

## Auricular fibrillation and its relationship to clinical irregularity of the heart

T. Lewis

*Br Heart J.* 1910;1:306-372

The first electrocardiographic recording of atrial fibrillation was made by Einthoven in 1906, but a significant background noise precluded the identification of atrial activity, although normal ventricular complexes were seen. With an improvement of the method, the fibrillatory f waves became clearly visible, but were not linked to atrial fibrillation until 1909 when Sir Thomas Lewis, independently of two German investigators, Rothberger and Winterberg, described an electrocardiogram in a patient with arrhythmia perpetua, an absolute ventricular arrhythmia and the presence of irregular waves seen in diastole replacing the P waves. He believed that these waves could result only from fibrillation of the auricle.

The question, however, remained as to whether the irregularity of ventricular contractions was secondary to atrial fibrillatory activity. There was no sufficient experimental evidence as to the origin of atrial fibrillation. James MacKenzie suggested that, in the case of arrhythmia perpetua, the heart was driven by the impulses originating from the atrioventricular node.

This hypothesis had prevailed until 1910 when Lewis noted that the R waves were usually normal in the presence of arrhythmia perpetua. From the detailed study of the chest leads, Lewis concluded that the f waves present throughout the cardiac cycle could only originate from the atria and not from the atrioventricular node with simultaneous conduction to both the atria and the ventricles as it was earlier suggested by MacKenzie. Atrial fibrillation was finally identified with the irregularity of the heart rhythm.

Lewis was the first to acknowledge a high prevalence of atrial fibrillation, describing it as "the commonest persistent irregularity exhibited by the human heart, constituting... approximately 50 per cent of all... cases." In the first part of his paper, he presented the results of his experiments in dogs with electrically induced atrial fibrillation, and showed that oscillations of the electrocardiogram occurring at a varying rate of 500 to 900 beats per minute that replaced the normal P waves were present through the

entire cardiac cycle and were the result of the continual, fibrillatory activity of the atrium. In the second part of his work, Lewis presented 31 clinical cases of atrial fibrillation. He described a "ventricular" form of the venous pulse characterized by the absence of the atrial a wave, but the presence of rapid undulations of venous pressure during slower heart rates associated with atrial fibrillation, and suggested a complete electrocardiographic picture of atrial fibrillation.

It was Lewis who formulated the first, "multiple heterotopous centers" hypothesis, whereby atrial fibrillation "might be regarded as a state in which stimuli are generated, at many separate and uncertain points and the incoordination of the contracting fibers may be held to result from the impact of contraction waves and the production of localized areas of block." Although his theory mixed electrical and mechanical phenomena, it was the best possible explanation of an increasing insight into atrial fibrillation. Eighty-five years prior to Allesie's experiments demonstrating that "atrial fibrillation begets atrial fibrillation" (see summary in this section), based just on circumstantial evidence, Lewis concluded that "the fibrillation itself aggravates the irritability of the auricular tissue. It is perhaps a factor of this nature which accounts... for long continued auricular incoordination in patients who are affected with it."

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1910

Johannes Diderik van der Waals,  
who discovered the weak attractive forces  
between electrically neutral atoms and molecules,  
wins the Nobel Prize for Physics;  
Portugal becomes a republic,  
and King Manuel II flees to England;  
and the Cape of Good Hope becomes part  
of the Union of South Africa



## Auricular fibrillation without other evidence of heart disease: a cause of reversible heart failure

E. Phillips, S. A. Levine

*Am J Med.* 1949;7:478-489

**A**trial fibrillation was first described in the association with congestive heart failure, but it was less commonly appreciated that it could be a cause and not only a consequence of severe left ventricular dysfunction. By the mid-thirties of last century, there was increasing evidence for atrial fibrillation occurring in the absence of identifiable underlying heart disease, with a reported incidence between 6% and 15% of all cases. Although the prognosis of "lone" atrial fibrillation is generally benign, some patients may develop overt congestive heart failure. The cessation of the arrhythmia or mere achievement of adequate rate control with digitalis can be followed by a complete recovery from heart failure.

