Why is the aging heart prone to atrial fibrillation, and what should be done about it?

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Atrial fibrillation—a major health problem, particularly among the elderly—is associated with an increased risk of stroke, death, and heart failure. Yet, despite more than 120 years of research, the detailed molecular, cellular, and pathophysiological mechanisms remain poorly understood. The major recent advance in the management of these patients has come from clinical trials, which have identified age >65 y, history of hypertension, stroke, diabetes, and poor ventricular function as factors that independently predict an increased risk of stroke. Thus, patients >75 y with or without risk factors or patients <75 y with a single risk factor derive benefit from anticoagulation with warfarin, with good blood pressure control. The remaining patients have a low risk of stroke on aspirin, 325 mg/day. Consideration should always be given to cardioversion and maintaining sinus rhythm.

Keywords: arrhythmia; atrial fibrillation; elderly patient; genetics; anticoagulation; warfarin; aspirin; cardioversion

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In Western societies, patients with atrial fibrillation (AF) are most often the elderly and not uncommonly women. AF is the most common arrhythmia found in adults,[1-3] and it is twice as common as all other arrhythmias combined. There are an estimated 2.2 million people in the United States with AF.[4] In developed countries, the prevalence of AF increases rapidly with age. The median age of patients with AF is approximately 75 years.[5] In the >70-year age-group, the estimated prevalence of AF is 9%.[5] In a community-based, Minnesota study, 16.1% of men and 12.2% of women >75 years of age had AF.[6] A British study of patients examined in a general practice setting was consistent with the above.[7] While the prevalence of AF is slightly higher in men, the absolute number of women and men with AF is approximately equal because there are more women than men in the older age-group.[3]

In addition to causing hemodynamic compromise, AF is a significant marker for higher incidences of stroke and increased mortality. In the Framingham heart study, the risk of stroke was 5.6 times greater in patients with AF than in comparably aged patients in sinus rhythm, and the risk increased from 1.5% in the 50- to 59-year age-group to 23.5% in the 80- to 89-year age-group.[3] The risk of stroke seems independent of whether AF is constant or intermittent.[5] Definitive clinical trials have shown that in selected patients protection from stroke using warfarin and to a lesser extent aspirin is highly effective.[8]

ATRIAL FIBRILLATION AS AN ELECTROPHYSIOLOGY PROBLEM

It has been more than 120 years since AF was first described.[9] This fascinating arrhythmia continues to defy a fundamental understanding. In this section, we provide a brief, and therefore incomplete, review of recent advances in AF-related research from the bench to the organ systems level. We focus on those advances that have contributed to our understanding of the mechanisms of *initiation, perpetuation (maintenance),* and *termination* of AF.

As regards initiation and maintenance, there is general agreement that AF is most likely a reentrant rhythm disturbance.[10] However, the precise pathophysiological bases for its initiation and maintenance have not been resolved. In addition, as newer and more sophisticated tools for the study of AF in experimental animals and in humans have become available, controversies such as whether AF results from focal or multiple reentrant mechanisms, or both, have reemerged.[11]

In the original description of the multiple wavelet hypothesis of AF, as put forward by Moe et al[12] and later substantiated by Allessie et al,[13] wavelets were thought to propagate randomly throughout the atria. However, more recent studies[14,15] that have applied high-resolution mapping of wave propagation in both the time and frequency domains provide evidence that AF is not random,[15] but is accompanied by a high degree of spatiotemporal periodicity. This has led to the hypothesis that maintenance of AF may depend on the uninterrupted periodic activity of a small number of discrete reentrant sites, established by the interaction of propagating waves with anatomical heterogeneities in the atria.[16] It has also been proposed that the rapidly successive wave fronts emanating from these sources propagate through both atria and interact with anatomical and/or functional obstacles, leading to fragmentation and wavelet formation.[16] In support of this idea is the observation in humans, which suggests that, in some patients, a single, repetitive focal source of activity propagates from an individual pulmonary vein to the remainder of the atrium as fibrillatory waves.[17,18]

In this regard, advances have occurred in the understanding of geometrical factors, such as wave front curvature[19] and sink-source relationships at areas of tissue expansion,[20] and in the application of nonlinear dynamics theory to the spatial and temporal organization underlying complex cardiac arrhythmias,[21] particularly during ventricular fibrillation. Such advances may be relevant to the ultimate understanding of the mechanisms of initiation of AF by the interaction of the propagating wave fronts with anatomic or functional obstacles in their paths.[13] Bioinformatics may provide analysis and modeling tools for research aimed at the study of the manner in which electrical "fibrillatory" waves interact with the highly complex three-dimensional structure of the atria.[13,21]

Exciting new information has become available about genetic abnormalities leading or predisposing to AF. Brugada et al[22] reported three families with inherited AF with a locus on chromosomal region 10q.[22,23] More recently, Roberts[23] found that several other kindreds with AF also linked to the same markers. It remains to be established what is the percentage of patients with AF who have genetic defects. How genetics impacts upon the aging process is not known.

