Ca\(^{2+}\) stores. Specialized sarcoplasmic reticulum Ca\(^{2+}\) channels (called ryanodine receptors [RyRs]) release Ca\(^{2+}\) in response to transmembrane Ca\(^{2+}\) entry. RyRs are normally closed during diastole but can open if they are functionally defective or if the sarcoplasmic reticulum is Ca\(^{2+}\) overloaded. When 1 Ca\(^{2+}\) ion is released during diastole, it is exchanged for 3 extracellular Na\(^{+}\) ions by the Na\(^{+}\)-Ca\(^{2+}\) exchanger, causing a net depolarizing inward positive-ion movement (called transient inward current [Iti]) that underlies DADs. Congestive heart failure, one of the most common causes of AF, produces atrial cell Ca\(^{2+}\) overload and DADs. RyR mutations, which typically cause catecholaminergic polymorphic ventricular tachycardias, also promote DAD-related AF.

**Basic Mechanisms Underlying Reentry**

**Functional Determinants**

Reentry can maintain AF by producing a rapidly firing driver with fibrillatory propagation (Figure 1B) or by producing multiple irregular reentry circuits (Figure 1C). Reentry can be conceptualized as either a leading circle (Figure 3A) or a spiral wave (Figure 3B). The maintenance of continuous activity in both models depends on atrial (substrate) properties, with an appropriate balance between refractory and excitability determinants. There are subtle but important distinctions between predictions of the models. In the leading-circle model, reentry circuits spontaneously establish themselves in a circuit length (the wavelength [WL]; Figure 3C) given by the distance the impulse travels in 1 refractory period (RP), given by the following equation: WL = RP \times CV, where CV is the conduction velocity. The shorter the wavelength is, the larger the number of simultaneous reentry circuits that the atria can accommodate. Increasing wavelength reduces the number of possible circuits (Figure 3E). Consequently, shortened RP and reduced CV promote reentrant AF, and drug-induced RP prolongation suppresses AF. Reduced RP also promotes spiral-wave reentry by accelerating and stabilizing spiral-wave rotors.

**Electric Remodeling**

Atrial remodeling refers to any alteration in structure or function that promotes arrhythmias. Remodeling is central to most acquired forms of AF.

**Figure 3. Conceptual models of reentry and implications for atrial fibrillation (AF). A, Leading circle. B, Spiral-wave reentry. C through E, Role of wavelength (WL) in AF maintenance based on leading-circle model. C, In normal atria, the number of reentrant waves that can be accommodated is small, and reentry easily terminates. D, When wavelength is reduced, by decreasing the refractory period (RP) or conduction velocity (CV), reentrant circuits are smaller and more can be accommodated; AF becomes unlikely to self-terminate. E, Drugs that increase wavelength reduce the number of circuits, favoring AF termination.**

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**Electric Remodeling**

Electric remodeling alters ion channel expression and/or function in a way that promotes AF. The most common form of electric remodeling is caused by AF or other very rapid tachyarrhythmias (Figure 5A). Because Ca\(^{2+}\) enters atrial cells with each AP, rapid atrial rates increase Ca\(^{2+}\) intracellular stores. Specialized sarcoplasmic reticulum Ca\(^{2+}\) channels (Ryanodine receptors [RyRs]) release Ca\(^{2+}\) in response to transmembrane Ca\(^{2+}\) entry. RyRs are normally closed during diastole but can open if they are functionally defective or if the sarcoplasmic reticulum is Ca\(^{2+}\) overloaded. When 1 Ca\(^{2+}\) ion is released during diastole, it is exchanged for 3 extracellular Na\(^{+}\) ions by the Na\(^{+}\)-Ca\(^{2+}\) exchanger, causing a net depolarizing inward positive-ion movement (transient inward current [Iti]) that underlies DADs. Congestive heart failure, one of the most common causes of AF, produces atrial cell Ca\(^{2+}\) overload and DADs. RyR mutations, which typically cause catecholaminergic polymorphic ventricular tachycardias, also promote DAD-related AF.

