Pathophysiology and Prevention of Atrial Fibrillation

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Atrial fibrillation (AF) is a ubiquitous yet diverse cardiac arrhythmia whose incidence increases with age; with most forms of cardiac and some pulmonary diseases; and with a number of metabolic, toxic, endocrine, or genetic abnormalities. Classification of clinical AF subtypes can be achieved on the basis of the ease by which episodes of the arrhythmia terminate as follows: “Paroxysmal” AF refers to episodes that generally stop spontaneously after no more than a few days. “Persistent” AF occurs less frequently than paroxysmal AF and, rather than self-terminating, requires cardioversion to restore sinus rhythm. “Permanent” AF cannot be converted to sinus rhythm. These terms apply strictly to chronic AF, because a single episode of the arrhythmia cannot be fully categorized. Although there are some mixed patterns, they generally derive from physician impatience for early cardioversion or from pragmatic clinical considerations (eg, to avoid thrombus formation or hemodynamic decompensation).

Patients initially presenting with paroxysmal AF often progress to longer, non–self-terminating bouts. An exception may be paroxysmal AF during intense vagotonia. Moreover, AF initially responsive to pharmacological or electrical cardioversion tends to become resistant and cannot then be converted to sinus rhythm. To some extent, the failure of the physician to suggest or the patient to accept further cardioversion tends to become resistant and cannot then be converted to sinus rhythm.14 These observations are disquieting because, in the absence of identifiable predisposing factors, targeting preventive therapy is difficult.

Clinical Risk Factors Predisposing to AF

AF derives from a complex continuum predisposing factors, summarized in Table 1. In the West, about 5% of the population >65 years of age is afflicted with AF. The most frequent causes of acute AF are myocardial infarction (5% to 10% of patients with infarct) and cardiothoracic surgery (up to 40% of patients). The most common clinical settings for permanent AF are hypertension and ischemic heart disease, with that subset of patients having congestive failure being most likely to experience the arrhythmia. In the developing world, hypertension and rheumatic valvular (usually mitral) and congenital heart diseases are also common associations.

Adrenergic and vagotonic forms of paroxysmal AF are uncommon. Nonetheless, lone fibrillators often have attacks against the background of parasympathetic predominance, whereas paroxysms in patients with structural heart disease more usually occur in a sympathetic setting. About half of the patients with paroxysmal AF have no obvious clinical cause (lone or idiopathic AF). This proportion falls to <20% in patients with persistent or permanent forms. These observations are disquieting because, in the absence of identifiable predisposing factors, targeting preventive therapy is difficult.

Pathophysiology of AF

Onset of AF

We consider the factors responsible for onset of AF to include triggers that induce the arrhythmia and the substrate that sustains it. The triggers are diverse yet do not cause AF in the absence of other contributors. Triggers include sympathetic or parasympathetic stimulation, bradycardia, atrial premature beats or tachycardia, accessory AV pathways, and acute atrial stretch. Recently identified as triggers are ectopic foci occurring in “sleeves” of atrial tissue within the pulmonary veins or vena cava! junctions. These regions likely resemble the juxtaposed islets of atrial myocardium and vascular smooth muscle in coronary sinus and AV valves that, under normal circumstances, manifest synchronous electrical activity but develop delayed afterdepolarizations and triggered activity on rapid pacing or acute stretch. Supporting this idea are clinical studies of impulses generated by single foci propagating from individual pulmonary veins or other atrial regions to the remainder of the atria as fibrillatory waves and...
abolition of AF by radiofrequency ablation to isolate the venous foci.17

Triggers propagating into atrial myocardium may initiate reentering wavelets if the wavelength is sufficiently short. Wavelength shortening can occur even in normal atria if the effective refractory period (ERP) or conduction velocity is decreased. Initiation and maintenance of AF may depend on uninterrupted periodic activity of a few discrete reentrant sources localized to the left atrium, emanating from such sources to propagate through both atria and interact with anatomical and/or functional obstacles, leading to fragmentation and wavelet formation.18,19 Factors such as wavefront curvature,20 sink-source relationships,21 and spatial and temporal organization22,23 all are relevant to our understanding of the initiation of AF by the interaction of the propagating wave fronts with such anatomic or functional obstacles. Indeed, all these factors, which differ from triggers, may be considered initiators of AF.

