Atrial Fibrillation

From Bench to Bedside

Edited by

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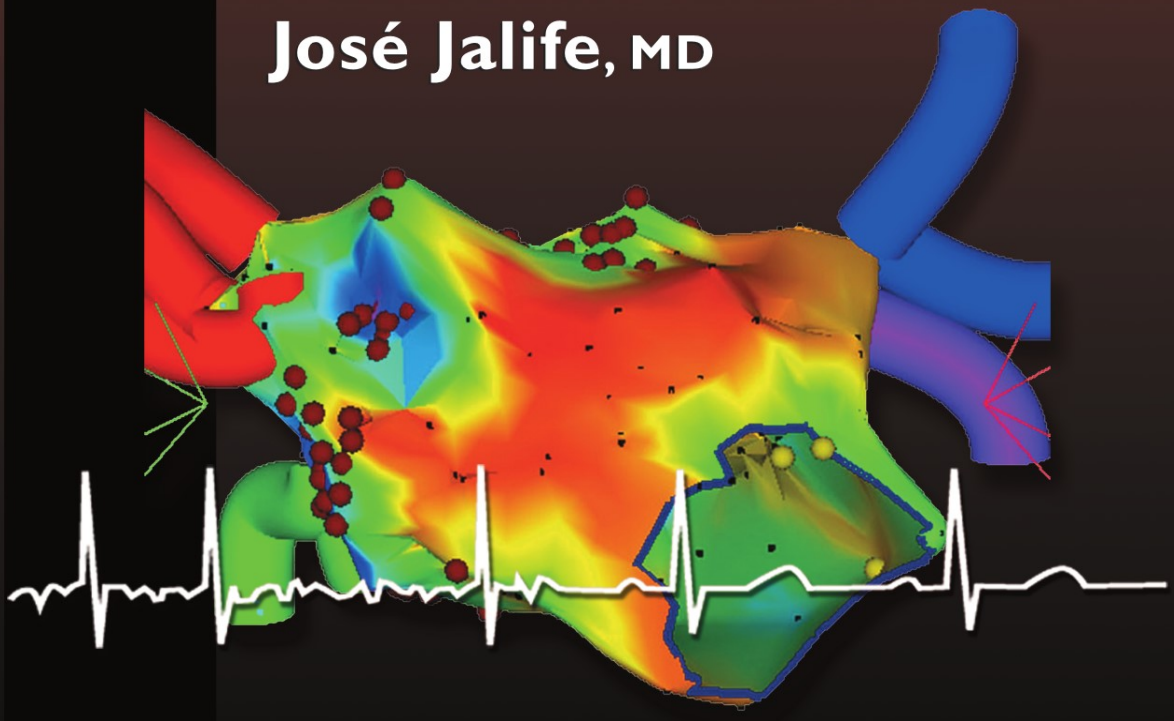

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Atrial Fibrillation

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To my father Domenico for his inspiration and guidance through his exemplary medical career and dedication to his patients. To my loving wife and family who have supported me in all my endeavors. AN

I dedicate the book to my wife Paloma Jalife whose support has been essential in everything I have done in my scientific career. Jose Jalife

Preface

"Fast", "chaotic", and "elusive" are used respectively to characterize the rate, rhythm, and presence of atrial fibrillation (AF). These same terms can be used to express the effect that AF has had on individuals, the healthcare industry, and society. The AF epidemic is a "ticking time bomb." It affects approximately 2.5 million individuals in the United States and is projected to affect 15 million individuals by 2050. Moreover, evidence is emerging that not only is AF associated with increased mortality and morbidity, but also it can be considered an independent risk factor as well. Therefore, there is an intense interest in this topic by clinicians, researchers, and patients. A clear understanding of the nature of AF may have a substantial impact on patient lives and may help lessen the societal and economic burden that AF currently causes. However, at present the mechanisms of AF are poorly understood, the number of individuals affected with AF is still rapidly increasing, and there is considerable debate regarding which treatment strategy is best for patients with AF. It is therefore important that clinicians thoroughly understand the indications for treatment, the latest technologies, the fundamental physiological principles, the epidemiology, and the pathogenesis of AF so that patients can be optimally managed and so that more discoveries can be made toward preventing and eradicating AF.

Our goal is to provide the latest information that is critically important in the daily care and for the potential cure of patients with AF. In essence, we have attempted to organize knowledge of a "disorganized rhythm." Each chapter deals with a different aspect of AF and is authored by internationally recognized experts in the evolving field of cardiac electrophysiology. Atrial fibrillation is a multidimensional disorder. To understand AF and to decide what is best for each patient one must understand the nature of AF from as many angles as possible. This book is a single source that provides a multiperspective look at and approach to AF. Because AF is so prevalent and affects all areas of medicine, the information in this book should be useful to cardiologists, cardiac surgeons, researchers, and all those in the medical field. We hope you enjoy reading this book as much as we have enjoyed the journey of putting it together.

Dimpi Patel, M.D.
Andrea Natale, M.D.
José Jalife, M.D.

Acknowledgment

To Dr. Dimpi Patel for her commitment and invaluable help in organizing this book.

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Section I

Introduction: Epidemiology of Atrial Fibrillation and Impact on Health System

1

Epidemiology of Atrial Fibrillation
The Rising Prevalence

Benzy J. Padanilam and Eric N. Prystowsky

Abstract: The prevalence of atrial fibrillation (AF) is increasing worldwide, resulting in a cardiovascular "epidemic." The rise in the prevalence of AF can be predominantly attributed to aging of the population and a higher incidence of cardiovascular diseases. The reasons for the increase in prevalence of AF has yet to be completely elucidated; age, gender, race, and cardiovascular disease have been shown to correlate with AF prevalence. It is estimated that AF affects 2.2 million individuals in the United States. However, the prevalence of AF may be underestimated because of a large number of asymptomatic individuals. It is projected that the aging of the population will result in 2.5-fold rise in the prevalence of AF by 2050. When considering both the aging of the population and the prevalence of AF, preventive measures that reduce the incidence of AF will have substantial economic and societal benefits.

Keywords: AF epidemic; Economic burden of AF; Incidence of AF; Prevalence of AF; Societal burden of AF.

Epidemic, a term generally used to describe a rapidly spreading infectious disease within a population, has recently been used to describe the rising prevalence of atrial fibrillation (AF).[1] The prevalence (and probably the incidence) of AF is rising for reasons that are not completely known.[2] The rising incidence of the etiological factors of AF, such as the aging population and a higher prevalence of cardiovascular diseases, only partly explains this phenomenon.[2] Several population follow-up studies and cross-sectional studies have affirmed AF to be primarily a disease of the elderly, affecting approximately 10% of people over 80 years of age. According to the Population Projections Program of the U.S. Census Bureau, the number of Americans aged 65 years or older will increase substantially by the year 2050 to more than 20% of the population (82 million).[3] Thus, the prevalence of AF will also rise, *pari passu*, with the rising elderly population in the United States.

Atrial fibrillation has been variously classified over the years, and the American College of Cardiology/American Heart Association/European Society

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of Cardiology (ACC/AHA/ESC) international guidelines distinguish three forms of AF: paroxysmal, persistent, and permanent.[4] Most epidemiological studies do not make distinctions between different types of AF when reporting prevalence and incidence. *Lone AF* is a term generally used to describe individuals with AF who are under 60 years of age and without significant cardiopulmonary disease.[5] Applying strict criteria for the definition of cardiopulmonary disease, lone AF encompassed only 2% to 3% of all patients with AF in one study.[6]

Prevalence

Prevalence of a disease is defined as the proportion of a population affected by the disease at a point in time. The medical community has been helped by the foresight of investigators who designed and executed several long-term population-based studies, including the Framingham study, that have provided valuable information about the epidemiology of AF. The original Framingham, Massachusetts, population cohort, initiated in 1948, followed 5,209 subjects free of cardiovascular disease at entry, between ages 28 and 62, with biennial examinations.[7] With up to 38 years of follow-up of 2,090 men and 2,641 women, 264 men and 298 women developed AF.[8] Data from Framingham clearly show AF to be a disease associated with progressive age. The prevalence rose from 0.5% in the age group 50 to 60 years to 8.8% in subjects 80 years or older.[9]

Three other large population-based studies have also reported age-specific prevalence for AF, and the data are remarkably similar to those of the Framingham study (Figure 1). The Cardiovascular Health Study[10] included 5,201 men and women aged 65 years or older examined annually between 1989 and 1993. Based on data from the four large population-based

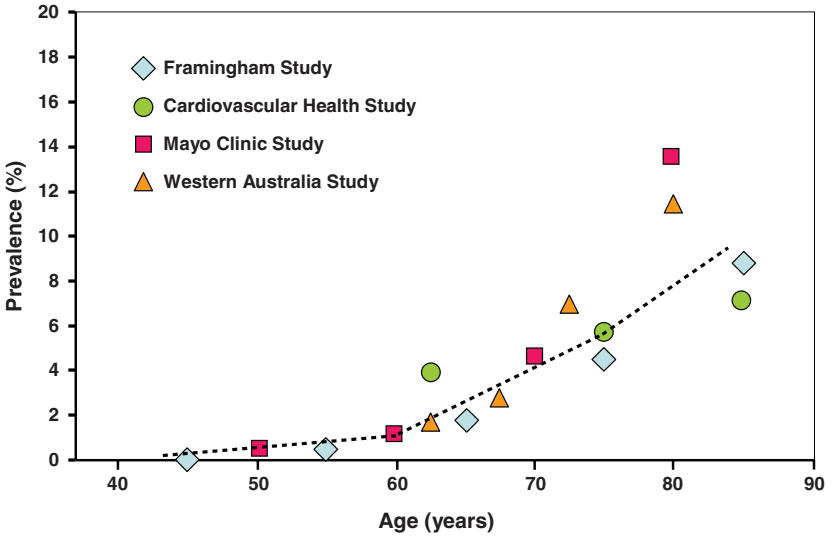

Figure 1 Prevalence of atrial fibrillation at various ages in four population studies. The dotted line represents the estimated prevalence values. (Reproduced with permission from ref. 14.)

Table 1 Comparison of prevalence of atrial fibrillation (AF) in published large studies.

Study	Year	Evaluation	Population (N)	AF cases (N)
Framingham study[9]	1948–1982	Biennial surveys, examinations, records review	5,070	311
Western Australia study[11]	1966–1981	Triennial surveys	1,770	87
Rochester, Minnesota, study[12]	1986	Population survey	2,122	86
Cardiovascular Health Study[10]	1989–1990	Screened adults for cohort study	5,201	277
PATAF[19]	1990	Screened adults for trial	36,165	1,837
ATRIA study[20]	1996–1997	Outpatient diagnoses and ECG findings in health plan database	1.89 million	17,242
Majeed et al.[16]	1998	Physician-reported diagnosis in the United Kingdom	1.4 million	7,218
West of Scotland[15]	1972–1976	Population (aged 45–65 years) examination	15,406	100

ATRIA Anticoagulation and Risk Factors in AF, *ECG* electrocardiogram, *PATAF* Primary Prevention of Arterial Thromboembolism in Non-rheumatic Atrial Fibrillation.

studies—Framingham, Cardiovascular Health Study, Western Australia study, and Rochester Minnesota study,[9,11–13] Feinberg et al. estimated that 0.89% of the U.S. population (2.23 million) was affected by AF.[14]

A subsequent large study from the west of Scotland[15] evaluated a population cohort of 15,406 middle-aged (45 to 65 years old) men and women initially examined between 1972 and 1976. The prevalence of AF in this age group (0.65%) was similar to the Framingham data. Other reports from the United Kingdom,[16] Denmark,[17] Iceland,[18] and the Netherlands[19] also showed similar findings. In the Anticoagulation and Risk Factors in AF (ATRIA) study,[20] a large cross-sectional analysis of 1.89 million people 20 years or older who were enrolled in a health maintenance organization in California, the overall prevalence of AF was 0.95%. As expected, age was a significant factor, and prevalence of AF was 0.1% and 9% for those younger than 55 years and older than 80 years, respectively.[20,21]

The major studies are summarized in Table 1. Even with significant differences in the methodology and populations studied, the remarkably similar results point to the rather homogeneous prevalence of AF in the Western world.

Correlates of Atrial Fibrillation Prevalence

Age

The previous discussion clearly demonstrates age as the strongest predictor of AF. About 75% of patients with AF are 65 years or older, and the median age of U.S. patients with AF is 75 years.[14,20] Several mechanisms may be operative in this age dependence of AF prevalence. Age-related changes in the atrial myocardium might provide a substrate for multiple reentrant wavelets maintaining AF. Increasing age is also associated with a higher prevalence of other etiological conditions causing AF, including hypertension, diabetes

mellitus, myocardial infarction (MI), valvular heart disease, and congestive heart failure.[22–24]

Gender

The prevalence of AF is higher in men when compared with women at all ages. The absolute number of women with AF, however, is equal to or greater than men in the older age groups because there are nearly twice as many women as men who live beyond 75 years in the overall population.[14]

Race

The racial or ethnic differences in the prevalence of AF are poorly understood as most studies have been conducted in Western countries. Available data suggest that AF is less frequent among African Americans compared with Caucasians. In the Cardiovascular Health Study, the incidence of AF among whites was approximately twice that among blacks.[10] Similar trends have been observed in other studies that corroborated the increased prevalence within white populations.[20,25] The prevalence of AF may be lower in Asia, and AF may account for a lower proportion of ischemic strokes among Indo-Asians.[26,27]

Cardiovascular Diseases

The key cardiovascular risk factors for the development of AF are hypertension, congestive heart failure, MI, and valvular heart disease.[8,10,28] Hypertension is probably the most common risk factor for the development of AF that is amenable to treatment.[29] The impact of valvular heart disease has been reduced significantly with the decline in the incidence of rheumatic fever in many countries.[30] Diabetes mellitus has also been associated with development of AF.[10,13,15] Less well established cardiovascular risk factors in the development of AF include increased left atrial size, left ventricular hypertrophy, and left ventricular dysfunction.[10,31,32] Some noncardiovascular risk factors have also been described and include obstructive sleep apnea,[33] hyperthyroidism,[34] elevated C-reactive protein levels,[35] and men with traits of anger and hostility.[36] Finally, the causal role of genetics in AF has been examined by a number of recent studies.[37–41]

Rising Prevalence

An increased prevalence of a disease must reflect an increase in incidence of the condition, an improved survival of persons with the disease, or both. Although there is evidence for a rising prevalence of AF, it is not clear whether this reflects an increasing incidence or improved survival.

Wolf and colleagues examined the prevalence of AF in persons aged 65 to 84 years from 1968 to 1989 in the Framingham study cohort.[2] Increasing prevalence of AF was noted even after adjusting for age, prior MI, or other comorbidities, with a doubling in prevalence during that time period among men. However, this increasing prevalence was not present in women (Figure 2). The reasons for the rising temporal prevalence were not apparent, although improved survival following MI was postulated as a possible cause.[2] An increase in the prevalence rates of AF has been reported in patients discharged between 1982 and 1993 from short-stay hospitals in the United States.[2,42,43] The Copenhagen City Heart Study from the 1970s to 1990s also demonstrated similar gender-specific increases in the prevalence of AF.[44]

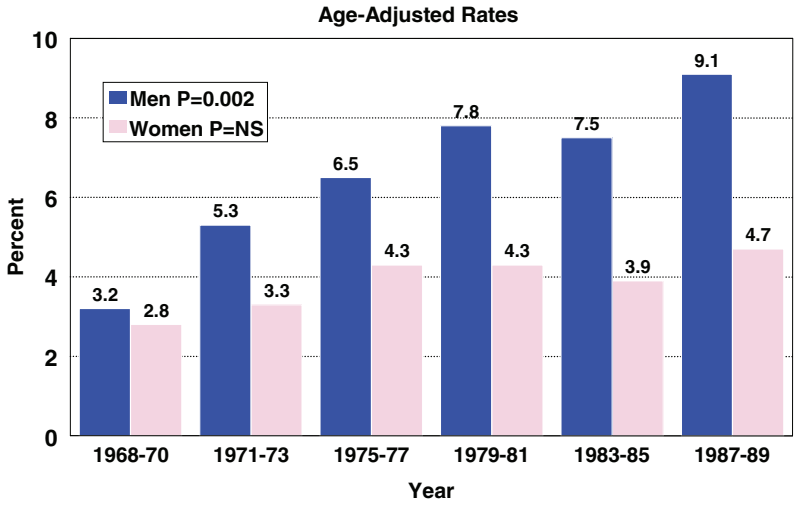

Figure 2 Secular trends in prevalence (percent) of atrial fibrillation among men and women aged 65 to 84 years (age adjusted). Data from Framingham study[2] was used to construct the bar graph. *NS* not significant

Implications for the United States

The estimated prevalence rates from the four aforementioned studies[9–12] were applied to the U.S. census data by Feinberg et al.[14] to derive the overall prevalence and age-specific prevalence for the entire country. An estimated 2.2 million people in the United States are affected based on these calculations. However, population studies may underestimate the prevalence of AF for two reasons: AF may not be present at the follow-up time, and a significant population may have asymptomatic episodes. According to the U.S. Census Bureau Population Projections Program,[3] the number of Americans aged 65 years or older will increase substantially to more than 20% of the population (82 million) by the year 2050. This aging of the population is projected to result in a 2.5-fold rise in AF prevalence.[20,21]

Incidence

Incidence of a disease is defined as the rate at which new cases occur in a population during a specified time period. The previously discussed Framingham study, which followed 5,029 men and women from 1948, observed an incidence of AF that was both age and gender dependent. There were 6.2 and 3.8 cases per 1,000 person-examinations for men and women aged 55 to 64 years, respectively, compared with 75.9 and 62.8 cases among persons aged 85 to 94 years[8] (Figure 3). The incidence was lower in the Manitoba follow-up study of 4,000 subjects,[45] while the Cardiovascular Health Study that followed a prospective cohort of 5,201 subjects reported a much higher incidence[10] compared with the Framingham study. Also, in a large general practice population of 703,730 subjects in 1996 in the United Kingdom, 1,035 new diagnoses of AF were identified, accounting for an incidence of 1.7 per 1000 person-years. The incidence was 3 cases per 1000 person-years in subjects aged 60 years or more and 8.6 in subjects aged 80 to 89 years.[46]

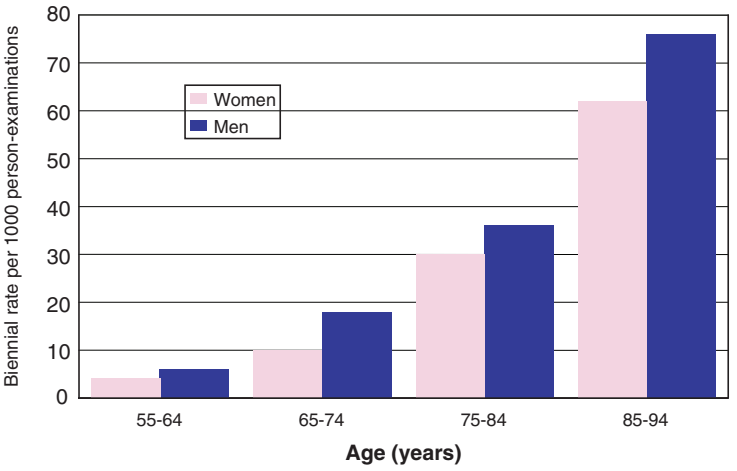

Figure 3 Incidence of atrial fibrillation according to age groups in the Framingham study 38-year follow-up. (Reproduced with permission from ref. 8.)

Another measure of the burden of a disease in a population is its lifetime risk assessment. The lifetime risk for development of AF was high in a study of the Framingham population: 1 in 4 for individuals 40 years of age and older.[47] The risks were similar in men and women at all ages.

Implications of Changing Epidemiology of Atrial Fibrillation

Atrial fibrillation is associated with significant morbidity related to symptoms, heart failure, and thromboembolic events. About 36% of all strokes in individuals aged 80 to 89 years are attributed to AF.[9] Although AF is generally considered a non-life-threatening arrhythmia, it was associated with a 1.5- to 1.9-fold excess mortality after adjustment for preexisting cardiovascular conditions in the Framingham Heart Study.[48] The economic consequences of this arrhythmia (discussed in Chapter 2) are highlighted by the fact that AF is the most common arrhythmia among patients hospitalized in the United States with a primary diagnosis of an arrhythmia.[49]

With the expected rise in the elderly population and the prevalence of AF, preventive measures to reduce its incidence will have profound societal benefits. Although proven preventive measures are lacking, control of risk factors such as hypertension and MI appear prudent. New areas of research are targeting the use of dietary agents (e.g., fish oil) and pharmacological agents (e.g., antagonists of the rennin–angiotensin system, HMG [3-hydroxy-3-methylglutaryl] coenzyme A reductase inhibitors) to prevent AF.[50]

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2

Economic Costs Associated with Atrial Fibrillation

Thomas M. Maddox, Ira S. Nash, and Valentin Fuster

Abstract: As the population ages, the incidence and prevalence of atrial fibrillation (AF) is expected to increase, resulting in significant societal and economic impact. By 2050, AF is projected to affect 15.9 million individuals in the United States. Atrial fibrillation results in a variety of adverse outcomes, including a fivefold increased risk of stroke, impaired quality of life, decreased work productivity, and increased rates of hospitalization. In 2005, there were 470,000 U.S. hospitalizations secondary to AF. In 2004, over 9 million working days were lost because of AF. Costs of AF and its associated complications are enormous. In 2006, costs attributable to AF-associated stroke equaled $12 billion. In addition, $41,000 to $105,000 per patient was spent on aggregate and individual AF care. Because of its increasing prevalence, numerous complications, and large costs, AF presents a significant challenge for patients, clinicians, and health care policymakers. Finding strategies to best care for these patients will become increasingly important.

Keywords: AF hospitalizations; AF cost; Incidence of AF; Prevalence of AF; Stroke.

The number of people affected by atrial fibrillation (AF) is large and growing, both in the United States and internationally. Approximately 2.2 million Americans, or 0.9% of the population, now suffer from AF, with an incidence rate of 75,000 new cases per year.[1–3] Both the prevalence and incidence rates of the condition increase with age (Figure 1). Among Framingham Heart Study participants, less than 0.1% of patients under the age of 40 were affected. However, AF incidence rates double with each increasing decade of life, independent of other cardiac conditions.[4] In those older than 85 years, the annual rate of AF exceeded 10%.[2] The AF incidence rates also differ by gender. Men were 1.5 times more likely to have AF than women in the Framingham cohort.[3] International cohorts illustrate similar findings. In the Renfrew/Paisley cohort, a survey of U.K. subjects conducted in 2000, AF affected 1% of the population. In addition, men were 1.8 times more likely to be affected than women.[4,5]

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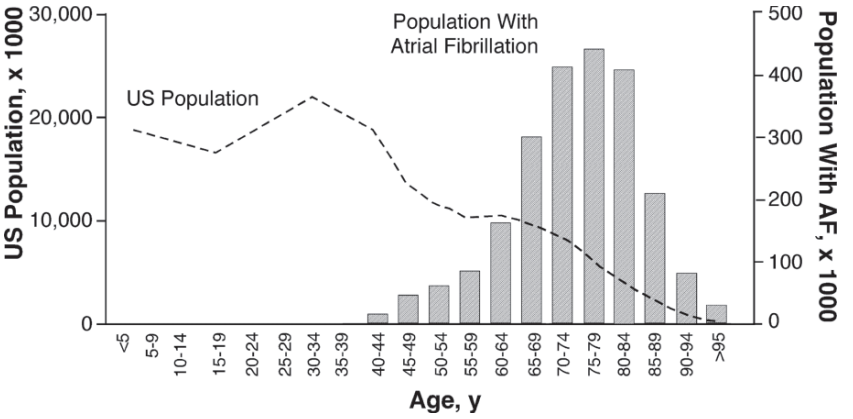

Figure 1 Prevalence of atrial fibrillation (AF) by age. *y* years. (From ref. 2.)

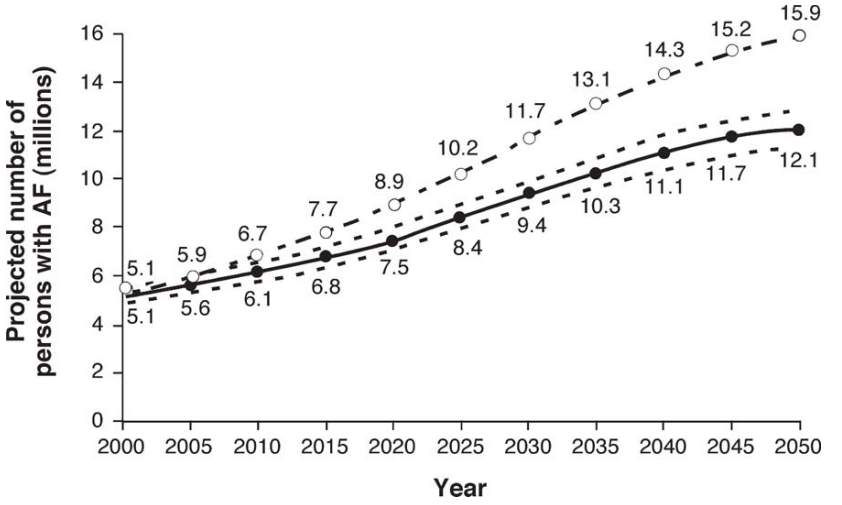

Figure 2 Projected number of persons with atrial fibrillation (AF) in the United States between 2000 and 2050 assuming no further increase in age-adjusted AF incidence (dark circles) and assuming a continued increase in incidence rate as evident in 1980 to 2000 (light circles). (From ref. 79.)

As the population ages and survival from other cardiac conditions improves, the AF burden will increase (Figure 2). For example, U.S. hospitalizations for AF in 2001 increased 34% from 1996 hospitalizations.[1] In the United Kingdom, AF rates among elderly men increased from 1.8 cases/1000 person-years in 1986 to 4.2 cases/1000 person-years in 1995. Similarly,[5] rates among elderly women increased from 1.8 cases/1000 person-years in 1986 to 3.7 cases/1000 person-years in 1995.

Economic Considerations

Given its large and growing prevalence, AF has substantial economic impact. Proper economic analysis of medical conditions such as AF requires explicit definitions of perspective, costs, and outcomes.

Perspective is the vantage point from which costs and outcomes are assessed. For example, costs can be quantified from the perspective of the patient. In this case, potential costs include AF symptoms, discomfort from therapy, and time lost from work. In contrast, potential costs from the perspective of a payor, such as a health insurance company, include covered services for hospitalization or other treatments and administrative costs in processing claims. Ultimately, a societal perspective, in which all costs and outcomes are assessed regardless of who pays the costs or experiences the outcomes, provides the most complete insight into the economic impact of AF.[6]

In cost accounting, costs should be clearly distinguished from the charges assessed by physicians, hospitals, and other health care providers and should reflect the actual financial resources required to provide care. Costs can be divided into direct and indirect costs. *Direct costs* are those incurred directly from medical care and include inpatient costs (hospital fees, physician fees, procedure and therapy costs) and follow-up costs (physician visits, outpatient testing, medications, home health care providers, long-term care, and future hospitalizations). *Indirect costs* quantify the remaining nonmedical impact of AF, such as missed days of work and lost productivity.[6] If possible, costs are usually presented in terms of dollar (or other currency) expenditure. When assessment of monetary costs is difficult, such as for mortality or decreased quality of life, proxy values such as lost years of work or lost productivity are used.

In this chapter, we focus primarily on the economic impact of AF and its treatment from a societal perspective. We present those costs associated with AF and its sequelae as well as its evaluation and treatment. Understanding these costs provides important information for both practitioners and policymakers.

Atrial Fibrillation Condition Costs

Atrial fibrillation increases the risk of a variety of adverse outcomes, most notably stroke. It also has an impact on mortality, impairs quality of life, decreases productivity, and increases hospitalization rates. All of these adverse outcomes have substantial costs (Table 1).

Table 1 Assorted atrial fibrillation and cerebrovascular accident costs.

Aggregate and individual CVA costs	
2006 (projected) U.S. CVA costs	$57.9 billion[1]
2006 (projected) U.S. CVA costs attributable to AF	$12 billion[1]
2004 U.K. CVA costs	£4.7 billion ($8.6 billion)[15]
2006 (projected) U.S. acute care CVA costs	$13,000-20,000/patient[1]
Aggregate and individual AF care and management costs	
2000 U.K. direct medical care costs	£459 million ($761.5 million)[18]
2000 U.K. nursing home costs	£110.7 million ($183.7 million)[15]
2004 indirect care costs (e.g., cost of caretakers)	£1.7 billion ($3.1 billion)[15]
2006 (projected) lifetime medical costs	$41,000 to $105,000/patient[1]
Aggregate lost productivity costs associated with AF	
2004 lost working years caused by AF mortality	44,000[15]
2004 lost working days caused by AF morbidity	9.0 million[15]

All costs and exchange rates valued in the respective study year; see exchanges rates calculator at http://eh.net/hmit/.
AF atrial fibrillation, *CVA* cerebrovascular accident.

Stroke

Stroke is the most debilitating complication of AF. With its associated hypercoagulable state, structural abnormalities in the fibrillating atria, and relative blood stasis, AF fulfills Virchow's triad for the development of thrombi and their subsequent embolization to the cerebral vasculature.[7,8] As a result, stroke is five times more likely to occur in AF patients than in age-matched controls.[1] Among the Framingham cohort, strokes were four to five times more likely to occur among AF patients than those without AF.[9] In the Renfrew/Paisley cohort, strokes were 2.5 to 3.2 times more likely in AF patients over a 25-year follow-up compared to those without AF.[5] Not only does AF predispose to strokes, but also these strokes are more often fatal, debilitating, and recurrent than those not associated with AF.[4,10–14] In aggregate, AF-related strokes account for 15% to 20% of all strokes annually in the United States.[1]

The economic consequences of stroke are massive. In the United States, total costs attributed to strokes in 2007 were projected at $62.7 billion.[1] Assuming 20% of these strokes are AF related, total costs attributable to AF are approximately $12 billion. In the United Kingdom, a 2004 survey calculated stroke costs of £4.7 billion ($8.62 billion). Approximately 44,000 working years were lost to mortality, and 9 million workdays were lost to morbidity. Indirect care costs (time and opportunity costs of nonpaid caregivers for cerebrovascular accident [CVA] patients) exceeded £1.7 billion ($3.12 billion).[15] For an individual patient, the mean estimated lifetime cost of a stroke, including inpatient care, rehabilitation, and follow-up care for lasting deficits, is $140,000.[1]

Acute care costs, such as hospitalization, diagnostic testing, initial therapy, and rehabilitation, are substantial. The average estimated cost for the first 30 days of stroke care is $13,000/patient for mild strokes and $20,000/patient for severe strokes.[1] In addition, inpatient costs can account for 70% of the overall cost of the first year after stroke.[1] Wolf and colleagues illustrated costs of acute care in the first year after stroke using 1991 Medicare data. Among men aged 65 to 74, Medicare spent $21,231 per patient, 95% of which was spent on acute care needs.[9]

Chronic long-term CVA costs are another major source of expense. One study evaluated lifetime costs of AF patients who suffered strokes. Costs varied from $41,257 (Australia) to $104,629 (United Kingdom) per patient.[16] In addition, these costs are increasing, possibly because of the increasing age of the population and a higher prevalence of comorbidities. For instance, the U.S. National Hospital Discharge Survey indicated that increasing numbers of patients are discharged from hospitalization to long-term nursing facilities.[17] In the United Kingdom,[18] nursing home costs associated with AF more than doubled from £46.4 million ($73.3 million) in 1995 to £110.7 million ($167.8 million) in 2000.

Mortality

Multiple national and international cohorts describe an independent association between AF and mortality. The mechanism by which AF confers this independent mortality risk is poorly understood. Nonetheless, the Framingham Heart Study illustrated an age-adjusted 1.5 to 1.9 hazard ratio for mortality among patients with AF compared with those without AF.[4] The U.K. Renfrew/Paisley cohort revealed a 1.5 increased hazard of time to death among patients with

AF.[5] A study of Canadian men with AF demonstrated a 1.3 to 1.4 increased hazard in time to all-cause and cardiovascular death.[14] A 4-year follow-up survey of the Marshfield Epidemiologic Study Area in the United States described a 2.4 increased hazard in time to all-cause death among AF patients.[19] The Valsartan in Acute Myocardial Infarction (VALIANT) study investigated the effects of valsartan, captopril, or both on patients with acute myocardial infarction (MI) complicated by heart failure or left ventricular (LV) systolic dysfunction. It showed an increased likelihood of mortality or major cardiovascular events (congestive heart failure, MI, resuscitated cardiac arrest, or stroke) among those patients who developed AF compared to those who did not.[20,21]

Mortality costs are difficult to compute and are generally unavailable. Regardless, the burden of AF, its associated mortality, and its effect on lost earnings and productivity imply substantial societal costs.

Postoperative Atrial Fibrillation

Atrial fibrillation is common in the postoperative recovery period. Between 20% and 50% of U.S. cardiac surgery patients develop AF postoperatively, resulting in prolonged hospital stays and increased treatment costs.[22–29] One survey revealed that patients with postoperative AF incurred $6,356 more in hospitalization charges than their AF-free counterparts.[22] Another survey demonstrated an adjusted increase in mean length of hospitalization for AF patients of 4.9 days, corresponding to increased costs of at least $10,005 per patient.[29] Yet another investigation concluded that the occurrence of AF after cardiac surgery independently increased the median length of hospitalization by 3.2 days.[30]

Many strategies have been tested to reduce the incidence and associated costs of postoperative AF.[31–33] Therapies such as metoprolol, amiodarone, sotalol, procainamide, and atrial pacing have all successfully reduced the incidence of postoperative AF.[33] A meta-analysis examining these various therapies found a 50% reduction in AF incidence and a decrease in length of hospitalization of 1.0 days. However, these clinical improvements did not correspond to a meaningful reduction in costs, possibly because of the expenses associated with the preventive therapies.[33] Only one small study demonstrated significant decreases in both length of hospitalization and costs of care.[34] Despite this lack of a clear cost reduction in postoperative AF prevention, prophylaxis may still be warranted to lessen lengths of hospitalization and to mitigate symptoms, especially among those patients who may not tolerate the arrhythmia well.[33]

Quality of Life

Atrial fibrillation adversely affects patients' quality of life. Patients with AF and poor rate control have palpitations, fatigue, shortness of breath, or lightheadedness, especially if they have underlying cardiac or pulmonary disease.[35] However, even asymptomatic AF patients experience lower perceived health and life satisfaction compared to patients without AF, possibly because of the burden of the diagnosis and its attendant needs for medical care and therapies.[36]

This reduction in quality of life has a direct impact on costs. Although quantification of quality of life in monetary terms is difficult, symptoms and poor functional status can lead to lost productivity, both professionally and personally. Fortunately, several randomized controlled trials have demonstrated quality

of life improvements with AF therapies.[37] Rate and rhythm control strategies were equally efficacious in providing quality-of-life benefits.[19]

Productivity

Atrial fibrillation results in significant indirect nonmedical costs, such as lost work and productivity. For example, a French survey of AF patients found that costs caused by missed work accounted for 6% of total AF costs.[38] In addition to the workers affected by this condition, employers face increased costs, not only from decreased productivity, but also from increased insurance premiums to cover affected employees. A U.S. study of 16 employers, conducted from 1999 to 2002, found large cost differences between employees with AF and those without. Annually, excess direct medical costs for AF patients were $12,349 per patient, and excess indirect medical costs were $2,524 per patient, as compared to patients without AF.[39] Although they account for a relatively small portion of overall AF costs, these indirect medical costs play a meaningful role in the overall economic impact of the condition.

Atrial Fibrillation Evaluation and Treatment

Acute Management

Patients with new-onset AF, or an exacerbation of previously diagnosed AF, often require extensive evaluation and treatment. Management approaches for AF vary dependent on patients' hemodynamic stability, symptoms and comorbidities, and the duration of the AF episode. A new diagnosis of AF, either in isolation or in association with another medical condition such as congestive heart failure, initiates an investigation into its cause. These investigations, which can include laboratory testing, monitoring, cardiac imaging, and hospitalization, play a significant role in the economic impact of AF.

One study analyzed costs between AF patients who were hospitalized and those discharged from an emergency department. Admitted patients incurred mean costs of $2,012 in their care compared to $1,878 among discharged patients.[40] A French survey of AF patients found that consultations and investigations for AF patients drove 9% and 8%, respectively, of their overall costs of AF care.[38]

Several interventions have been proposed to reduce these costs. Dell'Orfano and colleagues developed clinical practice guidelines to mitigate acute AF management costs.[41] Guidelines ensuring appropriate use of direct current cardioversion (DCCV), rate-controlling drugs, and expedited referrals to AF outpatient clinics resulted in decreased hospitalizations, reductions in health care costs of $1,400 per patient, and no increases in return visits or hospitalizations.[42]

Hospitalizations for AF management occur frequently. In 2005, AF resulted in 470,000 hospitalizations in the United States.[1] Similar data are seen internationally. Over a 25-year follow-up period in the Multifactor Primary Prevention Cohort in Sweden, 10.1% of male subjects in the cohort were hospitalized with a primary diagnosis of AF.[43] Over a 20-year follow-up period among the Renfrew/Paisley cohort in the United Kingdom, 3.6% of men and 3.4% of women were hospitalized with a diagnosis of AF.[5] In addition, AF hospitalizations, both nationally and internationally, have been

increasing. One study[22] found a doubling of U.S. AF hospitalizations between 1982 and 1993. From 1996 to 2001, the number of U.S. hospitalizations with AF as the primary diagnosis increased by 34%.[1] In Scotland,[44] AF admissions among elderly patients (>65 years) increased from 1.7/1000 person-years in 1985 to 5.5/1000 person-years in 1996, and among younger patients (age 46–65years) they increased from 0.7/1000 person-years in 1985 to 1.7/1000 person-years in 1996.

These hospitalizations account for a significant portion of the costs associated with AF. A review of U.S. patients admitted for a principal diagnosis of AF demonstrated a mean length of stay of 3.9 days, with average costs of $6,692 per patient.[45] In a French survey of 671 AF patients, hospitalization costs accounted for 52% of the expenditures per patient.[38] A 1995 U.K. survey revealed that 50% (£122 million, or $192.6 million) of total annual AF costs were because of hospitalizations.[18] Wolf and colleagues[9] found that 1-year Medicare hospitalization payments among men aged 65 to 74 years with AF were $12,654, and 3-year hospitalization costs were $18,365.

For AF episodes lasting 48 hours or less, cardioversion (either electrical or chemical) may be performed without prohibitive risk of thromboembolism.[46] Costs of the procedure include anesthesia, monitoring, or further treatments or hospitalization for those who fail to convert to sinus rhythm. In one study at a single center, the total cardioversion cost was $508 per patient.[41] Variations in the timing and method of cardioversion also affect costs. A single-center trial of AF cardioversion strategies found that patients randomized to a traditional care (hospitalization) pathway incurred median costs of $1,112 per patient, while those patients who received early DCCV in combination with low molecular weight heparin in the emergency department incurred median costs of $984 per patient.[47]

Pharmacological cardioversion is another treatment option for patients with recent-onset AF. Although these medicines cost less than DCCV, their cost advantage is attenuated by their inferior efficacy (average cardioversion success rates are reported from 21% to 71%).[48–50] One review found that, assuming a 45% efficacy rate with ibutilide use and DCCV use in those patients who failed two ibutilide doses, the average cost per patient undergoing chemical cardioversion was $506, equivalent to the cost of immediate DCCV.[41] Combining antiarrhythmics and DCCV offers another treatment strategy with favorable cost implications. One randomized trial illustrated improved success rates of DCCV with concomitant antiarrhythmic therapy (primarily quinidine) over DCCV alone.[51] The success of this combination approach reduced costs compared to DCCV alone ($1,240 vs. $1,917).[51]

Approximately 50% of initial episodes of AF convert spontaneously to sinus rhythm within 48 hours, with the majority occurring in the first 24 hours.[45,52] Accordingly, monitoring AF patients prior to DCCV, to allow for spontaneous conversion, is reasonable. In one center, 24 hours of monitoring cost $237 per patient. For those patients who failed to spontaneously convert and require DCCV, costs of care increased to $683 per patient. However, since 50% of patients spontaneously converted, the average cost per patient using the observational strategy was $460, which compared favorably to early DCCV management strategies.[41]

For AF patients presenting with episodes longer than 48 hours, cardioversion should not be attempted because of the excessive risk of thromboembolism.[53]

In these patients, 3 to 4 weeks of anticoagulation followed by cardioversion is the generally accepted practice. Alternatively, transesophageal echocardiography (TEE) can be performed to exclude intracardiac thrombi, followed by immediate cardioversion and 4 weeks of anticoagulation.[54] A comparison of these two strategies found similar costs for both ($6,508 for anticoagulation followed by cardioversion vs $6,235 for TEE followed by cardioversion).[55] The greater upfront costs of the TEE strategy were offset by the costs of bleeding complications in the anticoagulation-only strategy.

Chronic Management

After the initial evaluation and treatment of an acute AF episode, focus turns to arrhythmia control and anticoagulation. Arrhythmia control involves antiarrhythmic or atrioventricular (AV) nodal blocking medications. Rhythm control of AF with antiarrhythmic medications can reduce symptoms, improve functional capacity, and lower both stroke and mortality risk.[56] These benefits must be weighed against the potentially dangerous side effects associated with antiarrhythmic medications. An alternative method of AF management is rate control strategies with AV nodal blocking agents.

Five studies (Paroxysmal Atrial Fibrillation 2 study [PAF2],[57] Strategies of Treatment of Atrial Fibrillation [STAF],[58] Pharmacological Intervention in Atrial Fibrillation [PIAF],[59] Rate Control versus Electrical Cardioversion study [RACE],[60] and Atrial Fibrillation Follow-up Investigation of Rhythm Management [AFFIRM][61]) have examined the efficacy of rate vs rhythm control strategies.[56] In general, no differences in outcomes were detected between the two treatments. Both strategies appeared equivalent in mortality, stroke risk, functional capacity, and quality of life.[37,56] Costs, on the other hand, were less with a rate control strategy. Both RACE and AFFIRM demonstrated cost savings in the rate control arm, even after sensitivity analyses. In the 2000 RACE study, mean costs of rate control were 7,386 ($7,017), while mean costs of rhythm control were 8,284 ($7,870).[56] In the AFFIRM trial, the incremental cost of rhythm control over rate control was nearly $1,500 per patient per year.

Several interventional procedures are an alternative to medication-based antiarrhythmic strategies for AF management. Catheter-based AV node modification or ablation can be used to treat highly symptomatic patients or patients who cannot tolerate rate-controlling agents. The procedure can improve symptoms, functional capacity, and LV function.[62] In a 1997 report,[62] costs of AV node modification were $19,389, and costs of the AV node ablation were $28,485. Over time, with technical advances, these costs will likely decline, as evidenced by 2003 costs of $17,173 for AV nodal ablation.[63] Emerging technologies in AF ablation, such as maze procedures and pulmonary vein isolation, will also have significant cost implications.

Anticoagulation

Another crucial consideration in long-term AF management is anticoagulation. Among AF patients, warfarin reduced rates of stroke by 60% compared with placebo.[64–67] Despite this impressive efficacy, anticoagulation comes with a risk of hemorrhage. Warfarin use requires careful and frequent monitoring to ensure therapeutic levels of anticoagulation and to

avoid bleeding complications. Frequent laboratory testing is necessary to maintain a normalized prothrombin clotting time ratio (INR, international normalized ratio) of 2 to 3.

Not surprisingly, anticoagulation medication and its attendant monitoring drives a large portion of AF costs.[18] In a 1995 U.K. survey, drug therapy accounted for 20% (£56 million, or $88.4 million) of overall AF costs.[18] Similarly, a French survey of 671 AF patients found that 23% of overall AF costs were attributable to drug therapy.[38] Although these costs include all medications used in AF therapy, they point to the significant cost impact of anticoagulation

Anticoagulation complications also affect costs. The risk of bleeding complications increases with higher anticoagulation intensity, older patients, patients with a history of hemorrhage, and patients with serious comorbid conditions.[68,69] Overall, the reported annual incidence of warfarin-associated bleeding events ranges from 1% to 5%, with 0.5% to 1.0% incidence of fatal hemorrhage.[70–73] These bleeding events in turn increase costs. The average hospitalization cost for these bleeding events has been estimated at $15,988 per patient.[74]

Nonadherence to warfarin therapy is another large and costly problem in AF management. The fraction of eligible patients who actually receive anticoagulation is only 22% to 79%.[75,76] Even among those patients who receive anticoagulation, up to 60% of patients do not achieve therapeutic warfarin levels.[75] Taken together, these patients represent missed opportunities for stroke prevention and risk the significant costs and adverse outcomes of stroke morbidity and mortality.[77,78]

Future Directions

Although the current burden of AF, both in the United States and abroad, is already large, forecasts predict major increases over the coming decades. As the population ages and survival from other cardiac conditions that predispose to AF increases, the prevalence of AF will likely rise. Projections for the number of adults in the United States with AF in 2050 range between 5.6 and 15.9 million, as compared to 2.2 million in 2006 (Figure 2).[1,79] Approximately 50% of this projected population will be over the age of 85 years.[1]

As the numbers of AF patients increase, AF care costs will also increase. In the 2004 U.K. survey of AF patients, costs rose from 0.62% (£244 million, or $418 million) of the National Health Service (NHS) budget in 1995 to 0.97% (£459 million, or $788 million) of the 2000 NHS budget.[18]

Future developments in AF care, such as new anticoagulants and procedures, could have a significant impact on costs. For example, direct antithrombin agents or new antiplatelet combinations may show efficacy in AF-related stroke prevention. Since these new therapies do not require the intensive monitoring required by warfarin, substantial cost savings could be realized. Similarly, innovations or improvements in interventional procedures, both in efficacy and safety, could also affect costs.

Atrial fibrillation presents significant challenges to both individual practitioners and policymakers. With its substantial costs in diagnosis, treatment, and outcomes, it will become increasingly important to determine the best strategies in caring for these patients.

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Cost-Effectiveness of Catheter Ablation for Atrial Fibrillation

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Abstract: Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmia encountered in clinical practice. The incidence and prevalence of this arrhythmia continue to rise. Strategies for the management of atrial fibrillation include rate or rhythm control. Rhythm control can be attempted pharmacologically, surgically, or more recently by the use of catheter ablation. Catheter ablation of AF is now a widely accepted and practiced treatment modality. The cost-effectiveness of this technique hinges on procedural success rates, complication rates, up-front costs, and the stroke risk in the treatment population. There have been several studies of the cost-effectiveness of catheter ablation of AF compared with pharmacological management. Most of these studies projected a time horizon of at least 5 years before catheter ablation becomes cost-effective. As techniques become more uniform and widespread, the efficacy is likely to increase, with a reduction in complication rate, leading to a reduced time horizon for making this procedure cost-effective. A prospective, randomized, multicenter study is required to definitively establish the cost-effectiveness of this procedure.

Keywords: Cost-effectiveness; QALY; RF ablation; Atrial Fibrillation

Introduction

Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmia encountered in clinical practice.[1] It is associated with significant morbidity[2] and an increased mortality.[3] It can be defined as paroxysmal, persistent, or permanent. The incidence and prevalence of this arrhythmia continue to rise.[4]

Approaches to the management of AF include rate or rhythm control.[5] Rate control can be achieved by slowing the ventricular response rate with pharmacological agents or ablation of the atrioventricular (AV) node coupled with ventricular pacing. Rhythm control can be attempted pharmacologically with antiarrhythmic medications, with or without electrical cardioversion; surgically via the maze procedure; or more recently, utilizing catheter ablation of atrial tissue to restore sinus rhythm. Both rate and rhythm control strategies necessitate the use of anticoagulation to reduce the incidence of thromboembolic stroke.[5]

There are considerable costs involved with each of these strategies. As detailed in Chapter 2, there are several perspectives from which to quantify these

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costs: the perspective of the patient, the perspective of third-party payors, and the perspective of society as a whole. The patient's perspective includes symptoms, quality of life, and lost earnings. The third-party payor views the direct costs involved in hospitalization, specialist consultation, complications of therapy, and ongoing medical therapy. Society's perspective includes an assessment of all costs and outcomes, including indirect costs such as lost productivity. Assessment of the monetary value for indirect costs such as quality of life requires approximation.

Cost-Effectiveness Analysis

Cost-effectiveness analysis provides a way of comparing the efficacy of different treatment modalities with respect to the cost that can be assessed from each of these perspectives.[6] The different techniques for calculating cost-effectiveness include retrospective analysis and comparison of the costs incurred by two different treatment modalities, hypothetical decision analytical models, and prospective comparisons of the cost of randomized therapies.

Cost-Effectiveness of Pharmacological Rhythm vs Rate Control Strategies

Several authors have assessed the cost-effectiveness of rhythm control vs rate control for AF. Marshall et al. performed a retrospective economic evaluation from a third party payor's perspective of the data from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) clinical trial and found that rate control was more cost-effective than pharmacological rhythm control.[6] The number of hospital visits, inpatient hospital days, and cardioversions and the drug cost per day were all greater for the rhythm control group with no increase in efficacy. This reflects the fact that pharmacological rhythm control requires ongoing antiarrhythmic therapy with drugs that are relatively expensive, suboptimal in maintaining sinus rhythm, and have significant associated toxicities. An "on-treatment" analysis of the AFFIRM data concluded that if an effective method for maintaining sinus rhythm with fewer adverse effects than current antiarrhythmic therapy were available, such as catheter ablation of AF, it might be beneficial.[7]

Catheter-based atrial ablation techniques for the treatment of AF with the aim of maintaining sinus rhythm are being performed by an expanding number of practitioners. There is significant variability in the approach to this procedure; therefore, published estimates of efficacy and associated complications also vary.

Several authors have performed cost-effectiveness analyses of this procedure compared with pharmacological rhythm control strategies.[8,11,14]

Cost-Effectiveness of Radio-Frequency Ablation of Atrial Fibrillation

Weerasooriya et al. performed a retrospective comparison of the cost of radiofrequency (RF) ablation compared with that of antiarrhythmic drug therapy for paroxysmal AF in 118 consecutive patients.[8] The ablation technique

utilized a conventional multielectrode circumferential mapping catheter and an RF ablation catheter to electrically isolate the pulmonary veins. Costs were assessed from the payor's perspective. Cost of drug therapy was calculated on the basis of the antiarrhythmic medications utilized immediately prior to ablation. Ablation costs assumed a 5-day hospitalization stay. There were no significant complications of RF ablation in this series, and the efficacy of RF ablation was 72% at 32 ± 15 weeks after 1.52 ± 0.71 RF ablations. The initial cost of catheter ablation was 4,715 with a projected annual cost of 445 per year. Pharmacological rhythm control had a projected annual cost of 1,590 per year. A sensitivity analysis was also performed using pharmacological treatment costs for the Cost of Care in Atrial Fibrillation (COCAF) study.[9] The cost ratio favored catheter ablation after about 5 years and sooner using data from the COCAF study (Table 1).

Published first-attempt efficacy rates for RF ablation of paroxysmal AF using a similar technique have more recently exceeded 72% with much shorter durations of hospitalization, typically just an overnight stay.[10] This would suggest potentially even more favorable cost-effectiveness of RF ablation for paroxysmal AF if the analysis were performed with more recent data. However, the lack of complications in this series is exceptional, and any complications would of course reduce cost-effectiveness. Furthermore, this analysis compared RF ablation with pharmacological rhythm control, which has been shown to be less cost-effective than a rate control strategy. In comparing RF ablation to a rate control strategy, one would expect it to take longer to achieve an equivalent cost ratio. On the other hand, particularly in patients with paroxysmal AF, a rate control strategy may be poorly tolerated by a large number of patients. This would have to be taken into account when comparing the cost of RF ablation to the cost of pursuing a rate control strategy.

Khaykin et al. performed a cost-effectiveness analysis of catheter ablation compared with pharmacological rate and rhythm control in AF.[11] Again, this was a cost comparison from the payor's perspective. Costs related to medical therapy included the cost of anticoagulation, rate and rhythm control medications, noninvasive testing, physician visits, and hospital admissions and the cost of complica-

Table 1 Projected future costs (in euros) of ablation versus medical management (adapted from ref. 8).

Year	RFA cost	MED cost	Cost ratio	RFA cost (COCAF)	MED cost (COCAF)	Cost ratio (COCAF)
0	4715	0	-	4,715	0	-
1	5,160	1,590	3.24	5,349	2,263	2.36
2	5,583	3,101	1.80	5,951	4,413	1.35
3	5,985	4,536	1.32	6,523	6,455	1.01
4	6,367	5,899	1.08	7,066	8,395	0.84
5	6,730	7,194	0.93	7,582	10,238	0.74
6	7,075	8,424	0.84	8,072	11,989	0.67
7	7,403	9,593	0.77	8,538	13,653	0.62
8	7,714	10,703	0.72	8,980	15,233	0.59
9	8,010	11,758	0.68	9,400	16,734	0.56
10	8,291	12,760	0.65	9,799	18,160	0.54

COCAF Cost of Care in Atrial Fibrillation Study, *MED* medical management, *RFA* radio-frequency ablation.

tions related to medical therapy. Costs of RF ablation included those related to the procedure (the use of CARTO (Biosense Webster, Diamond Bar, California) or intracardiac echocardiographic [ICE] guided pulmonary vein isolation), hospital stay, and complications. Sensitivity analysis looked at a range of hypothetical initial success rates of 50% to 75% with attrition rates of 1% to 5%. Up to two additional catheter ablation procedures were accounted for depending on the initial success of the first ablation. In this study, costs of ongoing medical therapy and catheter ablation equalized at 2.5 to 5.5 years of follow-up. Subsequently, the ablation strategy is cost saving.

This analysis again suggests the cost-effectiveness of catheter-based ablation therapy occurring after 5.5 years with a conservative estimate of ablation efficacy at 50%, even when compared with rhythm and rate control strategies combined. Costs of ablation in this study also accounted for the use of CARTO or ICE, both of which are not uniformly utilized for this procedure. Therefore, this analysis may have somewhat overestimated initial ablation costs, and recalculation without the use of CARTO or ICE may reveal cost-effectiveness occurring earlier. The type of AF ablation (paroxysmal, persistent, or permanent) was not stipulated in this study. However, the analyzed efficacy range of 50% to 75%, allowing for multiple procedures, is comparable to those obtained for ablation of persistent and permanent AF that have previously been published.[12,13]

Chan et al.[14] published a Markov decision analytical model for the assessment of the cost-effectiveness of left atrial catheter ablation (LACA) compared with amiodarone rhythm control therapy and rate control therapy. This model assessed cost-effectiveness from the societal perspective in hypothetical cohorts of 65-year-old patients with a low or moderate risk of stroke. Moderate stroke risk was defined as the presence of one risk factor (hypertension, diabetes, coronary artery disease, or congestive heart failure). Low stroke risk was the absence of risk factors. A third cohort of 55-year-old patients with moderate stroke risk was also assessed.

A quality-adjusted life-year (QALY) is a composite measure of the length of life (life-years saved) and the quality of that life.[15] Cost-effectiveness in this study was defined at a traditional threshold of $50,000 to $100,000 per QALY. With warfarin therapy, estimated annual stroke risks of 1.3% and 0.7% were used for patients with moderate and low risk of stroke, respectively. This risk was adjusted linearly with age, with a relative risk of 1.4 for each decade. Complications of catheter ablation factored into this analysis included atrio–esophageal fistula, with a cost of $50,000 and 50% mortality. The efficacy of LACA was estimated at 80% with anticoagulation continued for 6 months and the subsequent stroke risk in patients with restored sinus rhythm estimated from data available in the literature.

In all three cohorts,[15] rhythm control was inferior to rate control, having worse efficacy and higher cost. This is congruent with the retrospective cost-effectiveness analysis of the AFFIRM data.[6] For moderate stroke risk, LACA had an incremental cost-effectiveness ratio of $51,800 per QALY and $28,700 per QALY in the 65- and 55-year-old cohorts, respectively. In the low-risk cohort, LACA had an incremental cost-effectiveness ratio of $98,900 per QALY (Table 2). As this approached $100,000, it was deemed not to be cost-effective.

This study[15] estimated cost-effectiveness in terms of a lifetime horizon; repeat examination of 5- and 10-year time horizons found that LACA was less cost-effective than rate control given its significant upfront costs. However, this study was deliberately conservative in the assessment of LACA

Table 2 Incremental cost-effectiveness ratios in base-case estimates, stratified by ischemic stroke risk.

Stroke risk	Strategy	Cost	Life-years	QALY	ICER ($/QALY)
Moderate (age = 65 yrs)	Rate control + warfarin	$39,391	11.47	10.81	Reference
	Amiodarone + warfarin	$43,358	11.45	10.75	Dominated
	LACA + warfarin	$52,369	11.55	11.06	$51,800/QALY
Moderate (age = 55 yrs)	Rate control + warfarin	$50,509	14.80	13.95	Reference
	Amiodarone + warfarin	$55,795	14.75	13.81	Dominated
	LACA + warfarin	$59,380	14.88	14.26	$28,700/QALY
Low	Rate control + ASA	$24,540	11.65	11.21	Reference
	Amiodarone + ASA	$38,425	11.60	11.02	Dominated
	LACA + ASA	$43,036	11.70	11.40	$98,900/QALY

Calculations for cost-effectiveness were performed by taking the incremental cost (difference between costs of compared strategies) divided by the incremental effectiveness (difference between quality-adjusted life-years [QALYs] of compared strategies). No calculations are needed for strategies that are dominated as they are less effective and more costly than the reference strategy. All ICER results are measured in 2004 U.S. dollars and are rounded to the nearest $100. Discrepancies in the ICER calculations are due to round-off error.

ASA aspiring, *ICER* incremental cost-effectiveness ratio, *LACA* left atrial catheter ablation.

cost-effectiveness. It biased cost-effectiveness in favor of rate control therapy using a significant rate of crossover to rhythm control therapy. This model also used similar health utility estimates for patients in AF and sinus rhythm, underestimating the effect of sinus rhythm on quality-of-life improvement in the ablation group. In addition, this model used digoxin and β-blockade alone for rate control, excluding more expensive calcium channel blockers to give a conservative cost estimate to the rate control group. Finally, the analysis is much more favorable for RF ablation under the assumption that the patient population consists of those who have tolerated a rate control strategy.

This study,[15] while based on a hypothetical model with numerous assumptions regarding costs, even with a deliberate conservative approach with a bias in favor of rate control therapy, suggested cost-effectiveness of LACA for patients with a moderate risk of stroke.

To date, the three previous studies are the only ones to have been performed specifically to assess the cost-effectiveness of catheter ablation for AF. Each used efficacy rates and costs that were either historically accurate or which are approximate estimates. For the first two studies, it appears that a time horizon of less than 6 years is required with the current catheter ablation success rates and costs involved for cost equivalence to be achieved. With further passage of time, ablation is not only cost-effective but also cost saving. With the deliberately conservative third study, a time horizon in excess of 10 years is required for cost-effectiveness of catheter ablation for AF.

Conclusions

Catheter ablation of AF is now a widely accepted and practiced treatment modality. Given the present increase in performance of this procedure, it is probable that in the future the upfront cost of this procedure may well decrease in excess of the discounting estimates used in these studies. Furthermore,

increasing procedural success rates are being observed, and together these factors will combine to make this technique more cost-effective over time, with time horizons for cost-effectiveness diminishing.

Clearly, the cost-effectiveness of this technique hinges on procedural success rates, complication rates, upfront costs, and the stroke risk in the treatment population. The study by Chan et al. suggests at least a moderate stroke risk is required in the treatment population with current success rates to demonstrate cost-effectiveness.[14] Operator experience also has a significant impact on these variables, and therefore cost-effectiveness is likely to vary depending on the volume and technique performed in individual centers. A prospective randomized study with long-term follow-up is required to definitively establish the cost-effectiveness of catheter ablation of AF. While such a study performed in a high-volume single center is likely to demonstrate cost-effectiveness, a multicenter study with pooled data may reflect more real-world outcomes.

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Section II

Pathophysiology, Molecular Mechanisms, and Genetics of Atrial Fibrillation

4

Cellular Electrophysiology and the Substrate for Atrial Fibrillation

Joachim R. Ehrlich, Pierre Coutu, Yung-Hsin Yeh, Xiaoyan Qi, and Stanley Nattel

Abstract: This chapter focuses on basic cellular atrial electrophysiology and tries to pinpoint the consequences of cardiac conditions that play a role in creating a substrate for atrial fibrillation. It touches on a series of cellular alterations that contribute to substrate and trigger formation. These include changes in ionic currents, cell–cell connections via connexins, calcium handling alterations, and genetic predispositions.

Keywords: Atrial cellular electrophysiology; Atrial substrate; Calcium handling alterations; Connexins; Ionic currents; Genetic predispositions.

Basics of Normal Atrial Cellular Electrophysiology

The resting membrane potential of excitable cells in the atrial working myocardium is set by the inwardly rectifying potassium current I_{K1}.[1] The ion channels that carry this current allow positively charged K^+ ions to leave the interior of the cell following the K^+ concentration gradient (K^+ is at much higher concentration intracellularly) and thus hold the resting intracellular potential at negative values. This current has a reversal potential (i.e., the potential at which the concentration gradient-generated chemical force moving K^+ out of the cell equals the electrical force tending to hold K^+ inside the cell) typical of a K^+ conductance about (−85 mV). In fact, in atrial cells I_{K1} is smaller than in ventricular cells, so that the resting potential is somewhat less negative (about −75 mV).

When a cell is depolarized (e.g., if an impulse is conducted from the sinoatrial node) and a threshold potential for firing is reached, voltage-gated Na^+ channels open and rapidly depolarize the cell membrane, causing an action potential (AP). Entry of Ca^{2+} through L-type Ca^{2+} channels is also triggered by depolarization, generating the AP plateau and triggering Ca^{2+} release from intracellular (sarcoplasmic reticulum, SR) Ca^{2+} stores, which causes myocardial contraction.

The AP initiated by cell depolarization consists of an orchestrated response of various time- and voltage-dependent ionic currents that returns the cellular membrane potential through various phases (Figure 1A) back to

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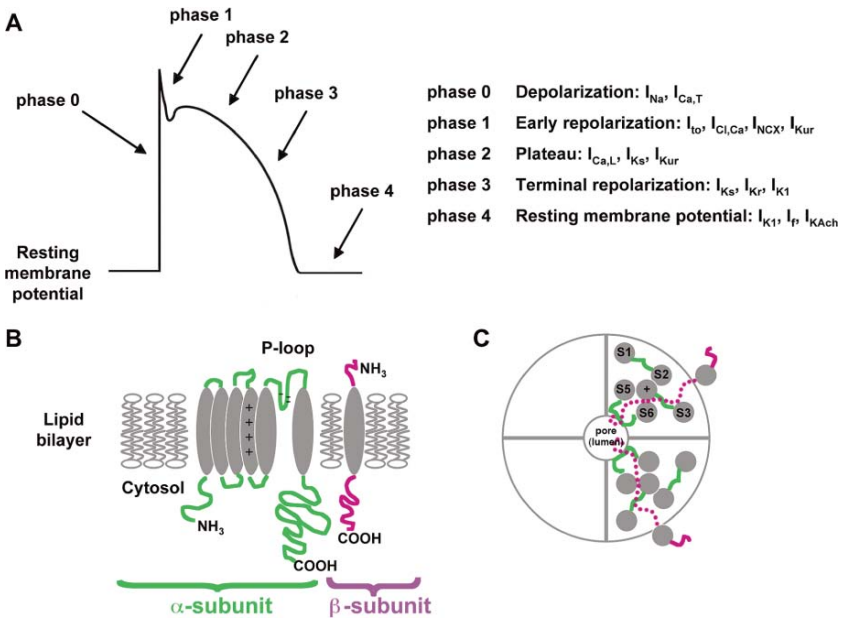

Figure 1 Atrial action potential and ion channel topology. **A** Phases of atrial action potential and ionic currents contributing to de- and repolarization. **B** Schematic of an ion channel α-subunit (six transmembrane domains) and a β-subunit (one transmembrane domain) in a cell membrane. **C** Orientation of four α-subunits within the membrane forming a channel pore with their respective P loops. S1 to S6 depict transmembrane segments, + denotes the voltage sensor of voltage-gated ion channels (S4). I_{Na} sodium current, $I_{Ca,T}$ T-type calcium current, I_{to} transient outward current, $I_{Cl,Ca}$ calcium-dependent chloride current, I_{NCX} sodium–calcium exchanger current, I_{Kur} ultrarapid delayed rectifier potassium current, $I_{Ca,L}$ L-type calcium current, I_{Ks} slow delayed rectifier potassium current, I_{Kr} rapid delayed rectifier potassium current, I_{K1} inward rectifier potassium current, I_f "funny" pacemaker current, I_{KACh} acetylcholine-dependent potassium current

the initial, fully repolarized state and restores cellular excitability. Important among these are a variety of potassium currents that contribute to early (I_{to}, I_{Kur}; see Figure 1 caption for definition of ionic current abbreviations) and late (I_{Ks}, I_{Kr}, I_{Kur}, I_{K1}) repolarization of atrial myocytes (Figure 1A). The depolarizing charge is transmitted from cell to cell because they are electrically coupled to each other via connecting channel proteins called connexins. Among these, connexin 40 (Cx40) and Cx43 are atrially expressed; Cx40 is found exclusively in atria and the conduction system.[2]

Sodium channels located at the intercalated disks then pick up the depolarization and carry on electrical activity. Each ionic current is conducted through pore-forming membrane proteins called ion channel α-subunits (Figure 1B). These proteins are membrane spanning with specific numbers of transmembrane domains, such as two transmembrane domains for I_{K1}-related α-subunits (Kir2.x) and six domains for voltage-gated currents like I_{to} (Kv4.x). The α-subunits assemble in tetramers and together conduct current through specific regions called the *pore* (Figure 1C).[3] α-Subunit proteins often assemble with accessory β-subunits that modulate their biophysical characteristics and

may also work as chaperones directing α-subunit trafficking to the appropriate site in the cell membrane.

The AP duration (APD) governs the time (the refractory period) from when the cell is fired to when excitability is restored by removing sodium channels from depolarization-induced inactivation. The APD thus has direct consequences for atrial fibrillation (AF) substrate formation as it governs tissue refractoriness. Cardiac diseases can modulate atrial refractoriness and conduction velocity; these changes are ultimately linked to AF occurrence.

Atrial electrophysiology has distinct characteristics differentiating it from the ventricular counterpart and also shows regional heterogeneity; for instance, the right atrial APD is longer than the left atrial APD. Atrial cells exhibit less I_{K1} and reduced Kir2.1/2.3 subunit expression compared to ventricular cells.[4] While pharmacological blockade of a current (i.e., like I_{Kr}) that is expressed in both atrium and ventricle exhibits effects at both levels, inhibition of a current present only in the atria theoretically carries the promise of no ventricular side effects.

Accordingly, atrially specific currents/proteins have recently been suggested for "atrial-selective" antiarrhythmic AF therapy. Such currents include the ultrarapid delayed rectifier current I_{Kur} (α-subunit: Kv1.5), the acetylcholine-dependent K^+ current I_{KACh} (heterotetramers of Kir3.1–3.4 α-subunits), its constitutively active form I_{KH}, and atrially expressed Cx40.[5–8] Figure 2 depicts this principle by showing the effect of blockade of I_{KH}, one of the above-mentioned potential targets, with a specific toxin inhibitor, tertiapin-Q.

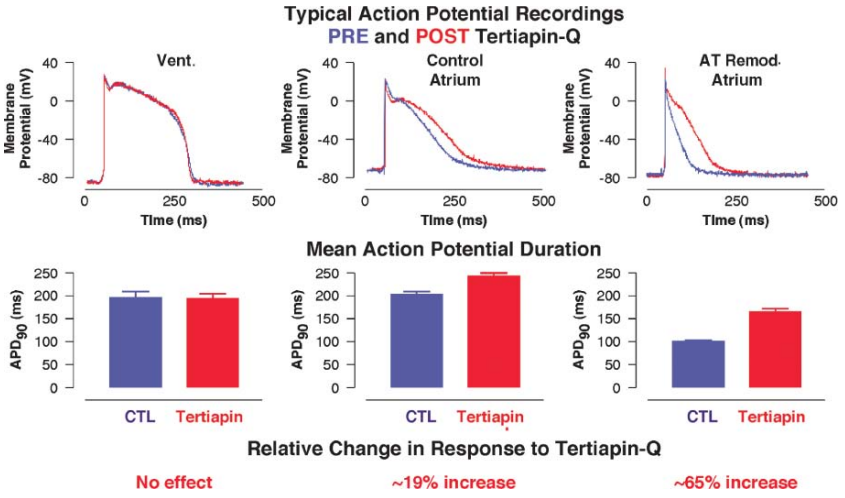

Figure 2 Principle of atrial-selective drug therapy. This figure exemplifies the effect of 100 nmol/l tertiapin-Q, a highly selective inhibitor of I_{KACh}, on the constitutively active form of the current I_{KH}. Shown are action potentials (APs) obtained with standard microelectrode technique from coronary artery perfused canine atrial or ventricular preparations in the presence of 200 µmol/l atropine. Top: APs recorded pre- (black) and post- (red) application of tertiapin-Q. Bottom: Action potential duration (APD) to 90% repolarization (APD_{90}) pre- and post-tertiapin-Q. *Left* Absence of effect on ventricular APs. *Middle* Functional role of I_{KH} in atrial cells under control conditions. *Right* Upregulation of the current by atrial tachycardia (AT) remodeling, with a correspondingly greater effect of current inhibition on APD_{90}. *CTL* control. (Adapted from ref. 34.)

Cardiomyocytes are not the only type of cells present in the atrium. Vessels, nerves, and structurally important fibrous tissue are also present. There is an important contribution of interstitial fibrous tissue to AF substrate formation, in particular in the setting of cardiac disease like hypertension or heart failure. Homogeneity of cardiac impulse propagation is important in maintaining regular rhythm. With arterial hypertension or congestive heart failure (CHF), an increasing amount of fibrotic tissue disturbs homogeneous impulse conduction and allows for the occurrence of reentry.[9]

Acquired Substrates for Atrial Fibrillation

The development of an AF substrate can be mediated by APD shortening, shortening of refractoriness with increased impulse conduction heterogeneity, and conduction slowing.[10] Each of these conditions favors reentry by decreasing the wavelength (minimum path length for reentry) or increasing conduction heterogeneity (for detailed discussion, see ref. 10). In a set of classical experiments, Wijffels et al.[11] showed that the duration of spontaneously sustained AF increases over a period of 2 to 4 weeks when the arrhythmia is maintained in goats by reinduction via implanted pacemakers. These results, described by authors with the colorful and informative term "AF begets AF," parallel a common natural history of AF in humans—AF as present initially in paroxysms and subsequently progressing to chronic persistent or permanent AF.

Several mechanisms contribute to maintenance of AF once a substrate has formed (like focal activation or single circles of macroreentry), but the final common pathway of these mechanisms is often multiple-wavelet reentry.[10] The ability to maintain reentrant arrhythmias generally depends on a short wavelength (distance traveled by an impulse during the refractory period; the shortest path length that can support reentry), which can be mathematically derived as the product of conduction velocity times refractory period. If a cardiac disease reduces speed of impulse conduction by changing Na^+ current availability, producing atrial fibrosis or altering constitution of connexins, the wavelength can be shortened and a substrate for reentry is created. Similarly, if the refractory period is shortened by decreasing APD, the likelihood of reentry increases. Furthermore, enhanced anisotropic conduction and heterogeneity of repolarization are important in establishing favorable conditions for reentry. Both are associated with disturbances in impulse propagation that may lead to reentrant arrhythmias.[10,12] Shortening of APD and decreased APD rate adaptation were described in human AF about 25 years ago.[13,14] Retrospectively, these changes were compatible with features of atrial remodeling[11] and underlying reductions in L-type calcium current,[15] documented a decade later.

Atrial fibrillation produces cellular changes in the atria that tend to sustain the arrhythmia and promote the occurrence of AF-related complications. Many of these alterations have been extensively studied in animal models of human disease. Larger mammals have been chosen for most of the work as their atrial electrophysiology is more similar to the human counterpart than that of small rodents. Table 1 lists a summary of commonly used animal models and their clinical correlate.

Alterations in ionic currents and properties of cellular excitability are termed *electrical remodeling*.[16] Other changes that include increases in

Table 1 Animal models and their clinical correlates.

Model	Animal	Clinical correlate
Sterile pericarditis	Dog	Postcardiac surgery
Atrial tachypacing	Dog, goat, rabbit	Lone AF
Ventricular tachypacing	Dog	CHF, sick sinus syndrome
Old age	Dog	Senescence
Acute atrial ischemia	Dog	Myocardial infarction and coronary disease
Atrial volume overload	Dog, sheep, rabbit	Acute severe volume overload
Mitral regurgitation	Dog	Mitral valve disease
Aortopulmonary shunt	Sheep	High-output failure
Cesium infusion	Dog	LQTS, abnormal automaticity

AF atrial fibrillation, *CHF* congestive heart failure, *LQTS* long QT syndrome.

extracellular connective tissue composition, cellular size, glycogen accumulation, myolysis, mitochondrial changes, or chromatin redistribution have been termed *structural remodeling*.[17] *Contractile remodeling* occurs because of modifications in intracellular Ca^{2+} handling and leads to impaired cellular contraction.[18,19] Finally, remodeling of the atrial endothelium occurs with AF. Atrial fibrillation is importantly associated with increased thromboembolic events.[20] In addition to causing contractile dysfunction and stasis of blood within the atria, AF downregulates endothelial nitric oxide (NO) synthase with subsequent reduction in NO bioavailability and increase of the prothrombotic plasminogen activator inhibitor 1 (PAI-1).[21] Furthermore, O_2 radical formation is increased in human AF, potentially promoting local inflammation and thrombosis.[22]

Changes in Repolarizing Currents that Affect the Refractory Period

Yue et al. were the first to analyze changes in APs and ionic currents caused by sustained atrial tachycardia (AT) as produced by AF.[23] The investigators used rapid atrial activation induced by pacemaker stimulation in a canine model to mimic AF-induced high-rate atrial excitation over a period of up to 6 weeks. They observed progressive downregulation of the transient outward current I_{to} and the L-type Ca^{2+} current $I_{Ca,L}$, leading to APD shortening and impaired APD rate adaptation. These properties accounted for shortening of atrial refractoriness that contributes to facilitating AF induction and maintenance. Other atrially expressed ionic currents were not affected and subsequent work identified transcriptional messenger RNA (mRNA) downregulation of the α-subunit of the L-type Ca^{2+} channel, as well as of the Kv4.3-I_{to} α-subunit, as the causative mechanism.[24] In line with these findings, the number of functional dihydropyridine receptors (indicating indirectly the quantity of L-type Ca^{2+} channel protein) at the membrane level is reduced.[25] A similarly prominent reduction of $I_{Ca,L}$ occurs in human AF.[26]

Reductions in L-type Ca^{2+} current are prominent in cells obtained from right atrial appendages of patients with persistent AF, leading to abbreviation of APD and APD rate adaptation.[15] In this work, stimulation of $I_{Ca,L}$ with 1 μmol/l isoproterenol led to equal relative increases in current density between

currents recorded from cells of patients with or without AF, while the absolute difference remained unchanged. In contrast with these findings, a more recent study suggested that protein levels of the pore-forming α_{1c} and regulatory β_{2a} channel subunits are not different between AF and SR patients.[27] These investigators found a state of decreased channel phosphorylation in AF caused by channel dephosphorylation via increased expression of type 2A phosphatase and higher phosphatase activity (Ca^{2+} channel phosphorylation enhances channel function).

Intracellular Ca^{2+} homeostasis is importantly altered by rapid atrial activation, decreasing systolic Ca^{2+} transients (determined primarily by the amount of Ca^{2+} released by the SR during the AP).[28] Intracellular Ca^{2+} loading by rapid atrial firing can lead to mitochondrial swelling and may jeopardize cell viability.[29] Slower and smaller Ca^{2+} transients occur as a consequence of rapid atrial rates, decrease atrial myocyte contractility, and underlie atrial contractile dysfunction ("atrial stunning") observed in clinical AF,[18] although they also help to defend against Ca^{2+} overload. Ca^{2+} transient reduction begins within minutes and represents an initial cellular "self-defense" mechanism linking reduced $I_{Ca,L}$ to mechanical dysfunction.[19]

The transient outward potassium current I_{to} is downregulated by human AF as well as in AT remodeling in animals.[23,26] Alterations of other ionic currents such as delayed rectifiers or I_{K1} were not initially documented in animals.[23,24] Human AF leads to an I_{K1} increase that has been suggested to add to APD shortening through a contribution to late repolarization,[26,30] and similar changes have subsequently been observed in animal studies.[31] Resting membrane potentials in right atrial trabeculae from patients with AF are more negative than in those from sinus rhythm patients, and Kir2.1 mRNA levels are increased,[32] consistent with larger I_{K1}.

Kir3.1 and Kir3.4 are channel α-subunits that form the acetylcholine-regulated current I_{KACh}, another important inwardly rectifying current. Kir3.1 mRNA levels are downregulated in human AF.[33] Compatible with a reduced expression of channel subunit mRNA, stimulation of atrial cells with the muscarinic agonist carbachol leads to blunted AP shortening in AF patients, indicating a reduction in available functional channels.[32] In contrast to reduced functional I_{KACh} and Kir3 subunit mRNA content, an increase in a constitutively active form of this current has been described as a potentially important contributor to the AF substrate.[6,7,34] A canine form of constitutively active I_{KACh} (called I_{KH}) shows regional heterogeneity (larger in pulmonary vein [PV] cardiomyocyte sleeves), contributes to atrial repolarization, and is absent in the ventricle,[7,34] suggesting that constitutively active I_{KACh} is a potentially interesting target for atrial-selective anti-AF therapy. The underlying Kir3 subunits are expressed much more in the atria than ventricles.[35] The AT remodeling increases I_{KH}, and I_{KH} inhibition terminates atrial tachyarrhythmias in tachycardia-remodeled canine atrial preparations.[34] While several antiarrhythmic drugs inhibit I_{KACh} in addition to other currents (e.g., amiodarone, dronedarone, AVE0118), the precise contribution of I_{KACh} inhibition to the antiarrhythmic potency of these drugs is unknown, and selective inhibitors are not yet available for clinical application.[36,37]

The ultrarapid delayed rectifier I_{Kur} is termed *ultrarapid* based on its activation kinetics[38] and in humans is solely expressed in atrial tissue.[5] I_{Kur} is carried by Kv1.5 α-subunits and represents a potentially interesting atrial-selective

target for anti-AF drug therapy.[5] Like constitutive I_{KACh}, as discussed, the atrial-selective expression of I_{Kur} makes it an anti-AF target that should be free of the acquired long QT syndrome risk that accompanies traditional antiarrhythmic agents that target I_{Kr}.[39]

For instance, AVE0118—an investigational $I_{to}/I_{Kur}/IK_{ACh}$ blocker—demonstrated promising selective efficacy to prolong atrial APD in pigs and reducing left atrial vulnerability to tachyarrhythmia induction.[40] In a goat model of sustained AF, application of AVE0118 led to strong atrial effective refractory period (ERP) prolongation and cardioversion, while dofetilide showed limited atrial class III effect and poor anti-AF efficacy.[41] Dofetilide increased the QT interval, while AVE0118 had no ventricular effect.

Downregulation of I_{Kur} in AF could limit the efficacy of I_{Kur} blockers. One study demonstrated reduced I_{Kur} with human AF[42]—a result that was not confirmed by subsequent investigators.[26,43] The latter investigators did not use a dedicated protocol to elicit I_{Kur} but analyzed the sustained end-pulse current I_{Ksus}, which consists largely but not exclusively of I_{Kur}, and did not find a difference between cells derived from patients with or without AF. However, Kv1.5 protein was reduced in two studies of human AF,[33,42] while mRNA expression remained unchanged, suggesting a posttranscriptional mechanism for reduced channel expression.[44] Given the relevance of alterations in I_{Kur} for anti-AF therapy, these discrepant findings still await final clarification. If anything, I_{Kur} appears not to be upregulated in AF and thus probably does not contribute to AF-induced APD shortening.

Human AF was found to reduce I_{KATP},[45] consistent with an observed reduction in Kir6.2 mRNA expression in atrial tissue from AF patients.[33] The pathophysiological role of I_{KATP} reduction in AF is not clear. I_{KATP} is activated in ischemia and contributes to ischemic APD shortening. Coronary artery disease and acute myocardial infarction are important risk factors for AF development,[46] and patients with right ventricular infarction are at increased risk for AF development.[47] In experimental animals, proximal occlusion of the right atrial artery increases AF propensity.[48]

Factors Affecting Conduction Velocity

The Na^+ current I_{Na} is the major determinant of upstroke velocity V_{max} of phase 0 of the AP and an important factor governing conduction velocity.[1] Reductions in I_{Na} reduce conduction velocity, shorten wavelength, and may thus help to maintain reentry. Canine atrial myocytes show a 52% reduction in I_{Na} density after 6 weeks of tachycardia-induced atrial remodeling.[49] No changes in voltage dependence of activation or inactivation are observed. Work in human atrial myocytes failed to document an AF-related I_{Na} reduction but found voltage-dependent current inactivation shifted to more positive voltages.[26] Workman et al. reported no difference in V_{max} at physiological rates between APs of atrial cells obtained from patients with or without AF.[43]

In line with these studies, Brundel and coworkers found no change in sodium channel α-subunit (NaV1.5) mRNA and protein expression in atrial tissue from AF patients.[33] However, a slight but statistically significant reduction in Nav1.5 mRNA was reported in another investigation of atrial tissue from AF patients,[50] indicating that further work is needed to unravel these discrepancies.

Atrial fibrillation frequently complicates CHF.[9] The AF substrate induced by CHF is different from that caused by AT, and several lines of evidence suggest that activation of the angiotensin system is of particular importance in this setting.[51] Angiotensin II binding to AT_1 receptors increases fibrosis by promoting TGF-β1 synthesis.[52] Selective cardiac overexpression of TGF-β1 in transgenic mice causes atrial but not ventricular fibrosis, along with a predisposition to AF.[53] There are greater local angiotensin II levels in atria than ventricles of CHF dogs, and atrial (but not ventricular) TGF-β1 is activated during the development of CHF.[54] Cardiac-specific ACE overexpression produces atrial enlargement and AF,[55] consistent with a link between angiotensin II, fibrosis, and AF.

The potential importance of altered tissue architecture and fibrosis is further exemplified by the changes induced by CHF in an animal model. Ventricular tachypacing-induced heart failure causes reductions in I_{to}, I_{Ks}, and $I_{Ca,L}$ with no net effect on APD—that is, unchanged refractoriness.[56,57] However, prominent atrial fibrosis caused by heart failure reduces homogeneity of impulse conduction and causes strong local conduction abnormalities. Treatment with enalapril during the development of heart failure attenuates fibrosis development and reduces impulse conduction heterogeneity.[58] Aldosterone blockade with eplerenone suppresses tachyarrhymia inducibility in a canine CHF model.[59] In addition to tissue fibrosis and reentrant AF, enhanced Na^+, Ca^{2+} exchange (NCX) activity occurs and could contribute to triggered activity.[58] With reversal of experimental heart failure, ionic changes (including NCX activation) reverse, but atrial fibrotic rearrangement remains unchanged, as does AF promotion,[60] suggesting that fibrosis is more important than ion current remodeling for heart failure-related AF, at least in this dog model.

Connexins are located at the intercalated disks, forming low-resistance pathways for the propagation of impulses between cardiomyocytes. Cx40 and Cx43 are the two main connexins expressed in the atrium.[2] Knockout of Cx40 in mice prolongs P wave and PQ interval, consistent with diminished atrial conduction velocity.[61] Atrial fibrillation-related Cx changes are controversial. Immunoblotting of human atrial protein extracts revealed no change in Cx43 content, but increased Cx40 expression in AF and immunohistologic analysis indicated that AF resulted in increased localization of both connexins at the lateral cell membrane, potentially contributing to anisotropic impulse conduction.[62]

Another study used confocal microscopy of immunostained sections for Cx protein quantification and found Cx40 significantly reduced in persistent AF with no significant changes in Cx43.[63] A reduction in Cx40 was also observed in a study involving patients with longstanding AF (mean 6.2 ± 5.3 years), along with a decrease in Cx43 and atrial fibrosis.[64] Despite methodological similarities—all three studies used tissue obtained from right atrial appendages—inconsistencies in changes in gap junctional protein expression remain and may be related to differences in the characteristics of patient populations.