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loading and initiate autoprotective mechanisms that reduce Ca\(^{2+}\) entry: Ca\(^{2+}\) current inactivation and \(I_{\text{CaL}}\) downregulation (which reduce Ca\(^{2+}\) entry directly) and inward rectifier K\(^+\) current enhancement (both \(I_{K1}\) and constitutive acetylcholine-dependent current \([I_{KACCH}]\)) that decreases Ca\(^{2+}\) loading by reducing APD.\(^2\)–5\(^,\) By decreasing APD, these changes stabilize atrial reentry rotors, increasing AF vulnerability and sustainability.\(^2\)–5,\(^18\) In addition, alterations in Ca\(^{2+}\) handling promote diastolic Ca\(^{2+}\) release and ectopic activity.\(^3\),\(^5\) Electric remodeling contributes to several clinically important phenomena, including early AF recurrence after cardioversion, progressive drug resistance of longer-lasting AF, and progression from paroxysmal to more persistent forms.

**Structural Remodeling**

Structural remodeling, particularly fibrosis (Figure 5B), is important in many forms of AF.\(^5\)–7,\(^19\)–\(^21\) Reactive interstitial fibrosis separates muscle bundles, whereas reparative fibrosis replaces dead cardiomyocytes, interfering with electric continuity and slowing conduction.\(^20\),\(^21\) Fibroblasts can couple electrically to cardiomyocytes and, when increased in number, promote reentry and/or ectopic activity.\(^19\) Fibroblast ion channels may provide novel therapeutic targets, both by suppressing arrhythmogenesis caused by fibroblast-cardiomyocyte electric interactions and by inhibiting collagen production.\(^19\) Fibrosis causes AF progression to permanent forms, so fibrosis development is potentially both a therapeutic target\(^7,\(^19),\(^20\) and a predictor of treatment response.\(^22\) AF itself may promote structural remodeling,\(^23\) creating a long-term positive feedback loop that contributes to the development of permanent forms.

**Neural/Autonomic Remodeling**

Autonomic nervous system factors are important in AF.\(^24\) Vagal discharge enhances acetylcholine-dependent K\(^+\) cur-
rent ($I_{K_{ACC}}$), reducing APD and stabilizing reentrant rotors. $^{25}$

$\beta$-Adrenoceptor activation increases diastolic Ca$^{2+}$ leak and promotes DAD-related ectopic firing by hyperphosphorylating RyR2s. $^{26}$ Atrial sympathetic hyperinnervation occurs in persistent AF patients and tachycardia-remodeled dogs. $^{27,28}$ Autonomic neural remodeling contributes to positive feedback loops that promote AF persistence and recurrence. $^{27-29}$ Suppression of autonomic signaling may contribute to the efficacy of PV-directed ablation procedures for AF, particularly in certain patient subsets; in experimental AF models, model-specific autonomic ganglion ablation effects depend on autonomic innervation changes. $^{29}$

**Anatomic Factors**

**Roles of Specific Structures**

Both the left atrium (LA) and right atrium possess structural features that contribute to the pathogenesis of AF (Figure 6). PVs are critical in AF initiation and maintenance. $^{6,10}$ Both nonreentrant (focal) and reentrant mechanisms have been suggested. $^{30,31}$ Properties favoring nonreentrant mechanisms include smaller $I_{K_{1}}$ in PV cells $^{32}$ and specialized cells with spontaneous activity. $^{33,34}$ Reentrant PV activity is favored by reduced resting potentials (which inactivate Na$^{+}$ channels and slow conduction), shorter APD, and abrupt changes in fiber orientation that promote unidirectional block and slow conduction. $^{32,35}$

The LA posterior wall and roof regions have unique characteristics favoring reentry. $^{36-38}$ Complex subendocardial fiber orientation properties favor conduction block, reentry, and wave break. $^{37}$ Heterogeneous fibrosis in the posterior LA anchors reentry and generates conduction delays, wave breaks, and signal fractionation. $^{38}$

Cardiac autonomic inputs pass through epicardial ganglionated plexuses. $^{39}$ Ganglionated plexuses are located close to PV ostia, and their destruction may contribute to the efficacy of PV-directed ablation procedures. $^{36,40}$ Both sympathetic and parasympathetic components coexist, have intrinsic activities that are independent of extrinsic neural input, $^{39}$ and play important roles in AF initiation and maintenance. Specialized LA structures like the ligament of Marshall also house autonomic ganglia and provide profibrillatory ectopic activity. $^{24}$