Having been initiated, AF may be brief. A variety of factors may act as perpetuators, ensuring the persistence of AF for longer periods. One is persistence of the triggers and initiators that induce AF,24 but at some point, AF persists even in their absence.25–27 Persistence here may result from factors acting as perpetuators, ensuring the persistence of initiators of AF.

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potentially also as contributors to AF. A, Altered stress/strain patterns on myocyte either directly or via cytoskeletal linkages to integrins open stretch-activated channels (SACs) and $I_{Ca,L}$ and stimulate muscarinic receptors (M2). Catecholamine release, which may be cause and/or effect of altered stress/stain, results in binding of $\alpha$- and $\beta$-adrenergic agonists to their respective receptors (recp). Additionally, angiotensin II (AT-1) receptor. These agonists, in binding to their respective receptors, activate $G$-protein–coupled pathways, with $\beta$-adrenergic and muscarinic pathways opposing another one in activating adenyl cyclase and turning on cAMP, synthesis, and $\alpha$-agonist and angiotensin II triggering phosphatidylinositol second messenger system that, via phospholipase C (PLC) action, synthesizes IP3 and diacylglycerol (DAG). Protein kinases A (PKA) and C (PKC), activated by cAMP and PI pathways, respectively, modulate Ca level, via opening of $I_{Ca,L}$ and sarcoplasmic reticulum (SR) calcium release. In addition, PKC activates mitogen-activated protein kinase (MAPK), which turns on immediate early gene (IEG) program to initiate hypertrophy. B, Simplified depiction of mechanical aspects of A, with prevailing explanations for mechanoelectric transduction or coupling. Starting from mechanical force-length ($F/L$) changes on left, transducers reside in force transmission, directly or indirectly via the focal proteins on cytoskeleton, to SACs or mechanosensitive channels. Force transduction may also be via myofilibrillar proteins. Calcium and cell signal transduction (see A) play central roles. Ach indicates acetylcholine; actomyo, actomyosin; and ET, endothelin.

Figure 1. Mechanoelectric feedback/coupling (mechanosensitivity) and heterogeneity as possible contributors to AF. A, Altered stress/strain patterns on myocyte either directly or via cytoskeletal linkages to integrins open stretch-activated channels (SACs) and $I_{Ca,L}$ and stimulate muscarinic receptors (M2). Catecholamine release, which may be cause and/or effect of altered stress/stain, results in binding of $\alpha$- and $\beta$-adrenergic agonists to their respective receptors (recp). Additionally, angiotensin II (AT-1) receptor. These agonists, in binding to their respective receptors, initiate $G$-protein–coupled pathways, with $\beta$-adrenergic and muscarinic pathways opposing another one in activating adenyl cyclase and turning on cAMP, synthesis, and $\alpha$-agonist and angiotensin II triggering phosphatidylinositol second messenger system that, via phospholipase C (PLC) action, synthesizes IP3 and diacylglycerol (DAG). Protein kinases A (PKA) and C (PKC), activated by cAMP and PI pathways, respectively, modulate Ca level, via opening of $I_{Ca,L}$ and sarcoplasmic reticulum (SR) calcium release. In addition, PKC activates mitogen-activated protein kinase (MAPK), which turns on immediate early gene (IEG) program to initiate hypertrophy. B, Simplified depiction of mechanical aspects of A, with prevailing explanations for mechanoelectric transduction or coupling. Starting from mechanical force-length ($F/L$) changes on left, transducers reside in force transmission, directly or indirectly via the focal proteins on cytoskeleton, to SACs or mechanosensitive channels. Force transduction may also be via myofilibrillar proteins. Calcium and cell signal transduction (see A) play central roles. Ach indicates acetylcholine; actomyo, actomyosin; and ET, endothelin.

Potential (AP) duration requires only 2 days,$^{25,36}$ it is likely that not only electrophysiological but other mechanisms, like reverse mechanical and/or structural remodeling, are involved in the prevention of AF by prompt cardioversion.