In this paper, Phillips and Levine reported on 84 patients (mean age 50 years) with atrial fibrillation with no evidence of organic heart disease. Of these, 47 underwent a detailed investigation during the arrhythmia and after reversion to sinus rhythm. Seven of these patients presented with overt congestive heart failure and the other 7 had asymptomatic left ventricular dysfunction determined as cardiomegaly on chest x-rays, a reduced vital lung capacity, and a slower velocity of blood flow. Seventy-three per cent of patients had sustained arrhythmia defined as one that lasted more than 7 days. None of the patients had a history of rheumatic heart disease, hypertension, angina, hyperthyroidism, or acute infection at the time of examination.

Oral quinidine restored sinus rhythm in 88.5% of patients. In patients with advanced heart failure, reversion to sinus rhythm was associated with a dramatic improvement in symptoms, a reduction in the diameter of the heart from 17.4 cm to 15.4 cm within 48 hours after the cessation of the arrhythmia, a nearly 50% increase in the vital lung capacity, a decrease in the venous pressure, and some acceleration of the velocity of blood flow. The same was true to a less dramatic degree in those with asymptomatic left ventricular dysfunction. The only patient, a 63-year old man, who showed no decrease in heart size had had 73 prolonged attacks of atrial fibrillation and presented with left ventricular hypertrophy. The mean time to relapse back

into atrial fibrillation was 26.9 months, significantly longer than was observed in patients with organic heart disease. In those under 50 years of age, sinus rhythm persisted for more than 5 years.

The authors concluded that "auricular fibrillation per se may produce cardiac dilatation and progressive congestive heart failure in patients with otherwise normal hearts. This is a truly reversible type of heart failure." The development of irreversible heart failure and the subsequent disability can, therefore, be prevented by early restoration of sinus rhythm in essentially asymptomatic patients. Interestingly, the duration of the arrhythmia was not a significant factor determining the progression to heart failure in patients with essentially normal hearts, whereas the actual ventricular rates seemed to have a definite influence on the development of heart failure.

This work was one of the first systematic reviews to show that poorly controlled atrial fibrillation could lead to left ventricular dysfunction, which was later termed "tachycardia-induced cardiomyopathy." It has been reported in as many as 25% of patients and was completely reversible after the institution of adequate rate control or restoration of sinus rhythm.

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1949

American writer William Faulker  
is awarded the Nobel Prize for Literature;  
Indonesia becomes independent  
from the Netherlands;  
and the USSR tests its first atom bomb

## Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge

G. K. Moe, J. A. Abildskov

*Am Heart J.* 1959;58:59-70

Since atrial fibrillatory activity on the electrocardiogram was linked to auricular fibrillation, there has always been a debate as to which mechanisms operate in sustaining atrial fibrillation: a single focus, multiple foci, or a fixed reentrant circuit. In 1959, Moe and Abildskov developed a cholinergic canine heart model of atrial fibrillation to find out at which frequencies atrial flutter, which was believed to be initiated by a single or multiple foci in the same way as fibrillation, would degenerate into fibrillation. The authors observed that atrial flutter induced either by electrical stimulation or by injection of aconitine terminated when the inciting agent was eliminated, but that atrial fibrillation could exist as "a stable state, self-sustained and independent of its initiating agency."

Moe explained this by differences in the atrial refractory periods, resulting in the presence of zones in the atrial myocardium in different states of excitability and recovery and characterized by different conduction velocities that made uniform propagation of the atrial impulse no longer possible. He was convinced that although atrial fibrillation could be initiated by a rapidly firing focus or even by a single atrial premature beat, the presence of such a focus was not sufficient, and in order to persist and propagate, fibrillation required multiple random reentrant circuits. In this paper, he described the formation of such multiple wavelets:

The grossly irregular wave front becomes fractionated as it divides about islets or strands of refractory tissue, and each of the daughter wavelets may now be considered an independent offspring. Such a wavelet may accelerate or decelerate as it encounters tissue in a more or less advanced state of recovery... Fully developed fibrillation would then be a state in which many such randomly wandering wavelets coexist.