Right atrial structures like the vena cavae and crista terminalis can also provide focal triggers. $^{41}$ Pectinate muscles contribute to wave breakup and fibrillatory activity. $^{42}$ and may act as anchor points for reentry. $^{43}$

**Regional Ion Current Differences**

The LA plays a predominant role in AF initiation and maintenance, particularly for paroxysmal AF. $^{44-46}$ Reentrant...
rotors are faster in the LA than in the right atrium, making them more likely to be drivers, partly because of larger K currents that reduce APD.44 PV cardiomyocytes have shorter APDs because of larger delayed rectifier K currents and smaller ICaL, along with reduced resting potentials because of smaller IK1.32 Regional ionic current properties in right atrial cells contribute to reentry-promoting AP heterogeneities.47

**Contractile Considerations**

**AF and Ventricular Function**

Atrial contraction contributes ≈20% of left ventricular stroke volume at rest48; this contribution is lost in AF. In addition, AF may cause left ventricular dysfunction as a result of inappropriately rapid49 and/or irregular50 ventricular rhythms (Figure 7). Coronary flow reserve may also be negatively affected.51 Thus, AF may contribute to ventricular decompensation, and suppressing AF may improve outcome in congestive heart failure patients. Although retrospective observations in AF ablation patients are encouraging,52 randomized trial results with drug therapy have been disappointing.53

**Ventricular Function and AF Risk**

Congestive heart failure increases AF prevalence.54 AF promotion occurs through factors that facilitate both reentry and ectopic firing, including fibrosis, cell stretch, impaired Ca2+ handling, and ionic current remodeling.2,5,13,21

**Atrial-Ventricular Contractile Interaction**

The effects of AF on ventricular function and the consequences of LV dysfunction on the atria lead to a vicious circle (Figure 7), with AF promoting ventricular dysfunction, ventricular dysfunction causing atrial remodeling changes that promote AF, and AF-induced atrial hypocontractility causing further atrial dilatation, stretch, and remodeling that make AF resistant to therapy. Earlier management may interrupt this cycle, with beneficial effects on both cardiac rhythm and function; prospective trials are needed to test this idea.

**Thromboembolic Determinants**

Thromboembolism is by far the most important complication of AF, and AF is the most common factor in stroke in the elderly.55,56 LA thrombi consist of red blood cells and fibrin, typical of low-flow venous thrombi and consistent with the superior efficacy of oral anticoagulants over antiplatelet drugs for stroke prevention in AF patients.55 The determinants of the Virchow triad, including stasis, endothelial damage, and coagulation properties (Figure 8), are centrally involved in AF-related thrombus formation.56 Blood stasis, particularly in the blind-pouch atrial appendage, is the most important determinant.55 AF impairs atrial contractile function through multiple mechanisms, including reduced Ca2+ stores because of decreased APD and reduced IcaL, altered intracellular Ca2+ handling, and abnormal myofilament protein phosphorylation.57 Delayed return of contractile function after cardioversion results in late thromboemboli.55 There is also evidence for atrial endothelial dysfunction resulting from reduced nitric oxide production, upregulated prothrombotic plasminogen activator-antigen; TFPAI, tissue-type plasminogen activator/plasminogen activator inhibitor, and β-TG, β-thromboglobulin.

**Management Implications**

The basic mechanisms underlying AF have important implications for AF management guidelines,50 including those relating to rhythm control, rate control, and prevention of thromboembolism.

**Pharmacological Rhythm Control**

Current rhythm control pharmacotherapy is limited by inadequate efficacy and serious adverse effect risk.16 Better
understanding of AF mechanisms may allow improved therapeutic approaches. Figure 9A lists the factors underlying AF, which act through the electric consequences presented in Figure 9B. Practical implications for AF therapy are presented in the gray boxes.

