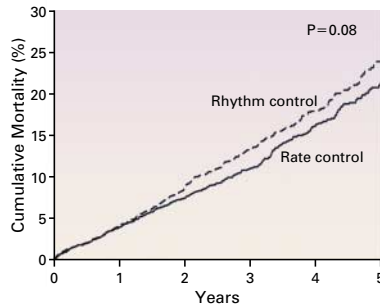




This Week in the Journal

December 5, 2002



Rate Control or Rhythm Control for Atrial Fibrillation

There are two approaches to the treatment of atrial fibrillation: rate control, allowing atrial fibrillation to persist, and rhythm control, with cardioversion and antiarrhythmic drugs. This North American study found that, contrary to prevailing practice, rhythm control offered no survival advantage and was associated with higher rates of adverse drug effects than rate control.

Atrial fibrillation is associated with substantial morbidity and mortality. This study, along with another, similar study in this issue of the Journal (see page 1834), will change the management of this common arrhythmia. As compared with rhythm control, rate control has advantages that have previously been underappreciated.

see page 1825 (editorial, page 1883; Perspective, page 1822)

“Our conclusion does not necessarily apply to patients seen for the first time with atrial fibrillation.”

Rate Control or Rhythm Control for Persistent Atrial Fibrillation

This study is the European counterpart of the North American study of atrial fibrillation reported in this issue of the *Journal*. Although the European study was smaller, the findings in the two studies were quite similar. Rate control was not inferior to rhythm control and should be regarded as appropriate for the management of persistent atrial fibrillation.

The results of the European and North American studies are mutually confirmatory and together provide good evidence that rate control is an acceptable, and in some cases the preferred, approach to therapy for persistent atrial fibrillation. Anticoagulant therapy should be maintained with either strategy.

see page 1834 (editorial, page 1883; Perspective, page 1822)



Eliminating Lymphatic Filariasis

In Papua New Guinea, approximately 2500 residents participated in a prospective, four-year study of the effects of a single dose of antifilarial drugs given annually for four years. The proportion of microfilariae-positive infections decreased by 86 to 98 percent, and the frequency of hydrocele declined from 15 percent to 5 percent.

*This study demonstrates that annual mass treatment of a population can virtually eliminate the reservoir of microfilariae and greatly reduce lymphatic abnormalities due to infection with *Wuchereria bancrofti*, which is transmitted by mosquitoes. New infections in children nearly disappeared during the course of the study.*

see page 1841 (editorial, page 1885)

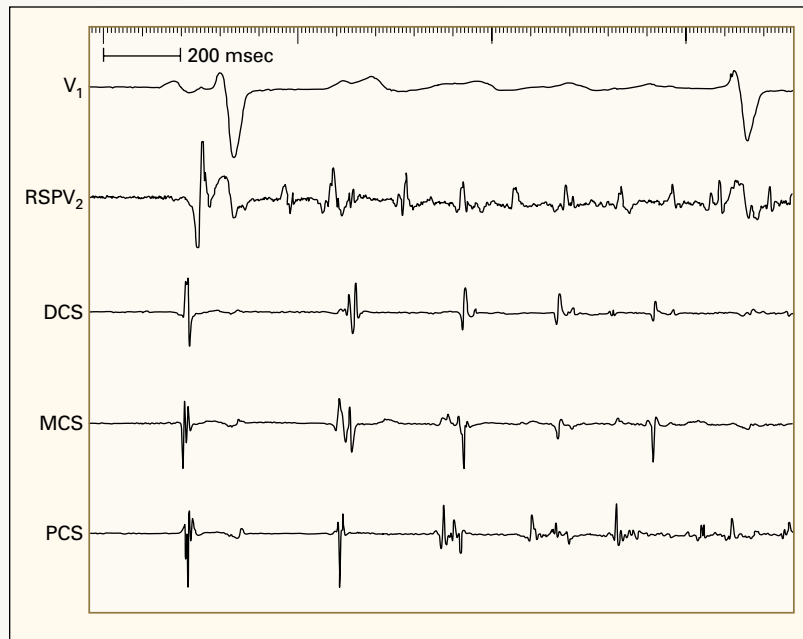
PERSPECTIVE

Atrial Fibrillation — Rhythm or Rate Control

The human heart has a complex electrical system that ensures coordinated propulsion of blood under a variety of physiologic conditions. Remarkable effort is expended with each heartbeat to maintain sinus rhythm. Arrhythmias are a system failure — and none more so than atrial fibrillation. It is the most common sustained arrhythmia, and people with atrial fibrillation have a mortality rate that is twice as high as that among people with sinus rhythm. The prevalence of atrial fibrillation increases with age, from 0.5 percent among young adults to more than 6 percent among those 80 years of age or older.