ATRIAL FIBRILLATION AS A MANIFESTATION OF THE AGING PROCESS

Attributing a condition to the aging process is always difficult because it is often impossible to separate physiological aging from the development of comorbid disease. There have been carefully conducted studies of the aging cardiovascular system.[24] A diligent attempt has been made to screen for latent coronary and other cardiovascular diseases.[24-27] Of relevance to AF is the observation of an age-associated increase in left atrial size. An enlarged left atrium predisposes to AF. The increase in size of the left atrium may be due to abnormalities of the left ventricular diastolic function, known to occur in the aging heart. Studies in animals suggest that overload in ionized calcium in the senescent myocardium may play an important role in arrhythmogenesis.[28] The older heart appears more susceptible to arrhythmias when calcium homeostasis is disturbed and especially under conditions that enhance calcium loading. Observations in patients, using echocardiographic measurements, confirm the histologic evidence of increasing prevalence of left ventricular wall hypertrophy in an aging population. Echocardiography reveals a progressive increase in diastolic dysfunction with aging. These changes explain the observation of an enlarging left atrium and higher incidence of atrial arrhythmias, including AF. Abnormalities of the conduction system have been reported in apparently healthy volunteers with the consistent finding of a prolongation of the PR interval and a higher prevalence of first-degree atrioventricular block.[25,26] In addition, unexplained sinus node abnormalities in apparently healthy nonathletic older individuals have been observed.[29] Exercise-induced ventricular arrhythmias have been associated with the development of spontaneous AF and supraventricular tachycardia.[27]

It is most likely that the increasing prevalence of AF with age is due to the influence of comorbid disease affecting a myocardium predisposed to AF. It is therefore of critical importance that diligent control of blood pressure is achieved, thereby reducing hypertrophy, which can result in diastolic dysfunction and left atrial enlargement. In addition, appropriate pharmacologic and more aggressive treatment of conditions such as mitral valve disease, which may also predispose to an enlarged left atrium, should lower the incidence with advancing age. The avoidance of certain drugs such as digoxin, bronchial dilators, tricyclic antidepressants, and caffeine-containing foods may also reduce the incidence in the elderly. Thyrotoxicosis is often present in the elderly without the usual clinical manifestations and is an important reversible cause of AF. Attention to electrolyte imbalance,

especially with diuretic therapy, may also reduce the incidence of AF in the elderly.

STROKE PREVENTION

Among patients over the age of 75, the prevalence of AF is about 15%.[6] Stroke is the most important complication in this age-group, robbing the elderly of their dignity and often resulting in significant morbidity, and may lead to heart failure and death.[8] The pivotal clinical question is to determine which patients would benefit from anticoagulation using warfarin and which patients from aspirin for prophylaxis against stroke. Guidance is provided by eight large prospective clinical trials.[8] The first five trials were primary stroke prevention, placebo-controlled, prospective, randomized trials.[8] The Stroke Prevention in Atrial Fibrillation–II (SPAF II) trial compared aspirin and warfarin[30] and the European AF trial[31] was directed at secondary prevention. There was a single trial evaluating warfarin and aspirin in combination.[32] These trials found that the elderly, simply by virtue of their age, automatically fall into a high-risk group with respect to the occurrence of stroke. Patients of any age who have a history of high blood pressure, diabetes, a previous transient ischemic attack or stroke, or poor ventricular function also qualify as high risk. Thus, among the elderly, the annual risk of stroke, untreated, can vary from 4% to 12% and above.[8] It is among these patients that the risk of stroke is not substantially reduced by aspirin.[8] Of critical importance, therefore, is to consider anticoagulation in this group of patients. The SPAF III study found that the risk of stroke, using international normalized ratio (INR)-adjusted warfarin in high-risk patients was 1.7 per year, a substantial reduction over the risk reduction achieved by aspirin and a subtherapeutic dose of warfarin when used in combination.[32] Physicians tend to use anticoagulation cautiously in the elderly because of the perceived risk of major bleeding, particularly intracerebral bleeding. However, the data would suggest that if the INR is maintained within a range of 2.0-3.0[33] and the blood pressure is controlled,[8,34] the risk of intracerebral and major life-threatening bleeds can be quite low and is far outweighed by the benefit of anticoagulant therapy. Minor bleeding is always more common in the anticoagulated patient. These non–life-threatening minor bleeds might unmask early malignancies, common in this patient population, which might not ordinarily be detected if it were not for the stress of anticoagulation. While this is not a proven cost-effective strategy, it is probably prudent to evaluate all anticoagulation-induced bleedings aggressively, particularly if they occur in the elderly, and particularly if they are a new finding.