**Underlying Conditions**

Earlier recognition and management of underlying conditions may prevent the development of AF. More than 70% patients with AF have structural heart disease like congestive heart failure, ischemic heart disease, myocarditis, pericarditis, cardiomyopathy, and hypertensive heart disease.61 Extrinsic determinants like hyperthyroidism, diabetes mellitus, sleep apnea, and obesity are important and may be overlooked. Autonomic signaling may provide new drug therapy targets. Vagal enhancement may be a key mediator of the AF-promoting effects of intense endurance exercise62; lifestyle modification may help in managing the arrhythmia. AF shares risk factors with other cardiovascular diseases like atherosclerosis, and epidemiological studies suggest that more than half of AF cases can be explained on the basis of risk factors like hypertension, diabetes mellitus, obesity, and cigarette smoking.63 Thus, effective primary prevention by risk factor modification may be a real (although as yet unproven) possibility. The role of genetic factors is rapidly becoming understood.3,64 Improved appreciation of the pathophysiology associated with specific genetic backgrounds promises exciting opportunities in personalized therapy.

**Atrium-Selective Therapies**

A principal concern with sinus rhythm–maintaining drugs is the risk of life-threatening ventricular proarrhythmia. Atrium-selective drug targets promise to reduce ventricular proarrhythmic risk. Drugs targeting ion channels primarily expressed in the atria, IKur and I KACh (Figure 4), are in early stages of development, so their real value is still uncertain.65,66 Atrium-selective67 or AF-selective68 Na⁺ channel blockade is also being studied. Na⁺ channel blocking properties likely underlie AF suppression for 2 recently introduced agents, vernakalant and ranolazine.16 Genetic findings point to the importance of Ca²⁺-dependent K⁺ channels, targeted by emerging atrium-selective compounds.69

**Compounds Targeting Focal Activity**

Existing sinus rhythm maintenance drugs act principally on reentrant mechanisms. Recent work points to DAD-related
triggered activity as a principal basis for ectopic beat formation in AF. Novel approaches to stabilize RyR2s and to prevent diastolic Ca$^{2+}$ leak are being explored. Ca$^{2+}$-calmodulin kinase-II hyperphosphorylation of RyRs causes diastolic Ca$^{2+}$ leak in many AF-promoting paradigms; interventions targeting Ca$^{2+}$-calmodulin kinase-II are under study.

Remodeling Prevention

Preventing atrial remodeling (so-called upstream therapy) could suppress the development and progression of the AF substrate. Clinically available drugs like statins, omega-3 fatty acids, and renin-angiotensin-aldosterone inhibitors prevent electric and/or structural remodeling in experimental models. Early therapy with such agents could prevent AF occurrence. Although retrospective analyses of clinical databases have been encouraging, prospective randomized trials have so far been inconclusive and/or disappointing. These unfavorable results may reflect ignorance of which patient populations to target and/or the limitations of presently available agents. Inefficacy may also reflect irreversibility of advanced forms of remodeling. We do not know enough about the processes that lead to AF in its early stages, which may be different from remodeling in the more advanced forms that are commonly seen. Focusing solely on the later stages of AF may render therapies less effective. Interrupting the AF-induced positive feedback loops that increase arrhythmia vulnerability and persistence may help to prevent the development of more advanced and intractable forms. Improved understanding of the molecular processes underlying remodeling may lead to more successful antiremodeling approaches.

Rate Control

Ventricular rate and rhythm regularity determine the functional consequences of AF (Figure 7), and rate control is as effective as currently available rhythm control therapies in preventing adverse outcomes. The optimal criteria for rate control are poorly understood. Recent work suggests that lenient rate control criteria are sufficient in patients with preserved ventricular function. Much more remains to be learned about optimizing the ventricular response in AF.

AF Ablation

The most effective therapy currently available for focal atrial ectopic activity is isolation of the source by ablation. More extensive procedures are required for persistent AF, in which atrial remodeling causes more complex substrates (Figure 1). However, interesting recent work suggests that sinus rhythm restoration before ablation of persistent AF may simplify the types of procedures that are necessary and improve outcome. Remodeling may also lead to AF recurrence after initially successful procedures and may explain the long-term fall-off in success rates from 87% at 1 year to 63% at 5 years. Studies of remodeling prevention after ablation have thus far been largely negative, perhaps because many AF recurrences are due to reconnection of previously isolated sources rather than remodeling. A benchmark paradigm for ablation procedures for persistent AF is the maze operation, which is extremely effective even in patients with longstanding AF.