Structure, Mechanics, and Signal Transduction

Attractive as it is to seek uniquely electrophysiological causes and therapeutic strategies for AF, reality imposes greater complexity, integrating mechanical, structural, and signaling processes. Incorporated in this mix are atrial architecture, including the extracellular matrix and cytoskeleton, which provide a source for transatrial force and stretch distribution (Figure 1). Yet given the micromechanics of normal atrium, with marked regional variation in the pattern of packing of cells within their connective tissue envelopes,$^{37}$ it is likely that dilatation and/or altered stretch affect some groups of myocytes differently than others. Uneven distribution of stretch on myocyte groups derives from variations in the collagen network and nonuniform excitation-contraction coupling. An example is the extensive interstitial fibrosis associated with macroreentry and fibrillatory conduction described in dogs with congestive failure–induced AF.$^{38}$ Age and atrial disease also are associated with increases in connective tissue elements$^{39}$ and/or scarring in atrium. Resultant changes in patterns of myocyte apposition may contribute to altered cell-cell interaction and redistribute the stretch that occurs (Figure 1A). However, fibrotic restructuring of the atrial wall may also be protective by shielding myocytes from abnormal stress and strain, depending on geometrical arrangement.

One starting point for considering the interactions of these factors is hemodynamic load, which, when chronically increased in diseases such as mitral valvulitis, hypertension, or congestive failure, is frequently associated with AF. Altered load is often accompanied by changes in myocardial segment length that, acutely, can result in decreased resting potential, AP amplitude and duration, and occurrence of afterdepolarizations causing extrasystoles that originate in the region of greatest stretch.$^{40}$

The effects of changes in stretch are many; even in normal hearts, regional stretch for <30 minutes turns on the immediate early gene program, initiating hypertrophy and altering AP duration in affected areas.$^{41}$ Moreover, acutely altered stress/stretch patterns augment the synthesis of angiotensin II, which induces myocyte hypertrophy.$^{42}$ By regionally increasing L-type Ca current ($I_{Ca,L}$) and decreasing the transient outward potassium current, $I_{to}$,$^{43}$ angiotensin II can contribute to arrhythmogenic electrical dispersion. These observations suggest that benefit might derive from preventing the remodeling effects of angiotensin II.

The effects of altered stretch on myocytes influence the internal machinery of the cell in part via stretch-activated channels (SACs)$^{44}$ as follows: Force transmits directly to SACs in the membrane or indirectly to them via cytoskeletal linkages to the integrins, resulting in channel opening (Figure 1A and 1B).$^{45}$ Stress and strain not only activate SACs$^{44,46}$ but may modify activity of other ion channels, receptors, and enzymes with cytoskeletal connections. For example, $I_{Ca,L}$ density increases in response to positive pressure or hypocontractile swelling in rabbit atrial myocytes,$^{47}$ providing a potential mechanism linking the cytoskeleton and this calcium channel. Moreover, $I_{Ca,L}$ in neonatal mouse cardiac myocytes is sensitive to agents that modulate the actin filament network.$^{48}$ Because $I_{Ca,L}$ is a critical regulator of atrial excitation-contraction coupling, it is quite conceivable that stretch in atrial myocardium contributes to its modulation.$^{47}$
Not only do acute mechanical changes produce electrophysiological alterations and arrhythmia, but once AF is induced, rapidly and inhomogeneously contracting and interacting atrial segments would tend to perpetuate electrophysiological dispersion. It is not difficult to visualize a geometry in which contractile dispersion (an earlier-activated segment stretching another) in the scarred matrix induces electrophysiological dispersion (Figure 1B). In addition, fibroblasts manifest mechanoelectric coupling in human atrium, and electrophysiological interactions between fibroblasts and myocytes are likely. Hence, stretch-induced depolarization of fibroblasts would facilitate depolarization of the myocytes, depending on the extent of fibroblast-myocyte coupling.

Changes in AF characteristics during evolving fibrosis also have a direct impact on why electrical and/or drug treatment ultimately fails to achieve conversion to sinus rhythm. The characteristics of fibrosis in infarct scars are a helpful paradigm here. Fibrotic myocardium exhibits slow conduction, whose low macroscopic propagation velocities are explained by microscopically zigzagging circuits or by the special conduction characteristics of tissues with discontinuous, branching architecture. Reentrant circuits can be only a few millimeters in diameter in discontinuously conducting tissue. Thus, atrial regions with advanced fibrosis can be local “sources” for AF. Such a hypothesis would not preclude the remainder of the atria from showing fibrillatory conduction and/or intact, functional reentrant waves. A highly fibrotic atrial region or regions would explain the refractoriness of AF to therapeutic interventions as follows.