A clinical study identified atrial tissue-specific mutations in GJA5 (the gene encoding Cx40) that predisposed individuals to idiopathic AF.[65] Mutant Cx proteins were not trafficked efficiently to cell membranes, accumulated intracellularly, and could not contribute to cell–cell coupling. Work in two

different canine models of AF (mitral regurgitation [MR] and CHF) evaluating the efficacy of rotigaptide (ZP123)—a drug augmenting gap junction conductance and improving cell-to-cell coupling—showed reduced AF vulnerability in the MR and no effect on AF vulnerability in the heart failure model.[66] Thus, altered Cx distribution and expression may contribute to the formation of an AF substrate, and therapeutic modification of gap junction conduction may represent a therapeutic option for certain conditions associated with AF.

Triggers of Atrial Fibrillation Initiation

In addition to factors that promote arrhythmia maintenance, AF development also depends on pathological mechanisms that initiate the arrhythmia. Recent work has emphasized the important role of triggered arrhythmias in the initiation of the arrhythmia.

Abnormal focal activity can arise from enhanced automaticity or from early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs). If afterdepolarizations move the membrane potential to the threshold for I_{Na} or $I_{Ca,L}$ activation, spontaneous APs may result and produce arrhythmic focal firing. The ionic basis of both EADs and DADs is complex and cannot be dealt with in detail here. $I_{Ca,L}$ and I_{Na} are the major carriers of EADs, and elevated cytoplasmic Ca^{2+} content can also play a significant role.[67,68] The DADs are related to abnormal diastolic intracellular Ca^{2+} transients, which activate a transient inward current I_{ti} carried mostly by inward I_{NCX}.[69]

The NCX is an electrogenic ion transporter that exchanges three Na^+ ions for one Ca^{2+} ion in either Ca^{2+} efflux or influx mode, depending on membrane potential. When diastolic Ca^{2+} release occurs, I_{NCX} can carry substantial depolarizing current after phase 3 repolarization, causing DADs.[70] Schotten et al. found increased protein levels of NCX (upregulated by 67%) in atria of AF patients,[71] but NCX mRNA expression was unaltered by chronic AF in another study.[72]

In humans with AF, increased spontaneous diastolic calcium release from the SR of atrial myocytes has been observed.[73] Spontaneous Ca^{2+} waves were associated with inward current generation. The SR Ca^{2+} content and NCX rate induced by a rapid caffeine application were comparable in cells from patients with or without AF. The authors attributed the increased spontaneous Ca^{2+} release in AF to altered function of the SR Ca^{2+} release channel.[73]

Recent work found spontaneous diastolic Ca^{2+} release from the SR via the ryanodine receptor (RyR), the SR Ca^{2+}-release channel.[74] Atrial tissue from animals with AT remodeling and humans with chronic AF showed a significant increase in RyR phosphorylation. The RyR channels isolated from dogs with AF exhibited increased open probability under conditions simulating diastole when compared with channels from control hearts, suggesting that these channels could cause a diastolic SR Ca^{2+} leak. Increased Ca^{2+} release from the SR, together with Ca^{2+} loading from the high atrial rate in AF, could lead to diastolic Ca^{2+} discharge and induce DADs.

Congestive heart failure is an important promoter of AF, and there is evidence pointing toward a particularly important role of Ca^{2+}-handling abnormalities in relation to AF in the setting of CHF. In a dog model of ventricular tachypacing-induced CHF, sustained atrial tachyarrhythmias could be readily

induced by burst pacing and suppressed by calcium antagonists and ryanodine, an SR Ca^{2+}-release channel blocker.[75] Isolated atrial cardiomyocytes from these animals showed prolonged APs, depolarized membrane potentials, and DADs. Upregulation of inward I_{NCX} and increased exchanger protein levels have been demonstrated in this model and could contribute to the generation of DADs.[57] Sites of earliest activation are located predominantly along the crista terminalis and within or near the PVs.[76] In human AF, these regions are important locations for AF triggers—therefore, anatomically defined variations may contribute to regional diversity in DAD susceptibility and AF induction.[77]

In experimental studies, atrial myocytes are capable of producing EAD during late phase 3 with shortened APD caused by acetylcholine stimulation.[78] Application of calcium antagonists reduced and ryanodine eliminated the post-rapid pacing (150-ms cycle length)-induced EADs and extrasystoles that initiated AF in this model. The authors suggested that rapid excitation rates, as occur during AF, may lead to intracellular Ca^{2+} elevation and that may contribute to late phase 3 EAD formation and EAD-induced extrasystoles mediated by inward I_{NCX}.

Triggers in the Pulmonary Veins

The regional distribution of triggers in the human heart is heterogeneous, with specific predilection sites in areas of the great cardiac veins, particularly PVs.[77] The PV cardiomyocytes are located in muscular sleeves extending from the atrium over PV smooth muscle. Arrhythmogenic EADs and DADs have been demonstrated in PV cardiomyocytes isolated from healthy dogs.[79] Both chronic atrial tachypacing and thyroid hormone exposure may enhance such arrhythmogenic activity.[80] These authors observed increased I_f and I_{ti} as potential underlying currents of triggered activity. However, other groups have failed to show this type of arrhythmogenic activity in PV cardiomyocytes.[31,81,82]

Honjo et al. showed that application of ryanodine at 0.5 to 2 μM, which maintains RyRs in a subconductance state and causes SR calcium leak during diastole, uncovers rapid pacing-induced spontaneous activity in rabbit PVs.[83] Both Ni^{2+} (a blocker of I_{NCX}) and niflumic acid (a blocker of I_{ClCa}) abolished the spontaneous activity. These studies indirectly pointed to abnormal PV Ca^{2+} handling, but direct studies suggested similar Ca^{2+}-handling properties in canine left atrial and PV cardiomyocytes.[84]

The PV myocardial sleeves may be particularly sensitive to vagal or adrenergic modulation.[85,86] These investigators demonstrated EAD formation in isolated, superfused canine PVs and suggested these were a physiological phenomenon enhanced by increased Ca^{2+} transients and inward I_{NCX} caused by short APDs. With combined application of norepinephrine and acetylcholine, frequent EADs and rapid firing could be induced in the PVs. Application of muscarinic antagonists, β-blockers, or ryanodine (10 μM) abolished rapid firing. Thus, local sympathetic and parasympathetic activity may play a role in generating AF triggers within the PVs.

Genetic Substrates for Atrial Fibrillation

Increasing attention has been directed to genetic predisposition to AF development. A decade ago, inherited familial AF (FAF) was considered

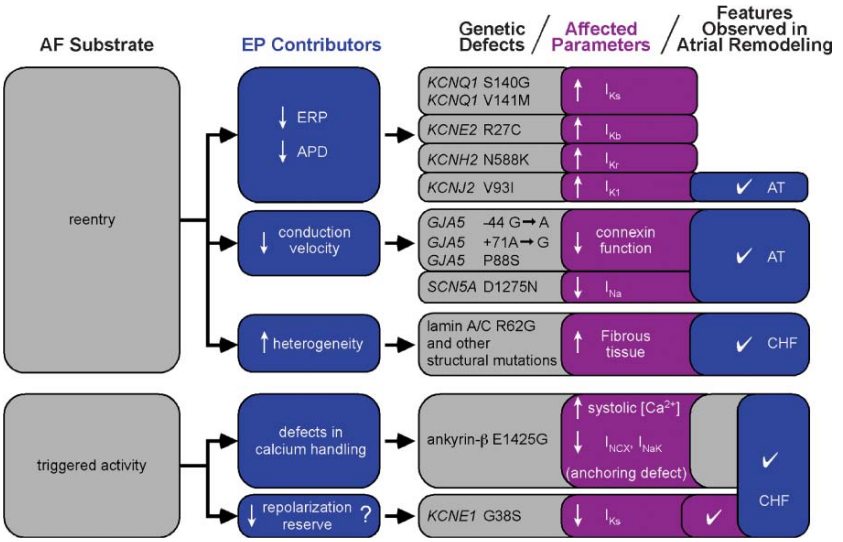

Figure 3 Genetic predisposition to atrial fibrillation (AF) substrate formation. Genetically transmitted changes in atrial cellular electrophysiology (EP) that lead to AF substrate formation, along with corresponding remodeling-induced functional changes shown by matching colors. *APD* action potential duration, *AT* atrial tachycardia remodeled paradigm, *CHF* heart failure paradigm, *ERP* effective refractory period, for abbreviation of ionic currents, see Figure. 1 caption

extremely rare.[87] However, mapping of gene loci to FAF either associated with other cardiomyopathies[88] or as the main pathological entity[89] stimulated the search for AF-related genetic defects. The developing evidence suggests that FAF may not be as uncommon as initially thought as more genetic mutations associated with AF have been unveiled.[90] In this section, we briefly review some of these mutations (which may occur in structural proteins or in ion channels) and attempt to establish a mechanistic link to AF. As outlined, the major determinants of the AF substrate are alterations in APD/ERP or in conduction velocity; mutations identified to date affect one or the other of these factors, and significant parallels to acquired AF substrates exist (Figure 3).

Alterations in Repolarization

Mutations located in various K^+ channel genes associated with FAF lead to gain of function in associated repolarizing potassium currents. Two adjacent missense mutations in the *KCNQ1* gene (encoding the α-subunit underlying the slow delayed rectifier current, I_{Ks}) located near the extracellular surface in the S1 segment, S140G and V141M, were found in a four-generation family and as a de novo mutation, respectively.[91,92] When heterologously expressed, both mutated α-subunits created a similar gain of function in I_{Ks}. Computer simulations of the mutant I_{Ks} properties demonstrated shortening of APD.[92] A change from arginine to cysteine at amino acid position 27 (R27C) of the MiRP1 β-subunit found in two Chinese kindreds led to an increased time-independent current component recorded from heterologously expressed *KCNQ1/KCNE2* subunits.[93]

Members of two families affected with the short QT syndrome were also frequently affected by AF potentially mediated by shortening of atrial APD.[94] The genetic defect underlying short QT syndrome in these families is a missense mutation (N588K) in the S5-P loop of the HERG channel, causing I_{Kr} increase that would be expected to abbreviate APD.[95]

An increase in I_{K1} was observed in a family affected by FAF and bearing the V93I mutation in *KCNJ2* gene (encoding Kir2.1 α-subunits). Thus, mutations that increase repolarizing ionic currents and shorten atrial APD create a substrate for AF and are among the most common presently recognized genetic bases for FAF.

A clinical study reported a common polymorphism within the gene encoding the minK β-subunit (*KCNE1* G38S) to be associated with an increased risk of AF.[97] The minK38G allele showed increased AF prevalence relative to the minK38S isoform. In a heterologous expression system, minK38G impaired membrane expression of the *KvLQT1* α-subunit and correspondingly reduced I_{Ks}, which would be expected to increase APD.[98] Mathematical modeling suggested that this allele would have little effect on human atrial APD under physiological conditions, but in individuals with increased baseline APD, this allele could be the cause of EADs that result from decreased repolarization reserve.[98] This hypothesis remains to be tested further. A loss-of-function mutation of Kv1.5 has been reported in association with FAF,[99] adding further support to the notion that genetically based APD-increasing alterations may sometimes create a substrate for AF.

Changes in Conduction Properties

Several mutations in *SCN5A* (encoding the α-subunit of cardiac I_{Na}) led to a variable phenotype, including cardiomyopathy, sinus node dysfunction, or AF.[100] Among these mutations, the one with the highest AF prevalence (D1275N) positively shifts activation voltage dependence, reducing current availability under physiological conditions. This alteration is compatible with reduced excitability and conduction velocity.[101] A Cx40 polymorphism (–44G → A, +71A → G) leads to AF predisposition in association with increased spatial dispersion of refractoriness.[102] Combination of the *SCN5A* mutation (D1275N) and the rare Cx40 polymorphism (–44A, +71G) resulted in atrial standstill in one large family.[101] Tissue-specific mutations in *GJA5* (gene encoding Cx40) underlies idiopathic AF by impairing gap–junction assembly or electrical coupling.[65]

Other mutations affecting structural proteins may promote atrial fibrosis and predispose to FAF. For instance, mutations in lamin A/C lead to dilated cardiomyopathy and FAF.[103,104] For a more detailed discussion of other cases of genetic predisposition to AF, refer to Chapter 10in this volume and recent articles.[90,105]

Triggers of Atrial Fibrillation Initiation

Genetic mutations causing increased automaticity in atrial tissue remain to be found. One mutation in an anchoring protein (ankyrin-β) was linked to long QT syndrome type 4.[106] Besides prolongation of the QT interval, this mutation is associated with abnormal calcium transients and impaired membrane localization of NCX and Na/K adenosine triphosphatase (ATPase). In a mouse model, ankyrin-β mutations caused triggered activity because of DADs and EADs.[106]

In summary, there is increasing awareness and understanding of the importance of genetic factors in AF. Significant parallels exist between mechanisms of genetic defects causing FAF and aspects of AF/AT remodeling observed in human or animal studies, as illustrated in Figure 3.

Conclusions

An enormous amount has been learned about the cellular electrophysiological basis for AF. The insights obtained have important implications for understanding why AF occurs and developing improved therapeutic approaches. Nevertheless, much more remains to be learned, particularly about the genetic predisposing factors that favor AF occurrence in individual patients, about the cellular basis for the important thoracic vein contribution to AF, and the relationship between clinical AF presentation in individual patients and underlying cellular mechanisms. Ultimately, improved understanding of the cellular mechanism of AF in individual patients should lead to more informed therapeutics on an individual patient basis.

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5

Electrical and Structural Remodeling in Atrial Fibrillation
The Role of Oxidant Stress and Systemic Inflammation

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Abstract: Intense research efforts since 1995 have sought to characterize the pathways that contribute to the occurrence and persistence of atrial fibrillation (AF). This chapter focuses on recent studies elucidating several of the molecular mechanisms that underlie the electrical and structural remodeling processes that promote persistent AF. Here there is a particular focus on the identification of signaling pathways that might be specifically and individually targeted for improved pharmacologic treatment or prevention of AF, perhaps simultaneously lowering the risk of stroke associated with AF.

Keywords: Antioxidants; Electrical remodeling in AF; Role of oxidant stress in AF; Role of systemic inflammation in AF; Structural remodeling in AF.

While atrial fibrillation (AF) can occur in the absence of structural heart disease (lone AF), it is more commonly associated with comorbidities including hypertension, diabetes, obesity, coronary artery disease, pulmonary disease, valvular heart disease, and congestive heart failure. The clinical course of AF is frequently progressive, often beginning with increased ectopy (premature atrial contractions), progressing to brief runs of AF that are typically transient and self-terminating. Over a period of time ranging from months to years, episodes of AF tend to increase in duration, sometimes becoming persistent. Progression from paroxysmal to persistent and then permanent AF involves both structural changes in the atria (with respect to the degree of dilation, trabeculation, fibrosis, fatty infiltration, etc.) and biochemical changes in the atrial myocytes (e.g., hypertrophy, changes in ion channel density or distribution, etc.). Pathophysiological adaptation of the atria to fibrillatory activity has been broadly termed *remodeling*. More specifically, the changes primarily affecting the excitability and electrical activity of the atrial myocytes have been termed *electrophysiological remodeling*, while the changes in myocyte number, chamber size, interstitial collagen deposition, and fibroblast proliferation have been termed *structural remodeling*. Here, we focus on the cellular mechanisms that underlie atrial electrophysiological and structural remodeling.

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Atrial Electrophysiological Remodeling

With the creation of a burst-pacing-maintained model of AF in goats,[1] Wijffels and colleagues stimulated great interest in the atrial electrophysiological remodeling process. Using this well-documented model system, they demonstrated that the atrial effective refractory period (ERP) could become reproducibly and rapidly abbreviated, with much of the effect evident within 24 hours of continuous AF. Changes in ERP were essentially complete within 1 week of high-rate activity. Because of the technical challenges involved in isolating myocytes from goat atria, cellular physiology studies were not performed. However, parallel studies in a canine rapid atrial pacing model revealed that significant reductions in the density of L-type calcium current (I_{Ca}) occur at a time compatible with many of the observed changes in action potential morphology, duration, and ERP.[2] In the canine rapid atrial pacing model, reductions in the density of the atrial sodium current (I_{Na})[3] and transient outward potassium current (I_{TO})[2] were also noted, with no significant changes in other currents evaluated.[2] The loss of I_{Ca} and I_{TO} that accompany rapid atrial pacing parallel changes in the density of these currents in human atrial myocytes with a history of persistent AF.[4–7] However, in the only study characterizing changes in sodium currents in persistent AF patients, no change in peak sodium current density was detected.[4]

Redox-Dependent Modulation of I_{Ca} and I_{Na}

What mechanisms underlie the functional changes in atrial electrophysiology observed in response to AF or rapid pacing? The answer is, in part, dependent on the time at which one evaluates the changes. Clinical studies have shown that even very brief periods (minutes) of high-rate pacing are associated with reversible abbreviation of the atrial ERP.[8] This suggests that metabolic influences may have an important impact on the earliest changes in channel activity. Consistent with this hypothesis, it has been documented that the human L-type calcium channel is sensitive to hypoxia,[9] and that the sensitivity to oxygen is mediated by redox-dependent modulation of channel activity.[10] Fearon and colleagues showed that, when the human calcium channel pore subunit was expressed in a recombinant system, thiol oxidants could reversibly attenuate I_{CaL}, and reducing agents could restore the current.[10] This type of regulation also occurs in intact human atrial myocytes.[11]

Is redox-dependent modulation physiologically relevant? While frank hypoxia may rarely occur, a substantial increase in oxygen consumption occurs in response to high-rate atrial activity. In studies performed on healthy dogs, blood flow was found to increase two- to threefold with acute episodes of AF, and oxygen consumption was estimated to increase at least threefold.[12] With a relatively modest coronary flow reserve, it is not difficult to envision a state of relative hypoxia following the onset of high-rate electrical activity. In patients with coronary artery disease, heterogeneous disturbances in coronary flow might lead to regional variations in Po_2 during AF that are not apparent during normal sinus rhythm. Regional heterogeneity might contribute to regional variations in I_{CaL} that promote dispersion of repolarization, facilitating creation of a highly arrhythmogenic substrate for reentrant arrhythmias.

Hypoxic modulation of ion channel activity is likely a function of the modulation of the oxidation state of specific thiol residues on the channel. The calcium channel is not unique in its sensitivity to redox state. Acute hypoxia (20 mm Hg Po_2) depresses peak cardiac sodium channel (SCN5a) current for recombinant channels expressed in Human Embryonic Kidney cells (HEK) cells, and delays the time to peak current, as well as slows the kinetics of channel inactivation. An increase in persistent sodium current (delayed inactivation) has been implicated in altered sodium handling and an increased propensity for arrhythmogenesis,[13,14] and drugs that suppress "late sodium current" are now under evaluation for antiarrhythmic efficacy.[13,15,16]

Oxidant Stress Subsequent to Atrial Fibrillation and Rapid Atrial Pacing

Acute responses to hypoxia are quickly reversed upon restoration of normal oxygen availability. However, sustained metabolic stress or high-rate activity may lead to more sustained alterations in the metabolic state of the myocyte. This may be caused by changes in mitochondrial function, leading to increased oxygen consumption, uncoupling, and production of oxidants subsequent to calcium overload. Altered mitochondrial structure and function is a characteristic response to both rapid atrial pacing[17] and human AF.[18,19]

Adaptation to increased production of oxidants requires increased production of cellular antioxidants or more rapid cycling of cellular reducing systems. In the absence of a suitable reserve, the balance of intracellular reducing and oxidizing agents will be altered, resulting in a more oxidized intracellular environment. In an evaluation of tissues from patients with persistent AF, we found direct evidence of increased oxidant stress (as revealed by increased abundance of 3-nitrotyrosine) in human atrial tissues.[20] One consequence of this is altered production of adenosine triphosphate (ATP) via creatine kinase.[20] Increased production of superoxide (a cytosolic oxidant) has been directly demonstrated in myocytes from patients with AF.[21] These authors have suggested that nicotinamide adenosine dinucleotide phosphate (NADPH) oxidase, and to a lesser extent, nitric oxide synthase (uncoupled) are primary contributors to the increased superoxide production.[21]

Superoxide can interact with nitric oxide in a diffusion-limited process to form peroxynitrite anions. Peroxynitrite is a semistable oxidant that can covalently modify cellular lipids and proteins. Proteins are typically modified by nitration of tyrosine residues. As a consequence of this interaction, increased superoxide production can lead to a decrement in bioavailable nitric oxide levels. In a porcine model of rapid atrial pacing, nitric oxide levels were reduced throughout the atria, although the changes were most marked in the left atrium.[22] A downregulation of endothelial nitric oxide synthase (eNOS) activity and expression, caused by the loss of endocardial shear during AF, is one factor proposed to contribute to the loss of atrial nitric oxide during AF. As observed in human atrial myocytes,[21] a second factor was increased superoxide production because of increased NADPH oxidase activity (but not expression).[23] It is important to note that activity of NADPH oxidase is increased by exposure to angiotensin II, a hormone critical to the development of hypertension.[24] Thus, patients with hypertension, heart failure, or other states characterized by increased angiotensin II levels are likely to suffer

from increased atrial (as well as vascular) oxidant stress. In the presence of increased oxidant stress, the ratio of oxidized to reduced glutathione, as well as the overall redox potential of the tissue, is shifted to a more oxidized state. This evidence suggests that regulation of the intracellular redox state may be a key event in the modulation of atrial electrical activity. It is notable that the transcription factor NF-κB (nuclear factor kappa B) is redox sensitive,[25] and this may indirectly confer redox dependence on the expression of a variety of genes (including ion channels and others) under its regulation.

Atrial-Specific Distribution and Redox-Dependent Modulation of Potassium Channels

Activation of sodium and calcium channels underlies the upstroke and plateau of the atrial action potential, respectively. Potassium channels provide the resting potential and underlie repolarization of cardiac myocytes following initiation of the action potential. Modulation of action potential duration and morphology is critical, both with respect to determining the wavelength for reentrant electrical activity and with respect to modulation of cardiac contractility. The atria are notable for their greater variety and greater density of potassium channels involved both in determining the resting potential and in modulating repolarization. Distribution of the muscarinic potassium current (I_{KACh}) and the ultrarapid delayed rectifier current (I_{Kur}) is essentially atrial specific, and the expression of the transient outward potassium current (I_{TO}) is much greater in atrial than in ventricular myocytes.

As noted, the current density of I_{TO} has been consistently reported to be attenuated in atrial myocytes from AF patients.[4,6] Li and colleagues showed that the transient outward current I_{TO} in rat ventricle (composed largely of Kv4.2 pore subunits) is subject to redox modulation.[26] The molecular composition of I_{TO} in human atrium is believed to include both Kv4.2 and Kv4.3 pore subunits as well as a variety of ancillary subunits. It is intriguing to note that one group of these subunits (Kv beta family) have structural homology with oxidoreductase enzymes and may confer redox-dependent modulation to cardiac K^+ channels.[27,28]

In rat ventricle, I_{TO} is attenuated during experimental heart failure, in diabetes, and following myocardial infarction.[29–31] Incubation of these stressed myocytes with exogenous glutathione (to restore intracellular levels of reducing agents and normalize an intracellular redox state) was able to restore the density of I_{TO} to control levels within 4 to 5 h. This time course is compatible with both altered transcriptional and posttranscriptional modulation of channel activity.

In dogs subjected to rapid atrial pacing, I_{TO} current density and Kv4.3 mRNA expression were significantly reduced by 7 days of rapid atrial pacing, consistent with a downregulation of channel expression. Interestingly, we could detect no change in the expression of the pore subunit protein in human atrial homogenates when using a pan Kv4 antibody.[6] It is possible that both transcriptional and nontranscriptional regulation of channel expression contributes to the longer-term changes in electrical activity in AF. Changes in the distribution of the ancillary subunit (K channel interacting protein 2, KChIP2) have been associated with altered I_{TO} in some, but not all, studies seeking to evaluate the mechanisms underlying the transmural gradient of I_{TO} in the ventricle. The impact of AF on KChIP2 expression has not yet been reported.

We also noted a reduction in the density of I_{Ksus}, the sustained component of the repolarizing K^+ current in human atrial myocytes. Kv1.5, which underlies I_{Kur}, is a major contributor to this current. In contrast to our results with I_{TO}, a reduction in the expression of Kv1.5 protein paralleled the reduction in I_{Ksus} current density.[6] It is notable that changes in K^+ channel currents were not observed in specimens from patients with paroxysmal AF who presented for cardiac surgery in normal sinus rhythm. This suggests that electrical remodeling is a dynamic process, and that changes in channel expression may reflect a response to the stress of AF more than a substrate that precedes AF onset.

Can Antioxidant Interventions Suppress Atrial Electrical Remodeling?

To test the hypothesis that oxidant generation is an important element of the electrophysiological remodeling process, we performed a series of experiments using the canine rapid atrial pacing model. Pretreatment and daily supplementation of dogs with large doses of supplemental ascorbate (a water-soluble antioxidant vitamin) was associated with significant preservation of the ERP at 24 and 48 h of rapid atrial pacing.[32] In tissues from these animals, the extent of protein nitration was increased with pacing, and ascorbate prevented this change.[32] Thus, pacing is a strongly prooxidant stimulus. Studies in the heart failure field utilizing rapid ventricular pacing have arrived at a similar conclusion.[33,34]

Ascorbate, because of its water solubility, has a short plasma half-life, and excess ascorbate is rapidly eliminated. Thus, it is not an ideal pharmacological agent for testing the hypothesis that electrophysiological remodeling can be modulated by antioxidants. Several studies from the laboratory of Dr. Stanley Nattel have characterized and compared the impact of other agents on the process of electrophysiological remodeling over a 1-week (7-day) time course. A comparison of several antioxidants, including vitamin C, vitamin E, and simvastatin (which suppresses NADPH oxidase activity) showed that simvastatin was the most effective agent at preserving the normal rate adaptation of the atrial ERP in response to rapid atrial pacing. The pharmacokinetics of statin therapy and the ability to suppress superoxide production (by suppressing prenylation of the small G-protein, rac, an essential step in the activation of NADPH oxidase[23]), rather than attempting to quench oxidants after their production, are two features that favor the efficacy of statins over simpler antioxidant vitamin interventions. In similar studies, it was shown that the putative T-type calcium channel blocker mibefradil was also able to suppress atrial electrical remodeling.[35]

While T-type calcium channel activity may contribute to excess calcium influx, it is notable that calcium channel blockers in general exhibit antioxidant activity.[36,37] In evaluation of a series of calcium channel blockers, mibefradil was the most potent and diltiazem was the least potent[38]; this correlates well with the documented efficacy of mibefradil and lack of efficacy of diltiazem with respect to modulating atrial ERP following rapid atrial pacing.[35] Thus, we postulate that antioxidant activity is a fundamental determinant of the atrial electrophysiological remodeling process. Consistent with this hypothesis, recent studies have shown that upregulation of heat shock protein 27 (HSP27) occurs in some patients with paroxysmal AF, and that experimental upregulation in cultured myocytes (HL-1 cells) is sufficient to prevent myolysis subsequent to rapid pacing.[39] Experimental upregulation of

HSP27 expression with administration of geranylgeranylacetate prevented electrophysiological remodeling in animals subjected to rapid atrial pacing.[40] Expression of HSP27 is stimulated by oxidant stress and provides protection from oxidant-mediated injury via increased glutathione production.[41]

Other classes of drugs have also been documented to suppress atrial electrophysiological remodeling. These include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers,[42,43] and anti-inflammatory steroids.[44] It is thus notable that angiotensin receptor activation is linked to activation of NADPH oxidase activity and increased superoxide production.[45,46] This activity has been linked to the etiology of hypertension,[46] a powerful independent risk factor for AF, as well as cardiac hypertrophy.[45] Significant changes in the expression of angiotensin receptors within the atria have been documented in patients with AF.[47]

Effects of Steroids and Statins in Surgical Models of Atrial Fibrillation

Prednisone can attenuate the atrial electrical remodeling process in the rapid atrial pacing model.[44] Interestingly, prednisone also attenuates the inducibility of atrial flutter in a canine cardiac surgery model in which arrhythmia inducibility is facilitated by atrial neutrophil infiltration and a systemic inflammatory response.[48] Neutrophil infiltration was associated with heterogeneous conduction and increased inducibility and duration of AF episodes. Prednisone treatment lowered plasma C-reactive protein (CRP) levels, neutrophil infiltration, and AF duration.[48] In the canine sterile pericarditis model of postoperative AF, epicardial tissue injury secondary to neutrophil infiltration also creates a substrate for AF. In this model, atorvastatin attenuated tissue injury, the elevation of plasma CRP, and the inducibility and duration of induced AF episodes.[49] Thus, agents with antioxidant efficacy also have anti-inflammatory actions with respect to modulation of neutrophil activation and infiltration in the atria.

Atrial Fibrillation and the Systemic Inflammatory Response

The above discussion documenting the impact of anti-inflammatory agents on AF in postsurgical models suggests an important link between the systemic inflammatory response and AF. This link is not only present in canine models of postoperative arrhythmias. Bruins and colleagues showed that levels of CRP complement complexes on postoperative day 2 predicted the occurrence of AF following surgery in patients undergoing cardiac bypass graft surgery. We have shown that leukocytosis similarly predicts the occurrence of AF in the postcardiac surgery patient.[50] A recent study has generalized leukocytosis as a predictor of AF following any type of thoracic surgery.[51]

The systemic inflammatory response is not only linked with AF in the perioperative setting. Frustaci and colleagues were the first to note inflammatory cell infiltration in biopsy specimens of lone AF patients.[52] In biopsy without obvious cellular infiltration, there was evidence of myocyte hypertrophy, necrosis, or interstitial fibrosis. These postinflammatory markers suggest that the inflammatory response may be involved in structural remodeling that increases the propensity of the atria to maintain persistent AF.

We evaluated the relationship between plasma CRP levels and the occurrence of AF in a series of healthy control patients and patients with paroxysmal or persistent AF.[53] The CRP levels were elevated in most of the AF

patients relative to the controls; they were more elevated in the patients with persistent than paroxysmal AF. This, again, is consistent with the hypothesis that the inflammatory response is related to atrial changes that increase the persistence of AF. In their studies on the goat model of AF, Allessie and colleagues postulated that a "second factor," beyond electrophysiological remodeling, must account for the delayed time course between induction of AF with burst pacing and its stabilization.[54] They postulated that increased tissue anisotropy, caused by either gap junction remodeling or accumulation of interstitial fibrosis because of structural remodeling, was a likely candidate for this second factor. Our results, in which the systemic inflammatory response seems to reflect increased persistence of AF, are likely consistent with this hypothesis. In a follow-up analysis of the Cardiovascular Health Study database, our group evaluated the relationship between baseline CRP levels and AF in 5,806 patients with a baseline CRP assessment.[55] At baseline, CRP was found to predict both AF at baseline and the development of AF during an approximately 7.5-year follow-up period.[55]

Cellular Mechanisms Underlying Atrial Structural Remodeling

Which factors contribute to atrial structural remodeling? In addition to modulation of atrial electrical activity, angiotensin II can modulate numerous intracellular pathways, including those regulating myocyte hypertrophy and those controlling the formation and degradation of intercellular matrix elements (fibrosis).[56] The extent of fibrosis contributes both to the inducibility of AF[57] and likely also to the persistence of the arrhythmia.[53] Angiotensin II levels are increased in hypertension, and it is likely that all neurohormonal factors that promote hypertension and hemodynamic overload (including valvular disease and heart failure) also promote atrial dilation and interstitial fibrosis and increase the risk of AF. It is important to note that the electrophysiological phenotype of atrial myocytes isolated from patients with dilated atria but without obvious AF (reduced I_{Ca}, I_{TO}, etc.) was essentially identical to that which we have observed in myocytes isolated from patients with well-documented AF.[6,7,58] Similarly, microarray expression studies in patients with valvular disease (with or without AF) suggest that hemodynamic overload can account for a majority of the changes in atrial gene expression relative to control (nonoverloaded) patients in normal sinus rhythm, and that a relatively small number of genes were specifically modulated by AF.[59]

Hemodynamic overload is associated with increased oxidant production (via NADPH oxidase and other pathways) and can lead to activation of matrix metalloproteinases.[60] Hemodynamic overload is frequently associated with accumulation of interstitial fibrosis in the atria, particularly in the setting of congestive heart failure. Changes in extracellular matrix composition can negatively affect cardiac myocyte function[61] as well as the interaction and electrical communication between myocytes. Once interstitial fibrosis has become established, it seems that the electrophysiological remodeling process becomes relatively less important. In a canine heart failure model subsequent to rapid ventricular pacing, atrial fibrosis is dramatically increased, in a heterogeneous manner, with the left atrium much more affected than the right, or Bachman's bundle.[62] Based on the above discussion, it is not surprising that development of fibrosis can be partially prevented by treatment with

enalapril, an ACE inhibitor that would suppress the formation of angiotensin II.[63] Importantly, once atrial fibrosis has become established, the relevance of electrophysiological remodeling (and by inference, the efficacy of drugs that modulate ion channel activity) is greatly reduced, with the duration of induced AF episodes identical in animals with or without AF-induced electrophysiological remodeling.[64]

Summary and Future Directions

Atrial fibrillation is a complex, multifactoral disease. The underlying etiology and optimal therapeutic approach likely vary between different patient populations. Young patients with lone AF in the absence of factors that promote atrial dilation (e.g., valvular dysfunction, hypertension, and ventricular dysfunction) are likely much less affected by structural remodeling than by atrial ectopy and electrophysiological remodeling. These patients are likely to derive benefit from therapies that focus on modulation of the mechanisms underlying ectopic triggers of AF and the electrophysiological remodeling process. Thus, drugs and procedures (e.g., pulmonary vein isolation, the maze procedure) that alter the ability of ectopic pacemakers to fire, or at least to drive the atria, are potentially effective in this group.

At the other end of the continuum, older patients with congestive heart failure and dilated, fibrotic atria are less likely to respond to drugs that modulate ion channel activity in an attempt to modulate the wavelength of reentrant activity or to interventions that attempt to isolate fixed triggers of arrhythmic activity. In these patients, structural remodeling (at both the subcellular and tissue levels) is present and likely is a dominant factor, with respect to regulation of arrhythmia persistence and AF maintenance.[65] The structural changes in these patients are much more difficult to ameliorate.[66]

Here, we have shown that oxidative stress and systemic inflammation are two interrelated processes that have important consequences on both the activity of atrial ion channels and the atrial structure and communication between atrial myocytes. From this perspective, efforts to identify and modulate atrial-specific elements of the oxidant-handling and inflammatory pathways may more directly address the fundamental mechanisms of AF. Targeting these pathways should improve the efficacy of pharmacological treatments aimed at controlling or preventing AF. Statins, ACE inhibitors, and angiotensin receptor blockers offer early glimpses of therapeutic efficacy in this regard. It is hoped that we can still do better.

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6

Genetics of Atrial Fibrillation: The Clinician's Perspective

Ramon Brugada and Stefan Kääb

Abstract: Atrial fibrillation (AF) remains one of the most challenging arrhythmias for the clinician and basic researcher. Different approaches have been undertaken from the basic standpoint to improve its understanding, from the development of animal models to the analysis of genetic backgrounds in individuals with familial and acquired forms of the disease. In recent years, a large body of evidence has shown that alterations in ionic currents are involved in the disease. Only recently, the genetic link between mutations in proteins responsible for these ionic currents and the familial disease has given the final evidence that AF can also be primarily an ion channelopathy. In this regard, despite the limited prevalence of inherited diseases, it has been shown that the knowledge gained from their study will be helpful in dealing with the most common acquired forms of the disease. Moreover, data from family studies and preliminary association studies stress the relevance of common genetic variants as modifiers of susceptibility to AF. Therefore, as new data continue to appear, clinicians can expect that soon better therapeutic and preventive options for this arrhythmia will emerge from basic science.

Keywords: AF associated with other monogenic disease; AF as a monogenic disease; Genetics of AF; Ion channelopathy; Molecular mechanism of AF.

Introduction

A balance between structural and ionic components is required for the electromechanical impulse to propagate orderly across the myocardial cells. When structural heart disease or genetic or iatrogenic factors modify this interaction, the result can be the formation of a highly complex and irregular chaotic electrical activity or fibrillation, which can affect either chamber of the heart, atria or ventricles. *Atrial fibrillation* (AF) is defined as an erratic and turbulent electrical activation of the atria causing an irregular heart rhythm at the ventricular level. Atrial fibrillation is the most common sustained arrhythmia encountered in clinical practice. It affects close to 3 million Americans, and its prevalence of 1% in the general population increases with age to about

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6% in people over the age of 65 years.[1] The disease doubles the mortality and accounts for over one third of all cardioembolic episodes.[2] It is usually associated with cardiac pathology, including hypertensive heart disease, cardiomyopathy, valvular disease, or atherosclerotic cardiovascular disease.

Atrial fibrillation can be transient (paroxysmal) or persistent. Paroxysmal AF accounts for 35% to 40% of all cases seen by physicians and is not a benign entity in individuals with underlying cardiac pathology. The disease carries high mortality and high incidence of stroke, and despite being a self-terminating arrhythmia, there is a 30% to 50% chance of converting to a chronic state depending on the underlying pathology.

In some instances, especially in the young, the disease has no apparent etiology and is called "lone" AF. Lone AF accounts for 2% to 16% of all cases and, in the absence of risk factors like hypertension, diabetes, or previous stroke, has a low risk of embolism and does not require the use of anticoagulation before the age of 65. Within the lone AF group falls the familial form of the disease, in which a genetic basis and no cardiac pathology are the main characteristics. Limited studies have shown that the familial form has also a higher risk of embolism after the age of 65, data that support the use of anticoagulation in these individuals.

There are three main goals in the therapy of AF: control of heart rate, prevention of thromboembolism, and restoration of sinus rhythm.[3] The first two are successfully achieved in the majority of cases with the use of medications. The last remains a challenge. While the pharmacological approach to restore sinus rhythm can be helpful in some cases, it carries a high recurrence rate and a potential proarrhythmic effect, especially in individuals with underlying cardiac pathology.[3] Surgery and ablation have emerged as promising techniques to terminate the arrhythmia, but to date they are very time consuming, lack long-time follow-up, and are reserved for selected patients who can benefit from these procedures.

Molecular Mechanisms in Atrial Fibrillation

The limited success in the therapy of AF is in part caused by our poor understanding of its molecular pathophysiology. Advances in genetics and molecular biology will likely give new insights into the development of the disease. In the human, research efforts to elucidate the molecular basis of AF are focused primarily on two main areas: genetics in the human and alterations in gene expression of ion channels and their regulatory subunits. The study on alterations in gene expression is usually performed in animal models of the disease but can also be performed, in a more limited scale, in the human (because of tissue availability). These experiments will mainly provide information on the molecular changes triggered by the disease and may explain some of the mechanisms that perpetuate the arrhythmia into a chronic form (see Chapter 5). However, it will be difficult to prove whether the molecular changes that occur in the atria are the etiology of the disease, a maladaptation, or a compensating mechanism.[4–6]

These doubts could in part be clarified by the identification of human genetic defects that play a role in the disease. Study in genetics of AF can also be attained from different perspectives: (1) the analysis of AF as a monogenic disease (rare genetic variants), in which different members of a family have

the arrhythmia as a primary electrical disease; (2) the analysis of the arrhythmia presenting in the setting of another familial disease (multiple rare genetic variants or common genetic variants modifying phenotypes in the context of rare variants); and (3) the analysis of genetic background that may predispose to the disease without it segregating in the family (multiple common genetic variants). The first two, analysis of familial forms of the disease, provide definitive insight into the etiology of the disease and require the analysis of families with the disease segregating in several members, with or without another pathology. The last one is achieved by comparing cases of nonfamilial AF to age- and gender-matched controls. The analysis is performed as an association study aimed at identifying differences in segregation of genetic backgrounds (common variants) between both groups that may explain the development of and susceptibility to the disease.

Atrial Fibrillation as a Monogenic Disease

Because of its increasing prevalence with age and the fact that AF in the majority of cases occurs in the context of structural heart disease, AF is not generally appreciated to be heritable or have a substantial genetic component to its pathophysiology. Nevertheless, in 1943 it was first reported as a familial form.[7] Recent analysis of the Framingham data and the Iceland population has shown that there is a genetic susceptibility to AF, shown by the fact that parental AF increased the risk of AF in the offspring to a relative risk up to 4.7 if parents were affected before age 60 years.[8,9]

A study by Darbar et al.[10] indicated that 5% of patients with AF and up to 15% of individuals with lone AF may have a familial form. This study indicated that the familial form of the disease may have a higher prevalence than previously suspected and emphasizes the importance to expand genetics studies.

In 1996, we identified three families in Catalonia, Spain, with AF inherited with an autosomal dominant pattern. These families were later expanded to six, with a total of 132 individuals. Fifty of them presented with AF, with an age of diagnosis of the arrhythmia from 0 to 45 years (two patients were diagnosed in utero). The echocardiograms were within the normal range when the patients were diagnosed. Some of them have subsequently developed dilation of the left atrium on follow-up. Two patients have mild left ventricular dysfunction, one of them probably related to her advanced age and the other to tachycardiomyopathy secondary to poorly controlled heart rate. In six patients, electrical cardioversion was unsuccessful despite a structurally normal heart. The majority of the individuals in these six families are asymptomatic, and only six patients presently suffer from palpitations but otherwise have a normal life. The disease is chronic in all but two individuals, one who has been progressively having more and longer episodes of paroxysmal AF, suggesting that the AF will probably become chronic. The second patient died suddenly while under treatment with antiarrhythmic drugs. With techniques of linkage analysis, the locus was identified in 10q22, which was segregating with the affected individuals.[11] The gene has not been identified yet.

The first genes for AF have been identified in these last years, providing the first links of ion channelopathies to the disease. A four-generation family from China was segregating the disease with a chromosome 11 locus.[12] The analysis of KVLQT1 (KCNQ1) identified a missense mutation resulting in the amino acid change S140G. Electrophysiological studies revealed a gain of

function in I_{Ks} (**slow delayed rectifier potassium current**) when the mutated channel was expressed with the β-subunits minK and MirP1. This gain of function explains well the shortening of the action potential duration and effective refractory period, which are thought to be the culprits of the disease. Mutations in KCNQ1 causing a loss of function had been described before as responsible for long QT syndrome type 1. Interestingly, despite the gain of function, 9 out of 16 individuals presented QT prolongation of the electrocardiogram.[12] This is an issue that is yet unresolved, and a gain of function mutation in codon 141, next to the one described in the family, is responsible for a severe form of AF in utero and short QT syndrome.[13]

Also from the same group in China, a link between KCNE2 and AF was provided with the identification of an identical mutation in two families with AF.[14] The mutation R27C caused a gain of function when coexpressed with KCNQ1 but had no effect when expressed with HERG. A third genetic defect was described in KCNE3[15]; however, the functional analysis did not demonstrate a different biophysical effect caused by the mutant genetic defect, indicating that it could be a rare polymorphism, and finally a gain of function mutation in Kir2.1, caused by a mutation in KCNJ2[16] was found in 2005 in a new kindred. The biophysical findings therefore indicated a role of gain-of-function mutations in potassium channels in AF, highlighting the pathophysiological role of shortened atrial action potentials. However, in 2006, Olson et al.[17] described a loss-of-function mutation in KCNA5, the gene that encodes KV1.5, opening the debate into the possibility of prolongation of the action potential as a mechanism for AF. New loci have been identified in 6q14–16[18] and 5p13[19], but the genes remain elusive.

Somatic mutations in *GJA5* in atrial tissues of a subset of patients with idiopathic AF have been identified.[20] The gene encodes the gap junction protein connexin 40, which is involved in electrical conduction in the atrial myocardium.

Atrial Fibrillation Associated with Other Monogenic Diseases

Atrial fibrillation has been described in other cardiac monogenic diseases as a concomitant disease. It has been identified in families with hypertrophic cardiomyopathy,[21] skeletal myopathies,[22] and familial amyloidosis[23] and in monogenic diseases predisposing to atrial abnormalities. In these cases, the disease is probably related to morphological changes in the atria caused by the underlying cardiac pathology.

The disease can also be present in other ion channelopathies like long QT 4,[24] Brugada syndrome[25] and short QT syndrome.[26] In the last, the mutations described in HERG cause a gain of function of I_{Kr} (**rapid delayed rectifier potassium current**), responsible for sudden cardiac death. One of the families, the one from the original paper on the short QT syndrome,[27] only presented with AF and no sudden cardiac death. In this family, the same gain-of-function mutation in HERG as in the previous families was identified.[28] The high incidence of atrial arrhythmias in patients with short QT syndrome and the data on gain-of-function mutations in I_{Ks} currents point to an important role for the shortening of the action potential in the development of AF. A mutation in KCNQ1 (V141M) was identified in 2005 as responsible for AF and short QT syndrome in utero, showing also a gain of function in I_{Ks}.[13]

Genetic Predisposition to Acquired Atrial Fibrillation

The familial form of AF is uncommon. The majority of the cases are acquired and related to structural abnormalities. However, not all individuals with the same cardiac pathology develop AF, indicating that there are probably genetic factors that predispose some of them to the arrhythmia. Few centers have been trying to unravel some of these genetic backgrounds with the use of association studies.

One report from Japan[29] tested the hypothesis that genetic factors that increase cardiac fibrosis would be a determinant for the development of lone AF. These investigators analyzed a polymorphism in the angiotensin-converting enzyme (ACE) gene, an enzyme that interacts with angiotensin II and affects cardiac remodeling. The ACE gene can be inherited with an intronic deletion, which has been linked to higher circulating levels of enzyme and a higher degree of hypertrophy and myocardial fibrosis.[30] While this cardiac fibrosis has been described at the ventricular level, they hypothesized that it would also affect the atria and cause the arrhythmia. They compared the genotypes of 77 patients with lone AF to 83 controls. They did not find any difference in the distribution of the ACE genotypes between the affected individuals and controls. There was no correlation with the type of AF, namely, paroxysmal or chronic, and the genotype. However, a larger study in 2004 showed that there may be a relation between nonfamilial structural AF and polymorphisms in the renin–angiotensin system.[31]

A second study looked at a polymorphism in minK and relation to the disease. There was an association with the 38G allele and AF. Interestingly, this is one of the rare exceptions for which an additional study could demonstrate the functional impact of this common variant on AF. When coexpressed with KCNQ1 in a heterologous expression system, the 38G allele is associated with decreased repolarizing I_{Ks}, potentially facilitating AF.[32] Further studies will be required to confirm this association.[33]

Another study is mentioned to highlight the importance of selecting a specific phenotype following a specific pathophysiological hypothesis as a prerequisite to identify genetic contributions to AF. This study has addressed the relationship between inflammation and the risk of developing postoperative AF. The authors investigated the role of the -174G/C interleukin 6 polymorphism in 110 patients undergoing coronary artery bypass surgery.[34] This polymorphism had been previously associated with postoperative interleukin 6 levels. Twenty-six patients developed AF in the postoperative period. Analysis of the polymorphism revealed a significant prevalence of the GG genotype (34% vs 10%) in patients with AF. Likewise, the levels of interleukin and fibrinogen were higher in patients with the GG phenotype. Therefore, this study showed a possible role of an inflammatory component in the development of AF. As in all association studies, larger patient populations with a comparable and homogeneous phenotype will be required to confirm the findings in independent replication studies.

Genetic Studies: Implications for the Future

The discovery of the structure of the ion channels, their function, and their pathophysiology have helped partly unravel the role played by the different

ionic currents in the electrical activity, electromechanical coupling, and arrhythmogenicity. With the advances in genetics and the discovery of mutations causing familial diseases, we have been able to jump from the most basic level to the clinical arena. Cardiac arrhythmias predisposing to sudden death, like long QT, Brugada syndrome, and short QT syndrome, have benefited tremendously from advances in genetics and molecular biology. The information gained in genetics, biophysics, and experimental models have opened new insights into preventive and therapeutic options. Rapidly expanding technology will allow for both large-scale candidate gene-driven systematic LD-based single-nucleotide polymorphism (SNP) association studies, as well as for whole-genome association studies, which hold the potential to identify novel genes and genetic variants that modulate the risk for AF.

Arrhythmias like AF will therefore undoubtedly benefit from the discovery of the genes that cause the familial forms of the disease and from the knowledge of the alterations in gene expression as a consequence of it. The study of the interaction of all these genes with the structural cardiac abnormalities will probably shed light not only on the factors that induce the first episode but also on the determinants that prolong this episode into a chronic form. The largest benefit that will be drawn from all such data is the much improved understanding of the disease, how it is initiated, how it perpetuates. As has happened in relation to the previously mentioned diseases, once the preliminary data are obtained, the development of better therapeutic and preventive measures will be a possibility.

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7

Dominant Frequency Mapping to Assess the Consequences of Remodeling in the Mechanism of Atrial Fibrillation

José Jalife and Omer Berenfeld

Abstract: The mechanisms underlying atrial fibrillation (AF) remain poorly understood. In some patients, AF initiation often occurs from arrhythmogenic foci arising at muscular sleeves in a pulmonary vein (PV). Either direct radio-frequency (RF) ablation of these foci or, more recently, their disconnection from the left atrium by ablation at venous ostia is the basis for curative AF ablation procedures. However, it is likely that, in most cases, the mechanism of AF maintenance is different from that which initiates it. Isolated animal heart experiments suggested that some cases of AF may be maintained by the uninterrupted periodic activity of a small number of discrete reentrant sites (rotors) located in the posterior left atrial (LA) wall, near the PV/LA junction. During sustained AF, such sources activate at an exceedingly high rotation frequency. Thus, rotors near the PV/LA junction dominate over any other slower sources that may form elsewhere and act as the drivers for the entire fibrillatory process. High-resolution spectral analysis of the spatial distribution of activation frequencies reveals a hierarchy with appreciable frequency gradients across the atria. Here, we briefly review our current understanding of the mechanisms and manifestations of AF and discuss the applicability of spectral analysis tools to the study of AF in patients with the idea of helping to improve the efficacy of ablation therapies. We focus in part on recent clinical studies that provide justification for the combined use of dominant frequency and electroanatomical mapping to systematically correlate the spatial distribution of excitation frequency with cardiac anatomy; provide mechanistic insight into different types of AF, particularly regarding the consequences of atrial remodeling leading to persistent AF; and facilitate ablation procedures.

Keywords: Ablation; CARTO; Dominant frequency; High-frequency sources; Rotors; Spectral analysis.

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in humans. It afflicts approximately 2% of the unselected adult population and 5.9% of the population over 65 years of age.[1] It is the most common cardiac cause of stroke.[2] In addition, the rapid heart rate resulting from AF can cause a number of adverse outcomes, including congestive heart failure and tachycardia-related cardiomyopathy.[3] Medications are only marginally effective in treating this arrhythmia and have the potential for serious side effects, including life-threatening proarrhythmia. On the other hand, it has recently been demonstrated that patients with paroxysmal AF can be cured by a catheter-based ablation procedure.[4] This is based on the observation that the mechanism of AF in these patients is initiated by focal triggers localized usually to one of the pulmonary veins (PV).[5] However, in persistent AF, the prevailing theory regarding its mechanism is that multiple random wavelets of activation coexist to create a chaotic cardiac rhythm,[6] and therapy is more challenging.[7–9] Our recent experimental studies of cholinergic AF in the isolated sheep heart[10] demonstrated that high-frequency sources in the PV region dominate and drive the fibrillatory activity throughout both atria.

Motivated by those results and by a growing body of work investigating how measurements of the cycle length (CL) of activity in patients during AF can contribute to its treatment,[11–13] we have begun to focus our analysis on the organization of spectral properties of the activity during AF in humans. We are also investigating the mechanisms that underlie the organization of such activity. As suggested in recent preliminary studies,[13,14] high-resolution spectral analysis offers the unique opportunity of the ability to correlate systematically the spatial distribution of excitation frequency with cardiac anatomy and ablation procedures and to provide mechanistic insight into different types of AF. In this chapter, we briefly review our current understanding of the mechanisms and manifestations of this complex arrhythmia and discuss possible approaches that may help to directly improve the efficacy of ablation therapies in certain groups of patients.

Mechanisms of Atrial Fibrillation

The exact mechanisms underlying AF are still poorly understood despite many years of research and speculation. Since the description of the multiple-wavelet hypothesis by Moe and Abildskov,[6] it became generally accepted that AF is the result of the random propagation of multiple wavelets across the atria, a process that is independent of the initiating event. Experimental support for this hypothesis came from Allessie et al.[15] in the 1980s; they estimated that four to six wavelets were needed for AF perpetuation in dogs. This theory was strengthened by the clinical observation that chronic AF could be cured in some patients by the placement of multiple surgical lesions (maze) to compartmentalize the atria into regions presumably unable to sustain the multiple random wavelets.[16] Indeed, this theory is virtually universally accepted by most clinical electrophysiologists.

However, in studies as early as the 1920s by Sir Thomas Lewis,[17] an alternative hypothesis for the mechanism of AF was proposed. Lewis suggested

that the mechanism was caused by activation by a rapidly firing reentrant circuit that resulted in wavefront fractionation and presented with a fibrillatory pattern on the surface electrocardiogram (ECG). More recently, Schuessler et al.[18] demonstrated in an isolated canine right atrial (RA) preparation that, with increasing concentrations of acetylcholine (ACh), activation patterns characterized by multiple reentrant circuits converted to a single, relatively stable, high-frequency circuit that resulted in fibrillatory conduction.

Studies from our laboratory[19,20] that have applied high-resolution mapping of wave propagation and analyzed long episodes of AF in both time and frequency domains have provided evidence that propagation during AF is not random[10] but has a high degree of spatiotemporal periodicity. This has led to the hypothesis that perpetuation of AF may depend on the uninterrupted periodic activity of a small number of discrete generators (rotors), most often localized in the left atrium (LA) and established by the interaction of propagating waves with anatomical heterogeneities in the atria. We have proposed also that, in the sheep heart, the rapidly succeeding wave fronts that emanate from such rotors propagate through both atria and interact with anatomical or functional obstacles, leading to fragmentation and wavelet formation.[10] As discussed in an "insight review article" in *Nature* by Nattel,[21] there is strong support in the literature for this hypothesis, including observations made during radio-frequency (RF) ablation of AF in humans suggesting that, in some patients, impulses generated by a single source of focal activity propagate from an individual PV or other atrial regions to the remainder of the atria as fibrillatory waves.[5,22,23]

Paroxysmal and Persistent Atrial Fibrillation

One reasonable interpretation for the seemingly contradictory results outlined is that paroxysmal AF is caused by a localized source leading to fibrillatory conduction, and persistent AF is caused by random multiple-wavelet reentry. Indeed, this is the prevailing accepted interpretation of the data. However, an alternative hypothesis is that most, if not all, patients with AF have a focal or reentrant mechanism as the initiating cause of the arrhythmia and a rotor or a small number of rotors as the drivers that maintain the arrhythmia. Perhaps the only differences between paroxysmal and persistent AF are the rotation frequency, stability, and location of such sources; that is, when the driving site is most stable and its frequency is highest, the clinical scenario of persistent AF will be manifest.

While this hypothesis has not been tested, there is evidence in the literature that supports it strongly.[24–26] Specifically, one report described the profound antiarrhythmic effect of cryoablation (using a handheld probe) to areas of shortest CLs in the posterior LA in open chest dogs with chronic AF.[24] While they attributed their success to the fact that the ablated areas were large enough to prevent reentry of multiple wavelets, this could really have represented empiric elimination of potential high-frequency sources. Roithinger et al.[25] used RF ablation to show that selective linear lesions in the LA significantly reduced AF frequency in a canine model, whereas RA lesions did not. Horvath et al.[26] reported on human cases of simultaneous LA flutter and RA fibrillation in which the mean LA CL of 173 ms (5.8 Hz) was nevertheless shorter than the

mean RA CL of 236 ms (4.2 Hz). Other studies have shown that refractoriness is shorter in the LA than in the RA.[20,27–29]

Recent experiments by Li et al.[30] strongly suggest that LA-to-RA differences in refractoriness at low frequencies correlate strongly with intrinsic differences in the action potential duration (APD) recorded from cells obtained from the two atria. A larger density of the rapid delayed rectifier current I_{Kr} in the LA seems to explain nicely such chamber-specific differences in APD during pacing at relatively low frequencies.[30] A number of studies in patients also support the idea that the LA may be the driver for AF in some cases. Harada et al.[31] mapped atrial activation in ten persistent AF patients who were undergoing mitral valve surgery. They demonstrated that the LA underwent regular and repetitive activations with CLs that ranged between 131 and 228 ms. In contrast, the activation sequence in the RA was extremely complex and dysrhythmic. More recently, the same authors[32] demonstrated that resection of the LA appendage or cryoablation of the orifice of the left PV terminated AF in 10 of 12 additional patients with mitral valve disease. These data support the hypothesis that at least some cases of persistent AF may be caused by a single or, at most, a few high-frequency periodic sources of activity in some regions of the LA.

Acute Atrial Fibrillation: The Sheep Heart Model

The general working hypothesis that AF results from activity of a small number of high-frequency reentrant sources localized in one atrium with fibrillatory conduction to the other atrium is based primarily on results obtained in our experimental model of the isolated, Langendorff-perfused, sheep heart, in which we have studied the mechanism of acute AF induced by burst pacing in the presence of ACh. Our initial work focused on the localization of the high-frequency sources thought to be responsible for maintaining AF in this model.[19,20,33.34]

Figure 1 shows a diagram of our experimental preparation for simultaneous optical and electrophysiological mapping of both atria. The optical fields are represented by the ovals on the LA and RA appendages. A biatrial electrogram (BAE) was used to monitor global activation frequency during AF. Electrodes were placed at various locations, including the base of the LA appendage, PV groove, epicardium and endocardium of the PV, Bachmann's bundle (BB), and RA free wall. Those studies demonstrated that there was a high degree of spatial and temporal organization during sustained AF. In addition, as illustrated in Figure 2, it was clear that the activation frequency in the LA was much higher than in the RA. Moreover, in many cases our optical mapping studies demonstrated self-sustaining rotors in the LA giving rise to periodic electrical waves[20] and strongly suggested that such rotors were the underlying mechanism of AF in the sheep heart model.

Subsequently, we hypothesized that waves emanating from relatively stable rotors in the LA undergo complex, spatially distributed conduction block patterns as they propagate toward the RA, manifesting as fibrillatory conduction and thus resulting in left-to-right frequency gradients. Our objectives here were in part to characterize impulse propagation and LA:RA frequency gradients across the BB and the inferoposterior pathway (IPP) along the coronary

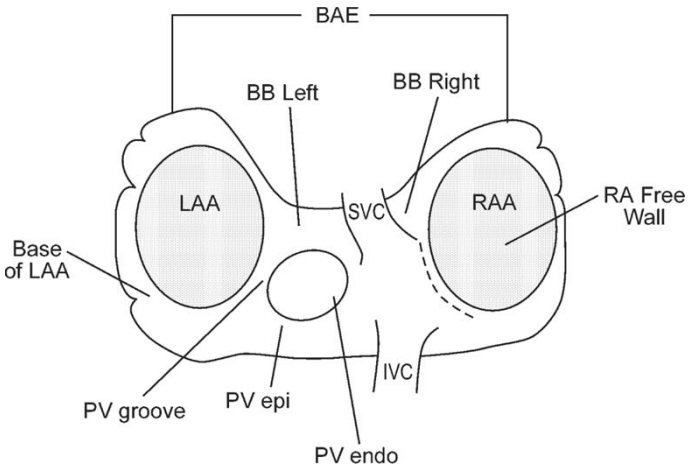

Figure 1 Diagram of the sheep or goat atria showing the location of optical mapping fields and bipolar recording electrodes. *BAE* biatrial electrogram, *BB* Bachmann's bundle, *epi* epicardium, *IVC* inferior vena cava, *LAA* left atrial appendage, *PV* pulmonary vein, *RAA* right atrial appendage, *SVC* superior vena cava. (Adapted from ref. 36 by permission of the American Heart Association.)

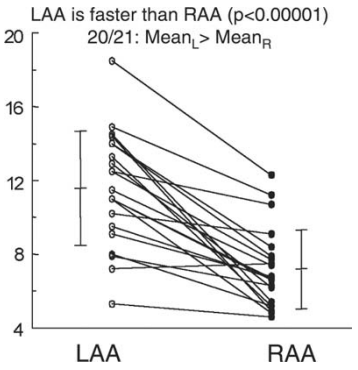

Figure 2 Differences in mean dominant frequency (DF) measured using spectral analysis of optical signals in left atrial appendage (LAA) and right atrial appendage (RAA) in the sheep heart. *L* left, *R* right.

sinus (CS). We induced AF by rapid pacing in the presence of 0.1 to 0.6 μ*M* ACh; 48 episodes of AF were analyzed. Simultaneous optical mapping of the LA and RA was done in combination with bipolar electrode recordings along the BB (6), the IPP (4), the RA free wall (2), the LA appendage (1), and the PV region (1). Power spectral analysis (fast Fourier transform, FFT) of all signals was performed.[35] A left-to-right decrease in the dominant frequencies (DFs) occurred in all cases along the BB and IPP, resulting in an LA:RA frequency gradient.

This is illustrated in Figure 3, which shows data obtained from a representative experiment.[36] In panels A and D are shown on the left single-pixel optical recordings obtained from the LA and RA during a 3-s episode of AF. Panels B and C show electrograms obtained, respectively, on the left and right portions of the BB. On the right are the corresponding power spectra, demonstrating a gradual decrease in DF from LA through the BB to the RA. In panel E, the color DF map illustrates the distribution of DF domains, demonstrating a

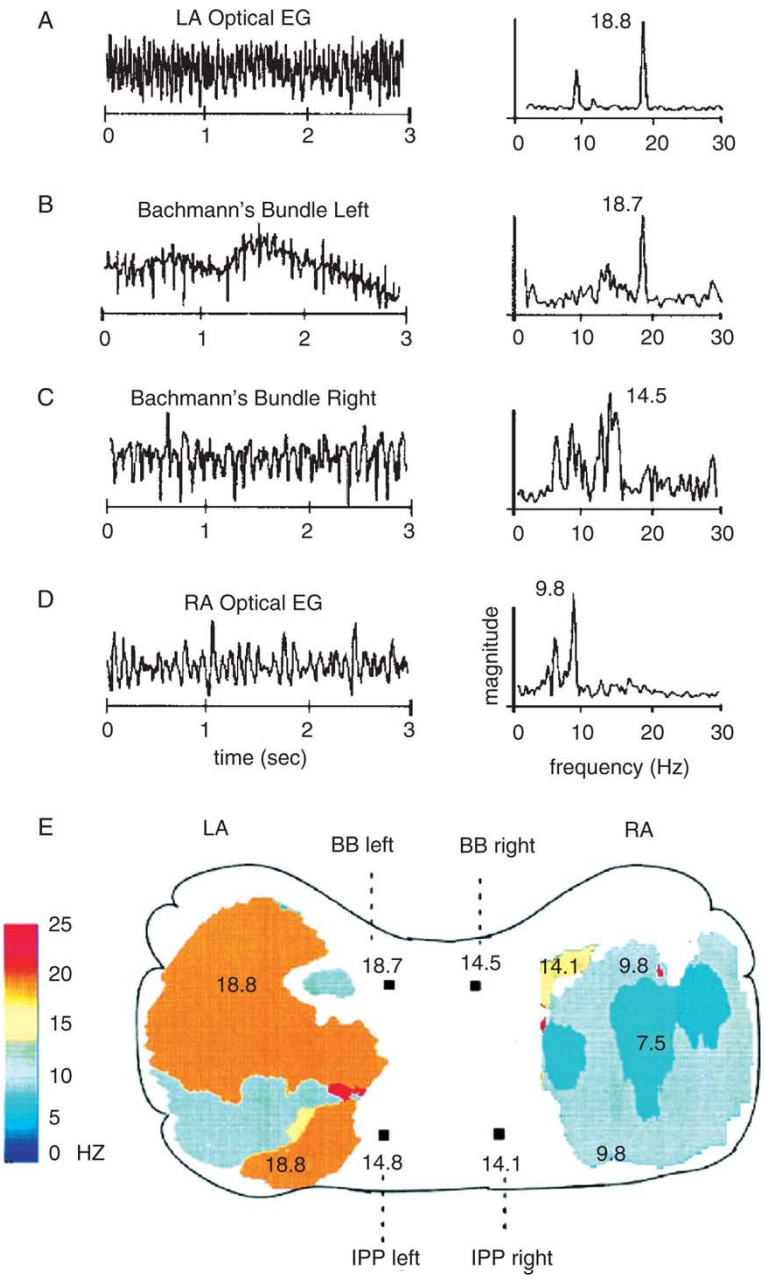

Figure 3 **A** Optical electrogram (EG) and fast Fourier transform (FFT) from LA. **B** and **C** True EGs and FFT from the BB left and right. **D** RA optical EG and FFT. **E** Color DF map of RA and LA including BB and inferoposterior pathway. Notice LA:RA frequency gradient. *BB* Bachmann's bundle, *DF* dominant frequency, *IPP* inferoposterior pathway, *LA* left atrium, *RA* right atrium. (Reproduced from ref. 36 by permission of the American Heart Association.)

gradient from LA to RA. The mean gradient, calculated as the difference between mean LA and RA DFs, was 5.7 ± 1.4 Hz. In these experiments, left-to-right impulse propagation was present in 81% ± 5% and 80% ± 10% of

cases along the BB and IPP, respectively. Overall, our results strongly supported the hypothesis that AF in the sheep heart is the result of high-frequency periodic sources located in the LA, with fibrillatory conduction toward the RA. This work has been published in *Circulation*.[19,20,36]

Role of Atrial Structure

At the macroscopic level, studies in animals suggest that the intricate three-dimensional (3-D) structure of the atrium is an essential component that contributes to the complexity of propagation patterns identified by high-resolution mapping during AF.[19,33,34,37,38] However, the information about how heterogeneous electrophysiology and heterogeneous anatomy interact to lead to AF initiation, maintenance, or perpetuation is incomplete at best. Advances have occurred in the understanding of geometrical factors, such as wavefront curvature,[39] nonuniform anisotropic coupling,[40] and sink–source relationships at areas of tissue expansion,[41] and in the application of nonlinear dynamics theory to the spatial and temporal organization underlying complex cardiac arrhythmias,[42] 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.[37] Computer modeling may provide useful tools for research aimed at the study of the manner in which electrical "fibrillatory" waves interact with the highly complex 3-D structure of the atria.[43,44]

A more recent study from our laboratory provided detailed analysis of the manner in which propagating waves initiated by high-frequency pacing in BB interact with the RA and result in fibrillatory conduction.[38] Our goal was to determine the underlying basis of the complex patterns of propagation that characterize AF. In other words, we wanted to answer the following question: What is the mechanism of fibrillatory conduction in this model in which activation by a high-frequency rotor in the LA is highly periodic?

We hypothesized that the left-to-right frequency gradient and fibrillatory conduction observed in our previous studies resulted from breakdown of waves traveling from the LA across interatrial pathways, into the pectinate muscle (PM) network of the RA. Thus, we expected to demonstrate that periodic repetitive input to the RA at increasing frequencies should result in increase in complexity and decrease in organization of wave propagation, compatible with fibrillatory conduction.

To this aim, we used simultaneous high-resolution endocardial and epicardial optical mapping (di-4-ANEPPS) in isolated, coronary-perfused sheep RA preparations.[38] Rhythmic pacing at the BB allowed well-controlled and realistic conditions for LA-driven RA. Pacing at increasingly higher frequencies (2.0 to 6.7 Hz) led to increasing delays in activation distal to major branching sites of the crista terminalis (CT) and PMs.[38] As shown by the frequency maps presented in panel A of Figure 4, stimulation of the BB at 5.0 Hz resulted in 1:1 activation of the entire preparation at 5.0 Hz. However, at 7.7 Hz, there were spatially distributed intermittent blockades with the establishment of well-demarcated frequency domains (compare DF maps on left and right) and significant discordance between epicardium and endocardium. In fact, as illustrated in panel B, stimulation at

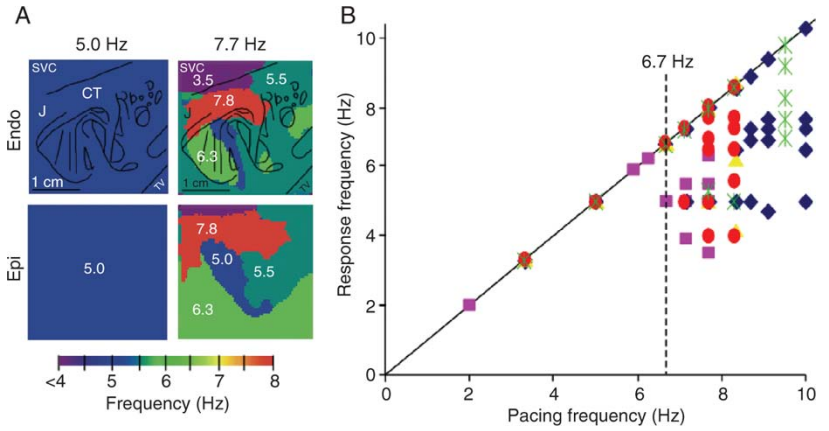

Figure 4 **A** Color DF maps of endocardium (endo; top) and epicardium (epi; bottom) of right atrium obtained during stimulation of Bachmann's bundle at 5 and 7.7 Hz. **B** Response frequency as a function of pacing frequency. Note breakdown at 6.7 Hz. (Reproduced from ref. 38 by permission of the American Heart Association.)

frequencies between 2 and 6.7 Hz resulted in rhythmic flutterlike activation of both epicardium and endocardium. However, above the "breakdown frequency" of approximately 6.7 Hz, RA activity underwent a significant loss of consistency in the direction of propagation and thus transformed into fibrillatory conduction.[38] Such frequency-dependent changes were independent of APD. Rather, the spatial boundaries between proximal and distal frequencies correlated well with branch sites of the PM.

From these experiments,[38] we concluded that there exists a breakdown frequency in the sheep RA below which activity is flutterlike and above which it is fibrillation-like. The data strongly supported the idea that, during AF, high-frequency activation initiated in the LA undergoes fibrillatory conduction toward the RA, and that branch points at the CT and PM play a major role in increasing the complexity of the arrhythmia. In addition, a loss of consistency in the propagation patterns demonstrates the difficulty of tracing the origin of the activation during fibrillation.

Role of Dispersion of Action Potential Duration and Refractoriness

Spatial dispersion in APD and refractoriness, measured at relatively slow stimulation rates, are usually invoked to explain complex wave propagation during AF.[45] Wang et al.[46] found that, at a CL of 250 ms in dogs susceptible to sustained AF, the dispersion of refractoriness in the RA epicardium was 19 ± 3 ms, with the longest refractoriness approximately 120 ms at the FW. Satoh and Zipes[47] reported that refractoriness was shortest at the lower portion of the CT relative to the superior vena cava (SVC). Yet, none of the above seemingly conflicting studies measured refractoriness in the PM region, and their data are therefore difficult to compare with our results.

We constructed high-resolution APD maps at a CL of 300 ms (3.3 Hz; not shown here) to assess indirectly the degree of spatial dispersion of refractoriness.[48]

In agreement with the results of Feng et al.,[49] our data also indicated that the CT has the longest APD during pacing at a slow rate (3.3 Hz). Spach et al.[50] also reported that, at 1.7 Hz, APD in the CT is longer than in the PM. In single cells, Yamashita et al.[51] showed that APD in the rabbit CT was longer than in the PM at 1 Hz. In our experiments, however, the CT consistently showed the largest DF when the BB is paced at a rate comparable to the frequency of the LA during AF (>7 Hz). Thus, the distribution of APD *under normal conditions* seems different from the distribution of DF domains during AF, which leads us to suggest that dispersion of refractoriness at normal frequencies is a poor predictor of the spatial distribution of intermittent block patterns that characterize AF.

However, both vagal stimulation and administration of ACh have been shown to result in AF.[52–54] In experimental animal models, vagal stimulation results in sustained AF as long as the vagus nerve is continuously stimulated,[53] and in dogs, catheter ablation of the cardiac parasympathetic nerves abolishes vagally mediated AF.[55] This has been attributed to the heterogeneous distribution of vagal innervation throughout the atria, which increases spatial dispersion of refractory periods.[56] Notably, any hypothesis put forth to explain the ionic mechanism of maintenance of AF must contend with the fact that local frequencies in some parts of the LA sometimes reach values as high as 16 to 18 Hz.[36] This means that APDs at such sites must abbreviate to about 60 ms or less to activate repeatedly at such frequencies in a 1:1 manner.

The work by Li et al.[30] demonstrated significant intrinsic differences in the APD of LA myocytes with respect to RA myocytes of the dog heart. In addition, they showed that LA myocytes have a larger I_{Kr} density and greater ERG protein expression compared to the RA. At a frequency of 6 Hz, APD in the LA and RA were approximately 100 and 110 ms, respectively. It is possible that such differences contribute somehow to the establishment of LA-to-RA frequency gradients during acute AF in the structurally normal heart through the resultant LA-to-RA differences in effective refractory period (ERP).

Yet, intrinsic APD differences alone are insufficient to explain the mechanism of AF maintenance or the exceedingly high frequency that can be achieved in some parts of the LA. A frequency of 16 to 18 Hz means that somewhere in the LA the atrial APD during AF is less than 60 ms, which cannot be explained on the basis of a relatively large I_{Kr}, which has a time constant that is about 135 ms at +10 mV.[30] Thus, under acute conditions, continuous vagal stimulation, ACh perfusion, or other profibrillatory ministrations that are capable of abbreviating atrial APD to extreme values are necessary for the arrhythmia to be established and maintained. Traditionally, the ability of cholinergic input to promote AF maintenance in the normal heart has been attributed to the heterogeneous distribution of vagal innervation and muscarinic ACh receptors throughout the atria, which increases spatial dispersion of refractory periods and results in complex patterns of activation and wavelet formation.[57]

Published data from our laboratory in the Langendorff-perfused sheep heart showed that increasing the ACh concentration from 0.2 to 0.5 μ*M* increased the frequency of the dominant source and rotors, as well as the LA-to-RA frequency gradient, suggesting that the LA and RA are indeed different in their response to ACh in this species.[58] In fact, work from Pappone et al.[59] suggests that, in patients with paroxysmal AF, isolation of the PVs together

with abolition of all evoked vagal reflexes around all PV ostia significantly reduces recurrence of AF at 12 months.

Atrial Fibrillation in Chronically Instrumented Animal Models

In 1995, Wijffels et al.[60] in Allessie's laboratory developed a goat model of chronic AF in which the animals were connected to an external automatic fibrillator (see also ref. 24). The device was programmed to deliver a 1-s burst of electrical stimuli (50 Hz) as soon as sinus rhythm was detected. As such, the automatic fibrillator was able to maintain AF for 24 hours a day, 7 days a week. On day 1 of the experiment, the paroxysms of AF induced by the fibrillator were short lived. However, in the continuous presence of high-frequency excitation for days or weeks, the rate and stability of AF increased, thus demonstrating that "AF begets AF." Importantly, with the persistence of AF, the atrial ERP shortened, and the slope of its frequency dependence became flat or inverted, which suggested the occurrence of a process of AF-induced electrical remodeling in the atria of these goats. More recently, the Allessie laboratory showed that electrical remodeling was not significantly affected by changes in autonomic tone or ischemia and concluded that high-frequency activation itself was responsible for the AF-induced changes in atrial ERP.[61] On the other hand, it was shown that the remodeling process is reversible, and the ERP normalizes completely within 1 week of resumption of sinus rhythm.[60]

The process of remodeling is reproducible in other animal models of chronic AF.[24,62,63] Moreover, recent studies in humans have shown that changes in atrial electrophysiology associated with persistent AF are reversible after cardioversion,[64] which provides convincing evidence for the existence of AF-induced remodeling in humans. However, to date investigators have been unable to rigorously correlate the electrical remodeling process to the molecular and ionic mechanisms underlying the perpetuation of AF.

Activation Rate in Atrial Fibrillation

In 1925, Lewis[17] postulated that fibrillation was similar to flutter in that a single circuit did exist in AF, but the path followed by the wave front was uneven. He also proposed that, in contrast to flutter, in fibrillation the circuit is completed in a shorter time. Since then, the differentiation between atrial flutter and fibrillation in patients is usually based on the regularity of the ECG signals, which is typically reduced with increasing rate. Although the upper limit of human atrial flutter rate varies considerably among investigators, its lower value relative to fibrillation is well documented.[26,65,66]

For example, according to Wells et al.,[65] type I and II atrial flutter have regular rates at less than 338 beats/min (5.6 Hz) and 433 beats/min (7.2 Hz), respectively. On the other hand, Roithinger et al.[66] found that frequency increased to a mean of 4.1 Hz during flutter after conversion from various types of AF with a longest CL of 184 ms (5.4 Hz). Horvath et al.[26] used an upper limit of 350 beats/min (5.8 Hz) to define atrial flutter. Very relevant to our study is the report these authors made on cases of simultaneous LA flutter

and RA fibrillation in which the mean LA CL of 173 ms (5.8 Hz) was shorter than the mean RA CL of 236 ms (4.2 Hz).

Our experimental work in the isolated sheep hearts[36] and RA preparations[38] provides mechanistic support to the idea put forth originally by Lewis[17] and demonstrates for the first time that there is a breakdown frequency below which activity is periodic and above which it is fibrillation-like. In the sheep RA, this breakdown frequency is 6.7 Hz, but it is important to note that the relevance of our results to the behavior of regions other than the sheep RA (e.g., the LA), or to other species, including humans, or even to diseased hearts,[67] remains to be determined. In the case of the LA of the sheep[19,35,36], dogs,[24] and humans,[11,22,26] there is substantial evidence that, during AF, activation frequencies are higher than in the RA. Therefore, one might expect that the general breakdown frequency in the LA should be higher than that demonstrated for the RA.

Radio-Frequency Ablation of Atrial Fibrillation

Radio-frequency ablation of atrial tissue by application of energy through intracardiac catheters has become a major therapeutic method for AF,[22,68–77] and there is significant clinical evidence that the PV region and the posterior LA are crucial for maintenance of AF in paroxysmal AF patients.[4,22,78] The RF ablation procedure consists of generating electrical barriers in various sites of the atria by altering the tissue properties in the vicinity of the ablating catheter tip. The extent of the altered tissue depends on the power and duration of the application as well as on the characteristics of the tissue itself. For a typical RF ablation, a power of 20 to 40 W is delivered for several minutes to create an altered substrate in a volume with a radius of about 5 mm around the catheter tip. The recognition that AF often depends on sources localized to the PVs resulted in the development of techniques designed to isolate those veins from the rest of the LA.[5] Together with cavotricuspid isthmus ablation, the so-called electrical isolation of the pulmonary veins (pulmonary vein isolation, PVI) is performed on many patients on a routine basis.[79]

Figure 5 shows schematically various configurations for combined limited linear ablation together with PVI performed in the laboratory of one of us.[79] A linear ablation joins the two superior PVs, connecting with a roofline that extends to the mitral annulus (MA) to interrupt the entire anterior interatrial band (left). In other patients, mitral isthmus ablation is performed to join the left inferior PV to the lateral MA (center); sometimes, an anterior line is added (right).

However, there is an ongoing debate among electrophysiologists regarding what is the most efficient strategy for the ablative treatment of AF. Haissaguerre and coworkers reported a success rate of 73% using limited ablation for segmental PVI in 70 paroxysmal AF patients.[80] Pappone and associates used a more extensive circumferential PV ablation and reported a success rate of 85% and 80% in 26[22] and 251[81] patients, respectively, with paroxysmal AF and persistent AF. Oral and colleagues[82] reported a 63% success rate in 70 paroxysmal AF and persistent AF patients with segmental PVI.

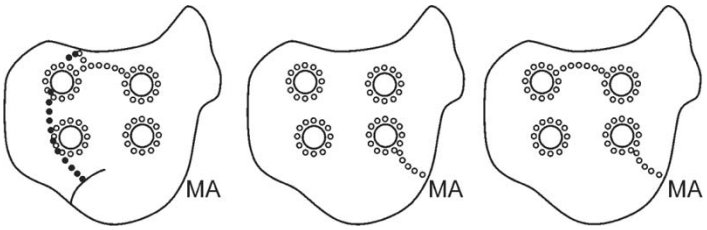

Figure 5 Limited biatrial ablation. *Left*: Pulmonary vein isolation (PVI), roofline and anterior line. *Center*: PVI and mitral isthmus line. *Right*: PVI and mitral isthmus line and roofline. *MA* mitral annulus. (Reproduced from ref. 79 by permission.)

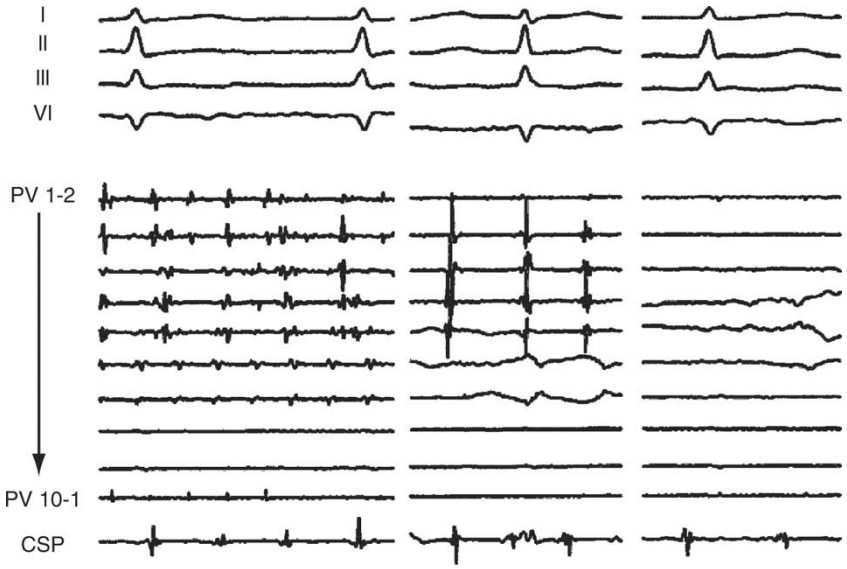

Figure 6 Pulmonary vein isolation (PVI) and atrial fibrillation (AF) termination. The initial target for this patient was the superior aspect of the PV, which led to a more organized PV activity (panel 2). Ablation at the site of earliest PV activity results in electrical isolation (panel 3). *CSP* proximal coronary sinus. (Reproduced from ref. 79 by permission.)

On the one hand, extensive ablation that is thought to modify the atrial substrate[83] can cure many types of AF, but it exposes the patient to a higher risk of complications[84] and to unacceptable fluoroscopy exposure times; on the other hand, more selective ablations that target localized "triggers" are safer but may be less likely to cure the AF, which may be become prone to recur.[73,85] Figure 6 shows surface and intracardiac recordings from a patient undergoing electrical PVI during AF.[79] On the left panel, bipolar electrograms from the catheter at the circumference of the PV show opposite polarity across adjacent bipoles, which in combination with the earliest activation indicate the site of a breakthrough.[86] After targeting the superior aspect of the PV, the activity slowed, with apparently more organized activity (middle panel). Further ablation of the site of earliest activation resulted in the electrical isolation of the PV and termination of AF.

Cycle Length During Atrial Fibrillation in Humans

Most recent work from Haissaguerre et al. described the changes in the CL measured at the CS during atrial fibrillation (AFCL) and different, progressive, ablation stages.[12] Prior studies of AFCL in animals[45,60,87] and humans[26–29,88,89] have emphasized its role as a surrogate measure of local atrial refractoriness. However, Morillo et al.[24] used a cryosurgical application to the posterior LA, where CL was the shortest, to terminate AF in dogs and demonstrate the link between the rate of local activity and its role in maintaining AF.