Five years later, Moe, Rheinboldt, and Abildskov, using a computer model to reproduce animal experiments, showed that multiple chaotic circuits widely scattered in myocardium and constantly varying in number, size, and location are likely to be the mechanism of established arrhythmia. These circuits, or wavelets, travel in changing

directions and are capable of extinguishing or reinitiating themselves or each other. Moe's hypothesis was enriched by systematic animal experiments by Allesie's group and, until recently, remained the most plausible hypothesis for understanding the mechanisms governing self-perpetuation of atrial fibrillation.

In his paper, Moe introduced what later was termed a "critical mass theory." He noted that the likelihood of persistence of fibrillation depended upon the number of circulating wavelets. This in turn is determined by the atrial mass capable of accommodating the sufficient number of wavelets. He observed that when a clamp was applied across the base of the fibrillating atrium disconnecting the right atrial appendage that was the site of stimulation that initiated the arrhythmia, fibrillation persisted in the atrium but terminated in the appendage. He concluded that the size of the appendage was too small to accommodate the sufficient number of circulating wavelets necessary for maintaining the arrhythmia, while the much larger mass of the rest of the atrium supported an adequate number of wavelets. He postulated:

Large mass, short refractory period, and slow conduction will all favor perpetuation of the arrhythmia by permitting the coexistence of many independent, randomly wandering wavelets. The results of the present study may be interpreted in terms of this multiple wavelet hypothesis.

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1959

General Charles de Gaulle

becomes president of France's 5th Republic;  
Alaska becomes the 49th state of the USA;  
and Billy Wilder's film "Some Like it Hot,"  
starring Marilyn Monroe and Jack Lemmon,  
premiers



## Electrical reversion of cardiac arrhythmias. Thomas Lewis Lecture

*B. Lown*

*Br Heart J.* 1967;29:469-489

It is now 40 years since the introduction of electrical cardioversion for cardiac tachyarrhythmias. Cardioversion was first employed in 1961, at the Peter Bent Brigham Hospital in Boston, for the treatment of refractory ventricular tachycardia in an elderly woman with acute myocardial infarction and left ventricular failure. A single 100 watt-seconds shock promptly reinstated sinus rhythm, resulting in almost immediate resolution of hypotension and pulmonary edema.

While cardioversion was introduced for ventricular tachycardia, by far the commonest arrhythmia treated in Lown's series of patients was atrial fibrillation. He reported a remarkable 94% success rate in converting 456 episodes of the arrhythmia in 350 patients. Rheumatic valvular disease was the underlying pathology in 70% and coronary artery disease in 12% of patients, while 10% were considered to have lone atrial fibrillation. The first patient with atrial fibrillation was treated on November, 1961, and continued to maintain sinus rhythm after 6 years of follow-up.

Although there had been attempts to cardiovert atrial fibrillation for more than 20 years, understanding of the factors conducing to success were only beginning to emerge. The duration of the arrhythmia became a key determinant of success or failure of therapy. The likelihood of failure increased from 2% for atrial fibrillation of less than 3 months to 39% when it had been present for a decade. A wide stream of unselected patients with atrial fibrillation permitted impartial insight into causes of failure of cardioversion. In 1967, Lown provided a comprehensive list of electrocardiographic features at the time of cardioversion auguring early recurrence of the arrhythmia. These include, but are not limited to, atrioventricular block with the PR interval greater than 280 ms, depressed sinus node function with profound bradycardia and junctional escape rhythm, sinus tachycardia, and multiple persistent atrial premature beats and bursts of atrial tachycardia or flutter. Cardioversion was more readily achieved with lesser energy requirement and better chances of maintenance of sinus rhythm when high-amplitude and discernable fibrillatory f waves were present.

Chronic atrial flutter was the easiest arrhythmia to terminate by means of cardioversion and it generally responded to a single low-energy shock. This held true in patients with atrial flutter as essential arrhythmia and those with atrial fibrillation organized into flutter on an antiarrhythmic drug. Lown has also suggested employing a 5-10 watt-seconds shock to deliberately induce atrial fibrillation in patients with atrial flutter, as the former was easier to manage.