1. In any markedly discontinuous tissue (discontinuous anisotropy, marked degree of gap junctional uncoupling, branching), the safety-factor for propagation is even higher than in normal tissue. Thus, blocking $I_{Na}$ to the same degree as is necessary for the termination of functional reentry might not terminate reentry caused by slow and fractionated conduction in fibrotic scars of remodeled atria.

2. That conduction in discontinuous tissue is mostly structurally determined will lead to excitable gaps behind the wave fronts. If a gap is of critical size, the effectiveness of ERP-prolonging drugs will be limited.

3. Scar tissue is likely to exhibit multiple entry and exit points and multiple sites at which unidirectional block occurs. This may lead to activity whose appearance in local extracellular electrograms changes from beat to beat, as well as beat-to-beat cycle length variability. Although such regions may be expected to respond to defibrillation, AF might resume after extrasystoles or normal sinus beats immediately after conversion, with unidirectional block recurring as a result of the presence of scar.

Apoptosis (programmed cell death) is another likely contributor to the structural substrate of AF. Apoptosis normally controls expression of specific cell types, but under pathophysiological conditions, it may occur inappropriately. When this happens in heart, myocytes die and contractile capacity and electrical activity are permanently altered. Although there is no apoptosis in the goat model after 19 to 23 weeks of AF, small numbers of apoptotic cells are identifiable in chronically fibrillating human atria. These cells are likely to be lost structurally and functionally when apoptosis is complete, causing irreversible atrial damage.

Figure 2. AF and cardiac AP. A, AP at cycle lengths of 2000 and 500 ms in normal right atrial endocardium (left) and that from chronically fibrillating dog (right). Note shorter AP duration (APD) in latter and failure to see any change in AP duration with changes in rate. B, APD to 50% repolarization in endocardium from normal (\textbullet) and fibrillating (\textcircled{C}) canine atria. Left, cycle length is changed abruptly from 500 to 1500 ms. Note initial prolongation of APD, secondary shortening, and then gradual prolongation. At all times, APD for AF is shorter than control. Right, cycle length is shortened abruptly from 1500 to 500 ms. Note again markedly shorter and attenuated APD in AF. Hence, there is abnormal rate adaptation in setting of AF. C, Same population but after treatment with the SR calcium release blocker ryanodine. Note that at both ranges of cycle lengths, early portion of rate adaptation is blocked by ryanodine. Later portion remains intact. This demonstrates importance of calcium release mechanisms in determining the rate adaptation in both normal and fibrillating atria. Modified from Hara et al.61
The Cellular Electrophysiological and Molecular Substrate

The cellular electrophysiological changes typifying AF are a decrease in AP duration and depression of the AP plateau (Figure 2). These occur in pacing-induced AF in animals\(^60,61\) and in AF in patients.\(^62\) A critical component of the cellular electrophysiological changes is altered restitution of AP duration, so that the response to rapid changes in rate is attenuated and vulnerability to the propagation of premature depolarizations is increased.\(^61\) Abnormalities in calcium handling as described above are important contributors to this altered restitution. In the setting of chronically diseased and dilated atria, decreases in resting potential and in AP upstroke velocity occur as well.\(^28\)

Explanations for these AP changes have been sought at the level of ion channels; those changes thus far identified as accompanying and/or predisposing to AF in human subjects are summarized in Table 2. Reductions in I\(_{\text{Na}}\) and in the sustained outward current, I\(_{\text{Ko}}\), which includes I\(_{\text{Kur}}\) as a major component,\(^63-65\) are seen in human tissues and animal models. However, reduction in these currents would tend to prolong AP duration, a change opposite to which typifies rapid atrial pacing or AF.\(^61\) In light of this, it is important that I\(_{\text{Ca-L}}\), which maintains a positive plateau voltage and sustains AP duration, decreases within 24 hours of rapid atrial pacing\(^66\) and in long-standing AF\(^67,68\) and that the outward currents I\(_{\text{Kr}}\) and I\(_{\text{Ko}}\) increase in myocytes from chronically fibrillating human atria.\(^69\) The sum of these changes in inward and outward currents likely explains the depressed AP plateau and accelerated AP repolarization.

