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The Excitable Heart Series

Part V: Atrial Fibrillation

By Dr. Charles Antzelevitch, Executive Director
Masonic Medical Research Laboratory

Racing faster and faster, the electrical impulses twist and turn tortuously through the upper chambers of the heart causing a fluttering sensation and an irregular heart rhythm. In some this arrhythmia goes unnoticed, in others it may cause dizziness, lightheadedness or even fainting spells. In many, it leads to fatigue, tightness in the chest and/or shortness of breath. The culprit is an arrhythmia known as atrial fibrillation (AF).

AF is the most common symptomatic abnormal heart rhythm. Over 2.5 million Americans are afflicted with the disease and its incidence is increasing, in part, related to increasing age of the population. AF is a particularly common in older individuals. At age 70, the incidence of atrial fibrillation is 5% (1 in 20). At 80 years of age 1 in 10 (10%) will develop AF.

The most important fact that you need to know about atrial fibrillation is that one third of all debilitating strokes in the United States are caused by untreated AF. For this reason, if you suspect AF, due to a fast and irregular heart rhythm, you should seek medical help without delay.

AF is caused by abnormal, rapid and irregular electrical activation of the upper chambers (atria) of the heart. Although the atria are activated hundreds of times per minute, many of the impulses generated are blocked at the level of the atrioventricular (AV) node, the safety valve of the heart, and are not transmitted to the ventricles, the main pumping chambers of the heart. The pulses that succeed in making it through the AV node emerge at an uneven pace, causing an irregular rhythm, most commonly at heart rates ranging between 100 to 175 beats per minute. Less commonly, particularly in the presence of drugs, a large fraction of the impulses may be blocked within the AV node, causing abnormally slow heart rates. Although both abnormally slow and rapid rates can be problematic, AF is usually not life-threatening, so long as both patient and doctor are vigilant about proper anticoagulation.

> AF can develop both in the presence and absence structural heart disease or systemic disease. Some cases of AF have no identifiable cause. Others are linked to dysfunction of the sinus node (the "natural pacemaker" of the heart) and a number of heart and lung disorders including coronary artery disease, rheumatic heart disease, mitral valve disorders, and pericarditis. It is a common but transient complication of coronary artery bypass graft surgery (CABG). Hypertension (high blood pressure), hyperthyroidism, and recent heavy alcohol use (binge drinking) or surgery of the heart, also predispose to the development of AF. Some forms of AF are inherited, in which case the arrhythmia may appear at a very early age, even in infants. Familial forms of AF are often associated with more deadly syndromes such Brugada, Short QT and Long QT syndromes.

Treatment of AF depends on the cause and on whether the arrhythmia is chronic or of recent onset. There are four distinct issues that are important to consider in patients with AF:

1. rate control (control of rate of beating of the ventricles);
2. rhythm control via conversion of the atrial fibrillation to sinus rhythm;
3. maintenance of sinus rhythm following conversion; and
4. prevention of embolic stroke from thrombi that form in the fibrillating atria.

Rate Control: Heart rate is commonly high during AF, due to the fact that the fibrillating atria beat at a rate of about 500-600 times per minute. At this rate the atria are not able to move blood effectively. Fortunately, most of the electrical signals are blocked at the level of the atrioventricular node. Nevertheless, enough impulses may get through to increase the ventricular rate to levels at which the pumping of blood by the ventricles is inefficient, causing shortness of breath, chest pain, or even loss of consciousness.

When a bypass tract is present between the atria and ventricles, as in individuals with the Wolff-Parkinson-White syndrome, the ventricles may beat so fast as to precipitate ventricular fibrillation, and thus cause sudden death.

Rate control can be effected in a variety of ways:

1. Rate control can be accomplished with drugs or radiofrequency ablation techniques that slow or partially blocks conduction through the atrioventricular node, so that the ventricles beat more slowly. Drugs used for this purpose include beta blockers and calcium channel blockers.
2. Radiofrequency ablation can reduce the number of beats passing through the AV node or be used to produce complete AV block. In the latter case, a permanent pacemaker will have to be implanted to drive the ventricles of the heart.
3. Radiofrequency ablation of the bypass tract is indicated in the case of patients with Wolff-Parkinson-White syndrome.

In some cases, the heart rate associated with AF is slower than normal. These patients often have diseased AV nodes and have been treated with drugs that block impulse transmission through the AV node. Changes in the activity of the “sympathetic” and “parasympathetic” nervous systems may also affect AV conduction. In some patients, atrial fibrillation is not constant; it starts and stops on its own. When it stops, the normal "sinus node” pacemaker of the heart may be slow to take over control of the heart, causing dizziness or fainting spells. This combination of rhythm abnormalities, termed “tachycardia-bradycardia syndrome” or “tachy-brady syndrome”, generally calls for the implantation of a permanent pacemaker. This syndrome accounts for approximately 25% of all pacemakers implanted in the United States annually.

Conversion of AF to Sinus Rhythm: Most people feel better when their hearts are in normal sinus rhythm than when their hearts are in AF. AF often stops by itself. If it fails to do

so, antiarrhythmic drugs may be used to convert the arrhythmia. When these agents fail to work, or when circumstances do not permit use of oral antiarrhythmic drugs, AF is converted with electrical cardioversion or with intravenous antiarrhythmic drugs such as ibutilide.