Of the first 100 patients reverted, 23% remained in sinus rhythm over the long term, but, with improvement in patient selection, 50% were expected to maintain sinus rhythm for at least 1 year. Of note, only quinidine, procainamide, and digitalis were available for prophylaxis of recurrence at that time. In conclusion, although Lown's name is invariably associated with the introduction and the development of the cardioversion technique, he has never patented the cardioverter.

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### 1967

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Vivian Leigh, the British actress who played Scarlet O'Hara in "Gone With the Wind," dies, aged 53; Billie Jean King completes a clean sweep of Wimbledon Tennis titles, winning the singles, doubles, and mixed championships; and the Beatles' "Sgt. Peppers Lonely Hearts Club Band" album is released

## Epidemiologic features of chronic atrial fibrillation: the Framingham study

W. B. Kannel, R. D. Abbott, D. D. Savage, P. M. MacNamara

*N Engl J Med.* 1982;306:1018-1022

The Framingham Study was the landmark study to appreciate the epidemiological significance of atrial fibrillation and to introduce the concept of risk factors for the arrhythmia. It was set up in late 1940s when a representative population sample of 5209 men and women aged 30 to 62 years had their initial examination between 1948 and 1952. This report presented data of a 22-year follow-up during which the participants were examined biennially, including medical histories, physical examinations, and electrocardiograms. The presence of atrial fibrillation was also determined from hospital records and subjects' physicians. The overall incidence of atrial fibrillation in both genders was 2 per thousand in each biennium and rose sharply with age, doubling with each advancing decade. Atrial fibrillation was predominant among the men and those with a history of cardiovascular disease. After adjusting for age and other risk factors, men were 50% more likely than women to develop the arrhythmia. Hypertension, congestive heart failure, rheumatic valve disease, ischemic heart disease with myocardial infarction, and diabetes were commonly associated conditions. Heart failure and valve disease posed as the most powerful risk factors for atrial fibrillation, with relative risks in excess of 6-fold, whereas hypertension was the most common antecedent disease, largely because of a higher prevalence in the general population. Hypertension was present in half the patients who developed atrial fibrillation, but was a strong predictor of atrial fibrillation only if accompanied by cardiac enlargement on chest x-rays or electrocardiographic evidence of left ventricular hypertrophy. When these factors were not present, hypertension was only weakly related to the occurrence of the arrhythmia, suggesting that myocardial damage was a prerequisite. Approximately one third of the patients developed atrial fibrillation in the absence of underlying cardiovascular disease.

This study was the first to show that the development of atrial fibrillation was also associated with a doubling of overall as well as cardiovascular mortality, providing a clear impetus for restoration and maintenance of sinus rhythm that governed the physicians' approach to the management

of atrial fibrillation. The Framingham Study has also provided strong evidence for the association between atrial fibrillation and stroke, with a 3- to 5-fold increased risk in the presence of the arrhythmia. With increasing age, the effects of hypertension, heart failure, and ischemic heart disease on the incidence of stroke decreased, whereas the impact of atrial fibrillation remained equally important in both younger and older patients. In fact, the proportion of strokes attributed to atrial fibrillation tended to grow with age. In subsequent publications from the Framingham Study, new-onset atrial fibrillation has been reported to be associated with an imminent risk of stroke.

The study is remarkable in that, by defining the risk factors for atrial fibrillation, it introduced the concept of arrhythmia prevention by preventing myocardial damage, progression of congestive heart failure, and atrial dilatation. This "upstream therapy" approach has been confirmed by the accumulating evidence of the beneficial effects of angiotensin-converting enzyme inhibitors on the development of atrial fibrillation in patients with overt heart failure and asymptomatic left ventricular dysfunction.