Although such changes in inward and outward ionic currents appear to provide a key to the AP alterations characteristic of AF, there are concerns about overinterpreting the roles of these currents. We state this because similar current changes occur in rapidly paced yet nonfibrillating atria, dilated and nonfibrillating atria, and atria that are chronically fibrillating. In other words, these ion channel changes are a response to a variety of stresses that, while contributing to the milieu favoring fibrillation, may not in and of themselves be the root cause. This observation may partially explain the limited success attained with the use of ion channel–blocking drugs in AF.

Channel function is partially controlled by metabolic changes. During rapid pacing or AF, atria are likely to reach a negative metabolic balance, characterized by diminished energy reserves and altered oxidative state. Under these conditions, several components of the cytosolic and interstitial milieu are altered, including pH\(^60\) and PO\(_2\). Interestingly, the \(\alpha_s\) subunit of human cardiac I\(_{\text{Ca-L}}\) is reversibly inhibited at clinically relevant, reduced PO\(_2\).\(^87\) The importance of this observation to AF is seen in patients after cardiac surgery in whom monophasic AP recordings demonstrate decreased atrial AP duration minutes to hours before AF onset.\(^88\) This period is one of increased metabolic demand, elevated sympathetic tone, and increased levels of circulating cytokines. These factors provoke hypoxia and/or ischemia and can suppress I\(_{\text{Ca-L}}\), thus playing important roles as initiators or triggers of AF. Also noteworthy is that the redox state is age dependent. Hence, decreased metabolic reserve may contribute to the age-related propensity to occurrence of AF.

Regulation of channels is also genetically determined. This is important because in families in which a high incidence of AF occurs in young people of one or more generations, genetic linkage indicates familial elements of susceptibility.\(^2\) As we learn more regarding the significance of specific DNA changes associated with AF, we may increasingly appreciate some of its fundamental determinants. Very importantly, the value of genetic information may not be restricted to family members of those individuals in whom inherited AF is expressed. Rather, it may extend to a significant subset of that 5% of the population that develops the arrhythmia during and after the seventh decade of life, thereby providing further clues regarding susceptibility to AF.

To sum up our consideration of pathophysiology, electrophysiological research, complemented by cellular electrophysiology and biophysics, has provided a detailed picture of AF and some of its determinants. Now being added to this information is literature incorporating mechanical and structural data, with a major focus on the molecular and genetic mechanisms associated with ongoing changes in cardiac function.\(^67-89\) The overall picture incorporates a variety of disease entities, as well as age and autonomic influences, individually and together altering the extracellular matrix and cytoskeleton and affecting individual myocytes at the multi-
ple levels depicted in Figures 1 and 2 and Table 2. The resultant fundamental reorientation of atrial structure and function provides the groundwork for AF. Given the profound changes that determine the likely progression from paroxysmal to persistent to permanent AF, it would appear that early detection and early prevention are the soundest strategies for combating the arrhythmia.

**Prevention of AF**

Given that AF is the final arrhythmic expression of a diverse family of diseases, preventive measures ideally must reflect the root causes of AF and be explored and administered in ways reflecting that diversity. High priority should be given to understanding epidemiological risk factors and diseases predisposing to AF and to managing them aggressively. Immediate goals are to recognize, and if possible prevent, the evolution of age-related, structural, and electrophysiological substrates favoring the progression of AF. Hence, preventive strategies should ideally focus on the comorbidity factors contributing to AF. These factors appear to involve disease processes that (1) contribute to the triggering of AF (eg, sympathetic and parasympathetic nervous systems, predisposing arrhythmias, ectopic foci in pulmonary veins); (2) increase atrial distension (eg, valvular heart disease, hypertension and heart failure); (3) decrease the ratio of atrial myocyte to fibrotic tissue, possibly including an increased rate of apoptotic cell death (hypertension and ischemic heart disease); (4) disrupt transmyocyte communications (pericarditis and edema); (5) increase inflammatory mediators (pericarditis and myocarditis); and (6) alter energy and redox states that modulate the function of ion channels and gap junctions.