More recent human studies have also analyzed the AFCL.[11,22,90] Pappone et al., while studying the effectiveness of PV ablation techniques, found that, indeed, the shortest local CL in all the atria is located in the PV region.[11,22] Wu et al. mapped human atria during surgery and consistently observed rapid repetitive activity in the posterior wall of the LA at or near the PVs. They concluded that, during permanent AF associated with organic heart diseases, the AFCL was shorter in the posterior wall of the LA than in the RA free wall. Overall, work on AFCL supported the finding that, concomitantly with the central role of the PV region in maintaining AF,[5,24] the posterior LA also shows the fastest activity, as measured by its CL.[11,22,24,89]

Many other patient studies also supported the idea that the LA may be the driver for AF in some cases. Harada et al.[31] mapped atrial activation in ten patients with persistent AF who were undergoing mitral valve surgery. They demonstrated that the LA underwent regular and repetitive activations with CLs that ranged between 131 and 228 ms. In contrast, the activation sequence in the RA was extremely complex and dysrhythmic. Later, the same authors[32] demonstrated that resectioning the LA appendage or cryoablation of the orifice of the left PV terminated AF in 10 of 12 additional patients with mitral valve disease.

The additional studies of Wu[90] and Haissaguerre[12] give further mechanistic support to our general hypothesis that the PV region in some patients hosts the source that maintains the AF. The recent work by Haissaguerre et al.[12] demonstrated that the sequence of vein-by-vein ablation in the PVI procedure resulted in a gradual increase in AFCL, with only 6 patients of 56 demonstrating an increase equal to or smaller than 5 ms (see Figure 7). This increase was observed with some variability from patient to patient and among PVs; in other words, while some PV ablations did not change the AFCL, a jump in the AFCL was observed with others. Figure 7 shows the AFCL before PVI, after sequential isolation of two and four PVs, and after a linear ablation was added. There was a significant increase in the AFCL in patients in whom AF terminated during PV ablation (186 ± 19 to 214 ± 24 ms, $p < 0.0001$) and to a lesser extent in patients with persistent AF after PV ablation (186 ± 20 to 194 ± 19 ms, $p = 0.002$). As shown in Figure 7, the cumulative change in AFCL after the procedure was completed in patients in whom AF terminated was greater than that in patients with persistent AF (30 ± 17 vs 24 ± 11 ms, $p < 0.005$).

These results conclusively demonstrate that the CL of the CS, when the AFCL was measured, depended on the activity in the remotely ablated sites. Since in this study the PV region was the fastest of all the regions in the atria, the findings strongly support the hypothesis that targeting for RF ablation of the regions that show the shortest AFCL may be a good strategy for

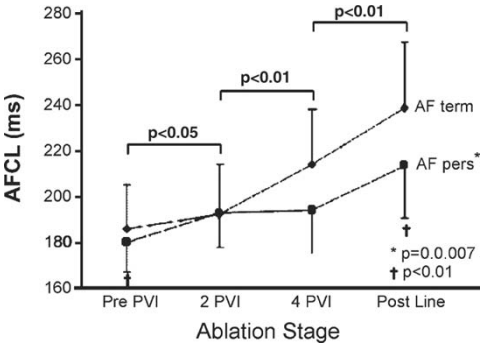

Figure 7 Atrial fibrillation (AF) cycle lengths in the coronary sinus as a function of progressive ablation stage. *AFCL* atrial fibrillation cycle length, *PVI* pulmonary vein isolation. (Reproduced from ref. 12 by permission of the American Heart Association.)

AF termination. As may be expected in patients with persistent AF, it would not be surprising to demonstrate that the region with the shortest AFCL lies somewhere other than the PV or the posterior LA. We surmise that, also in such cases, targeting the fastest activating site for ablation may lead to AF termination. Thus, as discussed next, research is currently ongoing with the objective of determining whether the use of spectral mapping[35,90–92] will make the analysis of the rate of excitation during AF more readily usable and efficient with greater chances of localizing in real time the high-frequency sources that maintain AF.

Mapping Dominant Frequencies in Patients with Atrial Fibrillation

The advancement from surface ECG tracings to highly sophisticated intracardiac, multisite mapping systems has no doubt contributed to the treatment of AF.[93] Various methods for nonfluoroscopic endocardial mapping systems and the localization of cardiac tissue critical for the arrhythmia are the basis for the success of the catheter ablation in terminating AF.[94] Three of the main advanced mapping methods currently used in the clinic are widely known as the multielectrode basket method,[95,96] the CARTO system,[97,98] and the Ensite noncontact mapping system.[99,100] While all three methods provide the clinician with spatial information on the electrical activity (i.e., electroanatomic mapping), the ability to successfully obtain such information varies considerably, and there are varying advantages and disadvantages of each technique.[93,94]

We collaborated with Haissaguerre's group in a study in which we utilized the CARTO system and a newly developed spectral analysis algorithm to investigate the spatial distribution of dominant excitation frequencies (DFs) in the endocardia of a group patients with AF.[13,14] Based on studies of AF progression and ablation, we hypothesized that, in humans, the predominance of DF values in the PV and LA regions over other regions would depend on the duration of the AF. Thirty-two patients undergoing ablation of symptomatic, paroxysmal (55.7 ± 9.3 years; n = 19) or persistent (58.0 ± 6.8; n = 13) AF

were studied. Patients were selected on the basis of the presence of spontaneous or inducible sustained AF (>10 min). The CARTO mapping system was utilized to acquire local electrogram and surface ECG recordings over 5 s during AF while creating a 3-D geometry. Points were acquired evenly throughout the atria and CS. The DFs and regularity of the electrograms were determined based on the power spectrum's highest peak and bandwidth, respectively. The point-by-point DFs of the electrograms were then color coded on the geometry map to characterize their spatial distribution. Electrograms showing low regularity were excluded from the analysis.

Data from two patients are presented in Figure 8. Figure 8A shows a DF map of a patient with paroxysmal AF; the image was obtained by spectral

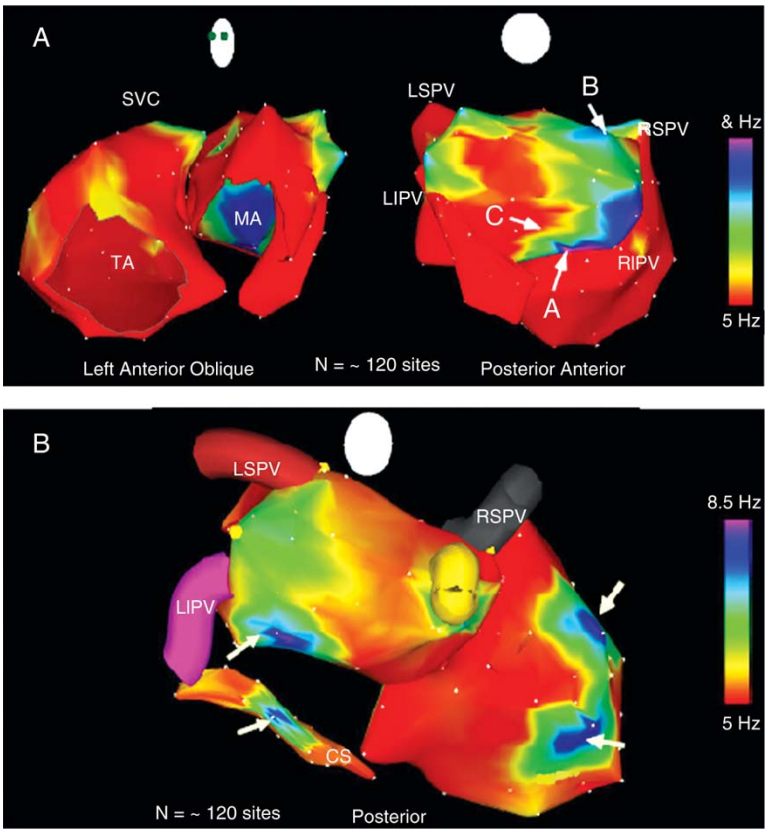

Figure 8 **A** Dominant frequency (DF) map in patient with paroxysmal atrial fibrillation (AF), with map obtained by spectral analysis of approximately 120 sites (white dots) in both atria. Note highest DF site at site A (purple) near the ostium of the right inferior pulmonary vein (RIPV). Ablation sequence in this patient was left superior (LS) PV, left inferior (LI) PV, right superior (RS) PV, and RIPV (site of AF termination); AF cycle length (CL) increased by 10, 25, 9, and 75 ms, respectively, before termination. **B** DF map in patient with persistent AF. Maximal DF and atrial frequency are slightly higher than in patient in **A**. In addition, many DF sites are located outside PVs (white arrows). Ablation sequence in this patient was RIPV, RSPV, LSPV, and LIPV; AFCL increased by 5, 2, 0, and 5 ms, respectively. *MA* mitral annulus, *SVC* superior vena cava, *TA* tricuspid annulus

analysis of approximately 120 sites (white dots) in both atria. The highest DF (purple) was localized to a small area near the ostium of the right inferior PV (RIPV). Subsequent RF ablation was carried out using the following sequence: left superior (LS) PV, left inferior (LI) PV, right superior (RS) PV, and RIPV (site of AF termination). After each ablation, the AFCL increased by 10, 25, 9, and 75 ms, respectively, before termination. In Figure 8B, the DF map is from a patient with persistent AF. Maximal DF and atrial frequency were slightly higher than in the patient in Figure. 8A. In addition, many DF sites were located outside the PVs (white arrows). The ablation sequence in this patient was RIPV, RSPV, LSPV, and LIPV; the AFCL increased by 5, 2, 0, and 5 ms, respectively.

The graph in Figure 9 shows a summary of our results using DF mapping. It reveals that, for both groups of patients, regions were organized with a similar hierarchy; the highest DF in the LA and the PVs was higher than the highest DF in the RA and the highest DF in the CS. In paroxysmal AF, the PV/ostial LA region was most likely to harbor a DF (42%); that probability decreased toward the rest of the atria and CS. In contrast, although persistent AF patients showed a similar incidence of DF sites in the RA and CS, the number tended to be reduced in the PV/ostial LA region, with only 26% of DF sites localized to that region. We concluded that, in that group of patients, paroxysmal AF was characterized by the hierarchical spatial distribution of DFs where the LA and PVs are always the fastest regions. By contrast, in persistent AF, a more uniform distribution of the DFs was observed, where the highest DF could not be found in the PV region, indicating the loss of this region's predominance. This may have implications in localizing a target for AF termination in patients.

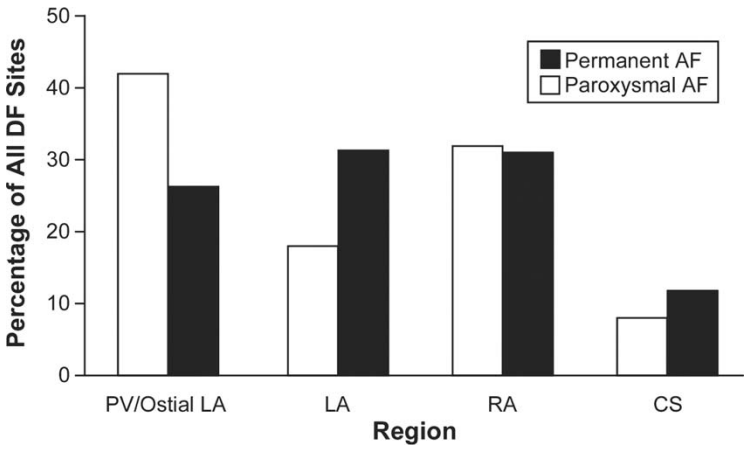

Figure 9 Spatial distribution of dominant frequency (DF) sites within pulmonary vein (PV)/ostial left atrial (LA) region, rest of LA, right atrium (RA), and coronary sinus (CS) in paroxysmal and permanent AF. (Reproduced from ref. 14.)

How Stable Is Atrial Fibrillation and How Reliable Is Dominant Frequency Mapping?

The sequential manner of data analysis is a significant limitation in the assessment of DF distribution. Intraoperative high-density recordings of AF do suggest epochs of regularity, but they are interspersed with periods of apparent chaos. It is therefore not convincing that a limited number of points were stable over the 5-s epochs needed to construct the power spectrum of a given episode. This observation needs to be verified over the entire mapping period. Thus, in 13 randomly selected patients, we recorded 30 s of data from each PV and analyzed this in terms of sequential 5-s intervals. After normalizing the variation in terms of the initial 5-s interval, each PV demonstrated no significant variation in the DF. In addition, in five randomly selected patients, we recorded 10 s of data for all points throughout the map and analyzed these data in terms of two 5-s intervals and compared with the total recording time (of 596 points). There was no significant difference in the DF determined for each point during the first (6.19 ± 0.79 Hz) and second (6.23 ± 0.82 Hz; $p = 0.4$) intervals or the entire recording interval (6.11 ± 0.81 Hz; $p = 0.5$). Comparison of sequential segments showed that the variability of 0.99 ± 0.41 Hz (range 0.21 to 1.79 Hz) and comparing the data obtained with the 5-s segments with those obtained by the full recording interval demonstrated that the mean variation was 0.56 ± 0.4 Hz (range 0.0 to 1.38 Hz), representing 14.8% ± 3.6% and 7.8% ± 0.6% of the mean and maximum DF in these patients, respectively. Further, in five additional patients we performed repeated sequential recordings from each PV, the CS, and the RA appendage for 15 min. Analysis of these sequential recordings demonstrated no significant variation in the DF for each of these sites. Finally, as illustrated in Figure 10, in ten randomly selected patients (five with paroxysmal AF, *left panel*; five with persistent AF, *right panel*), and we recorded and analyzed ten sequen-

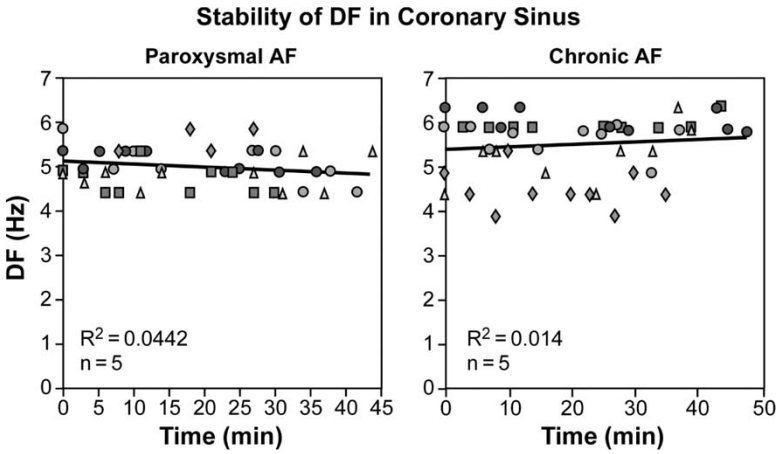

Figure 10 Atrial fibrillation (AF) dominant frequency (DF) stability analysis in ten randomly selected patients. For each patient, we recorded and analyzed ten sequential points taken from the start to the end of the mapping procedure from the coronary sinus. *Top*, individual data sets are from five patients with paroxysmal AF. *Bottom*, data are from five patients with chronic AF. While DF fluctuated in individual patients, the analysis showed no trend over 45 to 50 min of recording

tial points taken from the start to the end of the mapping procedure from the CS. These data in both groups of patients indicated stability of the DF within the CS for the duration of the study protocol. Altogether, these data demonstrated the short- and medium-term stability of the DF in humans with only minor fluctuations in the DF during the period of mapping. In addition, the data from our study strongly suggest that, at least in patients with paroxysmal AF, with 13 of 15 (87%) terminating at DF sites, temporal and spatial stability of DF did persist over the time frame of the study.

Thus, although the sequential nature of data acquisition of the CARTO system is a significant limitation, its use presented a relatively low risk for the patient. In addition, it generated accurate maps over a wide range of conditions of geometry and electrical activity, and its navigational system allowed for the reconstruction of the LA, RA, and CS in a single global coordinate system, thus allowing repeated catheter visits at specified locations in any atrium.[11] As suggested by the study described in this section, the combined use of the CARTO system with high-resolution spectral analysis promises to advance the field.

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Intracellular Calcium Dynamics and Atrial Fibrillation

Chung-Chuan Chou, Peng-Sheng Chen, and Shien-Fong Lin

Abstract: Intracellular Ca^{2+} (Ca_i) dynamics plays an important role in the initiation and maintenance of atrial fibrillation (AF). Specific intrinsic action potential properties and pacemaking cells within the pulmonary veins (PVs) contribute to PV arrhythmogenicity. Simultaneous sympathovagal activation could increase Ca_i and shorten action potential duration at the same time, resulting in triggered activity from the PVs and initiating AF. The maintenance of AF depends on both the triggered activity within the PVs and reentrant wave fronts in the atria and in the PVs. The reentrant wave fronts that conduct from the atria into the PVs increase the activation rate in the PVs, hence increasing Ca_i accumulation and triggered discharges. In the meantime, the wave fronts that conduct from the PVs into the atria may add complexities to atrial activations and support further wave break and reentry. Overload of Ca_i is likely to be a primary factor mediating both the short-term and chronic electrophysiological remodeling associated with AF.

Keywords: Atrium; Calcium; Dynamics; Ion channels; Fibrillation; Mapping; Triggered activity.

Atrial fibrillation (AF) is associated with multiple electrophysiological changes that may alter the excitability and contraction of atrial cells. Among the electrophysiological alterations associated with AF, cell membrane depolarization and downregulation of potassium channels I_{KACh} (acetylcholine-dependent potassium current), I_{to} (transient outward current), and I_{Kur} (ultrarapid delayed rectifier potassium current); L-type Ca current ($I_{Ca,L}$); and protein expression have been reported in atrial myocytes from patients with AF.[1–5] AF is also associated with the reduction in I_{CaL} and upregulation of IK_1; both changes may explain the observed decreases in action potential duration (APD) and effective refractory period (ERP) that are characteristic features of the remodeled atria.[6,7] In addition, the expression of sarcoplasmic reticulum (SR) Ca^{2+} adenosine triphosphatase (ATPase)[8] is reduced in AF patients, suggesting that intracellular calcium (Ca_i) cycling is affected, and Ca_i overload and perturbations in calcium handling play important roles in AF-induced

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atrial remodeling. The focus of this chapter is to review the importance of Ca_i dynamics on the generation and maintenance of AF.

Automaticity, Triggered Activity, and Reentry

Cellular electrophysiological studies in atrial tissue have shown that abnormal automaticity and triggered activity[9] are major mechanisms that lead to atrial arrhythmias in humans. Calcium sparks have been reported to activate latent pacemaker cells in cat atrial myocytes.[10] Increased frequency of spontaneous SR Ca^{2+} release observed in AF patients may also facilitate the induction of triggered activity.[11]

Atrial fibrillation is characterized by the coexistence of multiple activation waves within the atria.[12] The mechanisms by which the multiple wave fronts occur have been actively debated for many years. The original multiple-wavelet hypothesis posits that there is a random distribution of wave fronts, and that constant generation of new wave breaks underlies the mechanism of sustained AF.[13] According to this hypothesis, AF is a self-sustaining arrhythmia independent of focal discharge. However, clinical studies over the past ten years showed that paroxysmal AF can be cured by focal ablation of the triggers in the pulmonary veins (PVs).[14] Therefore, at least some paroxysmal AF episodes are clearly dependent on focal discharge.

An alternative hypothesis to the multiple-wavelet hypothesis is the focal discharge hypothesis. For example, persistent focal discharge induced by aconitine can cause sustained atrial arrhythmias, including AF.[15,16] Alternatively, a mother rotor could also produce sustained and rapid activation that triggers and sustains AF.[17]

While most of the studies of AF focused on the atria, the potential importance of the thoracic veins in generating atrial wave fronts has also been reported.[18, 19] Haissaguerre et al.[20] reported that rapid activations in the PVs may be responsible for triggering AF. Rapid activations in the PVs are also important in AF maintenance in animal models of sustained AF.[21] The success of PV isolation for AF conversion[22,23] has further supported the importance of PV myocardial sleeves in atrial arrhythmogenesis. While it is possible that reentry is responsible for these rapid activations,[24] nonreentrant mechanisms[25] such as triggered activity or automaticity can also be responsible for these focal discharges in the thoracic veins.

Electrophysiological Remodeling and Atrial Dysfunction in Atrial Fibrillation

The presence of AF was associated with a marked shortening of the APD and a decreased rate response of atrial repolarization.[26] In the canine rapid pacing model of AF,[7] a decrease of $I_{Ca,L}$ and I_{to} has been demonstrated as the underlying factor of APD shortening. The $I_{Ca,L}$ agonist Bay-K8644 restored the action potential (AP) plateau to myocytes isolated from an atrium rapidly paced for 42 days. In spite of the decreased current density of $I_{Ca,L}$, there were no detectable changes in the voltage-dependent properties of the current. In chronic human AF, it was also reported that $I_{Ca,L}$ and I_{to} were both significantly reduced, whereas an increased steady-state outward current was detected at

test potentials between −30 and 0 mV.[27] The inward rectifier potassium current (IK_1) and the constitutively active acetylcholine-activated potassium current (IK_{ACh})[6] were increased in AF at potentials that are relevant to repolarization. These changes contribute to electrical remodeling in AF and may be important for the perpetuation of the arrhythmia.

Atrial contractile dysfunction occurs after both short-term and chronic AF.[28] The atrial dysfunction after short-term AF might be caused by increased Ca_i during the high rate of atrial activation.[28,29] Rapid successive atrial depolarizations inhibit a proper SR Ca^{2+} reuptake, resulting in elevated Ca_i, impairing the excitation–contraction coupling and contractile function. Schotten et al.[30] reported that atrial contractility was reduced by 75% after prolonged AF in humans and suggested that the principal cause of AF-induced atrial dysfunction is the downregulation or altered function of $I_{Ca,L}$ and the associated depressed calcium transient. In a subsequent study[31] using human right atrial appendage thin muscle preparations of 59 consecutive patients who received mitral valve surgery (31 in sinus rhythm, 28 in chronic AF), it was suggested that downregulation or altered function of $I_{Ca,L}$ and an increased Ca^{2+} extrusion via I_{NCX} (**sodium–calcium exchanger current**) are responsible for the depressed contractility in AF-remodeled atria.

Intracellular Calcium Overload and Atrial Fibrillation

Van Wagoner et al. studied atrial $I_{Ca,L}$ in patients with and without chronic AF.[4] Whereas $I_{Ca,L}$ was significantly reduced in the myocytes of patients with chronic AF (11 patients), half of the patients in the control group (19/38 patients) with the greatest $I_{Ca,L}$ experienced postoperative AF. As catecholamines (high sympathetic tone at postoperative setting) enhance calcium influx through $I_{Ca,L}$, it was speculated that patients suffering from postoperative AF (with greatest $I_{Ca,L}$) may be more easily subjected to atrial calcium overload. Thus, Ca_i overload may be an important factor in the initiation of AF, and the reduction of functional $I_{Ca,L}$ density in myocytes from the atria of chronic AF patients may be an adaptive response to the arrhythmia-induced Ca_i overload.

Hove-Madsen et al.[32] reported a greater number of spontaneous Ca^{2+} sparks and Ca^{2+} waves in AF patients, whereas a comparable SR Ca^{2+} content was observed in patients with and without a history of AF. Thus, direct upregulation in the SR Ca^{2+} release channels is responsible for this observation.

Defective cardiac ryanodine receptor regulation in AF patients and dogs has been reported.[33] Atrial tissue from both the dogs with AF and humans with chronic AF showed a significant increase in protein kinase A (PKA) phosphorylation of ryanodine receptor 2, with a corresponding decrease in calstabin2 binding to the channel. Channels isolated from dogs with AF exhibited increased open probability under conditions simulating diastole compared with channels from control hearts, suggesting that these channels altered by AF could predispose to a diastolic SR Ca^{2+} leak. The increased frequency of spontaneous SR Ca^{2+} release or leak observed in patients with AF is expected to enhance the induction of triggered activity[11] and activate latent pacemaker cells.[34] In the meantime, the high rate in AF can induce Ca_i overload, contributing to a further increase of spontaneous SR Ca^{2+} release.[35] With respect to the chronology of the major electrophysiological changes, Ca_i overload is

likely to be a primary factor mediating both the short-term and chronic electrophysiological remodeling associated with AF.[36]

Spontaneous Electrical Activities of the Pulmonary Veins

Pulmonary vein cardiomyocytes play an important role in AF. Brunton and Fayer[37] first demonstrated independent PV contractions in rabbit hearts in 1872. After artificial respiration was discontinued in these anesthetized animals, the PVs pulsated at a rate of 119 beats/min, but the contraction of the PVs was asynchronous to the atria. They also noted that, while both atria subsequently ceased to beat, the PVs from both lungs continued to pulsate. These seminal observations have two important implications: The PVs have contractile muscle fibers, and the PVs are capable of generating electrical activity independent of the atria.

Findings by other investigators are compatible with these results. Cheung[38, 39] demonstrated that ouabain or norepinephrine infusion could trigger the onset of repetitive rapid activities from the distal PVs of guinea pigs. These studies also demonstrated that distal PV cardiomyocytes have shorter APD and small AP amplitudes than proximal cardiomyocytes and are capable of pacemaking but are usually dominated by sinus node activity. The electrical activity in the PVs was presumed to be a result of cardiac musculature because the smooth muscle present was noted to be electrically quiescent.

Pacemaking Cells in the Pulmonary Veins

Masani[40] showed that nodelike cells are present in the myocardial layer of the PVs of rats. In the rabbit sinocaval preparation, Ito et al.[41] demonstrated spontaneous diastolic depolarizations that could lead to automatic activity. Masani used an electron microscope to examine the myocardial layer of the PVs of adult rats. Among ordinary myocardial cells resembling those of the atrial myocardium, clear cells with structural features similar to those of sinus node cells were identified. They were distributed in the intrapulmonary, preterminal portion of the PV. They appeared either singly or in small groups among the ordinary myocardial cells. The authors proposed that the nodelike cells might have potential pacemaking activity and represent an ectopic pacemaker center in the PV.

To determine if nodelike cells are present in human PVs, Perez-Lugones et al.[42] obtained PV tissues from five autopsies, including those of four individuals with a history of AF. They also obtained five transplant heart donors without history of AF. They found some myocardial cells with pale cytoplasm by light microscopy in four of the five autopsy subjects. Electron microscopy confirmed the presence of P cells, transitional cells, and Purkinje cells in the PVs of these cases.

Chou et al.[43] stained canine PVs for glycogen with periodic acid–Schiff (PAS) stains. In a dog with focal discharge, there were many PAS-positive cells clustered in groups along the endocardial side of the PV muscle sleeve (Figure 1A). The PV myocytes in the midwall and in the epicardial aspect of the muscle sleeve were PAS negative (Figure 1B). Figure 1C shows that the PAS-positive cells were larger than the PAS-negative cells and had a

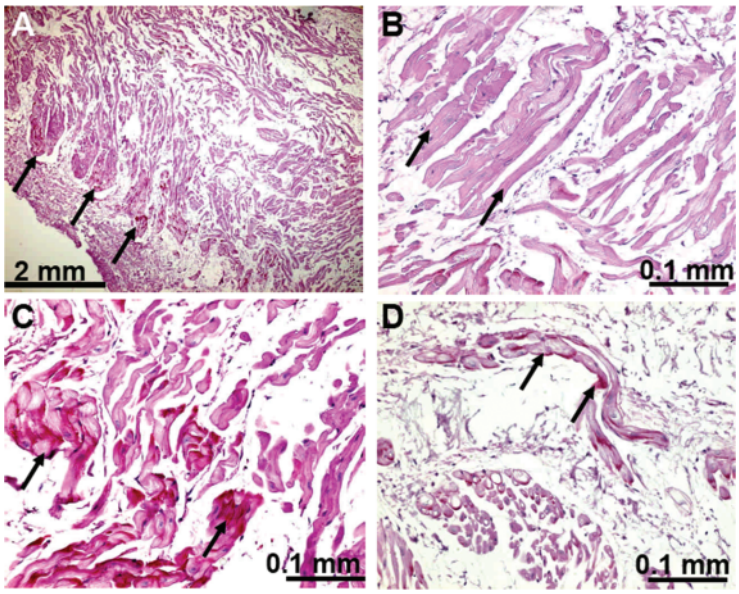

Figure 1 Results of periodic acid–Schiff (PAS0 staining in a discharging PV. **A** A low-power (×4) view of a PAS-stained slide. Clusters of PAS-positive cells (arrows) were seen on the endocardial side of the pulmonary vein (PV) muscle sleeve. The midwall and epicardial cells were mostly PAS negative. **B** PAS-negative cells (arrows) in greater detail. **C** PAS-positive cells with pale sarcoplasm. **D** PAS-positive pale cells at the PV–LA (left atrial) junction. The magnification of the objective lens was ×20 for **B–D**. (Reprinted from ref. 43 with permission.)

pale sarcoplasm. These cells are morphologically similar to the specialized conduction cells found in human patients.[42] In addition, some PAS-positive cells were identified on the endocardial aspect of the left atrium (LA) at the PV–LA junction (Figure 1D). The PV of the other dog without focal discharge contained only occasionally positive PAS cells

Cellular Electrophysiology of Pulmonary Vein Cardiomyocytes

Cellular determinants of PV electrical activity, especially the transmembrane ion currents associated with specific AP properties, have been studied with potential implications for understanding the PV electrophysiological properties in AF. Using standard glass microelectrodes, Chen el al.[44, 45] performed transmembrane potential recording of canine PVs. They reported several types of electrical activity within the PVs, including silent electrical activity, fast-response APs driven by electrical stimulation, and spontaneous fast- or slow-response APs with or without early afterdepolarizations (EADs). The incidences of APs with an EAD and of spontaneous tachycardias were much greater in dogs with chronic rapid pacing than in normal dogs.

Ehrlich et al.[46] demonstrated that PV cardiomyocytes have distinct electrophysiological properties compared to LA cells. Differences included smaller phase 0 upstroke velocity V_{max}, less negative resting potential, and shorter

APD in PVs. Ionic current differences were noted between the PV and LA cardiomyocytes, with smaller PV I_{K1} believed to contribute to the reduced PV resting potential and enhanced the development of delayed afterdepolarizations (DADs)[47] and larger I_{Kr}, $I_{Ks,}$ and smaller $I_{Ca,L}$ contributing to shorter APD. The intrinsic I_{NCX} is similar in PV and LA, and the PV and LA I_{NCX} protein expressions are similar.

Mechanisms of Focal Activities Underlying Pulmonary Vein Arrhythmogenesis of Atrial Fibrillation

With high-density (1-mm resolution) computerized mapping techniques, we have demonstrated that rapid focal activations are present in the PVs during sustained AF induced by LA pacing[25, 48, 49] and nonsustained AF in dogs with rapid right ventricle pacing-induced heart failure in vivo.[50] Arora et al.[24] first used optical mapping techniques with voltage-sensitive dye Di-4-ANEPPS for membrane potential V_m recording and showed sustained focal discharges from the endocardial surface in the presence of isoproterenol; each focus was localized near the venous ostium. With rabbit right atrial preparations, Honjo et al.[51] showed that rapid pacing and low-dose ryanodine shifted the leading pacemaker from the sinoatrial node to an ectopic focus near the right PV–LA junction. Both rapid pacing and low-concentration ryanodine can increase Ca_i, which may cause voltage-independent calcium release from SR and activate I_{NCX}. The pacing-induced activity was attenuated by either depletion of SR Ca^{2+} or blockade of the sarcolemmal I_{NCX} or Cl^- channels and potentiated by β-adrenergic stimulation. Because PV cardiomyocytes have a less-negative resting membrane potential than LA cardiomyocytes,[46] the depolarizing currents might result in triggered activity and focal discharge in the PV but not LA. It was concluded that PV myocardial sleeves have the potential to generate spontaneous activity, and such arrhythmogenic activity is uncovered by modulation of Ca_i dynamics.

Dual-Optical Mapping of Canine Pulmonary Veins

To gain further insight into the mechanisms of the nonreentrant focal discharge, we used dual-optical mapping techniques with simultaneous *V*m and Ca_i mapping in isolated canine PV–LA preparations.[43] The tissues were stained with the calcium indicator Rhod-2 AM and the voltage-sensitive dye RH237. The epifluorescence was collected simultaneously with two charge-coupled device cameras through a 715-nm long-pass filter for the *V*m image and a 580- ± 20-nm interference filter for the Ca_i image. We used low-dose ryanodine, isoproterenol, and rapid pacing to facilitate the induction of focal discharge from the PVs. Burst pacing tested the inducibility of arrhythmia, then ryanodine (0.5 μmol/l) was infused over a 15-min period. The same burst pacing protocol was then repeated with ryanodine alone. We then infused isoproterenol for 5 min and repeated burst pacing. Both spontaneous and pacing-induced arrhythmias were mapped to determine the source of the focal discharge, if any.

No focal discharge was induced at baseline. After ryanodine administration, rapid atrial pacing induced 26 episodes of focal discharge from the proximal

PVs. The cycle lengths were longer during ryanodine infusion (223 ± 52 ms) than during combined ryanodine and isoproterenol infusion (133 ± 59 ms). The major finding is that there was a rise of Ca_i preceding *V*m activation at the sites of focal discharge.

Figure 2 shows simultaneous Ca_i and *V*m mapping during left inferior PV (LIPV) focal discharge. The number below each frame is the frame number since the onset of data acquisition. The corresponding field of view of each map is shown in the top left schematics. Because there was a small angle between the two cameras, the shapes of the PV–LA preparation in Ca_i and *V*m maps look slightly different. We used registration points for spatial match. Onset of the Ca_i transient was recorded at frames 693 and 732 (white arrows, Figure 2A) preceding the earliest *V*m signal (white arrow, frames 696 and 735, Figure 2B) by three frames (12 ms). The activation then propagated toward the LA until it collided with a wave front from the LA (frame 701, Figure 2B) or encountered a line of conduction block near the LIPV–LA junction (frame 744, Figure 2B) In frame 693 of the Ca_i map, there was a region of low Ca_i (blue) above the two white arrows.

We found that a low Ca_i region often predicted subsequent fast propagation of impulses on the *V*m map. One possible reason is that a low Ca_i implies that more time has elapsed since previous activation. Because of a longer recovery time, the site with low Ca_i is less refractory. When activation propagates to a region with low Ca_i, it tends to generate a large-amplitude AP. This phenomenon can be observed in frame 697 on the *V*m map, where a large region of red color is present above the site indicated by a white arrow in frame 693 of the Ca_i map. The same phenomenon can be seen by comparing frame 735 on the Ca_i map and

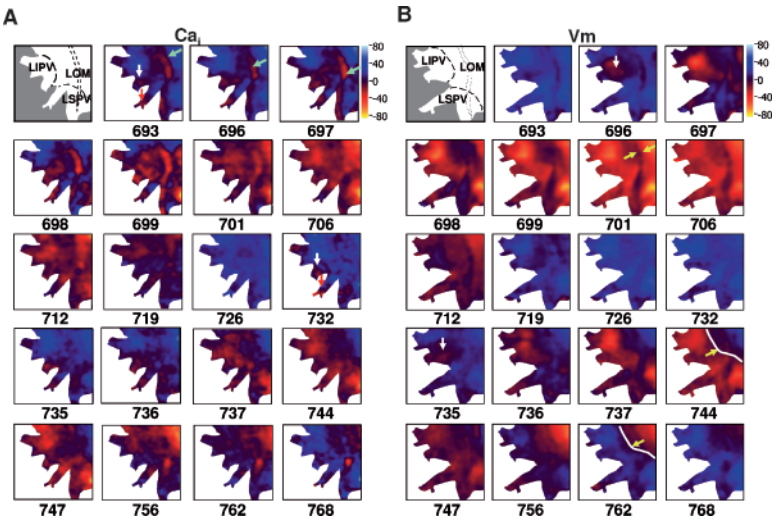

Figure 2 Dual-optical mapping of focal discharge from left inferior pulmonary vein (LIPV). The frames of intracellular Ca^{2+} (Ca_i) and voltage ratio (delta F/F) maps are shown in **A** and **B**, respectively. The number below each figure is the frame number, with the beginning of data acquisition as time 0. The time interval between the frames was 4 ms. *LOM* ligament of Marshall; *LSPV* left superior pulmonary vein. (Reprinted from ref. 43 with permission.)

frame 737 on the *V*m map. The blue region in the left upper corner of the former map predicted the subsequent large red region in the latter map.

In addition, at frames 696–699, there is a large calcium transient in panel a (green arrow) that does not seem to be accompanied by any changes in voltage. These calcium transients in fact represent the calcium transient within the ligament of Marshall (LOM) from the previous activation. The LOM often activates out of phase with the neighboring atrial myocardium because the impulse has to propagate from the atria into the coronary sinus muscle sleeve before activating the LOM. When the LOM activated later than the surrounding atrial myocardium, the calcium transient also occurred later. The three green arrows in frames 693–697 (Figure 2A) indicate the calcium transients within the LOM.

Also, the LOM does not have to activate with each AF wave front. When not activated, the LOM stayed repolarized (blue). This phenomenon can be observed in frames 706 and 712 of the *V*m map, in which a vertical blue region was present at the LOM. Yellow arrows (Figure 2B) indicate the directions of wavefront propagation, and red arrows (Figure 2A) point to a second site of calcium prefluorescence in a branch of the left superior PV (LSPV). However, the impulses did not propagate as far or as rapidly from this second site as from the site marked by the white arrows. In 6 of 12 focal discharge episodes from two dogs, there was a rise in Ca_i preceding *V*m activation (i.e., Ca_i prefluorescence) at the sites of focal discharge. The presence of Ca_i prefluorescence is compatible with voltage-independent spontaneous Ca_i release. The process by which spontaneous Ca_i release induces nondriven electrical activity is known as *reverse excitation-contraction coupling* (RECC)[52] and is responsible for inducing the triggered activity in the PVs.

A second important finding of this study is the clustering of phase singularities near the PV–LA junction, where complex myocardial fiber orientation was noted on the histological sections, that is, wave break occurred preferentially at the sites of increased anisotropy. We also showed that rapid sustained reentrant activations can induce spontaneous Ca_i release at the proximal PV, leading to PV focal discharge in the same preparation. It suggests that separating the PVs and the LA with ablation techniques or reducing the PV–LA interaction by pharmacological therapy[48, 49] may reduce the activation rate in PV, Ca_i accumulation, and triggered activity.

Late Phase 3 Early Afterdepolarization Contributing to Initiation of Atrial Fibrillation

Burashnikov and Antzelevitch[53] showed that Ca_i overload conditions present after termination of vagally mediated AF contribute to the development of late phase 3 EADs, which was suggested to be the underlying mechanism responsible for the extrasystolic activity that reinitiates AF in an acetylcholine-induced canine right atrial model. Marked APD abbreviation, rapid rate of excitation, and strong SR Ca^{2+} release were required to elicit EADs in the initiation period following termination of AF. These extrasystolic activities were eliminated by 1 μmol/l ryanodine, further supporting the underlying intracellular and SR Ca^{2+} overload mechanism to reinitiate AF. Based on the time course of contraction, the levels of Ca_i would be expected to peak during the plateau phase of AP

under normal control but during the late phase of repolarization in the presence of acetylcholine. In the latter condition, I_{NCX} and Cl^- become strongly inward currents and are able to generate late phase 3 EADs. This unique mechanism combines properties of both EADs and DADs, in which abbreviated repolarization permits "normal" rather than "spontaneous" SR Ca^{2+} release to induce an EAD-mediated closely coupled triggered response.[54]

The late phase 3 EAD mechanism has also been demonstrated in the PVs from canine PV preparations. Patterson at al.[55] reported that autonomic nerve stimulation decreased PV APD (APD_{90} = 160 ± 17 to 92 ± 24 ms; $p < 0.01$) and initiated rapid (782 ± 158 beats/min) firing from EADs in 22 of 28 PV preparations. Failure to induce arrhythmia was associated with a failure to shorten APD_{90} (151 ± 18 to 142 ± 8 ms; $p = 0.39$). Muscarinic receptor blockade (atropine: 3.2×10^{-8} mol/l) prevented APD_{90} shortening in eight of eight preparations and suppressed firing in six of eight preparations, whereas β_1-adrenergic receptor blockade (atenolol: 3.2×10^{-8} mol/l) suppressed firing in eight of eight preparations. Suppression of the calcium transient with ryanodine (10^{-5} mol/l) completely suppressed firing in six of six preparations. Inhibition of forward I_{NCX} by a transient increase in $[Ca^{+2}]_o$ completely suppressed firing in four of six preparations. The data demonstrated combined parasympathetic and sympathetic nerve stimulation triggered firing within canine PVs, and enhanced calcium transient and increased I_{NCX} may be required for arrhythmia formation.

In another study,[56] electrophysiological bases for triggered rhythms initiated by combined adrenergic–cholinergic stimulation were examined in isolated superfused canine PVs using extracellular bipolar and intracellular microelectrode recordings. Early afterdepolarizations were observed with pacing, catecholamines, and interventions increasing contractile force and I_{NCX}. With further abbreviation of the APD of PV after catecholamines plus acetylcholine, tachycardia-pause-initiated focal arrhythmias (1,132 ± 53 beats/min) were observed originating within the PV sleeves. Ryanodine and inhibition of I_{NCX} suppressed both EADs and pacing-induced firing initiated by catecholamines plus acetylcholine.

The intrinsic short APD of PV cardiomyocytes in favor of reentry has been well recognized.[57,58] From the point of late phase 3 EADs, the brief APDs of PV cardiomyocytes also provide an intrinsic vulnerability to "Ca^{2+} transient triggering" under conditions exaggerating temporal asynchrony between repolarization and the Ca^{2+} transient; that is, triggered activities could result from an inward current (I_{NCX}) activated by Ca_i overload, a circumstance favored by accelerated repolarization and enhancement/delay of the Ca^{2+} transient.[56] Thus, the I_{NCX} inhibitor may be able to reduce the PV arrhythmogenicity, especially the reinitiation of AF after its termination.

Conclusion

Intracellular Ca^{2+} dynamics are an important factor that contributes to both the initiation and the maintenance of AF. Simultaneous sympathovagal activation could increase Ca_i and shorten APD at the same time, resulting in triggered activity from the PVs[56] and initiation of AF. The maintenance of AF depends on both the triggered activity within the thoracic veins and reentrant wave

fronts in the atria and in the PVs. The reentrant wave fronts that conduct from the atria into the PVs may increase the activation rate in the PVs, hence increasing Ca_i accumulation and triggered discharges. In the meantime, the wave fronts that conduct from the PVs into the atria may add complexities to atrial activations and support further wave break and reentry. Severing the connections between the PVs from LA therefore reduces the activation rates in both chambers, decreases Ca_i accumulation, and prevents further AF. We conclude that Ca_i dynamics are important in the generation and maintenance of AF.

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9

Role of the Vagus in AF
Pathophysiology and Therapeutic Applications

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Abstract: The autonomic nervous system, especially the vagus (parasympathetic) nerve, is postulated to play an important role in the initiation and maintenance of atrial fibrillation (AF). However, the supporting experimental evidence was mostly obtained in animals without concomitant deceases, which are usually AF resistant and require vagal stimulation to induce and maintain AF. Accordingly, it is self-evident that vagal denervation would prevent or reduce AF inducibility in such a model. On the other hand, the role of the vagus in patients with AF is more circumstantial and less clear. This chapter reviews current evidence for the role of the vagus in the pathophysiology of AF, the potentials and controversies of the role of vagal denervation during AF ablation, and the possibility for utilization of vagal nerve stimulation to control the ventricular rate during AF.

Keywords: Ablation; Atrial fibrillation; Autonomic nervous system; Vagal denervation; Vagal stimulation; Vagus nerve.

Introduction

The vagus nerves, representing one of the two branches of the autonomic nervous system, play a very important role in regulating normal cardiac rhythmicity. Normally, the vagus exerts and controls the negative chronotropic and dromotropic effects on the sinus and the atrioventricular nodes, respectively. However, under certain pathophysiological conditions, enhanced vagal tone could become arrhythmogenic. It has been known for long time that electrical vagal stimulation can greatly facilitate atrial fibrillation (AF) induction and its maintenance.[1]

Atrial fibrillation is known as the most common clinically significant cardiac arrhythmia. Management of patients with AF basically involves the choice of ventricular rate control or efforts to restore and maintain sinus rhythm in addition to prevention of thromboembolism.[2] The past decade witnessed two very important advances in clinical management of AF. On the rhythm control side, catheter ablation, specifically around the pulmonary veins, has been demonstrated as effective for curing AF in many patients.

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On the rate control side, it has been established that AF rate control is not an inferior strategy compared to rhythm control and has its own merits and suitability.[2] It is interesting that the application of either of these treatment options might have mechanistic links with the vagus and its role in the arrhythmia.

Since experimental vagal stimulation has been demonstrated as proarrhythmic in AF and because clinical AF ablations are associated with a certain degree of denervation,[3–5] there is renewed interest in the role of cardiac autonomic nerves, particularly the vagus, during AF ablation. On the other hand, studies suggested that vagal stimulation could become a novel strategy to control the ventricular rate in AF when restoration of the sinus rhythm fails.[6–8] Thus, depending on the disease condition, modulation of the vagus nerve function could play an important role in either rhythm or rate control during AF.

This chapter focuses on reviewing current evidence for the role of the vagus in the pathophysiology of AF, the possible role of vagal denervation during AF ablation, and finally the novel approach of applying vagal stimulation for control of the ventricular rate during AF.

The Cardiac Autonomic Nervous System

The cardiac autonomic nervous system consists of parasympathetic (vagal) and sympathetic nerve branches. A detailed description of autonomic innervation to the heart and the extensive complex interactions between vagal and sympathetic neural functions is beyond the scope of this review. However, it is necessary to summarize some important aspects of cardiac autonomic innervation, especially the epicardial ganglia, to understand better the discussion.

Vagal innervation of the heart is carried by cranial nerve X (the vagus nerve). The axons of parasympathetic preganglionic neurons in the medulla region of the brain stem travel along the right and left vagi and synapse with postganglionic neurons in cardiac ganglia located on epicardial fat pads. These fat pads are distributed mainly between the ascending aorta and pulmonary trunk, around pulmonary veins and the superior and inferior vena cava.[9–12] From these fat pads, postganglionic neurons project to the target cells. The atria are more densely innervated by vagal nerves than the ventricles. Reports have shown that, in humans as well as in canine hearts, there are seven major ganglionated subplexuses,[11,12] among them five subplexuses innervating the atria and two innervating the ventricles (Figure 1).

In contrast to the vagal innervation, sympathetic preganglionic neurons in the spinal cord project to postganglionic neurons located outside the heart in the stellate ganglia and the caudal halves of the cervical sympathetic trunks (extrinsic cardiac nerves and ganglia), which in turn project to the heart.[13]

It should be noted that the epicardial fat pads contain mainly vagal ganglia; however, some sympathetic nerve fibers and even sympathetic neurons exist inside the fat pads. There are also afferent neurons and interconnecting local circuit neurons inside the heart.[14] Thus, the “intrinsic cardiac nerves” (nerves within the heart) constitute a much more complex network than it was originally thought. Despite this complexity, electrical stimulation of the epicardial fat pads usually evokes a predominantly vagal effect; the sympathetic nerve excitation by such stimulation can usually be demonstrated when vagal effects are blocked by atropine.[15] However, removal of the fat pads by surgery or radio-frequency (RF) ablation not only damages vagal innervation, but also affects sympathetic innervation.

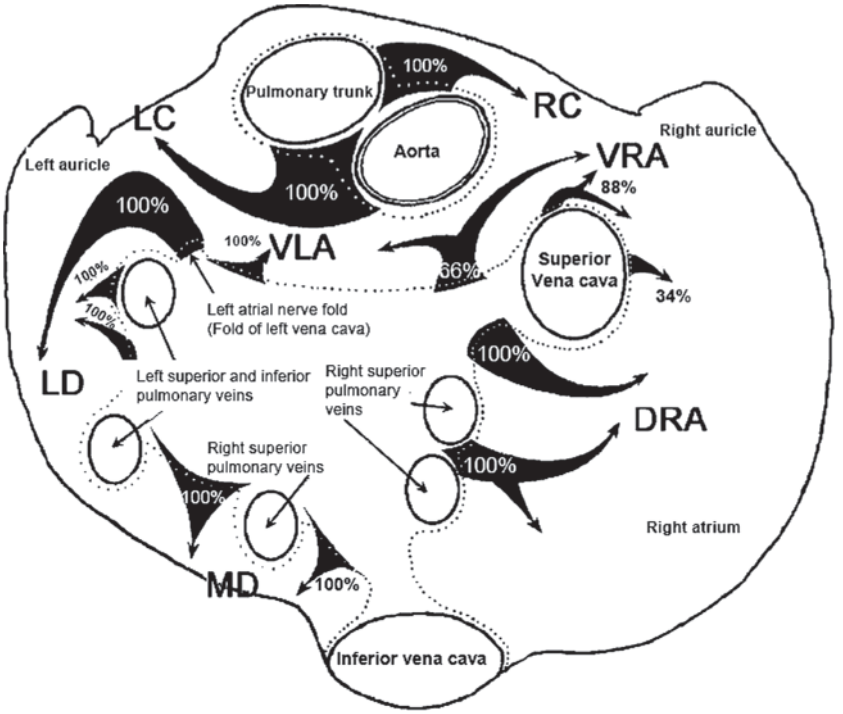

Figure 1 Schematic illustration of the location and direction of the mediastinal nerves (arrows) accessing seven epicardial ganglionated subplexuses identified by the abbreviations. Numbers indicate the percentage of the examined hearts with nerves directed into one of the seven subplexuses. *DRA* dorsal right atrial, *LC* left coronary, *LD* left dorsal, *MD* middle dorsal, *RC* right coronary, *VLA* ventral left atrial, *VRA* ventral right atrial. (Reproduced ref. 11 with permission.)

Pathophysiology of Vagal Control in Atrial Fibrillation

To initiate and maintain AF, both focal triggers and a proper substrate that can sustain fibrillatory activation are necessary. The fact that vagal stimulation can produce an arrhythmogenic substrate favoring AF is well known. The major parasympathetic neurotransmitter, acetylcholine, shortens the action potential duration of atrial myocytes.[16] It has been known for a long time that vagal stimulation dramatically shortens the atrial effective refractory period (ERP), increases its heterogeneity, and greatly augments the ability of single atrial premature beats to induce AF in dogs.[1] Vagal stimulation achieves this by shortening the atrial reentrant wavelength (the product of a substantially reduced ERP and a slightly increased conduction velocity).[17,18] The shorter atrial wavelength enhances the probability that sustained fibrillatory activation can be established in the atrial myocardium.[19]

Although both vagal and sympathetic stimulations could produce similar effects on atrial ERP and wavelength, vagal stimulation appears much more arrhythmogenic than sympathetic stimulation in promoting AF.[17] One reason could be that vagal stimulation has more potent effect on atrial ERP heterogeneity. A direct relationship has been demonstrated among the intensity of vagal stimulation, the spatial disparity of refractory periods, and the AF inducibility.[20] Because of this AF facilitation capability, vagal stimulation has been

used for decades as a common experimental tool to induce and maintain AF in animal models.[21,22] However, it is not known whether such (usually strong) vagal activation evoked by electrical stimulation is comparable with the vagal status in patients with spontaneous AF, although an incident of transient AF associated with vagus nerve stimulator implanted in a patient has been reported.[23]

While the term *vagal AF* implies a causal relationship, the clinical descriptions are usually based solely on patients' clinical characteristics and manifestation.[24,25] Vagal AF is categorized when it occurs in young patients without structural heart disease and at a time when increased vagal tone is expected, like at night, after a meal, or after exercise. In addition, there is also sympathetic AF.[24,25]

It has been thought that these AF types constitute only a small portion of the AF population. However, even in this group a direct link between autonomic fluctuations and the onset of spontaneous AF appears inconsistent.[26–29] By using heart rate variability (HRV) analysis, Bettoni and Zimmermann[26] found in 77 paroxysmal AF patients a primary increase in adrenergic tone followed by an abrupt shift toward vagal predominance immediately before AF onset. Fioranelli et al.[28] reported 36 episodes of AF in 28 patients; 50% of these episodes were associated with an increase in sympathetic drive, and the remaining 50% of the episodes were associated with an increase in parasympathetic drive.

Tomita et al.[27] studied the HRV in patients with nighttime paroxysmal AF. They found a progressive increase in both the low-frequency (LF; a sympathetic tone index) and the high-frequency (HF; a vagal tone index) components before AF onset, with no change in LF/HF ratio. In contrast, in patients with daytime paroxysmal AF, the same authors found an increase in the LF/HF ratio before the onset of AF. Other studies reported only sympathetic prevalence before AF, without parasympathetic activation even when AF occurred during sleep.[29] There is also a report that baroreflex sensitivity, but not HRV, was higher in patients with paroxysmal AF than in those without paroxysmal AF.[30] Despite these inconsistencies, however, no reports found significant sinus bradycardia or sinus arrest before AF.[26,29] This is in contrast to experimental AF induced by vagal stimulation, in which a strong vagal chronotropic response is usually sought. The Framingham Heart Study found that autonomic dysregulation at baseline as reflected by HRV was not associated with risk of AF after adjusting for potential confounders, suggesting that the link between HRV and AF is mediated by other traditional risk factors.[31]

Atrial electrophysiological remodeling induced by AF is another important factor for sustaining AF. Atrial fibrillation itself can result in remodeling by shortening atrial ERP, which in turn would perpetuate AF.[32] The current knowledge about the role of the vagus nerve in atrial electrophysiological remodeling is very limited. It has been found that vagal stimulation could actually prevent atrial remodeling in AF.[33] However, vagal stimulation might delay the process of reverse remodeling. Thus, it has been reported that goats with high vagal tone had shorter atrial ERP and attenuated atrial recovery from remodeling.[34] In line with this, another study found that parasympathetic blockade by atropine promoted faster recovery from atrial electrical remodeling induced by rapid atrial pacing in patients.[35]

Paroxysmal AF is usually triggered by premature atrial contraction,[36] and pulmonary vein foci are believed to be important in most cases.[37] There are

few reports about the direct effect of the vagus nerve on pulmonary vein triggers. Tai et al.[38] demonstrated that vagal activation could actually suppress the pulmonary vein trigger for AF. In ten patients with AF foci originating in the pulmonary veins, phenylephrine administration, which is known to evoke the vagal reflex because of an increase in blood pressure, resulted in suppression of the pulmonary vein ectopic activity. The authors hypothesized that the triggers for AF originating from the pulmonary veins might be sensitive to autonomic changes in a manner resembling the sinus node. A similar result was observed in another clinical report.[39]

However, in a canine superfused pulmonary vein–atrial preparation, stimulation of the autonomic nerves innervating the pulmonary veins decreased pulmonary vein sleeve action potential duration and initiated rapid firing from the pulmonary vein preparations,[40] presumably involving excitation of both vagal and sympathetic nerves. Atropine could prevent action potential duration shortening in all preparations as expected, and it also suppressed pulmonary vein firing in most cases.

Vagal excitation is associated with shortening of fibrillatory cycle length, suggesting that vagal excitation would enhance the driving role of pulmonary vein foci.[41] In contrast, however, it was also reported that pulmonary vein isolation had lower efficacy in patients with vagotonic paroxysmal AF than in patients with adrenergic or random episodes of paroxysmal AF, questioning the role played by the pulmonary vein region in vagotonic paroxysmal AF.[42]

The experience accumulated from AF ablation lesions used to isolate pulmonary veins[43–45] or to eliminate complex fractionated electrograms[46] deserves special attention. These lesions have general anatomical locations that coincide with the locations of epicardial fat pads in the vicinity of the pulmonary veins,[9–12,47] and high-density autonomic nerves were found near the pulmonary veins–left atrium junction.[48] Ablations around the pulmonary vein ostia diminish the left atrial response to vagal stimulation and decrease atrial vulnerability to AF induction.[49] Thus, vagal attenuation accompanying pulmonary vein isolation may contribute to suppression of AF.[3]

Fat pads also coincide with areas where complex fractionated electrograms have been recorded near the pulmonary veins, the interatrial septum, the roof of the left atrium, and the coronary sinus ostium.[46] These complex fractionated electrograms could be related to vagal innervation in the area. Vagal stimulation could result in an increase in left atrial rotor frequency, and the outer border of these HF rotors coincides with the area where fractionated activity occurs.[50–52] However, whether ablation of complex fractionated electrograms' regions produces beneficial effects because of altering of vagal function is unclear at this point. Similarly, even though ganglionic fat pads colocalize with most common triggers around the pulmonary veins, superior vena cava, inferior vena cava, and coronary sinus,[53,54] the direct link between those triggers and the vagal innervation remains obscure.

Vagal Denervation and Inducibility of Atrial Fibrillation

Because of the proarrhythmic potential of vagal nerve stimulation as just discussed, it is intuitive to speculate that blocking vagal effects by denervation would be beneficial in preventing AF. This notion is supported by experimental studies.

Chiou et al.[55] reported that most efferent vagal fibers to the atria travel through a fat pad located between the medial superior vena cava and the aortic root, superior to the right pulmonary artery. These fibers then project onto two other fat pads, one at the inferior vena cava–left atrial junction (IVC-LA, or atrioventricular [AV] nodal fat pad), the other at the junction of the right pulmonary vein and right atrium (RPV, or sinus node fat pad). Radio-frequency catheter ablation of these three fat pads eliminated major vagal innervation to the atria and prevented the inducibility of sustained AF during bilateral cervical vagal stimulation.[55]

Schauerte et al.[56]demonstrated that using transvenous catheter stimulation to identify and ablate the parasympathetic pathways that innervate the atria blunted the atrial ERP shortening, abolished the increase in atrial ERP heterogeneity during vagal nerve stimulation, and led to an increase of the baseline atrial ERP. Before RF neural ablation, AF could be induced and maintained as long as vagal stimulation was continued, whereas after ablation, AF was no longer inducible during vagal stimulation.

However, partial vagal denervation might be proarrhythmic in AF. Hirose et al.[57] reported that vagal denervation of the high right atrium was achieved using RF catheter ablation of the fat pad at the right pulmonary vein–atrial junction (RPV fat pad). Programmed stimulation was performed at each of four atrial sites to measure ERP and inducibility of AF during vagal stimulation. Ablation of the RPV fat pad increased only the high right atrium ERP during vagal stimulation. It also increased measures of refractoriness dispersion during vagal stimulation and increased the incidence of AF. The authors concluded that partial right atrial vagal denervation facilitated rather than prevented initiation of vagally mediated AF.

The clinical role of vagal denervation in the genesis of AF is similarly inconclusive. Four major left atrial ganglionated plexuses (GPs) located 1 to 2 cm outside the pulmonary vein ostia (Figure 2) have been identified in patients.[47] Unfortunately, clinical data about ablation of these ganglia (without concomitant isolation of the pulmonary vein) and its impact on AF is very limited. In a preliminary study[5] of 26 consecutive patients with persistent/chronic AF, the GPs clustered at the base of the pulmonary veins were identified by electrical stimulation through a Lasso catheter in the antrum proximal to each pulmonary vein ostium. After RF ablation of the ganglia, AF noninducibility was achieved in 23/26 patients (89%). It should be noted, however, that these ablations unavoidably created lesions to the posterior wall of the left atrium, although not enough to achieve pulmonary vein isolation. Whether the success was purely because of ablation of GPs or lesions inflicted to the posterior left atrium remains unclear because such lesions have been shown effective in treatment of AF.[46]

Limited clinical data are also available about the role of vagal denervation that accompanies ablation for isolation of the pulmonary veins. Pappone et al.[3] reported in a series of 297 patients that vagal reflexes (induced during RF application) were observed in 102 (34.3%). In addition to complete circumferential pulmonary vein isolation, the vagal reflexes were fully eliminated in 100 of the 102 patients. Interestingly, there was an apparent overlap of AF ablation lines with locations of vagal reflexes (Figure 3). After 12-month follow-up, the authors found that the success rate (free of symptomatic AF) was better in

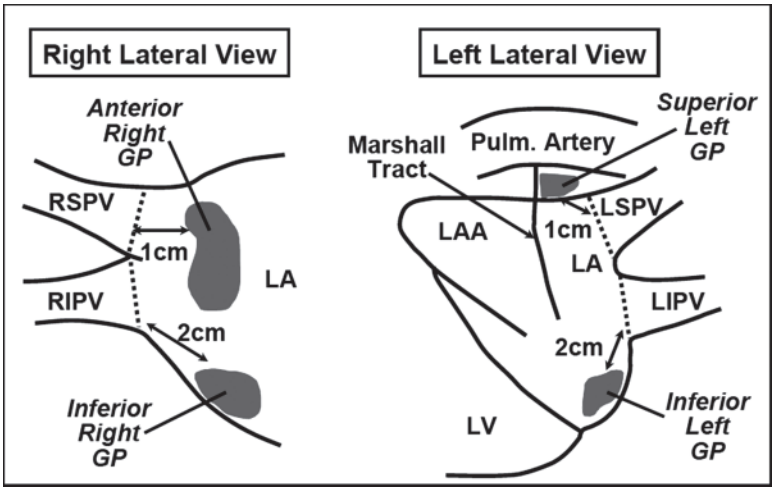

Figure 2 Schematic illustration of four major left atrial ganglionated plexuses (GPs) located within fat pads identified by high-frequency electrical stimulation. *LA* left atrium, *LAA* left atrial appendage, *LIPV* left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *LV* left ventricle, *RIPV* right inferior pulmonary vein, *RSPV* right superior pulmonary vein. (Reproduced from ref. 47 with permission.)

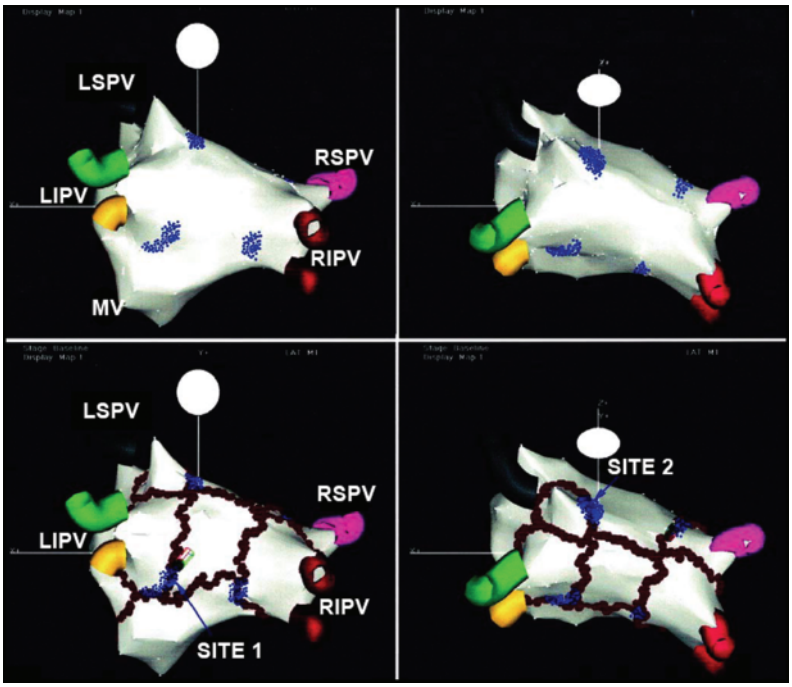

Figure 3 Three-dimensional left atrium electroanatomic maps (postero-anterior view on left and coronal postero-anterior view on right) show location and number of sites at which vagal reflexes were evoked (dots, top panels) and pulmonary vein ablation lines overlapping with common locations for vagal reflexes (dots, bottom panels). Application of radio-frequency energy at 2 separate sites (site 1 and site 2) induced transient AF, hypotension, and high-grade atrioventricular block. *LIPV* left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *MV* mitral valve, *RIPV* right inferior pulmonary vein, *RSPV* right superior pulmonary vein. (Reproduced from ref. 3 with permission.)

patients with vagal denervation (99%) compared with patients without vagal reflexes (85%).

Similar results were found in a smaller group of 60 patients.[4] In this case, left atrial GP were identified by endocardial HF electrical stimulation and were subsequently ablated in 33 patients as part of the RF application that also achieved pulmonary vein antrum isolation. Another 27 patients were treated with pulmonary vein antrum isolation alone. Testing in this small number of patients with very short follow-up suggested that adding GP ablation to PV antrum isolation may increase ablation success (absence of AF recurrence) from 70% to 91%.

These clinical reports suggested that adding vagal denervation might be beneficial during AF ablation. However, the better success rate with concomitant vagal denervation could be explained by the fact that a larger area of the left atrium was ablated.[3] In addition, it remains puzzling why using the same techniques did not evoke vagal reflexes in a majority of patients (about 66%). Moreover, in all but 5 of the 102 patients with evocable vagal reflexes, no AF was induced, and the patients remained in sinus rhythm during the entire procedure.[3]

Finally, it is unclear whether vagal denervation has long-term effects. Although vagal reflex-guided AF ablation could be associated with decreased vagal tone (reflected in the HF component of HRV), the vagal index usually recovered within 1 to 3 months after ablation.[3,58] We have also reported that, in canines, RF denervation of the sinus and AV node fat pads had only transient effect on AF inducibility.[59] It is worth noting that the cholinergic and adrenergic nerves are highly colocalized at the pulmonary vein–left atrium junction. Since it is difficult to selectively target either vagal or sympathetic nerves during ablation procedures,[48] denervation attempts would unavoidably damage some sympathetic elements as well. The resulting regional heterogeneous sympathetic denervation may increase dispersion of refractoriness and enhance vulnerability to induced AF.[60]

Vagal Denervation and Postoperative Atrial Fibrillation

Postoperative AF is a unique and important issue for patients undergoing cardiac surgery. It prolongs hospital stay and increases cost of care.[61] Initial reports suggested that cardiac denervation might be beneficial for these patients. However, the results were inconsistent. Melo et al.[62] reported that, in 426 patients undergoing low-risk coronary artery surgery, ventral cardiac denervation was performed in 207 patients, and the remaining 219 served as controls. The clinical profiles were comparable between the two groups. The additional time for the denervation was 5 ± 2 min, and there were no associated complications. Postoperative AF was present in 15 (7%) patients undergoing ventral cardiac denervation and in 56 (27%) control subjects. The authors concluded that ventral cardiac denervation significantly reduced the incidence and severity of AF after routine coronary artery bypass surgery.

These findings, however, were not confirmed by later observations. Alex and Guvendik[63] compared 70 consecutive patients who underwent coronary artery bypass grafting with 70 consecutive subsequent patients who in addition underwent ventral cardiac denervation. There was no significant difference in the incidence of AF: 34% vs 29%. Davis and Jacobs[64] reported that retention or removal of the aortic fat pad had no effect on the incidence of postoperative

AF in 320 patients after coronary artery bypass surgery. Moreover, selective and limited denervation has also been reported as proarrhythmic. The study of Cummings et al.[65] was performed on 55 patients undergoing coronary artery bypass grafting, with 26 patients randomized to anterior fat pad preservation and 29 to its dissection. Anterior fat pad functioning before and after denervation was confirmed by the ability of electrical stimulation to induce heart rate slowing. The incidence of postoperative AF in the preservation group (7%) was significantly less than that in the dissection group (37%). It was concluded that preservation of the human anterior epicardial fat pad decreases incidence of postoperative AF.

From these studies, it remains unclear whether cardiac denervation is an effective tool in prevention of postoperative AF. Notably, the degree of denervation has not been functionally or otherwise quantified in any of the available clinical reports. Even more importantly, none of the available studies provided an evaluation of the autonomic status after denervation. It is obvious that complete cardiac denervation is not feasible by removal of one or several ganglia, but the role of partial denervation in the arrhythmogenesis has been only conceptually addressed.[57]

In addition, it is not clear if and to what degree the autonomic nerves play a mechanistic role in postoperative patients. It has been reported that focal atrial activity, rather than changes in autonomic tone, usually triggered postoperative AF.[66] In fact, low vagal tone and supraventricular ectopic activity predicted AF after coronary artery bypass grafting.[67] Finally, AF occurred frequently (24% during follow-up) even in fully denervated transplanted hearts,[68] although results varied in different reports.[69] It seems therefore that the autonomic nerves might not be a major, or at least not the only, factor involved in the genesis of postoperative AF. Thus, preexisting histopathologic changes of the right atrium might play a very important role.[70]

Vagal Nerve Stimulation: A Novel Strategy for Ventricular Rate Control During Atrial Fibrillation

Ventricular rate control remains the only option in patients wit a sinus rate that cannot be restored.[2] For this purpose, vagal nerve stimulation could be a viable strategy. The negative dromotropic effect of the vagus is well known. It has been shown that the vagal neurotransmitter acetylcholine causes cellular hyperpolarization in AV nodal cells and thus prolongs the AV nodal conduction and ultimately produces AV nodal block.[71] The AV nodal area is richly supplied with vagal nerves. A high concentration of acetylcholinesterase exists particularly around the central compact nodal domain.[72] It has been discovered that the vagal innervation to the AV node is highly selective. Vagal fibers to the AV node project from a discrete epicardial ganglion (the AV nodal fat pad). The AV nodal fat pad is located at the junction between the inferior vena cava and the left atrium, at the crux of the heart.[73,74] Because of this unique arrangement of the cardiac vagal network, selective AV node vagal stimulation (AVN-VS) is possible[55,75–78] and has been demonstrated as effective in slowing the ventricular rate during AF.[79]

Use of vagal stimulation to control the ventricular rate during AF has been studied extensively. Mazgalev et al.[80] demonstrated in isolated rabbit hearts that when subthreshold postganglionic vagal stimulation was applied directly onto

the endocardial surface above the AV node, the depressive vagal effect could be maintained during simulated AF and resulted in slowing of the ventricular rate. A similar depressive effect on AV conduction can be achieved when electrical stimulation is applied to the AV node fat pad in dog hearts in situ.

Wallick et al.[79] reported that, in 11 anesthetized, open-chest dogs, selective AVN-VS through the epicardial fat pad produced slowing of the ventricular rate during AF that was associated with significant hemodynamic improvement. Zhang et al.[81] further demonstrated that, by using a feedback control algorithm, different predetermined levels of ventricular rate slowing could be achieved and maintained by this approach. Moreover, it has been demonstrated that ventricular rate slowing by selective AVN-VS was hemodynamically superior to currently used AV nodal ablation followed by regular right ventricular pacing.[82] In addition to the epicardial fat pad stimulation, vagal effects could be evoked using endocardial catheters at different locations.[7,8]

Long-term vagal stimulation to achieve rate control has been reported in chronic and conscious animals. Zhang et al.[6] established a chronic AF model in 18 dogs using high-rate right atrial pacing, and AVN-VS was applied to the epicardial AV nodal fat pad using implantable devices. It was found that AVN-VS had a consistent effect on ventricular rate slowing for up to 6 months of observation period. The vagally induced ventricular rate slowing was associated with improvement of hemodynamic responses (Figure 4). Importantly, AVN-VS therapy was well tolerated by conscious animals, causing no signs of distress or discomfort. Thus, it seems that AVN-VS could be an attractive alternative to other methods of rate control.

Selective vagal nerve stimulation has been explored clinically as well. Carlson et al.[83] reported that electrical stimulation of parasympathetic nerve fibers in a fat pad near the sinoatrial node (presumably the sinus node fat pad) affected only the sinus rate without affecting AV nodal conduction. Keim et al.[84] applied subthreshold burst stimulation on the endocardial surface of the AV node during clinical electrophysiological studies and reported stimulation-induced AV nodal conduction delay, which prolonged with increasing current strength. The observed effect was fully reversed by atropine, consistent with postganglionic vagal nerve stimulation and release of acetylcholine.

Quan et al.[85] identified optimal sites for stimulation of efferent parasympathetic nerve fibers to the human AV node via an endocardial catheter (from the proximal coronary sinus as well as from the posteroseptal right atrium) and investigated the synergistic interaction between digoxin and vagal activation at the end organ. Again, Quan et al.[86] provided identification of a functional human AV node fat pad and stimulated this structure during cardiac surgery, producing complete heart block but no change in the sinus rate.

Schauerte et al.[8] reported interesting data in 25 patients; it confirmed that human vagal efferent nerve stimulation induces reversible negative chronotropic and dromotropic effects. Vagal nerves were stimulated via a multipolar electrode catheter placed in the superior vena cava or the coronary sinus. A significant sinus rate decrease and strong dromotropic effects were achieved during these procedures. The results from this study[8] indicated that autonomic modification of the AV nodal transmission may serve as an adjunctive tool for the diagnosis/treatment of supraventricular tachycardias and may be beneficial for ventricular rate slowing during tachycardic AF in patients with congestive heart failure.

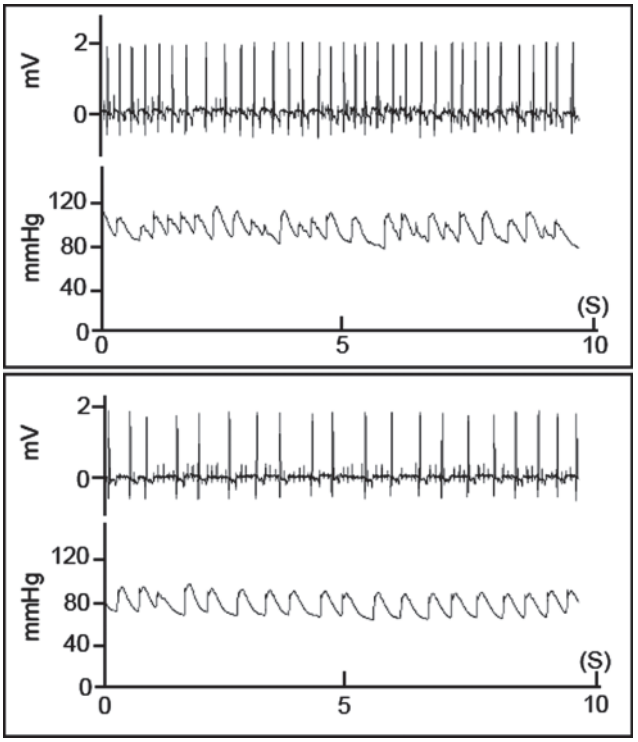

Figure 4 Electrograms and blood pressure tracings recorded by a telemetric device from a conscious dog receiving chronic atrioventricular nodal vagal stimulation (AVN-VS) during atrial fibrillation. The top panel shows tracings taken when the AVN-VS was temporarily turned off, and the bottom panel shows tracings taken when the AVN-VS was on. Note that AVN-VS decreased the ventricular rate from 205 beats/min (top panel) to 122 beats/min (bottom panel), which was associated with more stable blood pressure readings. (Reproduced from ref. 6 with permission.)

These clinical studies, along with the rich body of experimental knowledge accumulated during the last 5–10 years, suggest that vagal nerve stimulation could be a novel technology for modulation of AV node transmission. This approach may offer transient or longer-term control of the ventricular rate in certain populations of patients with AF and warrants further investigation.

Conclusion

The role of the vagus nerve in AF initiation and maintenance is largely based on experimental studies in normal animals. These animals are usually AF resistant, and to induce and maintain AF, concomitant vagal stimulation is necessary. Therefore, it seems self-evident that vagal denervation would prevent or reduce AF inducibility in such a model. However, the role of the vagus nerve in AF patients is less clear. Thus far, the evidence supporting the role of vagal denervation in AF ablation is only circumstantial. Atrial fibrillation ablation, in particular around the pulmonary veins, unavoidably causes a certain degree of vagal denervation. Similarly, primary vagal denervation targeting epicardial ganglia would inflict some damage to the atria. Thus, there is a dilemma about which procedure, the atrial structural remodeling or the

denervation, causes the subsequently observed effects on arrhythmogenesis. This dilemma will undoubtedly stimulate experimental efforts to solve the puzzle. Clinically, it would be useful to propose a simple trial and determine the effect of vagal blockade by atropine on paroxysmal AF.

If vagal denervation proves beneficial for curing AF, many questions still would remain to be answered: How much vagal denervation is needed to achieve AF cure? What is the best way to achieve vagal denervation? Would reinnervation occur, and would it lead to AF recurrence?

While vagal denervation carries the risk of irreversible neural damage, vagal stimulation might be a much easier and more practical approach under certain conditions. Current evidence indicates that vagal stimulation is a promising alternative for ventricular rate control during AF when rhythm control is not feasible. Nevertheless, further human studies are needed before this novel technology could become a clinical option.

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Atrial Fibrillation Genetic Considerations: The Basic Scientist's Perspective

Qing K. Wang

Abstract: Common atrial fibrillation (AF) is a complex disease, and its pathogenesis involves multiple genetic factors, environmental factors, and interactions among these factors. Genetic factors clearly contribute to the risk of common AF. Parental AF increases by more than threefold the risk of AF under age of 75 years in offspring, and first-degree relatives have almost fivefold more risk of developing AF before the age of 60 years. Candidate gene case–control studies investigated the roles of several genes in common AF and thromboembolism in AF, including *KCNE1, KCNE4, KCNE5, GNB3, AGT, CETP, coagulation factor II, α-fibrinogen, factor XIII*, and *IL6*. Genomewide single nucleotide polymorphism association studies is the state-of-the art study design for dissecting the common complex AF trait and have successfully identified two SNPs on chromosome 4q25 that are associated with risk of atrial fibrillation. Rare families with AF have been reported, and studies of these families identified mutations in several genes for AF, including *KCNQ1, KCNE2, KCNE3*, and *KCNJ2*. Two autosomal dominant AF genes were mapped to chromosome 10q and 6q, and one autosomal recessive gene for AF was mapped to 5p, but these genes have not yet been identified. Also, AF can occur in patients with dilated cardiomyopathy with *SCN5A* and *LMNA* mutations, long QT syndrome patients with an *ankyrin-B* mutation, and short QT syndrome patients with a *KCNH2* mutation. Genetic studies of AF will continue to provide insight into molecular mechanisms for the pathogenesis of AF and will facilitate realization of genetic testing and genotype-based therapies (personalized medicine) for AF patients.

Keywords: Atrial fibrillation; Case-control association study; Genetics; Linkage analysis; Mutation.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia associated with increased mortality and substantial morbidity. Genetic studies of other types of cardiac arrhythmias, mainly long QT syndrome (LQTS) and Brugada

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syndrome (BrS), have driven the realization of personalized medicine, known as the right drug/therapy for the right patients, in this specific medical field. To date, disease-causing genes have been identified for an estimated 50% to 75% of LQTS and 25% of BrS cases. The genes identified for LQTS include potassium channel genes *KCNQ1* (LQT1),[1] *KCNH2* (LQT2),[2] *KCNE1* (LQT5),[3,4] and *KCNE2* (LQT6)[5] and the cardiac sodium channel gene *SCN5A* (LQT3).[6,7] Mutations were also identified in LQTS patients and were associated with other diseases in genes, including a structural ankyrin gene *ANK2* (LQT4, sick sinus syndrome with bradycardia); a potassium channel gene *KCNJ2* (LQT7, Anderson syndrome); a calcium channel gene *CACNA1C* (LQT8, Timothy syndrome); and a potassium channel gene *HCN4* (LQT9, sick sinus syndrome).[8] The LQTS mutations in *SCN5A* are gain-of-function mutations, whereas loss-of-function mutations in *SCN5A* cause BrS.[9] More than 90% of genotyped LQTS patients belong to LQT1, LQT2, and LQT3 types, and genotype–phenotype correlation was well defined in these three types of LQTS.

Commercial genetic testing called Familion is now available for LQTS and BrS patients (http://www.familion.com/). The testing results have a direct impact on treatment options for individual patients. The LQT1 patients respond to β-blockade, LQT2 patients respond to β-blockade and elevated serum potassium levels, and LQT3 patients respond to sodium channel blockers.[10] Symptomatic LQTS and BrS patients (*SCN5A* positive) may be managed with implantation of ICDs (implantable cardioverter-defibrillators).[10,11]

Genetic studies of AF have made some progress, but much remains to be done. This chapter reviews recent advances and discusses future perspectives in the field of AF genetics. We are optimistic that, in the future, personalized medicine will be a reality for AF patients as it is for LQTS and BrS patients.

Genetic Component of Atrial Fibrillation

Studies have clearly demonstrated that genetic factors contribute to the development of AF. Familial forms of AF were reported but were very rare. The AF in these large families is inherited in a Mendelian fashion. Two forms of inherited AF have been reported, autosomal dominant and autosomal recessive forms. Large families with autosomal dominant AF have been reported,[12,13] but autosomal recessive AF has been reported in only one family to date.[14] Simplex cases of AF are common in clinical practice. Some simplex cases may represent autosomal recessive AF, but most of them may simply be sporadic AF. No X-linked AF has been reported.

The common form of AF is most likely to be a complex disease, which is believed to be caused by multiple genetic factors, environmental factors, and interactions among these factors. Indeed, many risk factors have been identified for AF, including advanced age, male gender, valvular heart disease, coronary artery disease, hypertension, heart failure, left ventricular dysfunction, hyperthyroidism, and diabetes.[14] Studies showed that there was a genetic component in the common form of AF. Fox et al. reported the first population-based study to estimate heritability of AF and found the odds ratios (ORs) for the parent–offspring pair based on a prospective cohort of 2,234 offspring involved in the Framingham Heart Study.[15] Seventy of the offspring developed AF during follow-up.[15] Atrial fibrillation in at least one parent significantly increased the risk of AF in offspring, with an OR

of 1.85, which increased to 3.23 with study participants younger than 75 years or to 3.17 when offspring with overt heart disease were excluded.[15] Interestingly, maternal AF was a stronger risk factor than paternal AF. These results demonstrate that there is a genetic predisposition to AF, and parental AF increases the risk of AF in offspring.

The second population study to examine the heritability of AF was carried out in Iceland by Arnar et al.[16] The risk ratios (RRs) of AF were estimated based on studies of 5,269 AF patients and 10,000 controls (RR is defined as the risk of AF in the relatives divided by the risk in the general population). Familial aggregation was demonstrated. The RRs for the first-degree through fifth-degree relatives were 1.77, 1.36, 1.18, 1.10, and 1.05, respectively. Although these RRs are statistically significant values, the risk of AF is very small for the third-degree to fifth-degree relative (RR < 1.18). Interestingly, the RR for first-degree relatives increased to 4.67 in study subjects under the age of 60 years, indicating that the first-degree relatives of AF patients have an almost fivefold higher risk to have AF than the general population. The RRs for second-degree through fifth-degree relatives in subjects under 60 years were 2.13, 1.34, 1.35, and 1.02, respectively. The risk of AF disappeared for the fifth-degree relatives.

Ellinor et al. studied 110 patients with lone AF (AF without structural heart disease). The RRs were very high, 8.1 for sons, 9.5 for daughters, 70 for brothers, 34 for sisters, 4 for mothers, and 2 for fathers.[17] Because the population used for this study was an ascertained population for genetic studies (not random), selection bias may have augmented the RRs, and precaution should be taken to extrapolate the findings from this study to the general population of AF.

In summary, the studies discussed demonstrated that AF has substantial familial aggregation and strong heritability, indicating that there are genetic variants that predispose to the risk of common AF.

Classification of Atrial Fibrillation Genes: Disease-Causing Genes, Susceptibility Genes, and Disease-Linked Genes

We can classify the genes that are associated with AF into three major categories: disease causing, susceptibility, and disease linked. Disease-causing genes are referred to as the genes with mutations that are directly responsible for the pathogenesis of disease, most often single-gene disorders.[18] In this case, the mutations are clearly defined as the primary cause of the disease. For example, *KCNQ1* mutations cause LQTS,[2,7] and *SCN5A* mutations cause BrS.[9] Disease-causing genes for AF are discussed in detail in a separate section.

Susceptibility genes are more often related to common complex disease traits (e.g., the common form of AF). Variants or single-nucleotide polymorphisms (SNPs) in these genes increase the risk for development of disease and may or may not cause the disease in the context of other genetic and environmental factors.[18] The susceptibility genes are commonly identified by a case–control association study showing significantly different allelic or genotypic frequencies of SNPs between control and patient populations. Susceptibility genes for AF are discussed in a separate section.

Disease-linked genes are referred to as the genes with expression or function that is linked to the disease by molecular biology studies or microarray or proteomic analyses.[18] Northern blot, Western blot, reverse tran-

scriptase polymerase chain reaction (RT-PCR), and other molecular biological techniques can be used to identify candidate genes with expression that differs between AF patients and controls. Examples include genes encoding heat shock proteins *HSP10, HSP60*, and *HSP70*[19] and *sarcolipin* (a homologue of phospholamban). At least five studies reported oligonucleotide microarray analysis for profiling expression of thousands of genes from AF tissues and non-AF tissues,[20–24] and two complementary DNA (cDNA) microarray studies were also reported for studying AF.[25,26] Each study identified many genes with expression that is associated with AF; however, the relationship of these genes to the disease as a cause or a consequence was not established. Furthermore, each study identified a different set of genes associated with AF. The main problem may be related to the small number of samples used in each study. Future studies with an expanded sample size (e.g., hundreds of patients and controls) may eventually identify a common set of genes with expression that is truly associated with AF (signature pattern). Some of these genes may serve as excellent biomarkers for the disease.