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### 1982

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Several thousand Argentinean troops seize the disputed Falkland (Malvinas) Islands; the Zimbabwean capital Salisbury is renamed Harare; and biologists discover a thriving ecosystem supported by geothermal energy 8600 feet beneath the sea off the Californian coast



## Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials

*Atrial Fibrillation Investigators*

*Arch Intern Med.* 1994;154:1449-1457



bsence of organized mechanical contraction of fibrillating atria with a consequent increase in atrial pressure and atrial stretch and dilation due to multiple pathophysiological mechanisms compensating for reduced cardiac output create conditions for blood stasis. The unique anatomical and physiological properties of the left atrial appendage render it the major site of thrombus formation, particularly in nonvalvular atrial fibrillation. The hypercoagulable state, including endothelial dysfunction and platelet hyperactivation, is additive to increased risk of thromboembolism.

Five large randomized trials (AFASAK, BAATAF, CAFA, SPAF, and SPINAF\*) published between 1989 and 1992 evaluated oral anticoagulation, and two tested aspirin for primary prevention of thromboembolic events in patients with atrial fibrillation. There was also a sixth trial, EAFT,† which focused upon secondary prevention in patients who had survived stroke or transient ischemic attack and was not included in this meta-analysis. For warfarin therapy, the target intensity of anticoagulation ranged from a prothrombin time ratio of 1.2-1.5 to an international normalized ratio (INR) of 2.8-4.2. The dose of aspirin varied from 75 mg to 325 mg.

Meta-analysis of these five trials had an unsurpassed effect on physicians' attitude to anticoagulation in atrial fibrillation. It has shown that adjusted-dose warfarin is highly efficacious for prevention of stroke, with a 68% risk reduction (95% confidence interval [CI], 50% to 79%). The annual rate of stroke was 4.5% for the control group and 1.4% for the treatment group. The efficacy of warfarin was consistent across all studies and subgroups of patients. Aspirin showed less impressive results, with the risk reduction of 36% (95% CI, 4% to 57%).

\* AFASAK, Atrial Fibrillation, ASpirin AntiKoagulation; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; SPAF, Stroke Prevention in Atrial Fibrillation; SPINAF, Stroke Prevention In Nonrheumatic Atrial Fibrillation.

† EAFT, European Atrial Fibrillation Trial.

The incidence of major bleeding was, however, higher with warfarin, and the investigators have expertly developed the conception of risk stratification for stroke, which is essential for decision making in favor of anticoagulation. The independent risk factors for stroke were age >75 years, previous stroke or transient ischemic attack, hypertension, and diabetes. For example, a 75-year-old patient with hypertension would theoretically have an 8% annual event rate, compared with a 1% rate in a 60-year-old with no risk factors. Anticoagulation would be expected to reduce the event rate to 1.2% in a high-risk individual, whereas a low-risk subject would not gain sufficient benefit from anticoagulation to outweigh the attendant risks and the inconvenience of close anticoagulation monitoring. For completeness, there was also excess of stroke if ischemic heart disease, myocardial infarction, or congestive heart failure were present, and left ventricular dysfunction was found to be a risk factor in subsequent analyses. It is also worth noting that the threshold risk of stroke warranting anticoagulation and the need for routine anticoagulation in patients with intermediate risk (eg, 2%-6%/year) are still controversial.

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### 1994

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President Mitterrand of France becomes the first world leader to visit South Africa since the ending of apartheid;  
the Sumo Wrestling Association bans the use of silicon scalp implants to permit wrestlers to reach the minimum height requirement of 172.7 cm; and presidential elections in two of the former Soviet Union republics see Leonid Kuchma win in Ukraine and Alexander Lukashenko in Belarus

## Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats

M. C. Wijffels, C. J. Kirchhof, R. Dorland, M. A. Allesie

*Circulation.* 1995;92:1954-1968

**P**aroxysmal atrial fibrillation is a recurring disease: the first attack will not be the last in over 90% of patients. It also tends to progress to a permanent form over time, the transition rate varying considerably with the etiology. The epidemiological studies have shown that even in the absence of cardiovascular disease almost one fifth of patients are bound to develop sustained arrhythmia. Ever since electrical cardioversion for atrial fibrillation was introduced by Bernard Lown (his work is discussed above), the duration of atrial fibrillation has been recognized as an important predictor of successful restoration and maintenance of sinus rhythm. These intriguing epidemiological and clinical observations lacking a complete and satisfactory explanation have motivated Allesie and his team to pose the question of whether atrial fibrillation itself may produce electrophysiological and structural alterations in the atria that would make atrial fibrillation a self-perpetuating arrhythmia and explain its progressive nature.