To optimize recognition of comorbidity factors, standard tests like ECG, echocardiography, clinical electrophysiological studies, and x-ray or ventriculography should be used. Of these, clinical electrophysiological techniques are rightfully receiving increased attention, given their success in diagnosing and treating conditions such as pulmonary venous ectopy.16,17 In addition, more widespread application of techniques like signal-averaged ECG, fast Fourier transforms, high-resolution mapping, and autonomic testing should be explored.

1. **Fast Fourier transforms.** Digital analysis of surface, endocardial, or epicardial electrograms recorded during AF has already provided useful clinical information in some patients. Fibrillatory oscillations can be analyzed in detail, especially after the QRS-T deflections have been eliminated by subtraction techniques. Frequency and morphology analyses can demonstrate the origin of the most rapid atrial activity, information that can then guide assessment of the mechanisms of the initiation and maintenance of AF.

2. **High-resolution mapping.** Activation maps can be constructed during sinus rhythm or AF. Maps during sinus rhythm may reveal areas of abnormal conduction or refractoriness that might point to the need for a specific therapy, eg, ablation or pacing. During ongoing AF, activation maps might demonstrate areas of rapid focal activity, frequently engaged reentrant pathways, or areas of consistent activation and organization that give clues to mechanism of the arrhythmia and its therapy. Increasingly detailed high-resolution technologies are now being deployed to map the atrial endocardium rapidly. Epicardial mapping from the right pulmonary artery, esophagus, and pericardial space is now being developed.

3. **Autonomic testing.** Autonomic tone can be investigated by baroreceptor sensitivity testing, analysis of heart rate variability, and posture- or exercise-induced or spontaneous changes in heart rate. Considering autonomic input is important, because it may contribute significantly as a trigger as well as to alteration of the atrial substrate.

Importantly, each comorbidity factor does not specifically target ion channel, gap junctional, or electrophysiological substrates but diversely affects myocardial structure and contractile function. Hence, exploration of potential interventions needs to become more far ranging and should take into account the observation that different interventions are of varying effectiveness at different times in the evolution of AF. Therefore, we make the following suggestions.

1. More active investigation is needed of the role of angiotensin II as a possible signal transduction factor and of ACE inhibition and angiotensin II receptor blockade in delaying onset and preventing recurrences of AF.90 That ACE inhibition appears to reduce the incidence of AF90,91 may result from actions on the cardiac signal transduction cascades of angiotensin II but also could occur via effects on hemodynamic load. If ACE inhibitors slow or reverse mechanical remodeling and create more homogeneous contraction patterns, this would promote homogeneous mechanoelectric coupling and reduce electrophysiological dispersion. Other hypertrophic and arrhythmogenic hormones (eg, endothelin, catecholamines) also need study in greater detail.

2. More information is needed regarding why calcium blockade shows mixed results as a preventive measure.92,93 In an animal model, verapamil delays the shortening of the atrial ERP during the first 24 hours of rapid atrial pacing.92 However, after a longer period of rapid pacing or AF, verapamil no longer has a preventive effect.94 Nonetheless, clinically, calcium-lowering drugs may reduce the number of early recurrences of AF after cardioversion.92 Increasing the complexity here is that the shortened AF of remodeling atria is restored to normal by an ICa,L agonist.96 Although this might suggest the use of calcium agonists as a preventive intervention, these agents can induce early afterdepolarizations and torsade de pointes.95 Clearly, the complex changes in calcium handling in AF constitute one of the keys to formulating new approaches to prevention.

3. Metabolic status before AF onset may influence the propensity of atrium to undergo electrophysiological remodeling once AF begins. Interventions that alter the redox state of fibrillating atria may prevent the short-term electrophysiological remodeling that accompanies AF initiation and decrease the propensity of AF to reinitiate after cardioversion. Moreover, the time required to recover normal electrophysiological function on termination of AF may relate to its metabolic state at
TABLE 3. Stratification of Risk and Its Relationship to Modalities for Prevention