Disease-Causing Genes for Atrial Fibrillation

Disease-causing genes are discussed in detail in Chapter 6. In brief, a gain-of-function mutation (S140G) in *KCNQ1* was associated with autosomal dominant AF in a Chinese family.[27] More than 50% of the affected members (9/16) in the family are also affected with LQTS, which is caused by loss-of-function or dominant-negative mutations in the *KCNQ1* gene.[1] Another gain-of-function *KCNQ1* mutation, V141M, was identified in a patient with both AF and short QT syndrome.[28] A heterozygous mutation R27C of *KCNE2* was identified in two AF patients.[29] Mutation R27C did not affect KCNH2–KCNE2 I_{Kr} (rapid delayed rectifier potassium current) current, but it had a gain-of-function effect on the KCNQ1–KCNE2 potassium current. The mutation did not alter the functions of the hyperpolarization-activated cyclic nucleotide-gated (HCN) potassium channel family either.

Mutation R53H in *KCNE3* was identified in three patients in a very small Chinese family with AF (note that a 40-year-old normal family member also carried the mutations).[30] A mutation in *KCNJ2*, V93I, was identified in three patients carrying the mutation, as well as two other normal family members aged 42 and 33 years, in one Chinese family.[31] Although the V93I mutation increased inward potassium current at –90 to –80 mV and outward potassium current at –60 to –40 mV, the hypothesis that *KCNJ2* mutations cause AF needs to be further tested considering the minor change from a valine to isoleucine and the finding that two normal family members also carried the V93I mutation.

These studies suggest that mutations in ion channels can cause AF. Interestingly, some mutations in non-ion channel genes are also associated with AF in the context of other diseases. Mutations in the lamin A/C gene (*LMNA*) were identified in families with both dilated cardiomyopahty and AF.[32] A mutation in the *ankyrin-B* gene was identified in a family with LQT4, sick sinus syndrome with bradycardia, and AF.[33] Mutations in *SCN5A* were identified in families with both dilated cardiomyopathy and AF.[34] A mutation in *KCNH2*, N588K, was identified in a small family with both short QT syndrome and AF.[35]

Two genetic loci for autosomal dominant AF have been mapped to chromosome 10q22–24,[12] and 6q14–16[13]; however, the specific genes have not been identified yet.

Atrial fibrillation can also inherit as an autosomal recessive trait.[14] The first autosomal recessive AF gene has been mapped to 5p13,[14] but the specific gene remains to be identified.

Susceptibility Genes for Atrial Fibrillation

The most frequently used method for identifying the susceptibility genes for a common complex disease is the candidate gene case–control association studies. In this study design, a candidate gene is selected based on its potential involvement in the disease.[18,36] Single-nucleotide polymorphisms (SNPs) are identified in the candidate gene by searching the HapMap database (www.hapmap.org) and literature or by direct DNA sequence analysis of a panel of patients. The SNPs are genotyped in a group of patients (cases) and matched controls, and the frequencies of SNP alleles or genotypes are then analyzed by a χ^2 test or a Fisher exact test. An allele or genotype is associated with the disease if its occurrence in the cases is significantly different from that in the controls. Several case–control studies were reported for AF, and are summarized next.

Ion Channel Genes

In a Chinese population in Taiwan, Lai et al. showed a significant association between the *KCNE1* SNP G38S and AF.[37] The 38G allele increased the risk of AF, with an OR of 2.16 in heterozygotes and 3.58 in homozygotes. The functional effect of this SNP was reported.[38] The 38G allele reduced the I_{Ks} (slow delayed rectifier potassium current) potassium current, which is consistent with a finding that *KCNE1* null mice developed AF.[39] However, this result contradicts the finding that the gain-of-function mutations in *KCNQ1* were associated with AF in the familial form of AF.[27] Further studies are needed to clarify the discrepancy. Of note is that *KCNE1* SNP G38S was not associated with AF in a different Chinese population from mainland China.[40]

Other members of the *KCNE* potassium channel subunit genes were also investigated for their association with AF. The SNP E145D in the *KCNE4* gene was associated with AF in a Chinese population (OR = 1.66, $p = 0.044$).[40] The SNP T97C in *KCNE5* was associated with AF in a population from Denmark.[41] The 97T allele was associated with a reduced risk of AF, with an OR of 0.52.

G-Protein Gene

Schreieck et al. showed that the C825T SNP in the G-protein β3 subunit gene (*GNB3*) was significantly associated with AF in a German population.[42] The TT genotype plays a protective role in AF, with an OR of 0.46 ($p = 0.02$).

Genes in the Renin–Angiotensin System

In a Chinese population in Taiwan, Tsai et al. reported that three SNPs (M235T, G-6A, and G-217A) in the angiotensinogen (*AGT*) gene were associated with risk of AF, with ORs ranging from 2.0 to 3.3, but the insertion/deletion polymorphism in the angiotensin I-converting enzyme (*ACE*) gene and the A1166C polymorphism of the angiotensin II type I receptor gene (AT_1R) were not associated with risk of AF.[43] The study implicates involvement of the renin–angiotensin system in the pathogenesis of AF. In a different study

in Japanese patients with hypertrophic cardiomyopathy, the insertion/insertion (I/I) genotype of the (*ACE*) gene was a significant risk factor for AF.[44,45] The earlier study was supported by a report showing that the expression of *ACE* was threefold increased during chronic persistent AF.[46] Furthermore, in a population from the Netherlands, the *ACE* insertion/deletion polymorphism did not show any significant risk of AF.[47]

Gene in Lipid Metabolism

The *CETP* gene encodes the cholesteryl ester transfer protein that enables the transfer of cholesteryl esters from high-density lipoprotein (HDL) to low-density lipoprotein (LDL), which lowers HDL cholesterol. The TaqIB SNP in *CETP* was associated with AF in a cohort from the Netherlands (OR = 0.35, $p = 0.008$).[47]

Genes Involved in Thrombosis and Hemostasis

Because AF is associated with increased risk of stroke and thromboembolic events in AF, several candidate genes involved in thrombosis were analyzed for their association with AF. Factor V Leiden is a SNP in the coagulation factor V gene, R506Q, that produces a resistance to degradation by activated protein C and increases the risk of venous thrombosis. Factor V Leiden was not associated with the risk of AF or with the risk of left atrial thrombus formation in a Japanese population.[48] In a large U.S. population with 13,559 adult patients with nonvalvular AF, factor V Leiden was not significantly associated with risk of stroke in AF.[49] In a study with 1,531 participants involved in the Stroke Prevention in Atrial Fibrillation III Study (SPAFIII), the factor V Leiden SNP and levels of prothrombin fragment F1.2 (F1.2), β-thromboglobulin (BTG), and fibrinogen were not associated with thromboembolism in AF.[50] This finding was confirmed in two independent Italian populations.[51,52]

Factor II is another coagulation factor and a leading risk factor for venous thrombosis. Pengo et al. showed that SNP G20210A in the *factor II* gene was associated with systemic thromboembolism (OR = 3.0, $p < 0.05$).[51] Poli et al. showed that the same SNP was associated with AF (OR = 2.4, $p < 0.05$) but not with cerebral or peripheral embolic events in AF.[52] Hatzinikolaou-Kotsakou et al.[53] showed that both factor II SNP G20210A and factor V Leiden were associated with AF, with ORs of 4.9 and 4.6, respectively, but the study population was small (55 patients and 17 controls).

The T312A SNP in the *α-fibrinogen* gene was associated with poststroke mortality in a U.K. AF population.[54] In patients with AF, individuals with the A allele showed decreased survival, whereas in the normal population, it did not affect the survival. SNP T312A is close to the FXIIIa crosslinking site at A328. A common SNP in *factor XIII*, V34L, was associated with rapid FXIII activation but was not associated with AF.[55] However, patients with allele 34L showed higher plasma levels of *IL6*, which may induce a prothrombotic state in AF patients.[55] Patients with AF had higher blood levels of IL6 and fibrinogen after surgery, and the –174G/C SNP in the promoter of *IL6* was associated with postoperative AF (GG genotype, OR = 3.25, $p = 0.006$).[56]

It is important to note that the results from the case–control association studies should be interpreted with caution as many of these studies are compounded by the selection bias of cases and controls, population admixture, imperfect matching of cases with controls, phenotyping errors, and small sample sizes.

Genomewide Single Nucleotide Polymorphism Association Studies

To date, case–control association studies for AF have been limited to candidate genes. Recent technological advances in high-throughput genotyping of SNPs have driven down the costs to perform genomewide case–control association studies and make genomewide SNP association studies practical reality. The genomewide association study has the advantage of identifying novel genes associated with AF. More than 50,000 SNPs are required to provide the genome coverage, and a p value less than 5×10^{-7} was proposed to be the cutoff value for achieving significance (80% power).[57]

On average, sequence variants occur every 1,000 bp in the human genome,[58] and approximately 90% of sequence variants are SNPs.[59] Over 5 million SNPs have already been reported[60] and can be identified at the National Center for Biotechnology Information (NCBI) database and the HapMap database (http://www.hapmap.org/). High-throughput genotyping technologies have been developed for genomewide SNP genotyping, and an example is Affymetrix microarrays, with 500,000 SNPs. Successful genomewide SNP association studies were reported for age-related macular degeneration (the complement factor H gene),[61] type 1 diabetes (the innate immunity viral RNA receptor gene region),[62] and the QT interval trait (the NOS1 regulator *NOS1AP*).[63] In July, 2007, Gudbjartsson et al. reported the results from a genome-wide SNP association study for 550 patients with atrial fibrillation and 4,476 controls from Iceland.[64] Genotyping was carried out using the Illumina Hap300 Beadchip with 316, 515 SNPs. A strong association was identified between two SNPs on chromosome 4q25 and atrial fibrillation.[64] The result was replicated in three other European populations and a Chinese population from Hong Kong.[64] However, the SNPs were not located in any know or putative gene, thus, the specific gene at the locus was not identified.

Future Perspectives

In the next 5 to 10 years, the field of genetics of AF will witness advances in the following research areas:

1. Genetic studies of rare large families will continue to provide important insights into the pathophysiological mechanisms of AF. In particular, identification of novel non-ion channel genes will be critical to pinpoint other signaling pathways involved in AF.
2. Genomewide SNP association studies will be a new innovative tool to identify many susceptibility genes for AF.
3. Candidate gene case–control association studies will continue to identify some susceptibility genes for AF.
4. Molecular characterization of disease-causing genes, susceptibility genes, and disease-linked genes for AF using a variety of technologies, including transgenic/knockout/knockin mouse models, will provide insight regarding the pathogenesis of AF.
5. Genotype–phenotype correlation studies will lead to genotype-specific therapy (personalized medicine) in AF and move the basic scientific findings to the clinic.

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Section III

Medical Treatment in Atrial Fibrillation

11

Review of Recent Trials of Medical Therapy for Atrial Fibrillation

Carlo Stuglin and D. George Wyse

Abstract: Medical therapy remains the mainstay for treatment of most patients with atrial fibrillation (AF). The three aspects of such therapy for AF are rhythm management, antithrombotic therapy, and so-called upstream therapies. This chapter reviews rhythm management and upstream therapies. Rate control refers to control of the ventricular rate during AF without any specific attempt to restore or maintain sinus rhythm. Rhythm control refers to restoring and maintaining sinus rhythm. Upstream therapy refers to drug treatments not usually considered antiarrhythmic but that help to maintain sinus rhythm. Trials of drug therapy in these categories are reviewed as are trials comparing pharmacological rate control to pharmacological rhythm control. Antiarrhythmic drugs in particular have limited efficacy and a number of unattractive adverse effects. Thus, there tends to be an advantage to the rate control approach for many patients. However, limitations of pharmacological approaches have been a major impetus to the development of nonpharmacological therapies

Keywords: Atrial fibrillation; Antiarrhythmic drugs; Medical therapy; Pharmacological rate control; Pharmacological rhythm control; Upstream therapies.

Introduction

Atrial fibrillation (AF) is the most prevalent sustained tachyarrhythmia. Since apothecaries offered digitalis plant extracts more than 200 years ago, it has been a struggle to find a highly efficacious, nontoxic, safe, and easily used medical treatment for rhythm management of AF. In earlier times, rhythm management of AF aimed at controlling symptoms and eliminating other consequences that resulted from the inappropriately rapid and irregular ventricular rate usually associated with it (rate control). With the discovery and development of antiarrhythmic drugs in the latter half of the last century, there was great optimism for restoration and maintenance of sinus rhythm (SR; rhythm control) as primary rhythm management. The subsequent identification of issues such as thromboembolic risk, cardiac remodeling, different

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clinical subsets of AF, epidemiology, the complex and incompletely understood pathophysiology of AF, and several other factors has led to the current bewilderingly complex therapeutic armamentarium used to treat AF. Included in this armamentarium is a long list of variably effective pharmaceutical options for rhythm management, both rate and rhythm control.

The failure of antiarrhythmic drug treatment to match the optimism for it 30 to 40 years ago has led to a reevaluation of some of our most fundamental concepts about rhythm management of AF. New modalities of therapy for rhythm management have emerged. Yet, drug therapy has not been a total failure. Medical therapy for rhythm management remains an important part of the treatment of AF for the majority of patients who suffer from it. Antithrombotic therapy for AF, although an important part of the medical treatment of AF, is not reviewed here. The focus of the present discussion is review of the medical therapies for rhythm management of AF, with emphasis on recent trial data.

Trials of Pharmacological Rate Control

Heart Rate Control—What Is it?

The control of ventricular rate (rate control) during AF is broadly defined as prevention of inappropriately rapid and irregular ventricular rates during AF without making any specific attempt to restore and maintain SR. Of course, restoring SR also accomplishes such a goal, but that is not what is under discussion here. More specific goals given for heart rate control tend to be quite arbitrary because, for the most part, they are not based on an abundance of scientifically sound experimental information.

Rate control in AF has three targets: control of the heart rate at rest, control of the heart rate during activity, and regularization of the heart rate. Some aspects of these targets have been recently reviewed.[1] Pharmacological rate control can be reasonably effective with respect to the first two targets but less so in the case of the third target. Pharmacological heart rate control is much more difficult in the case of atrial flutter (AFL) in comparison to AF or when AFL and AF coexist.

AFFIRM[2] (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and RACE[3] (Rate Control vs Electrical Cardioversion for Persistent Atrial Fibrillation), the two largest AF trials utilizing a rate control arm in their design, had very different heart rate targets: 80 beats/min or less at rest and 110 beats/min or less with mild activity in the former and simply 100 beats/min or less at rest in the latter. Strict vs more lenient rate control targets were assessed in a post hoc analysis of the AFFIRM and RACE rate control arms.[4] There was an average 7 beats/min lower heart rate in the AFFIRM patients (76.1 vs 83.4 beats/min), which did not translate into any difference in the rate of occurrence of the primary outcome (death, cardiovascular hospitalization, or myocardial infarction [MI]) or individual endpoints of the composite. However, when compared to a subset of patients who did not achieve even the more lenient RACE targets, achieving heart rate targets was associated with a decrease in the primary endpoint. AFFIRM patients, with stricter heart rate targets, had a higher rate of pacemaker implantations. These data would suggest that a more lenient heart rate target may be as effective as a stricter target, may be easier to achieve, and would

spare atrioventricular (AV) junction ablations and pacemaker implantations in a significant minority of patients with difficult-to-control heart rate. This finding awaits confirmation from prospective randomized studies before firm recommendations can be made.

Heart Rate Control—Review of the Trials

The trial data evaluating the efficacy of various agents for the rate control of AF were largely published in the mid-1980s to mid-1990s. The studies tend to have fewer than 50 subjects, and several had fewer than 10 subjects enrolled. Fortunately, there were many studies, such that the overall number of subjects studied across various drug regimens allows some reasonable conclusions to be drawn.

Segal et al. reviewed 45 articles evaluating 17 drugs.[5] This review was subsequently updated by Tamariz and Bass[6] with new literature published up to May 2003. A summary of pharmacological agents commonly used for rate control in AF is provided in Table 1.

Acutely, intravenous digoxin can control the ventricular rate once a full loading digitalization dose is given, but this can take several hours. With chronic oral use, its efficacy is observed only for resting heart rate, but it fails to control heart rate with activity.

When diltiazem or verapamil alone are compared to a combination with digoxin, higher doses of these agents can achieve heart rate control similar to that of the combination, and these agents have a better effect on activity heart rates than digoxin alone. Both diltiazem and verapamil have a rapid onset of action when given intravenously for acute rate control. Diltiazem and verapamil should be used with caution in the setting of depressed systolic function or hypotension as both may be exacerbated.

The β-blockers as a group are probably best at controlling heart rate with activity. Trials using atenolol, metoprolol, pindolol, and nadolol were all effective at controlling heart rates at rest and with exertion. Newer β-blockers like carvedilol have only been evaluated in small and uncontrolled studies, although there is evidence of efficacy for reducing heart rate at rest and with exertion in the setting of congestive heart failure (CHF).[7] Excess β-blockade is associated with reduced exercise capacity.

Sotalol, amiodarone, propafenone, and flecainide have been evaluated for heart rate control in various trials, although that is not their primary action. Sotalol controls heart rate in AF at rest and with exertion, but because of its proarrhythmic effect (QT prolongation and torsades de pointes ventricular tachycardia [VT]), it offers little advantage over simpler β-blockers when the goal is simple heart rate control. Propafenone and flecainide have weak efficacy for heart rate control. Their potential side effect profiles make them unattractive for simple rate control in AF. Amiodarone is used in special circumstances (see Table 1) or is sometimes added in low doses as a second or third drug when rate control is difficult to achieve with β-blockers, digoxin, or diltiazem and verapamil. Atrioventricular junction ablation and a pacemaker probably offer a better alternative, however.

Since 2003, there have been scant new trial data concerning rate control of AF. Post hoc analysis of the AFFIRM trial[8] evaluated use of rate control medications in its rate control arm. Most patients achieved adequate heart rate control, with β-blockers most efficacious (70%), followed by digoxin alone

Table 1 Intravenous and orally administered pharmacological agents for rate control of atrial fibrillation (modified from ref. 65).

Drug	Route	Loading dose	Onset	Maintenance	Side effects	Class recommendation[a]
Digoxin	IV	0.25 mg IV Q 2 h up to 1.5 mg	≥1 h	0.125–0.375 mg IV or oral daily	Digitalis toxicity, heart block, bradycardia	IIb, LOE B; I LOE C in CHF
Digoxin	PO	0.25 mg PO Q 2 h up to 1.5 mg or 0.5 mg a day	2 d	0.125–0.375 mg PO daily	Digitalis toxicity, heart block, bradycardia	IIb, LOE B; I, LOE C in CHF
Diltiazem	IV	0.25 mg/kg IV over 2 min	2–7 min	5–15 mg/h IV	Hypotension, heart block, CHF	I, LOE B
Diltiazem	PO	N/A	2–4 h	120–360 mg daily in divided dose; slow release available	Hypotension, heart block, CHF	I, LOE B
Esmolol	IV	0.5 mg/kg over 1 min	5 min	0.06–0.2 mg/kg per min	Hypotension, heart block, CHF, bradycardia, asthma	I, LOE C
Metoprolol	IV	2.5–5 mg IV over 2 min; may repeat twice Q 5 min	5 min	N/A	Hypotension, heart block, CHF, bradycardia, asthma	I, LOE C
Metoprolol	PO	N/A	4–6 h	25–100 mg bid	Hypotension, heart block, CHF, bradycardia, asthma	I, LOE C
Propranolol	IV	0.15 mg/kg IV over 15–30 min	5 min	N/A	Hypotension, heart block, CHF, bradycardia, asthma	I, LOE C
Propranolol	PO	N/A	60–90 min	80–240 mg daily in divided dose; sustained release available	Hypotension, heart block, CHF, bradycardia, asthma	I, LOE C
Verapamil	IV	0.075–0.15 mg/kg IV over 2 min	3–5 min	N/A	Hypotension, heart block, CHF	I, LOE B
Verapamil	PO	N/A	1–2 h	120–360 mg daily in divided dose; slow release available	Hypotension, heart block, CHF, digoxin interaction	I, LOE B
Amiodarone	IV	150 mg IV bolus over 10 min; may be repeated 2 or 3 times 30 min apart	Days	0.5–1 mg/min	Hypotension, bradycardia, heart block, pulmonary toxicity, skin discoloration, corneal deposits, optic neuropathy, warfarin interaction, hypothyroidism, hyperthyroidism, and others	IIa, LOE C with accessory pathway or in CHF
Amiodarone	PO	800 mg daily for 1 wk, 600 mg daily for 1 wk, 400 mg daily for 4–6 wk (various regimens exist)	1–3 wk	200 mg daily	Hypotension, bradycardia, heart block, pulmonary toxicity, skin discoloration, corneal deposits, optic neuropathy, warfarin interaction, hypothyroidism, hyperthyroidism, and others	IIa, LOE C in CHF

Check the *Physicians Desk Reference* or package insert for dosages. *bid* twice a day, *CHF* congestive heart failure, *IV* intravenous, *LOE* level of evidence, *N/A* not applicable, *PO* orally.
[a]Modified from ref. 65.

(58%), then diltiazem/verapamil (54%). More patients switched to β-blocker use from another agent than from β-blocker use to an alternative agent.

Intravenous magnesium sulfate in addition to usual care for the control of heart rate during AF was recently studied in the emergency room setting.[9] The magnitude of the clinical effect of adding magnesium was small (≤15 beat/min reduction) and of uncertain clinical importance. There was an increase in adverse events in association with magnesium use, which may negate any potential benefit to its use.

Trials of Pharmacological Rhythm Control

Pharmacological rhythm control for AF is most easily discussed by separating two pharmacological effects: pharmacological cardioversion to terminate AF and maintenance of SR. In general, however, the agents used to achieve these effects are often the same.

Issues in Pharmacological Cardioversion

Pharmacological cardioversion of AF has been reviewed.[10,11] Some newer agents used for cardioversion of AF have been evaluated since these reviews. Before discussing the specific drugs, a brief discussion is needed about pharmacological cardioversion itself.

Pharmacological cardioversion is most likely achievable when AF has been present for a short period of time. The time taken to achieve pharmacological cardioversion can be an important consideration. Pharmacological agents vary greatly in the time they take to convert AF to SR. Intravenous formulations in general work more quickly than the oral formulations of the same. However, specific agents are known to act rapidly (e.g., Ibutilide[10]), and some are known to act slowly (e.g., amiodarone[12]). A drug that takes hours or days to produce cardioversion is not useful in many settings. When studies include only patients with "recent onset" AF, there will be many patients included who have paroxysmal (self-terminating) AF, and therefore a placebo control arm is essential for assessment of the true rate of efficacy. Drugs also have differential efficacy for conversion of AF and AFL. Finally, the risk of thromboembolism around the time of cardioversion is the same for both electrical and pharmacological cardioversion. For these and other reasons, a distinction is often made between AF of recent onset (<48 h in duration) and long-lasting AF (>48 h but usually greater than 1 week).

A novel strategy capitalizing on pharmacological cardioversion is the "pill-in-the-pocket" approach.[13] Conventionally, cardioversion of AF, whether via pharmacology or electricity, is performed under the supervision of a physician and medical staff and with electrocardiographic (ECG) monitoring. Alboni et al.[13] reported safe and efficacious AF conversion in the outpatient setting using oral self-administration of propafenone or flecainide. Their cohort had minimal or no heart disease, had recurrent episodes of AF for which onset could be accurately determined, and had demonstrated safety and conversion efficacy in the hospital for an episode with duration less than 48 h using the same medication that they used with the pill-in-the-pocket approach. With recurrence of typical palpitations, patients self-administered the medication at the same previously given dose, now in the outpatient setting. Unfortunately, the technique can probably only be applied to a minority of the patients with AF.

Pharmacological cardioversion of long-lasting AF has much lower success rates than that for recent-onset AF, likely because of electrical and mechanical remodeling of the heart during persistent AF. The alternative is electrical cardioversion, but even in this case antiarrhythmic drugs can have an adjunctive role. Electrical cardioversion has significant efficacy for long-lasting AF (67% to 100% success rate) but is burdened by a significant relapse rate (70% to 80%).[10] Patients are frequently preloaded with an antiarrhythmic drug with both AF conversion efficacy and utility for maintenance of SR, such as amiodarone or dofetilide, the two drugs with some efficacy for conversion of long-lasting AF. If the drug does not convert the AF, an electrical shock can be offered and the medication continued, at least temporarily, to prevent relapse of AF.

Pharmacological Cardioversion of Atrial Fibrillation: Review of the Trials

There are two fundamental mechanisms by which antiarrhythmic drugs are thought to terminate AF: slowing of conduction and prolonging refractoriness of the atrial myocytes. Sodium channel blockers such as flecainide and propafenone slow conduction and probably terminate AF by widening the excitable gap. Potassium channel blockers such as ibutilide terminate and prevent recurrences of AF by prolonging the refractory period.[14]

Table 2 summarizes some of the drugs used for pharmacological cardioversion of recent-onset AF. Digoxin had been used for many years for "cardioversion" of AF, but it has been shown that it has little or no efficacy in this regard when used by itself. The class IA antiarrhythmic drugs quinidine, procainamide, and disopyramide have moderate conversion efficacy but are limited by either side effects (frequent gastrointestinal upset and QT prolongation for quinidine) or a lack of significant supportive data (procainamide and disopyramide) and are rarely used for this purpose in North America.

The class IC antiarrhythmic drugs propafenone and flecainide have been demonstrated to have moderately high conversion efficacy, always superior to placebo, with a relatively rapid onset of effect. The IC agents should be used with caution or not at all in those with ischemic heart disease, conduction system disease, sinus node insufficiency, or left ventricular (LV) systolic dysfunction and heart failure. The combination of widening of the QRS and 1:1 conduction of a "slow" AFL can produce a confusing wide-complex tachycardia when IC agents are used for this purpose. These agents are generally well tolerated except for occasional mild gastrointestinal upset or hypotension. They have better efficacy for AF than AFL.

Class III antiarrhythmic drugs have been investigated for the conversion of AF to SR. Amiodarone has similar overall conversion efficacy to other antiarrhythmic drugs, but its time to effect is longer. At 1 to 2 h, its effect is comparable to placebo; at 6 to 8 h, it is slightly superior to placebo (56% AF conversion vs 43%), and at 24 h it is superior to placebo (83% AF conversion vs 56%).[10] In a direct head-to-head comparison between oral amiodarone and oral propafenone, the mean conversion times were 6.9 h and 2.4 h, respectively, although the overall efficacy was similar.[10] Amiodarone's well-known and numerous toxicities are largely related to chronic use, but acutely bradycardia, hypotension, or phlebitis from intravenous formulations may occur. For these reasons (slow onset and adverse effects), amiodarone is not widely recommended for pharmacological cardioversion.

Table 2 Intravenous and orally administered pharmacological agents for pharmacological cardioversion of atrial fibrillation (modified from refs. 10 and 65).

Drug	Route	Loading dose	Time to conversion	Efficacy	Adverse effects	Class recommendation by duration of AF[a]
Quinidine	PO	750–1,500 mg in divided doses over 6–12 h	<24 h	59–92%	3–46%	IIb, LOE B for ≤ 7 d and > 7 d
Procainamide	IV	5–15 mg/kg (maximum 1,000 mg) at 0.2–0.4 mg/kg/min	<1.5 h	43–88%	2–12%	IIb, LOE B for ≤ 7 d; IIb, LOE C for > 7 d
Propafenone	IV	1.5–2 mg/kg over 10–20 min	<4 h	43–89%	0–17%	I, LOE A for ≤ 7 d; IIb, LOE B for > 7 d
Propafenone	PO	600 mg	<5 h	72–86%	10–14%	I, LOE A for ≤ 7 d; IIb, LOE B for > 7 d; IIb, LOE B for > 7 d
Flecainide	IV	1.5–3 mg/kg bolus over 10–20 min	<2 h	65–96%	7–31%	I, LOE A for ≤ 7 d; IIb LOE B for > 7 d
Flecainide	PO	200–300 mg	<5 h	78–95%	21–23%	I, LOE A for ≤ 7 d; IIb, LOE B for > 7 d
Amiodarone	IV	5–7 mg/kg over 30–60 min, then 1.2 to 1.8 g per day until 10 g total	>8 h	25–89%	7–27%	IIa, LOE A for ≤ 7 d and > 7 d
Amiodarone	PO	Inpatient: 1.2–1.8 g per day divided dose to total of 10 g Outpatient: 600–800 mg per day divided dose to total of 10 g	Up to 30 d	25–89%	7–27%	IIa, LOE A for ≤ 7 days and > 7 d
Dofetilide	PO	125–500 µg bid	36–72 h	43%	15%	I, LOE A for > 7 d
Ibutilide	IV	1 mg over 10 min; repeat once	<1.5 h	31–60%	25%	I, LOE A for ≤ 7 d; IIa, LOE A for > 7 d

Check the *Physicians Desk Reference* or package insert for dosages. *bid* twice a day, *IV* intravenously, *LOE* level of evidence, *PO* orally.

[a]Modified from refs. 10 and 65.

Dofetilide is only available in oral form in North America and has modest conversion efficacy in AF but more effect in conversion of AFL. Its significant limitation is a linear relationship between plasma dofetilide levels and the QTc interval, which results in an overall 3.6% torsades de pointes VT incidence.[10]

Ibutilide in intravenous form is moderately effective for conversion of AF but also much more effective for conversion of AFL. Its advantage is rapid effect (usually within 60 to 90 min) but is limited by significant cost and QTc interval prolongation, which results in a 2.7% torsades de pointes VT incidence.[10]

Sotalol is widely used and is efficacious for maintenance of SR but has little efficacy for cardioversion. Its inefficacy is probably at least partly because of its "reverse use dependence" effect, by which it tends to prolong atrial refractoriness more at lower heart rates than at higher rates. Almost all randomized

trials testing the ability of sotalol to convert AF demonstrated that it is only slightly better than placebo. It is also burdened by QTc interval prolongation and torsades de pointe VT risk, and it is generally not recommended for pharmacological cardioversion.

There are some newer agents in testing for cardioversion of recent-onset AF. Tedisamil was originally developed as an antianginal agent, although its ability to block numerous ion channels led to its investigation as an antiarrhythmic drug. It has predominantly class III activity and is relatively selective for atrial tissue. In intravenous formulation, it has an AF conversion efficacy of 57% and an AFL conversion efficacy of 27% (51% total for AF and AFL) vs a placebo conversion rate of 9% at 2.5 h from dosing. The average time to conversion is 35 min. The QTc interval was prolonged in a dose-dependent manner with a ventricular proarrhythmia rate of 1.8%.[15]

RSD1235 is an investigational drug that has novel mixed frequency-dependent Na^+ channel and atria-preferential K^+ channel blocking activity. In preclinical studies, it has been shown to prolong atrial refractoriness without significant effects on the ventricular refractoriness or the QTc interval. It has an excellent safety profile and is well tolerated. Early data demonstrated very good conversion efficacy within 30 min of infusion completion for recent-onset AF (61% vs placebo 5%; mean time to conversion 14 min).[16]

Dronedarone and azimilide are two other class III agents undergoing evaluation for rhythm management of AF (see discussion of investigational agents), but there are no data on pharmacological cardioversion. There are several other drugs under development that have novel mechanisms for conversion of AF or maintenance of SR: connexin modulators, stretch receptor antagonists, Na^+/H^+ exchange inhibitors, 5-hydroxytryptamine receptor inhibitors, Na^+/Ca^{2+} exchange inhibitors, and thyroid antagonists.[17]

Pharmacological Maintenance of Sinus Rhythm

The efficacy and safety of pharmacological agents for the maintenance of SR in patients with AF have been the subject of two reviews.[11,18] The more recent review[18] reported on 91 randomized controlled trials published prior to August 2001. This review reported aggregate superior efficacy of class IA (treatment difference 21.5%), class IC (treatment difference 33.1%), and class III agents (treatment difference 17.4%) for maintaining SR when compared to placebo. These trials and most of those discussed next focus on the endpoint of recurrence of symptomatic AF because the current Food and Drug Administration standard for efficacy of an antiarrhythmic drug for this indication is reduction of recurrent symptomatic AF compared to placebo.

A number of trials assessing the comparative ability of various agents to maintain SR have been published more recently. Amiodarone was evaluated in three of them.

The Canadian Trial of Atrial Fibrillation (CTAF)[19] was the first large trial evaluating the efficacy of amiodarone for maintaining SR in AF patients. When compared to patients receiving sotalol or propafenone, patients treated with amiodarone showed decreased recurrence of AF over the 17-month follow-up (63% vs 35%, $p < 0.001$).

The AFFIRM First Antiarrhythmic Drug Substudy[20] was a substudy of those 661 patients randomized to a rhythm control strategy in the parent

study. The patients were randomized to one of three drug choices as the initial therapy: amiodarone, sotalol, or a class I agent. Amiodarone (60% to 62% SR at 1 year) was found to be superior to either sotalol (34% to 38% SR at 1 year) or class I agents (23% SR at 1 year). With serial therapy, 80% of patients could be maintained in SR at 1 year.

The Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T)[21] randomized patients on anticoagulation and with persistent AF to amiodarone, sotalol, or placebo therapy. Amiodarone and sotalol had equal efficacy for cardioversion of AF, with both superior to placebo—a finding for sotalol that is a little surprising given previous studies (see above). For maintenance of SR, sotalol was superior to placebo, and amiodarone was superior to placebo and sotalol. In patients with ischemic heart disease, amiodarone and sotalol were equally efficacious.

These trials all demonstrated the superiority of amiodarone compared to other drugs for maintenance of SR, although its adverse effects profile remains problematic.

A sustained-release formulation of propafenone was evaluated in two trials. The European Rythmol/Rytmonorm Atrial Fibrillation Trial (ERAFT)[22] demonstrated an increase in arrhythmia-free periods in AF patients with sustained-release propafenone (mean time to recurrence 35 to 44 days) vs placebo (mean time to recurrence 9 days). The Rhythmol Atrial Fibrillation Trial (RAFT)[23] demonstrated an increase in arrhythmia-free periods in AF patients with sustained-release propafenone (mean time to recurrence 112 to more than 300 days, in a dose-dependent fashion) vs placebo (mean time to recurrence 41 days).

The drug combination of quinidine plus verapamil was evaluated in two European trials published in the same issue of the *European Heart Journal* in 2004. The Prevention of Atrial Fibrillation After Cardioversion (PAFAC) trial[24] randomized patients with persistent, successfully electrically cardioverted AF to either sotalol, quinidine plus verapamil, or placebo. After a follow-up of 266 days, quinidine plus verapamil was found to be superior to sotalol and placebo for the recurrence of AF (recurrence rates of 38%, 49%, and 77%, respectively). The Suppression of Paroxysmal Tachyarrhythmias Trial (SOPAT)[25] randomized patients with frequent symptomatic episodes of paroxysmal AF to either high-dose quinidine plus verapamil, low-dose quinidine plus verapamil, sotalol, or placebo. After a follow-up of 233 days, all active treatments were found to be superior to placebo and not different from each other.

Table 3 lists the doses of typical drugs used for maintenance of SR.

Investigational New Agents for Maintenance of Sinus Rhythm

There a few new agents currently or recently in phase II and III trials and several others that are at an earlier stage of development. Some are thought to hold promise, some are used elsewhere in the world but not in North America, and some appear to have been abandoned.

Bidisomide is a class I antiarrhythmic drug thought to hold promise for the treatment of supraventricular arrhythmias including AF because of its atrial selectivity. The Atrial Fibrillation Investigation with Bidisomide (AFIB) trial[26] enrolled patients with symptomatic nonpermanent AF who were in SR at enrollment. Bidisomide unfortunately was not found to have any efficacy

Table 3 Typical orally administered pharmacological agents for maintenance of sinus rhythm in atrial fibrillation[a].

Drug[b]	Contraindications and precautions	Class recommendations	Daily dose[b]	Adverse effects
Amiodarone	Lung disease	I, LOE A	100–400 mg	Photosensitivity, pulmonary toxicity, polyneuropathy, gastrointestinal upset, torsades de pointes (rare), hepatic toxicity, thyroid dysfunction, eye complications
Disopyramide	Reduced systolic function and CHF	IIa, LOE C for vagal AF	400–750 mg	Torsades de pointes, heart failure, glaucoma, urinary retention, dry mouth
Dofetilide[c]	Long QT interval	I, LOE A	250–1,000 µg	Torsades de pointes
Flecainide	Structural heart disease, particularly ischemic	I, LOE A	200–300 mg	Ventricular tachycardia, CHF, enhanced AV nodal conduction (conversion to atrial flutter)
Propafenone	Structural heart disease, particularly ischemic	I, LOE A	450–900 mg	Ventricular tachycardia, CHF, enhanced AV nodal conduction (conversion to atrial flutter)
Sotalol[c]	Reduced systolic function and CHF; long QT interval	I, LOE A	240–320 mg	Torsades de pointes, CHF, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease

AF atrial fibrillation, *AV* atrioventricular, *CHF* congestive heart failure, *LOE* level of evidence.
[a]Modified from the ACC/AHA/ESC guidelines for managing AF.[65]
[b]Drugs and dosages given have been determined by consensus based on published studies.
[c]Dose should be adjusted for renal function and QT-interval response during in-hospital initiation phase.

for suppressing AF compared to placebo at any of the three doses tested and has been abandoned.

Azimilide has been tested for efficacy in maintaining SR in AF patients. At the higher doses tested, it appeared to have some efficacy.[27] However, in the Azimilide Post-Infarction Survival Trial (ALIVE)[28] demonstrated that, in 3,381 patients with AF, recent MI, and LV systolic dysfunction, azimilide was only marginally superior to placebo ($p = 0.04$) in preventing the development of AF and maintaining SR over the 1-year follow-up and only with the 100-mg dose. The Azimilide-Cardioversion Maintenance Trial I (A-COMET-I)[29] also evaluated the efficacy of azimilide for maintaining SR in symptomatic non-permanent AF patients. This trial failed to show superiority of azimilide over placebo for suppressing the recurrence of symptomatic AF in the previously effective 125-mg dose. Thus, azimilide appears to have weak and inconsistent efficacy for this indication, and there is some risk of proarrhythmia.

Dronedarone is an amiodarone-like benzofuran derivative without the iodine moiety. The Dronedarone Atrial Fibrillation Study After Electrical Cardioversion (DAFNE) trial[30] was designed to assess the optimal dose for prevention of AF recurrence after cardioversion of patients with persistent AF. Dronedarone at the 400-mg dose twice daily was superior to placebo in preventing recurrent AF. Higher doses were no better than placebo, mostly because of poor adherence as a result of gastrointestinal adverse effects. This same 400-mg twice-daily dose of dronedarone was used in the ADONIS

(American–Australian–African Trial with Dronedarone in Atrial Fibrillation or Flutter for the Maintenance of Sinus Rhythm)[31] and EURIDIS[32] (European Trial in Atrial Fibrillation or Atrial Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) trials. These trials remain unpublished at the time of this writing, but the results have been presented at major meetings[66]. Time to recurrence of AF was prolonged significantly in both trials. No proarrhythmia or end-organ toxicities were noted in either study. ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease), a double-blind, placebo-controlled, phase III clinical trial (evaluating dronedarone in high-risk patients with CHF and ventricular dysfunction) was discontinued in January 2003 by the steering committee following the Data Safety Monitoring Board's recommendation.[33] The results indicated a potential excess risk of death, with 24 deaths out of the active treatment group vs 10 deaths on placebo. Dronederone has not been approved for use, and it is unknown if it will proceed to registration in one or more countries. It could be an alternative to other drugs but has not been demonstrated to have the same efficacy as the parent drug, amiodarone; its dosage is limited by tolerability, and it is unlikely to be safe in those with poor ventricular function and CHF.

Other new agents under more preliminary investigation include piboserod, an atrial-selective 5-HT_4-blocker; ZP123, a gap junction conduction facilitator; and CVT-510, a long-acting intravenous selective A-1 adenosine agonist.[34] Data evaluating these drugs and others are awaited.[35]

Adjunctive Medical Therapies for the Maintenance of Sinus Rhythm

Interest has grown in identifying drugs that may have efficacy for preventing AF recurrence through mechanisms that are poorly understood but are not traditional "antiarrhythmic" modes of action. These agents and the data that support their potential utility in treating AF are reviewed in two publications.[36,37] Space does not permit a detailed discussion, and the interested reader is referred to these reviews for more details.

Inflammation, increased oxidative stress, and an association between increased levels of C-reactive protein (CRP) and AF have been reported several times. Dernellis and Panaretou tested the hypothesis that decreasing inflammation would decrease recurrence of AF after pharmacological or electrical cardioversion. In 104 patients with first symptomatic persistent AF and elevated CRP levels, they reported a decrease in AF recurrence over 30 months when methylprednisolone was added to propafenone for the first 5 months of therapy. Higher CRP levels in both treatment groups predicted recurrence of AF.[38] These data support the hypothesis that inflammation is related to and promotes AF.

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are of interest in this regard because studies have shown that they demonstrate the ability to decrease CRP and have anti-inflammatory effects, at least partially independent of statins' lipid-lowering effects. Data in animal models showed that atorvastatin can prevent the occurrence and maintenance of AF in a sterile pericarditis model. Clinical observations of coronary disease patients and CHF patients demonstrated decreased risk of AF in both primary and secondary prevention settings and several large databases. However, the

only randomized, controlled trials reported to date did not conclusively demonstrate efficacy of statins in preventing AF after cardioversion. Pravastatin was not found to be superior to placebo in preventing recurrence of AF in 114 patients cardioverted from persistent AF.[39] Atorvastatin was found to be superior to placebo over a short period of follow-up in a study involving only 48 patients.[40] Further trials are in progress.

Angiotensin II increases afterload and LV wall stress, which increase atrial chamber size, dispersion of refractoriness, reduce action potential duration, and promote afterdepolarizations. Angiotensin II also promotes growth of cardiac myocytes, vascular smooth muscle cells, and fibroblasts, promoting structural remodeling of the heart. High tissue levels of angiotensin-converting enzyme (ACE) have been described in AF.[36] These and other collective changes in the electrical and structural milieu of the atria, as a result of an activated renin–angiotensin–aldosterone system (RAAS), predispose to development and maintenance of AF.

Retrospective analysis of the Trandolapril Cardiac Evaluation (TRACE) study[41] and Studies of Left Ventricular Dysfunction[42] demonstrated a decreased incidence of the development of AF in these two post-MI populations with decreased LV ejection fraction treated with ACE-I. A retrospective cohort study[43] also demonstrated a lower incidence of AF from treating hypertensive patients with ACE-I rather than a calcium channel blocker but with a smaller effect size than seen in CHF patients.

A retrospective analysis of the Valsartan Heart Failure Trial[44] (Val-HeFT), by which angiotensin receptor blocker (ARB) was added to standard therapy in patients with moderate-to-severe stable heart failure showed a 33% relative risk reduction for the development of new AF with the addition of valsartan. A prospective trial of the addition of irbesartan to amiodarone vs amiodarone alone showed this ARB reduced the time to first recurrence of AF in patients with persistent AF who were cardioverted.[45] The LIFE study (Losartan Intervention for End Point Reduction in Hypertension) compared losartan to atenolol for treatment of hypertension in patients with LV hypertrophy. Retrospective analysis revealed that new AF developed more frequently in the atenolol arm compared to the losartan arm, reducing the risk by 33% despite similar blood pressure reductions.[46] In the setting of lone AF, a small trial evaluated irbesartan in addition to amiodarone vs amiodarone alone for the prevention of recurrence of AF. The addition of irbesartan reduced the risk of AF recurrence.[47] Finally, two meta-analyses summarized the ACE-I/ARB treatment effect for the prevention of AF. In 24,849 AF patients across seven trials, the risk of AF was reduced by 43%.[48] In a newer and larger meta-analysis of 56,308 patients,[49] ACE-I or ARBs reduced the development of AF by 28%.

More and stronger trial data are required before these therapies move into the mainstream of clinical AF treatment without their usual indications. So far, the data suggest this type of adjunctive therapy is more effective in heart failure patients than it is in patients with uncomplicated hypertension. There are some large trials currently in progress. The GISSI-Atrial Fibrillation trial[50] is an Italian multicenter trial designed to assess the use of valsartan added to best therapy vs placebo for preventing recurrence of AF in 1,402 patients with symptomatic, recent-onset AF. The ACTIVE-I trial[51] is studying irbesartan vs placebo in 9,000 patients with AF and at least one risk factor for stroke. Other trials are also in progress or are planned.

The β-blockers are generally regarded as rate control treatment but probably also have an antiarrhythmic effect. Elevated sympathetic nervous system may be a contributing factor to development of AF in some patients. A post hoc analysis of the CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) trial studied the effect of carvedilol on AF in 1,959 post-MI patients with LV systolic dysfunction who were treated with ACE inhibitors. Carvedilol reduced the incidence of AF or AFL by 59% (hazard ratio [HR] 0.41, 95% CI 0.25–0.68, $p = 0.0003$).[52]

Trials of Pharmacological Rate vs Rhythm Control

There are now seven published trials[2,3,53–57] that have addressed the question of rate vs rhythm control, and three published meta-analyses[1,58,59] have pooled data from either four or five of the original studies with similar patient populations. At least two other ongoing trials are awaiting completion[60,61] (Table 4).

The results of the seven trials can be discussed according to the patient populations enrolled in them. CRAAFT[57] (Control of Heart Rate vs Rhythm in Rheumatic Atrial Fibrillation Trial), was distinct in that it enrolled only patients with rheumatic heart disease and AF. The 144 subjects enrolled were much younger and more frequently women than in the other trials, with a mean age of 39 years; 70% had received valve surgery. The three randomized arms of the study were heart rate control with diltiazem, electrical cardioversion plus amiodarone, and electrical cardioversion plus placebo. The primary endpoint was the presence of SR at 1 year, which was obviously not a reasonable goal in the rate control arm. Amiodarone use resulted in higher rates of SR at 1 year. Further analyses compared patients in SR with those still in AF, regardless of treatment allocation, making interpretation of the other findings problematic.

The PAF2 (Paroxysmal Atrial Fibrillation 2) trial[54] had a unique patient population: highly symptomatic paroxysmal AF patients who had failed pharmacological therapy and had the pace and ablate strategy for their AF. They were then randomized to pharmacological therapy for rhythm control or to no further medical therapy. The 137 subjects were followed for a mean of 16 months for the primary endpoint of development of permanent AF and for several secondary endpoints, including clinical events, echocardiographic parameters, and time in AF. Fewer patients in the rhythm control arm progressed to permanent AF but at a price of increased CHF and hospitalizations. There were no differences in quality of life or echocardiographic measurements between the groups. There was no difference in other patient outcomes between permanent AF and paroxysmal AF subjects over the term of this trial. It is not surprising that there was little overall clinical benefit in trying to maintain SR given the obligatory failure of medical therapy leading to enrollment in the trial and given that ablation and pacing have such a high impact on symptoms in such patients.

The other five trials, PIAF (Pharmacological Intervention in Atrial Fibrillation),[53] AFFIRM,[2] RACE,[3] STAF (Strategies of Treatment of Atrial Fibrillation),[55] and HOT CAFE (How to Treat Chronic Atrial Fibrillation)[56] were fairly similar with respect to the patients they enrolled: older, mostly men, and mostly with persistent AF. The most common rhythm control drug used was amiodarone,

Table 4 Overview of published and ongoing trials and meta-analyses of trials of rate vs rhythm control in the management of atrial fibrillation (adapted from ref.[1]).

	Duration of follow-up	Subjects (N)	Patients' characteristics	Patient AF characteristics	Rhythm control therapies[a]	Rate control therapies[b]	Anti-coagulant use	Primary endpoints	Other endpoints	Summary of results
Completed trials of rate vs rhythm										
PIAF (2000)	1 yr	252	60 yr old; 92% male, 50% HTN, 23% CAD, 16% normal heart; few with CHF	Persistent: 7 d to 1 yr	A, ECV	Dit, BB, Dig, RFA	Yes, for duration of study	Proportion symptomatically improved	QoL; functional capacity; hospitalization; adverse drug effects; bleeding	No difference in primary endpoint and QoL; rhythm = slightly ↑ functional capacity; rate = ↓ hospitalizations and adverse drug affects
PAF2 (2002)	1.3 yr	141	68 yr old; 42% male, 30% HTN, 16% CAD, 35% normal heart; few with CHF	Paroxysmal, severely symptomatic	A, P, F, S; ECV not allowed	RFA	Yes, but discontinuation for SR permitted by guidelines	Development of permanent AF	QoL; echo measures; worsening CHF; hospitalization; bleeding	Rhythm = ↓ permanent AF, no difference in QoL and echo; rate = ↓ progression of CHF & ↓ hospitalizations
AFFIRM (2002)	3.5 yrs	4,060	70 yrs old; 61% male, 71% HTN, 38% CAD, 13% normal heart; 9% CHF	Persistent (>69%) & paroxysmal	A, S, P, other Class I AADs; ECV; few non-pharmacologic	BB, Dit, V, Dig, RFA	Yes, but discontinuation for SR permitted by guidelines	Death	Composite of clinical events; QoL; functional capacity; bleeding; hospitalization; adverse drug effects; cost	No difference in 1° endpoint (trend favors rate) & QoL; rate = ↓ hospitalizations and adverse drug effects; rhythm = slightly ↑ functional capacity
RACE (2002)	2.3 yr	522	68 yr old; 63% male, 50% HTN, 27% CAD, 21% normal heart; 50% CHF	Persistent (median 32 d) and recurrent after ECV	S, F, P, A; ECV (prescribed sequence)	BB, Dit, V, Dig, RFA	Yes, but discontinuation for SR permitted by guidelines	Composite of clinical events	Individual components of the composite; QoL; bleeding; cost	Rate not inferior for primary endpoint; no difference in QoL; rate = ↓ hospitalizations and adverse drug effects

STAF (2003)	1.7 yr	200	65 yr old; 65% male, 64% HTN, 44% CAD, 21% normal heart; 46% CHF	Persistent > 4 wk	A, P, F; ECV	BB, Dit, V, Dig, RFA	Yes, but discontinuation for SR permitted by guidelines	Composite of clinical events	Individual components of the composite; QoL; echo measures; worsening heart failure; bleeding	No difference in primary or secondary endpoints; rate = ↓ hospitalizations
HOT CAFE (2004)	1 yr	205	61 yr old; 92% male, 50% HTN, 23% CAD, 16% normal heart; 62% CHF	Persistent: 7 d to 2 yr	ECV followed by P, S or Dis; repeat ECV, new drug or A for recurrence	BB, Dit, V, Dig, RFA	Yes, but discontinuation for SR permitted by guidelines	Composite of death and clinical events	Measures of rate control and rhythm; discontinuation of therapy; bleeding; hospitalization; new or worse CHF; exercise tolerance; echo measures	No difference in primary endpoint; rate = ↓ hospitalizations; rhythm = ↑ exercise tolerance and slight ↑ in LVEF; all 3 strokes in rhythm
CRAAFT (2004)	Not provided	144	39 yr old; 39% male, 100% rheumatic heart disease, 70% previous valve surgery, 49% prosthetic valve, 100% normal EF	Average duration AF > 5 yr	ECV alone (control group), A + ECV (rhythm control group)	Dit	Yes, for duration of study	Restoration and maintenance of SR at 12 mo	Exercise test; functional class; QoL; bleeding; thromboembolism; hospitalization; death	More patients in SR at 1 yr with amiodarone; other comparisons included only rate control subjects to those in SR at 1 yr; SR = ↑ exercise tolerance, functional class, QoL, and ↓ deaths
Meta-analyses										
Wyse (2005)		5,034	PIAF, AFFIRM, RACE, STAF					Death; thrombotic stroke		Rhythm = trend toward ↑ death (HR 1.12, $p = 0.09$) and ↑ thrombotic strokes (HR 1.63, $p = 0.2$)

(continued)

Table 4 (continued)

	Duration of follow-up	Subjects (N)	Patients' characteristics	Patient AF characteristics	Rhythm control therapies[a]	Rate control therapies[b]	Anti-coagulant use	Primary endpoints	Other endpoints	Summary of results
de Denus et al. (2005)		5,239	PIAF, AFFIRM, RACE, STAF, HOT CAFE					Death		Rate = trend toward ↓ death (HR 0.87, $p = 0.09$) and ↓ thrombotic strokes (HR 1.63, $p = 0.2$)
Testa et al. (2005)		5,239	PIAF, AFFIRM, RACE, STAF, HOT CAFE					Death or thromboembolic stroke		Rate = ↓ in primary endpoint (HR = 0.84, $p = 0.02$, NNT = 50)
Ongoing trials of rate vs rhythm										
AF-CHF (2007)	≥2 yr	1,378	CHF (NYHA I–IV), EF ≤0.35, AF	Paroxysmal or persistent, but not permanent	ECV + AADs (amiodarone or other class III agents) ± nonpharmacological therapy	BB, Dig, RFA	Yes, as per guidelines for anticoagulation in AF	Cardiovascular death	All-cause death; stroke; hospitalization; QoL; cost; composite endpoint of CV death, stroke, and hospitalization	
J-RHYTHM (2006)	≥3 yr	1,065 (885 with paroxysmal AF)		Paroxysmal or persistent, but not permanent	ECV + AADs as recommended by Japanese AF Guidelines	Dig, BB, CCB	Yes, as per guidelines for anticoagulation in AF	Composite of all-cause death, symptomatic stroke, systemic embolism, bleeding, CHF hospitalization, justifiable discontinuation of therapy	Composite of AF-specific QoL, efficacy and safety of drugs used	

AADs antiarrhythmic drugs, *AF* atrial fibrillation, *CAD* coronary artery disease, *CHF* congestive heart failure, *CV death* cardiovascular death, *EF* ejection fraction, *HR* hazard ratio, *LVEF* left ventricular ejection fraction, *HTN* systemic hypertension, *NNT* number needed to treat, *NYHA* New York Heart Association, *QoL* quality of life, *SR* sinus rhythm.

[a]Rhythm control therapies: *A* amiodarone, *Dis* disopyramide, *ECV* electrical cardioversion, *F* flecainide, *P* propafenone, *S* sotalol.

[b]Rate control therapies: *BB* β-blockers, *CCB* calcium channel blockers, *Dig* digitalis, *Dit* diltiazem, *RFA* AV junction ablation, *V* verapamil.

with sotalol and propafenone used much less frequently. Only a minority (<5%) of the rate control patients proceeded to a pacing-and-ablation strategy for rate control. Given the similarity in subject populations and trial design, these five trials are more suitable for inclusion in meta-analysis. Three meta-analyses[2,58,59] have been published pooling data from four or five of these trials. Notably, AFFIRM was by far the largest trial with 4,060 patients enrolled, more than three fourths of the total of all five trials combined, and thus will skew the meta-analysis results toward the findings of the AFFIRM trial.

The first of these,[1] published in June 2005, analyzed the endpoints of death or thrombotic stroke in the rhythm control and rate control arms. The PIAF, AFFIRM, RACE, and STAF trials were included in the pooled analysis. A trend toward increased mortality (HR 1.12 [0.98–1.28], $p = 0.09$) and increased thrombotic strokes (HR 1.63 [0.81–3.28], $p = 0.2$) was shown. HOT CAFE was not included, and because in it there were no strokes in the rate control arm (vs three in the rhythm control arm) it could not have contributed to the calculation of hazard ratio for stroke. A sizable minority of the pooled sample for the rhythm control arm had their anticoagulation stopped with the apparent restoration and maintenance of SR or had a subtherapeutic international normalized ratio,[2] probably because of the mistaken belief that apparently successful rhythm control ameliorates the risk of stroke. Discontinuation of anticoagulation has been proposed as an explanation for the trend toward increased thrombotic stroke in this arm of these trials. A key finding is the requirement to continue indefinite thromboprophylaxis in AF patients with the presence of independent thrombotic risk factors regardless of the perceived status of the heart rhythm. Recent evidence suggests the reason for this is that many patients continue to have prolonged episodes of asymptomatic AF.[62]

The subsequent two meta-anlyses[58,59] used all five trials in their pooled analyses for a total of 5,239 patients, of which AFFIRM again contributed 4,060. The first of these also found a nonsignificant trend to increased mortality in the rhythm control arm. The second found an endpoint of all-cause mortality or thromboembolic stroke significantly decreased in the rate control arm (HR 0.84 [0.73–0.98], $p = 0.02$ with a number needed to treat to prevent one endpoint of 50).

PIAF, AFFIRM, and HOT CAFE reported a slight improvement in functional status in rhythm control patients. Subgroup analyses of AFFIRM and RACE suggested that some groups did better with a rate control strategy (females, hypertensives, patients with ischemic heart disease or without a history of CHF), while others did better with a rhythm control strategy (younger patients or those with a history of CHF).[2] As always, subgroup analyses have lower power and generate hypotheses that need further investigation rather than providing clear proof. Nonetheless, these results were impressive enough to some bodies to allow their incorporation into new AF guidelines, recommending rate control as the initial choice for treatment strategy.[63]

However, these five trials underrepresented certain important patient groups, including the young; those with paroxysmal AF, especially if highly symptomatic; those with moderate or advanced clinical CHF (New York Heart Association [NYHA] class II or above); or those with significantly impaired LV systolic function. The CRAAFT and PAF2 studies enrolled younger patients with surgically treated rheumatic valve disease and highly symptomatic patients with paroxysmal AF, respectively, but small size, trial design, and the

methodological issues discussed make it difficult to generalize the results of these trials to those populations. Similarly, it is difficult to extrapolate the findings of AFFIRM, RACE, and the other three major trials to patient populations that include an increasing number of individuals underrepresented in those trials—patients under 60 years of age because of the "baby boom" bulge in the population and those with heart failure caused by the epidemic of CHF.

Thus, for now it seems inappropriate to deem one strategy for rhythm management of AF the preferred therapy for all patients, and a number of factors need to be considered in selection of the initial strategy.[64] In the future, there may be additional information to help with this decision. The AF-CHF (Atrial Fibrillation and Congestive Heart Failure) trial,[60] similar to the AFFIRM trial but enrolling patients with CHF and significant LV systolic dysfunction, will address some of these underrepresented patients. J-RHYTHM (Japanese Rhythm Management Trial for Atrial Fibrillation),[61] a Japanese AF trial under way, will enroll significant numbers of patients with paroxysmal AF but primarily uses different drugs (pliscainide [class IC] and disopyramide [class IA] compared to those commonly used in North America and Europe, where amiodarone (classes III, II, and I), flecainide/propafenone (class IC), and sotalol (classes III and II) tend to dominate.

Summary and Conclusions

Recent years have seen an explosion of research clarifying the pathophysiology of AF and its clinical correlates. Paralleling that research effort is an equally large number of trials testing various management strategies and specific pharmacological therapies for a diverse range of AF patients. None of the antiarrhythmic drugs used for the rhythm control strategy for rhythm management of AF have turned out to be a panacea—highly effective with little or no adverse effects. This review presents a summary of the available data on drug therapy for rhythm management of AF. The failure of antiarrhythmic drug therapy has a number of consequences. These include development of nonpharmacological therapy and emergence of alternative strategies, such as intermittent therapy and heart rate control without any specific effort to restore SR, to emerge or be reevaluated. The pharmacological therapies used in these last two strategies have also been reviewed, as has the literature comparing rhythm control to rate control in selected populations. Whereas clinical intuition suggests that restoring and maintaining SR must be better than allowing AF to continue, current drug therapies are flawed enough that, in a large proportion of patients, drug therapy to control heart rate along with anticoagulation are at least equivalent to drug therapy to restore and maintain SR.

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12

Antithrombotic Treatment and Cardioversion of Patients with Atrial Fibrillation

Boris S. Lowe, Mina K. Chung, and Allan L. Klein

Abstract: Systemic thromboembolism is the most serious clinical consequence of atrial fibrillation (AF). The arrhythmia is a potent independent risk factor for ischemic stroke. Because of the potentially incapacitating and fatal consequences of embolic stroke, antithrombotic therapy in patients with AF has been a major focus of research. The safety and efficacy of oral anticoagulants has been established by multiple randomized placebo-controlled clinical trials.

Keywords: Anticoagulation; Antithrombotic treatment; Atrial fibrillation; Cardioversion.

Stroke Risk in Atrial Fibrillation

Uncoordinated contraction of the left atrium leads to blood stasis and abnormalities of coagulation, platelets, and fibrinolysis. Two thirds of ischemic cerebrovascular events are caused by thromboemboli from within the left atrial appendage in patients with atrial fibrillation (AF)[1]; left atrial thromboemboli, coexisting atherosclerosis of the large arteries, and valvular abnormalities account for the remainder.

The very high 17-fold increased risk of thromboembolic complications and stroke in patients with AF and rheumatic valve disease has been appreciated for many years. Even in nonrheumatic AF, the thromboembolic risk is significantly increased, 5.6-fold, compared to healthy controls[2] and is responsible for up to 15% to 25% of all ischemic cerebrovascular accidents.[3–5] Recurrent paroxysmal AF is associated with a stroke risk comparable to permanent AF.[6] Patients with AF who have a stroke have higher mortality, greater disability, longer hospital stays, and lower rates of discharge compared to those who have a stroke in the absence of AF.[7–11]

Patients who have AF comprise a heterogeneous group, and the risk of ischemic stroke varies widely depending on the patient population. Clinical and echocardiographic risk factors for stroke in patients with AF are well established (Table 1, Figure 1, Figure 2). Consideration of these factors with

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Table 1 Risk factors for thromboembolic events in atrial fibrillation.

Clinical
Prior embolic event, transient ischemic attack, or stroke
Hypertension
Age > 65 years
Diabetes mellitus
Heart failure
Coronary artery disease
Prosthetic valve
Echocardiographic
Rheumatic heart disease (mitral stenosis)
Left ventricular dysfunction
Increased left atrial size
Left atrial thrombus, severe spontaneous echocardiographic contrast
Left atrial mechanical dysfunction (emptying velocities < 20 cm/s)
Complex aortic atheroma

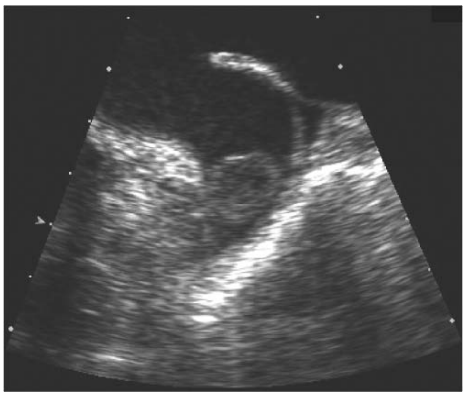


Figure 1 Transesophageal echocardiography of the left atrial appendage illustrating left atrial appendage thrombus.

comorbidities and contraindications allows identification of individual patients who are likely to benefit from anticoagulant therapy. The stroke risk is lowest in "lone" (no underlying cause) AF at 0.5% per year.[12] A prior history of an embolic event and age are the two most powerful predictors of increased stroke risk in nonvalvular AF.[5,13] The annual risk of AF-associated embolic events is 1.5% in patients younger than 60 years old and increases to 23.5% in octogenerians.[3] Several risk stratification schemes have evolved to direct treating physicians in their decision-making process (Table 2).

Stroke prevention in AF can be approached by restoration and maintenance of sinus rhythm, anticoagulant therapy, and mechanical isolation of the left atrial appendage. Five recent randomized trials failed to show a decreased risk of embolic events with a rhythm control strategy compared to one of rate control.[19–23] The larger Atrial Fibrillation Follow-up Investigation of Rhythm

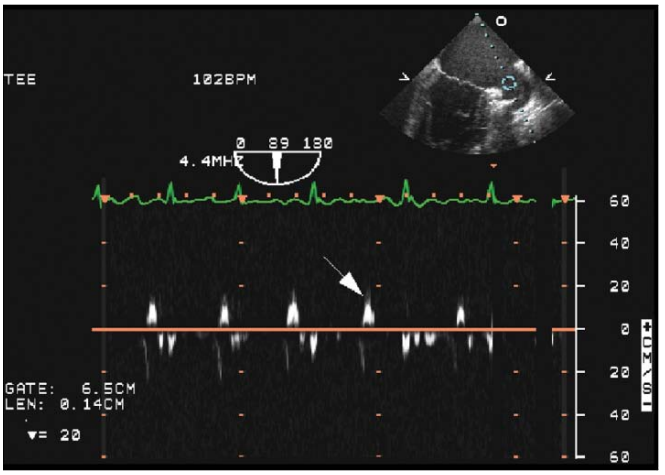


Figure 2 Transesophageal echocardiography (TEE) of the left atrial appendage showing pulsed Doppler low left atrial appendage emptying velocities of approximately 8 cm/s during atrial fibrillation. *BPM* beats per min.

Table 2 Stroke risk stratification schemes for patients with atrial fibrillation.

Scheme	High risk	Intermediate risk	Low risk
AFI[5] (1994)	Age ≥ 65 years	HTN	Age < 65 years; no high-risk features
	DM	CAD	
SPAF[14] (1995)	Women aged > 75 years	HTN; no high-risk features	No history of HTN; no high-risk features
	SBP > 160 mm Hg		
	LV dysfunction (clinical or echo)		
ACC/AHA/ESC[15] (2001)	Age ≥ 60 years with DM or HTN	Age < 60 years with CAD but no high-risk factors	Age < 60 years and no risk factors
	Age ≥ 75 years (especially women)	Age ≥ 60 years with risk factors	
	Any age with CHF, LVEF ≤ 35%, thyrotoxicosis, or HTN		
	Rheumatic heart disease		
	Prosthetic heart valves		
	Prior thromboembolism		
	Persistent atrial thrombus on TEE		
CHADS2[16,a] (2001)	3–6	1–2	0
	Score 1 for each of recent CHF, HTN, age ≥ 75 years, DM; score 2 for history of stroke or TIA; total score /6		
Framingham[17] (2003)	Complicated weighted point scoring system: ↑age (maximum score ≤10); gender (female = 6, male = 0); ↑ HTN (≤4); DM (6)		

(continued)

Table 2 (continued)

Scheme	High risk	Intermediate risk	Low risk
	Total score corresponds to a predicted 5-year stroke risk		
ACCP[18] (2004)	prior stroke, TIA, Systemic emboli event	Age 65–75 years with no other risk factors	Age < 65 years with no risk factors
	Age >75 years		
	Moderate-to-severe LV dysfunction ± CHF		
	HTN		
	DM		

ACC American College of Cardiology, *ACCP* American College of Chest Physicians, *AFI* Atrial Fibrillation Investigators, *AHA* American Heart Association, *ESC* European Society of Cardiology, *SPAF* Stroke Prevention in Atrial Fibrillation.
CAD coronary artery disease, *CHF* congestive heart failure, *DM* diabetes mellitus, *HTN* hypertension, *LV* left ventricle, *LVEF* left ventricle ejection fraction, *SBP* systolic blood pressure, *TEE* transesophageal echocardiography, *TIA* transient ischemic attack.
[a] Score 1 for each of the following: recent congestive heart failure, hypertension, age ≥ 75 years; score 2 for a history of stroke or transient ischemic attack.

Management (AFFIRM)[21] and Rate Control vs Electrical Cardioversion (RACE)[20] trials have highlighted a broader approach to anticoagulation of patients with AF. Previously, it had been presumed that a rhythm control strategy prevented the development of embolic strokes. Both trials demonstrated that thromboembolic risk is not reduced despite apparent restoration and maintenance of sinus rhythm. Most strokes in the rhythm control group occurred in those with subtherapeutic or no anticoagulation. Furthermore, the trials highlighted how frequently AF can be asymptomatic and the poor efficacy of current antiarrhythmic drugs to maintain sinus rhythm and prevent recurrences of AF. Studies examining the long-term safety and stroke reduction efficacy of surgical ligation or stapling and percutaneously deployed occluder devices are ongoing. Currently, anticoagulant therapy remains the cornerstone of preventing vascular events in patients with AF.

Warfarin

Warfarin inhibits the vitamin K γ-carboxylation of coagulation factors II, VII, IX, and X, resulting in the synthesis of inactive coagulation proteins of the prothrombin complex. Anticoagulation with warfarin is the current standard of care for prevention of stroke and other vascular events in patients with all forms of AF, rheumatic or nonrheumatic, persistent or permanent.

Warfarin vs Placebo

The role of warfarin is derived from clinical trial data summarized in Figure 4A. Five randomized controlled clinical trials have compared warfarin (mean achieved international normalized ratio [INR] 2.0 to 2.6) with either control or placebo for the primary prevention of stroke among patients with nonvalvular AF. One randomized trial compared phenprocoumon or acenocoumarol (mean achieved INR 2.9) and placebo in the secondary prevention of stroke

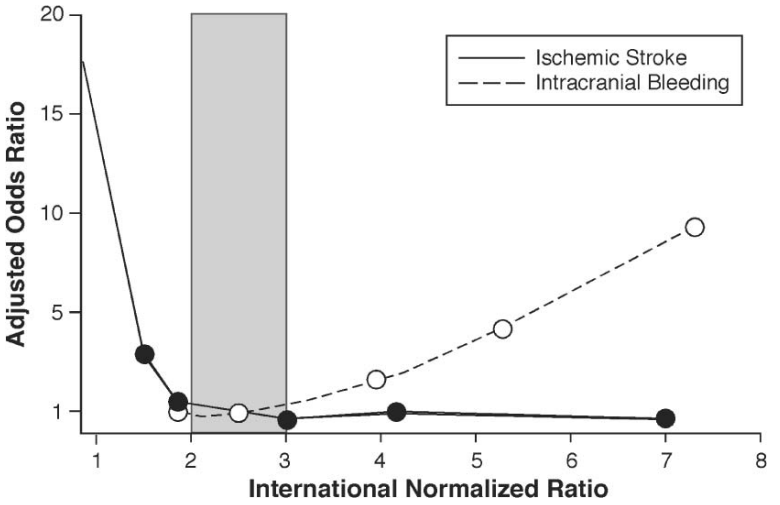


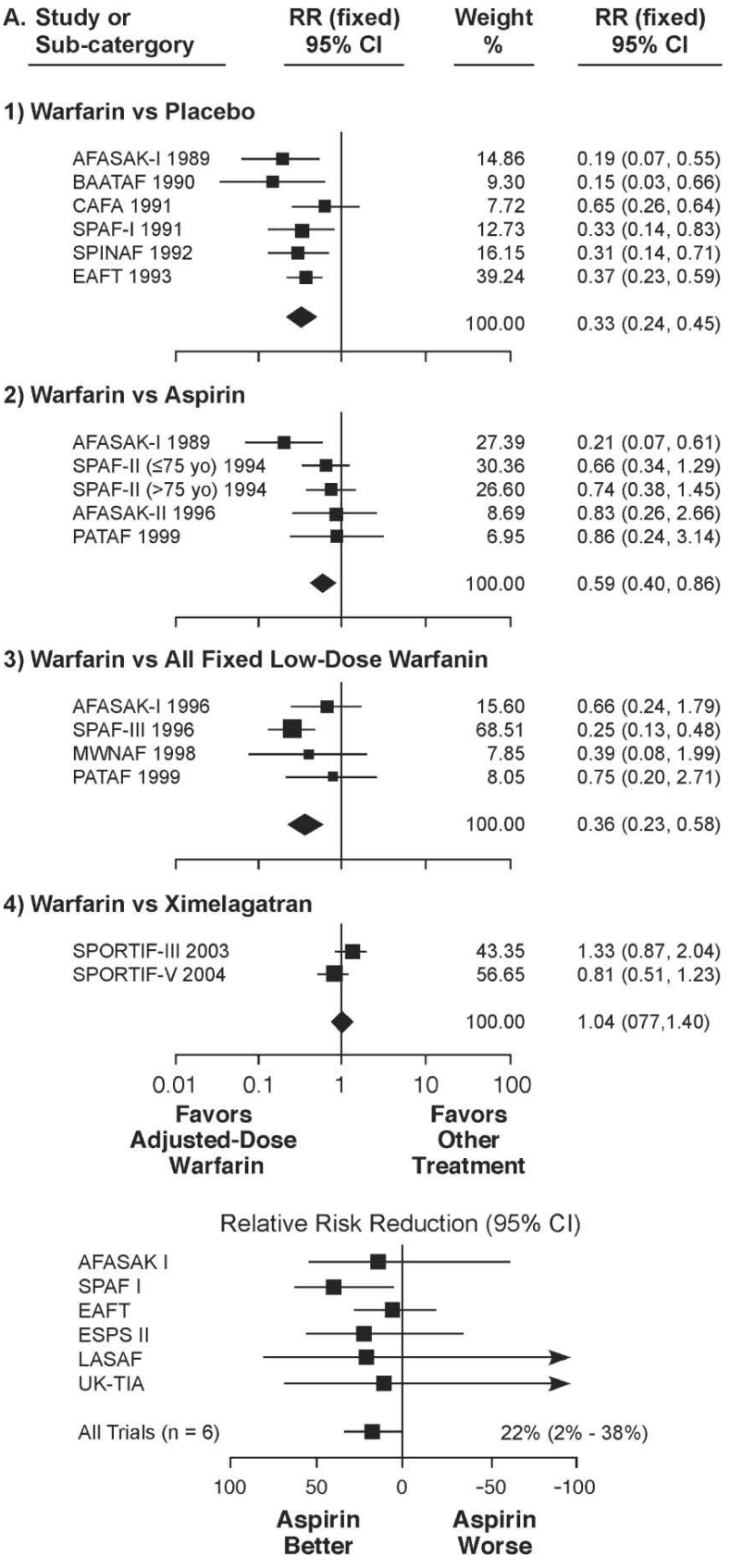
Figure 3 Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation in randomized trials of antithrombotic therapy for patients with atrial fibrillation (AF). (Data from ref. 28.)

among patients with nonvalvular AF. In a meta-analysis of these six trials, adjusted-dose warfarin reduced the relative risk of ischemic stroke or systemic embolism by two thirds (relative risk reduction [RRR] 67%, 95% CI 55% to 77%; $p < 0.00001$).[24] When only ischemic strokes are considered, treatment with adjusted-dose warfarin was associated with a 65% (95% CI 52 to 74) relative risk reduction and was equally effective in preventing disabling and nondisabling strokes.[25] The absolute benefit conferred by warfarin in an individual is greater with increasing risk of a cardioembolic event. The absolute risk reduction for all strokes is far greater for secondary stroke prevention (8.4% a year; number needed to treat for 1 year to prevent one stroke, 12) than for primary prevention (2.7% a year; number needed to treat for 1 year to prevent one stroke, 37).[25] Furthermore, unseen with other antithrombotic therapies, adjusted-dose warfarin significantly reduced all-cause mortality compared with placebo in patients with AF (RR 0.69, 95% CI 0.53 to 0.89; $p = 0.005$).[24]

Adjusted-dose warfarin (target INR 2.0 to 3.5) has also been compared with low or fixed doses of warfarin in a pooled analysis (mean achieved INR 1.1 to 1.4). Adjusted-dose warfarin was superior in reducing the relative risk of stroke or systemic embolism (RRR 64%, 95% CI 42% to 77%; $p < 0.0001$) without a significant excess of major hemorrhages (RRR 24%, 95% CI 58% reduction to 40% increase; $p = 0.38$).[24]

Warfarin vs Aspirin

The superiority of adjusted-dose warfarin compared to aspirin in the primary and secondary prevention of ischemic stroke or systemic embolism in nonrheumatic AF has been confirmed in a meta-analysis of five randomized trials (RRR 41%, 95% CI 14% to 60%; $p = 0.006$).[24] As expected, major (RRR 42%, 95% CI 3% to 65%; $p = 0.04$) and minor (RRR 55%, 95% CI 36% to 68%;


A. Study or Sub-catergory
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
1) Warfarin vs Placebo
AFASAK-I 1989 14.86 0.19 (0.07, 0.55)
BAATAF 1990 9.30 0.15 (0.03, 0.66)
CAFA 1991 7.72 0.65 (0.26, 0.64)
SPAF-I 1991 12.73 0.33 (0.14, 0.83)
SPINAF 1992 16.15 0.31 (0.14, 0.71)
EAFT 1993 39.24 0.37 (0.23, 0.59)
100.00 0.33 (0.24, 0.45)
2) Warfarin vs Aspirin
AFASAK-I 1989 27.39 0.21 (0.07, 0.61)
SPAF-II (≤75 yo) 1994 30.36 0.66 (0.34, 1.29)
SPAF-II (>75 yo) 1994 26.60 0.74 (0.38, 1.45)
AFASAK-II 1996 8.69 0.83 (0.26, 2.66)
PATAF 1999 6.95 0.86 (0.24, 3.14)
100.00 0.59 (0.40, 0.86)
3) Warfarin vs All Fixed Low-Dose Warfanin
AFASAK-I 1996 15.60 0.66 (0.24, 1.79)
SPAF-III 1996 68.51 0.25 (0.13, 0.48)
MWNAF 1998 7.85 0.39 (0.08, 1.99)
PATAF 1999 8.05 0.75 (0.20, 2.71)
100.00 0.36 (0.23, 0.58)
4) Warfarin vs Ximelagatran
SPORTIF-III 2003 43.35 1.33 (0.87, 2.04)
SPORTIF-V 2004 56.65 0.81 (0.51, 1.23)
100.00 1.04 (077,1.40)
0.01 0.1 1 10 100
Favors Adjusted-Dose Warfarin
Favors Other Treatment
Relative Risk Reduction (95% CI)
AFASAK I
SPAF I
EAFT
ESPS II
LASAF
UK-TIA
All Trials (n = 6)
22% (2% - 38%)
100 50 0 -50 -100
Aspirin Better
Aspirin Worse

$p < 0.00001$) bleeding occurred significantly less with aspirin. There was no significantly increased hemorrhagic stroke risk with warfarin compared with aspirin (RR 2.1, 95% CI 1.0 to 4.6).[25]

Limitations of Warfarin

Although warfarin is unequivocally favorable in the vast majority of patients with AF, it has a number of shortcomings, including bleeding and the inconvenience of regular blood testing and dose adjustments. Patients with an INR of 1.7 have twice the odds of stroke (95% CI 1.6 to 2.4), and those with an INR of 1.5 have 3.3 times the odds of stroke (95% CI 2.4 to 4.6 times) as those with an INR of 2.0.[26] An INR above 3.0 increases the risk of major bleeding threefold (OR 3.21, 95% CI 1.24 to 8.28)[27–29] (Figure 3). In addition to its narrow therapeutic window, warfarin has an unpredictable dose–response relationship, delayed onset and offset of action, and significant drug–drug and drug–food interactions.

Overall, if 1,000 patients with nonvalvular AF are treated with warfarin for 1 year, about five intracranial or major extracranial hemorrhages are likely to occur, but 27 strokes will be prevented. Participants with AF in randomized controlled trials anticoagulated with warfarin had a 0.2% per year absolute increase for hemorrhagic stroke and 0.3% per year increase for major extracranial hemorrhage.[1] Patients at high risk of bleeding have the following characteristics: INR values 4.0 or higher; age above 75 years; hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 100 mm Hg); alcoholism or liver disease; poor drug adherence; presence of bleeding lesions (e.g., peptic ulcer disease, intracranial hemorrhage, bleeding diatheses); concomitant use of nonsteroidal anti-inflammatory drugs or specific antibiotics. There is no significant increased hemorrhagic stroke risk with warfarin compared with aspirin.

The elderly are a subset of patients in whom AF is common and with a high attendant thromboembolic absolute risk, but these individuals are also at the highest risk for bleeding complications. Physical frailty, recurrent falls, cognitive impairment, polypharmacy, and other diseases that increase the risk of bleeding not uncommon in this age group mandates individualization of the therapeutic approach after an integrated clinical assessment of each patient.

Figure 4 Anticoagulation for cardioversion of persistent atrial fibrillation. **A** Meta-analysis of ischemic stroke or systemic embolism for adjusted dose warfarin compared with placebo, aspirin, fixed low-dose warfarin (with or without aspirin), and ximelagatran in patients with nonvalvular atrial fibrillation. **B** Meta-analysis of trials comparing aspirin with placebo in reducing risk of thromboembolism in patients with atrial fibrillation. *AFASAK* Copenhagen atrial fibrillation, aspirin, and anticoagulation study, *BAATAF* Boston Area Anticoagulation Trial for Atrial Fibrillation, *CAFA* Canadian Atrial Fibrillation Anticoagulation study, *EAFT* European Atrial Fibrillation Trial, *ESPS* European Stroke Prevention Study, *LASAF* Low-Dose Aspirin, Stroke, and Atrial Fibrillation pilot study, *MWNAF* Minidose Warfarin in Non-rheumatic Atrial Fibrillation, *PATAF* Primary Prevention of Arterial Thromboembolism in Non-rheumatic Atrial Fibrillation, *SPAF* Stroke Prevention in Atrial Fibrillation study, *SPINAF* Stroke Prevention in Non-rheumatic Atrial Fibrillation, *SPORTIF* Stroke Prevention Using the Oral Thrombin Inhibitor in Patients with Non-valvular Atrial Fibrillation, *UK-TIA* United Kingdom Transient Ischemic Attack. (From *Heart* 2006;92:155–161.)

Conversely, the severe disability and cost of rehabilitation and long-term care for survivors are substantial.

In the absence of adequate anticoagulation, cardioversion is associated with a 5% to 7% risk of thromboembolic complications, which may be effectively reduced by adequate anticoagulation to less than 1%.[30–33] For patients with AF duration of 48 h or longer or unknown or uncertain duration, for whom elective cardioversion is planned (electrical or pharmacological), therapeutic warfarin (target INR 2.0 to 3.0), for at least 3 weeks before elective cardioversion and continued at least until sinus rhythm has been maintained for 4 weeks after successful cardioversion, is recommended. The importance of achieving a therapeutic anticoagulation status prior to cardioversion is underscored by studies showing up to a 14% incidence of left atrial or left atrial appendage thrombus in the presence of abbreviated courses or subtherapeutic international normalized ratios.[34,35] An alternative strategy is anticoagulation and screening multiplane transesophageal echocardiography (TEE); if no thrombus is seen, cardioversion can proceed, and therapeutic anticoagulation is continued for at least 4 weeks. Warfarin is still required for at least 4 weeks after cardioversion owing to variability in the return to fully coordinated function; but the total duration of anticoagulation can be significantly reduced with the screening TEE strategy. Therapeutic anticoagulation may need to be given long term in patients with stroke risk factors or those at high risk of AF recurrence, which may be asymptomatic. In patients presenting with a shorter duration of AF (<48 h), the risk of thromboembolism following cardioversion is lower. While anticoagulation before cardioversion is generally recommended in these patients, TEE is usually not mandated unless patients are at high risk for thromboembolism.

Anticoagulation for Acute Stroke

There have been few trials involving anticoagulant treatment of patients with AF presenting with acute stroke. A computed tomogram or magnetic resonance image to confirm the absence of intracranial hemorrhage is mandatory. In patients with AF and no evidence of hemorrhage or a small infarct, anticoagulation with a target INR of 2.0 to 3.0 can be initiated provided the patient is normotensive. If a large infarct is revealed, the initiation of anticoagulation should be delayed for 2 to 4 weeks because of the potential risk of hemorrhagic transformation. The presence of intracranial hemorrhage is a contraindication to immediate and possibly future use of anticoagulation for thromboprophylaxis in AF. Randomized trials comparing aspirin with heparin during the first 2 weeks of acute ischemic stroke among patients in AF showed no benefit from early anticoagulation because any net gains from reduction in ischemic strokes were offset by the excess hazards of hemorrhagic stroke.[36,37]

Bridging Antithrombotic Therapy

Randomized controlled trials of bridging therapy in patients with AF in the periprocedural period are lacking. When cessation of warfarin therapy is required because of a surgical procedure, it is necessary to stratify the vascular invasiveness of the procedure and the short-term risk of thromboembolism.

For minor procedures, warfarin can be continued at a decreased dose. Warfarin is usually withheld for 4 to 5 days before a major procedure as the INR will usually remain above or close to 2.0 for up to 2 days after cessation. Patients at high risk of thromboembolism (e.g., with a prosthetic mitral valve, who had a prior thromboembolism while on subtherapeutic anticoagulation) should receive unfractionated or low molecular weight heparin during warfarin cessation. Warfarin should be recommenced as soon as possible after an invasive procedure unless there is evidence of bleeding. It will take 4 or 5 days before therapeutic anticoagulation will be achieved after restarting warfarin, so heparin should be restarted 12 h after surgery and continued until the INR is therapeutic in patients at high risk of thromboembolism. There is no consensus on whether bridging thromboprophylaxis should be applied to intermediate- and low-risk patients.