The authors conducted a series of elegant experiments in a goat model of atrial fibrillation continuously induced by high frequency burst atrial pacing via an external pacemaker ("fibrillator"). In normal goat atria, electrically induced atrial fibrillation lasted only a few seconds and terminated spontaneously. The device detected spontaneous conversion by sensing an atrial electrogram, and delivered a burst of stimuli to promptly reinduce the arrhythmia. Multiple electrodes sutured to the epicardium enabled the researchers to map both atria and measure atrial effective refractory periods at baseline and after 6 and 24 hours, and then at regular intervals for a few days of sustained fibrillation. The reversibility of changes in effective refractory periods and the vulnerability of the atria were studied 1 day, and 1 and 2 weeks following restoration of sinus rhythm.

Already within the first 24 hours, both the duration and the rate of fibrillation increased significantly, accompanied by low-amplitude and fragmented atrial electrograms, suggesting a shift to a more complex activation of the atrium. The atrial effective refractory periods shortened by one third,

but also displayed a reversion of the normal adaptation to increased pacing rates (ie, a lesser degree of shortening at higher pacing rates). The inducibility of fibrillation by a single premature stimulus increased from 24% to 76%. The atrial fibrillation cycle length shortened progressively at a rate of 1 to 2 ms per every hour and continued to decrease at a lower rate, until after about 4 to 6 days when a new steady state was reached. A critical fibrillation cycle length (120 ms in a goat model) was required for the arrhythmia to become sustained. Thus, it has been demonstrated that the most important electrophysiological changes leading to persistent fibrillation involve a progressive shortening and reversion of rate adaptation of the atrial effective refractory period resulting from prolonged exposure to rapid atrial rates. This phenomenon was termed "electrical remodeling."

The same group continued their experiments to investigate the time course of metabolic, electrical, and structural remodeling of the atria during fibrillation. While structural changes may take months to develop, metabolic adaptation occurs virtually immediately and can rapidly reverse. Electrical remodeling develops later and persists longer than metabolic changes and is believed to arise from alterations in ion channel protein expression in atrial myocytes. It should, however, be acknowledged that the time course of electrical remodeling, its prevention by prompt cardioversion, and reversibility have not yet been studied in the human heart.

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1995

Quebec narrowly rejects independence from  
Canada; the Nobel Peace Prize is awarded  
to scientist and antinuclear campaigner  
Joseph Rotblat; and the United Nations celebrates  
its 50th anniversary with a major gathering  
of world leaders in New York



## Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins

M. Haissaguerre, P. Jais, D. C. Shah, A. Takahashi, M. Hocini, G. Quiniou, S. Garrigue, A. Le Mouroux, P. Le Metayer, J. Clementy

*N Engl J Med.* 1998;339:659-666

For the best part of the last century, Moe's multiple wavelet reentry hypothesis prevailed in our understanding of the mechanism of sustained atrial fibrillation. But Moe's hypothesis does not tell why atrial fibrillation occurs. Until recently, little attention has been paid to triggers of the arrhythmia because many landmark studies in humans have focused on atrial fibrillation induced in the electrophysiological laboratory and because spontaneous initiation of atrial fibrillation is rare in animal models. Of note, Moe himself considered that multiple wavelet reentry did not provide a satisfactory explanation for mechanisms of clinical arrhythmia and thought a single focus or multiple foci to be equally conceivable in the genesis of atrial fibrillation.

The French electrophysiologists who authored this paper have revived the old concept by Rothberger that a rapidly firing single focus may produce atrial fibrillation. Such a focus can drive the atria fast enough that atrial tissue fails to respond in a 1:1 fashion, resulting in fibrillatory conduction. The focus may also act as a trigger (an equivalent of burst pacing in a lab) and the arrhythmia may then become sustained due to multiple wavelets. However, their most important finding was that 80% to 95% of rapidly firing foci are clustered within the pulmonary veins, and this resulted in the development of a new curative ablation technique for atrial fibrillation: pulmonary vein isolation. Firstly applied in patients with lone paroxysmal atrial fibrillation where no identifiable substrate often can be seen, this method has been extended to cure more persistent forms by preventing the initiation instead of modifying the substrate of the arrhythmia. Thus, this paper opened up a new field of research in the management of atrial fibrillation.