“Delirium cordis” and “pulsus irregularis perpetuus” were terms once used to characterize the irregular pulse associated with mitral-valve disease. Cushny, in 1899, described atrial fibrillation in experiments in open-chest dogs. In 1909, Lewis used Einthoven’s string galvanometer to record irregular electrical wave forms from the body surface of a patient with pulsus irregularis perpetuus, linking this disease to atrial fibrillation.

Valvular heart disease, heart failure, hypertension, and diabetes predispose persons of both sexes to atrial fibrillation. Myocardial infarction is associated with atrial fibrillation in men. Other conditions that increase the risk are alcohol ingestion, thyrotoxicosis, and in susceptible persons, increased vagal tone (causing postprandial atrial fibrillation) or increased sympathetic tone (causing exercise-related atrial



Electrocardiographic and Intracardiac Recordings at the Onset of Atrial Fibrillation.

Electrocardiographic lead V_1 is shown, with intracardiac electrograms from the right superior pulmonary vein ($RSPV_2$) and indirectly from the left atrium with the use of a catheter with three recording electrodes positioned in the coronary sinus. The coronary-sinus electrodes are located at distal, middle, and proximal sections of the coronary sinus (DCS, MCS, and PCS, respectively). Recordings were made during a normal sinus beat (left) and during the initiation (middle) and onset (right) of atrial fibrillation. Atrial activation during sinus rhythm is organized and sequential. After the sinus beat, rapid, irregular depolarizations from a sleeve of atrial myocytes extending into the pulmonary vein conduct intermittently to the left atrium. This rapid activation of the left atrium initiates atrial fibrillation, resulting in rapid and disorganized atrial wavelets.

fibrillation). Patients with “lone” atrial fibrillation (accounting for 17 percent of all patients with atrial fibrillation) have no clinical, electrocardiographic, or echocardiographic evidence of these risk factors. Familial cases are rare and have been associated with abnormalities of chromosome 10.

In 1962, Moe suggested that electrical activation in atrial fibrillation proceeds as multiple reentrant wavelets that arc around the atrium. Wavelets range from a few large loops to many small circuits. Small circuits are easier to sustain and less likely to terminate sponta-

neously. The wavelength of a circuit is the product of the conduction velocity and the refractory period. Short wavelengths facilitate atrial fibrillation. They may be caused by fibrosis and inflammation (resulting in slow conduction), thyrotoxicosis (resulting in shortened refractoriness), or ischemia and autonomic tone (resulting in both of these changes). Atrial enlargement helps sustain atrial fibrillation by accommodating more wavelets. Inflammation may also contribute to the pathogenesis of atrial fibrillation. The important new discovery that some episodes of atrial fibrillation

are initiated by rapid, repetitive firing of atrial myocytes in muscle sleeves located in the pulmonary veins (see Figure) has led to the use of catheter-based approaches to isolate these structures electrically, which cures atrial fibrillation in some cases.

Atrial fibrillation induces anatomical and electrical remodeling of the atria. Myocyte degeneration, focal accumulation of endoplasmic reticulum and mitochondria, widening of portions of the intercalated disks, and replacement of myofibrils lead to patchy fibrosis and dilatation. The refractory period shortens, and there is loss of the normal adaptation of refractoriness to alterations in heart rate. Both changes contribute to the recurrence of the arrhythmia.

The clinical presentations of atrial fibrillation and the terms describing them vary. Recently, the American College of Cardiology, American Heart Association, and European Society of Cardiology standardized the definitions of paroxysmal, persistent, and permanent atrial fibrillation. Atrial fibrillation is associated with palpitations, decreased exercise tolerance, and dyspnea. Hemodynamic impairment results from the loss of synchronous atrial contraction and rapid, irregular ventricular rates. A further decrease in cardiac output can occur in patients with stiff ventricles, such as those with hypertension, mitral stenosis, or hypertrophic or restrictive cardiomyopathy. Rapid rates depress atrial function and delay the recovery of contractility after sinus rhythm has been restored.

Thromboembolism and stroke are serious complications. In patients with rheumatic heart disease, atrial fibrillation increases the risk of stroke by a factor of 17. Non-rheumatic atrial fibrillation increases the risk of stroke by a factor of five, to 5 percent per year (independently accounting for 15 percent of all

cases of stroke). Risk factors for stroke are additive and include previous stroke and transient ischemic attack (relative risk, 2.5), diabetes (1.7), hypertension (1.6), and increased age (1.4). Thromboembolism is thought to follow hemodynamic stasis. Atrial fibrillation may induce a hypercoagulable state, indicated by raised plasma concentrations of fibrin D-dimer and β -thromboglobulin, which becomes more pronounced as episodes lengthen.