Aspirin

The importance of platelet activation in the setting of AF is ill defined. Atrial fibrillation commonly coexists with vascular disease, and the benefits of aspirin in AF may relate to the effect on vascular disease rather than thrombogenesis in AF. No trial has shown antiplatelet therapy to be equivalent to adjusted-dose warfarin in patients at high risk for embolic events.

Aspirin vs Placebo

When the effects of aspirin are compared with those of placebo, aspirin confers modest protection against stroke in patients with nonvalvular AF. In the large Antithrombotic Trialists' Collaboration meta-analysis,[38] the proportional reduction in vascular events was 19% with 500 to 1,500 mg aspirin daily, 26% with 160 to 325 mg daily, and 32% with 75 to 150 mg daily; however, 75 mg aspirin daily had a somewhat smaller effect with a proportional reduction of 13%. In a pooled analysis of the six main randomized trials, aspirin (dose ranged from 25 mg twice daily to 1,300 mg daily) showed a 22% relative risk reduction (95% CI 2% to 38%) in the incidence of stroke when compared with control in patients with vascular disease risk factors (Fig. 4B).[25] Although all of the six randomized trials showed a trend toward reduced stroke with aspirin compared to placebo, only one study showed a significant benefit. Aspirin appeared to best serve those younger than 75 years and did not prevent severe disabling or recurrent strokes.[14]

The optimal dose of aspirin for AF thromboprophylaxis is controversial. Many clinicians administer low-dose aspirin (<100 mg daily) or clopidogrel (75 mg daily) concurrently with warfarin in AF patients with concomitant coronary artery or peripheral arterial disease. Such a strategy has not been evaluated by randomized controlled trials and may be associated with an increased risk of bleeding. With the increasing use of coronary stents, the likely bleeding risk associated with warfarin, aspirin, and clopidogrel has prompted many patients with AF to have warfarin temporarily stopped after coronary stent implantation while they are treated with the aspirin–clopidogrel combination for 2 to 4 weeks, followed by warfarin and 75 mg clopidogrel daily. Evidence is lacking on how best to manage anticoagulation prophylaxis in patients with AF who have a drug-eluting stent (current guidelines recommend 12 months of aspirin–clopidogrel).

Implementation of Trial Evidence to Clinical Practice

Current guidelines for anticoagulation in AF have been published by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Table 3).[15] Despite the overwhelming evidence in favor of adjusted-dose warfarin for the prevention of stroke in patients with AF, numerous clinical observational studies have confirmed that fewer than half of all patients eligible for warfarin for AF actually receive it.[39] Furthermore, even among patients who are prescribed warfarin for AF, therapeutic anticoagulation is achieved only about 30% to 50% of the time.[40,41] Poor application of clinical guidelines by physicians, limited availability of anticoagulation monitoring systems, patients' poor understanding of the importance of anticoagulation, inconvenience of dosing and monitoring, and perceived increased bleeding risk all contribute to the underutilization of anticoagulation for AF in clinical practice.

Low Molecular Weight Heparin

There is a paucity of randomized controlled trials assessing the efficacy of low molecular weight heparin for prevention of thromboembolism in AF. The subcutaneous route of low molecular weight heparin has practical limitations for use in long-term anticoagulation. Results from a small randomized ACE (Anticoagulation for Cardioversion Using Enoxaparin) trial could only demonstrate enoxaparin to be noninferior to heparin and phenprocoumon, an oral vitamin K antagonist with a serum half-life longer than warfarin.[42]

The Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) II randomized trial compared the safety and efficacy of enoxaparin with unfractionated heparin as antithrombotic bridging therapy in patients with AF of greater than 48 h duration undergoing TEE-guided cardioversion.[43] Preliminary results suggest similar safety between the two anticoagulation

Table 3 Recommendations of the ACC/AHA/ESC guidelines for long-term anticoagulation.

Risk	Patient characteristics	Therapy
Very low	<60 years old, no structural heart disease (lone AF)	Aspirin 325 mg/day or no therapy
Low	<60 years old, structural heart disease but no risk factors for embolism	Aspirin 325 mg/day
	≥60 years old, no risk factors for embolism	
High	≥60 years old, diabetes mellitus or coronary artery disease	Warfarin (INR 2.0–3.0) ± aspirin 81–162 mg/day
	≥75 years old (especially women)	Warfarin (INR ~ 2.0)
	Heart failure, EF ≤ 35%, hyperthyroidism, hypertension	Warfarin (INR 2.0–3.0)
Very high	Rheumatic valve disease (mitral stenosis)	Warfarin (INR 2.5–3.5)
	Prosthetic valve	
	Previous thromboembolic events	
	Left atrial thrombi confirmed	

ACC American college of Cardiology, *AHA* American Heart Association, *ESC* European Society of Cardiology.
EF ejection fraction, *INR* international normalized ratio.

strategies in terms of ischemic stroke, transient ischemic attacks, peripheral embolism, major and minor bleeding, and death. The duration of hospitalization in the low molecular weight heparin group was less, which has important cost-saving implications.

Thrombin Inhibitors

Ximelagatran is an oral direct thrombin inhibitor with a prompt onset and offset of anticoagulant action, wider therapeutic window, lower potential for food and drug interactions, and no need for dosage adjustments or anticoagulant monitoring compared to warfarin. The Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and V trials randomized more than 7,000 patients with nonvalvular AF to adjusted-dose warfarin (INR 2.0 to 3.0) or fixed-dose ximelagatran.[44] These trials concluded that ximelagatran was not inferior to warfarin for the prevention of stroke and systemic embolic events, with an absolute risk reduction of 0.7% (95% CI –0.1 to 1.4, $p = 0.13$). Rates of major bleeding were similar between the two groups, but minor bleeding was lower in the ximelagatran group. However, an increase in the liver enzyme alanine aminotransferase in 6% of patients and rare cases of hepatic failure were reported.

Factor Xa Inhibitors

A phase III study of the pentasaccharide idraparinux subcutaneously once weekly vs warfarin (AMADEUS) was prematurely terminated because of increased severe bleeding in the idraparinux-treated patients.

Combination Antiplatelet Drugs

Given the effectiveness of aspirin plus clopidogrel in cerebrovascular and cardiovascular disease,[45,46] investigators have initiated studies of combination therapies in patients with AF. In the ACTIVE W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) study, 6,706 patients with AF were randomly assigned to aspirin plus clopidogrel or to warfarin.[47] This trial was stopped prematurely because of a lack of efficacy relative to warfarin. The ACTIVE A is an ongoing randomized trial of aspirin plus clopidogrel vs aspirin alone in patients with AF not willing or capable of using oral anticoagulants.

Direct Current Cardioversion

Electrical cardioversion is recommended if the patient is hemodynamically unstable because of hypotension, cardiac ischemia, or heart failure attributable to AF. It is also reasonable to cardiovert patients with intrusive lethargy or poor exercise capacity in an attempt to maintain sinus rhythm. When AF has been continuously present for more than a week, electrical cardioversion is the preferred method for achieving sinus rhythm.

Pharmacological cardioversion with class Ic, III, and Ia antiarrhythmics are less effective than electrical cardioversion, but these are acceptable alternatives for recent-onset AF (<7 days, preferably < 72 h). Hospitalization is often recommended for initiation of class Ia or III antiarrhythmic drugs, which prolong repolarization.

Transthoracic electrical cardioversion has an overall success rate of 75% to 93%, which is inversely related to the chest wall impedance, duration of AF, left atrial size, and underlying heart disease.[48–50] Higher success rates and a lower energy requirement are reported with the anteroposterior electrode placement compared to an anteroapical position for monophasic direct current cardioversion.[51,52] Biphasic defibrillators reverse current polarity 5 to 10 ms after the shock delivery begins and are more effective with less energy delivered than monophasic devices.[53,54] Less total energy is delivered when a higher initial shock is used, with 200 J recommended using a monophasic waveform. Lower energy is required (e.g., 75 to 120 J) when a biphasic waveform is used. Pretreatment with antiarrhythmic therapy prior to electrical cardioversion can enhance immediate success and suppress early recurrences of AF.

The Future

In recent years, significant progress has been made in understanding the electrophysiological mechanisms of AF. Ideally, this would lead to effective preventive and curative therapies. However, it is uncertain whether this will necessarily translate into reduction of stroke risk and abolish the need for antithrombotic therapy. New antithrombotic agents, pacing techniques, and surgical and catheter-based procedures under development should be rigorously compared before superseding warfarin.

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13

Current Role of Medical Therapy for Prevention or Termination of Atrial Fibrillation

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Abstract: Antiarrhythmic drug therapy is the mainstay for managing atrial fibrillation (AF). The main limitations of antiarrhythmic drug therapy include limited efficacy, potential adverse effects, and the palliative nature of this treatment option. Nevertheless, substantial evidence has emerged suggesting that drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor-blocking agents can reduce the frequency of AF episodes and may even prevent its development. There have been several trials conducted to assess the efficacy and risks of several antiarrhythmic agents. Amiodarone has clearly been shown to be the most effective in the majority of these trials; however, it is associated with several cardiac and noncardiac adverse effects. Propafenone is considered to be the best-tolerated drug currently available; however, class 1c agents are associated with increased risk of ventricular fibrillation in patients who have survived a myocardial infarction. Sotalol and dofetilide prolong the QT interval and in some patients can cause torsades de pointes. The efficacy of pharmacological conversion depends on the duration of AF. Dofetilide, flecainide, ibutilide, and profenone are considered first line and amiodarone second line for pharmacological conversion. In trials, dofetilide and ibutilide appear to have the highest rate of conversion to sinus rhythm. In patients with structural heart disease or prolonged QRS duration, dofetilde and amiodarone are the first choice. In the absence of structural heart disease, ibutilde, flecainide, and propafenone can be used. The "pill-in-the-pocket" approach suggests that patients with new-onset AF should be treated in the emergency room with an oral class 1c agent. Treatment with both flecainide and propafenone was successful in 94% of episodes, the time to resolution of symptoms was 113 ± 84 min, and 7% of patients reported adverse effects. Newer agents, such as dronaderone and azimilide, are still in the investigational stage.

Keywords: Adverse effects; Amiodarone; Angiotensin-converting enzyme inhibitors; Angiotensin receptor blocking; Antiaarhythmic agents; Dofetilide; Flecainide; "Pill-in-the-pocket" concept; Propafenone.

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Antiarrhythmic Drugs to Prevent Atrial Fibrillation

Antiarrhythmic drugs continue to be the most widely used means to control atrial fibrillation (AF) even though several clinical trials have not shown any reduction in mortality or other cardiovascular events with their use.[1,2] The reasons for this are that there are many patients who want to be relieved of the symptoms associated with AF, which can include palpitations and occasionally other more severe manifestations, such as angina or heart failure. Rate control approaches are not always optimal for doing this or produce a less-desirable result because of side effects of rate-slowing drugs.[3–9] Compared to ablation, the antiarrhythmic drugs have the appeal of being simple and more widely available to apply with no surgical risks. The main disadvantage of pharmacological therapy is the limited efficacy and significant rate of adverse effects that frequently lead to intolerance and discontinuation. In addition, these agents do not cure AF but merely suppress its occurrence to a greater or lesser extent.

A new concept is that we may be able to prevent or suppress AF by means of agents that do not primarily target the substrate of AF, as has been approached by traditional antiarrhythmic agents. There is now substantial evidence that some of the antihypertensive agents, in particular the angiotensin receptor blocking (ARB) agents and the angiotensin-converting enzyme (ACE) inhibitors, can reduce AF and possibly even prevent its development.[10] The present chapter reviews the current role of medical therapy for the management of AF.

Currently Available Agents for Long-Term Use

There are several effective antiarrhythmic agents in clinical use, including amiodarone, propafenone, flecainide, sotalol, and dofetilide. Of these, amiodarone is by far the most effective. The Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) compared amiodarone to sotalol and placebo in patients with paroxysmal AF lasting more than 72 h.[11] The median time to recurrence of AF was markedly increased by amiodarone compared to either sotalol or placebo.[11] The superiority of amiodarone was first shown in the Canadian Trial of Atrial Fibrillation (CTAF).[12] Recurrence of AF after a mean follow-up of 16 months was 35% in the amiodarone group compared to 63% in either the propafenone or sotalol group.[12] These results have been replicated in a substudy of Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) in which amiodarone maintained sinus rhythm after 1 year in 62% compared to 38% and 23% taking sotalol or class I agents, respectively.[13]

The other agent is dofetilide, available only in the United States. It has been shown to be better than placebo against intermittent AF but has not been systematically compared to the other agents. A substudy of the DIAMOND trial[14] has investigated the efficacy of 250 μg dofetilide vs placebo in converting AF/atrial flutter to sinus rhythm and maintenance of sinus rhythm in both groups. Cardioversion occurred in 44% of the dofetilide group and in 14% of the placebo group over the course of the study ($p < 0.001$). A 1-year probability of maintaining sinus rhythm was 79% in the dofetilide group and

42% in patients receiving placebo. Dofetilide was a strong predictor of maintaining sinus rhythm (relative risk [RR] 0.30, 95% CI 0.19 to 0.48; $p < 0.001$). Mortality was similar in both groups; however, maintenance of sinus rhythm was a predictor of lower mortality (RR 0.44, 95% CI 0.30 to 0.64; $p < 0.0001$). Although these agents are clearly more effective than placebo, it is also clear that these agents typically work very well in only a limited number of patients or only partially suppress AF recurrences. Maintenance of sinus rhythm markedly declines over time, as shown by AFFIRM, in which 62% were in sinus rhythm after 5 years.[2] In contrast, rate control improved over time.[2]

Five randomized trials comparing rhythm vs rate control and including over 5,000 patients have been published,[7–9] and all have demonstrated that both strategies yield similar results. Of note, these studies underrepresented younger patients with lone AF and patients with heart failure.

Adverse Effects of Antiarrhythmic Drugs

All antiarrhythmic agents have adverse effects or potential adverse effects that limit their use.[15,16] Propafenone is perhaps the best tolerated of the currently available drugs, although some annoying side effects may occur, such as foul taste.[17–20] However, the concern with propafenone is that it is a member of the group of drugs that partially block the sodium channel. This class of drugs, which included flecainide[21,22], a drug similar to propafenone and available for use, was shown to increase mortality in patients who survived myocardial infarction in the Cardiac Arrhythmia Suppression Trial (CAST).[23] The increased mortality may be because of an increase in the propensity to have ventricular fibrillation (the so-called proarrhythmic effect) (Table 1). Therefore, current guidelines restrict the use of propafenone to patients without coronary

Table 1 Proarrhythmia: mechanism, incidence and complications.

Drug	Type or class	Mechanism	Estimated incidence	Complication
Propafenone[15,16,18–20]	IC	Slow atrial flutter cycle length, 1:1 conduction	6–9%	Rapid atrial flutter
Flecainide[15,16,21–23]	IC	Widening of the QRS interval Inducing VT*	10–30% when given intravenously Up to 60%	Paroxysmal AV block VT arrest/SCD
Sotalol[24,26]	III	QT prolongation + bradycardia	2–7% (dose dependent)	TdP
Amiodarone[26,27]	III	QT prolongation + bradycardia	2%	TdP
Dronaderone[54]	III	–	0%	–
Azimilide[58,59]	III	QT prolongation	1.5–2%	TdP
Dofetilide[14]	III	QT prolongation	1.6%	TdP
Ibutilide[47,49,50]	III	QT prolongation + bradycardia	1.8–8.3%	TdP

*CAST I trial[40] showed a higher fatality rate in the treated group (flecainide/encainide) (55% vs 17%; $p < 0.0001$).
AV atrioventricular, *SCD* sudden cardiac death, *TdP* torsades de pointes, *VT* ventricular tachycardia.

artery disease and depressed left ventricular function. These drugs can also exacerbate heart failure, and their use must be avoided in patients with left ventricular dysfunction; although safe in carefully selected patients, the safety of propafenone and flecainide remains of some concern.[15,20,22]

Proarrhythmia is also a concern with the use of sotalol[24–26] and dofetilide,[14] although the mechanism is different. Both of these agents prolong the QT interval and in some patients cause fatal arrhythmias, primarily torsades de pointes. These drugs can interact with other mechanisms that prolong the QT interval, such as low serum potassium. Some individuals are predisposed to excessive QT prolongation but are hard to identify reliably before the potentially lethal arrhythmia occurs. Women and patients on potassium-losing diuretics are at risk for excessive QT prolongation.[15,24,25] Therefore, sotalol and dofetilide must be used cautiously and monitored carefully to reduce the risk of this serious outcome.

The amiodarone safety profile is a study of contrasts. Despite the fact that it prolongs the QT interval extensively, it is largely free of risk of proarrhythmia, although torsade de pointes can very rarely occur.[26,27] Furthermore, it can be used safely in heart failure and indeed is the drug of choice in heart failure patients who need an antiarrhythmic drug. On the other hand, amiodarone has several potentially serious cardiac and noncardiac adverse effects. It causes some bradycardia in all patients, and occasionally this can be extreme. Amiodarone causes hepatotoxicity rarely and pulmonary fibrosis in about 1% of patients.[28] These effects are dose dependent and occur less frequently at doses that may be effective against AF (200 mg per day or less). Amiodarone may cause either hypo- or hyperthyroidism. This potential for serious adverse effects limits the use of this drug.[26] Table 1 summarizes the most frequent drugs involved in proarrhythmia with their proposed mechanism and associated complications.

Inhibition of the Renin–Angiotensin System for the Prevention of Atrial Fibrillation

Even though agents that block the renin–angiotensin system (RAS) cannot be considered traditional antiarrhythmic agents, beneficial effects of ACE inhibitors in preventing ventricular arrhythmias in patients with coronary artery disease and left ventricular dysfunction were suggested more than 20 years ago.[29–32] More recent data also described such a benefit for ACE inhibitors and ARBs in preventing supraventricular arrhythmias such as AF. In the Trandolapril Cardiac Evaluation (TRACE) study, trandolapril treatment for 2 to 4 years was associated with an odds ratio (OR) of 0.45 vs placebo ($p<0.01$) in reducing the risk of AF,[33] which was also confirmed by data from studies of Left Ventricular Dysfunction (SOLVD).[34] for enalapril and after a mean follow-up of 2.9 ± 1.0 years (hazard ratio [HR] 0.22 vs placebo, $p<0.0001$).

Clinical efficacy of ARBs in preventing the occurrence of AF episodes has been shown for valsartan,[35] candesartan,[36] losartan,[37,38] and irbesartan.[39] The most comprehensive analysis, published by Healey et al.,[10] analyzed a total of 11 randomized, controlled, parallel-design studies and included 56,308 patients. Overall, ACE inhibitors and ARBs reduced the relative risk of AF occurrence by 28% (95% CI 15% to 40%; $p=0.0002$), showing a similar

benefit for ACE inhibitors (28%; $p = 0.01$) and ARBs (29%; $p = 0.00002$). However, the largest effect was seen in patients with heart failure (relative risk reduction [RRR] 44%; $p = 0.007$). Although not significant, relative risk ratios of 12% and 27% were detected in patients with hypertension and postmyocardial infarction, respectively. Only two small prospective studies in patients with AF (most of the patients had hypertension with preserved systolic function) showed a reduction in AF recurrence after electrical cardioversion. However, there were only a short follow-up period and no placebo control group in both studies.

Several potential mechanisms explaining the clinical efficacy of ACE inhibitors and ARBs in preventing AF have been proposed.[40] Cardiac structural remodeling because of an activated RAS system, leading to left ventricular hypertrophy, heart failure, left atrial enlargement, and subsequent AF could be one potential target for RAS-blocking agents in the prevention of AF. Another mechanism, strongly interrelated with structural remodeling, is electrical remodeling, describing changes in the electrophysiological properties of the atria, such as shortening of the atrial effective refractory period (AERP) and slowing of atrial conduction velocity.[41,42] A growing body of evidence suggests that RAS-blocking agents may attenuate or even reverse aspects of cardiac structural remodeling as ACE inhibitors and ARBs have been shown to reduce left ventricular hypertrophy among patients with hypertension. However, data on the efficacy of RAS-blocking agents on electrical remodeling in humans are sparse, mainly because serial electrophysiological testing is difficult to perform. Furthermore, certain genetic polymorphisms of RAS genes seem to be more frequent in patients with AF, suggesting also a genetic predisposition to developing AF.[43]

In summary, data from several larger but also smaller clinical trials suggest similar effects of ACE inhibitors and ARBs on the prevention of AF in patients with heart failure, postmyocardial infarction, and hypertension. However, the largest risk reduction (RRR 44%) was seen in patients with heart failure; there is currently insufficient data to support the use of ACE inhibitors or ARBs for prevention of AF recurrence after electrical cardioversion. More data from prospective clinical trials will be required to assess the clinical value of RAS-blocking agents in AF. The largest study ongoing is Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-I) (n = 9,000 patients), which is investigating not only the effects of irbesartan vs placebo in patients with AF on the primary composite outcome of stroke, myocardial infarction, and vascular death, but also the occurrence of paroxysmal AF and structural cardiac remodeling.

Pharmacological Cardioversion

Pharmacological cardioversion has been used for decades, but the bulk of evidence is limited by small studies with varied inclusion criteria, doses, and duration of drug administration, making it difficult to compare among studies. No direct comparisons between pharmacological and electrical cardioversion are available; however, the introduction of biphasic electrical cardioversion seems to be clearly superior.[44] The main caveat with pharmacological cardioversion is the risk of developing toxic effects. The risk of thromboembolic events is comparable between pharmacological and electrical cardioversion

(<1%), particularly when attempted within 48 h of onset.[45] Successful restoration of sinus rhythm depends primarily on the duration of AF and has been estimated as between 60% and 90%.

The most effective time window in which pharmacological cardioversion appears to be indicated is within 7 days of onset of newly detected AF.[46] Efficacy is markedly reduced after 48 h of onset of AF (less than 50%). Persistence of AF is also a factor that limits the success of pharmacological cardioversion. Selection of antiarrhythmic agent is largely a matter of preference and not evidenced based. Underlying heart disease, presence of left ventricular dysfunction as well as evidence of electrocardiographic (ECG) abnormalities such as conduction disorder or widened QRS aid in the selection of the agent.

The recently revised American Heart Association/American College of Cardiology/European Society of Cardiology (AHA/ACC/ESC) AF guidelines provide recommendations for the use of pharmacological cardioversion of AF detected less than or longer than 7 days after occurrence. The agents with proven efficacy for pharmacological cardioversion of recent-onset AF (<7 days) include dofetilide, flecainide, ibutilide, and propafenone with a class I, level A recommendation. Amiodarone is a second-line choice, with a class IIa, level A recommendation. Other class I antiarrhythmic agents were considered less effective or poorly studied and given a class IIb, level B recommendation. Of note, digoxin and sotalol were considered contraindicated for pharmacological cardioversion of AF.[44] Similar recommendations were provided for cardioversion of AF lasting more than 7 days, with only dofetilide receiving a class I, level A recommendation. Amiodarone and ibutilide have a class IIa, level B recommendation, with the rest of the antiarrhythmics all considered less effective and with a class IIb, level B recommendation.

The success rate of conversion into sinus rhythm with the most effective agents (ibutilide and dofetilide) is only in the range of 30% to 40%.[47,48] Side effects include polymorphic ventricular arrhythmias caused by excessive QT interval prolongation in up to 8%.[47,49–50] The main shortfall with the most effective agent, dofetilide, is the need to adjust the dose according to creatinine clearance, making its widespread use cumbersome.[14]

Oral amiodarone has similar success rates of conversion to sinus rhythm when compared to sotalol in persistent AF: amiodarone 27% vs sotalol 24%. However; both were superior to placebo (0.8%) ($p < 0.001$).[11]

Pharmacological Cardioversion for Paroxysmal Atrial Fibrillation

Pharmacological restoration of sinus rhythm in paroxysmal AF lasting less than 48 h can be achieved in up to 40% of cases. Selection of agent can be based on the presence or absence of structural heart disease. In the presence of structural heart disease or prolonged QRS duration, dofetilide and amiodarone are the first choice. In the presence of minimal or no structural heart disease, ibutilide, flecainide, and propafenone are acceptable options.[44,46]

The Pill-in-the-Pocket Concept

The efficacy of both oral flecainide and propafenone (in-hospital administration) is similar to that reported for intravenous administration (58% to 95%). However; the conversion to sinus rhythm may take longer (2 to 4 h). The incidence of

serious adverse events such as atrial flutter with rapid 1:1 conduction is exceptional (<1%), and this approach is contraindicated in patients with left ventricular dysfunction or heart failure.[51,52] A multicenter Italian trial[53] tested the hypothesis of treating patients with new-onset AF with the "pill-in-the-pocket" approach.

Patients were initially treated at the emergency room with flecainide (200 to 300 mg) or propafenone (450 to 600 mg). During a follow-up of 15 ± 5 months, 165 patients (79%) had a total of 618 episodes, and 92% of these episodes were treated. The mean time for treating the episode after the onset was 36 ± 93 min. Treatment with both flecainide and propafenone was successful in 94% of the episodes, and the time to resolution of the symptoms was 113 ± 84 min. Adverse events were reported in 7%, with only 1 patient experiencing atrial flutter with 1:1 conduction. The pill-in-the-pocket approach requires stratifying the patient (left ventricular function, QRS duration, female gender) to select the appropriate candidate.

In patients with lone AF and normal structural heart, IC drugs maybe initiated in an outpatient basis. For patients with structural heart disease, long QT interval, wide QRS, or suspected Brugada syndrome, drugs can be started once proved safe in hospital.[44]

Newer Agents

Several newer agents have been tested in patients with AF. This section briefly reviews some information regarding ongoing trials.

Dronaderone

Dronaderone is a new antiarrhythmic agent analogous to amiodarone but lacking an iodine moiety, thus reducing amiodarone's side effects.

Only one published randomized controlled trial, the Dronaderone Atrial Fibrillation Study After Electrical Cardioversion (DAFNE)[54]is available. Another two ongoing trials have presented preliminary results; the European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronaderone for the Maintenance of Sinus Rhythm (EURIDIS)[55] and the American–Australian–African Trial with Dronaderone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS).[55] Other ongoing randomized trials include the Efficacy and Safety of Dronaderone for the Control of Ventricular Rate during Atrial Fibrillation (ERATO) trial[56]) and finally another ongoing trial assessing the efficacy of dronaderone in prevention of hospitalization and death in high-risk AF patients A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation (ATHENA).

The DAFNE trial[54] compared three different doses of dronaderone (800, 1,200, 1,600 mg/day) vs placebo. Dronaderone at 800 mg/day prolonged the time to first recurrence after pharmacological or electrical cardioversion (5.3 days in the placebo groups vs 60 days in the dronaderone group; RR 55%, 95% CI 28% to 72%; $p = 0.001$) and increased the rate of spontaneous cardioversion ($p = 0.026$). In addition, a lower ventricular rate response was documented during AF recurrence (0.0001).

Preliminary data from EURIDIS and ADONIS,[55–57] comparing 400 mg dronaderone twice daily to placebo, demonstrated a reduction in the risk of

recurrence of AF/atrial flutter (EURIDIS RR 0.78, 95% CI 0.64 to 0.95; $p = 0.0318$ and ADONIS RR 0.78, 95% CI 0.59 to 0.89; $p = 0.0017$). Other significant advantages were shorter time to first recurrence in the dronaderone group and a slower ventricular rate during AF recurrence (EURIDIS $p = 0.0001$, ADONIS $p = 0.001$). Preliminary data from ERATO indicated that dronaderone in addition to β-blockers, calcium channel blockers, or digitalis is effective to control the ventricular rate in permanent AF. The ATHENA trial will provide further information on the role of dronaderone in the reduction of Cardiovascular (CV) hospitalizations and death of any cause in more than 3,500 high-risk AF patients.

Azimilide

Azimilide is a new class III antiarrhythmic agent that blocks both the slow and fast components of the cardiac-delayed rectifier potassium currents. A meta-analysis of four randomized trials[58] demonstrated that azimilide in doses of 100 and 125 mg/day significantly prolonged the time to first symptomatic recurrence of AF (for 100 mg/day, HR 1.34, 95% CI 1.05 to 1.72; $p = 0.02$, and for 125 mg/day, HR 1.32, 95% CI 1.07 to 1.62; $p = 0.01$). The treatment effect was superior in patients with congestive heart failure. A randomized, placebo-controlled trial comparing 125 mg/day azimilide vs placebo[59] in patients with and without congestive heart failure or coronary artery disease was unable to document any differences in the primary endpoint (time to first symptomatic AF recurrence). The results of this study do not support use of azimilide for the prevention AF in the setting of structural heart disease.

Conclusions

Antiarrhythmic agents have been the mainstream form of therapy for AF for decades in spite of limited efficacy and risk of side effects. Newer developments are in the horizon and will indeed enhance the management of AF. In addition, the recognition that non-antiarrhythmic agents such as ACE inhibitors and ARBs may play a significant role in the prevention of AF opens a new path for its medical therapy.

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Section IV

Atrial Fibrillation Ablation

14

Applied Cardiac Anatomy for Catheter Ablation of Atrial Fibrillation

Kalyanam Shivkumar

Abstract: Catheter ablation for atrial fibrillation (AF) has emerged as a promising treatment strategy. A thorough understanding of cardiac anatomy is vital to prevent complications and for procedure success. Complications secondary to catheter ablation of AF such as atria–esophageal fistula, phrenic nerve damage, pericardial effusion, pulmonary vein stenosis, and tamponade can possibly be prevented by detailed knowledge of cardiac anatomy.

Keywords: Bronchus; Esophagus; Phrenic nerve; Pulmonary veins; Recurrent laryngeal nerve; Transseptal puncture.

Introduction

Catheter ablation procedures for atrial fibrillation are now a well-established therapeutic option for the management of atrial fibrillation. Catheter ablation of atrial fibrillation has also highlighted the need for electrophysiologists to understand cardiac anatomy (with respect to orientation of the atria in relationship to cardiac structures, to each other, and to pericardiac structures such as the esophagus and mediastinal nerves, which can and have been injured because of collateral damage during ablation procedures). Despite variations in specific approaches used by different institutions, the concepts that relate to ablation and potential complications have some common threads and are reviewed in this chapter. The aim of this chapter is to outline key anatomical concepts that relate to various parts of catheter ablation procedures, and strategies to prevent and manage complications are also reviewed. We have tried to use the ECWG (European Working Group) and NASPE (North American Society of Pacing and Electrophysiology) criteria for defining the atrioventricular junction location[1] if appropriate.

Anatomy of the Atrial Septum and Transseptal Catheterization

A central concept for transseptal catheterization involves the recognition of the fact that the true "interatrial" portion of the septum is primarily the fossa

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ovalis. The flap of the fossa ovalis and the anterior rim of the limbus are the only atrial septal structures that are truly interatrial.[2] Other areas of the septum do not ensure safe passage from the right to the left atrium.

Entry into the aorta and the pericardial space pose extremely serious risks. The medial wall of the right atrium has several structures of anatomical significance. The fossa ovalis is immediately recognizable as a membranous structure (Figure 1A,B). The right atrial aspect of the fossa shows a clear

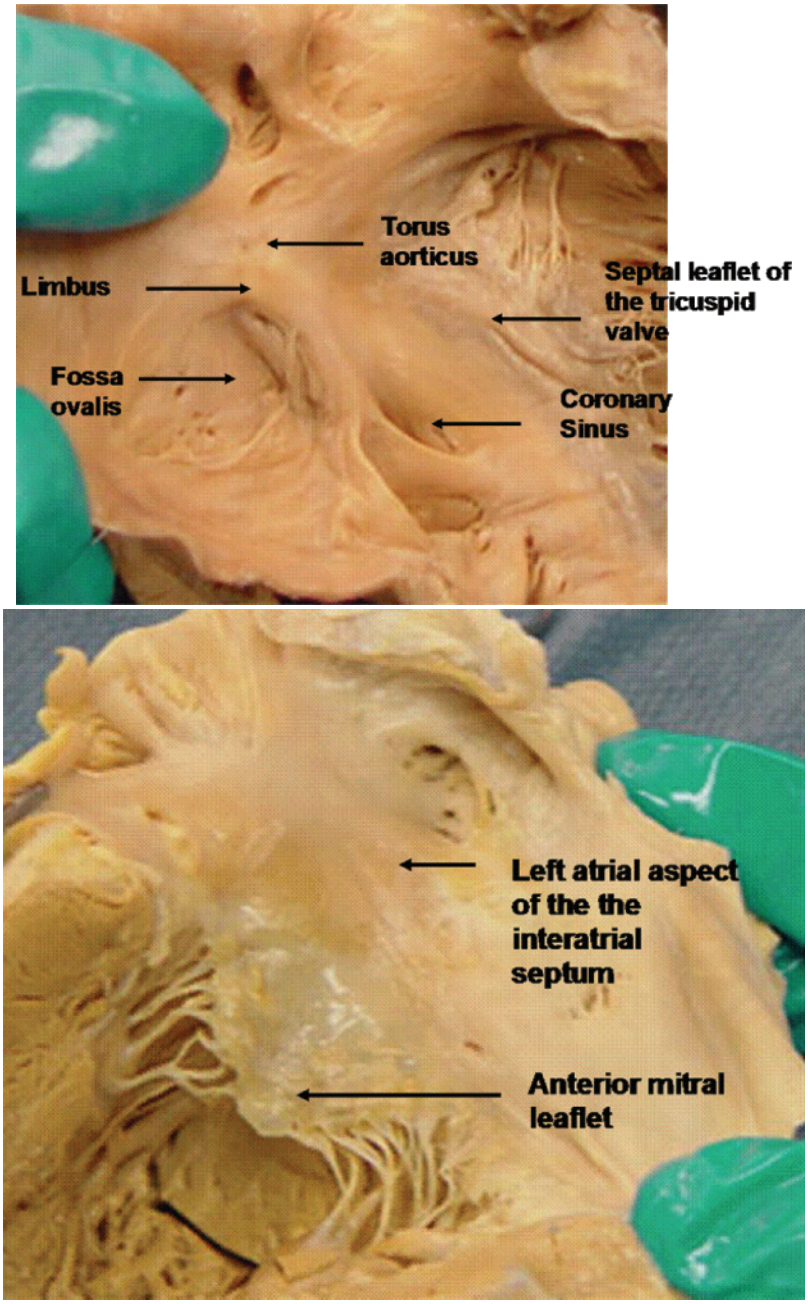

Figure 1 Anatomy of the interatrial septum viewed from the right atrium (**A**) and the left atrium (**B**)

ridge (the limbus), which is not seen on the left atrial side of the septum. The relationship of the aorta to the atria is very intimate, and the atria wrap around the aorta with only the transverse sinus of the pericardium between the atrial walls and the aorta in many places (Figure 2). Aortic entry can occur if the needle is extended superior to the limbus. This results in entry of the needle into the transverse sinus and perforation of the aorta. It is critical to use pressure and contrast injection/staining of structures before advancing sheaths into the presumed left atrium (this remains one of the most avoidable complications in transseptal procedures). Pericardial effusions and tamponade also result from aortic entry because of the interposed transverse sinus.

Further, there is an added risk of entry into the ascending and descending aorta via the left atrium as the aorta wraps around the atrium (Figure 3). Structures that surround the heart provide useful landmarks during transseptal access (Figure 4). The left main bronchus is a reasonably good marker of the roof of the left atrium. It is useful to make a note of this structure during transseptal access to assess the range of movement possible when the left atrium is entered. In the early days of catheterization, transbronchial and suprasternal notch needle entry (via the aortic arch) were used to enter the left atrium.

Several variants of this region have an impact on transseptal catheterization; these include lipomatous hypertrophy, fibrosis (which is noted in repeat transseptal procedures),[3] and interatrial septal aneurysms. Further, the presence of a persistent left superior vena cava also makes left atrial access challenging, mainly by the deformation of the medial right atrial wall by the large coronary sinus. The fossa ovalis and these anatomic variants are instantly recognizable on intracardiac echocardiography (ICE), and this imaging modality can facilitate safe transseptal puncture.[4,5]

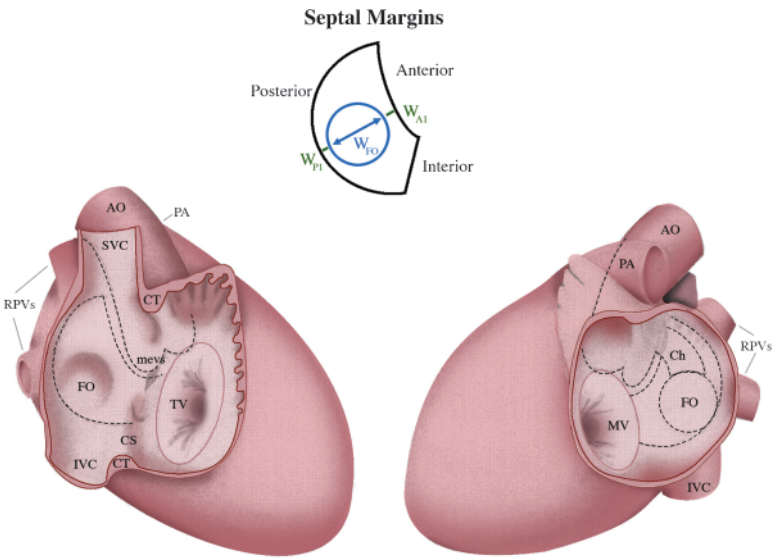

Figure 2 The anatomy of the human atrial septum in relation to the aorta

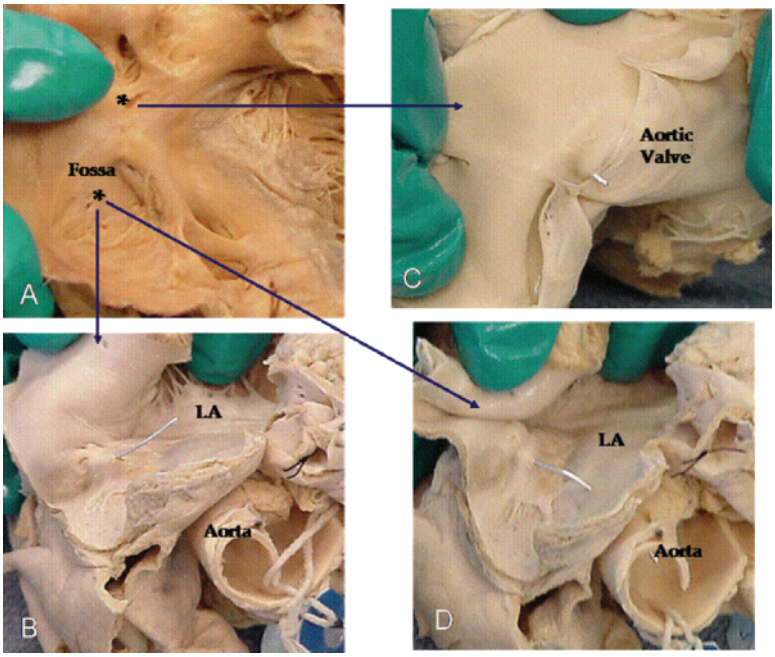

Figure 3 A–D Risks of transseptal puncture. The asterisk shows site of entry. **C** Aortic entry when the region beyond the superior limbus is penetrated. **C** and **D** Access of the LA and perforation of the aorta (which can occur by overcorrection of the needle to less than 3 o'clock after transseptal crossing). *Fossa* fossa ovalis, *LA* left atrium

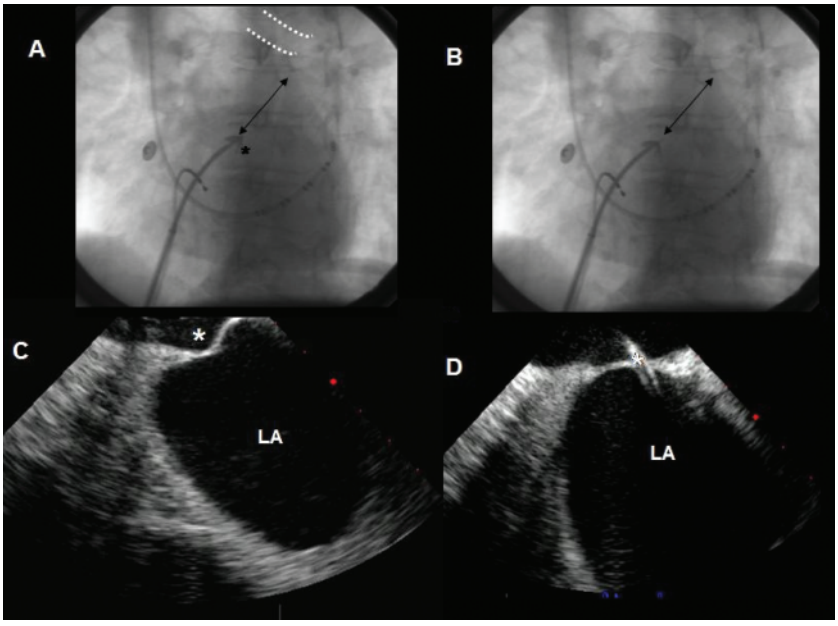

Figure 4 A–D Fluoroscopy and intracardiac echocardiography (ICE) for transseptal access. **A** Contrast staining of the septum (asterisk) and the left bronchus (interrupted line). The arrow in **B** shows the available room to move within the left atrium (LA)

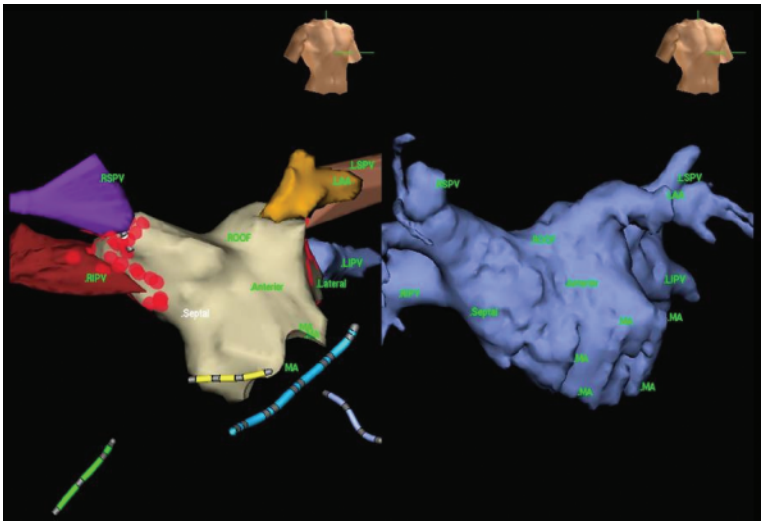

Figure 5 Electroanatomical map and three-dimensional computed tomographic (CT) reconstruction of the left atrium (LA) and pulmonary veins (PV). *MA* mitral annulus

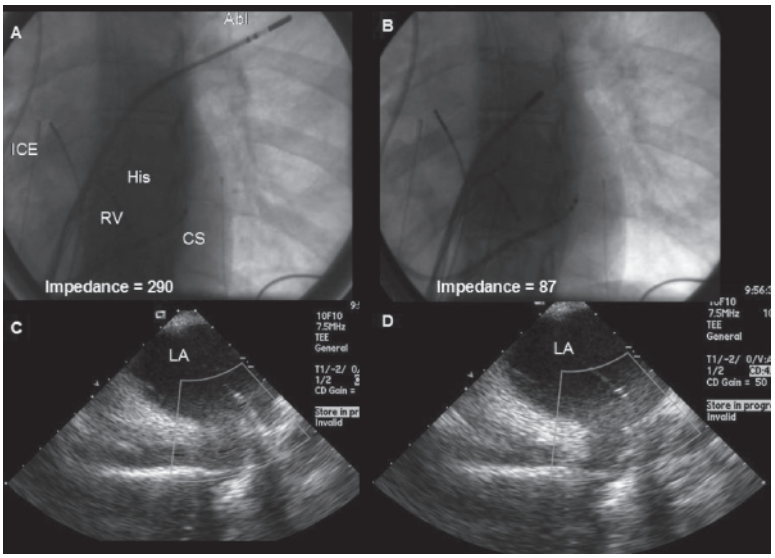

Figure 6 A–D Fluoroscopy and intracardiac echocardiography (ICE) images showing location of the ablation catheter and corresponding ICE view. *Abl* ablation catheter, *CS* coronary sinus, *His* His bundle catheter, *LA* left atrium, *RV* right ventricle. (Adapted from ref. 12 with permission.)

Anatomy of the Atria and the Pulmonary Veins

The true atria are normally thin-walled structures (~4 mm); however, the atrial wall can become thinner and taper (2.0 mm) near the atrioventricular grooves.[6] There is considerable anatomic heterogeneity with respect to atrial thickness within the anterior, superior (dome), posterior, and lateral portions of the left

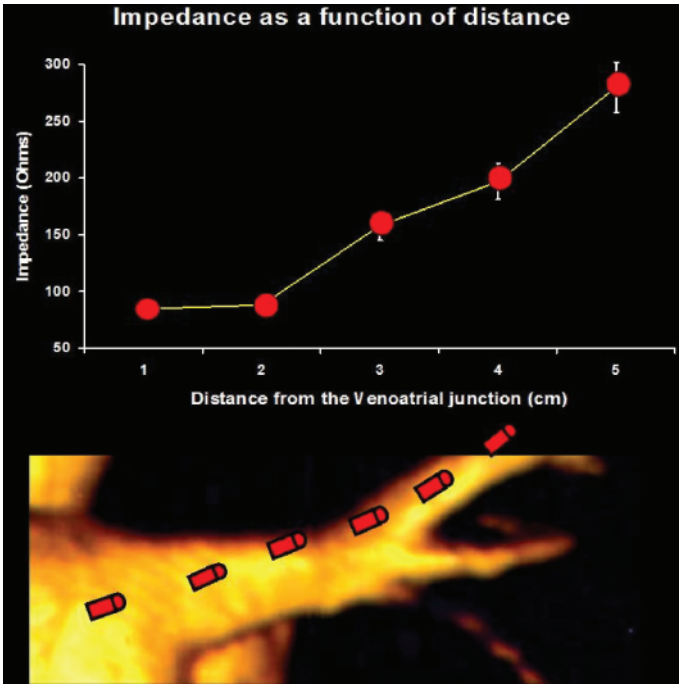

Figure 7 A,B The effect of catheter location and impedance values obtained during continuous impedance monitoring. The upper panel shows impedance values as a function of distance, and the lower panel shows catheter tip location superimposed on the magnetic resonance image (MRI) of the pulmonary vein

atrium[6,7] (Figure 5). There exists a complex anatomical relationship between the posterior left atrium, pericardium,[8] transverse and oblique sinuses, and adjacent structures such as the aorta,[9] esophagus and left bronchus,[10] and the recurrent laryngeal nerve.[11] During catheter ablation procedures involving the superior and posterior left atrium (Figure 6), any of these structures may be inadvertently damaged. The pulmonary veins (PVs) are posterior structures and have muscle sleeves that surround them.[6] The PVs can be readily imaged by ICE, and their location within the vein vs the atrium can be ascertained by impedance monitoring (Figure 7).[12]

Anatomy of the Major Structures Surrounding the Heart

Almost all energy sources used for catheter ablation of atrial fibrillation are "outwardly directed," thereby increasing the risk of collateral damage to structures that surround the heart. The key structures are the esophagus (Figure 8), mediastinal nerves (Figure 9), and the bronchus. Surgical approaches minimize the risk of damage to these structures by direct visualization and by the use of "inwardly directed" energy sources.

Esophagus

The esophagus is directly posterior to the left atrium and is at risk for any lesion that targets the posterior left atrial wall.[13] Injury to the esophagus can

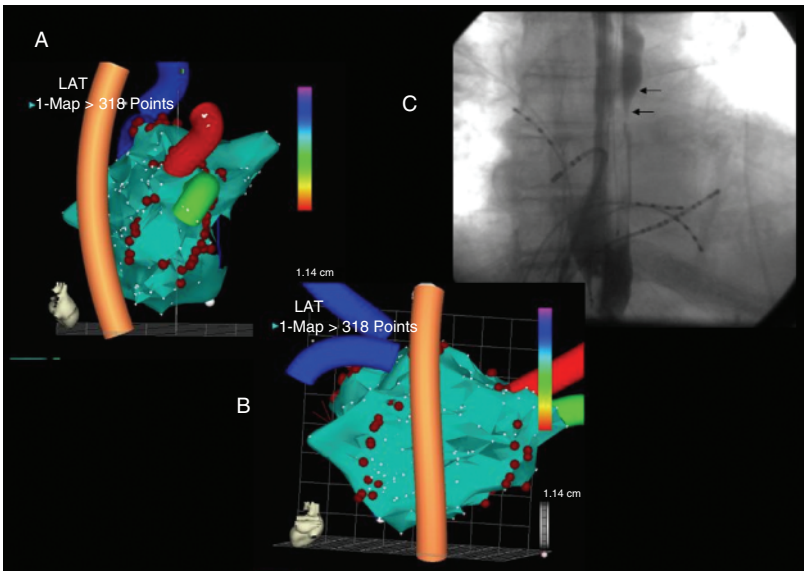

Figure 8 Electroanatomical maps in the right lateral view (**A**) and posterior view (**B**) and fluoroscopic (**C**) views of the esophagus. The arrows in **C** show contrast in the esophagus

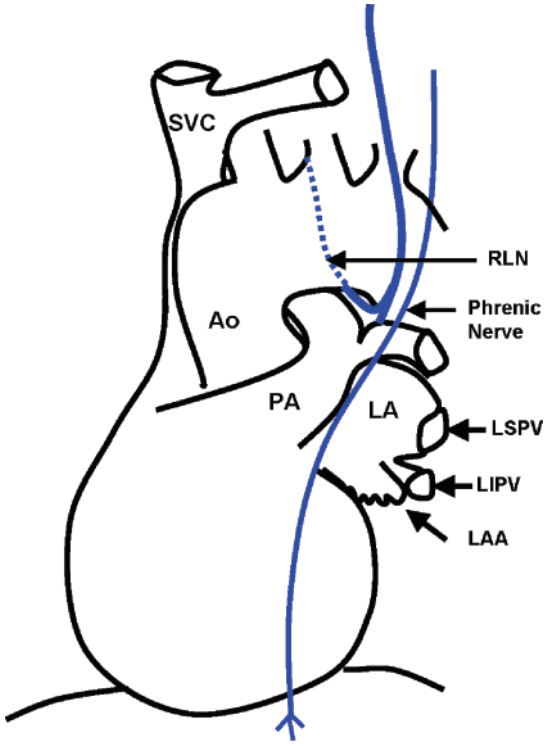

Figure 9 Mediastinal nerves and the heart: schematic diagram showing the course of the recurrent laryngeal and phrenic nerves (viewed from the left side). *Ao* aorta, *LA* left atrium, *LAA* left atrial appendage, *LIPV* left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *PA* main pulmonary artery, *RLN* recurrent laryngeal nerve, *SVC* superior vena cava. (Reproduced from ref. 11. with permission.)

be fatal.[14] The esophagus is fairly mobile and can be visualized by the use of contrast agents during the ablation procedure.[15] The esophageal blood supply is located in the anterior wall of the esophagus, further increasing the risk caused by energy application in this region.[16]

Phrenic Nerve, Recurrent Laryngeal Nerve, and Cardiac Vagi

The phrenic nerves on either side are closely related to the atria and can be injured during ablation procedures.[17] The right phrenic nerve is related to the superior vena cava right atrial junction, antero-inferior Right Superior Pulmonary Vein (RSPV) ostium, and the left phrenic nerve is related to the left atrial appendage (Figure 9). High-output pacing should be performed before energy delivery in these locations. In addition to the phrenic nerves, lesions along the roof of the atrium can damage the recurrent laryngeal nerve.[11] Finally, the vagal plexus is located behind the left atrium, and injury to this plexus can result in pyloric spasm and gastric hypomotility.[18]

Bronchus

The left bronchus is closely related to the left atrium. Catheter ablation in this region has the potential to cause atriobronchial fistula.[10]

Conclusion

Detailed knowledge of cardiac and mediastinal structures is a key prerequisite for interventional electrophysiologists and is crucial for improving the safety of catheter ablation procedures.

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15

Selection of Ablation Catheters, Energy Sources, and Power Delivery

David Cesario, Osamu Fujimura, Aman Mahajan, Noel G. Boyle, and Kalyanam Shivkumar

Abstract: The primary purpose of lesion-forming technologies in atrial fibrillation is to create safe and effective myocardial lesions in a reasonable time frame while avoiding collateral damage. The complex anatomy of the left atrium creates unique difficulties for any lesion-forming technology employed in the ablation of atrial fibrillation. Unfortunately, the ideal energy source for the treatment of atrial fibrillation has yet to be developed, and thus multiple different technologies are still used. Lesion-forming technologies currently employed in the treatment of atrial fibrillation include radio-frequency energy, cryothermal energy, and high-intensity focused ultrasound. This review touches on the basic principles behind each of these technologies and highlights the advantages and limitations of their use in the treatment of atrial fibrillation. Finally, we briefly review some evolving strategies for the treatment of atrial fibrillation, including the use of lasers, microwaves, and Beta-irradiation as well as the injection of autologous fibroblasts.

Keywords: Biophysics; Catheter ablation energy source; Lesion formation; Radio frequency.

Introduction

The ability to safely and effectively treat atrial fibrillation (AF) using catheter-based methods has greatly increased interest in the development of technologies for the management of this arrhythmia. The general goal of these technologies is to create myocardial lesions that are effective, can be created in a reasonable time frame, and result in minimal or no collateral damage. An ideal energy source for catheter ablation is yet to be defined. All the energy sources currently in use for lesion formation in AF were initially developed for creating discrete focal lesions for arrhythmias such as atrioventricular nodal (AV) reentrant tachycardia and accessory pathways. The various energy sources currently applied to the treatment of AF and some of their individual properties are outlined in Table 1.

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Table 1 Comparison of energy sources for catheter ablation.

Energy source	Catheter based	Contact	FDA approved for AF
RF	Yes	Critical	No
Cryo	Yes	Critical	No
HIFU	Yes	Not critical	No
Laser	Yes	Not critical	No
Microwave	Yes	Not critical	No

AF atrial fibrillation, *Cryo* cryothermal, *FDA* Food and Drug Administration, *HIFU* high-intensity focused ultrasound, *RF* radio frequency.

The purpose of this chapter is to highlight the biophysical principles of lesion formation and to give a framework for assessing new technologies. Although catheter-based and handheld surgical tools for AF management share similar energy sources, specific technologies that are currently used exclusively for surgical treatment are outside the scope of this chapter.

The lack of a clear mechanistic understanding of AF is reflected in the pattern of development of multiple different technologies for its cure. It is unlikely that a single ablative platform will be available in the near future capable of meeting the multiple demands necessary for a successful catheter-based ablation strategy for AF, given the need for sufficiently deep lesions, linear lesions, and circular lesions in the antrum of the pulmonary veins. Despite apparent differences in ablation strategies, a common thread is the recognition that ablation does have a useful effect.[1]

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of AF incorporate catheter ablation as a valid therapeutic option.[2] Early studies looking at AF ablation as primary therapy have also been reported.[3] Global evolution of AF ablation indicates that these therapies[4,5] have already shown some efficacy in the treatment of this arrhythmia, and the future holds much promise for a potential catheter-based cure of AF.

The complex anatomy of the left atrial structures plays an important role in how technology is deployed in the left atrium for ablation procedures.[6] As discussed in Figure 1, catheter-based ablation strategies for the treatment of AF have evolved over the years, from procedures focusing mainly on ablation of ectopic foci, to electrical isolation of the pulmonary veins, to left atrial substrate modification. As procedural techniques have evolved, the tools available to the clinician have also been modified to meet the unique challenges of these various approaches. The initial procedures developed for pulmonary vein isolation (PVI) utilized standard 4-mm tip radio-frequency (RF) catheters. Subsequently, cooled-tip RF and 8 -mm tip RF catheters were used. Multipolar catheters (to ablate via several poles) and balloon-based technologies (to approximate the pulmonary vein atrial junction) have been more recently developed. In contrast to surgical technologies, all catheter-based technologies have the inherent disadvantage of being "outwardly directed" energy sources, which directly increases the risk of collateral damage to surrounding structures.

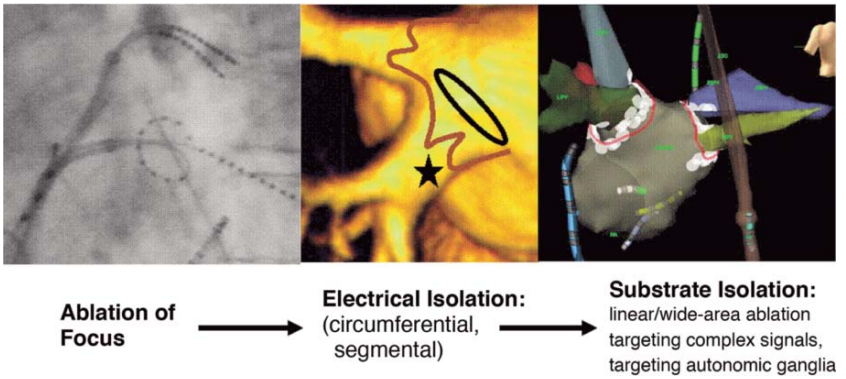

Figure 1 Evolving strategies for catheter ablation of atrial fibrillation. Procedures have evolved and have moved away from ablation within the vein

Evolution of Technology

The original catheter-based energy delivered was direct current (DC) shocks. Although now mostly of historical interest, DC shocks were successfully applied from an electrode catheter percutaneously positioned adjacent to the His bundle to successfully ablate the AV node.[7] Electrode shocks were delivered to the catheter from an external defibrillator. However, this procedure suffered from serious collateral damage, resulting in unacceptably high in-hospital mortality rates, approaching 6%.[8] It became clear that if catheter-based ablation was to advance as a therapeutic technique, safer forms of energy would need to be applied to create ablative lesions.

Radio-Frequency Ablation

Radio-frequency energy was one of the earliest energy sources used for catheter ablation and by far has the greatest patient-year experience.[9] Subsequently, bipolar RF, high-intensity focused ultrasound (HIFU), catheter-based cryoablation, laser ablation, and microwave have been proposed as potential therapies for the treatment of arrhythmias. Radio frequency is the energy source that has been most extensively studied. Radio-frequency generators typically deliver unmodulated sine wave alternating current (AC) at frequencies too high to depolarize the myocardium, between 500 and 1000 kHz (1 MHz).[10,11]

In most currently used RF ablation systems, unipolar current is delivered from the ablation catheter tip to a dispersive patch on the patient's skin (typically placed over the liver or on the thigh). The passage of this AC current from the ablation catheter through tissues to the dispersive patch causes resistive heating, resulting in lesion formation at the catheter tip. Because the surface area of the ablation catheter tip is relatively small compared to the dispersive patch, the site of highest current density and heating occurs at the catheter tip.[10] This feature helps minimize collateral damage by limiting resistive heating to the immediate catheter tip–tissue interface and a small rim or surrounding tissue (~1 mm). Conductive heating of surrounding tissues

results in additional lesion depth because of the "virtual electrode" of resistive heating.[10]

Experimental data suggest that temperatures above 50 °C irreversibly damage myocardial tissue.[11] Deeper lesions are produced as the catheter tip–tissue interface temperature increases, until the interface temperature reaches approximately 100 °C, at which point plasma boils, resulting in coagulum formation at the catheter tip. This can result in clot embolization, a sudden increase in impedance, loss of thermal conductivity, and ineffective tissue heating. Thermocouples and thermistors at the catheter tip allow monitoring of catheter tip temperature in an attempt to avoid excessive tissue heating. The ability to monitor catheter tip temperature has been available since the second generation of RF generators became clinically available. Subsequent RF generators have allowed delivered power to be titrated up or down until a chosen catheter tip temperature is reached. Delivery of RF in this mode is referred to as *temperature -guided RF ablation*.[10] More recent RF generators can deliver RF in either temperature- or power-guided modes.

One of the limitations of standard RF energy is the complex interplay between the resistive heating temperature of tissue adjacent to the RF catheter tip and the convective cooling caused by local blood flow. This complex interaction makes the relationship between catheter tip temperature and lesion depth an oversimplification and may result in reported RF generator values underestimating local tissue temperatures.[12] In certain situations, excessive heating of deep tissue layers can result in the production of steam within the tissue, ultimately leading to a steam pop and potentially to crater formation in the adjacent tissue, which can result in significant collateral damage and even cardiac perforation.

As the ablation strategy for AF has evolved, electrophysiologists have desired to make deeper lesions to improve ablation success rates. As mentioned, boiling of plasma at the electrode tip–tissue interface limits power delivery with standard RF. Two approaches have been devised to increase electrode cooling and thus allow effective levels of RF power to be maintained even in areas of low blood flow (see Figure 2A).

The first approach is to increase the electrode surface area exposed to the blood, thus initiating the development of 8- to 10-mm tip catheters. This greater surface area increases convective cooling without a change in blood flow. The second approach to this problem is to cool the electrode tip with infused saline. Saline infusion allows greater power delivery to the tissue and shifts the point of maximal heating into the tissue itself. Ultimately, this results in deeper conductive heating and the production of deeper lesions.[12,13] The production of deeper lesions may limit the total number of lesions necessary in the left atrium, and a reduction in the number of lesions can potentially help minimize collateral damage and reduce both total procedure and fluoroscopy times.

In general, there are two types of irrigated catheters (Figure 2A). The first is closed-loop irrigation catheters, which have an internal thermocouple and continuously circulate saline within the electrode tip, internally cooling the electrode tip. The second type of irrigated catheters is open irrigation catheters, which have an internal thermocouple and multiple irrigation holes located around the electrode, through which saline is continuously flushed, providing both internal and external cooling. In a direct comparison between open and closed irrigation RF ablation catheters, Yokoyama et al. found

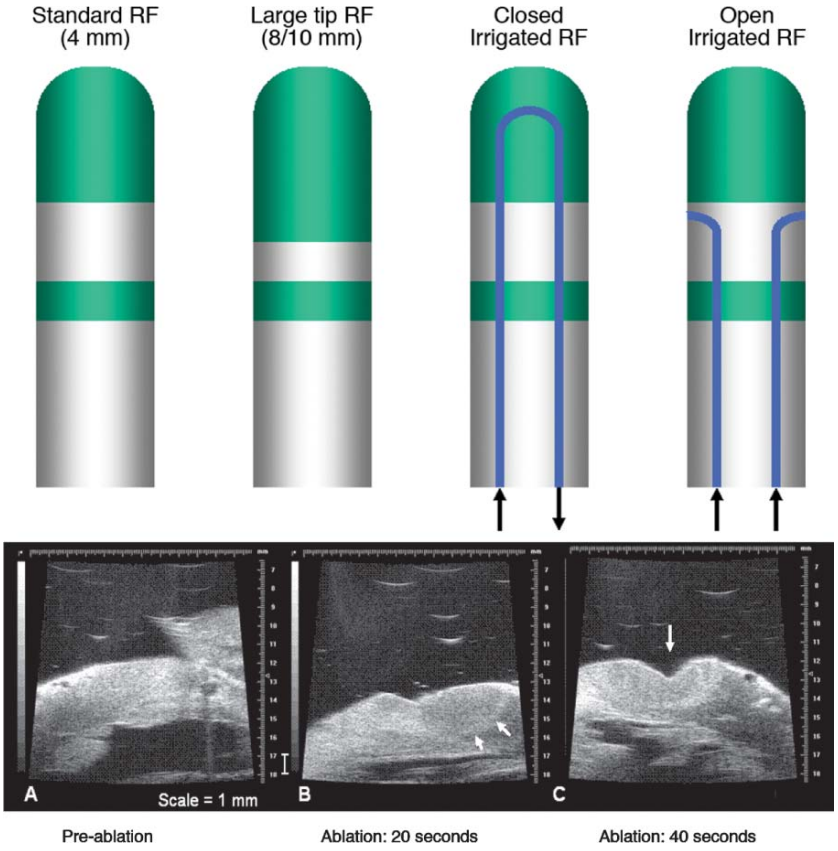

Figure 2 A. Radio-frequency (RF) ablation catheter designs. Increasing the size of the electrodes and methods to cool the ablation electrode. **B.** Imaging lesion formation during RF ablation. The three panels show lesion formation during RF delivery on the epicardial surface of a Langendorff-perfused rabbit heart imaged with a 30-MHz system (Visualsonic)

that open irrigated systems resulted in greater interface cooling with lower interface temperatures, and a lower incidence of both thrombus formation and steam pops, than seen with closed-loop irrigation catheters.[14]

Newer catheter designs are attempting to address some of the special obstacles encountered during ablation within the left atrium for AF. Long linear catheters have been designed with multiple electrodes that can ablate in a sequential or simultaneous fashion. In addition, catheters have been designed that can deliver current between two adjacent electrodes in a bipolar fashion.[15] If the electrodes are of similar size, current density will be similar, allowing the production of longer single lesions, which will minimize gaps between lesions.

Phased RF has been applied to form deeper and more continuous lesions. Phased RF delivers unipolar RF via alternating electrodes, resulting in AC sine waves that are out of phase, producing a potential difference between electrodes similar to bipolar RF.[15] In vitro studies comparing lesions produced

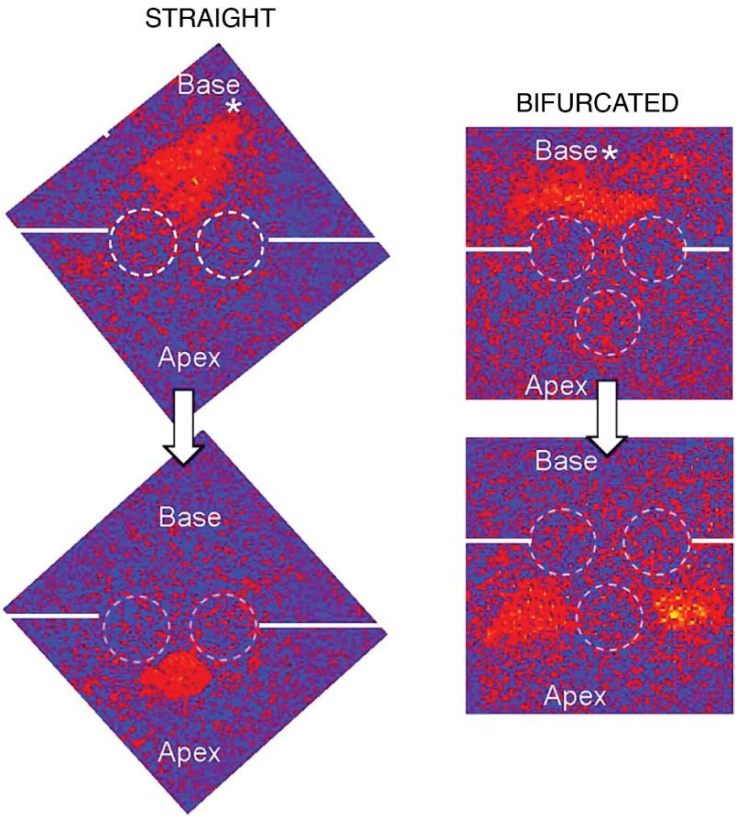

Figure 3 Optical mapping of gaps formed by radio-frequency (RF) ablation. The images show optical maps illustrating conduction across straight and bifurcated gaps. The upper panels show orange wave fronts of depolarization that have progressed from the pacing sites (asterisks) to the gaps. The lower panels demonstrate that the wave fronts have crossed these gaps (straight and bifurcated in 4 and 8 ms, respectively)

by multielectrode unipolar RF, bipolar RF, and phased RF revealed that phased RF resulted in the highest tissue temperatures and most uniform and deepest lesions.[15] A consistent problem with all RF catheters is the inability to form contiguous lesions. Gaps in lines can be proarrhythmic, and technologies such as phased RF may be able to address some of these concerns (see Figure 3).[16]

Cryoablation

The application of cryothermal energy (cryoablation) has long been a part of the regimen for the treatment of cardiac arrhythmias. The use of epicardial cryoablation was first described by Klein et al. for the surgical ablation of accessory pathways.[17] In these early surgeries, intraoperative mapping localized the arrhythmogenic substrate, and then a refrigerated cryoprobe was applied to this site. This method proved to be safe and effective; however, it was time consuming and required highly invasive surgical procedures for the treatment of arrhythmias.

More recently, percutaneous cryoablation systems consisting of a steerable ablation catheter and a dedicated ablation console have become available.

Cryoablation catheters have terminal segments capable of reaching temperatures less than −70 °C. Catheter tip cooling is achieved via the delivery of liquid refrigerant, typically nitrous oxide, under pressure to the catheter tip. Nitrous oxide is delivered through a hollow injection tube that runs through the entire length of the ablation catheter into a sudden luminal widening at the catheter tip. Decompression and expansion of nitrous oxide within a small chamber located at the catheter tip result in cooling based on the Joule–Thompson effect.[18] Ultimately, this creates a liquid-to-gas-phase interface within the catheter tip, resulting in heat extraction from the local tissue in contact with the distal electrode. Gas is constantly removed, via vacuum, through a second coaxial lumen inside the catheter. Catheter tip temperature can be constantly monitored on the console, and in turn the nitrous oxide flow can be adjusted to obtain a preset temperature. "Cryomaps" can be obtained by moderate reversible cooling of tissue to temperatures between −28 °C and −32 °C. For successful cryoablations, resulting in irreversible myocardial tissue damage, tissue–tip interface temperature is typically maintained at −80 °C.

Lesion formation with the delivery of cryoenergy has been well characterized and occurs through both direct cellular injury and a vascular -mediated tissue injury.[19] The direct cellular injury is likely the result of ice formation, and the distribution of lesions is related to temperature reached during cooling.[20] Ice formation results in a hyperosmotic extracellular environment and a resultant shift of water from the intracellular to the extracellular space, ultimately causing cell shrinkage and damaging the plasma membrane. Cooling to temperatures resulting in extracellular ice formation (>−40 °C) can result in cellular death if cryoenergy is applied for prolonged periods; however, with limited application this cell damage is largely reversible, and cellular function can recover. This feature allows cryoablation systems the attractive option of delivering a functionally reversible lesion in many cases. However, by cooling tissue to −40 °C and below, ice is formed in both the intracellular and extracellular spaces, resulting in irreversible damage to the plasma membrane as well as internal organelles. These lesions ultimately result in localized cell death and can lead to the propagation of intracellular ice between cells via intracellular channels, potentially resulting in lesion growth.

Cryoablation also results in vascular-mediated tissue injury. The initial response to the application of cryothermal energy is vasoconstriction and decreased blood flow. As the tissue freezes, circulation ultimately ceases uniformly in the frozen areas. Ultimately, this could result in tissue damage via ischemic necrosis; however, this cannot be easily distinguished from damage produced by intracellular ice formation. As the tissue rewarms, there is a subsequent hyperemic response with increased vascular permeability and edema. In addition, endothelial damage can result in platelet aggregation and microthrombus formation.

In percutaneous closed-chest cryoablation systems, the coldest area is located adjacent to the catheter tip, and thus effects of energy delivery are observed earlier in these areas. Less-cooled areas are located at the periphery of the cryolesion. Because of limited cooling in these outer areas, reversible

tissue damage is more likely to occur in such regions. Thus, effects noted late during cryoablation are likely to revert on rewarming. In general, ablation success is correlated with early functional modification (within the first 30 s of cryoenergy application).[20]

Cryoenergy has been delivered in several different forms to various areas of the left atrium as a targeted treatment for AF. The surgical approach to AF using cyroablation to isolate the pulmonary veins has been well described.[21] In this procedure, a T-shaped cryoprobe is applied to the epicardial side of the left atrium, around the pulmonary veins, through a median sternotomy. This is done in combination with endocardial cryoablation through a right-sided left atriotomy to completely isolate the left superior pulmonary vein. More extensive cryoablation in combination with RF ablation, creating a lesion set similar to the Maze II procedure, has also been described, with success rates approaching 90% maintenance of sinus rhythm at 9-month follow-up.[22] Milla et al. reported using an argon-based cryoclamp and linear probe to epicardially isolate the pulmonary veins and left atrial appendage in the beating heart of six dogs.[23]

Cryothermal energy has also been applied endocardially via a percutaneous transvenous catheter-based approach to electrically isolate the pulmonary veins.

Successful complete PVI was achieved in 41 of 45 veins ablated using cryothermal energy delivered via novel 7F circular catheters, guided by Lasso catheters, in 18 patients.[24] Furthermore, several authors have recently described the use of a balloon catheter to deliver cryoenergy to the pulmonary vein ostia in animal models.[25,26]

High-Intensity Focused Ultrasound

High-intensity focused ultrasound is an extracorporeal technique that is capable of creating thermal ablation lesions in subsurface regions without having an impact on intervening tissues and blood vessels. Ultrasound energy can be precisely focused in a targeted region of a tissue to induce molecular vibration and friction, absorptive heating, and ultimately necrosis of the targeted region by thermal coagulation.[27,28] Other currently utilized techniques for thermal ablation, such as argon cryotherapy or interstitial laser therapy, cool or heat tissues primarily by thermal conduction and create a graded response depending on the distance from the thermal source. Since this mechanism is relatively slow, it is susceptible to cooling from the nearby blood vessels. In contrast, HIFU has an advantage over these techniques because focusing the ultrasound acoustic energy in the targeted tissue by a remote ultrasound transducer allows rapid heat ablation while the intervening tissue is not damaged.[27,28]

High-intensity focused ultrasound induces tissue damage primarily by two mechanisms.[29] The primary mechanism for ablating tissue with focused ultrasound is coagulative necrosis by thermal absorption. Temperature increase (~55 °C to 60 °C) in tissues, assumed to be linearly proportional to the delivered acoustic energy, is achieved by controlling the ultrasound acoustic power and wavelength. The other mechanism, cavitation-induced damage (thermal or mechanical), incurs much greater tissue destruction, and

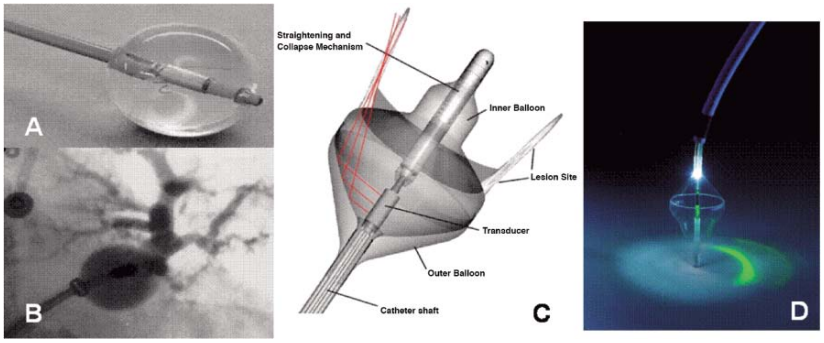

Figure 4 Balloon-based high-intensity focused ultrasound HIFU (**A–C**) and laser (**D**) delivery technologies. (Figure 4A and 4B reproduced from ref. 32 with permission of the American Heart Association; Figure 4C reproduced from ref. 33 with permission of the *Journal of Interventional Cardiac Electrophysiology*; Figure D reproduced courtesy Cardiofocus Inc.)

in the past, it had generally been avoided because of variable intensity values and unpredictable lesion sizes. However, the idea of promoting cavitation for enhancing the level of ablation and reducing required exposure times is under investigation.[30,31]

The technology of focusing ultrasound into tissue to induce temperatures high enough to achieve tissue ablation is relatively simple. The primary objective of the HIFU delivery system is to deliver frequencies that are high enough to allow significant energy absorption at the point of focus, yet not so high that they cause appreciable energy loss in the intervening tissue. High-intensity focused ultrasound can be achieved with a spherically curved transducer operating at frequencies approximately between 1 and 10 MHz, with most cardiac ablation procedures performed around 5 to 8 MHz.[32–34]

Currently, intracardiac catheter-based technology incorporating balloons to focus the ultrasound beams is utilized in delivering HIFU for cardiac ablations (see Figure 4).[32,33] Unfortunately, tissue heterogeneities can alter the intended focal point in the tissue as well as make the actual temperature rise at the targeted tissue difficult to predict. The intensity achieved at the targeted tissue varies with the procedure (range of 7 to 20 W/cm^2) and is usually sustained for 30 to 120 s.

Other Energy Sources and Approaches for Lesion Formation

Other energy sources, such as lasers, microwave, and β-irradiation have been proposed for lesion formation. Microwaves are electromagnetic waves with frequencies from 100 to 10,000 MHz, much higher than RF waves.[10] When microwaves are applied to myocardial tissue, heating occurs via the dissipation of absorbed energy into the adjacent tissues. Heating occurs mainly through the oscillation of water molecules, which produces kinetic energy in the tissues that is eventually released as heat. Microwaves have greater depth

penetration than RF waves, resulting in the potential advantage of producing larger and deeper lesions without resulting in tissue heating beyond 100 °C and the associated potential for collateral damage.[35] To date, the majority of experience with microwave ablation has been during open surgical procedures[36–38]; however, because of its potential to produce deep linear lesions, further investigations using catheter-based percutaneous microwave ablation in the treatment of AF are warranted.

Another potential alternate to RF energy in the treatment of AF is laser energy. Direct resistive heating caused by the application of laser energy has the potential to produce very large and deep lesions. Several different laser sources have been investigated during surgical ablation to date, including Nd:YAG, excimer, and CO_2.[10] The potential for collateral damage caused by excessive surface heating and crater formation has limited the use of this technology until recently.

A laser balloon has been developed for pulmonary vein ablation and potential use in AF.[39] This laser system is similar to the ultrasound balloon ablation system. It employs a low-cost diode laser, potentially making it more financially viable for routine clinical use. However, at this time additional clinical trials are necessary to further evaluate the safety and efficacy of laser energy in the treatment of AF.

In addition, experimental catheters are currently in the development stage that will allow the electrophysiologist to both image using a phased array intracardiac echo and ablate through the same catheter (see Figure 5). Biological approaches such as the injection of autologous fibroblasts has also been suggested as an approach for the creation of lesions[40] (see Figure 6).

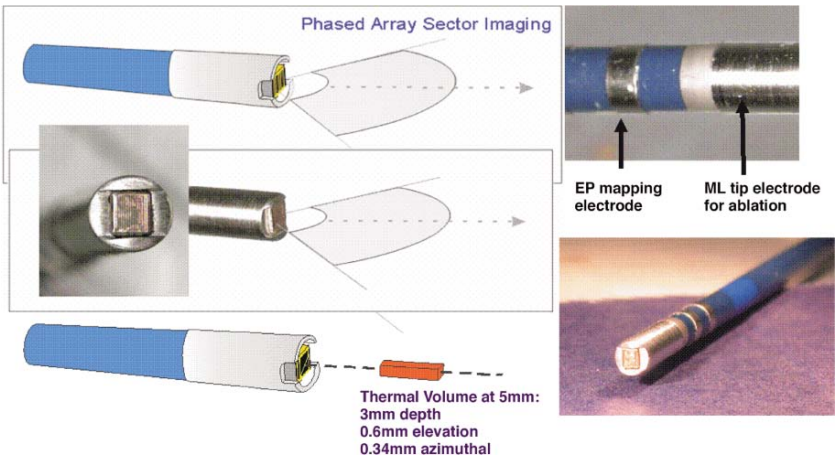

Figure 5 Experimental imaging/ablation microlinear catheter. (Courtesy Doug Stephens, University of California Davis, and David Sahn, Oregon Health and Science University (OHSU), NIH Bioengineering Research Partnership Grant.) This catheter design allows imaging via the tip of the catheter and the ability to ablate using the same ultrasonic array. EP; Electrophysiologic, ML; Microlinear

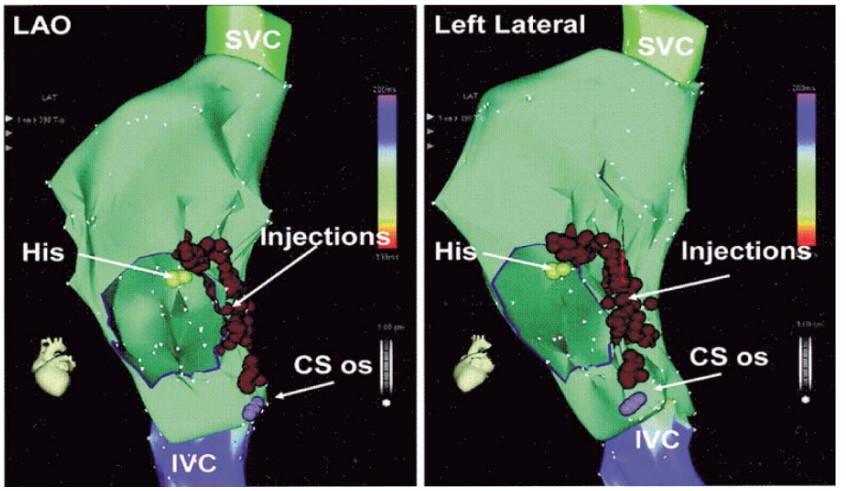

Figure 6 Biological "lesion" formation. *CS* coronary sinus, *IVC* inferior vena cava, *SVC* superior vena cava, *LAO* Left anterior oblique. (Reproduced from ref. 40 with permission of the American Heart Association.) In this animal model, injection of autologous fibroblasts resulted in targeted areas of conduction block

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16

Anatomically Guided Catheter Ablation for Atrial Fibrillation

Hakan Oral and Fred Morady

Abstract: In recent years, radio-frequency catheter ablation has emerged as an effective treatment option for patients with paroxysmal and chronic atrial fibrillation (AF). Based on advances in the understanding of the pathogenesis of AF, catheter ablation has evolved primarily into two general approaches: (1) ablation strategies that create a predetermined set of lesions usually at or around specific anatomical landmarks (anatomically guided ablation) and (2) ablation strategies that attempt to identify and eliminate specific mechanisms that initiate and perpetuate AF (tailored ablation). A tailored ablation strategy also has been combined with anatomically guided ablation. In this chapter, anatomically guided ablation is discussed.

Keywords: Atria–esophageal fistula; Catheter ablation for AF; Circumferential PV ablation; Ganglionated plexi; Linear ablation; Mechanism of AF; PV stenosis; Segmental ostial ablation; Tailored approach.

Mechanistic Background

The premise of anatomically guided ablation is that mechanisms critical to initiation and perpetuation of atrial fibrillation (AF) (i.e., triggers and drivers) are likely to involve certain anatomical locations and structures in the majority of patients with paroxysmal and chronic AF. The basis of this approach can be summarized as follows: multiple-wavelet hypothesis, pulmonary veins (PVs) and other thoracic veins, rotors/anisotropic reentry/focal drivers, and ganglionated plexi.

Multiple-Wavelet Hypothesis

As proposed by Moe,[1] a minimum number of wandering wavelets may be critical to perpetuation of AF. Because atrial size has to be greater than the wavelength (Conduction velocity × Effective refractory period), AF can no longer exist if the atrium is anatomically divided into smaller compartments. Moe's hypothesis forms the basis for the classic surgical Cox maze proce-

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dure,[2] which compartmentalized the atria such that AF could not sustain itself. The clinical efficacy of the Cox maze procedure is consistent with the wandering wavelet hypothesis. However, the Cox procedure may also eliminate other potential mechanisms of AF, for example, the PVs.

Pulmonary Veins and Other Thoracic Veins

As a result of the observation that premature depolarizations from the PVs) can initiate AF,[3] the PVs have been targeted for ablation. Subsequent studies have demonstrated that PVs not only may trigger AF but also can perpetuate AF.[4,5] Rapid electrical activity (PV tachycardias) have been shown to be critical drivers of AF (Figure 1).[5] Furthermore, the presence of a dynamic interplay between the left atrium and the PVs has been demonstrated (Figure 1).[5]

The potential arrhythmogenicity of the PVs led to empirical electrical isolation of all PVs.[6,7] Subsequently, a variety of approaches have been performed to electrically isolate all PVs and sometimes other thoracic veins, such as the superior vena cava or the coronary sinus, as well.

In addition to PV triggers, spontaneous depolarizations outside the PV ostia may initiate AF. These non-PV triggers have often been mapped to the antrum of the PVs and the posterior left atrium.[8,9] Therefore, a set of encircling lesions around the PV antrum may also eliminate non-PV arrhythmogenic foci.