Haissaguerre and coworkers mapped the left atrium during spontaneous initiation of atrial fibrillation in 45 patients with frequent recurrence of the arrhythmia and identified 69 sites with the earliest electrical activity preceding the atrial ectopic beat that initiated atrial fibrillation. Ninety-four percent of these foci were located 2 to 4 cm inside the pulmonary veins, and the application of radiofrequency energy at these sites resulted in interrupting conduction

to the rest of the atria and abolishing atrial fibrillation. The reasons why pulmonary veins become arrhythmogenic are unknown. The ability to accommodate various electrophysiological mechanisms, notably automaticity, thanks to their architectural topography augmented by modifying factors such as dilatation and stretch, has been implicated, but this hypothesis not completely satisfactory.

Limitations of pulmonary vein ablation have been immediately recognized as this approach supposes initiation of atrial fibrillation during atrial mapping and the elimination of one focus does not necessarily cure atrial fibrillation because it may be induced by another focus in the same or spared veins. However, the solution has been found for both problems: firstly, the earliest local depolarization can be seen during sinus rhythm and isolation of all four pulmonary veins may achieve the curable goal. Additional maneuvers, such as pacing from the coronary sinus, can help to differentiate between far field atrial potentials and left pulmonary vein spikes.

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### 1998

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The UN International criminal tribunal for Rwanda finds Jean-Paul Akayesu guilty of genocide and crimes against humanity; death of the celebrated Japanese film director Akira Kurosawa; and Mark McGuire of the St Louis Cardinals scores his 62nd home run of the baseball season to break the all-time record

## Atrioverter: an implantable device for the treatment of atrial fibrillation

H. J. Wellens, C. P. Lau, B. Luderitz, M. Akhbar, A. L. Waldo, A. J. Camm, C. Timmermans, H. F. Tse, W. Jung, L. Jordaens, G. Ayers

*Circulation.* 1998;98:1651-1656

The demand for effective therapeutic strategies for atrial fibrillation has always been high and is anticipated to further increase. Until recently, anticoagulation and pharmacological antiarrhythmic therapy or radiofrequency catheter ablation with permanent ventricular pacing remained the mainstay of treatment for atrial fibrillation. The considerable limitations of existing therapeutic options and promising results with internal low-energy cardioversion have prompted interest in implantable devices capable of restoring sinus rhythm expediently in patients with recurrent symptomatic arrhythmia failing on conventional therapies.

A stand-alone atrial defibrillator (Metrix Atrioverter system) was the first in a series of such devices to enter the clinical investigation. The device, with a weight of 79 g and a volume of 53 cc, is implanted in the pectoral region. The system consists of a pulse generator connected to the right atrial and coronary sinus defibrillation leads and a bipolar ventricular pacing lead. The device detects and converts atrial fibrillation with a synchronized low-energy (up to 6 J) atrial shock. It may be either programmed in an automatic mode with a preset delay of shock delivery from onset of the arrhythmia, or it can be activated by the patient or a physician.

The first atrial defibrillator was implanted on October 30, 1995. As of May 1997, a total of 51 systems had been implanted as a part of the phase I Metrix multicenter clinical trial in patients with drug-refractory atrial fibrillation and no or little underlying heart disease. Wellens and Metrix coinvestigators have reported prompt and safe restoration of sinus rhythm with the atrial defibrillator. In this study, shock was administered in-hospital under physician observation. The device terminated 96% episodes of atrial fibrillation.