CARDIOVERSION VERSUS RATE CONTROL AND STROKE PREVENTION

There is an ongoing and unresolved debate concerning the wisdom of cardioverting patients with AF and maintaining them in sinus rhythm. The essence of the debate is centered around the success of cardioversion and the success of maintaining sinus rhythm in the long term and the side effects of the drugs that are used for this purpose. Definitive data concerning the success of cardioversion and maintenance of sinus rhythm are not available and are being collected in the SAFETY and Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trials, which are ongoing. It is estimated that taking the best case, only about 50% of patients successfully cardioverted remain in sinus rhythm 12 months after the cardioversion.[35] In addition, many of the drugs that are used to maintain patients in sinus rhythm have important side effects that preclude their use. A commonly used medication in this setting is amiodarone. Even at low dose, it may be associated with hypothyroidism and hyperthyroidism, as well as pulmonary fibrosis, hepatic dysfunction, and skin sensitivity to sunlight. Sotalol, another drug commonly used to maintain sinus rhythm, is associated with prolongation of the QT interval, risk of ventricular tachycardia, and typical problems associated with all β-blockers, which are brachycardia, asthma, and deterioration of ventricular function. Propafenone and mexiletine should only be used in patients who have normal ventricular function and who do not have overt coronary disease because of risk of proarrhythmia. Dofetilide also carries a risk of QT prolongation and proarrhythmia. Among the elderly, AF is often associated with a more generalized conduction system disease. Drugs such as sotalol and amiodarone may induce significant brachycardia, particularly when used in association with other agents that block the atrioventricular node. In these patients, the use of a backup pacemaker may be indicated.

The counterargument supports the use of cardioversion, particularly early cardioversion, and is based on the work of Allessie et al[13] in goats. They demonstrated that AF begets AF because of the development of irreversible changes to the atrial wall. Extrapolating these data to humans, it appears that early cardioversion is more likely to be successful in the long term than cardioversion in patients that have had AF for a long period of time.

The approach of rate control and stroke prevention is therefore a viable alternative, particularly if the AF is well tolerated clinically, which is often the case in the elderly. This approach is limited by the difficulty in using warfarin because of its many interactions with food and other pharmacological agents, as well as the fear of using warfarin in an elderly population.

THE ROLE OF ECHOCARDIOGRAPHY AT THE TIME OF CARDIOVERSION

Transesophageal echocardiography, from the time of its early development,[36] was shown to be useful for identifying masses in the left atrium, and therefore was proposed by Manning and his colleagues as the best test to evaluate clot prior to cardioversion in order to minimize the risk of postcardioversion stroke.[37] It was believed that in the absence of clot in the left atrium the risk of stroke following cardioversion would be low. The use of echocardiography can therefore shorten the 4-week period of anticoagulation required to avoid left atrial clot formation prior to cardioversion. Transesophageal echocardiography does not preclude the use of anticoagulation; however, because it has been demonstrated that, while cardioversion may restore patients to the sinus rhythm, it may also result in stunning to the atrium, leading to stasis and formation of clot after the cardioversion and the risk of developing an embolic stroke.[38] Thus, the protection from stroke using anticoagulation during and for at least 1 month after cardioversion is essential. Rapid anticoagulation is achieved by either using fractionated or low-molecular-weight heparin until a therapeutic level can be achieved with warfarin.

AGGRESSIVE MANAGEMENT STRATEGIES

In a minority of patients, particularly those elderly that remain symptomatic, a more aggressive approach may be needed. Ablation of the atrioventricular node with pacing improves hemodynamics and symptoms.[39,40] More recently, implantable left atrial defibrillators have been developed and are under evaluation.

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