These complications are compelling reasons to maintain sinus rhythm. The literature is replete with treatment strategies for this purpose. Antiarrhythmic drugs were initially the mainstay of the rhythm-control approach. With this approach, escalating doses of increasingly potent drugs are administered until atrial fibrillation is abolished or toxic effects develop. The champions of rhythm control argued that patients who remain in atrial fibrillation have a worse outcome than those treated with drugs that maintain sinus rhythm. A second but intuitively less appealing approach is ventricular rate control. Proponents of this approach noted that rate control is achievable in most patients, the avoidance of antiarrhythmic drugs is desirable, and the risk of stroke can be reduced with anticoagulant therapy. Over time, a low rate of efficacy, side effects, and ventricular proarrhythmia dampened enthusiasm for the use of antiarrhythmic drugs in patients with atrial fibrillation and finally led to randomized trials comparing the two approaches.

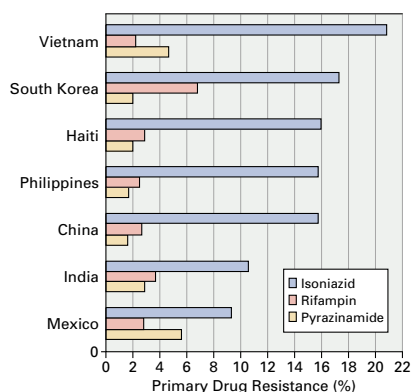
In this issue of the *Journal*, two groups of investigators, one in North America (pages 1825–1833) and one in Europe (pages 1834–1840), report the outcomes in more than 4500 older patients with atrial fibrillation who were randomly assigned to rhythm control or rate control. In both studies, rhythm control provided no advantage over

ventricular rate control with respect to survival. On the basis of these data, rate control can now be considered a primary approach to the treatment of atrial fibrillation, and rhythm control, if used, can be abandoned early if it is not fully satisfactory. These options are important to physicians who treat patients with atrial fibrillation. It is no longer necessary to prescribe a drug with a borderline benefit–risk ratio for an individual patient because of the belief that rate-control therapy does the patient a greater disservice.

Fortunately, the saga of atrial fibrillation management does not end here. The disappointment with antiarrhythmic drugs that led to the North American and European trials also catalyzed the development of nonpharmacologic approaches to the maintenance of sinus rhythm. These two trials focused on older, high-risk patients with atrial fibrillation. Curing atrial fibrillation and maintaining sinus rhythm may still be the goal, at least in some groups of patients.

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Special Article: Improving the Management of Latent Tuberculosis in Immigrants

There is considerable variation in the patterns of resistance to anti-tuberculosis drugs around the world. This decision-analysis study incorporated data on region-specific drug-resistance profiles. The results show that detecting and treating latent tuberculosis in new immigrants to the United States with the appropriate regimens was cost-saving in the case of immigrants from seven regions and was highly cost effective for immigrants from other developing nations.

This analysis focuses on the United States, but the results have implications for other industrialized countries where many cases of tuberculosis occur in foreign-born persons. Optimal treatment decisions should reflect what is known about the pattern of drug resistance in the new immigrant's country of origin. Screening can lead to health benefits for the immigrants and cost savings for the health care system.

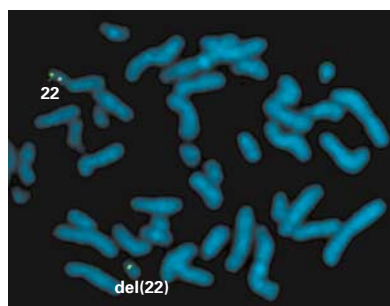
see page 1850



Clinical Practice: Latent Tuberculosis Infection

A 44-year-old man who recently immigrated from Peru is found to have induration of 16 mm on a tuberculin skin test. He received bacille Calmette–Guérin vaccine as an infant and is asymptomatic. Chest radiography shows fibronodular opacities in the upper lobe. In another case, a 27-year-old schoolteacher born in the United States has induration of 17 mm on a tuberculin skin test, no symptoms, and a normal chest radiograph. How should these patients' cases be managed?

see page 1860



Genomic Medicine: Genetic Testing

Classic genetic tests indicate, either directly or indirectly, the presence of DNA variants associated with rare but highly penetrant disorders such as Huntington's disease or multiple endocrine neoplasia type 2. This article not only reviews these classic tests but also shows how novel genetic tests can reveal the presence of DNA variants that are more logically considered risk factors for a given condition.

see page 1867



Clinical Problem-Solving: The Unusual Suspect

A 17-year-old boy awakes with left-sided pleuritic chest pain. He also notes mild dyspnea during track-and-field practice. Over the ensuing months, symptoms progress to dyspnea when he is at rest, accompanied by three-pillow orthopnea.

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