<table>
<thead>
<tr>
<th>Modalities for Prevention</th>
<th>Stratification of Risk and Its Relationship</th>
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</thead>
<tbody>
<tr>
<td>Primary prevention (risk factors present but AF not documented)</td>
<td>Predisposing disease identified</td>
</tr>
<tr>
<td>Disease-free but risk factor(s) present and evolving</td>
<td>ACE inhibitor?</td>
</tr>
<tr>
<td>Other (including pacing)?</td>
<td>Antiarrhythmic drug</td>
</tr>
<tr>
<td>Secondary prevention (documented AF)</td>
<td>Paroxysmal or persistent AF</td>
</tr>
<tr>
<td>Care of primary disease process (if identified)</td>
<td>Care of disease process</td>
</tr>
<tr>
<td>ACE inhibitor? Ca blocker? Pacing?</td>
<td>Other (including pacing)?</td>
</tr>
<tr>
<td>Ablation*</td>
<td>Electrical</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>Pharmacological</td>
</tr>
<tr>
<td>Care of primary disease (if identified)</td>
<td>Ablation*</td>
</tr>
<tr>
<td>Maze procedure*</td>
<td>Catheter</td>
</tr>
<tr>
<td>Other (including pacing)?</td>
<td>Surgical</td>
</tr>
</tbody>
</table>

*Areas that are under active investigation and/or used at some centers but are not yet in routine use over a wide range of centers.

that time, as well as to factors such as autonomic remodeling.96

4. The basis for the initial success and ultimate failure of antiarrhythmic drugs and their inconsistencies in prevention93,97 must be better understood. Do channel changes evolve to a point beyond the range at which antiarrhythmic drugs can be expected to be effective, or is there excess fibrosis and/or uncoupling of gap junctions? It is possible that AF prevention may be achieved with better ion channel–targeted drugs. Not only might new drugs like ibutilide, dofetilide, and azimilide effectively supplement the existing armamentarium, but given the important downregulation of I_{Kr} and I_{Ca,L} in remodeled atria,62,63 development of atrium-selective drugs that upregulate or open these channels might be appropriate.

5. As the role of mechanoelectric coupling in AF is defined, additional targets can be identified. One is the transducer residing in SACs, although extensive drug discovery is required to permit clinically rational approaches. The cytoskeleton may be an opportune target, given its mechanical linkage to SACs and other mechano-sensitive signal sources. Because depolymerization of cytoskeletal F-actin filaments promotes stretch-induced AF,98 cytoskeletal stabilizers may curtail AF.

6. We must learn whether molecular genetic information from families with congenital AF characterizes only those who are biallelic for genes that confer susceptibility and whether and to what extent genetic heterogeneity may contribute to acquired disease. It is likely that information gained from studying such families will provide leads for discovering more widespread DNA alterations detectable in the general population via soon-to-be-available screening techniques. Potential genetic associations with age, sex, disease, and other determinants of AF may provide highly sensitive identifiers of risk and new means for prevention.

Conclusions

Modalities selected for prevention ultimately depend on risk stratification. Table 3 overviews approaches currently used and being explored clinically. Primary prevention of AF is difficult to comment on, because it requires stratification of risk factors with better selectivity and sensitivity than are now the case. It calls for preventive measures for patients in whom risk factors are present but AF has not been documented. When a causative disease is diagnosed, primary prevention rests largely on treatment of that disease. When no disease is identifiable but a risk factor is present and evolving (eg, pulmonary venous foci inducing paroxysmal AF), novel means for prevention based on some of the approaches discussed above need be identified and tested for therapeutic potential.

Secondary prevention of AF incorporates approaches that maintain patients with paroxysmal or persistent AF in sinus rhythm. Most of the approaches in Table 3 are used clinically today. Those not explored or not sufficiently explored include ACE inhibitors and angiotensin II receptor blockers, calcium blockers, and pacing, as well as some of the experimental approaches mentioned above. With respect to permanent AF, the only methods currently in use or on the horizon involve surgical or catheter maze procedures to restore regular atrial rhythms.

Finally, it is equally important to understand when preventive measures no longer can be expected to succeed and a point of no return has been reached. Ideally, this point of no return should be identified by objective pathophysiological markers supplementing clinical judgment. With this in mind, studies focusing on the time course and extent of structural change, fibrosis, and apoptosis may be valuable in determining when efforts to restore sinus rhythm have no expectation of success.

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