However, the primary efficacy of the defibrillator was marred by frequent early recurrence of the arrhythmia, which occurred in 27% of all episodes in half the patients and required repeat shock. The median number of shocks was 3 per episode. Thus, after adjustment for early recurrence,

the clinical efficacy of defibrillation therapy was reduced to 86%. For completeness, the clinical efficacy of ambulatory cardioversion, either executed automatically or initiated by the patient, was approximately 80%. Of importance is the fact that the frequency of atrial fibrillation tends to subside over time, probably because prompt restoration of sinus rhythm prevents advanced electrical and structural remodeling.

This paper is significant as it was the first to show that atrial fibrillation can be successfully and safely treated by implantable devices. It must, however, be emphasized that the use of solely atrial defibrillators is limited to patients with minor heart disease and infrequent, but highly symptomatic recurrence of atrial fibrillation. Dual-chamber cardioverter-defibrillators with capacity to prevent and interrupt atrial fibrillation, including painless antitachycardia pacing, may offer more comprehensive and successful treatment for patients with advanced heart disease, frequent recurrence of the arrhythmia, concomitant ventricular tachycardia, and the risk of drug- or shock-induced proarrhythmia.

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### 1998

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Former Chilean ruler Augusto Pinochet is arrested in a London hospital and charged with the murder of Spanish citizens during his 17-year rule; the Japanese government passes bank reform legislation, associated with a \$513 billion aid package to help economic recovery; and British Poet Laureate Ted Hughes dies, aged 68



## A comparison of rate control and rhythm control in patients with atrial fibrillation

D. G. Wyse, A. L. Waldo, J. P. DiMarco, M. J. Domanski, Y. Rosenberg, E. B. Schron, J. C. Kellen, H. L. Greene, M. C. Mickey, J. E. Dalquist, S. D. Corley; Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Investigators

*N Engl J Med.* 2002;347:1825-1833

There are two main approaches to the management of atrial fibrillation: the first, most often pursued in patients with new-onset and persistent atrial fibrillation, is rhythm control aimed at restoration and maintenance of sinus rhythm; the second is to minimize symptoms by merely administering agents blocking the atrioventricular node. Rhythm control has generally been accepted as theoretically preferable, but there has been no direct evidence for the superiority of this strategy in terms of improved survival and reduced thromboembolic events.

Among the recent studies comparing the two strategies, the AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management) was the largest and was powered to detect the mortality benefit. Its population of over 4000 patients 65 years of age and older or with a risk factor for stroke was representative of the majority of patients with atrial fibrillation, and the antiarrhythmic drug was chosen by the treating physician. The investigators hypothesized that rhythm control would decrease the risk of stroke and the need for lifelong anticoagulation, improve symptoms, functional status, and quality of life, and ultimately reduce mortality. The results of the trial proved the opposite. There was a trend to excess mortality and more strokes, hospital admissions, and torsades de pointes in the group assigned to rhythm control. There was no difference in generic and cardiac-specific quality of life measures between rhythm and rate control.

Given the strength of this evidence, an important consideration is whether the conclusions drawn from the AFFIRM trial can be applied to all patients with atrial fibrillation. The trial pertained to older patients who are likely to have modest symptoms and in whom rate control has generally been presumed (but not proven) preferable. The results cannot be readily extrapolated to younger individuals who are more likely to be symptomatic and have impaired quality of life, even if good rate control is achieved. In the subgroup analysis, the point estimate of the hazard ratio was shifted toward benefits of rhythm control in patients under 65 years. Furthermore, the mere fact that more than one

third of patients in the rate control arm had sinus rhythm at the end of follow-up made the comparisons ambiguous. A significant proportion of patients presented with paroxysmal or recent-onset atrial fibrillation, suggesting that the benefits of being in sinus rhythm can be offered to many more patients than participated in the trial.

Finally, it must be recognized that the AFFIRM trial and other studies compared predominantly pharmacological therapies. Greater use of nonpharmacological therapies, resulting in more effective rhythm control and less side effects compared with traditional antiarrhythmic drugs, might shift the balance in favor of the rhythm control strategy.

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### 2002

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Iraq delivers a 12 000-page document to the United Nations stating that the country possesses neither weapons of mass destruction (WMD) nor programs to create them;  
South Korea elects Roh Moo-hyun as its new president; and the first comparison of the complete mouse and human genomes reveals striking similarities