Rotors/Anisotropic Reentry/Focal Drivers

Jalife et al. proposed that rotors or high-frequency sources caused by anisotropic reentry may be drivers of AF.[10–13] The presence of rotors has

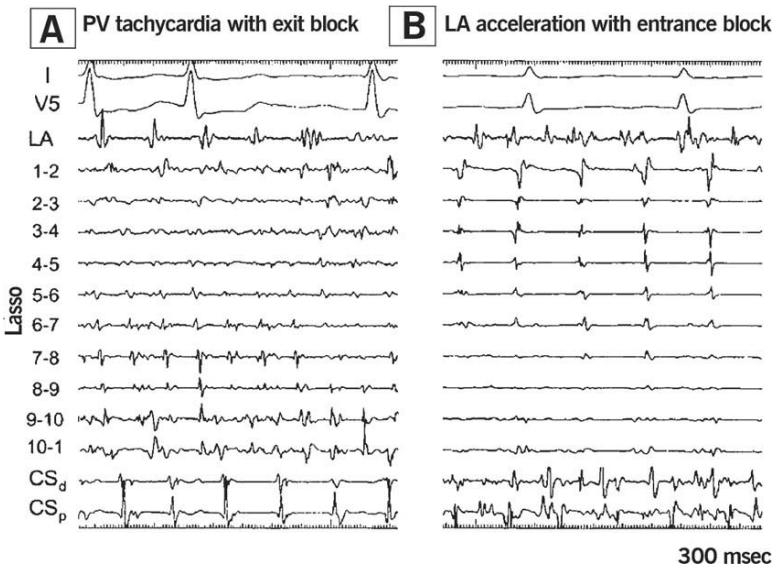

Figure 1 Pulmonary vein (PV) tachycardia. Leads I and V5 and intracardiac recordings from the left atrium (LA), a decapolar ring catheter positioned at the ostium of the left superior PV, and the coronary sinus are shown. The LA catheter was positioned in the posterior LA adjacent to the ostium of the left superior PV. A PV tachycardia with a cycle length shorter than in the adjacent LA and coronary sinus was recorded (**A**). The site of shortest cycle length alternated between the PV (**A**) and the LA (**B**). (Reproduced from ref. 5 with permission.)

been demonstrated in computer simulation and animal models. Rotors or high-frequency sources are believed to form in the atria with spiral spread from a core that has the highest frequency. As the wave spreads, eventually wave-break and fibrillatory conduction occur, resulting in complex and fractionated electrograms. A frequency gradient from the antrum of the PVs to the left, then to the right atrium has been reported in both animal models and human subjects, suggesting that rotors may have anchor points within the PV antrum close to the PV ostia.[14,15] Therefore, empirical extra-ostial anatomical ablation that includes part or all of the PV antrum may also result in elimination of rotors and other high-frequency sources.

Ganglionated Plexi

Vagal innervation of the atrium facilitates AF. Increased vagal tone may facilitate premature depolarizations almost anywhere in the atria and may shorten the effective refractory period.[16–23] As a matter of fact, acetylcholine has often been used to facilitate AF in experimental models. Clinically, episodes of AF that exclusively occur during states of heightened vagal tone, such as postprandial or nocturnal AF, have been recognized.[20,21,24–26] Coincidental ablation of ganglionated plexi during circumferential PV ablation, as manifest by elimination of vagal influence on heart rate variability parameters, may be associated with a higher probability of freedom from recurrent AF.[27] However, dissection of fat pads that contain ganglionated plexi during surgery[28] has had mixed results in preventing postoperative AF.[29] Furthermore, vagal denervation by endocardial and epicardial left atrial catheter ablation as a stand-alone therapy for paroxysmal AF has had poor results.[30] It appears that ganglionated plexi may be more abundant in the posterior left atrium and around the PV antrum,[23] and empirical anatomical lesions around the PVs may also result in ablation of ganglionated plexi.[27]

Clinical Applications

Based on the multiple mechanisms that may contribute to the initiation and perpetuation of AF, a variety of ablation strategies have been proposed and performed in patients with AF.

Segmental Ostial Ablation for Pulmonary Vein Isolation

Because arrhythmogenic foci within the PVs may initiate and perpetuate AF, systematic empirical isolation of all PVs has been performed both in patients with paroxysmal and in those with chronic AF. Myocardial sleeves that extend from the left atrium on to the PVs are often discontinuous around the perimeter of PV ostia, and isolation is performed by ablation of the electrical breakthrough points at the ostium with the guidance of a multipolar circular catheter.[6] Segmental ostial ablation for PV isolation can be performed during sinus rhythm or AF.[4,6,7]

Segmental ostial ablation has had a modest efficacy of 60% to 70% in patients with paroxysmal AF and is not effective for chronic AF. Possible explanations for the clinical outcome of patients after segmental ostial ablation may include (1) PV isolation by segmental ostial ablation eliminates only one mechanism of AF (i.e., PV-dependent arrhythmogenicity); (2) because of the risk of PV stenosis,[31,32] only limited amounts of radio-frequency energy can be delivered safely at the ostium of the PVs. This contributes to the high recurrence rate of conduction through previously ablated PV fascicles.

Segmental ostial ablation may be technically challenging. Misdiagnosis of left atrial appendage and superior vena cava potentials as PV potentials[33,34] may result in unnecessary applications of radio-frequency energy and increase the risk of PV stenosis. Furthermore, ablation in or around the right superior PV is associated with a risk of phrenic nerve palsy.[35]

Circumferential Pulmonary Vein Ablation, Wide-Area Circumferential Ablation, Left Atrial Circumferential Ablation, Pulmonary Vein Antrum Isolation

Circumferential PV ablation has been performed to encircle the left- and right-sided PVs 1 to 2 cm away from the ostia of the PVs, with additional linear lesions along the roof or posterior left atrium and along the mitral annulus (Figure 2).[36–38] Because of the proximity of the left atrial appendage to the ostium of the left-sided PVs, the left circle often is created at the ostium of the PVs anteriorly rather than 1 to 2 cm away where the left atrial appendage is. From a technical perspective, because the lesions are delivered away from the PV ostia, it is possible to deliver more energy using cooled-tip or large-tip catheters without a significant risk of PV stenosis. Therefore, the probability of recovery of conduction may be low. Furthermore, there may be anatomical variations in the number of PVs, and a common ostium for the left-sided PVs may be encountered in 10% to 15% of patients.[39,40] Circumferential ablation encircles all PVs without having to know the exact number of PVs, whereas during segmental ostial ablation each PV ostia must be cannulated.

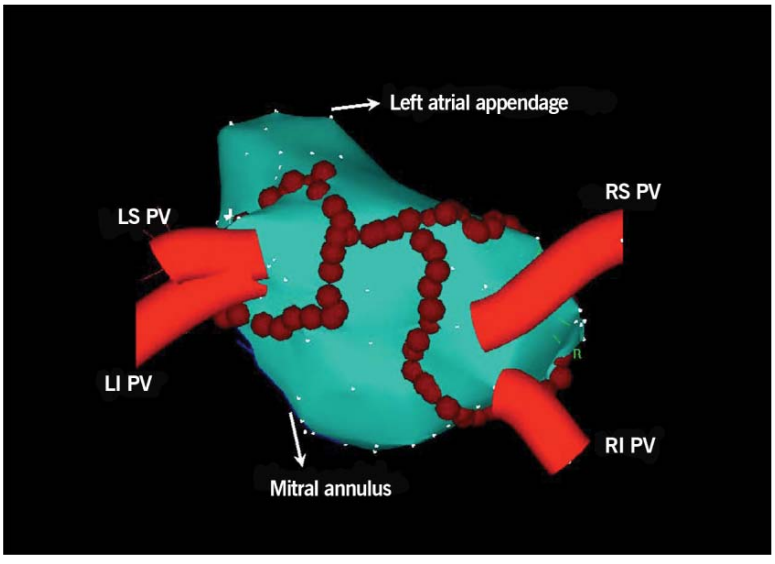

Figure 2 Circumferential pulmonary vein (PV) ablation. Shown is a three-dimensional reconstruction of the left atrium on an electroanatomical mapping system. The left- and right-sided PVs are encircled (red tags) 1 to 2 cm away from the ostia except for the anterior part of the left-sided circle, where there is the left atrial appendage. *LI* left inferior, *LS* left superior, *RI* right inferior, *RS* right superior. (Reproduced from ref. 40 with permission.)

From a mechanistic perspective, circumferential PV ablation attempts to eliminate a number of potential mechanisms of AF, such as PV arrhythmogenicity, rotors and high-frequency sources within the antrum of PVs, and non-PV arrhythmogenic foci that originate from the antrum and posterior left atrium. In addition, circumferential PV ablation may also result in atrial debulking since approximately 25% to 30% of left atrial tissue may be electrically excluded from the remaining left atrium. Consistent with its multimechanistic effects, circumferential PV ablation was found to be more effective than PV isolation in patients with paroxysmal AF in a randomized study.[37]

Circumferential PV ablation also was found to be effective in patients with chronic AF.[41] In a controlled, randomized study that utilized daily transtelephonic monitoring for 1 year, 74% of the patients with chronic AF were found to be in sinus rhythm without any antiarrhythmic drug therapy postablation, compared to only 4% of patients in the control group (Figure 3). Maintenance of sinus rhythm postablation was associated with a decrease in left atrial size and improvement in left ventricular ejection fraction and quality of life.

A critical aspect of circumferential PV ablation is the mapping and ablation of residual drivers, particularly PV tachycardias inside the encircling lesions, once the lesion set is completed (Figure 4). If residual drivers are eliminated, complete isolation of the PVs may not be necessary for the clinical efficacy of circumferential PV ablation.[42]

Modifications of this technique have been proposed. A recent study utilized double circular catheters positioned in the ipsilateral PVs to assess the completeness of PV isolation and conduction block across the encircling lesions.[43,44] Mapping with two circular catheters may facilitate identification of residual drivers inside the encircling lesions. However, the technique requires three transeptal punctures and multiple catheters in the left atrium.

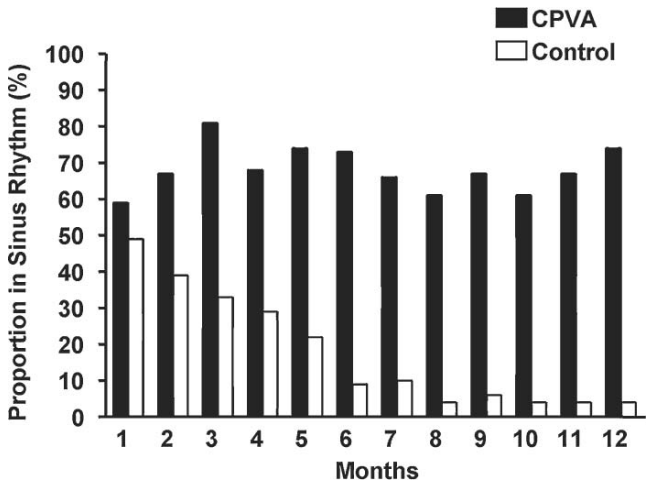

Figure 3 Proportion of patients with chronic atrial fibrillation (AF) who were free of AF and atrial flutter on a monthly basis in the circumferential pulmonary vein ablation (CPVA) and control groups. Therapy with amiodarone was discontinued at 3 months in both groups. (Reproduced from ref. 40 with permission.)

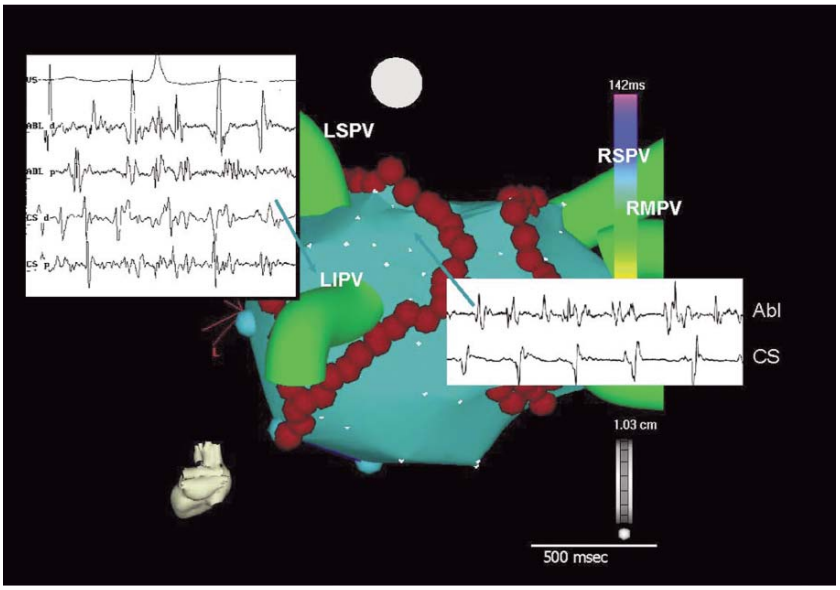

Figure 4 Residual drivers after circumferential pulmonary vein (PV) ablation. After completion of the encircling lesion sets, the inside of the circles should be carefully mapped, and residual drivers that have a cycle length shorter than in the coronary sinus (CS) or left atrium and complex electrograms should be ablated. *Abl* ablation catheter, *LIPV* left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *RMPV* right medial pulmonary vein, *RSPV* right superior pulmonary vein

Pulmonary vein antral isolation that targets potentials in the antrum of PVs identified by a roving ring catheter also has been reported to have high efficacy in patients with paroxysmal and chronic AF.[45,46] To better identify the PV antrum and titrate power, intracardiac echocardiography is used to guide this approach. It appears that a larger portion of the posterior left atrial wall may be ablated during PV antral isolation than during conventional circumferential PV ablation.

Circumferential PV ablation requires technical expertise and may be associated with two major complications: left atrial flutter and atrioesophageal fistula. Because contiguous lesions are created within the left atrium without necessarily achieving complete conduction block, left atrial flutters have been observed in 10% to 20% of the patients after circumferential PV ablation.[47] Nearly 50% of these tachycardias resolve spontaneously within a few months after ablation, and eventually 5% to 10% of the patients require a repeat ablation procedure to ablate the flutter. The majority of atrial flutters after circumferential PV ablation are perimitral.[47,48] However, other mechanisms are possible (Figure 5).[47,49] In an attempt to prevent perimitral left atrial flutter, an ablation line along the mitral isthmus often is performed during the initial ablation procedure.[48] However, achieving complete conduction block across the mitral isthmus can be quite challenging.

An infrequent but often fatal complication is atrioesophageal fistula.[50,51] The esophagus lies close to the posterior left atrium, and the distance between the endocardial surface of the left atrium and the lumen of the esophagus

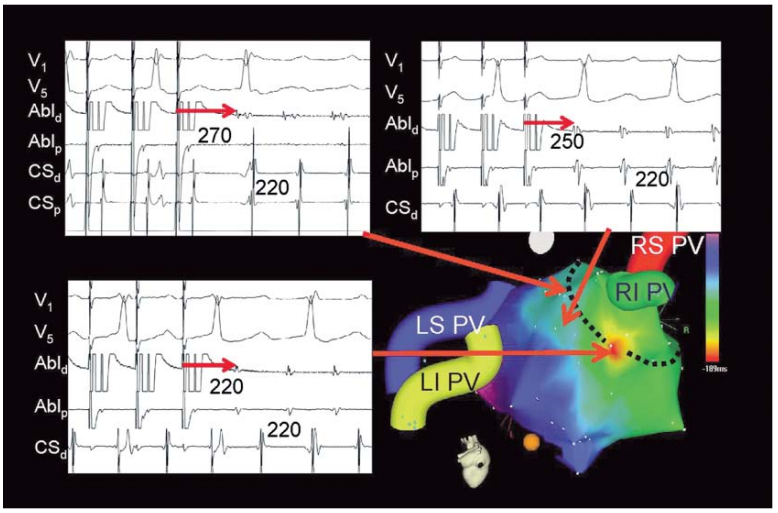

Figure 5 Left atrial flutter to focal microreentry after circumferential pulmonary vein (PV) ablation. Activation mapping suggested a focal tachycardia originating near the prior right-sided encircling lesion set (dashed black line). However, entrainment mapping from the distal bipole of the ablation catheter positioned in the left atrium demonstrates reentry as the mechanism, most likely because of a gap along the prior ablation line. Abl_d distal bipole of the ablation catheter, Abl_p proximal bipole of the ablation catheter, *CS* coronary sinus, *LI* left inferior, *LS* left superior, *RI* right inferior, *RS* right superior

may be less than 5 mm and well within the reach of a typical radio-frequency energy application.[52] Although underreported, the incidence of atrioesophageal fistula appears to be low, 0.2% in one large series of more than 4,000 patients.[50] The risk of atrioesophageal fistula is not limited to circumferential PV ablation. It can also develop after any type of ablation along the posterior left atrial wall even when ablation is performed at the PV ostia.[51,53] However, because encircling lesions during circumferential PV ablation often extend to the posterior left atrium and intersect the course of the esophagus, the risk may be higher. To minimize the risk of atrioesophageal fistula, a posterior left atrial ablation line has been moved to the left atrial roof.

The esophagus has a variable course along the posterior left atrium and can migrate during ablation (at least when ablation is performed under conscious sedation).[52,54,55] It is unclear whether there are upper thresholds of maximum power, temperature, and duration of radio-frequency energy applications that are safe to deliver in the posterior left atrium. Therefore, the most effective technique for avoiding esophageal injury may be not to deliver any energy near the esophagus by utilizing real-time dynamic imaging of the esophagus. A simple and safe technique may be a barium swallow under light conscious sedation using a thick barium paste.[54]

A variety of esophageal probes also has been proposed to monitor the position of the esophagus. However, these probes do not accurately reflect the actual width of the esophagus, which is quite variable and dynamic.[54] Temperature probes have been used to look for a rise in temperature, but this may not accurately detect intramural esophageal temperature. To minimize

the risk of esophageal injury, it would be advisable either to avoid delivering radio-frequency energy near the esophagus or at least to markedly reduce the power, temperature, and duration of radio-frequency energy applications.

Linear Ablation

The surgical Cox maze procedure is effective in eliminating AF in the majority of patients with AF. However, it is technically challenging and time consuming and therefore has not been used on a widespread basis. Attempts to create linear lesions in the atria more often have been part of percutaneous catheter-based approaches. Initially, linear lesions were limited to the right atrium, but it quickly became clear that right atrial ablation alone was not sufficient (and probably not necessary in the majority of patients) to eliminate AF.[56–59]

Percutaneous left atrial ablation with linear lesions was pioneered by Schwartz et al.[60] Because of very long procedure durations and a high risk of serious complications, this approach was not adopted into clinical practice. However, linear ablation can be performed in the operating room with relative ease using a handheld radio-frequency energy or cryo probe.[61–65] Efficacy rates of more than 90% have been reported with intraoperative anatomical linear ablation in the left atrium for paroxysmal and chronic AF, in which ablation lines are created to connect the PVs, and in the mitral isthmus. As in the electrophysiology laboratory, radio-frequency energy delivery near the esophagus is associated with the risk of atrioesophageal fistula formation.[66]

Three important observations during and after intraoperative linear anatomical ablation may be noteworthy: (1) Despite the fact that complete PV isolation was not attempted or achieved by linear ablation connecting the PVs, a high success rate still was achievable,[61] consistent with reports from percutaneous circumferential PV ablation.[42] (2) After linear left atrial ablation without complete PV isolation, despite the persistence of triggers from the PVs, AF was no longer sustainable, suggesting that left atrial substrate modification is sufficient to eliminate AF.[67,68] Linear ablation is likely to exert its beneficial effects by compartmentalizing the left atrium; eliminating anchor points for reentrant circuits or rotors; eliminating some but probably not all PV tachycardias; and possibly ablating ganglionated plexi. (3) Atrial fibrillation localized to the posterior left atrium, dissociated from sinus rhythm elsewhere in the atria, was observed after encircling all PVs en bloc. This observation demonstrates the arrhythmogenic potential of the posterior left atrium as an extension of the PVs.

The major limitations of intraoperative ablation for AF are the need for chest incisions and the inability to assess acute procedural endpoints. Completeness of conduction block or PV isolation is not routinely assessed during intraoperative ablation.

Linear ablation also has been performed by percutaneous radio-frequency catheter ablation.[67,69,70] The availability of three-dimensional navigation and mapping systems has greatly facilitated linear ablation. However, despite the availability of these mapping systems and large- or cooled-tip catheters capable of delivering more radio-frequency energy than conventional catheters, complete conduction block is difficult to achieve.[69] Nevertheless, in a randomized study, nonencircling left atrial linear ablation was found to have an efficacy similar to that of circumferential PV ablation in patients with chronic AF (Figure 6).[70]

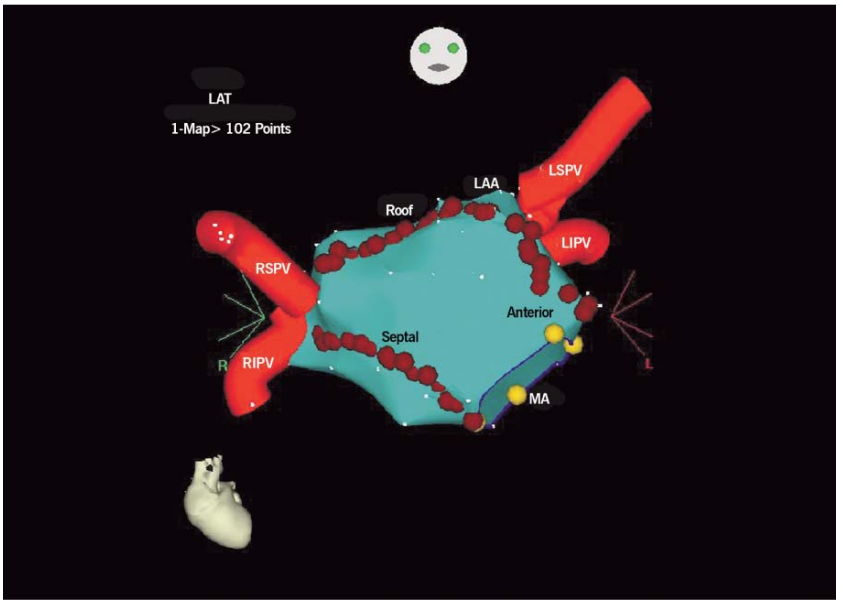

Figure 6 Nonencircling linear ablation for chronic AF. Shown is a three-dimensional reconstruction of the left atrium with nonenecircling roof and septal and anterior lines. *LIPV* left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *RIPV* right inferior pulmonary vein, *RSPV* right superior pulmonary vein, *MA* mitral annulus, *LAA* left atrial appendage. (Reproduced from ref. 69 with permission.)

The complications and limitations of linear ablation include the risk of proarrhythmia in the form of left atrial macroreentry, the possibility of residual triggers that may be symptomatic, and the potential for unnecessarily extensive left atrial ablation, which increases the risk of thromboembolic complications, atrioesophageal fistulas, and impairment of left atrial transport function.

Conclusions

As a result of the recognition of the role that the PVs play in the genesis of AF and development of three-dimensional navigation systems and ablation catheters capable of creating effective lesions, left atrial ablation based primarily on predetermined, anatomically determined lesions has evolved into an effective ablation strategy for paroxysmal and chronic AF. However, as the specific mechanisms of AF become better identified and physiologically guided ablation tailored to eliminate specific mechanisms continues to evolve, the role of purely anatomical ablation may gradually diminish.

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Chronic Atrial Fibrillation and Catheter Ablation

Pierre Jais, Mark O'Neill, Meleze Hocini, Frederic Sacher, Nicolas Derval, Jacques Clementy, and Michel Haissaguerre

Abstract: Catheter ablation is an effective treatment for atrial fibrillation (AF). The majority of cases of paroxysmal AF can be resolved by electrically disconnecting the pulmonary veins. While electrical disconnection is a cornerstone for all AF ablative strategies, patients with chronic AF may require targeting additional sites. Several groups have reported the use of a predetermined ablation schema that is used independent of electrophysiological, anatomical, or other considerations. Pulmonary vein antrum isolation, complex fractionated atrial electrograms, and circumferential ablation of pulmonary veins are widely used ablation schemas for paroxysmal and chronic AF. All of these strategies report good results; thus, certain aspects of each strategy may be desirable depending on type of fibrillation. Moreover, it is likely that any ablation strategy will need modification depending on the degree of underlying structural heart disease and the histological and electrophysiological remodeling created by the arrhythmia. Regardless of which strategy is used, it is of paramount importance to create lesions that are electrically complete to prevent additional arrhythmia and to avoid applying lesions that are not needed because they can be counterproductive and can be associated with resistant iatrogenic arrhythmias. We have proposed a sequential procedure based on the following order of ablation: (1) PVI guided and confirmed by a circumferential mapping catheter; (2) linear ablation at the left atrium roof between the left and right upper pulmonary veins; (3) ablation of the inferior left atrium and coronary sinus; (4) left atrial ablation at any atrial site that exhibits continuous electrical and complex fractionated activity, any focal site that appears to be a driver for AF; (5) mitral isthmus ablation (if necessary); and (6) optional right atrial/superior vena cava ablation. The endpoint of the ablation procedure is termination of AF, which can be achieved by passing directly from AF either to sinus rhythm or, more commonly, to AT, which is then mapped and ablated. With this stepwise strategy, we report an unprecedented conversion rate of 87%.

Keywords: Catheter ablation for chronic AF; Circumferential pulmonary vein ablation (CPVA); Complex fractionated atrial electrograms (CFAE); Left

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atrial linear lesions; Pulmonary vein antrum isolation (PVAI); Stepwise ablation approach for chronic AF.

Introduction

Emerging evidence suggests a significant benefit for the maintenance of sinus rhythm in patients with atrial fibrillation (AF).[1] Although antiarrhythmic drugs have to date been the mainstay of achieving and maintaining sinus rhythm in such patients, their limited efficacy and potential for significant adverse effects has led to renewed interest in nonpharmacological strategies to maintain sinus rhythm.[2–4]

One decade after the original description of the success of catheter ablation as a means of restoring and maintaining sinus rhythm, our techniques continue to evolve.[5,6] Multiple different strategies and technologies have been investigated over the years with variable success. This chapter covers the most recent techniques used for patients with persistent or permanent forms of AF.

Techniques and Strategies for Chronic Atrial Fibrillation Ablation

Role of the Pulmonary Veins in Atrial Fibrillation

It is now recognized that the pulmonary veins (PVs) have a dominant role in AF, with focal discharges from the PV musculature implicated in the initiation of 60% to 94% of AF paroxysms.[7–9] As a consequence, strategies of electrically isolating all PVs to prevent any interaction of these triggers with the atrial substrate have emerged with complete isolation, demonstrated by the disappearance or dissociation of PV potentials, as the most desirable endpoint. While PV isolation (PVI) has become the cornerstone of the ablation procedure, with a favorable safety/efficacy ratio, in patients with paroxysmal AF there is a growing body of evidence suggesting that the veins are in fact critical for maintenance of AF.[10,11]

In the context of persistent or permanent forms of fibrillation, the results of PVI are usually limited.[12] One exception to this rule is encountered in patients selected on the basis of immediate reinitiation following external electrical cardioversion, probably because of a prominent role of the PV triggers in such a situation.[13] However, using a randomized order of ablation targeting the PVs; thoracic veins, including the coronary sinus (CS) and superior vena cava (SVC); and left atrial (LA) tissue, we have demonstrated that PVI was one of the three ablation sites associated with the greatest impact on the AF cycle length and termination of AF.[14] In other words, PVI alone is certainly too limited for treatment of chronic AF but should not be abandoned and in fact remains the first step of the procedure in many laboratories.

Predetermined Strategies

Several groups have reported the use of a predetermined ablation schema for AF that is applied to the patient independently of electrophysiological, anatomical, or other considerations. Frequently, the ablation strategy used for paroxysmal or chronic AF is the same. Excellent results have been reported

by the Cleveland clinic group; guided by a circular mapping catheter, PVI is associated with extensive ablation at the posterior LA. Intracardiac echocardiography was systematically used not only to improve catheter localization but also in an attempt to optimize tissue lesions by monitoring microbubble formation during radio-frequency (RF) delivery. Fifty percent of 152 patients treated with this approach had chronic AF, and 90% of the total population was considered successfully treated.[15]

Nademanee et al., based on the demonstration of regional and temporal heterogeneity of endocardial atrial activation, hypothesized that complex fractionated atrial electrogams (CFAEs) may represent a substrate for AF perpetuation and therefore be a target for catheter-based ablation procedures. By applying this ablation strategy to patients with all forms of AF (i.e., paroxysmal, persistent, and permanent), they reported a high success rate[16]; however, in our experience, targeting CFAE following PVI is almost invariably associated with conversion of AF to atrial tachycardia (AT), which then requires further mapping to permit restoration of sinus rhythm by ablation. In other words, this strategy needs to be combined with linear lesions in more than 80% of patients with persistent or permanent AF when restoration of sinus rhythm is the procedural endpoint. Therefore, for persistent/permanent AF, we consider targeting of CFAE alone to constitute but one part of a stepwise ablation strategy rather than the strategy itself.

Another widely practiced ablation schema involves wide encircling of the PVs in combination with linear ablation at the LA roof and mitral isthmus, which have both been shown to improve outcome following ablation.[17,18] This strategy is often applied to all patients irrespective of the type of AF; however when used in chronic AF, 74% of patients were free from AF without antiarrhythmic drugs at 1 year follow-up.

The impressive results mentioned, using quite different ablation strategies, suggest that certain aspects of each procedure may be desirable to achieve the best result in any given patient, depending on the type of fibrillation seen. Furthermore, it is likely that the ablation strategy will need modification depending on the degree of underlying structural heart disease and the histological and electrophysiological remodeling produced by the arrhythmia. To some extent, the current catheter-based procedures are comparable to surgical procedures in which no attempt to map the arrhythmia is made, and the completeness of linear lesions is rarely assessed. In the context of a catheter-based procedure, the isolation of PVs and completeness of linear block are easy to document once converted to sinus rhythm. This point is of paramount importance as the arrhythmogenic role of incomplete lesions has been well described and is largely accepted. In addition, applying lesions that are not needed, as may be the case with a predetermined ablation schema, can be counterproductive (in addition to the increased risk they carry) and associated with resistant iatrogenic arrhythmias. Several groups have therefore investigated the role of mapping during AF to tailor the procedure to the patient.

Stepwise Strategy as a Synthesis of Current Approaches

It has been demonstrated that when ablation is performed in a random order, the steps most frequently associated with a conversion from AF to AT or to sinus rhythm are PVI, ablation at the inferior LA/CS and the LA appendage

mouth, followed by linear lesions at the LA roof and mitral isthmus.[14] Accordingly, we propose a sequential procedure based on the following order of ablation:

1. Pulmonary vein isolation guided and confirmed by a circumferential mapping catheter.
2. Linear ablation at the LA roof between the left and right upper PVs. Although linear ablation at this site is infrequently associated with termination of AF, it is not highly technically demanding and can usually be performed in less than 10 min. In view of the very narrow isthmus created at the LA roof by the wide encircling performed to isolate PVs, linear conduction block across this isthmus is certainly desirable to prevent roof-dependent atrial flutter.
3. Ablation o the inferior LA and CS (Figure 1). The endpoint of ablation at the inferior LA (i.e., the endocardial LA surface facing the CS and bordered by the interatrial septum and mitral isthmus) is organization of local activity as well as of activity within the CS. Once ablation of the inferior LA is complete, the ablation catheter is used to map within the CS, and further ablation is performed as required to organize and slow local electrical activity.
4. Left atrial ablation (incorporating the orifice of the LA appendage) at any atrial site showing one of these characteristics: (a) continuous electrical activity (Figure 2), defined as atrial activity without a return to electrical baseline for a minimal duration of 100 ms; and (b) fractionated or fragmented electrical activity, defined as the presence of at least two deflections traversing the baseline and with a total duration of less than

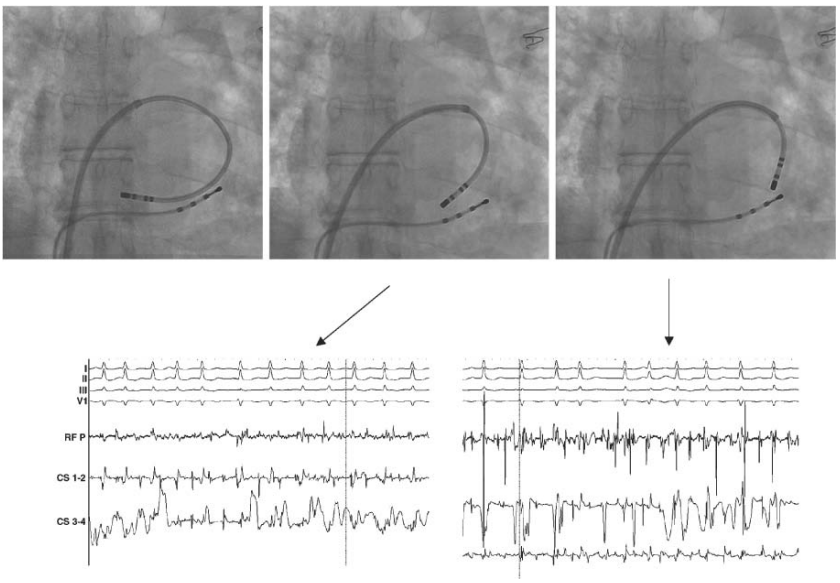

Figure 1 Ablation of the inferior LA and along the CS. The endpoint is organization of the local and CS recordings. Once ablation of the inferior LA is complete the ablation catheter is used to map within the CS, and further ablation is performed.

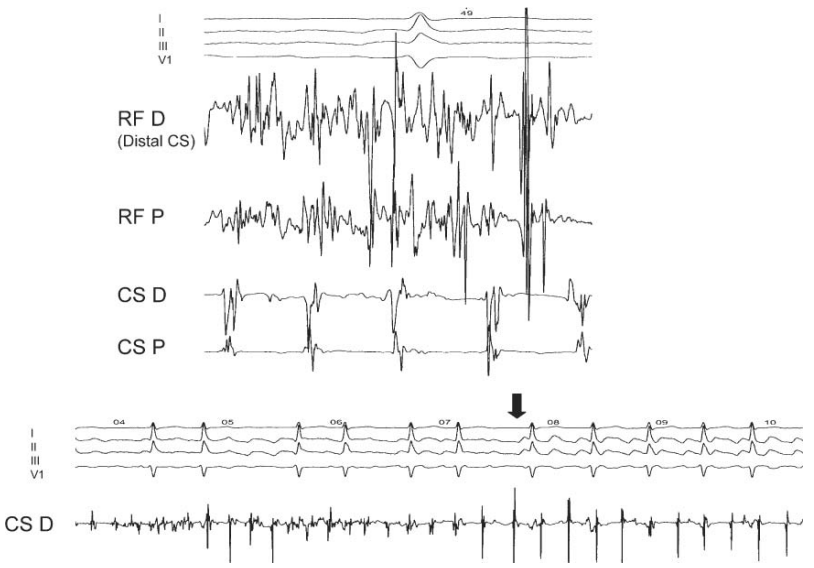

Figure 2 Left atrial ablation is performed at any atrial site consistent with the definition of continuous activity (shown in figure) or complex fractionated activity during atrial fibrillation. As shown on the surface ECG tracings (I,II,III and IV) organization into atrial flutter may occur after targeting these sites (arrow).

100 ms. Potential sources or drivers perpetuating AF are targeted based on identification of: (c) rapid activity (i.e., a locally recorded cycle length with a frequency gradient to the surrounding tissue); (d) focal and consistent centrifugal activation during AF as demonstrated by a single site of earliest activity with radial spread of activation to the surrounding tissue; and (e) a temporal gradient of activation, defined as a clearly visible phase difference between the local electrograms recorded on the proximal and distal bipoles of the mapping catheter and potentially representing a rotor.

5. Mitral isthmus ablation. Ablation at the mitral isthmus is required in about 80% of patients, either for ongoing AF after completion of steps 1 to 4 or, more frequently, for perimitral reentry.

The endpoint of the ablation procedure is termination of AF (Figure 3). This can be achieved by passing directly from AF either to sinus rhythm or, more commonly, to AT, which is then mapped and ablated. Once sinus rhythm has been restored, PVI and linear lesions are checked for completeness and reablated if needed.

Using this approach, all components of the more conventional schemas listed above are targeted, with the added advantage that discrete but critical sites that are frequently not incorporated by these standard schemata can be identified and treated. As a consequence, sinus rhythm can be restored by ablation alone and maintained in about 90% of patients, albeit at the cost of a repeat procedure in 50% of patients. However, it should be emphasized that these are extensive procedures associated with significant risks and require careful and individualized risk–benefit assessment. In addition, even if restoration of atrial mechanical function is observed in over 90% of patients

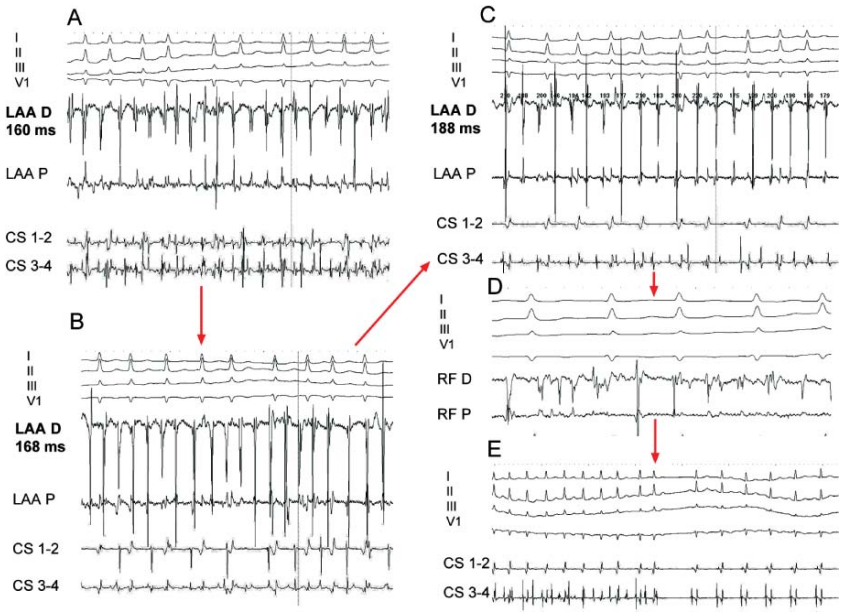

Figure 3 The mode of termination of AF during catheter ablation for chronic AF. Termination of AF can be accomplished by either passing from AF to sinus rhythm (SR) or in the majority of patients from AF to AT and then with further mapping and ablation to SR. The above figure shows the organization of AF (A) to AT (B,C,D) and finally to SR (E).

in whom sinus rhythm is restored, less-extensive and less time-consuming procedures are certainly desirable. Technical improvements such as mapping during AF could be of significant help in better defining specific targets, but this remains to be demonstrated (Figure 4).

Given the important differences in methodology and definitions for success, comparing approaches used for AF ablation has always been challenging. However, the increase in AF cycle length, and perhaps even more the percentage of conversion of AF, reflect the impact of ablation on the substrate for fibrillation. Using these markers, the stepwise strategy described is highly effective, with an unprecedented conversion rate of 87%. Further refinement of the procedure to limit the extent of ablation (and thereby preserve LA tissue) in combination with electrical or chemical cardioversion could be advocated. Of note, though, is the fact that patients in whom the conversion is not achieved by ablation have a lower long-term success rate with more repeated procedures for AF recurrences.

Another recently reported strategy tailored to the patient consisted of ablating only those PVs showing PV tachycardia.[17] Left atrial tissue, the CS, and SVC were targeted only if AF persisted or could be reinduced after elimination of all PV tachycardias, although complete isolation of the PVs was not a required endpoint. The rationale for this tailored strategy was to spare as much as possible the posterior LA in an effort to prevent fistulas between the LA and the esophagus. Accordingly, CFAEs are targeted everywhere in the LA with the exception of the posterior LA. This approach has been restricted to paroxysmal AF and remains untested in long-standing AF.

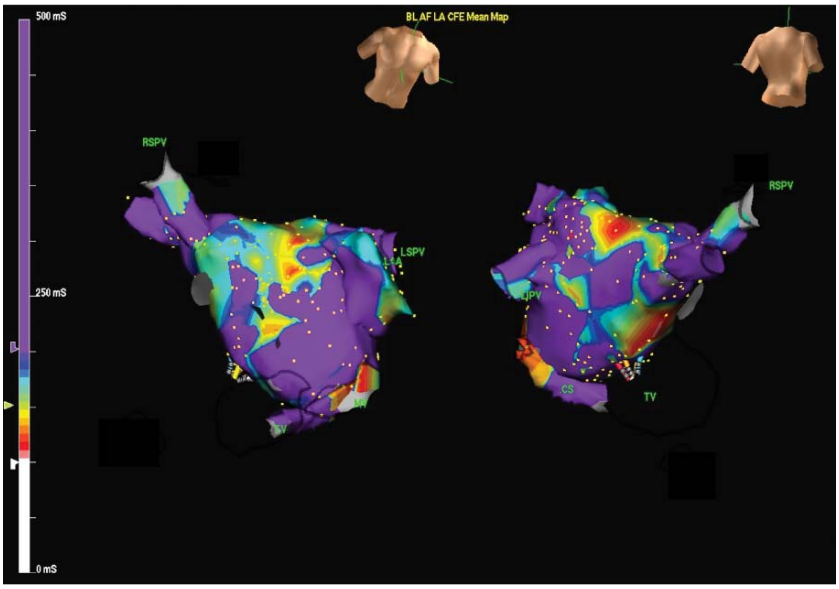

Figure 4 The left atrium (LA) geometry posterior and anterior views showing the CFAE map obtained with the EnSite NaviX system. Note that CFAE areas are shown at the RSPV, LSPV, LAA, LA Roof, inferior LA and CS.

Conclusion

Catheter-based ablation of chronic AF is not perfect and is probably the most technically challenging procedure currently performed in electrophysiology labs worldwide. Although extensive ablation procedures are associated with higher conversion rates and possibly with better clinical outcomes, we must acknowledge the significant associated risk to the patient. Shorter and less technically challenging procedures are desirable prior to a wider dissemination of the technique. In spite of this cautionary note, catheter ablation offers a unique opportunity to restore sinus rhythm in patients resistant to drugs, with a favorable impact on symptoms, quality of life, and heart function, particularly in patients with heart failure.

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Hybrid Strategies for Ablation of Permanent AF
Targeting AF Nest in Sinus Rhythm and CFAE in AF

Mauricio Arruda, Claude Elayi, Jose Carlos Pachon, and Andrea Natale

Abstract: Catheter ablation for atrial fibrillation (AF) has emerged as an effective treatment for paroxysmal AF. However, permanent AF ablation success rates are dramatically lower, thus fostering an interest in alternate and adjunctive strategies, such as targeting the complex fractionated atrial electrograms (CFAEs), CFAE in addition to pulmonary vein antrum isolation (PVAI), ablation of AF nests guided by real-time spectral mapping, and ablation of AF nests in addition to PVAI.

Keywords: AF Ablation; CFAE; AF Nest; Catheter Ablation.

Complex fractionated atrial electrogram (CFAE) ablation has been shown to terminate atrial fibrillation (AF) in 95% (28% required concomitant ibutilide) of patients. At 1-year follow-up, 91% of patients were free of arrhythmias and symptoms, with 20% requiring a second procedure. In our initial study assessing the efficacy of CFAE plus PVAI in patients with permanent AF (PM-AF), success rate after a single procedure and off antiarrhythmic drugs (AADs) at 7-month follow-up was 64%. This adjunctive CFAE approach decreased overall recurrences in comparison to our conventional strategy of PVAI plus superior vena cava isolation (SVCI).

Ablation of atrial nests, without intentional pulmonary vein isolation (PVI), has been shown to maintain 94.1% of patients in sinus rhythm (SR) at 9.9 ± 5 months postprocedure (41.1% remained on a previously ineffective AAD). When AF nest ablation is performed in combination with PVAI and SVC, 75% of paroxysmal AF (PAF) patients and 64% of persistent or permanent AF (PS/PM-AF) patients were maintained in SR in comparison to 67% of patients who maintained SR with PVAI in addition SVCI. Initial studies assessing these alternative and adjunctive approaches appear promising; however, the long-term clinical implications of these strategies remain to be shown prospectively in larger series of patients.

The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study concluded that SR is either an important determinant of survival or a marker for other factors associated with survival. Antiarrhythmic

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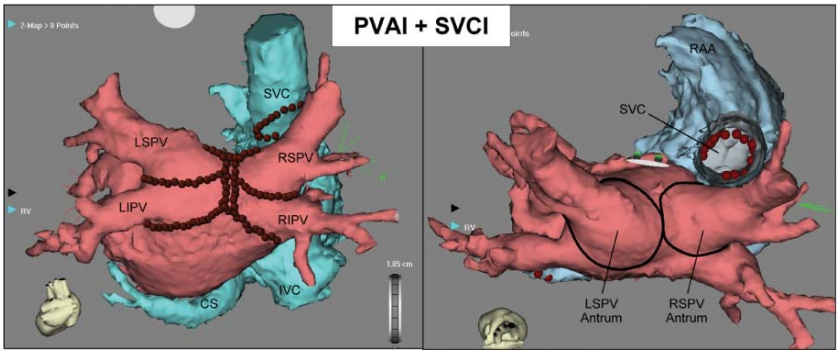

Figure 1 The segmented three-dimensional contrast cardiac computed tomography(CT) of a patient presenting for atrial fibrillation (AF) ablation is used to illustrate our approach for pulmonary venous isolation at their antrum (PVAI) and superior vena cava isolation (SVCI). **A** The lesion continuity along the posterior wall and at the anterior aspect of the left atrial (LA) roof. **B** Pulmonary vein (PV) antra (dotted circles) seen from the superior view. Also, note the close proximity of the superior vena cava (SVC) to the right superior PV (RSPV) and the circumferential lesion created for SVCI. *CS* coronary sinus, *IVC* inferior vena cava, *LIPV* left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *RIPV* right inferior pulmonary vein

drugs are not associated with survival, and benefits are offset by adverse effects. In addition, the investigators suggested that an effective method for maintaining SR is warranted.[1]

Catheter ablation for the treatment of AF has been evolving with innovative approaches and technologies. Pulmonary vein isolation, initially limited to the pulmonary veins (PVs), has been modified to encompass the left atrial (LA) myocardium surrounding the PV ostia, namely, the LA–PVAI. Our current intracardiac echo (ICE)-guided PVAI approach, including the adjunct of SVCI[2–4] (Figure 1), has likely accounted for higher success rates by electrically isolating further AF trigger sites, modifying the substrate for AF maintenance, and possibly by modulating a dysfunctional autonomic cardiac nervous system.

Adjunctive Strategies to Improve Long-Term Outcome of Atrial Fibrillation Ablation

Atrial Fibrillation Ablation Targeting Complex Fractionated Atrial Electrogram

The CFAEs were identified during surgical epicardial mapping at sites expressing slow conduction, functional conduction block, and pivot points.[5] These complex electrical activities exhibit short cycle lengths and heterogeneous temporal and spatial patterns.[6]

Nadamanee et al.[7] performed mapping and ablation of CFAEs as a substrate-modifying strategy without PVI in patients with induced AF (lasting ≥ 5 min) or presenting in AF. The investigators defined CFAEs as low-amplitude potentials (0.06 to 0.25 mV) exhibiting relative spatial and temporal stability: (1) fractionated atrial electrograms (EGMs) composed of two deflections or more or continuous deflections; or (2) atrial EGMs with cycle length of 120 ms or less.

Customized software was developed and incorporated into the CARTO electroanatomic system (Biosense-Webster). The CFAEs are displayed in a color-coded manner in respect to (1) interval confidence level (ICL), which is the degree of fractionation during a signal recording time of 2.5 s; and (2) shortest complex interval (SCI). Ablation is first targeted at sites with SCI and high ICL.

Three types of CFAE were described based on their right atrial (RA) and LA distributions. Type I CFAEs were found in only one area, and focal ablation terminated AF. Type II was in two areas. Type III required three or more areas of ablation (PV was one area). The CFAE ablation terminated AF in 95% of patients (28% required concomitant ibutilide). Type III distribution was more commonly identified in patients with chronic AF. The interatrial septum was the most common site for CFAEs, whereas CFAEs were not present in the appendages. At 1-year follow-up, 91% of patients were free of arrhythmias and symptoms, with 20% requiring a second procedure.

Ablation of Complex Fractionated Atrial Electrogram as an Adjunctive Approach to Pulmonary Vein Isolation

Oral et al. described a hybrid ablation approach in patients with PAF.[8] Large circumferential ablation (CFAE), by voltage abatement, combined with posterior inter-PVs and mitral isthmus linear lesions was initially performed. If AF was still present or inducible (60% of patients), additional ablation lines (1 to 4) along areas of CFAEs were created, resulting in 86% freedom of AF at 6 months postprocedure.

The same investigators randomized patients undergoing ablation for chronic AF to linear LA lesions across CFAEs (nonencircling) or LACA (encircling) plus mitral isthmus, posterior wall, or roof linear lesions.[9] Three to five nonencircling linear lesions (using voltage abatement without assessing for conduction block) through areas of CFAEs showed equal efficacy as encircling plus, with 60% and 68% AF and atrial flutter freedom at 9 ± 4 months.

These investigators have also described a tailored approach for ablation of PAF targeting initially only the culprit PVs, without empirical PVI. If AF persisted or was reinduced, CFAEs were targeted, but sparing the posterior LA to avoid esophageal injury.[10] Haissaguerre et al. described a stepwise sequential ablation approach for patients with long-lasting PS-AF.[11] It includes PVI and linear ablation across the roof and along the isthmus between the mitral annulus and the left inferior PV; in addition, ablation was performed at atrial sites exhibiting (1) continuous electrical activity; (2)fractionated or fragmented electrical activity (at least two deflections traversing the baseline and with a total duration of less than 100 ms); (3)rapid activity with a frequency gradient to the surrounding tissue; (4)focal and consistent centrifugal activation during AF as demonstrated by a single site of earliest activity with radial spread of activation to the surrounding tissue; (5)temporal gradient of activation (visible phase difference between local EGMs recorded on the proximal and distal bipoles of the mapping catheter, potentially representing a rotor).

Using this extensive ablation strategy, AF termination was typically preceded by prolongation of AF cycle length (AFCL). Only 13% converted directly to SR, while the majority organized into residual atrial tachyarrhythmias. Focal atrial tachycardias (ATs) were ablated at the PVs, left atrial appendage (LAA), and coronary sinus (CS). Macroreentrant ATs were ablated at the mitral isthmus, LA roof, and occasionally at the cavotricuspid isthmus.

To further assess CFAEs, the investigators used a 20-electrode catheter, distributed in five spines with 4 electrodes each (PentaRay, Biosense-Webster). This provided for high-resolution mapping of CFAEs in a small series of patients with PAF.[12] Interestingly, it was observed that the same anatomic region may have short nonfractionated EGMs during an episode with a slow AFCL, whereas it could have a complex fractionation when AFCL is accelerated.

Nakagawa et al. targeted the autonomic ganglionated plexuses (adjacent to the PVs) as an adjunct approach to PVI. The typical endocardial stimulation sites used to identify the ganglionated plexuses seem to have a spatial correlation to three major LA areas exhibiting CFAEs.[13] At the Cleveland Clinic, we have been evaluating the adjunctive role of CFAE ablation to our ICE/EGM guided approach to PVAI and SVCI in a prospective randomized study including patients presenting for ablation of long-standing or PM-AF. In summary, PVAI is performed in AF. Typically there are no significant changes in the level of fragmentation in the anterior LA, CS, and RA; in addition AF rarely converts into SR during PVAI, and following empirical PVAI we extensively target sites exhibiting CFAEs.

We use a multielectrode circular catheter for mapping CFAEs in the LA and RA. A multielectrode linear catheter is used for CFAE mapping in the CS and SVC–RA junction. We define CFAEs as atrial sites exhibiting continuous electrical activity, fragmented electrical activity (complex EGMs with two or more deflections), or atrial EGMs with cycle length of 120 ms or longer. We have also used the NaviX system (St. Jude Medical) along with its CFE (Complex Fractionated Electrogram) mapping algorithm in which the index of fragmentation is based on EGM average detection (acquisition intervals 1 to 8 s) (Figures 2 and 3). Our initial study group consisted of 51 consecutive patients

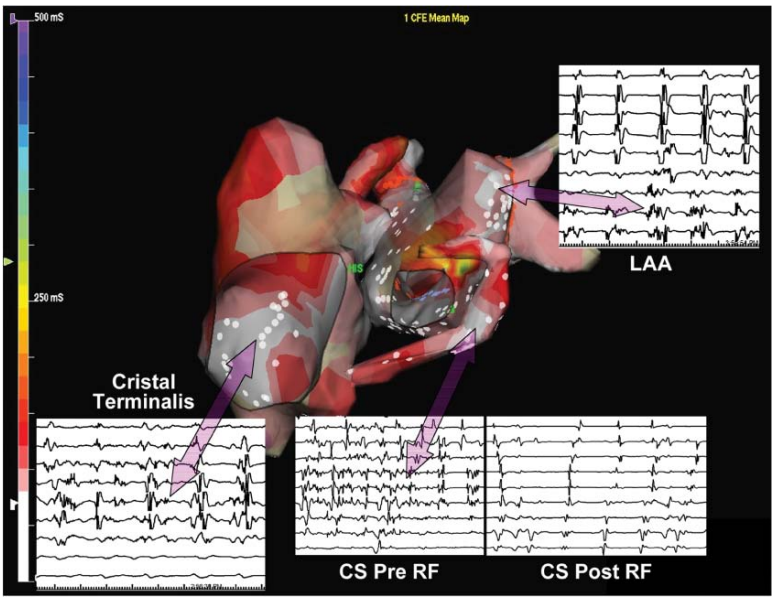

Figure 2 Tridimensional right and left atrium geometry obtained with the EnSite NaviX system using software (CFE) to detect complex fractionated electrograms (EGMs). The distribution of fractionated EGMs is color coded within 50 and 150 ms in this patient. Note that the crista terminalis, coronary sinus (CS), left atrial appendage (LAA), septum, and floor of the left atrium exhibited highly fractionated EGMs. *RF* radio frequency

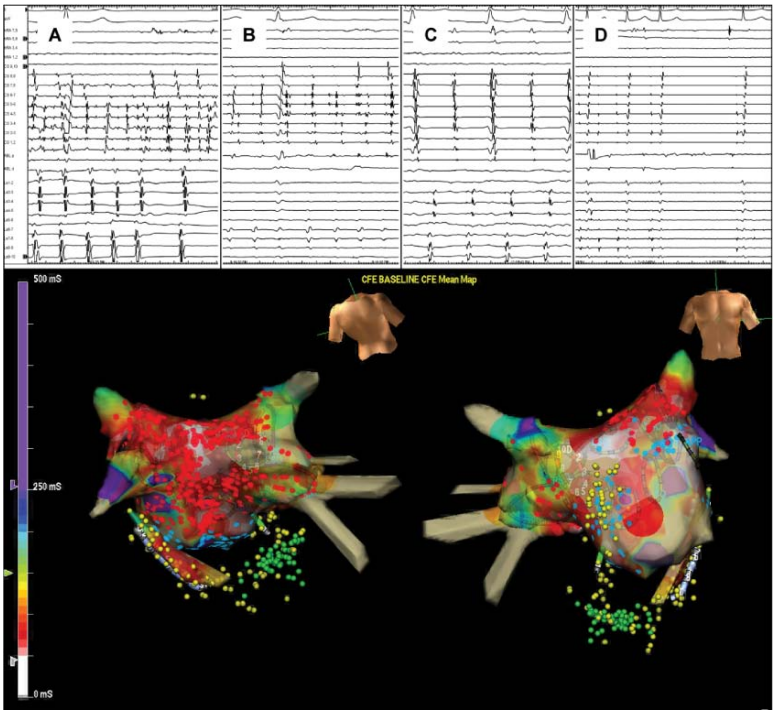

Figure 3 Left atrium (LA) geometry (posterior and anterior views) showing the CFE map obtained with the EnSite NaviX system. **A** and **B** The EGMs before and after isolation of all four PVs (PVI). **B** Note that the coronary sinus (CS) remains fractionated following PVI. Extensive ablation at fragmented areas, including the CS and right atrium, eventually organized the tachycardia (**C**), which was later terminated by ablation at the anterior septum LA (**D**)

who underwent PVAI plus CFAE ablation. The AF converted into SR in only 2 patients (4%), remained in 25%, but organized in a tachyarrhythmia (AT) in 71% of patients (Figure 3). In a median follow-up of 7 months following a single procedure without AADs, there was a 36% recurrence rate (22% recurred with AF and 14% with an organized AT). Of the patients that remained in AF requiring direct current (DC) cardioversion at the end of the procedure, 46% had recurrences, while of the patients in whom AF organized into AT, 33% had recurrences. Nevertheless, the adjunct of CFAE ablation (extensively at the LA and CS and some at the RA; Figure 3) decreased overall recurrences compared to our conventional PVAI plus SVCI.

Ablation of Atrial Fibrillation Nests Guided by Real-Time Spectral Mapping in Sinus Rhythm

Pachon et al. have developed a system for real-time spectral mapping using fast Fourier transform (FFT) in SR. This mapping strategy identifies sites in which the unfiltered, bipolar atrial EGMs contain unusually high-frequency components, namely, fibrillar myocardium or the so-called AF nest. The investigators described a new AF ablation approach targeting solely the atrial sites exhibiting the AF nests without intentional PVI. In their patient series, 94.1% were maintained in SR at 9.9 ± 5 months postprocedure. However, 41.1% remained on a previously ineffective AAD.[14]

Atrial Fibrillation Nest Ablation as an Adjunctive Approach to Intracardiac Echo-Guided Pulmonary Vein Antrum Isolation and Superior Vena Cava Isolation

In the attempt to further modify the AF substrate and to improve long-term ablation success, we have been evaluating the adjunctive role of AF nest ablation to our ICE/EGM guided approach in a prospective randomized study. Patients with PAF and PS/PM-AF underwent PVAI plus SVCI alone (control group) or PVAI plus SVCI plus AF nest ablation (study group). Patients presenting in AF underwent DC cardioversion during PVAI or after its completion and prior to spectral mapping and AF nest ablation in SR at the LA, RA, and CS. A customized amplifier and software (Pachon) was used for real-time spectral mapping. The system applies FFT to the unfiltered bipolar atrial EGMs from the distal pair of electrodes on the ablation catheter. The full spectrum of each EGM is continuously displayed in three dimensions (Figures 4 and 5). Radio-frequency (RF) current was delivered via a 3.5-mm irrigated-tip electrode (Biosense-Webster) up to 45 W (35 W in the CS) for 20 s at all sites exhibiting AF nests except at the sinus and atrioventricular (AV) nodal regions.

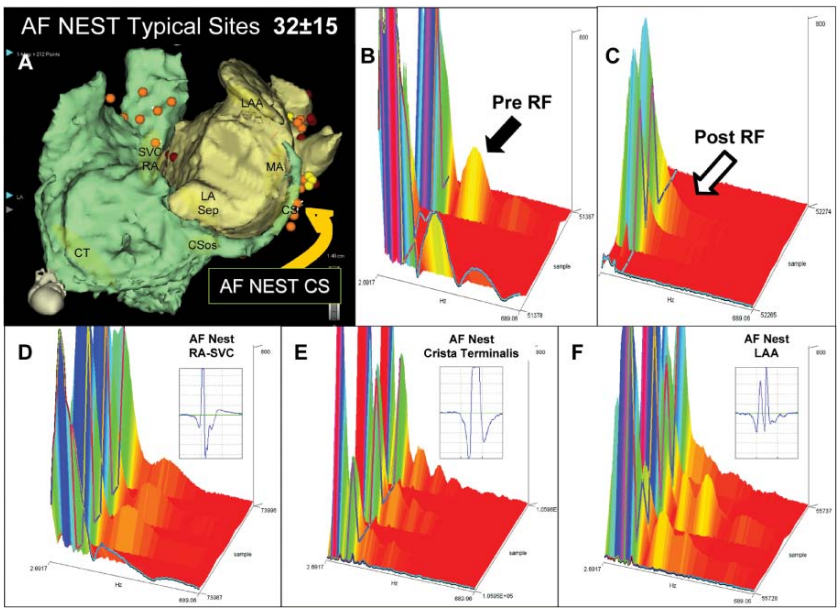

Figure 4 **A** The typical locations exhibiting fibrillar myocardium (atrial fibrillation [AF] nest) during real-time spectral mapping in sinus rhythm, following pulmonary vein (PV) and superior vena cava (SVC) isolations, are shown in a segmented three-dimensional contrast cardiac computed tomograph (CT) of a patient presenting for AF ablation. **B** Note the frequency spectra of two consecutive bipolar electrograms recorded from the coronary sinus (CS; arrow in **A**). The high-frequency components characteristic of AF nests are indicated by the arrow in **B**. Radio-frequency (RF) delivery up to 35 W for 20 s eliminated the fibrillar pattern, shown in **C. D–F** Additional examples of AF nests recorded from other regions. *LAA* left atrial appendage, *RA* right atrium

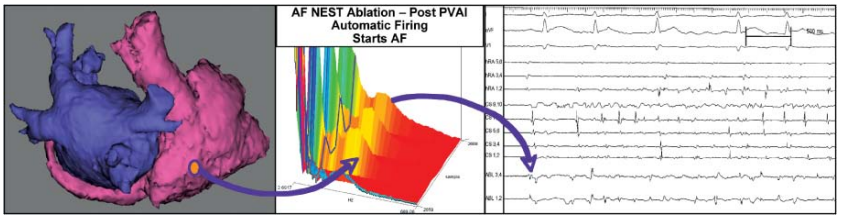

Figure 5 The segmented three-dimensional contrast cardiac computed tomographic (CT) scan indicating a site at the crista terminalis in which an atrial fibrillation (AF) nest was recorded following isolation of all four pulmonary veins (PVs). Note that radio-frequency (RF) current delivery at this AF nest promptly induced local automatic firing and subsequently AF. This is a common response observed while ablating AF nests located in the coronary sinus (CS), low right atrium (RA) free wall anterior to the crista terminalis, and at the crista itself. *PVAI* pulmonary vein antrum isolation.

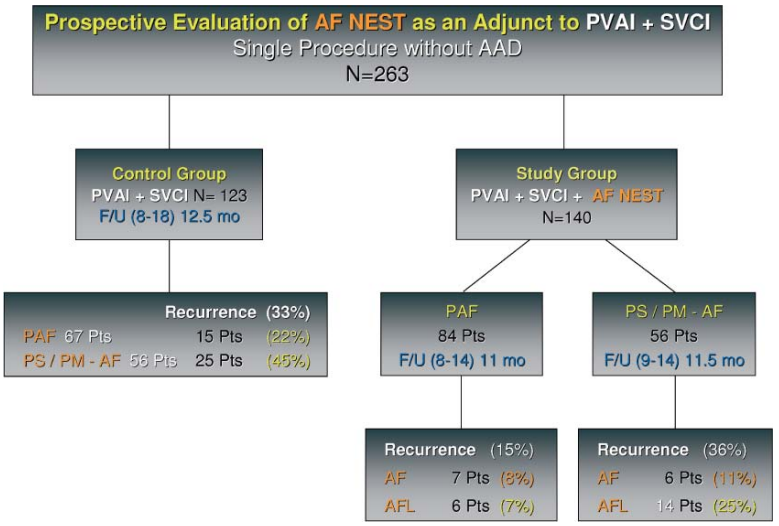

Figure 6 Prospective Evaluation of AF Nests as an Adjunct to PVAI+SVCI *Abbreviations*: AF=Atrial Fibrillation, PVAI-Pulmonary Vein Antrum Isolation, SVCI-Superior Vena Cava isolation, AAD-antiarrhythmic drugs, F/U-follow up, PAF-Paroxysmal Atrial Fibrillation, PS/PM-AFPersistent/ Permanent atrial fibrillation, Pts-patients, AFL-Atrial Flutter.

Automatic firing is commonly induced during RF delivery at AF nest sites (particularly at the low CT), LAA, and CS (Figure 5).

The adjunct of AF nest ablation had a favorable impact on the long-term outcome following a single procedure without AADs. The study results are summarized in Figure 6.

Clinical Implications

Innovative techniques for mapping and catheter ablation of AF have improved long-term outcomes and allowed a more thorough understanding of this prevalent arrhythmia.

Our conventional approach of PVAI with anteroseptal extension and SVCI has likely accounted for higher success rates by electrically isolating further AF trigger sites, modifying the substrate for AF maintenance, and possibly modulating a dysfunctional autonomic cardiac nervous system.

Ablation of AF nests decreases recurrence rates following a single ablation procedure for PAF, PS, and PM-AF. Likewise, extensive CFAE ablation, as an adjunct to PVAI plus SVCI, decreases AF recurrence. Alone, CFAE ablation had no impact on AF termination, but PVAI followed by CFAE ablation converted AF into AT in most patients; nevertheless, ablation of the residual AT or its DC cardioversion resulted in similar recurrence rates.

Typically, for AF nest ablation, RF delivery for 20—30 s abolishes the high-frequency potentials, normalizing the spectrum of the local bipolar EGM. Importantly, full lesion thickness or linear lesions are not required; therefore, this approach is less likely to create a substrate for macroreentrant ATs while sparing viable atrial myocardium.

Interestingly, recurrence of an organized atrial tachyarrhythmia, typically focal, is more common following AF nest ablation, while for patients who have undergone CFAE ablation, it recurs most commonly with AF, but also with focal or macroreentrant AT.

These adjunctive hybrid strategies may be considered in patients with more frequent AF episodes refractory to AADs and certainly in those with PS/PM-AF. The SR approach may be preferable to targeting continuous electrical activity or CFAE since these low-amplitude EGMs may be unrecognized because of their temporal variability.

The typical electrophysiological characteristics of AF nests, exhibiting a heterogeneous spectral shift toward high frequencies, are not yet correlated by any histopathological, neurological, or endocrine changes. The AF nests may simply be an expression of anisotropic conduction and short refractoriness or other more complex mechanisms yet to be investigated. These highly resonant, localized atrial sites may harbor CFAEs during AF.

Delivery of RF at AF nest sites often induces rapid localized atrial firing, but whether this automatic or triggered response is associated with direct neurological stimulation or with intracellular calcium overload or yet whether AF nest ablation modulates the cardiac autonomic nervous system, potentially responsible for initiation and maintenance of AF, remains to be demonstrated.

The independent or combined value of these innovative hybrid strategies for AF ablation and their long-term clinical implications remain to be shown prospectively in large series of patients.

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Isolation of Pulmonary Vein Antrum Triggers

Mohamed Kanj, Atul Verma, Dimpi Patel, and Robert Schweikert

Abstract: Atrial fibrillation (AF) triggers are repetitive bursts of ectopic atrial activity that can induce AF. These triggers are often located in the pulmonary vein antra (PVA). The latter are tubular structures arising from the posterior wall of the left atrium and giving rise to the pulmonary veins. Multiple imaging modalities have been used to define the PVA, including intracardiac echocardiography along with computed tomographic scans and magnetic resonance imaging. Isolation of AF triggers by performing PVA isolation has been shown to be superior and safer than focal ablation of these triggers. The PVA isolation procedure is often performed using two catheters, a circular mapping catheter and an ablation catheter. The endpoint of this procedure is to electrically isolate the pulmonary vein antra.

Keywords: Atrial fibrillation; Atrial fibrillation triggers; Catheter ablation; Pulmonary vein antrum isolation; Pulmonary veins.

Introduction

Catheter ablation of atrial fibrillation (AF) has emerged as an increasingly effective and safe procedure for the treatment of this common arrhythmia. The technique for ablation originated from an understanding that AF is frequently triggered from focal regions of the left atrium (LA).[1] By elimination of these focal triggers, AF may be cured in a substantial number of patients, particularly those with paroxysmal AF. The pulmonary veins (PVs) have been identified as a major source of these focal triggers of AF.[1] Bands of atrial-like tissue extend out into the PVs and act as a source of spontaneous activity, which if rapid enough, can result in chaotic atrial activation.[2] Both electrical and anatomical properties of the PVs contribute to the arrhythmogenicity of these structures. However, the PV–LA interface may also play an important role in the perpetuation of AF once it is triggered.[3] This important junctional region is frequently the site of vortexlike microreentry, or "rotors," that are critical to sustaining AF, particularly in patients with more persistent or permanent forms of the arrhythmia. As such, most techniques

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of catheter-based AF ablation have focused on the electrical disconnection of the PVs from the LA.[4]

To achieve thorough isolation of the PVs from the LA, a good understanding of the anatomy of the PVs and their junction with the LA is essential. Through this understanding, the entire interface between the PVs and the LA, also called the PV "antrum," can be targeted and ablated, leading to long-term cure. In fact, the failure of PV isolation-based techniques to cure AF has frequently been linked to inadequate achievement of isolation of the entire PV antrum.

In this chapter, the rationale for isolating the PV antra is explained, and the importance of achieving complete PV antral isolation (PVAI) is emphasized. The chapter also describes the evolution of approaches used for PV isolation, culminating in a description of a successful approach to PVAI used in over 4,000 patients.

Pathophysiology of the Pulmonary Veins in the Triggering and Maintenance of Atrial Fibrillation

A complete review of the electrophysiology of the PVs is beyond the scope of this chapter 4 and is covered elsewhere in chapter 4. However, a brief overview is warranted to emphasize the important role that the PVs play in both the triggering and the maintenance of AF.

It has been known for a long time that rapid, repetitive bursts of ectopic atrial activity can induce AF.[5] Bursts of rapid atrial pacing can also induce AF and cause paroxysmal AF to become persistent.[6] Since the publication of the seminal article by Haissaguerre et al. in 1998, increasing attention has been focused on the PVs as the primary source of ectopic atrial activity triggering AF.[1] The article demonstrated that in the majority of AF patients (94%), the focus was in one or more of the PVs. Observations from other studies have confirmed the importance of the PVs as a source of AF triggers in both human and animal models.[7,8] Although non-PV sites may also trigger AF, the incidence of such non-PV triggers appears to be low. Human studies have suggested that non-PV sites trigger AF in no more than 6% to 10% of patients.[9] The PV is a complex anatomical structure with muscular extensions of the atrium extending into the PV and providing a complex substrate for both automatic and reentrant activity that promotes the initiation and perpetuation of AF.

Triggered activity has been demonstrated in the PVs, which may be an important contributor to PV ectopy leading to AF. Studies performed on human embryonic tissues have shown the presence of pacemaker-type cells and conduction system tissue in the region immediately surrounding the common PV.[10] In fact, Perez-Lugones et al. specifically demonstrated the presence of Purkinje-type cells in human PV samples.[11] Thus, the region around the PV origin may be morphologically similar to the conduction system and be capable of pacemaker-like activity. Studies in isolated PV tissue models have also shown that the PVs are capable of spontaneous triggered activity with phase 4 depolarization.[8,12,13] In human studies, overdrive suppression of PV activity provides strong evidence that such activity may be secondary to a triggered activity mechanism.[14,15]

In addition to triggering AF, the electrical and anatomical structure of the PVs may facilitate the occurrence of reentry, which may contribute to the maintenance of AF.

Atrial fibrillation is perpetuated by microreentrant circuits, or rotors, that exhibit high-frequency, periodic activity from which spiral wave fronts of activation radiate into surrounding atrial tissue.[3,16] Conduction becomes slower and less organized with increasing distance from the rotors, likely because of atrial structural remodeling, resulting in fibrillatory conduction. Interestingly, the dominant rotors in AF are localized primarily in the junction between the LA and PVs, as demonstrated by several investigators.[16–18] Optical mapping in isolated heart preparations has also directly visualized the presence of reentry circuits at the PV–LA interface.[18] Kumagai et al. demonstrated that the PV–LA region has heterogeneous electrophysiological properties capable of sustaining reentry (micro or macro).[19] Specifically, Hocini et al. suggested that it is the abrupt changes in muscle fascicle orientation that create zones of delay facilitating reentry.[20] Finally, autonomic inputs may be important in both triggering and maintaining AF, and many of these inputs are clustered close to the PV–LA junction.[21]

Thus, the PVs play a critical role in both triggering and maintaining AF. This was elegantly confirmed using both electrophysiological and histological data in an open-heart, human model involving patients undergoing AF surgery.[22] The mechanism also applies to a wide spectrum of AF patients, including adolescents[23] and adults with structural heart disease.[24,25] It seems quite reasonable, then, that the primary target of catheter-based AF ablation should be the PVs and the PV antrum.

Anatomy of the Pulmonary Vein Antrum

A detailed understanding of the PV–LA interface is important because this interface is ultimately the target of most catheter ablation approaches. Failure to completely isolate the entire interface is a common cause for procedural failure.

On a simplistic level, the PVs may be thought of as tubular extensions arising from the posterior wall of the LA. This is indeed the impression one gets when the LA and PVs are imaged by PV angiography. Angiograms clearly define the tubular portion of the veins and their extension away from the LA. However, as imaging techniques for the LA have evolved, so has our understanding of the interface between the LA and PVs.

Embryologically, the PVs originate from the posterior LA wall so that a continuum between the atrial wall and PVs exists.[4] During the fourth week of development, a primordial common PV appears as a blind diverticulum in the dorsal wall of the LA. Within days, the common PV anastomoses with the venous plexus around the lungs, and the common PV is absorbed into the posterior LA wall to create two separate openings of PVs and eventually four separate openings. It is not surprising, then, that muscular sleeves of the atrium are found along the lengths of all of the PVs. It is also not surprising that the transition from LA to PV is a gradual one and not simply a tubular attachment to a chamber. In fact, studies of PV anatomy from pathological specimens and three-dimensional (3-D) computed tomography (CT) have shown that the PV is shaped like a funnel that starts distally as a tube, but then fans out into a proximal "cup" that blends gradually into the posterior atrial wall[26] (Figure 1). It is this proximal cup that we refer to as the PV antrum.[4] Furthermore, the PV

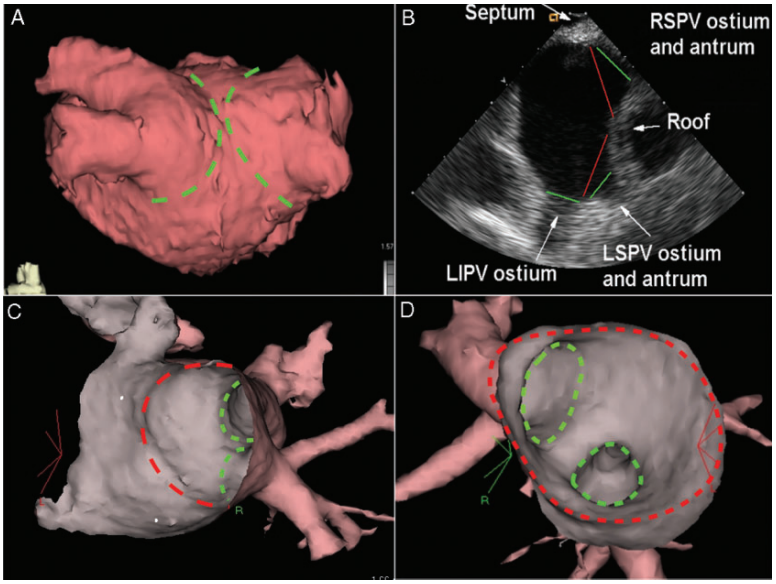

Figure 1 Pulmonary vein antra. **A** Postero-anterior view of the left atrium showing the left and right pulmonary vein (PV) antra (in blue) erupting for the posterior wall. Note that the PV antra constitute most of the posterior wall. **B** Two-dimensional intracardiac echocardiographic picture of the pulmonary vein ostia and antra. **C** Right anterior oblique view of the left atrium showing the left PV ostia (in blue) and antra (in red). **D** Left anterior oblique view of the left atrium showing the right superior PV (RSPV) and right inferior PV (in blue) and the right PV antrum (in red). Note the extensions of the right PV antrum anteriorly and superiorly. *LIPV* left inferior pulmonary vein; *LSPV* left superior pulmonary vein

antrum connects to the LA wall at an oblique angle. The posterior aspect of each PV is more "proximal," while the anterior segments of the PVs are more "distal." The diameter of the antrum is considerably larger than that of the distal tubular PV. Studies from CT have shown that the diameter of the tubular PV may range from 1 to 2 mm in most normal subjects, while the cross-sectional diameter of the PV antrum may range from 2 to 2.5 mm.[27] Several anatomical variations may also occur, with superior and inferior divisions of a PV occurring distal to a single common PV antrum that inserts into the LA, sometimes referred to as a *common os*. Obviously, with the diameter of the antra so large, the right- and left-side antra frequently converge on one another, with very little posterior LA wall separating the two sides (Figure 1A).

This last point is important because of evidence that confirms the critical role that the posterior LA plays in both the triggering and the maintenance of AF. Dominant frequencies during AF are frequently mapped to the posterior LA wall.[28,29] A frequency gradient has been demonstrated in human models of AF between the posterior LA and other parts of the atria.[30,31] The posterior LA has also been identified as a common site for non-PV AF triggers.[32] This all makes sense, however, in the context that the PV antra occupy most of the posterior LA wall. The very properties described that make the PVs so arrhythmogenic are also the properties that make the PV antra, and thus the posterior LA wall, so important in the triggering and maintenance of AF.

Newer imaging techniques have played an important role in visualizing the PV antra. In contrast to angiography, intracardiac echocardiography (ICE) is able to define the proximal edge of the PV antrum. Figure 1B shows the definition of the antrum by ICE compared to the tubular ostium demonstrated on angiography. By using ICE, we can see how proximally the PV antra extend. Three-dimensional CT and magnetic resonance imaging (MRI) of the LA have also been pivotal in showing the gradual transition of the PV–LA interface

Evolution in the Technique of Pulmonary Vein Isolation

When targeted ablation of PV triggers was first performed, extensive mapping was performed distally in the PVs to identify the exact origin of the PV trigger.[1] While the technique made intuitive sense, it required extensive and time-consuming mapping of the PV. It also required the presence of frequent ectopic beats or multiple AF initiations to map the source; unfortunately, this is not common during ablation of AF in the electrophysiology laboratory. Furthermore, identification and ablation of one focal PV source did not exclude triggers occurring from other sites within the same PV causing AF. One of the biggest drawbacks of ablation within the PV, however, was the unacceptably high incidence of symptomatic PV stenosis.[33]

The procedure therefore evolved so that instead of targeting foci distally within the vein, ablation was performed at the ostium of the tubular PV, targeting muscle sleeve connections between the PV and LA. By ablating these sleeves, electrical "disconnection" of the PV could be achieved, and triggering impulses would no longer be able to reach the LA and initiate AF. This procedure was commonly referred to as *segmental ostial ablation*.[34] Initially, only arrhythmogenic PVs (as identified during the procedure) were targeted in this fashion. However, over 85% of patients have multiple arrhythmogenic PVs,[35] and thus operators quickly moved to empiric isolation of all PVs to minimize recurrences. Segmental ostial ablation of all PVs resulted in higher success rates, but symptomatic PV stenosis remained an important and not infrequent risk. Furthermore, ablation only at the tubular ostium failed to address any of the potential triggers and rotor sites in the more proximal antral region of the PV.

To include the more proximal regions of the PV antrum and to move even further away from the PVs to avoid inducing stenosis, newer techniques of PV isolation started creating large, circumferential lesions well outside the veins, often along the posterior wall of the LA. Whether this lesion set was created by electroanatomical mapping or ICE guidance, the procedure had the advantage of incorporating and isolating the entire PV antrum. Instead of targeting specific muscular connections between the PVs and the LA, the entire PV antrum was ablated along its border, increasing the amount of radio-frequency (RF) delivery required. However, by ablating well outside the PVs, operators felt more comfortable using higher-power outputs (or irrigated ablation), allowing for shorter ablation times despite the increase in RF delivery. Higher outputs also meant more thorough lesions that were less likely to recover. Pulmonary vein stenosis also became an increasingly rare complication. Studies comparing the efficacy of segmental ostial ablation to a wide, circumferential antral

isolation clearly demonstrated a benefit to the latter approach, and success rates of AF ablation were consistently published in the 75% to 80% range.[34] At the present time, PVAI remains the cornerstone of the most widely adopted approach to catheter ablation of AF.

Pulmonary Vein Antrum Isolation Technique

Patient Selection

Currently, most centers are performing AF ablation only on patients with symptomatic AF who have failed at least one antiarrhythmic drug. In this group of patients, the morbidity of ongoing AF and antiarrhythmics required to treat it outweigh the risks of performing the procedure. Data from pilot studies have been published that suggest both the efficacy and the safety of performing ablation as first-line therapy for paroxysmal AF patients. Larger clinical trials are currently ongoing to answer this question more definitively. Until the results of these trials are available, AF ablation remains second-line therapy for most centers.

Most of the published data to date on outcomes of AF ablation have been in paroxysmal AF. However, the procedure may be offered to patients with paroxysmal, persistent, or permanent AF. Analysis of outcomes at the Cleveland Clinic has shown that the recurrence rate postprocedure is higher in patients with nonparoxysmal AF but is similar to those with paroxysmal AF after two procedures. A randomized, multicenter trial showed that circumferential PV ablation can be very effective in patients with permanent AF.[36] Others have also reported on the efficacy of PV-based ablation procedures in patients with nonparoxysmal AF.[37]

From the Cleveland Clinic experience of over 4,000 patients, no age, LA size, or ejection fraction (EF) cutoffs have been shown to consistently predict procedural failure. Regardless of age or EF, PVAI can be performed in most patients with reasonable success rates.[24,38]

Preablation Preparation

Patients are asked to stop their antiarrhythmic medications more than 5 days in advance of the procedure. For amiodarone, patients stop it 2 to 4 months pre-PVAI because of its tendency to reduce the presence of PV potentials (PVPs) at the time of ablation.

Prior to ablation, all patients have a Holter monitor, 12-lead electrocardiogram (ECG), and transthoracic echocardiogram performed to document AF and the presence/absence of structural heart disease. Three-dimensional, multislice CT scans of the LA may be performed to accurately depict the PV anatomy and to serve as a baseline for comparison with postprocedure scans looking for PV stenosis. The CT scans may also be imported into nonfluoroscopic mapping systems to allow for image integration (see next section).

Patients should be therapeutically anticoagulated with coumadin to maintain an international normalized ratio (INR) of 2 to 3 for at least 6 to 8 weeks prior to ablation. Coumadin is then stopped 2 days prior to the procedure. Assuming compliance with this protocol, the incidence of LA thrombus or

periprocedural embolus is very low. More recently, the Cleveland Clinic has been performing procedures on those with an INR between 2.0 and 2.5, and there have not been any significant complications with this approach. Many centers are routinely performing transesophageal echocardiography (TEE) on patients the day of the procedure to rule out LA thrombus. This may not be necessary in all patients. If patients are in sinus rhythm the day before the procedure, TEE may be forgone. If thrombus is documented on TEE, then the procedure should be cancelled, and an additional 3 to 4 weeks of anticoagulation should be given prior to attempting PVAI again. In the presence of echo contrast without thrombus, PVAI may still be performed.

Guidance by Imaging Technology

Given the complexity of the LA anatomy and the necessity of isolating the entire circumference of the PV antrum, the ablation procedure needs to be guided by imaging beyond 2-D fluoroscopy to better define the PV antral anatomy. As mentioned, PV angiography is not adequate for defining the full proximal extension of the PV antrum–LA interface. The most commonly employed modalities include ICE and 3-D nonfluoroscopic mapping systems with or without CT/MRI image integration software.

As mentioned, ICE is an excellent imaging modality for defining the full extent of the PV antra. The Cleveland Clinic technique typically uses a 10F, 64-element phased-array ultrasound catheter (Acuson Siemens AG Inc.) positioned in the middle of the right atrium (where it remains for the procedure duration). Clockwise rotation of the ICE catheter from the standard transseptal view allows imaging of the left lower, then left upper, then right upper and lower PVs in order (Figure 2). As the operator images each vein, the Lasso and ablation catheters can be positioned at the antral–LA interface for ablation, knowing that the risk of stenosis here is low. Furthermore, the operator can ensure that the full extension of the PV antrum is electrically isolated, maximizing procedural success.[39] Also, ICE has the advantage of being able to reduce the incidence of complications other than PV stenosis.[39] Double transseptal puncture can be performed under real-time imaging guidance (Figure 3A). Microbubbles seen on ICE directly correlate to cerebral microembolic events detected by transcranial Doppler, tissue disruption, and char formation (Figure 3B).[40,41] Absolute temperature and impedence readings do not correlate to microbubbles and cannot reliably predict tissue disruption and cerebroembolic events. By titrating RF energy to avoid microbubble formation, these complications may be minimized.