Blood clots (thrombi) that form in the atria during a prolonged period of AF can break away and enter the brain or other parts of the body when normal sinus rhythm is restored. The result is an embolic stroke. The consequences can be so dreadful that cardioversion of AF is rarely attempted unless the patient is treated with a "blood thinner" (anticoagulant, usually heparin or warfarin) for two to three weeks. In many cases, a transesophogeal echocardiogram (TEE) is performed to ensure that the atria are free of clots. After cardioversion, anticoagulant medication is usually continued for a period of time because the atria may not contract mechanically for some time after the electrical abnormality is corrected.

Maintenance of Sinus Rhythm following Conversion: One of the greatest challenges of AF therapy is to prevent the arrhythmia from recurring. As a general rule, patients who do not take antiarrhythmic medication or have ablation procedures have a 75% chance of returning to AF within one year, although this often depends on the duration and frequency of previous episode(s). Older antiarrhythmic drugs such as quinidine or procainamide and newer drugs such as sotalol and dofetilide can reduce the chance of AF recurring. In a small fraction of patients, these drugs may cause more serious ventricular arrhythmias, known as Torsade de Pointes, which can lead to sudden death. This often occurs when heart rate is abnormally slow, plasma potassium levels are abnormally low, and/or other drugs are administered which interfere with the metabolism of the antiarrhythmic drugs, causing blood levels to rise to very high levels. Class IC antiarrhythmic drugs such as flecainide and propafenone are useful in some cases of AF, although these agents should not be used in patients with structural heart disease. Many physicians prescribe beta blockers alone or in combination with these other antiarrhythmic agents. An approach that has become popular with some physicians is the "pill in the pocket" approach, which involves the self administration of propafenone when an individual senses that AF has recurred. Co-administration of beta blockers or calcium channel blockers to "protect the AV node" is recommended by some. Recent studies have shown that one of the most effective agents in preventing recurrence of AF is amiodarone. Although this agent can produce some very serious adverse effects, these side-effects are minimized when relatively low maintenance doses of the drug are used (e.g., 200 mg/day). An analog of amiodarone, dronedarone, was approved by the FDA in 2010 for the management of AF. Although safer than amiodarone, dronedarone is not as effective as amiodarone in preventing the recurrence of AF. Recent experimental studies at the Masonic Medical Research Laboratory have identified ranolazine, an anti-anginal agent, as effective in rhythm control of AF. MMRL scientists have also identified that a combination of dronedarone and ranolazine leads to potent synergistic antiarrhythmic effects.

A surgical procedure developed by Dr. James Cox of Washington University, St. Louis, known as the *maze procedure,* is capable of curing atrial fibrillation. Because it requires access to the inside of the heart, it is reserved principally for those undergoing open heart surgery. Electrophysiologists are attempting to mimic this surgical procedure using ablation techniques, designed to destroy segments of heart tissue. Ablation can be accomplished by delivery through a catheter of radiofrequency energy, ultrasound, or cryothermy (freezing technology).

In 1998 Michelle Haissaguerre made the seminal observation that pulmonary spontaneous extra beats arising from the pulmonary veins are the most common triggers of AF and that catheter

ablation of these foci can cure atrial fibrillation in some patients. This technique is commonly employed as a measure of rhythm control.

Prevention of Embolic Stroke: Much of the morbidity and some of the mortality associated with AF are due to blood clots (thrombi) that form in the atria due to hemostasis (stagnating blood due to interruption of normal blood flow through the atria). When these clots leave the heart and enter the brain, they can cause a stroke. The risk of stroke from AF is estimated to be 1.5% for those 50-59 years of age, and approaches an incredible 30% for those 80-89 years of age. The risk of stroke increases with age over 65 and the presence of hypertension, heart failure, previous stroke or blood clot, myocardial infarction, diabetes, mechanical valves and mitral stenosis. There has been no distinction in stroke risk between chronic atrial fibrillation and a more intermittent form of atrial fibrillation.

This risk can be significantly reduced, but not eliminated, by administration of anticoagulants

(e.g., heparin or warfarin) and/or antiplatelet (e.g., aspirin or clopidogrel) agents. **Careful**

attention to proper anticoagulation, most commonly warfarin (coumadin), is a critically

important part of the approach to therapy of AF. The target level for anticoagulation is

generally an INR between 2 and 3.

Future Directions:

The knowledge that has made these advances and therapies possible emanated from decades of painstaking research conducted at medical research laboratories worldwide. Among the laboratories contributing fundamentally to our present day knowledge of cardiac electrophysiology and arrhythmias is the **Masonic Medical Research Laboratory (MMRL)**. On-going research is focused on cardiac arrhythmias, the single most prevalent mechanisms of mortality and morbidity in the United States. In recent years, the MMRL has contributed importantly to identification of the genetic basis for atrial fibrillation and the mechanisms responsible for the development of this arrhythmia. MMRL investigators are actively engaged in research to develop a novel pharmacologic approach to the treatment of AF. These new agents are designed to be cardio-selective and specific for distinct ion channels in the atria of the heart, and will therefore be able to terminate AF as soon as it begins, without the danger of producing life-threatening arrhythmias in the ventricles or side effects in other organs.

The Masonic Medical Research Laboratory (MMRL) is a 501(c)3 not-for-profit corporation founded and sponsored by Freemasonry. Recognized as a one of the finest biomedical research centers in the world, the MMRL has contributed importantly to the modern day practice of cardiology. Over the past five decades MMRL investigators have been credited with either discovering or unraveling the mechanisms of a majority of known cardiac arrhythmias and is currently one of a handful of medical research institutes worldwide capable of studying the genetic causes of the lethal cardiac arrhythmias responsible for sudden death in young adults, children and infants. The MMRL is leading the way in the development of innovative safe and effective pharmacological treatment for atrial fibrillation, one of the greatest unmet medical needs facing our society.

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