Substrate modification approaches for persistent AF include LA linear lesions targeting the LA roof and mitral isthmus (Figure 6), complex fractionated electrogram targeting, and autonomic ganglion ablation. The most common approach involves sequential lesions, and the role of individual components is poorly understood. There is great interest in specific procedural end points and targeting lesion sets according to mechanistic or patient-selective criteria. Autonomic ganglion ablation is receiving increasing recognition. Substrate-selective efficacy of ganglion ablation suggests that patient criteria may help in case selection. Further understanding of the anatomic and functional determinants of AF in individual patients is needed. Noninvasive assessment of fibrotic structural remodeling may help to predict AF ablation outcome.

Prevention of Thromboembolism

Vitamin K–dependent oral anticoagulants effectively prevent AF-related thromboembolism, consistent with underlying red-thrombus pathophysiology. Newer agents targeting factor Xa or thrombin will increasingly replace vitamin K–dependent oral anticoagulants in the future. The pathophysiology of AF-related thrombus formation (Figure 8) suggests interesting additional/ancillary approaches. If remodeling-related inflammatory and endothelial protection–suppressing changes are important, upstream therapies may be valuable. Changes in the coagulation system may also provide targets. AF-related stasis clearly plays a central role in thrombus formation. There has been much interest in preventing AF-induced atrial hypocontractility, but the multiplicity of underlying mechanisms suggests that any single target may be limited and upstream targeting may be more effective. The primary role of the LA appendage is consistent with the predictive value of LA thrombus on echocardiography and with the usefulness of LA exclusion procedures in thromboembolism prevention.

Our present understanding of atrial thromboembolism places great importance on the consequences of atrial dysrhythmia. Several clinical observations raise questions about this notion. If AF per se is central, sinus rhythm maintenance should prevent thromboembolism, but currently available clinical trial data do not support this expectation. Furthermore, paroxysmal AF patients may be as predisposed to thromboembolism as persistent AF individuals. One explanation may lie in the enhanced risk of thromboembolism when mechanical contraction returns after rhythm normalization, dislodging fresh thrombus. Paroxysmal AF episodes that last long enough to cause thrombus formation (eg, 24–48 hours) may be followed by a several-day period of increased thromboembolic risk. Thus, incompletely effective drug therapy that converts sustained AF to repetitive paroxysmal AF episodes may paradoxically increase thromboembolic risk.

The Future of Translational Research on AF Mechanisms

A great deal has been learned about AF mechanisms in the last 10 to 15 years. It is reasonable to ask, in light of this rapid
expansion of knowledge, where it has gotten us and where future research may lead. One could reasonably argue that the direct impact of mechanistic insights on clinical practice has thus far been limited. This limited practical impact may relate to delays in translating new ideas into practical clinical applications. Drugs that have been developed against novel ion channel targets are in either preclinical or early clinical investigation phases. Prospective upstream therapy trials are just beginning to be reported, and it appears that identifying the right patient population/drug intervention combinations may be challenging. Exciting new areas include microRNAs and their role in atrial remodeling, gene and cell therapies, and personalized medicine approaches. Exploiting the specific pathophysiology of AF in individual patients to prescribe optimized therapy remains a major, largely elusive, goal, but one worth pursuing.

Acknowledgments

We thank France Thériault and Luce Bégün for secretarial help with the manuscript.

Sources of Funding

This work was supported by the Canadian Institutes of Health Research (MGP 6957, MOP 44365) and Fondation Leducq (EUFAR: 07/CVD/03).

Disclosures

AstraZeneca funded research on a remodeling-preventing drug by Dr Nattel. Dr Nattel served on the advisory boards for Xention, Merck, and Pierre-Fabre. The Montreal Heart Institute/Université de Montréal a patent to await Dr Nattel for AF (inventor, Dr Nattel).

References


86. Lam YY, Ma TK, Yan BP. Alternatives to chronic warfarin therapy for the prevention of stroke in patients with atrial fibrillation. Int J Cardiol. 2011;150:4–11.