Systems for 3-D nonfluoroscopic mapping may also be used to define the PV antral anatomy and guide placement of ablation lesions. Creation of a point-by-point shell of the LA on a magnetically based mapping system may not provide adequate resolution to define the PV antrum. In fact, guidance of ablation by such a shell alone may cause the operator to ablate closer to the tubular PV than desired. However, integration of such a shell on an actual CT or MRI image of the LA can improve resolution and allow reasonably accurate delineation of the antral borders. Mapping systems can definitely improve lesion placement, but they do not provide some of the real-time, "dynamic" information (like microbubbles) that ICE can provide.

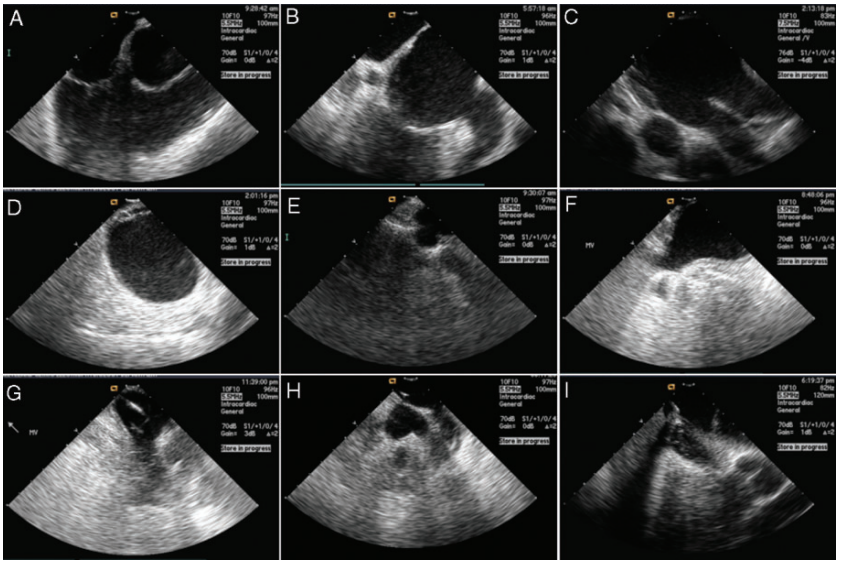

Figure 2 Standard intracardiac views: *View 1* (*home view*) This is the reference view (**A**), obtained while the catheter was in the mid-right atrial cavity facing anteriorly. The right atrium and ventricle, tricuspid valve, and aortic valves will be imaged. *View 2* Obtained by clockwise rotation of the catheter from the *home view* position (**B**). The cardiac structures visualized include the anterior portion of the interatrial septum, mitral valve, left atrium and ventricle, and left atrial appendage. Often, the fossa ovalis is seen in this view. *View 3* Obtained by clockwise rotation from *view 2* without changing the depth settings (**C**). It images the mid-interatrial septum and the left superior and inferior pulmonary veins along their longitudinal axis. We routinely use this view to perform the transseptal punctures. Moreover, the left atrial size in this view is used for selecting ablation and mapping catheter morphology (curve size). *View 4* Obtained with a clockwise rotation of the catheter from *view 3*. Often, one should decrease the depth to 8 to 10 cm to improve the spatial resolution. This is the best view to visualize the posterior wall and posterior portion of the pulmonary vein antra (**D**). *View 5* Obtained with a clockwise rotation from *view 4*. This view is used to visualize the inferior and superior pulmonary veins in cross section along with the very posterior portion of the interatrial septum (**E**). The depth is usually adjusted to around 6 to 8 cm in this view because of the proximity of the right-sided veins to the posterior right atrium. *View 6* Obtained from *view 4* position by a posterior tilt (extension) on the catheter to position it just above the tricuspid valve while keeping the clockwise tension on the catheter. This often visualizes the right inferior pulmonary vein in its longitudinal axis (**F**). Slight clockwise turn of the catheter while slightly retracting it will bring the right superior pulmonary vein in view in its longitudinal axis (**G**). Superior vena cava–right atrial (SVC–RA) junction: We advance the catheter transducer into the superior vena cava where the SVC will be visualized along its longitudinal axis. We then rotate the catheter to the anteroseptal region to bring the right pulmonary artery in cross section. We define the SVC–RA junction at the level of the bifurcation of the right pulmonary artery (**H**). Cavotricuspid isthmus: A slight anterior tilt from the *home view* will usually visualize the central isthmus (**I**). A clockwise rotation is usually needed to visualize the septal portion of the tricuspid isthmus

Mapping and Targeting Pulmonary Vein Antral Potentials

The PVAI procedure is best performed using two catheters through two separate transseptal accesses. The mapping catheter of choice is a deflectable, circular, decapolar catheter that can be inserted into the PVs and moved

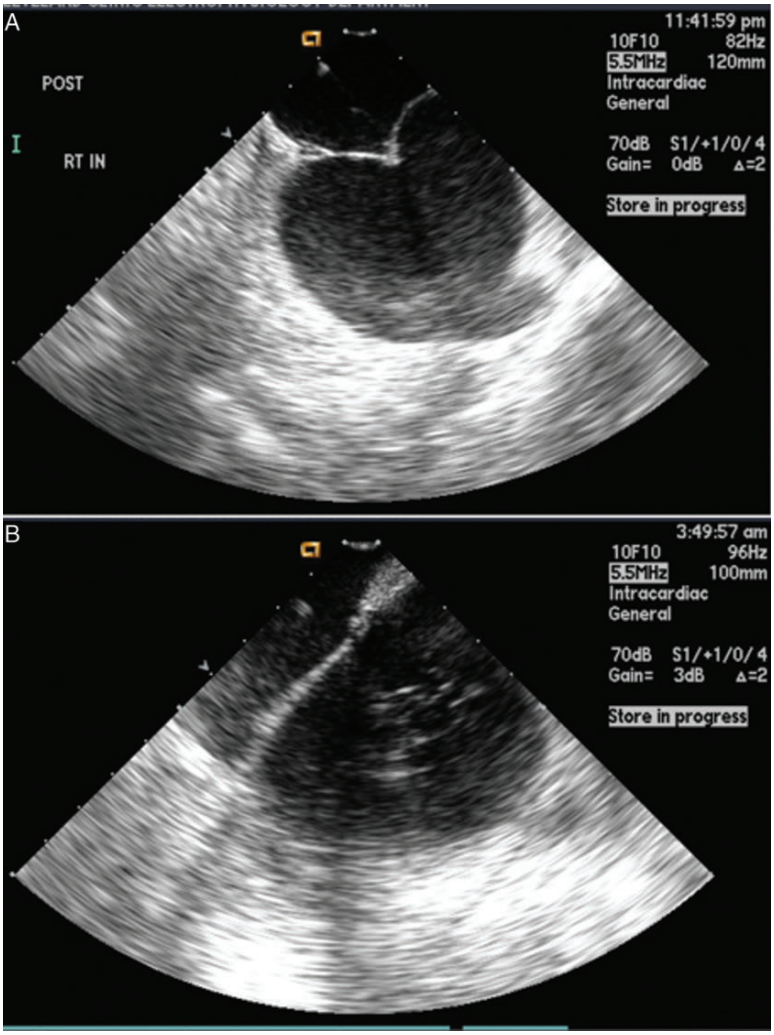

Figure 3 **A** Transseptal puncture performed under intracardiac echocardiography guidance. **B** Microbubbles seen during catheter ablation

sequentially along the border of the PV antra to identify all PVPs that need to be ablated (Figure 4). The ablation catheter may be either an 8-mm tip or and irrigated 3.5-mm tip, which allows for rapid, transmural ablation of the large regions of LA that need to be ablated.

The PVPs identify muscular sleeves that extend from the atrium into the PVs, and these are responsible for transmitting triggering impulses from the vein to the LA. These potentials/sleeves are seen extending proximally to the antral–LA junction and are not restricted to the tubular portion of the PV. The PVPs are identified during mapping of the antrum with the circular multipolar catheter. They are often fused with the atrial electrogram (EGM) but can be identified by their high-frequency appearance. Coronary sinus (CS) pacing may help separate PVPs from the atrial EGM for the left-sided veins, but this separation may be less evident in the posterior PV antrum,

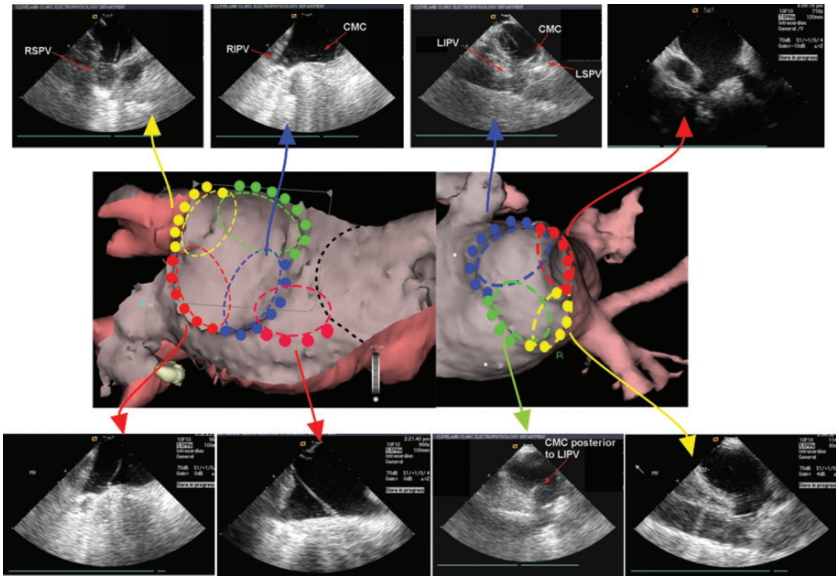

Figure 4 Cartoon illustrating the circular mapping catheter (CMC) movement during isolation of the right and left pulmonary vein antra with corresponding intracardiac image to verify the catheter position. The circular mapping catheter is represented by dashed circles, and the dots represent the radio-frequency ablation delivered at the respective circular mapping catheter position. *LIPV* left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *RIPV* right inferior pulmonary vein, *RSPV* right superior pulmonary vein

which is closer to the CS. The PVPs may also be confused with LA appendage potentials, especially around the left-side veins. However, if pacing from the appendage causes the potential to advance to the pacing stimulus, then the EGM is appendageal and not from the PV. Sinus rhythm or CS pacing is usually preferred for mapping because AF reduces PVP amplitude, making PVPs harder to identify. If mapping must be performed in AF because the patient cannot be cardioverted, attempts to cardiovert later in the procedure after some of the PV antra have been isolated are often successful and allow for more detailed PVP mapping.

Given the large diameter of the PV antrum, its entire circumference cannot be mapped using a stationary circular mapping catheter fixed in one position. Instead, the circular catheter should be sequentially positioned along each segment of the antral circumference (Figure 4) to look for PVPs—a so-called roving catheter technique. Since the catheter is not wedged into the tubular portion of the PV for stability, an operator's assistant must often hold the circular catheter in position while ablation is performed. When mapping the anterior segments of the left PVs or the septal segments of the right PVs, the circular catheter must be advanced slightly because of the oblique nature of the antral–LA interface.

The goal of ablation is to eliminate all PVPs within and around the PV antra by ablation. As the circular catheter is moved from one segment of the LA–antral interface to the next, ablation is performed at the poles that demonstrate PVPs. The ablation catheter is moved to the target pole on the circular

catheter, taking care to keep it in the same plane. Ablation is only performed along the specific antral segment that the circular catheter is mapping. Seeing ablation artifact on the recording from a specific circular catheter pole confirms which pole your catheter is on and that you are in the right plane. Ablation is continued in one spot until no more PVPs can be seen. The catheter is then moved to the next adjacent position on the circular catheter until the entire segment has been ablated. After ablating all segments of a PV antrum, the circular catheter is used to again map the vein's interface with the LA to confirm the absence of any PVP. During sinus or CS pacing, the circular catheter is also advanced deep into each PV tube to confirm an absence of EGM recordings or entrance block. One may also pace within the vein to confirm that there is also exit block; however, if the PV antrum is totally quiet and there is complete entrance block, then exit block almost universally exists.

Some operators have suggested maintaining the circular catheter within the tubular PV while ablation lesions are placed along the antral circumference until no further PVPs are seen on the circular catheter. This may be used as an alternative technique but would still require the circular catheter to be moved and placed in different regions around the antrum postablation to confirm the absence of PVPs in all areas of the PV antra (not just the tubular portion). Any PVPs still present would then require further ablation.

The endpoint of the procedure should be isolation of all PV antra (four or more) in every patient. When PV isolation was initially performed, operators went to great lengths to identify specific "arrhythmogenic" PVs, which were preferentially isolated. However, over 85% of patients have multiple arrhythmogenic veins, and while one PV may appear arrhythmogenic on a given day, another may be the culprit in the future.[35] Complex muscular connections may exist between the PVs that allow for inter-PV conduction and may explain why more than one PV may be responsible for triggering AF.[42,43] Therefore, pharmacological challenges with high-dose isoproterenol or adenosine are not routinely required to demonstrate culprit ectopic activity. These challenges may be used for redo procedures, however, to confirm total PVAI and to look for potential sites of non-PV ectopy. To ensure complete elimination of all triggering ectopy for redo procedures, doses of up to 20 μg/min isoproterenol may be used.

During isolation of the PV antrum, dissociate firing may be seen inside the PV (Figure 5). The presence of dissociate firing is an indication of exit block from that part of the PV antrum. However, breakthrough from other parts of the antrum may be observed simultaneous to the appearance of dissociate firing. Thus, the presence of dissociate firing alone is not enough to confirm total antral isolation, and a full mapping of the entire antral region is still required to search for breakthrough points.

Procedural Anticoagulation and Radio-Frequency Delivery

As soon as double transseptal access is obtained, systemic anticoagulation should be started to maintain an activated clotting time (ACT) of 350 to 400 s. Studies have shown that the risk of cerebroembolic complications is lower when higher ACT targets are used, particularly given the often-extensive amount of ablation that needs to be performed during PVAI.[44] Given the safety of performing transseptal puncture under ICE guidance, anticoagulation should

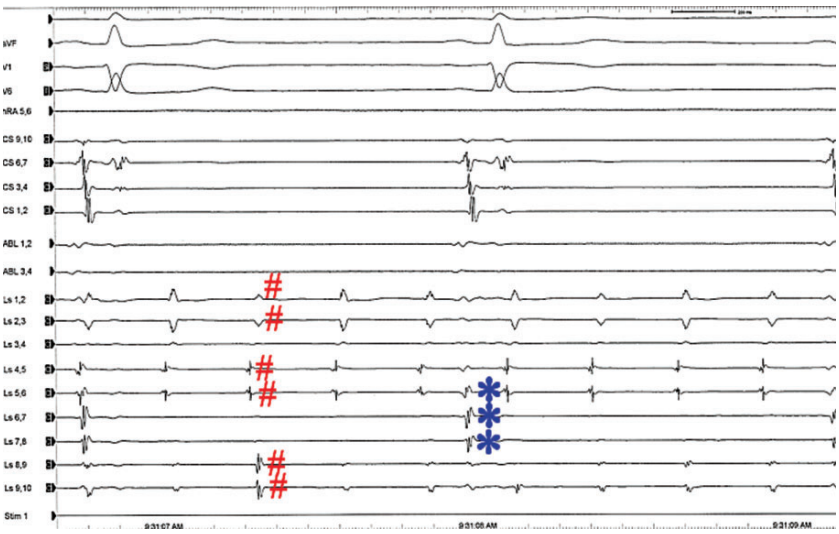

Figure 5 Intracardiac electrographic recordings after pulmonary vein antrum isolation. The circular mapping catheter (Lasso) is in the left superior pulmonary vein. There are automatic pulmonary vein discharges (dissociated potentials) with block into the left atrium; the left atrium is in sinus rhythm, as evident from the coronary sinus (CS) recordings. Note the far-field electrograms on the anterior electrodes of the circular mapping catheter corresponding (Ls 5 to 7) to left atrial appendage depolarization (sinus rhythm)

ideally be started even before puncture to avoid clot on the needle/introducer. Before the first transseptal puncture, a 140-IU/kg heparin bolus is given, and a heparin infusion of 15 IU/kg/h is started. An additional 70-IU/kg bolus is given before the second transseptal. The ACT is then checked every 20 min, and the heparin infusion is titrated with boluses to maintain the target ACT.

To ablate, RF energy is initially delivered at 30 W (8-mm tip) or 20 W (irrigated tip) with a temperature of 55 °C. If using ICE monitoring for microbubbles, power may be increased by 5 W every 5 s as long as no microbubbles (8-mm tip) are seen or no increase in microbubble density (irrigated tip) is observed. If bubbles occur, the power should be titrated down by 5 W every 5 s until no bubbles are seen. If a brisk shower of bubbles is detected, RF power should be terminated immediately. If ICE monitoring is not used, power may be gradually titrated up as above until the local EGM is eliminated. Each lesion typically lasts 30 to 50 s to achieve local EGM elimination. Occurrence of intense pain, cough, profound vagal response (asystole), sudden impedence rise above 10 ohms, or occurrence of any complication all necessitate abrupt termination of RF delivery.

To avoid the rare complication of esophageal injury, some operators have proposed limiting the power output when ablating in the vicinity of the esophagus, particularly on the posterior wall.[45] No specific guidelines exist regarding how much power output should be limited to avoid injury. However, some have proposed limiting output to less than 50 W (8-mm tip) or less than 35 to 40 W (irrigated tip) when ablating in the periesophageal region. In general, power greater than 70 W (8-mm tip) or greater than 50 W (irrigated tip) should be avoided when ablating anywhere in the LA during AF ablation.

Postablation Care and Follow-up

At the end of the procedure, the heparin is stopped, and a maximum of 15 mg protamine is administrated to achieve partial reversal of the anticoagulation before removal of the sheaths. Venous sheaths can be safely removed at an ACT below 300 s.

Patients resume coumadin the same night post-PVAI. They are given twice their usual dose for the first 3 days and continued on coumadin for at least 4 months. For persistent or permanent AF patients, they are also given 0.5 mg/kg enoxaparin twice daily for the first 3 days, which is started about 3 to 4 h post-PVAI. This half dose of enoxaparin is used because the full dose (1.0 mg/kg twice daily) results in an increased risk of bleeding.

In many centers, patients with persistent or permanent AF are placed on antiarrhythmic medication for the first 2 months after PVAI. This is because early recurrences are common, but they do not necessarily predict failure of the procedure. Most centers have reported that only recurrences beyond 2 months postprocedure represent true failure. Typically, one of a class Ic agent, sotalol, or dofetilide is chosen for the first 2 months, and amiodarone is avoided completely. If the patient has contraindications to all of these, then a β-blocker is used.

The patient has a 24-h Holter and outpatient assessment performed day 1 and 3, 6, and 12 months post-PVAI. The patient may also wear a rhythm transmitter (if available) for the first 3 months to instantly transmit the patient's rhythm if the patient feels any symptoms. Recurrence is documented either by symptoms or from ECG/Holter/transmitter data.

A contrast-enhanced, multislice CT scan of the LA should be performed at 3 months to assess for PV stenosis. Scans may be performed serially at 3-month intervals thereafter if any degree of narrowing is detected.

Coumadin is continued for a minimum of 4 to 6 months post-PVAI. Coumadin should not be stopped until at least 6 months of sinus rhythm have been confirmed post-PVAI, although practices do vary. In high-risk patients with previous stroke or other indications for anticoagulation, coumadin may be continued indefinitely.

Efficacy of Pulmonary Vein Antrum Isolation

With time, operator experience, and greater consistency in the technique, PVAI has proven itself to be a very effective treatment for AF, with similar success rates reported by several different groups. From the Cleveland Clinic experience in over 4,000 patients, the off-drug success rate after one procedure is about 80%. If recurrence or either AF or atrial flutter is documented beyond 2 months after the initial procedure, a second PVAI is performed, and the off-drug success after the second procedure climbs to over 90%. Success at the Cleveland Clinic and many centers is defined as the absence of both AF and all atrial flutters (after the first 2 months post-PVAI) off antiarrhythmic medication; however, differences in defining success remain. Recent publications from several groups employing ablation of all four PVs outside the tubular portion show consistency in the outcome, with an off-drug cure rate of 80.5% overall (Table 1).[34,39,40,46–49,61] A further 10% to 20% of patients may become responsive to previously ineffective antiarrhythmic medications (AAM).[50]

Table 1 Freedom from atrial fibrillation following pulmonary vein catheter ablation.

Author	Year	Ostial (%)	Segmental/ circumferential (%)	Antral (%)
Oral et al.[34]	2003	67	88	
Marrouche et al.[39]	2003	80.4		90.2
Pappone et al.[46]	2003		84	
Ouyang et al.[47]	2004	75.6		
Hassaigairre et al.[48]	2004	74	83	
Mansour et al.[49]	2004	60	75	
Wazni et al.[40]	2005			87
Pappone et al.[61]	2006		93	

The highest success rates are seen in younger patients with paroxysmal AF and no structural heart disease. Lower, but still acceptable, success rates in the 70% to 75% range can be seen in patients with impaired EF, valvular heart disease, and even hypertrophic cardiomyopathy. Patients with persistent and permanent AF may have initially lower success rates after one procedure but tend to have comparable results after two procedures compared to those with paroxysmal AF.

Advanced age, large LA size, and nonparoxysmal AF have all been reported as predictors for procedural failure.[51] However, multivariate analysis has not shown these to be consistent predictors in and of themselves. The presence of LA scar at the time of PVAI, as determined by a paucity or complete absence of LA voltage during mapping, is the single most negative prognostic factor, with a success rate of about 50% even after two procedures.[51] Left atrial scar is often associated with more chronic AF, larger LA size, and advanced age.

Complications of Pulmonary Vein Antrum Isolation

Complications from PVAI include vascular complications secondary to venous access, cardiac perforation/tamponade, valvular injury, embolic stroke or systemic embolism, esophageal injury, PV stenosis, and proarrhythmia caused by reentrant tachycardias arising from incomplete ablative lesions. Finta and Haines pooled data from 63 clinical studies between 1994 and 2003 on AF ablation encompassing 3,339 patients.[52] Cerebrovascular events occurred in 1.0% of patients, manifest PV stenosis in 0.9%, and atrial macro reentry tachycardia in 29%. When only the more recent reports using a more consistent technique were reviewed, the complication rates are similar, if not lower.

The complication rates continue to fall with more recent modifications to the technique and presently available technologies. For example, aiming for higher ACT levels of 300 to 400 s can reduce the chance of thromboembolism without increasing bleeding risk,[53] and ablation outside the tubular portion of the veins greatly minimizes the risk of PV stenosis. Char formation, tissue disruption, and esophageal injury can also be avoided with strict limitations on RF energy output[45] and avoidance of ablating directly on top of the esophagus.

Intracardiac echocardiography has been demonstrated to be a particularly effective (and readily available) tool to minimize procedural complications. By providing real-time imaging, ICE allows one to perform safe transseptal access and avoid ablating within the PVs to prevent stenosis.[39] Furthermore, by titrating RF energy output to prevent microbubble formation on ICE, tissue disruption and coagulum formation causing stenosis and embolic events can be minimized.[39]

Procedural-related atrial flutters can also be avoided if care is taken to document total electrical isolation of the PVs at the level of the antra, thereby eliminating the triggers for flutter. Using an ICE-guided PVAI technique, the rate of flutter recurrence postablation is very low, less than 3%.[54] In patients with both typical atrial flutter and AF, both arrhythmias can be treated with PVAI alone by eliminating the common trigger[55] in most cases. Other groups have successfully used additional linear ablation lesions to avoid postablation flutters, such as a line across the mitral valve isthmus.[48]

Newer technologies to reduce complications and improve the ease of performing ablation are also imminent, including real-time 3-D CT and electroanatomical mapping integration, robotic/magnetic-controlled catheter systems, and balloon-guided systems.

Relationship of Recurrence to Pulmonary Vein–Left Atrium Reconnection

The importance of isolating the PV antra is reinforced by recently published data demonstrating the direct relationship between AF recurrence postablation and PV–LA reconnection. Several small studies have demonstrated recurrent PV–LA conduction in patients who demonstrate AF recurrence.[56–58] However, these studies did not definitively prove that the reconnection was responsible for the clinical recurrence. Verma et al. reported a more direct relationship between recurrence and PV–LA reconnection.[59] Three subsets of patients were studied with a repeat procedure: patients without recurrence (group I), patients with recurrence but maintaining sinus rhythm on antiarrhythmics (group II), and patients with recurrence despite drugs (group III). While recurrent PV–LA conduction was seen in at least one PV in groups II and III, almost all of the patients in group I did not have any reconnection. In the few isolated group I patients who had reconnection, the conduction delay was so long between the PV and LA that slightly faster pacing resulted in blocked PV–LA conduction. Group II patients also had long PV–LA conduction delays compared to group III patients, who had almost no delay. Ouyang et al. also showed a direct relationship between PV–LA reconnection and AF recurrence.[60] In the few patients with recurrence patients without reconnection, non-PV triggering foci were identified. Such evidence supports the importance of isolating the PV triggers for successful outcome and reinforces why PVAI remains a cornerstone of AF ablation today.

Conclusions

The PV antra are important structures for both the triggering and maintenance of AF. Thus, the foundation of most AF ablation performed today remains

electrical isolation of these structures from the rest of the LA. To completely isolate the antra from the LA, a thorough understanding of the antrum anatomy is requisite. With this knowledge and the appropriate use of technology, PVAI can be performed effectively and safely with reliable outcomes.

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Complications and Definition of Success

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Abstract: Major complications related to atrial fibrillation (AF) ablation have been reported in 3% to 6% of procedures. These include pulmonary vein stenosis, thromboembolic events, phrenic and recurrent laryngeal nerve injury, cardiac perforation and tamponade, and atrio–esophageal fistula. A better understanding of the pathophysiology of these events has decreased the current incidence to 1% to 2%. Formal evaluation of procedural efficacy includes assessment of AF-free survival, although the format and extent of postprocedural rhythm evaluation and the significance of asymptomatic AF remain controversial. Consensus guidelines for defining successful AF ablation are under development.

Keywords: Atrio–esophageal fistula; Cardiac perforation; Phrenic and recurrent laryngeal nerve injury; Pulmonary vein stenosis; Tamponade; Thromboembolic events.

Over the past decade, techniques for ablation of atrial fibrillation (AF) have evolved and multiplied, resulting in improved efficacy and more widespread application.[1–9] The growth in AF ablation mandates a careful understanding of procedural risks and complications as well as explicit and objective outcome criteria. These efforts will facilitate comparisons between various methods and optimize selection of safe and effective ablation techniques. This chapter provides a brief review of the complications of AF ablation and the methodologies employed to assess long-term outcome.

Complications

Cappato and colleagues surveyed complications of AF ablation performed between 1995 and 2002 in 8,745 patients (30% with multiple procedures) from 181 centers worldwide.[10] The most serious complications included death (0.05%), cardiac tamponade (1.22%), permanent diaphragmatic paralysis (0.11%), pulmonary vein (PV) stenosis greater than 50% (1.63%, symptomatic

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in 40%), stroke or transient ischemic attack (0.94%), and pseudoaneurysm or atrioventricular (AV) fistula (0.95%).

Pulmonary Vein Stenosis

Histologically, PV stenosis is characterized by intimal thickening, thrombus formation, endocardial contraction, and elastic laminae proliferation.[10] Dense fibrosis and scar contraction are pathological endpoints in the development of clinically manifest PV stenosis.[11] During the initial experience with AF ablation, the reported prevalence of PV stenosis following a linear ablation procedure ranged from 2% to 7%,[7,12,13] while the prevalence in patients undergoing focal or segmental ostial ablation was approximately 5%.[3,4,14–19] These reports differ in the methodology and definitions employed to identify PV stenosis. With the use of anatomic imaging techniques such as magnetic resonance imaging (MRI) or computed tomography (CT), PV stenosis can be characterized as severe (>70%), moderate (50% to 70%), or mild (<50%). In one large study, 608 patients underwent PV isolation; 3.4% had severe PV stenosis, 4.4% had moderate stenosis, and 7.7% had mild stenosis.[19,20] When transesophageal echocardiography is used to diagnose PV stenosis based primarily on elevated flow velocities, rates of PV stenosis as high as 33% to 42% have been observed.[4,17] However, this technique significantly overestimates stenosis severity compared to anatomically based techniques.

Operator experience may significantly reduce the incidence of PV stenosis. Haissaguerre and coworkers reported a decrease in the rate of PV stenosis from 5% to less than 1% with additional operator experience.[3] Similar outcomes have been reported by other investigators.[19,21] Careful power titration with reduced maximal temperature and power when energy is delivered in the vicinity of the pulmonary ostia are also important in reducing the incidence of PV stenosis. Power reduction may be particularly important with the use of irrigated-tip catheters, for which electrode temperature is an unreliable guide to tissue heating. Additional measures, such as monitoring the appearance of microbubbles with intracardiac echo, may also be useful.[19] Not all investigators have found a close correlation of applied power and the subsequent development of stenosis.[22]

In addition to intracardiac echo, three-dimensional (3-D) imaging techniques and image integration with CT and MRI that help delineate the location of the PV ostia throughout the procedure may have a favorable impact on the risk of PV stenosis. The risk of PV stenosis is particularly high when energy is delivered at the orifice or within the tubular portion of the PV,[19] either as a deliberate strategy or as a result of inadequate definition of the ostia during the procedure. Ablation strategies that avoid the vicinity of the ostia (so-called wide-area and antral ablation) have contributed to the declining risk of PV stenosis.

Clinically, PV stenosis evinces protean, nonspecific manifestations that often elude rapid diagnosis; in one series, the median duration from symptom onset to diagnosis was 16 weeks.[23] Pulmonary vein stenosis can cause symptoms of dyspnea with exertion (83%) or dyspnea at rest (30%); it may be accompanied by cough (39%), hemoptysis (13%), flulike symptoms (13%), and chest pain (26%).[20,21] The mean onset of symptoms is 2 to 5 months postprocedure.[20,21,23] Symptoms occur most commonly when the stenosis is severe

and when multiple veins are involved. However, even totally occluded vessels can occur without symptoms. Because of nonspecific or absent symptoms, routine surveillance of AF patients with anatomic imaging techniques is advocated.[24,25] Perfusion MRI demonstrates decreased pulmonary perfusion in the presence of PV stenosis, and perfusion decreases substantially in PVs less than 7 mm in diameter.[25] Radionuclide lung perfusion imaging is usually abnormal in patients with severe stenosis and typically normal in patients with less-severe stenosis.[21]

Percutaneous angioplasty and stenting for PV stenosis are highly effective acutely and lead to significant and rapid symptom improvement for those patients with significant symptoms attributed to a stenotic PV.[20,21,23] However, late restenosis or occlusion remain problematic. Whether all patients with severe stenosis in the absence of symptoms should undergo treatment remains unclear. Arentz et al. reported long-term outcome in 11 patients with severe PV stenosis 1 month post-ablation for AF.[26] An MRI repeated 2 years after diagnosis demonstrated no change in stenosis severity. Right heart catheterization at rest and during exercise was also performed. No patient had resting pulmonary hypertension, although 7 demonstrated pulmonary hypertension with maximum exercise. These patients were more likely to have stenosis of multiple veins, preexisting left ventricular dysfunction, or clinical symptoms. In patients with mild-to-moderate stenosis on CT scans at 3 months, subsequent progression to severe stenosis is rare; late regression of stenosis may be observed in up to 30% of patients.[19]

Atrioesophageal Fistula

Atrioesophageal fistulae (AEF) are rare but devastating complications associated with intraoperative or percutaneous ablation performed in the posterior left atrium (LA), with an incidence as high as 1% during surgical procedures[27-29] and approximately 0.1% following percutaneous AF ablation.[30–33] Mortality exceeds 50% related to widespread esophagoatrial air and septic embolization.

The anatomy of the posterior wall of the LA renders the esophagus particularly vulnerable to thermal-induced injury. In a study of 50 patients with CT-based imaging of the chest with 3-D reconstruction, Lemola and coworkers demonstrated that the mean length and width of the esophagus in contact with the posterior LA were 58 ± 14 and 13 ± 16 mm, respectively.[34] The mean thicknesses of the posterior LA and anterior esophageal walls were 2.2 ± 0.9 and 3.6 ± 1.7 mm, respectively, with 98% of the patients demonstrating a discontinuous layer of fat between the esophagus and posterior LA. Of note, these thickness values are less than those obtained from postmortem evaluation of formalin-preserved posterior LA wall thickness (mean 4.1 ± 0.7 mm).[35] Another postmortem study found that the esophageal wall was less than 5 mm from the LA endocardium.[36] The position of the esophagus is variable and may underlie both the right and left PV ostia or any position in between.

Risk factors for the development of AEF are poorly defined. While radio-frequency (RF) energy applications were greater than 40 W in the large majority of cases, applied power does not clearly differ between cases with and without fistula formation.[28] The common finding of a latency period of 3 to 7 days (generally within 2 weeks) that exists between ablation and symptom

onset suggests that vascular injury or ischemic necrosis rather than direct thermal injury may be responsible for AEF formation.[34,40] Other potential risk factors include a thin posterior LA wall in slim patients, a paucity of soft tissue between the esophagus and LA,[27] a heterogeneous distribution of the fat pad between the esophagus and posterior LA wall,[34] and mechanical trauma induced by transesophageal echocardiographic probes.[29]

The clinical presentation of an AEF is variable and is based on multiple case reports and small studies.[28–33,41] The most common symptoms are fever, marked leukocytosis, chest or epigastric pain, difficult or painful swallowing, and neurologic symptoms. Diagnosis requires a high degree of clinical suspicion. The initial diagnostic procedure should be MRI or CT with water-soluble contrast. Esophageal instrumentation or insufflation should be avoided as these procedures may lead to catastrophic deterioration.[27,29]

Various approaches can be employed to minimize the potential risk of esophageal injury, although none have been well validated. One tactic involves imaging of the esophagus and avoidance of energy delivery to adjacent areas. Fixed images, as obtained from electroanatomic tagging or digital fusion imaging, have been used to establish the location of the esophagus as it courses posterior to the LA.[32,42,43] However, the esophagus can move during an ablation procedure, migrating from one set of PVs to the other. Rendering the esophagus relatively immobile via general anesthesia could counter this problem by limiting peristalsis and inhibiting the swallow reflex.[44] Real-time imaging using MRI or fluoroscopic monitoring of an esophageal probe or retained barium contrast may provide more certainty regarding esophageal position throughout the procedure.[45–48] Esophageal location can also be identified by intracardiac echo, which may provide a more practical guide for proximity to potential ablation sites.

Monitoring of intraluminal esophageal temperature has been proposed as a method to abort energy delivery as esophageal temperatures begin to rise.[49] However, data regarding "safe" temperature thresholds are limited. Reduction in maximum power and duration of applied energy in regions where the esophagus cannot be avoided is sensible, but clear guidelines are lacking.[30,44] Avoidance of routine linear lesions in the posterior LA or displacement of the lines to the LA roof not directly apposed to the esophagus can be an additional preventive strategy.[29,30,34,50]

Expeditious surgical evaluation and esophageal reconstructive surgery are critical because of the high attendant mortality. Bunch et al. reported a case in which temporary esophageal stenting was performed after an ablation-induced AEF with complete defect resolution after 3 weeks of antibiotics and nasogastric tube feedings, ultimately permitting stent removed. The 18-month follow-up was reported to be uneventful.[41]

Thromboembolic Events

Thromboembolic stroke has been reported in 1% to 2% of patients undergoing AF ablation, although rates as high as 5% have been reported in some series.[51,52,55,57] The large majority of these events occur within the first 2 weeks, often within the first 24 h. Radio-frequency energy application may precipitate clot development at the site of endocardial ablation as the heat generated from energy application to the endocardial surface can denature

fibrinogen to fibrin.[58,59] Alternatively, thrombogenic sheaths and catheters in the left-side circulation, as well as transeptal puncture, a procedure that denudes the septal endothelium, may precipitate thrombus formation.[59–62] The duration of intracardiac catheter presence as opposed to energy delivery has been directly correlated with activation of hemostasis and fibrinolysis.[52,61] Clinical risk factors associated with an increased risk of clot formation include patient age, longer procedure duration, presence of spontaneous echo contrast, greater number of catheters, and greater number of energy applications.[52,59]

Only a small percentage of intracardiac emboli produce explicitly manifest neurological deficits. This observation was initially made in patients following coronary artery bypass graft surgery and, more recently, in patients following AF ablation. Lickfett and coworkers tested 20 post-PV isolation patients with diffusion-weighted magnetic resonance imaging (DW-MRI) as a means to detect acute ischemic cerebral lesions.[63,64] Ten patients underwent pre- and postablation imaging, and ten patients underwent postablation imaging only. The authors observed three embolic events in 2 of the 20 patients. No patient had clinically evident neurological symptoms. This 10% incidence of DW-MRI embolic events is consistent with other investigations into the prevalence of intracardiac thrombi during AF ablation.[52] The primary implication of clinically silent embolic events may be their propensity to give rise to more subtle cognitive deficits, including memory impairment and early dementia.[65]

Thromboembolic events can be prevented by multiple strategies. Irrigated catheters reduce the incidence of char formation at the electrode tissue interface and are associated with a reduced risk of stroke.[54,58] Cryoablation and ultrasound have the potential to improve safety by limiting disruption of the endothelial surface.[66,67] Downward power titration and impedance monitoring respectively avoid and warn of excessive tissue heating. Intracardiac ultrasound can be used not only to monitor energy delivery but also to detect early thrombus formation on intracardiac structures and nonablation catheters, thus allowing clot retrieval and vascular protection.[52,68,69] Early heparin administration either prior to or immediately following transseptal puncture and maintenance of high activated clotting times (300 to 400 s) throughout the procedure are also essential. Finally, heparin alternatives such as fibrinogenolytic agents or combination protocols of antiplatelet, antithrombin, and antifibrinogen therapies have also been proposed.[70]

Phrenic and Recurrent Laryngeal Nerve Injury

Phrenic nerve injury is a well-described complication of catheter ablation procedures, including ablation of accessory pathways[71] and right atrial free wall tachycardia.[72] With the increasingly widespread use of ablation for AF, the issue of phrenic nerve damage has again arisen,[73,74] as has the complication of recurrent laryngeal nerve palsy.[75] Right phrenic nerve damage has been noted most commonly during ablation in and near the right superior PV.[73,74] The right phrenic nerve follows a path that approximates the superior vena cava, right atrium, and often the right superior PV.[76] Left phrenic nerve injury, although less common, may occur with ablation near the LA appendage.[74] The recurrent laryngeal nerve courses below the aorta, near the ligamentum arteriosum, and then ascends in the groove between the trachea and esophagus,

near the roof of the LA.[77] Trauma to this nerve, while rare, may occur during the creation of a posterior LA roof line.

Sacher and colleagues reported the clinical features and outcome of 18 patients with phrenic nerve injury (16 right, 2 left) following AF ablation at five high-volume centers.[74] The overall incidence of phrenic nerve injury was approximately 0.5%. The diagnosis was made at the time of the procedure in 50%, and in the remaining patients was detected only during follow-up, with the predominant symptom of dyspnea. Of importance, complete (66%) or partial (17%) recovery was noted in the majority of patients, often within days but occasionally requiring 1 year or more. Palsy of the recurrent laryngeal nerve typically leads to hoarseness, a breathy sounding voice, and dysphagia. Left-side vocal cord paralysis and paramedian position may also be observed.[75]

Damage posed to these nerves by application of RF energy is caused by several, perhaps synergistic, mechanisms. Direct thermal injury can result from heat transfer from the ablation catheter contact site to the nerve.[78] The resulting edema and inflammation may also be of significant consequence.[75] Supporting the hypothesis of an inflammatory and edema-related etiology of nerve damage are clinical observations[73–75] of late symptom onset (greater than 24 h after time of ablation). The effect of the high intensity electromagnetic field transiently generated at the catheter tip[79–80,] and the production of a resonance current around the heart[81] during radiofrequency energy application may also contribute to nerve damage. Nerve function recovers once the resonance current is no longer present.[73] Higher-power, repeated applications may be more likely to produce phrenic nerve injury as evidence from experimental canine models indicated that heat dissipation, particularly near the right phrenic nerve, is delayed beyond that of nearby atrial tissue.[82] Nerve tissue appears to be more vulnerable to thermal injury, which can occur at relatively low tissue temperatures (47 °C ± 3 °C). Alternative energy sources do not appear to ameliorate the risk of phrenic nerve injury. Ultrasound, laser, and cryoenergy have all been associated with phrenic nerve damage despite less thermal and electrical energy.[83–86] Balloon-mounted energy sources for PV isolation pose a particular risk since it is often difficult to avoid proximity to the right phrenic nerve even when careful attempts are made to ensure a proximal balloon position.[85,86]

Techniques to prevent phrenic nerve injury are largely empiric. Use of the lowest effective power is particularly important near the right superior PV. In experimental models, there is evidence that nerve injury is reversible in its early stages,[82] so that fluoroscopic monitoring of diaphragmatic motion during energy delivery in high-risk areas is prudent. Hiccoughs or coughing may also be an early sign of impending nerve injury. It has also been suggested that high output pacing that results in diaphragmatic capture identifies sites adjacent to the phrenic nerve where subsequent energy delivery poses a risk of nerve injury. The sensitivity of this technique is unclear as one preliminary study demonstrated that pacing from outside the right superior PV orifice resulted in phrenic nerve capture in only 20% of patients.[87]

Cardiac Perforation and Tamponade

Cardiac perforation is a recognized complication of atrial ablation, although it occurs uncommonly.[88–91] Reported rates of perforation specifically during AF

ablation range from 0.5% to 4%[7,8,19,92–95] but are typically 1% to 2%. There is evidence that linear lesions, particularly the mitral isthmus line, and irrigated RF ablation with high power (>40 W) increase the risk of perforation.[93] There are few patient characteristics that reliably predict risk of perforation during AF ablation; in particular, older age has a minor, if any, contribution to risk.[94]

Bunch and coworkers reported an incidence of perforation requiring pericardiocentesis in 2.4% (15 patients) of 632 AF ablation procedures; 60% of perforations occurred in the LA, 33% in the right ventricle, and 7% in the right atrium.[92] These investigators suggested that continuous intracardiac echo monitoring was more helpful in detecting enlarging pericardial effusions heralding tamponade than either arterial blood pressure or surveillance of the left heart border. Two patients required open surgical repair. Both perforations appeared to be in the LA dome, a region where the pericardium is loosely adherent. Because of the lack of apposition of the pericardium to the LA dome, negative pressure created by suction through an intrapericardial pigtail catheter was less likely to create a pericardial seal over the perforation, leading to reaccumulation of blood in the pericardial space. Late morbidity caused by inadequately drained hemopericardium was limited to pericarditis, which resolved over a period of days to weeks.

Intracardiac echo may also be useful at the time of transseptal puncture, a maneuver that bears particular risk related to inadvertent puncture of the right atrial or LA free wall with pericardial entry, penetration into the ascending aorta, and damage to the left circumflex artery.[95]

Definitions of Success for Atrial Fibrillation Ablation

Restoration and long-term maintenance of sinus rhythm is the principal therapeutic goal of AF ablation. Potential benefits of sinus rhythm maintenance include symptom reduction and improved quality of life, enhanced cardiac performance and the prevention of heart failure, reduction in thromboembolic risk and the need for long-term anticoagulation, decreased hospitalizations and health care utilization, and improved survival. The large majority of studies to date have employed an intermediate endpoint of procedural success—AF free survival. However, experience over the past 5 years has made clear that this seemingly simple endpoint is both elusive to define and difficult to quantify in practical day-to-day clinical care. Yet, objective and consensus definitions of success are sorely needed if practitioners are to choose, among an increasing array of techniques and strategies, those that offer the best long-term outcomes with the least risk.

Detection of Recurrent Atrial Fibrillation

Although most candidates for AF ablation are identified because they have highly symptomatic AF (palpitations, dyspnea, dizziness, or syncope), even in this population, more than 50% of patients may also have asymptomatic episodes during prolonged ambulatory monitoring prior to the procedure.[96] This finding is consistent with those in other "symptomatic" AF populations.[97–100] Following ablation, asymptomatic AF remains common and may even increase.

Hindricks and colleagues prospectively examined 114 patients following PV isolation and additional linear lesions with serial 7-day Holter recordings and found that the incidence of exclusively asymptomatic AF increased significantly from 5% preablation to 36% to 38% at 3, 6, and 12 months postablation.[96] Reliance on symptoms alone would have substantially overestimated procedural success.

Senatore and coworkers demonstrated similar findings in 72 patients undergoing AF ablation.[101] By comparing daily transtelephonic electrocardiographic (ECG) monitoring for 90 days to both serial Holter and ECG monitoring postablation, the authors found that AF-free survival at 3 months was 72% with intensive monitoring and 86% with standard monitoring. Of the 20 patients with recurrent AF, 8 had exclusively asymptomatic episodes.

Following AF ablation, Vasamreddy et al. investigated 19 patients with a mobile cardiac telemetry device that performed continuous monitoring for 5 days of each month for 6 consecutive months.[102] At 6 months, AF-free survival was 70% in patients using symptomatic AF as the endpoint but only 50% when asymptomatic recurrences were included. Symptoms were not specific for AF; only 40% of patient-triggered symptomatic events were confirmed to be AF. This study also demonstrated the practical difficulties of implementing intensive long-term monitoring. Nearly half the patients failed to complete the entire 6-month protocol.

Drug therapy for AF may contribute to this high incidence of asymptomatic AF by shortening episode duration of the recurrent episode to a threshold below symptom detection or by slowing the ventricular response during the episode.[98,101,103] However, in these studies, antiarrhythmic drug use either was held constant or declined over time. Other factors, including changes in autonomic innervation or a placebo effect may play a contributing role. Not surprisingly, quality-of-life studies following AF ablation showed consistent improvements that correlate poorly with objective indices of arrhythmia recurrence.[104,105] The incidence of asymptomatic AF postablation remains controversial, and other investigators have reported a significantly lower incidence (<5%).[106,107] However, these studies employed less-intensive monitoring regimens. While it is clear that symptoms alone with sporadic ECG monitoring are insufficient to document AF recurrences following ablation, a practical surveillance regimen acceptable both to patients and to health care professionals, who must bear the data-processing burden, remains to be defined.

Temporal Patterns of Atrial Fibrillation Recurrence and Delayed Responders

Assessment of procedural success is also complicated by several temporal patterns of recurrence that confound selection of the optimal time point for evaluation of success. One phenomenon is the early recurrence of AF (ERAF) in the initial 2 to 4 weeks following the procedure. This time period is based on the resolution of acute inflammatory changes because of RF energy application and the formation of well-delineated scar.[108–110] During this time, pericardial inflammation (which may potentiate the arrhythmogenicity of the PVs),[111,112] delayed therapeutic effects with lesion consolidation, and the transient stimulatory effects of energy applications run their respective full pathogenic courses.[97,113] By contrast, AF recurrence because of incomplete ablation, recovery of conduction, and persistence of arrhythmogenic foci

outside the sites targeted by ablation would be expected throughout the early and late follow-up period, not just within the initial weeks postablation.

The incidence of ERAF is between 35% and 45% in patients who undergo PV isolation for paroxysmal or persistent AF.[113–117] This incidence appears to be independent of specific ablation technique. Persistent AF, LA enlargement, and the presence of structural heart disease have all been identified as predictors of ERAF.[113,116,117] Of patients with ERAF within the first month postablation, 30% to 55% will remain free of AF during subsequent medium-term follow-up.[113,116,117] These findings form the rationale for excluding recurrences within the first month postablation when evaluating procedural success. Limited data suggest that patients undergoing more extensive LA ablation, including linear lesions, may experience a more gradual and progressive reduction in AF episodes for up to 1 year following ablation.[118] The mechanism of this delayed response is unclear but has prompted some investigators to prolong the time window of the healing phase or "blanking period" to 3 or more months.

Recurrences of AF after the initial year postablation have been considered uncommon.[119,120] However, others have reported a progressive cumulative increase in AF recurrence over several years of follow-up.[121] Differences in the intensity or completeness of follow-up over time may account for some of these disparities.

Definition of Successful Ablation

At present, there is no consensus on the optimal criteria for successful ablation. At a minimum, to permit comparisons between techniques, reporting of case series should include long-term follow-up (1 or more years) from a single procedure after incorporating an appropriate blanking period of 1 to 3 months postablation. Evaluation should include periodic objective assessment for asymptomatic as well as symptomatic recurrence, preferably in the absence of antiarrhythmic drug therapy.

Complete elimination of AF episodes may be neither a reasonable nor a necessary therapeutic endpoint. Clinical trials currently in the planning phase will compare AF ablation to alternative therapy with respect to other clinical endpoints, including heart failure, stroke, and mortality. Data from these trials may provide a better perspective on the magnitude of AF reduction required to improve clinical outcomes.

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Strategies on How to Diagnose, Prevent, and Treat Pulmonary Vein Stenosis

Douglas L. Packer

Abstract: Imaging strategies used to facilitate catheter ablation for atrial fibrillation (AF) have provided a deeper understanding of the anatomy of the pulmonary veins (PVs). Pulmonary vein stenosis (PVS) is a possible complication of AF ablation and can present either asymptomatically or symptomatically. Symptoms such as dyspnea, cough, hemoptysis, chest pain, or the generalized appearance of bronchitis or pneumonia can be present in clinically relevant PVS. Magnetic resonance imaging and computed tomography are the best imaging strategies for establishing the presence and severity of PVS. Ventilation/profusion nuclear scanning can provide insight into the physiology of blood flow within the stenosed PV. Intervention for PVS is indicated in patients with significant symptoms or progressive stenosis in more than one vein and in patients with more than 85% to 95% stenosis in the absence of symptoms. Risks of pulmonary vein dilation include infection, bruising, pain, hematoma, deep vein thrombosis, pulmonary embolism, or peripheral artery damage. When stenosed vessels are appropriately dilated, the lesions typically decrease from the prestenosis level down to 0% to 20%. However, follow-up studies have shown a high rate of in-stent and in-segment restenosis, and because of the unavailability of coated stents 10 mm or larger in diameter, stenting on the first procedure is not currently recommended or practiced in large centers undertaking frequent interventional vein dilation procedures. Patients must be aware that two or three procedures could be required to complete the dilation process with or without stenting. Long-term follow-up studies have shown that extensive collateralization of vessels over time can be a chief factor in reducing symptoms. A careful assessment of the risk of the procedure must be weighed against the potential likelihood of success prior to intervention.

Keywords: CT for diagnosis of pulmonary vein stenosis; MRI for diagnosis of pulmonary vein stenosis; Pulmonary vein dilation; Pulmonary vein stenosis; Pulmonary vein stenting; Ventilation/profusion scan.

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Introduction

Over the past decade, an enhanced understanding of the anatomy of the left atrium (LA) has emerged as a by-product of the quest to ablate atrial fibrillation. Although initial interventional attempts were based on the identification and elimination of repetitively firing foci within the pulmonary veins,[1–6] this approach has since undergone evolution to the more anatomically based isolation of pulmonary veins using circular catheter guidance or wide-area circumferential ablation or antral isolation.[7–9]

This has in turn been fostered by better imaging of the LA and pulmonary veins. A variety of intracardiac ultrasound and computed tomographic (CT) or magnetic resonance (MR) imaging studies have chronicled the number and distribution of these veins[10–18] (Table 1). While initial studies suggested only a 5% to 20% occurrence of antral fusion of the left pulmonary veins, the wider-scale application of CT and MR imaging has verified that up to 70% of patients have this venous formation. These imaging studies have also demonstrated more clearly the characteristics of tissue around the pulmonary veins, including the dome of the LA and the lateral LA isthmus.[19–21]

These anatomic investigations have also identified the location of collateral structures and their relationship to the LA. The location and course of the pulmonary veins, phrenic nerve, coronary arteries in the left atrioventricular grove, and the esophagus are all better established than 5 years ago.[22–26] Such an understanding is of critical importance to avoid inadvertent injury to these structures during the course of an ablation. This chapter focuses on the pulmonary veins with a basic premise that increased understanding of the process will lead to decreased risk of untoward damage occurring in the course of the ablative intervention.

Pulmonary Vein Injury

The occurrence of clinically relevant pulmonary vein stenosis is heralded by the emergence of dyspnea, dyspnea on exertion, cough, hemoptysis, chest pain, or the generalized appearance of bronchitis or pneumonia.[27] The prevalence of each of these symptoms or findings is as noted in (Figure 1).[28] In many cases, patients with marked symptoms and consistent x-ray changes were misdiagnosed as having other pulmonary illnesses but were found to have stenosis well within the pulmonary veins following radio-frequency ablation. Accompanying abnormalities on physical examination are uncommon. While the emergence of this new clinical entity at first seemed alarming, subsequent studies have provided the perspective needed to view this complication as problematic but not typically catastrophic.

The studies of Chen et al.[4] suggested that this problem occurred in up to 35% of patients. This was based on transesophageal echocardiographic evaluation in a group of patients who had undergone ablation at the site of focal targets well within the veins. In other early experience, pulmonary vein stenosis in similarly targeted veins appeared to be as high as 10% of all ablated patients.[3,4,29–34] With the abandonment of primary ablation within pulmonary veins, use of lower-power ablation, application of intracardiac ultrasound, and the accumulation of greater general experience, this risk came down rapidly to a 2% to 4% range.[30,32,35]

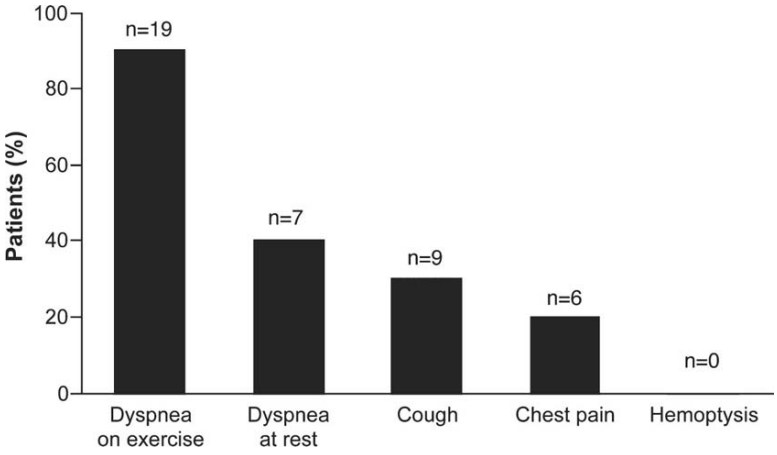

Figure 1 Symptoms on presentation of PV stenosis in 23 patients.

Table 1 Anatomic variations of pulmonary veins (PVs)

Supernumerary PVs	
Righ	18–29%
Left	3%
Common Ostium of	
Right PVs	<1%
Left PVs	3–35%
Early branching of right inferior PV	66–99%
"Right top" PV	3%

The application of each of these factors was based to a large degree on an emerging appreciation of the anatomy of the pulmonary veins. The application of real-time intracardiac ultrasound also allowed a more precise delineation of the venoatrial junction (Figure 2). These studies also demonstrated more clearly the true location of this junction in the right superior and left superior pulmonary veins and revealed discrepancies and miscalculations made using fluoroscopic measures.[30,35,36] The creation of actual geometries of pulmonary veins with the electroatomic mapping to create more accurate anatomy has also helped in establishing this important anatomic marker. To this end, merging preacquired CT imaging with segmented pulmonary veins is also useful in recognition of the same anatomic delineations (Figure 3).[37,38]

Diagnosis and Pulmonary Vein Stenosis

Again, the role and relevance of anatomy is illustrated by the emergence of CT and MR anatomic imaging as the best means of establishing the presence and severity of pulmonary vein stenosis. Initial studies[4,27–29,39] not only allowed the characterization of the underlying pulmonary veins, but also demonstrated the location and severity of pulmonary vein stenosis. Although each ablation laboratory has tried to target tissue at or outside the pulmonary veins, the

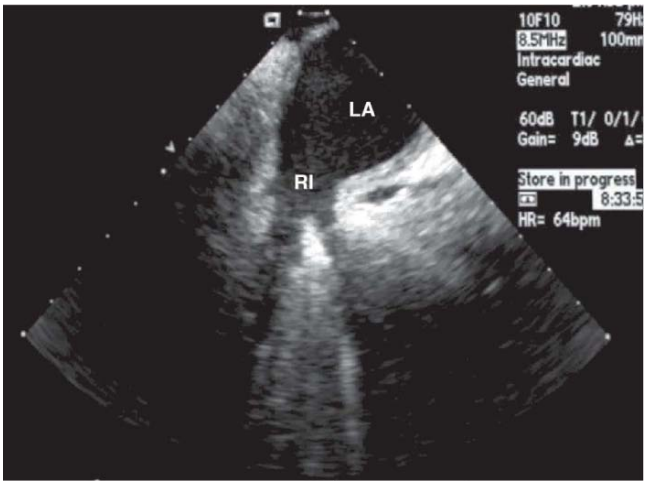

Figure 2 Intracardiac ultrasound image showing long axis view of the right inferior (RI) pulmonary vein. Also seen is the left atrium (LA) during imaging from the right atrium

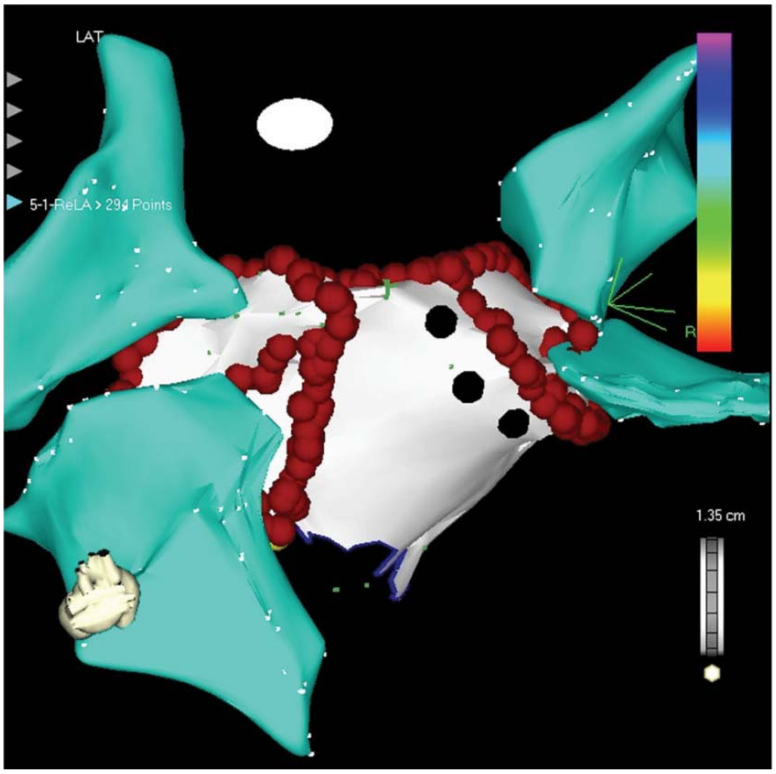

Figure 3 Posterior view of the left atrium and four pulmonary veins following wide area circumferential ablation for atrial fibrillation. The geometry of each vein is created as a separate chamber providing a more authentic image of the pulmonary veins

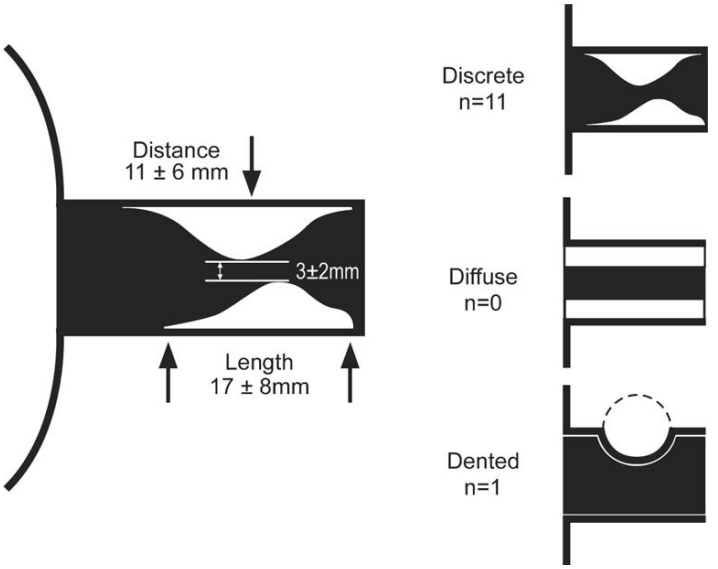

Figure 4 Characteristics of maximal pulmonary vein stenosis in the initial Mayo experience. Because of focal or lasso guided ablation, maximum stenotic distance was 11 ± 6 mm into the vein. Lesions were typically 17 ± 8 mm in length. The majority showed discrete stenosis

point of maximum stenosis has been documented to occur anywhere from the orifice of the vein to a point 20 to 30 mm into the pulmonary vein (Figure 4). Typical lesions are cylindrical, albeit frequently eccentric, and taper at the site of maximal narrowing. Recent studies have demonstrated that the lesions may be anywhere from 2 to 3 mm in length with a weblike morphology, but more commonly have a length of 10 to 30 mm.

The CT and MR imaging studies also demonstrate the presence of apparent accompanying tissue inflammation occurring around the pulmonary veins. Sequential studies have shown that this inflammatory process can progress to the point of complete fibrotic occlusion of the pulmonary veins related to extensive fibrosis about the vessels and in perihilar tissue.[40] Recent animal studies have clarified the accompanying cascade of protein precursors present in the inflammatory process[41] (Figure 5).

Studies from several centers showed that the emergence of symptoms, as expected, is a function of the extent and distribution of pulmonary vein stenosis. Occurrence of stenosis greater than 65% to 75% of the luminal diameter can be followed by the above-mentioned symptoms. This is substantially more likely if more than one vein is affected. In contrast, pulmonary veins may go on to completely occlude without symptoms if only one vessel is stenosed.[42–45] This is less likely to be the case if two or three vessels have extensive stenoses (Figure 6). That this "one-vessel rule" is not foolproof is the finding that some patients are highly symptomatic with pleuritic chest pain and hemoptysis, indicating infarcted tissue, occurring in the setting of occlusion of a single vessel or even a branch. This again highlights the relevance of the underlying anatomy and importance of surveillance of lung parenchyma in considering the cause and effect of the patient's symptoms.

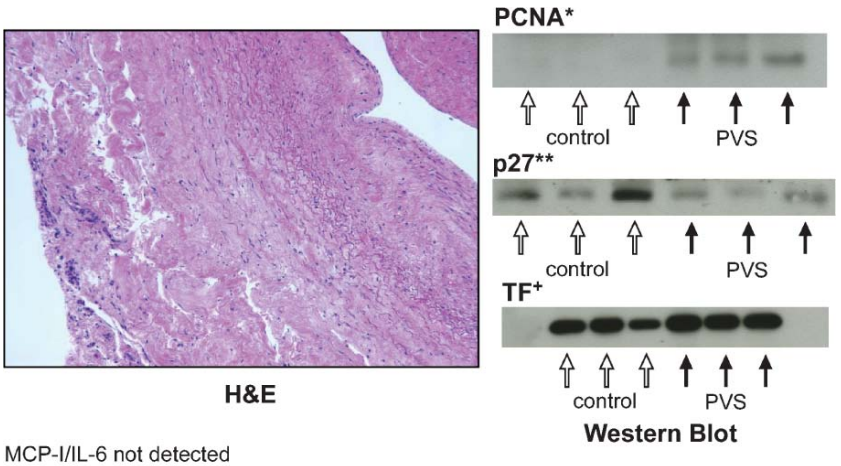

Figure 5 Marked cellular proliferation observed on hemotoxalin / eosin staining of pulmonary vein stenosis in a canine model. Also shown are the western blot analyses of inflammatory factors with an increase of proliferating cell nuclear annogens (PCNA), a decrease in P27 a cyclin-dependent kinase inhibitor, and a marked increase in tissue factor (TF). (Ref: Milton, MA Heart Rhythm 2004;1(1S):S109)

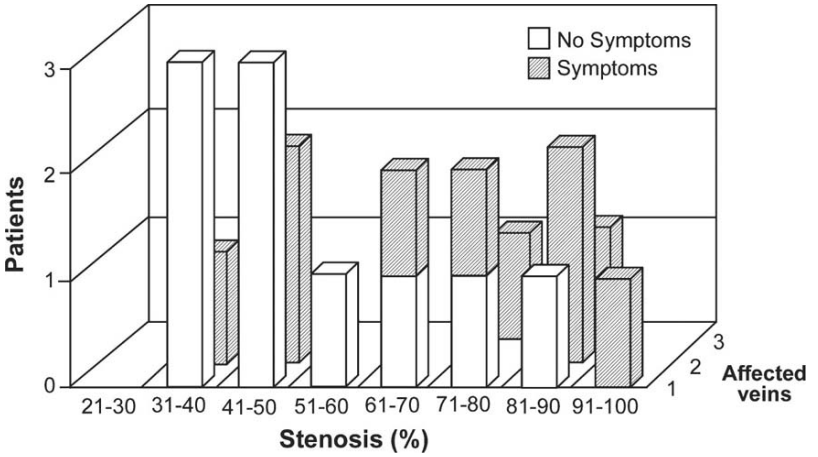

Figure 6 Impact of stenosis severity and affected vein number on symptoms in pulmonary vein stenosis. Symptoms emerged at 60–70% stenosis, particularly in patients with more than one affected vein. (Ref: Packer DL, Asirvatham S, Seward JB, Robb RA, Breen, JF. Imaging of Cardiac and Thoracic Veins. In: Thoracic Vein Arrhythmias: Mechanisms and Treatment. Eds. Chen S-A, Haissaguerre M, Zipes DP. Blackwell Publishing, Futura Division. Elmsford, NY: an imprint of Blackwell publishing. 2004.)

Ventilation/profusion nuclear scanning provides more robust characterization of the physiology of blood flow within the distribution of a stenosed pulmonary vein. Local perfusion diminishes substantially with stenosis greater than 65% to 75%. The percentage contribution of local blood flow within the

affected pulmonary vein distribution to the overall imaging counts can be as low as 3% to 4%, where the normal range for apparent blood flow of one third of a lung is between 15% and 30%, depending on the pulmonary vein under imaging (Figure 7).[28,39,46] The application of perfusion scanning is most useful in objectively identifying the presence of stenosis in the setting of largely subjective symptoms and other clinical findings.

Transesophageal echocardiographic imaging may be useful in establishing the presence of pulmonary vein stenosis, although the largest studies to date have suggested a lack of utility in the identification of the severity of the stenosis.[28,47] The occurrence of turbulence and aliasing in the region of the pulmonary vein orifice is useful, but the ability to image deeply into the pulmonary veins, particularly the inferior veins, makes this imaging modality less useful in clearly establishing the extent and location of the pulmonary vein stenosis.

Interventional Approach to Pulmonary Vein Stenosis

Intervention appears indicated in patients with significant symptoms, in more than one vein, and is reasonable in those with 85% to 95% stenosis in the absence of symptoms. Of note, even in the setting of lesions reaching the 65% to 75% range, there is approximately a one-third chance that the vessels will remain stable; one third will show improvement, and the final third will show progression over 3 to 12 months of follow-up. With evidence of progression, however, to the 75% range, follow-up within 3 months with repeat scanning is required to avoid missing a lesion that would otherwise progress to complete occlusion without intervention.

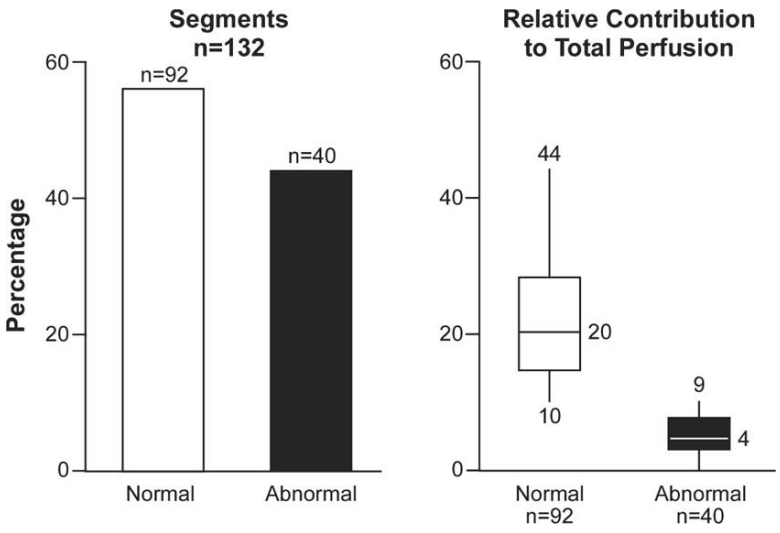

Figure 7 Perfusion abnormalities in 22 PV stenosis patients. Panel A shows the number of normal and abnormal segments on ventilation perfusion scanning. Panel B shows the relative contribution of normal and abnormal segments to total profusion. Typically, a normal segment contributed a mean 20% to overall profusion. Abnormal segment showed a substantial reduction in contribution to 2–7%. (Ref: Circulation 2005;111(5):546–54.)

Angiographic evaluation has been highly effective in patients with progressive symptoms. Direct venography is most useful in establishing the extent of the stenosis as well as the precise anatomic location with reference to the orifice of the vessel (Figure 8). Using selected 8F sheaths, along with more directional catheters (multipurpose, Williams, or other catheters) along with specific guide wires (Stork, Glide, straight tip), the lesions can be crossed. This can even be true if a CT or MR prestudy suggested total occlusion of the vessel, providing there is clear-cut evidence of contrast agent within the LA and reconstitution of pulmonary vein contours in the lung field on the other side of the stenosis. At that point where the pulmonary veins within the lung parenchymal appear replaced by apparent inflammatory or scar tissue, this becomes singularly unlikely. Selected pulmonary arterial injections to visualize the stenosis are less useful.

Once a hemodynamic catheter is positioned across the stenosis, typical gradients of 6 to 12 mm are seen when comparing the pulmonary vein to LA pressures. Given the "apparent anatomy" seen on CT and angiographic imaging, balloons of 10-mm diameter and 20 mm in length are most useful for eliminating the stenosis. The dilation of the balloons to 6 to 10 atm may be required to eliminate the "fibrotic waist" of these lesions. It should be noted that the use of balloons greater than 12 mm in diameter and higher pressure can result in dissection of the vein with substantial bleeding (personal experience). The use of smaller balloons is unlikely to achieve long-term patentcy. Dilation for a period of at least 1 min is usually required, with all interventions performed with Activated Clotting Time (ACTs) above 250 to 300, given the possibility of thrombus in or about the stenotic segment. The occurrence of such a clot has been reported to produce transient myocardial ischemia or even stroke, in part related to the absence of availability of distal protection devices for the LA and aorta.[27,28]

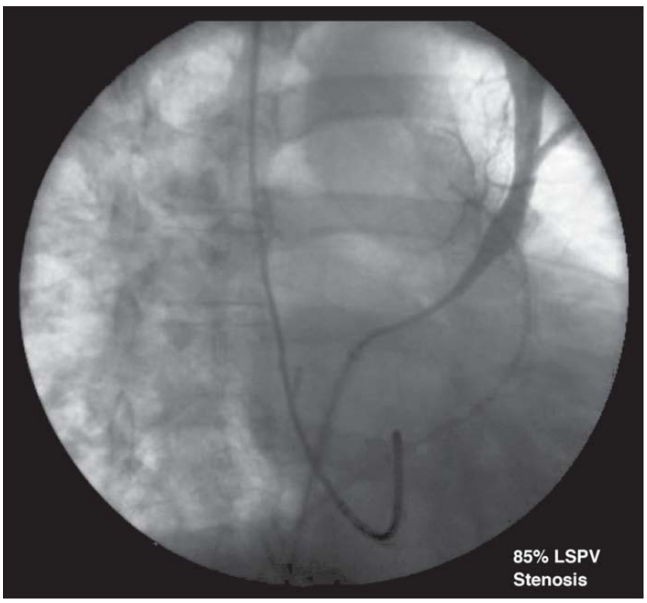

Figure 8 Venographic examination of the LSPV showing an 85% stenosis. Also seen is collateralization to normal vasculature. (Ref: Circulation 2005;111(5):546–54.)

With appropriate dilation, the lesions typically decrease from the prestenosis level to 0% to 20% (Figure 9). Because follow-up studies have shown a high rate of in-stent and in-segment restenosis and because of the unavailability of coated stents larger than 10-mm diameter, stenting on the first procedure is not currently recommended or practiced in large centers undertaking frequent interventional vein dilation procedures.[28,45] Nevertheless, with restenosis occurring following the initial procedure, stenting may be necessary, albeit accompanied by a 60% to 70% recurrence of both in-stent or in-segment restenosis.

Intracardiac ultrasound can be highly useful in guiding stent placement. This is particularly critical in matching the proximal edge of the stent to the pulmonary vein orifice without extension into the LA. This is also critical with the orthogonal position of the left pulmonary veins, where a stent extending out into the LA or antrum can block access to an ipsilateral vein. Intracardiac ultrasound can also guide the "fluting" of the most distal portion of the pulmonary vein to allow a better form fit to the underlying expanding pulmonary vein anatomy. The location of the balloon and its continual apposition to the stent are readily seen on intracardiac ultrasound. The alternative backward projection of the balloon out into the LA is also readily identifiable.

Long-Term Outcome of Stenosed Vein Intervention

As noted, the limitation of pulmonary vein interventions in the absence of drug-eluting stents is recurrent stenosis of a balloon-dilated vessel. As such, patients must be aware that two or three procedures could be required to complete the dilation process, with or without stenting. This may be particularly relevant given the possibility of progressive lesions within other vessels not

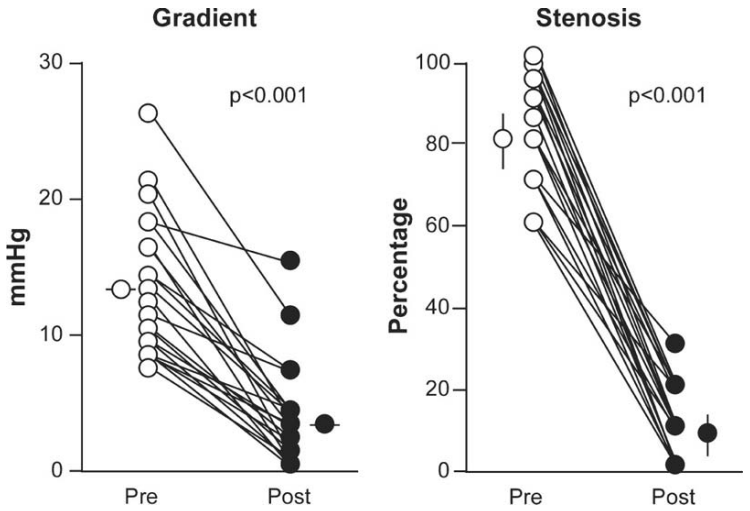

Figure 9 Outcome of intervention for pulmonary vein stenosis in 23 patients with 34 affected veins. Panel A shows the trans-stenosis gradient both prior to and following intervention for pulmonary vein stenosis. Panel B shows the percent of stenosis dropping from 80 to 10% with balloon dilatation. (Ref: Circulation 2005;111(5):546–54.)

warranting intervention at the time of the first catheterization. Despite this, over 80% of vessels do remain sufficiently patent to dramatically decrease patients' symptoms and ameliorate risk of pulmonary artery hypertension, which is only infrequently reported, including in patients with multiple vessel abnormalities. It should be noted, however, that currently available follow-up described in the literature is limited to less than 9 years duration.[27,28,39]

Long-term follow-up studies nevertheless demonstrated the occurrence of extensive collateralization over time, which appears to be a chief factor in reducing symptoms from a class 3 to 4 level to a more tolerable 0 to 2 region (Figure 10).[44] This positive factor typically occurs via collaterals to an ipsilateral vessel. It appears important to maintain patency of at least one vessel of a given lung to permit this collateralization process.[44] Obviously, much additional work is required to more completely define the long-term clinical outcomes and importance of each of these factors in managing patients with pulmonary vein stenosis.

Postinterventional Patient Management

Because of the risk of re-stenosis, careful patient evaluation is important postprocedure. A CT or MR study obtained following the procedure will disclose the propensity of early restenosis, which occurs in a minority of patients. Scans at the 3-month mark are more useful, however, for reintervention decision making.

Given thrombus risk, patients following pulmonary vein stenosis should be anticoagulated to traditional international normalized ratio (INR) levels of 2 to 3. There have been several cases of pulmonary artery thrombus occurrence in the distribution of affected pulmonary veins. Of note, however, is the possibility of misdiagnosis of the presence of arterial thrombus because of the streaming effects of contrast delivery during CT evaluation. In the presence of equivocal findings, MR imaging with alternative contrast may be useful.

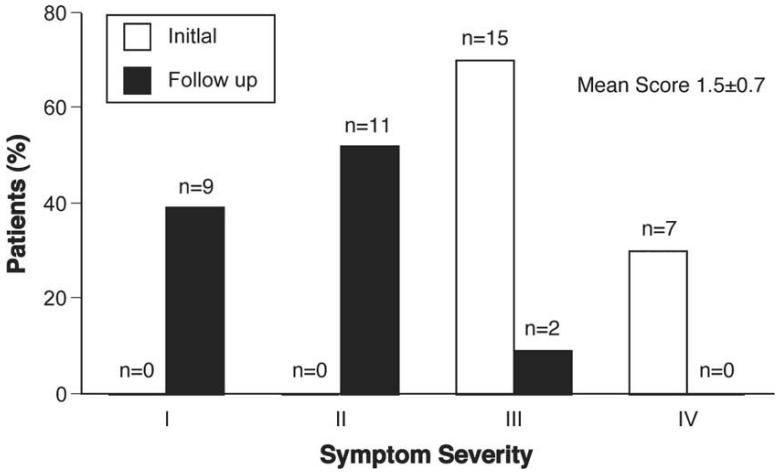

Figure 10 Overall symptom level at 24 months in 22 patients with pulmonary vein stenosis. Here the percentage of patients and their class I through IV symptom level at baseline and follow up. The majority of patients that showed class III-IV symptoms, showed a decrease to class I-II symptoms at two years of follow up. (Ref: Heart Rhythm 2004; 1(1s):S88.)

Several centers with extensive experience also employ clopidogrel (Plavix) in these patients over an indefinite period of time. Obviously, follow-up longer than 3 to 5 years would be required to more completely establish indications for anticoagulation following the occurrence of pulmonary vein stenosis. The fact that strokes have occurred in these patients indicates that caution is mandated. Whether anticoagulation can be stopped in patients with stents or with excellent results and no restenosis over the long term must be established on an individual patient basis. Extensive follow-up over a period of years appears prudent before making that decision. Because of thrombus risk, we do not currently recommend discontinuing warfarin anticoagulation.

Asymptomatic Stenosis

A word regarding asymptomatic stenosis is warranted. Some patients with pulmonary vein stenosis have no or limited symptoms in the setting of a single-vessel process (Figure 11). In the absence of evidence for late pulmonary artery hypertension or other untoward events such as infection or uncontrolled bleeding, an argument could be made for simply observing patients with single-vessel asymptomatic disease without intervention. At this point, however, we have been unwilling simply to allow progression to occlusion without intervention, particularly if the ipsilateral vessel is also involved in the stenotic process. In most cases to date, dilation of a single apparently asymptomatic vein has been accompanied by symptomatic improvement. While that could be

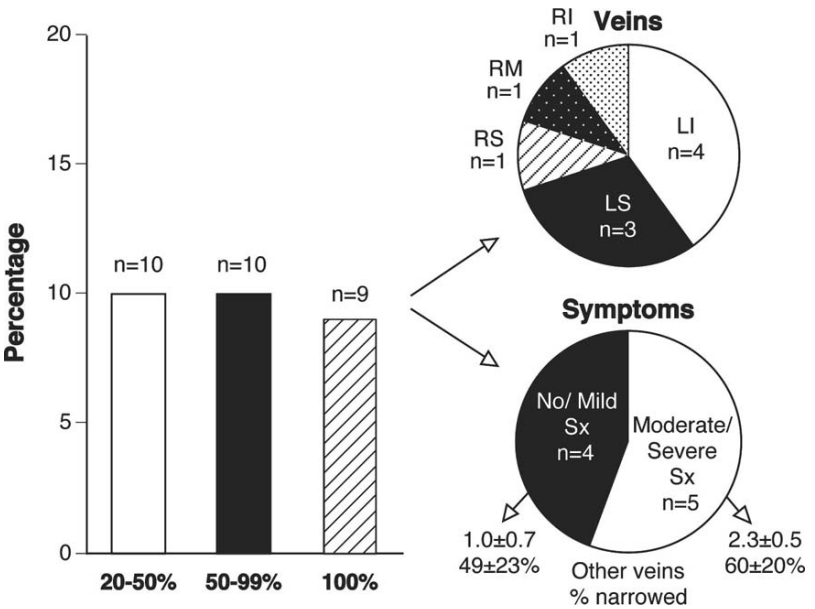

Figure 11 Implications of total pulmonary vein occlusion after RF ablation in 29 affected veins. Panel A shows 9 veins (30%) were totally occluded. Panel B shows the distribution of the veins and the symptom level. The majority of patients with total occlusion with no other affected veins and mild narrowing showed minimal or no symptoms. Patients with moderate or severe symptoms had multiple vessels affected with a higher degree of stenosis in accompanied vessels

caused by a placebo effect, it may also be related to the insidious progression of pulmonary vein stenosis in some patients, which occurs over a long enough period of time that the change in symptoms is not completely recognized. In the absence of symptomatic improvement or any evidence of untoward effects from the pulmonary vein stenosis itself, the alternative strategy in such a case could be to forgo repeat dilation, although that approach has not been tested even in observational studies.

Risk of Intervention for Pulmonary Vein Stenosis

Obviously, the quest to intervene in these patients must be weighed against the risk of the procedure itself. Pulmonary vein dilation can be accompanied by the typical risks accompanying any vascular intervention, with local complications at the catheterization site such as infection, bleeding, bruising, pain, hematoma formation, deep vein thrombosis (DVT), pulmonary embolism (PE), or peripheral artery damage requiring surgical repair. The risk of heparinization during the procedure and that of contrast agent utilization and anesthesia used during the procedure are not negligible. Furthermore, risks of myocardial perforation with tamponade are possible with the manipulation of interventional catheters or guide wires. Bleeding from the vein dilation or because of guide wire perforation into lung parenchyma is also possible.[39] Of note, the risk of stent embolization, vessel stenosis aggravation, and pulmonary vein dissection have been reported.[48,49] These are sufficiently uncommon, however, to be uncertain of their occurrence rate. In our own experience with 50 patients, 2 patients had extensive intrapulmonary bleeding requiring extended intubation and repeat bronchoscopy to deal with intrabronchial bleeding. Surgical intervention for such cases has not been required but has been reported in the case of severe acute thrombus.[50] Clearly, the risk of the procedure must be weighed against the potential likelihood of success, the anticipated benefit to the patient, and the likelihood of occurrence of complications.

Conclusion

Although the treatment process was once feared, most patients with pulmonary vein stenosis show a favorable outcome over time.[28,29,39] Nevertheless, ongoing anatomic surveillance with CT and MR imaging is warranted, as is additional long-term follow-up with transthoracic echocardiography to monitor for the possibility of long-term pulmonary artery hypertension or other problems. As with any other interventional complication, the best approach to patients with atrial fibrillation is to avoid the problem in the first place through careful targeting of ablation outside the pulmonary vein, monitoring during ablation with intracardiac ultrasound or other measures, and use of caution in selecting energy delivery parameters. In so doing, the risk of this process can be minimized to a level below 1% to 2%.

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Section V

Surgery for Atrial Fibrillation

22

Ablation of Atrial Fibrillation with Cardiac Surgery

A. Marc Gillinov and Adam E. Saltman

Abstract: When present in cardiac surgical patients, atrial fibrillation is associated with increased morbidity and decreased early and late survival. Today, cardiac surgeons have a variety of new techniques and technologies that facilitate ablation of atrial fibrillation at the time of concomitant heart surgery. Based on the biatrial lesion set of the Cox –maze procedure, newer operations employ alternate energy sources to create extensive lesion sets that include wide pulmonary vein isolation, a mitral isthmus lesion, and right atrial lesions. In addition, surgical ablation includes excision or exclusion of the left atrial appendage. In many cases, combined mitral valve surgery and ablation can be performed with a minimally invasive approach. For the patient seeking stand-alone therapy for atrial fibrillation, surgeons offer minimally invasive approaches that do not require cardiopulmonary bypass or a sternotomy. These procedures may be particularly applicable to patients who are not candidates for catheter ablation, patients who have failed catheter ablation, and patients who might benefit from excision of the left atrial appendage.

Keywords: Atrial fibrillation; Cardiac surgery; Left atrial appendage; Maze.

Introduction

Although it has long been recognized that atrial fibrillation (AF) is common in patients presenting for mitral valve and other forms of cardiac surgery, routine ablation of AF in such patients is a recent phenomenon. This change in surgical practice is attributable to new data clarifying the pathogenesis and dangers of untreated AF and development of new ablation technologies that facilitate ablation. For cardiac surgical patients presenting with AF, surgeons now offer a more complete operation that corrects both the structural heart disease and the AF. With this comprehensive approach, it was estimated that surgeons would perform ablation procedures in more than 10,000 cardiac surgical patients in 2007. The purposes of this review are to (1) review the rationale for surgical ablation of AF in cardiac surgical patients, (2) describe the classic

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maze procedure and its results, (3) detail new approaches to surgical ablation of AF, (4) emphasize the importance of the left atrial appendage (LAA), and (5) consider challenges and future directions in the ablation of AF in cardiac surgical patients.

Rationale for Surgical Ablation

Atrial Fibrillation Prevalence

Atrial fibrillation is present in up to 50% of patients undergoing mitral valve surgery and in 1% to 6% of patients presenting for coronary artery bypass grafting (CABG) or aortic valve surgery.[1–4] Because AF is particularly common in patients with mitral valve dysfunction, most studies examining concomitant ablation focus on this group. As in the general population, the prevalence of AF in patients with mitral valve disease increases with increasing patient age (Figure 1). In patients with mitral valve dysfunction, AF is a marker of advanced cardiovascular disease. Compared to mitral valve patients without AF, those with AF have higher New York Heart Association functional class, more severe left ventricular dysfunction, and greater left atrial enlargement.[4–7] Data examining CABG patients confirmed similar associations of AF in this population.

Atrial Fibrillation Dangers

Atrial fibrillation is associated with increased mortality and morbidity in mitral valve and CABG patients.[3,4,8] In nonsurgical patients with degenerative mitral valve disease, AF is an independent risk factor for cardiac mortality and morbidity.[3] In patients undergoing mitral valve surgery, persistence of postoperative AF is both a marker and a risk factor for increased mortality; in addition, AF is associated with morbidity that includes stroke, other thromboembolism, and anticoagulant-related hemorrhage.[8–11] In some patients, AF

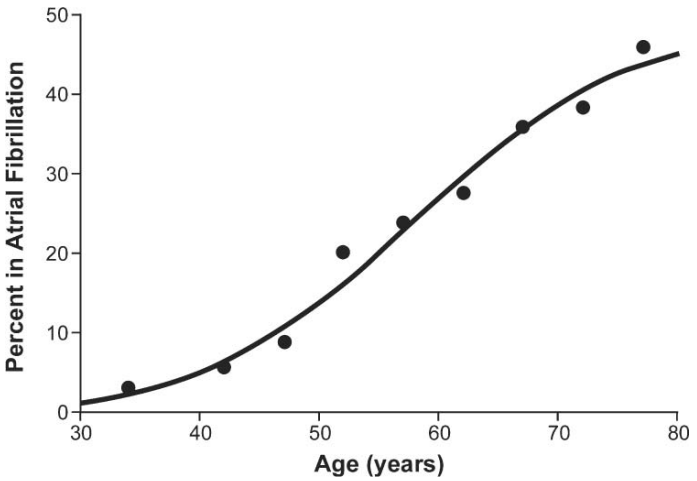

Figure 1 Prevalence of atrial fibrillation vs age in patients with degenerative mitral valve disease

causes symptomatic tachycardia, reduced cardiac output, and tachycardia-induced cardiomyopathy. This is particularly deleterious in patients with structural heart disease and reduced cardiac output. For these reasons, the presence of AF should be factored into the operative strategy in cardiac surgical patients.

The onset of AF is a relative indication for mitral valve surgery in those with mitral valve dysfunction.[2] In most instances, however, mitral valve surgery alone does not ablate AF.[5–7,12] When duration of preoperative AF exceeds 6 months, 70% to 80% of patients will have AF after mitral valve surgery alone.[5,6,12] In contrast, when AF has been present for 3 months or less, particularly if it is paroxysmal, mitral valve surgery results in 80% conversion to sinus rhythm.[5,6] Therefore, ablation should be added to the mitral valve procedure in any patient with AF of greater than 6-month duration or in any patient with AF that is not paroxysmal.

Atrial Fibrillation Mechanisms and Implications for Surgical Ablation

Because the pathogenesis of AF in cardiac surgical patients is incompletely understood, there is no consensus concerning ablation strategy in these patients. It is recognized that clinical presentation of AF varies between individuals, and current guidelines account for this by classifying AF as paroxysmal, persistent, or permanent.[13] Alternatively, AF may be classified as intermittent or continuous.[14] It is certain that, like clinical presentation, the pathogenesis of AF varies between patients; however, the extent to which mechanisms of focal activity and reentry contribute to the initiation and maintenance of AF is disputed.[15] While the electrophysiological causes of AF require further investigation, the anatomical basis of AF is increasingly clear.

Endocardial electrophysiological mapping data demonstrate that the pulmonary veins and posterior left atrium are the critical anatomic sites in humans with isolated AF.[16,17] Because creation of intraoperative epicardial maps to characterize AF in cardiac surgical patients is time consuming and technically demanding, there is less direct evidence supporting this concept in patients with mitral valve and other cardiac surgical patients. Nevertheless, available mapping studies support the importance of the left atrium as the driving chamber in mitral valve patients.[18–23] In many mitral patients with permanent AF, regular and repetitive activation can be identified in the posterior left atrium in the regions of the pulmonary vein orifices and LAA.[18–22] However, the spectrum of AF is more complex than this as such foci are not identified in all mapped patients, and some patients also manifest right atrial focal or reentrant activation.[18]

Although routine real-time intraoperative mapping is currently not available to guide AF ablation in cardiac surgery patients,[23] an anatomic approach to ablation based on our understanding of pathophysiology and empiric results is reasonable. In fact, such an anatomic (rather than map-guided) approach is rapidly becoming the foundation for catheter-based ablation of AF.[24–26] A left atrial procedure that includes a boxlike lesion around all four pulmonary veins and a lesion to the mitral annulus appears to eliminate AF in 70% to 90% of mitral valve patients.[22,27–30] The addition of right atrial lesions in these patients is controversial.[31,32] Omission of a right atrial isthmus lesion leaves some patients at risk for typical atrial flutter.[33] Because creation of right atrial lesions is simple and does not appreciably increase operative time, AF ablation in cardiac surgical patients usually entails creation of a biatrial lesion set.

The Maze Procedure

The Cox Maze III operation, or maze procedure, is the gold standard for surgical treatment of AF, and other approaches to AF ablation should be measured against it. The maze procedure has an 18-year history and is the most effective curative therapy for AF yet devised.[34–36] Cox and colleagues designed the procedure empirically based on the limited understanding of AF available at the time.[34] To improve results and simplify the operation, they modified the procedure twice, culminating in the Cox Maze III.[34]

In the maze procedure, multiple left and right atrial incisions and cryolesions are placed to interrupt the multiple reentrant circuits of AF (Figure 2). The maze procedure includes isolation of the pulmonary veins and posterior left atrium and excision of the LAA; these maneuvers are critical to the efficacy of the maze procedure in restoration of sinus rhythm and reduction of the risk of thromboembolism.

Although the maze procedure is a complex operation that requires 45 to 60 min of cardiopulmonary bypass and cardiac arrest, experienced surgeons have performed the classic operation in large numbers of patients having concomitant cardiac surgery.[1,2,35,36] The addition of a maze procedure does not increase operative mortality or morbidity.[37–39] However, it is associated with a 5% to 10% need for implantation of a permanent pacemaker, most commonly in those with preexisting sinus node dysfunction or in patients having multivalve surgery. Data demonstrated that the maze procedure has equivalent long-term efficacy in patients undergoing both lone operations and concomitant procedures. Results of a concomitant maze procedure vary somewhat between different groups; successful restoration of sinus rhythm has been achieved in 70% to 96% of patients.[37–39]

Early postoperative AF is common after a maze procedure, usually abating by 3 months. However, over time, some patients develop recurrent AF.[37–39] The pathogenesis of this is unclear, but risk factors have been identified (Figure 3).

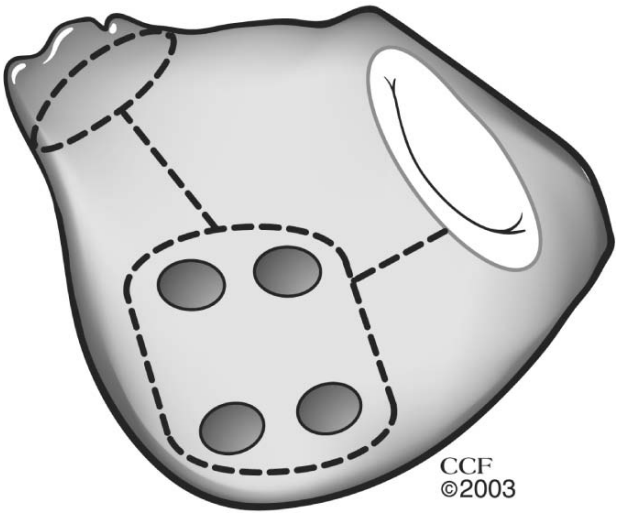

Figure 2 Left atrial lesion set of the maze procedure. Small circles represent pulmonary vein orifices and white oval represents the mitral valve. Dashed lines represent surgical incisions

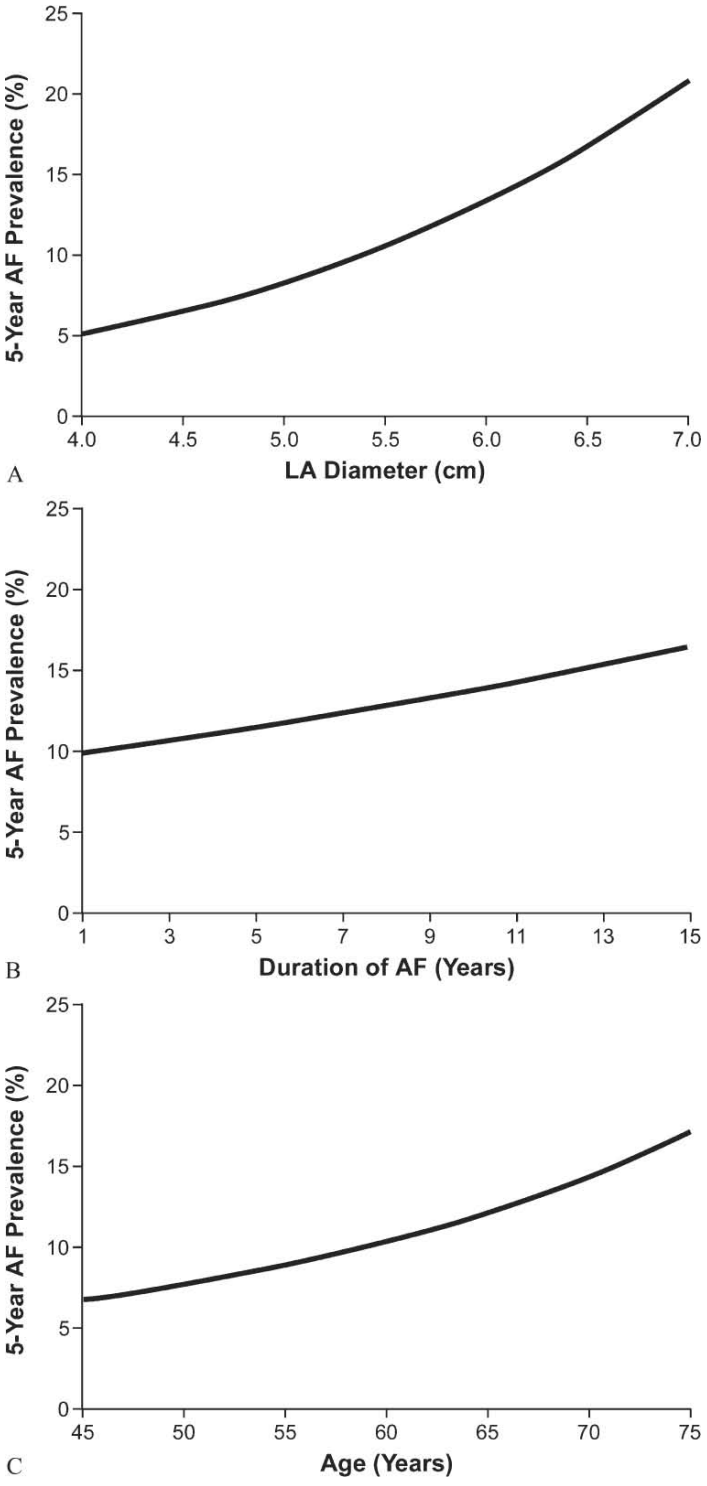

Figure 3 Prevalence at 5 years of postoperative atrial fibrillation (AF) in patients having combined mitral valve surgery and a maze procedure demonstrating effects of selected preoperative factors. **A** Left atrial (LA) diameter. **B** Preoperative duration of AF. ***C*** Age. (From ref. 39.)

Increasing left atrial diameter, longer duration of preoperative AF, and advanced patient age all increase the late prevalence of AF. Thus, 5 years after a concomitant maze procedure, the predicted prevalence of AF is only 5% in mitral valve patients with a 4-cm left atrium; in contrast, the predicted prevalence is 15% in similar patients with a 6-cm left atrium. Others have identified similar risk factors for AF after the maze procedure, suggesting the possibility that earlier operation and left atrial size reduction in those with left atrial enlargement (>6 cm) might improve results.[40–43]

The temporal pattern of AF (paroxysmal, persistent, or permanent) does not have an impact on results of the maze procedure.[39] Similarly, in mitral valve patients, etiology of mitral valve dysfunction does not influence results, and there is general agreement that the maze procedure is effective in patients with rheumatic valve disease, as well as in those with degenerative mitral valve disease.[44,45] Even in patients with rheumatic disease, biatrial contraction is usually restored.[44]

The maze procedure is associated with important clinical benefits in patients with mitral valve disease. Data demonstrated that restoration of sinus rhythm improves survival in patients with AF and mitral valve disease.[9] This survival benefit requires confirmation by further study. Other advantages of the maze procedure in mitral valve patients with AF are well documented, including reduced risks of stroke, other thromboembolism, and anticoagulant-related hemorrhage.[9–11,46]

The reduced risk of late stroke after a maze procedure deserves particular emphasis. In the largest series focusing on this outcome, Ad and colleagues noted a single late stroke at a mean follow-up of 5 years in 300 patients having a classic maze procedure.[46] This remarkable late freedom from late stroke is likely attributable both to restoration of sinus rhythm in the majority of patients and to excision of the LAA, which is an integral component of the maze procedure.

These results confirm the safety of the maze procedure, its efficacy at restoring sinus rhythm, and the resulting clinical benefits, most notably the virtual elimination of late strokes. Despite these excellent results, the maze procedure has been relatively underutilized, and today it is almost obsolete. Most surgeons have been reluctant to add a maze procedure to the operative course of patients having mitral valve or other cardiac surgery. However, with recent advances in our understanding of the pathogenesis of AF and development of new ablation technologies, surgeons are increasingly likely to ablate AF using simpler techniques that require only a few minutes of operative time.

New Approaches to Surgical Ablation of Atrial Fibrillation

Lesion Sets

Like recent approaches to catheter-based ablation, new surgical techniques for AF ablation are anatomically focused, concentrating on the creation of lines of conduction block in the left atrium.[47–49] Because the left atrium is opened for mitral valve procedures, precise creation of lesions is possible. A variety of lesion sets have been employed to ablate AF in patients with mitral valve disease. Most include pulmonary vein isolation, excision or exclusion of the

LAA, and linear left atrial connecting lesions.[47–51] The pulmonary veins may be isolated with a boxlike lesion as in the maze procedure, or, with separate right- and left-side ovals around the pulmonary veins. With the advantage of direct vision, the surgeon can easily create a lesion from the left pulmonary veins to the mitral annulus; this lesion improves results, particularly in patients with permanent AF and mitral valve disease.[52,53] In patients with left atrial enlargement (>6 cm), we recommend left atrial reduction as this may increase restoration of sinus rhythm.[40]

The issue concerning the creation of biatrial lesions (more closely mimicking the Cox Maze III set) vs creating left atrial lesions alone remains contentious. It is clearly easier and faster to create a more limited lesion set; yet, data indicated that patients undergoing both right and left atrial treatment have a better long-term result at maintaining sinus rhythm.[32] Through the judicious selection of a technology or multiple technologies, as discussed in this section, it is now becoming possible to create right-side lesions without opening the right atrium or prolonging cardiopulmonary bypass time or aortic cross-clamp time. In this manner the largest number of patients can be treated in the most efficacious and safest fashion.

A Review of the Available Energy Sources

The classical lesion creation method is cutting and sewing tissue. Once the healing process is complete, there remains a scar composed mostly of collagen and little to no cellular material. It is not electrically conductive, and the lesion is, by definition, *transmural*. The goal of any energy source, therefore, is to create a similar scar by exposing tissue to extremes of temperature, inducing thermal injury, coagulation necrosis, and healing.

To produce such an injury, the tissue must be either heated to 50 °C or frozen to −60 °C.[54,55] The quantity of tissue injured is usually directly proportional to the duration the tissue is held at either temperature. The various energy sources discussed differ mainly in the method by which they transfer energy to the tissue and how deeply that energy is conducted into the tissue. A summary review of some characteristics, advantages and disadvantages of each method are given in Table 1. (It should be noted that, as of 2006, the devices discussed are Food and Drug Administration [FDA] labeled for the ablation of soft tissues but not for the treatment of AF. The specific treatment of AF is therefore considered “off-label” usage.)

Despite clearly different energy forms and application methods, it is interesting to note that when applied with the left atrium open, from the endocardial aspect with full cold cardioplegic arrest, there seems to be very little difference in the safety or efficacy of any one device over the others.[56] The most extensive experience has been with the dry unipolar radiofrequency (RF) devices, mainly Boston Scientific’s Cobra® probe. The probe consists of a malleable 6 cm long × 2-mm diameter active tip that can be shaped as the operator desires. Surveying its reported use in 16 studies including 1,187 patients, Khargi and colleagues found that dry unipolar RF was effective at freeing patients from AF 78% of the time (reported success ranged from 42% to 92%).[56] There have been several complications attributed to the use of the probe; the most worrisome were esophageal injuries, resulting in death 60% of the time.[57,58]

Table 1 Characteristics, advantages, and disadvantages of methods of tissue ablation.

Energy source	Method	Advantages	Disadvantages	Brand name
Dry unipolar RF	Contact resistive heating	1. Well understood technology 2. High tissue temperatures achieved 3. Flexible delivery system	1. Poor temperature control 2. Fat does not heat or conduct well 3. No transmurality feedback 4. Dosimetric energy delivery 5. Collateral damage from conduction into surrounding structures	Boston Scientific Cobra®
Irrigated unipolar RF	Contact resistive heating	1. Higher energy delivery at lower operating temperature 2. Small tip can make many lesions 3. Complete operator control over lesion set	1. Highly operator dependent (otherwise same as dry unipolar RF)	Medtronic Cardioblate®
Dry bipolar RF	Contact resistive heating	1. Shielded energy source 2. Very localized lesion 3. Possible transmurality feedback; used to control energy delivery 4. Very fast ablation times	1. Fixed device shape, limiting lesion types 2. Large device, making minimal access difficult	Atricure®
Irrigated bipolar RF	Contact resistive heating	1. Device more malleable than dry bipolar RF 2. Irrigation avoids char (otherwise as with dry bipolar RF)	Same as dry bipolar RF (except more flexible delivery system)	Medtronic Cardioblate® BP
Microwave	Radiation into tissue	1. Shielded energy source 2. Flexible probe 3. Penetrates fat well 4. Does not require direct tissue contact	1. Dosimetric energy delivery 2. No transmurality feedback	Guidant Flex 4® and Flex 10®
High-intensity focused ultrasound	Radiation into tissue	Same as microwave	Same as microwave	St. Jude Medical Epicor™
Laser	Radiation into tissue	Same as microwave	Same as microwave	Edwards Lifesciences OptiWave
Cryothermy	Direct tissue freezing	1. Wide safety margin (otherwise as with microwave)	1. Question about energy "sink" problems (otherwise similar to microwave)	Cooper Medical Frigitronics®; CryoCath SurgiFrost™

RF **radio frequency.**

Of course, adverse events can occur with any technology when incorrectly applied,[59] but as more experience has been gained and safer methods of ablation have been developed, such as placing a cold, wet sponge between the posterior wall of the left atrium and the esophagus or shielding the probe in nonconducting sheaths, these injuries have become an extreme rarity.

The Left Atrial Appendage

Because 60% to 90% of stroke-causing emboli in AF patients originate from the LAA, this structure has been termed "our most lethal human attachment."[60] Therefore, excision or exclusion of the LAA is a critical component of operations to treat AF; this may explain in part the exceedingly low risk of stroke after the Maze procedure. In fact, ligation of the LAA in mitral valve patients with AF reduces the late risk of thromboembolic events even if the patient does not have intraoperative ablation.[61]

Surgical technique has an impact on results of LAA ligation, with incomplete ligation increasing the risk of thromboembolism.[62,63] Currently employed techniques include exclusion by suture ligation or noncutting stapler and excision with suture closure or stapling.[64] We currently favor surgical excision of the appendage with standard cut-and-sew techniques. Development of devices designed specifically for management of the LAA will facilitate this procedure. Published preclinical experience with a LAA clip is promising, and clinical trials are anticipated[65] (Figure 4).

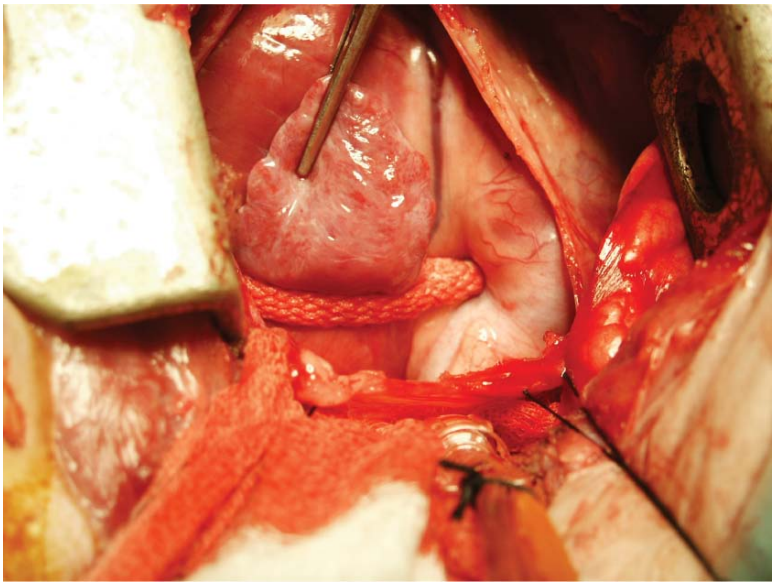

Figure 4 Exclusion of the left atrial appendage with a specially designed, cloth-covered clip. **A** Clip placed on canine left atrial appendage

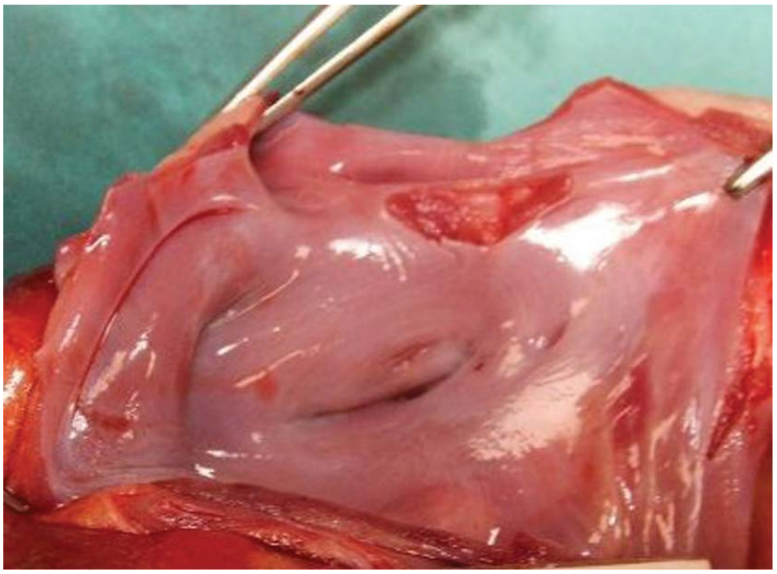

Figure 4 B View of orifice of the excluded left atrial appendage from inside the left atrium 90 days after clip application

Challenges and Future Directions

Advances necessary to improve AF ablation in cardiac surgical patients include uniform definitions and methodology for reporting results, improved technology to facilitate ablation and its intraoperative assessment, and refinement of minimally invasive procedures.

Reporting Results

Standard terminology and methodology for reporting results is absent from the cardiac surgery and electrophysiology literature, and current reporting is haphazard and subject to criticism.[66] While there are now guidelines for categorizing the clinical pattern of AF (paroxysmal, persistent, or permanent), these are inconsistently applied. Techniques for postablation rhythm assessment vary, with no generally accepted standard. Ideally, simple and convenient technology for long-term and continuous rhythm monitoring will be developed. Data obtained with such systems could be analyzed in uniform fashions to determine (1) absolute freedom from AF, (2) AF burden in individual patients, and (3) prevalence of AF in treated populations.[66]

Ablation Technology and Intraoperative Assessment

Current surgical ablation technology has several limitations. No single ablation device enables creation of all lesions from the epicardial aspect with ease of use, absence of collateral damage, and guaranteed lesion transmurality. In addition, because we do not yet have the capability to perform real-time epicardial mapping in the operating room, we cannot tailor ablation to patients' particular electrophysiological characteristics. Although anatomically

based approaches are usually successful, it is likely that a strategy based on both anatomic and electrophysiological findings will improve results.

Minimally Invasive Approaches

While most operations that include both mitral valve surgery and ablation are performed through a sternotomy, it is now possible to perform minimally invasive procedures. This may be achieved via a small right thoracotomy[67] or through a partial upper sternotomy. These procedures have been performed with bipolar RF, unipolar heat-based systems, and cryothermy.[67,68] However, they are technically challenging as minimally invasive or keyhole approaches using current technology are hampered by difficult access to the posterior left atrium and LAA. Refinement in ablation technology is necessary to facilitate widespread application of minimally invasive cardiac surgery with ablation.

Conclusions

Atrial fibrillation is common in patients presenting for cardiac surgery. Left untreated, AF increases morbidity and jeopardizes survival. Recent data demonstrated that AF ablation improves outcomes in these patients. Therefore, virtually all cardiac surgery patients with AF should have AF ablation. The cut-and-sew maze procedure is obsolete, replaced by operations that use alternate energy sources to create lines of conduction that block rapidly with little risk of bleeding. Minimally invasive cardiac surgery with AF ablation is now possible. Continued progress will facilitate tailored ablation approaches for individual patients and further improve results.

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23

Epicardial Atrial Fibrillation Ablation

Patrick M. McCarthy and Jane Kruse

Abstract: Since the first Cox maze procedure was performed in 1987, the success of the surgery has consistently been demonstrated by surgeons at many institutions. Despite the impressive outcomes, this surgery has not been widely adopted because of the complexity of the procedure. Development of energy sources to produce scar lines that replace the "cut-and-sew" incisions has generated interest in development of minimally invasive beating heart surgical approaches. Using these energy sources with only an epicardial, off-pump approach is still in the early state but is an area of intense clinical investigation. Hybrid approaches combine surgical epicardial ablation with endocardial catheter ablation by electrophysiologists to perform more of the Cox maze lesions and utilize mapping to ablate gaps. While early follow-up data suggest success rates of 85%, lesion sets to provide the best outcome are not yet defined. Data on the long-term effectiveness of these approaches are not yet available.

Keywords: Epicardial ablation; Ganglionated plexuses; Left atrial appendage; Maze procedure; Surgery for atrial fibrillation; Thoracoscopic.

Introduction

The excellent freedom from late symptomatic atrial fibrillation and freedom from stoke associated with the classic Cox maze procedure has set a level of success that surgeons would like to reproduce with simpler techniques, using new technologies through smaller incisions, without using cardiopulmonary bypass.[1–5] Progress toward less-invasive maze procedures have been iterative, first using a right thoracotomy with cryoablation from an endocardial approach, then with partial sternotomy incisions, and now small thoracotomy or port access epicardial beating-heart approaches.[6–9] This chapter describes what is known about these procedures and the reported results. However, the technologies to facilitate reproducible, epicardial, transmural lesions are in their infancy and are rapidly evolving. Much of what is currently attained in the field is not yet published.

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Concepts Behind Epicardial Approach to Atrial Fibrillation Ablation

There are three potential targets for epicardial ablation: the creation of transmural ablation lesions under direct or thoracoscopic visualization; closure or obliteration of the left atrial (LA) appendage, the source of strokes in many patients; and ablation of the ganglionated plexuses (GP), the underlying mechanism of atrial fibrillation in some patients.[7–11] The minimal transmural ablation is bilateral pulmonary vein isolation (PVI), similar to wide-area circumferential ablation (WACA) performed in catheter ablation. This most commonly is performed using bipolar radio-frequency clamps to isolate the left and right pulmonary veins.[8] This can be performed with small bilateral thoracotomies with direct visualization or additional visualization using a thoracoscope. Nascent attempts to perform this through port access are also ongoing.[46] Using a bipolar radio-frequency clamp, it is currently difficult to perform more extensive lesions, especially through a small thoracotomy; however, using purse-string sutures placed in various locations in the LA and RA, more extensive lesions can be performed by placing one jaw of the clamp within the heart (endocardial surface) and the other jaw outside the heart (epicardial) to create a long lesion.

While PVI is the minimal lesion, new technologies try to create a more extensive "box" lesion that encircles and electrically isolates a cuff of posterior LA wall and the four pulmonary veins.[9] A variety of unipolar technologies can be used, including cryoablation, unipolar radio-frequency, microwave, laser, and high-intensity focused ultrasound (HIFU).[7,10,12] Laser and HIFU energy are focused; the others are unfocused. Unfocused energy sources, in particular when they are not applied with direct visualization, may lead to collateral damage, including to the esophagus and left main coronary artery.[13–15] Most important, epicardial unipolar energy sources may have a difficult time creating transmural lesions.[16–21] Circulating intracavitary warm blood can make it difficult to create reproducible transmural lesions with each of these energy sources. Focused unipolar energy sources such as HIFU and laser have theoretical advantages but have a fixed depth of penetration, which may be a problem considering the variability of normal and pathological atrial wall thickness.[22] These energy sources also may be applicable to other ablation lines in the LA and RA.[9,22]

There has been a remarkably low incidence of late stroke in patients who had the classic maze procedure.[2–5] The reason patients have such a low stroke rate may be multifactorial, including the resumption of sinus rhythm and LA systole and the contribution from removal of the LA appendage.[5,23] The LA appendage has been a surgical target to reduce strokes and for new percutaneous LA appendage closure devices.[24–26] As part of the epicardial approach, surgeons can treat the LA appendage either via suture ligation, ligation with a loop, stapling, or new devices developed for this but not yet released.[27,28] It has never been clearly demonstrated, however, whether closure of the LA appendage in itself significantly reduces the risk of stroke. Furthermore, suture ligation is sometimes incomplete and may lead to thrombus formation in the LA appendage with extension into the LA.[29,30] Stapling may be dangerous in some patients with a broad-based LA appendage, especially in elderly patients

with a fragile appendage that may suddenly bleed, with severe consequences. New devices that have been developed for epicardial application through port access may allow for a more complete closure of the LA appendage, ease of use, and safer application, but these have not yet clinically been tested and are in development.[31,32]

The GPs contain efferent parasympathetic and sympathetic neurons and afferent neurons, which are found in the ligament of Marshall, which is easily identified by the surgeon, and in the fatty epicardial tissue at the junction of the pulmonary veins and LA.[11,33,34] Stimulation of the GPs has been shown to result in changes in cardiac rhythm, including the onset of atrial fibrillation.[33–35] It was noted during catheter ablation for atrial fibrillation that pulmonary vein denervation enhanced the long-term success when treating patients with lone atrial fibrillation.[33,36] Many surgeons therefore have now added GP mapping and ablation to the epicardial approach to atrial fibrillation.

In concept, then, epicardial approaches to atrial fibrillation include at minimum the equivalent of WACA and frequently are associated with closure of the LA appendage and ablation of the GPs (Figure 1). Unipolar energy sources allow for a "box" lesion (Figure 2) that encircles all four pulmonary veins and isolates the posterior LA wall, another potential source for atrial fibrillation triggers. Unipolar energy can also be used to create an ablation line from the superior vena cava down to the inferior vena cava and across the free wall of the RA (similar to the Cox maze lesion). Currently, all epicardial approaches have limited effectiveness in creating the LA and RA isthmus lesions because of overlying structures, including the circumflex and right coronary arteries and the potential for injury to branches of these vessels by the energy source. Theoretically, HIFU does not cause this injury but has not been tested in this

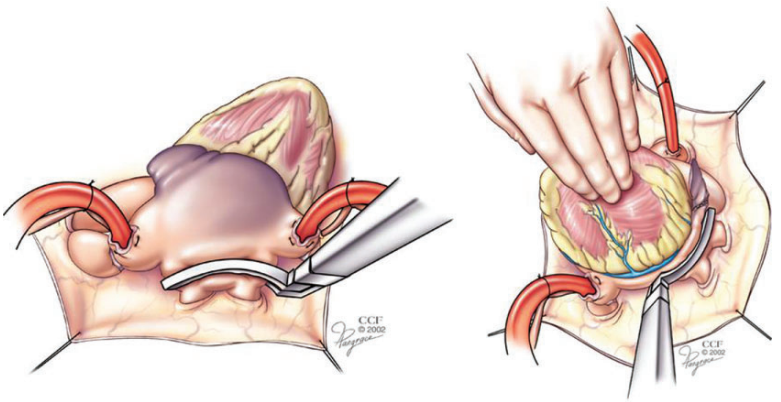

Figure 1 The right (*right panel*) and left (*left panel*) pulmonary veins can be electrically isolated using bipolar radio-frequency clamps. On the right side, the dissection has to be carried out below the inferior vein cava and above the right superior pulmonary vein at the pericardial reflection. On the left side, the ligament of Marshall is divided in the space above the left upper pulmonary vein and dissected free of the pericardial reflection. In both instances, the clamps are placed on the antrum and not directly on the pulmonary veins

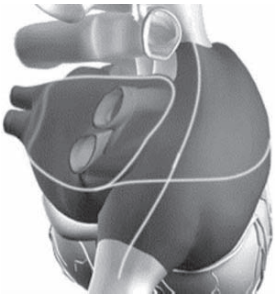

Figure 2 All four pulmonary veins and the posterior left atrial wall can be electrically isolated with a "box" lesion by applying energy just above all four pulmonary veins. In addition, with unipolar energy sources such as laser, microwave, and high-intensity focused ultrasound, additional right atrial lesions can be placed, such as the ablation line from the superior vena cava down to the inferior vena cava and another across the free wall of the right atrium. (Reproduced from ref. 9 with permission *Ann Thorac Surg*.)

setting, particularly not for patients who may have a nonobstructive burden of atherosclerotic plaque that potentially could be disrupted.[22]

Experimental Studies

Bipolar radio-frequency clamps have been used to create transmural lesions on the beating heart in animals.[37,38] Using purse-string sutures, lesions nearly identical to the Cox maze procedure were performed without cardiopulmonary bypass. In six minipigs, magnetic resonance imaging (MRI) assessment revealed no coronary artery stenosis, despite clamping the circumflex coronary artery and applying bipolar radio-frequency energy. Furthermore, there was no histological damage to the arteries or to the coronary sinus (Figure 3). Despite the experimental work, clinicians have been reluctant to cross the coronary arteries using the bipolar radio-frequency devices until this is more clearly demonstrated to be safe.[37–40]

Microwave has also been used to create lesions from the epicardial surface in animals. In one experiment in 14 dogs, epicardial microwave ablation was performed using the intuitive surgical robot.[41] Complete PVI, however, was difficult to perform. The authors noted that incomplete isolation decreased atrial fibrillation duration and lengthened the atrial fibrillation cycle length. However, complete isolation was necessary to prevent induction of atrial fibrillation. Again, emphasizing the importance of creating transmural lesions, microwave was shown to be effective in cardioplegia-arrested hearts.[42] It was not consistently effective in the beating-heart model. Despite 90 s of prolonged ablation, only 20% of the atrial fibrillation lesions were transmural in the beating heart. In the arrested heart, however, 94% of atrial lesions were transmural after 45 s, and 100% were transmural at 90 s.

Additional studies have been performed using an infrared coagulator.[43] The overlapping linear lesions were demonstrated by both electrophysiological and

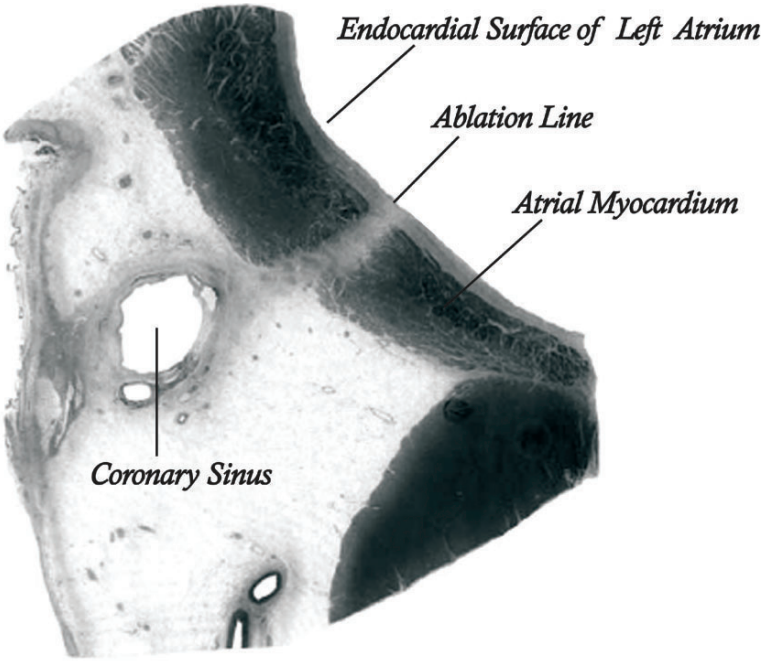

Figure 3 In an experimental study, bipolar radio frequency was placed across the coronary sinus and the circumflex coronary artery, and ablation energy was applied. The ablation line is well demarcated, and there was no apparent damage to the coronary sinus or to the coronary arteries. Although experimentally this has been demonstrated, clinicians have been reluctant to compress and ablate the coronary artery. (Reproduced from ref. 38 with permission *Ann Thorac Surg*..)

histological study to be transmural, and atrial fibrillation could not be induced after ablation. An argon-based linear cryoablation clamp was used to isolate the pulmonary veins and LA appendage in six dogs.[44] Additional linear lesions were also placed with a malleable probe. Conduction block was demonstrated acutely for 30 days; however, tissue sections showed transmurality in 63% of cryoclamp lesions and 84% of linear lesions. Areas of thickened tissue (such as the RA appendage) were more prone to failure than thinner tissue because of the "heat sink" of warm blood. Achieving epicardial transmural lesions using cryoablation is problematic.

Early Clinical Results

There is currently a moderate amount of clinical activity in epicardial approaches to atrial fibrillation ablation. There is little in the literature at this point, although several manuscripts are in progress. In 2005, the first series of bilateral PVI was reported.[8] Through bilateral thoracotomy incisions, using endoscopic visualization for a portion of the procedure, both pairs of pulmonary veins were electrically isolated using a bipolar radio-frequency clamp. This was performed off pump on the beating heart in 27 patients, and in this

early report only 3-month follow-up was available. Of the patients, 91% were free from atrial fibrillation, and 65% were off antiarrhythmic drugs. The method of follow-up on these patients was by electrocardiogram (ECG) (n = 10) or transtelephonic monitoring (n = 11).

In 2006, a series of 50 patients who were treated using a box lesion set of all four pulmonary veins employing epicardial microwave energy was reported.[9] Of this group of patients, 33% had paroxysmal atrial fibrillation, and 17 patients had "continuous" atrial fibrillation. At last follow-up, 79.9% of the patients were in sinus rhythm, but this included patients who had reintervention (27%, including catheter ablation or a classic maze procedure). The freedom from atrial fibrillation and reintervention was only 49%. There was no operative mortality in either series.[8,9] In the series with bilateral PVI through thoracotomy, the LA appendage was stapled; GP ablation was not routinely performed at that time.[8]

A prospective series of 103 patients received treatment with HIFU concomitant to other operations, including 46 mitral valve, 7 coronary bypass, and 2 atrial septal defect (ASD).[22] Atrial fibrillation was permanent in 74% and paroxysmal in 21%. In 35 (34%), an additional lesion was placed to the mitral valve annulus from the epicardial surface using a HIFU handheld probe. As judged by ECG or Holter monitor, at 6 months freedom from atrial fibrillation overall was 85%. For those with the additional mitral valve annular lesion, freedom from atrial fibrillation was 88%. There were no complications related to the use of bipolar radio frequency, microwave, or HIFU in these series.[8,9,22] In a series of patients with stand-alone surgery for atrial fibrillation at Northwestern Memorial Hospital, HIFU was utilized in 16 patients from February 2005 to June 2005. Freedom from atrial fibrillation at 12 months was 75%, but freedom from atrial fibrillation and reintervention was only 37% at 10- to 22-month follow-up.

Limitations to Epicardial Approach

There are several practical problems with the epicardial approach to atrial fibrillation ablation. For patients with prior mediastinal surgery, adhesions may not allow ideal contact with the LA epicardial surface. If bilateral PVI is performed, these adhesions can be lysed under direct visualization to allow for bilateral PVI, but this will be much more difficult with port access procedures. Similarly, visualization is difficult, especially through small bilateral thoracotomies, in obese patients. Patients with congenital heart abnormalities also may be difficult to treat from the epicardial approach, such as a left superior vein cava. Finally, the technology must be in direct complete contact with the pulmonary veins to create the box lesions using unipolar energy, and anatomic variations in the structure of the LA just superior to all four pulmonary veins potentially lead to areas of incomplete contact (Figure 4). The technologies themselves need to be able to create a complete transmural lesion on the beating heart despite variations in LA wall thickness and other factors such as the "heat sink" that affects cryoablation. Managing the LA appendage can be difficult, and stapling may be dangerous and has led to occasional major bleeding episodes and fatalities. The LA appendage has variations in the orifice width and quality of tissue; older patients may have friable tissue that may be prone

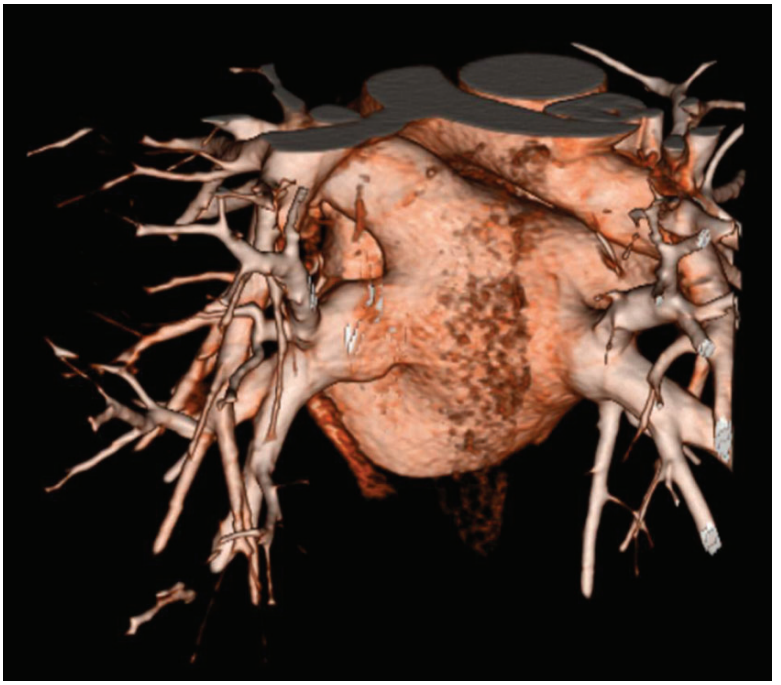

Figure 4 The pulmonary vein anatomy is not always uniform. Irregular areas at the sites of ablation can lead to poor contact of the ablation source with the wall of the atrium. Furthermore, there is variable thickness of the atrial tissue. Both of these practical issues must be dealt with when developing epicardial ablation strategies with the goal to achieve 100% transmural lesions

to bleeding. New devices should help address the appendage in a more routine fashion with safer application and more complete obliteration.

Future Directions

Work continues on approaches to create a box lesion through a small right thoracotomy or through ports. Steps to the procedure would include opening the right side of the pericardium, dissecting underneath the superior and inferior vena cavae, passing a guide from the right side to the far left side of the pericardium (underneath the LA appendage) and using this guide to advance the energy delivery system to create a 360° circumferential ablation. Potential energy sources include HIFU, laser, or microwave. Through the right side, additional lesions also can be placed along the RA (superior vena cava down to inferior vena cava and RA free wall lesions). The technologies are still not standardized to create transmural lesions at the LA or RA isthmus from the epicardial approach. Research is under way to employ technology through a separate port access left thoracic incision such that the LA appendage can be occluded with new devices. Through both approaches, the GP can be mapped and ablated. Our approach at Northwestern Memorial Hospital is to do a "hybrid" procedure with the surgeons creating box lesions of all four pulmonary

veins, closing the LA appendage, and ablating the GPs. The electrophysiologist will create LA and RA isthmus lesions, map to confirm conduction block, and perform focused ablation of any additional triggers.

Reporting "success" also needs to be standardized between catheter and surgical ablation. Recent publications will help in this regard.[12,45] Only through rigorous analysis of our results will we be able to identify the risk factors for failure, identify the sources of those failures, and then correct them in the future.

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24

Minimally Invasive Surgical Treatment of Atrial Fibrillation

Randall K. Wolf

Introduction

Over the last decade, there have been important advances in the interventional treatment of atrial fibrillation (AF). Success with catheter ablation led cardiac surgeons to explore concomitant surgical left atrial isolation for treatment of AF as an adjunct to open heart surgery for valve or coronary revascularization procedures.[1] Prior to this paradigm shift, patients with AF were treated medically with either rhythm control or rate control with anticoagulation or, occasionally, surgically with a Cox maze procedure. Although reported long-term results of the Cox maze are good, the method of long-term follow-up has been challenged.[2–5] In addition, the invasiveness and technical aspects of the Cox maze procedure have limited its application.

Most surgical ablation is performed in the concomitant setting. However, when one considers all the patients who present to the operating room with AF and if all underwent concomitant ablation, at most 40,000 individuals would be treated annually. At present, 2.3 million individuals have AF in the United States, and this number is exponentially increasing. Therefore, there is growing interest in stand-alone surgical ablation of AF. The lone AF patient who is symptomatic usually has intermittent AF and often has pulmonary vein (PV) triggers. This is in contrast to the concomitant patient who has long-standing persistent or permanent AF and more extensive changes in the atrial substrate. Our focus has been on minimally invasive, epicardial approaches to the patient with paroxysmal AF and potential PV triggers.

Minimally Invasive Epicardial Ablation

Bipolar Radio Frequency

Initial laboratory experiments in 1999 demonstrated that a bipolar radio-frequency (RF) clamp can be used to isolate the PVs and their antra. The acute results were promising, and the lesions reliably transmural (Figs. 1 and 2). Chronic preclinical studies confirmed these findings.[6] Building on this work, clinical application of bipolar RF for surgical ablation in the concomitant setting became common. Subsequent advances in technique and technology led

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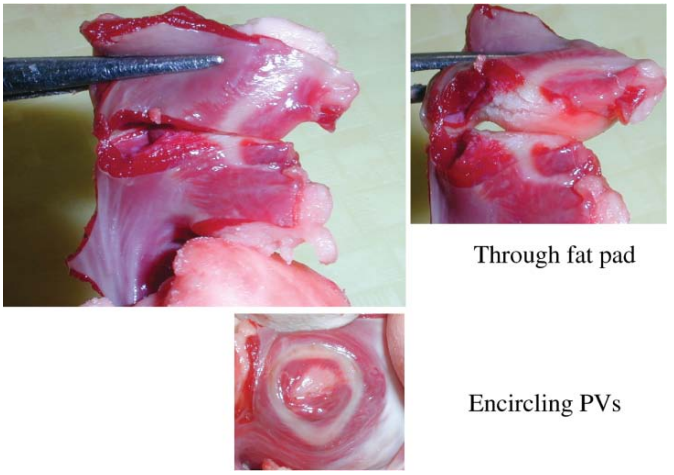

Figure 1 Gross pathology after dry bipolor clamp technique in the acute beating heart porcine model: transmural lesions. *PV* pulmonary vein.

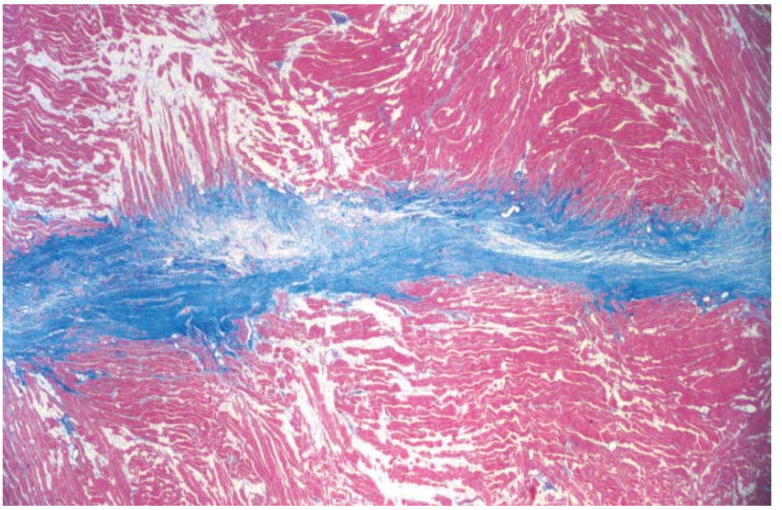

Figure 2 Histology with trichrome staining in the acute beating heart porcine model: transmural lesions.

to the development of a stand-alone procedure that included video-assisted bilateral PV isolation and left atrial appendage (LAA) exclusion for the minimally invasive treatment of AF.[7] The PV isolation was achieved bilaterally by using a dry RF device (Atricure, Cincinnati, OH) applied through a bilateral VATS approach. Endoscopic instruments (Cardiovations, Ethicon Inc.) were used through ports. The surgeon's hands did not enter the chest. The LAA was removed with a surgical stapler (Ethicon-Endosurgery, Cincinnati, OH). At average 3-month follow-up in 23 patients treated with this procedure, 21 were free of AF by objective endpoints (electrocardiographic [ECG] and home monitoring); the short-term success was 91%.

The current bilateral dry bipolar VATS technique (Wolf minimaze) is designed to allow cardiac surgeons to achieve minimally invasive surgical AF cures safely without the absolute necessity of mastering totally thorascopic skills. The bilateral non-rib-spreading working ports in the third intercostal spaces are positioned directly over the PVs and on the left side over the LAA to allow direct (three-dimensional) visualization of these important structures. A camera provides additional illumination as well as visualization outside the area covered by the working port. In our experience, patients can be discharged on the second postoperative day with little or no discomfort.

Intraoperative electrophysiological (EP) testing is an important component of minimally invasive epicardial ablation. Following a collaboration with Drs. Jackman and Scherlag at the University of Oklahoma, we have incorporated intraoperative ganglionic plexus (GP) testing, partial cardiac denervation, and objective confirmation of block (B. J. Sherlag, personal communication).[8]

Based on the technology developed to localize GPs in a canine model, Dr. Scherlag and our team created a map to record the epicardial position of these GPs in each patient during the minimally invasive AF procedure. After isolation, we confirm GP isolation. A second part of the intraoperative EP testing is designed to objectively document PV block after PV isolation. If the patient is in sinus rhythm, attempting to pace the atrium from the isolated PV can easily confirm isolation. If the patient is in AF, testing for block can be achieved with sensing (Fig. 3).[9]

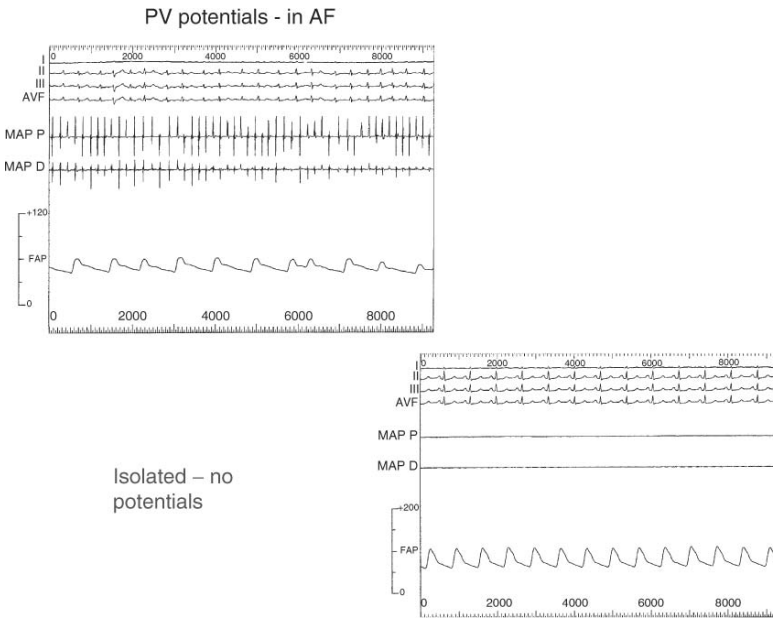

Figure 3 Introperative pulmonary vein electrocardiographic (ECG) documentation of pulmonary vein (PV) potentials and subsequent isolation after dry clamp application. *AF* atrial fibrillation.

We recommend the electrophysiologist be involved with testing and assessment in the operating suite. We have also found that in surgical cases referred after failed catheter ablation for AF, we have been able to identify the nonisolated PV(s) at the time of testing during the minimally invasive surgical AF procedure. This is helpful feedback to the electrophysiologist. This testing will also help ensure some consistency when reporting results. This GP isolation during the AF procedure addresses one of the possible mechanisms of AF. Directed partial cardiac denervation has the possibility of revolutionizing our concept of the triggers and targets in the surgical treatment of paroxysmal AF.

Our routine preoperative workup includes transthoracic echo within the past year, ECG, and stress test if history dictates. All patients undergo 64-slice computed tomography (CT) 1 to 2 days prior to the minimally invasive procedure to rule out significant coronary artery disease (CAD), PV stenosis (in patients with a history of catheter ablation), and thrombus in the LAA and to evaluate the PV anatomy.[10] We no longer rely on transesophageal echocardiography (TEE) as the CT gives additional information, is noninvasive, and helps tremendously in planning the procedure, such as documentation of posterior PV branches and anomalous coronary anatomy.

Although catheter-based techniques are the least invasive approach to the heart from the aspect of skin incisions, it can be argued that epicardial discrete surgical isolation of the antrum utilizing a bilateral VATS technique with dry bipolar RF (Wolf minimaze) is less operator dependent and therefore could result in more consistent transmurality of lesions with lower risk for proarrhythmia. Indeed, scarring, especially without consistent transmural lesions and skip lesions, can explain the marked proarrhythmias experienced by some patients after catheter ablation techniques. We believe this difference in approach accounts for the low proarrhythmia rate after minimally invasive surgical antrum exclusion. The surgical approach also reliably treats the autonomic nerves, which are epicardial. We hypothesize that treatment of the GPs has played a factor in the high cure rates we are experiencing in both short-term and long-term follow-up. Postoperative EP diagnostic mapping has been performed on three patients at least 6 months after Wolf minimaze procedure (Fig. 4). In these three patients, complete isolation of all PVs was documented, supplying further evidence that the dry bipolar VATS technique is durable.

Other Approaches to Epicardial Ablation

A variety of alternative minimally invasive surgical approaches has been developed for stand-alone ablation of AF. Microwave, cryotherapy, and dry bipolar RF have been used in concomitant ablation and have been adapted for minimally invasive approaches. However, not all energy sources that perform adequately in open procedures on the arrested, empty heart provide transmural lesions in the beating heart. Doll et al.[11] found that microwave and cryotherapy applied epicardially to the beating heart were not reliable, and that they resulted in histological damage to the esophagus and coronary arteries. In contrast, dry bipolar RF resulted in complete transmural lesions and no histological damage to surrounding tissues. These findings can be explained. Blood in the beating heart acts as an infinite heat sink, making transmural lesions problematic. Using a bipolar clamp and dry RF, there is no heat sink as the blood is excluded from the treated area. In addition, using a dry bipolar

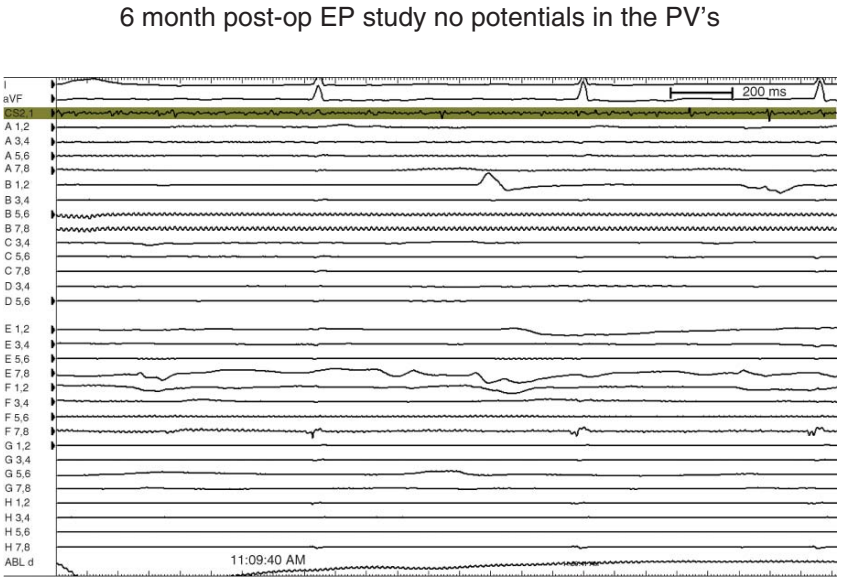

Figure 4 A 6-month postoperative electrophysiological (EP) study demonstrating no potentials in the pulmonary veins (PVs), documenting the efficacy of the dry bipolar technique.

clamp there is minimal lateral thermal spread, so the energy application is limited to the treated area.

Incomplete lesions (nontransmural) and skip lesions with certain energy sources have clinical consequences. Pruitt reported one-year results of attempted AF ablation utilizing a minimally invasive microwave thorascopic procedure. The cure rate was a dismal 42% (J. C. Pruitt, personal communication).

The various "minimally invasive" techniques used currently also differ in LAA treatment. We have been a strong proponent of LAA exclusion or excision. Some patients are referred because of inability to tolerate coumadin in the background of transient ischemic attacks or stroke. The main reason for surgical referral in this subset of patients is to exclude the LAA as a source of repeated cerebral events. In addition, until we achieve 100% cures with these minimally invasive surgical AF techniques, it seems prudent to incorporate LAA treatment during the minimally invasive procedure.

It is anticipated that over time minimally invasive epicardial AF ablation will evolve to a thorascopic beating heart procedure applying devices that reliably deliver transmural lesions with short application times (to avoid the use of intraoperative anticoagulants). However, it must be kept in mind that patients who choose a minimally invasive AF surgical approach generally are otherwise in good health. This scenario is akin to operating on a healthy 8-year-old with an atrial septal defect (ASD). There is no room for error, and the mortality must be zero. Evolution of minimally invasive AF techniques must be safe and effective, and the desire to achieve smaller incisions must be tempered by the absolute need to ensure safety with a less-invasive procedure.

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Section VI

Imaging, Technologies, and Associated Arrhythmias

25

CT and MR Images in Atrial Fibrillation

Hsuan-Ming Tsao and Shih-Ann Chen

Abstract: Catheter ablation of the left atrium (LA) has emerged as an important therapeutic option to treat atrial fibrillation (AF). The efficacy and safety of this technique highly depend on the understanding of morphological characteristics of pulmonary veins (PVs) and the LA. Magnetic resonance angiography (MRA) and multidetector computed tomography (CT) can readily provide the useful information in terms of (1) the anatomic variations of PV and LA, (2) the topographic relationship between LA and the adjacent structure, (3) procedure-related complications, and (4) the morphological remodeling process. Interventional electrophysiologists should be familiar with the normal and variant patterns of PVs, the important landmarks within the LA, and the spatial relationship among the LA, esophagus, and surrounding vascular structures before the ablation. In addition, we can understand the morphometric alterations of PV/LA and drawbacks after ablation by utilizing the CT/MRA images.

Keywords: Atrial fibrillation; Computed tomography; Left atrium; Magnetic resonance angiography; Pulmonary vein.

Introduction

Evolving techniques in catheter ablation of atrial fibrillation (AF) have led to expansion of the knowledge of left atrial (LA) anatomy.[1–4] Understanding the morphological characteristics of the LA in detail not only can help achieve a more efficient and successful ablation but also can prevent potential procedure-related complications. Noninvasive imaging modalities, including magnetic resonance angiography (MRA) and multidetector computed tomography (MDCT), are good and powerful for depicting the pulmonary veins (PVs) and LA and provide a valuable road map before the catheter ablation of AF.[5–11] The advantages of cardiac computed tomography (CT)/MRA are as follows: (1) provide preprocedural imaging of the anatomic characteristics of PV and LA; (2) disclose the anatomic relationship between LA, esophagus, and adjacent vascular structures; (3) understanding the morphological remodeling of PV and LA in AF; (4) detect postprocedural complications.

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Anatomic Characteristics of Pulmonary Veins

It has been well recognized that the ectopic foci from the myocardial sleeve of PVs can initiate AF. Elimination of these ectopic triggers can cure a subset of AF. Therefore, the interventional therapy of paroxysmal AF has been first focused on the interruption of electric conduction by isolating the AF initiators of PVs from LA tissues. The detailed information of PV anatomy and the relationship between PV and LA is mandatory for the mapping and ablation procedures.

The PV ostia are ellipsoid with a longer superio-inferior dimension, and funnel-shaped ostia are frequently noted in AF patients.[7] The right superior PV is close to the superior vena cava or right atrium; the right inferior PV projects horizontally. The left superior PV is close to the LA appendage, and the left inferior PV courses near the descending aorta. These observations are essential for a transseptal procedure, placement of a circular mapping catheter, and application of energy around or outside the PV ostia.

Morphology Patterns of Pulmonary Vein Trees

Although the morphologies of PVs have a certain basic pattern, they are more variable than the arteries. Variations of PVs can be readily demonstrated by cardiac CT/MRA (Table 1). The variability can substantially influence the success rate of catheter ablation if the variant veins are inadequately treated. Several studies reported the existence of supernumerary right PVs, with the incidence ranging from 18% to 29% (Figure 1A).[5,8,11–14] Tsao et al. utilized MRA to demonstrate the PV variant of a discrete right middle PV (RMPV) with an independent orifice other than the typical two PV ostia on the right side. The ectopic focus originating from the RMPV could initiate AF, which was cured by catheter ablation of the RMPV.[8] In addition, a significantly longer distance between the PV ostium and first branch was demonstrated for left versus right PVs.[5] Perez-Lugones et al. showed that multiple ramifications and early branching of right inferior PV were observed and this might explain the low incidence of firing of right inferior PV.[15]

A common trunk of the left or right PVs was also disclosed by the CT/MRA images. The common ostium is more frequently found on the left-side PVs (6% to 35%) and results in a broad PV–atrial junction (Figure 1B). The common left PV was reported to be a consistent origin of arrhythmogenic ectopy.[16]

Table 1 Anatomic variations of pulmonary veins (PVs).

Supernumerary PVs	
Right	18–29%
Left	3%
Common ostium of	
Right PVs	<1%
Left PVs	3–35%
Early branching of right inferior PV	66–99%
“Right top”PV	3%

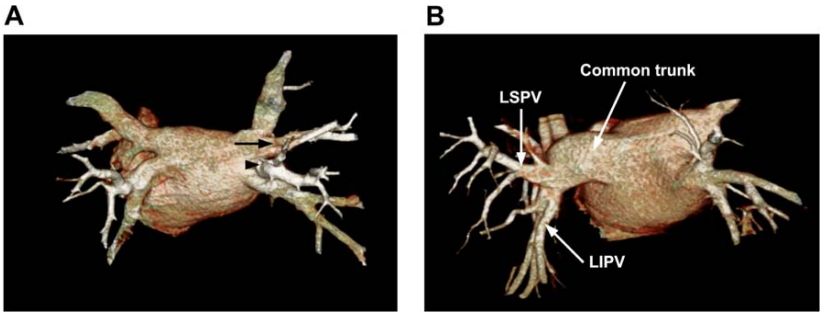

Figure 1 Volume rendering technique of multidetector computed tomography shows the pulmonary vein (PV) variants. **A** Additional right PVs caused by a right middle PV (arrow), and superior segment right inferior PV (arrow head). *LIPV* left inferior pulmonary vein, *LSPV* left superior pulmonary vein. **B** A common trunk of left PVs results in a broad PV–atrial junction

These anatomic variations are important in planning catheter ablation of AF. Localization of the true PV–atrial junction in these patients can be more accurate with the assistance of the three-dimensional (3-D) images prior to mapping and ablation procedures.

Anatomic Relationship Between the Left Atrium, Esophagus, and Adjacent Vascular Structures

Atrioesophageal fistulas have been reported during intraoperative radio-frequency ablation of AF using the endocardial approach, percutaneous PV isolation, and LA ablation.[17–19] An atrioesophageal fistula can cause an air embolism with a stroke, mediastinitis, or gastrointestinal bleeding and is associated with a high mortality rate. Thus, understanding the anatomic relationship between the esophagus and PV/LA may provide useful information for avoiding esophageal injury during the catheter ablation procedure. Several studies had demonstrated the close relationship between the posterior LA, coronary sinus (CS), PVs, and esophagus by CT scan (Figure 2A–C).[20–23] Although the peristalsis and dynamic movement of the esophagus was suspected to influence the results, the anatomic parameters about the relation between esophagus, PV, and LA posterior wall are useful for deciding the location of the ablation lesions in the LA and understanding the possible risk of esophageal injury.

The closeness of the LA roof and right pulmonary artery (RPA) was also revealed by CT imaging (Figure 3A). Although there were no reported cases of injury to the RPA, it may be another potential structure that can be damaged when more powerful energy sources are introduced to make a deep lesion in the LA roof. It is likely that the cooling effect of the rapid blood flow may protect the RPA from heat injury. However, to avoid the potential hazard of RPA injury, ablation at LA roof, especially near the right superior PV orifice where the distance to the RPA is the shortest compared to the other parts of the roof, should be performed with care.

In addition, the closeness of the LA appendage orifice and the proximal left circumflex artery has been demonstrated by CT images (Figure 3B).

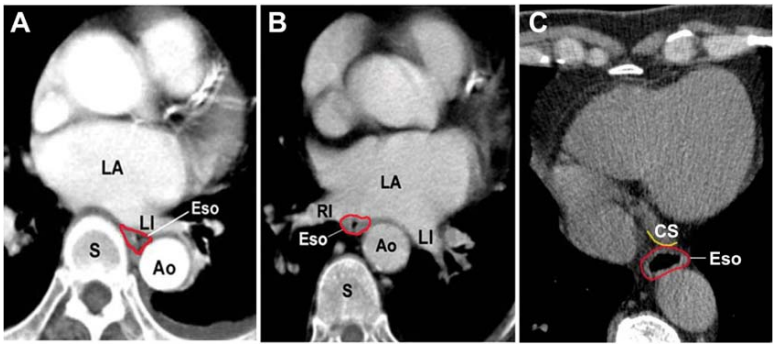

Figure 2 Cardiac computed tomographic (CT) scan with axial views that show the esophagus (Eso; red circle) courses close to the left inferior (LI) pulmonary vein (PV) and posterior left atrium (LA) (**A**), right inferior (RI) PV and posterior LA (**B**), and coronary sinus (CS) (**C**). *Ao* aorta, *S* spine

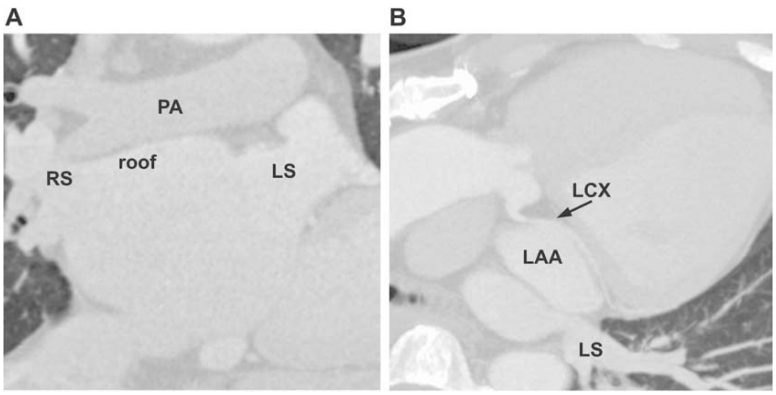

Figure 3 The close anatomic relationship between left atrium (LA) and adjacent vascular structures revealed by computed tomographic (CT) scan. **A** LA roof and pulmonary artery (PA). **B** LA appendage (LAA) and left circumflex (LCX) coronary artery. *LS* left superior, *RS* right superior

Takahashi et al. reported that the left circumflex coronary artery was occluded acutely during ablation within the CS.[24] Because energy applications around the LA appendage had been recently proposed to increase the success rate in treating persistent AF, ablation near the anterior base of the LA appendage orifice must be carried out with caution to avoid any potential risk of left circumflex artery injury.

Morphological Remodeling of Pulmonary Veins and Left Atrium in Patients with Atrial Fibrillation

The ostial geometries of PVs have been comprehensively evaluated by CT and MRA. Tsao et al. first reported the different sizes on MRA images of PVs in control, paroxysmal AF, and chronic AF patients.[25] Furthermore, the significant

dilation of both superior PVs with simultaneous LA enlargement was demonstrated among patients with paroxysmal AF and chronic AF. After successful ablation of arrhythmogenic PV, the dilated (nonablated) PVs could regress during a long-term follow-up.[26] Several reports also proved the morphological remodeling and reverse remodeling process of LA and PVs in AF patients.[27,28]

Detection of Complications After Catheter Ablation

The feasibility and safety of catheter ablation of PVs and LA have been well documented. However, procedure-related major complications, including cerebral emboli, PV stenosis, and pericardial effusion with tamponade, could be encountered occasionally. MRA and CT scan play an important role in disclosing PV stenosis after ablation of AF.[29–33] Acquired PV stenosis after PV ablation was a major concern when radio-frequency energy was applied around or inside the PV ostia. The clinical manifestations of PV stenosis include chest pain, dyspnea, cough, hemoptysis, recurrent lung infection, and pulmonary hypertension. Although a single PV stenosis can be asymptomatic, the severity of clinical symptoms may be related to the number, stenotic degree, and chronicity of the involved veins. MDCT and MRA can effectively delineate the lesions and provide the information for justification of treatment, and these two tools are better than transesophageal echocardiography to detect PV stenosis.[30–33]

Conclusion

The successful outcome of catheter ablation of AF highly depends on the realization of LA and PV anatomy. Advances in imaging technology have improved the quality of cardiac CT/MRA and provided crucial information for electrophysiologists to perform ablations within the LA efficiently and safely. Before the ablation procedures, we should be familiar with the normal and variant patterns of PVs, the important landmarks within the LA, and the topographic relationship between LA, esophagus, and surrounding vascular structures. In addition, we can understand the morphometric alterations of PV/LA and procedure-related complications after ablation by utilizing CT/MRA images.

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26

Integrative Approaches to Imaging
Fluoroscopy, CT, MRI, Echocardiography, and Three-Dimensional Electroanatomical and Noncontact Mapping

Hakan Oral and Fred Morady

Abstract: As a result of the better understanding of the mechanisms in recent years, ablation strategies evolved to eliminate complex arrhythmias such as atrial fibrillation. However, the genesis of atrial fibrillation is often multifactorial and effective treatment may require complex and technically challenging procedures. To better appreciate that anatomy, facilitate mapping and catheter navigation, and minimize radiation exposure, imaging has evolved to play an important role during catheter ablation of atrial fibrillation. In this chapter a variety of imaging modalities and recent developments are discussed.

Keywords: atrial fibrillation, catheter ablation, imaging, CT, MRI, fluoroscopy, anatomy, navigation

Because of the complexity and the multitude of mechanisms that play a role in the genesis of atrial fibrillation (AF), catheter ablation often requires complex lesion sets in the atrium and a three-dimensional (3-D) perspective of the left atrium may be particularly helpful. Therefore, there has been much emphasis on imaging of the heart, specifically the left atrium, to facilitate catheter ablation. Imaging provides (1) identification of the number, location, and size of the pulmonary veins (PVs) and their ostia; (2) a 3-D perspective of the left atrial geometry and anatomical landmarks; (3) the ability to create complex circular or linear ablation lines; (4) identification of the location, proximity, and size of critically important adjacent structures such as the esophagus; (5) a guide for transeptal puncture; (6) less reliance on fluoroscopy, with a decrease in radiation exposure to both the patient and the operator. In this chapter, imaging modalities commonly used in clinical practice are discussed.

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Fluoroscopy

Fluoroscopy has been the time-honored, primary imaging modality for catheter ablation of AF. It is readily available and provides real-time imaging. However, even when biplane fluoroscopy is used, a 3-D appreciation of the left atrial geometry is difficult. Fluoroscopy results in cumulative radiation exposure for both the patient and the operator, which can be substantial when the duration and number of procedures performed are considered. Nevertheless, fluoroscopy has been successfully used as the primary and often the only imaging modality in some centers for PV isolation and linear ablation, with fluoroscopy exposure often longer than 1 h.[1–5]

Pulmonary venography is often performed to define the PV anatomy prior to ablation. Although caution should be exercised to accurately interpret the exact location and number of pulmonary venous ostia, venography provides useful anatomical landmarks. Furthermore, venography can be repeated postablation if there is suspicion of acute PV narrowing or stenosis. Venography can be performed by selective cannulation of each PV using an National Institutes of Health (NIH) or multipurpose catheter. A more practical approach may be nonselective hand injection of contrast material toward the posterior left atrium during adenosine-induced asystole.[6] This approach obviates the need to cannulate each PV. However, adenosine should not be used in patients with asthma or severe obstructive pulmonary disease.

Fluoroscopy has also been used to visualize the position of the esophagus to avoid atrioesophageal fistula as a complication of radio-frequency catheter ablation along the posterior left atrial wall.[7,8] Because it is not clear whether there is a maximum amount of radio-frequency energy or any other type of energy that is safe to deliver near the esophagus, the safest method to avoid atrioesophageal fistula may be not to deliver any energy adjacent to the esophagus.

To determine the position of the esophagus, either a radiopaque probe is placed through the esophagus or the patient is asked to swallow a small of amount of a thick barium paste, which adheres to the mucosa of the esophagus for at least 30 to 60 min (Figure 1).[7,8] The esophagus is a mobile structure in the mediastinum. Fluoroscopy enables real-time dynamic imaging of the position of the esophagus. Since the width of the esophagus may change during the course of ablation, barium paste is useful because it provides real-time imaging of the position of the esophagus in relation to the left atrium.

Rotational angiography has been proposed to facilitate 3-D visualization of the anatomy and catheter manipulation.[9–12] The advantages of this approach is that it can be performed in real-time in the electrophysiology laboratory and may provide a more accurate assessment of the anatomy. However, further improvements in technology will be necessary to be able to record and tag catheter position on the 3-D fluoroscopic image. Obviously, this technique may not completely eliminate the associated radiation exposure. The accuracy of registration of 3-D CT images with fluoroscopic projections was validated.[13] Larger clinical studies will be necessary to determine the utility of this technique during AF catheter ablation.

During AF catheter ablation, lower frame rates (7.5 frame/s) and pulsed fluoroscopy significantly reduce radiation exposure.[14] In one study, the peak skin dose was 1.0 ± 0.5 Gy and 1.5 ± 0.4 Gy in the right anterior oblique and left anterior oblique projections, respectively, during a mean of 68 min of

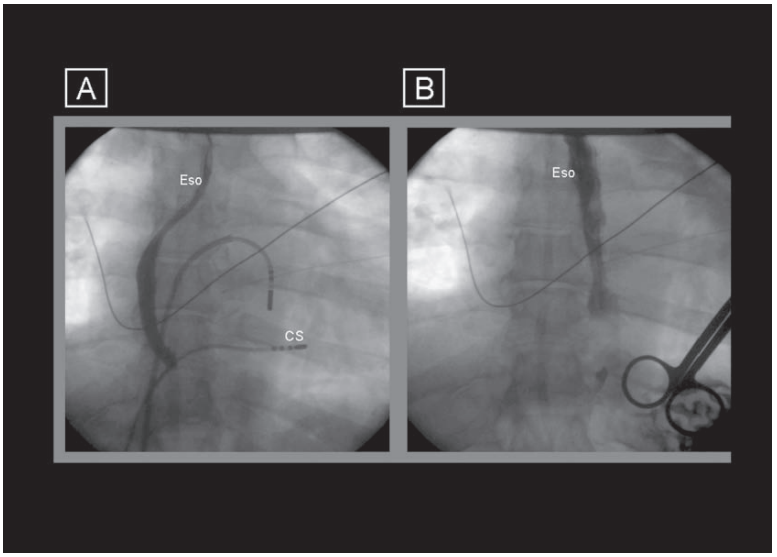

Figure 1 Barium swallow. Barium paste is used to visualize the lumen of the esophagus. The esophagus migrated during the ablation procedure. **A** Before ablation. **B** After ablation. *CS* coronary sinus catheter, *Eso* esophagus. (Reproduced from ref. 7 with permission)

fluoroscopy.[14] The increase in the lifetime risk of malignancy for each 60 min of fluoroscopy exposure was 0.07% for women and 0.1% for men.

Computed Tomography

With the availability of ultrafast 4-, 16-, and 64-row CT scanners and 3-D reconstruction of the scanned images, CT is playing an increasing role in AF catheter ablation.

Computed tomographic images acquired prior to ablation facilitate identification of the number, size, and location of the PV ostia and provide a road map during AF catheter ablation.[15] For example, a separate ostium of the right middle lobe PV is easily recognized and not missed during ablation. Other variations in left atrial anatomy can also be identified using CT imaging. Pouches in the left atrial roof were reported in 15% of patients, and a septal ridge was recognized in 30% of patients in one study.[16] Ridges and variability between the left atrial appendage and the left-side PVs also were recognized.[16,17]

Three-dimensional reconstruction of the CT images has led to better understanding of the anatomical relationship between the esophagus and the left atrium in vivo (Figure 2).[18] Detailed analysis of the CT images demonstrated that the distance between the endocardial surface of the posterior left atrium to the lumen of the esophagus may often be less than 5 mm (Figure 3).[18] Furthermore, the esophagus has a variable course along the posterior left atrium, making it difficult to predict the exact location of the esophagus without any imaging.[18] The correlation between the measurements obtained by CT imaging[18] and during postmortem analysis of human hearts is remarkable and underscores the accuracy of CT imaging.[19] It has been suggested that the position of the esophagus can be identified during the ablation procedure by

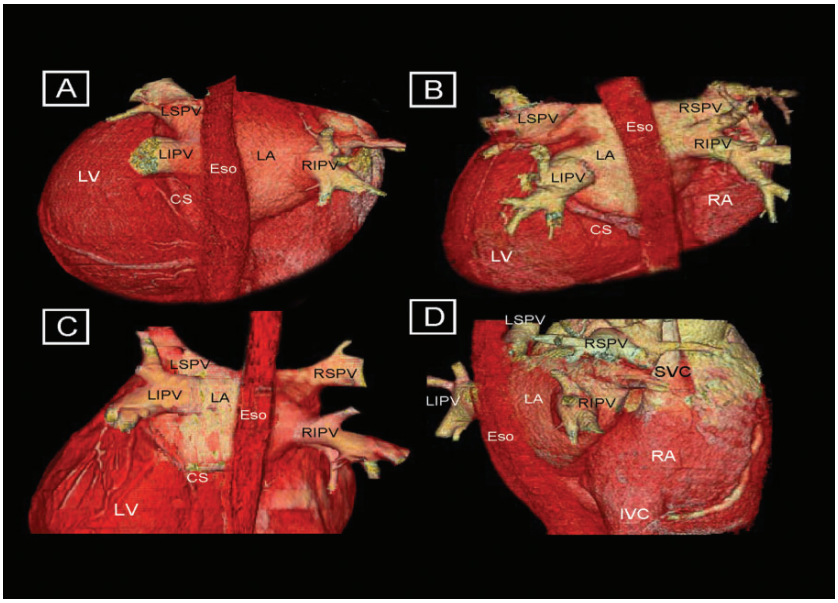

Figure 2 Three-dimensional computed tomographic (CT) images of the esophagus and its relationship to the posterior left atrial wall. The esophagus may be close to the ostia of the left-side pulmonary veins (PVs) (**A**, postero-anterior (PA) projection), may have an oblique course (**B**, PA projection), or may be closer to the right-side PVs (**C**, PA projection). The esophagus wraps around the posterior left atrium along its entire length (Panel **D**). *CS* coronary sinus, *Eso* esophagus, *IVC* inferior vena cava, *LA* left atrium, *LIPV* left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *LV* left ventricle, *RA* right atrium, *RIPV* right inferior pulmonary vein, *RSPV* right superior pulmonary vein, *SVC* superior vena cava. (Reproduced from ref. 19 with permission.)

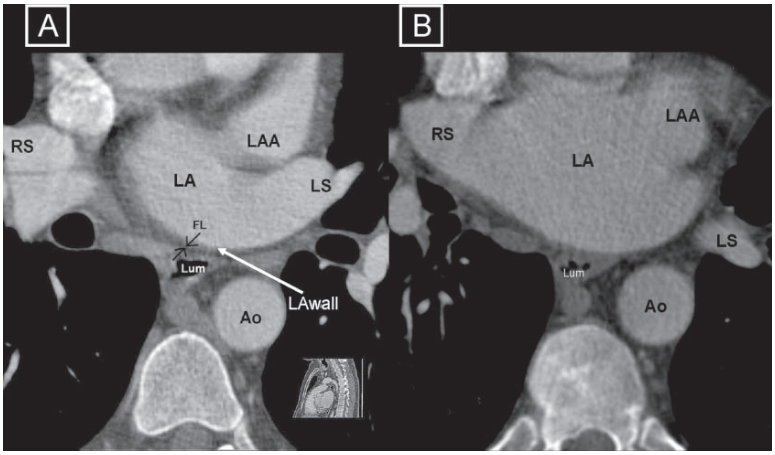

Figure 3 Axial image of the esophagus and the posterior left atrium (LA). Between the left atrial and esophageal lumen (**A**), four different layers are visible: radio-contrast agent within the LA (most radiodense), a thin layer of posterior LA wall (less radiodense than the LA), a thin layer of adipose tissue (radiolucent), and anterior esophageal wall (radiodense). **B** There is no fat layer visible between the LA and the esophagus. Measurements were made using digital calipers. *Ao* aorta, *FL* fat layer, *LAA* left atrial appendage, *LAwall* posterior left atrial wall, *Lum* lumen of the esophagus, *LS* left superior, *RS* right superior. (Reproduced from ref. 19 with permission.)

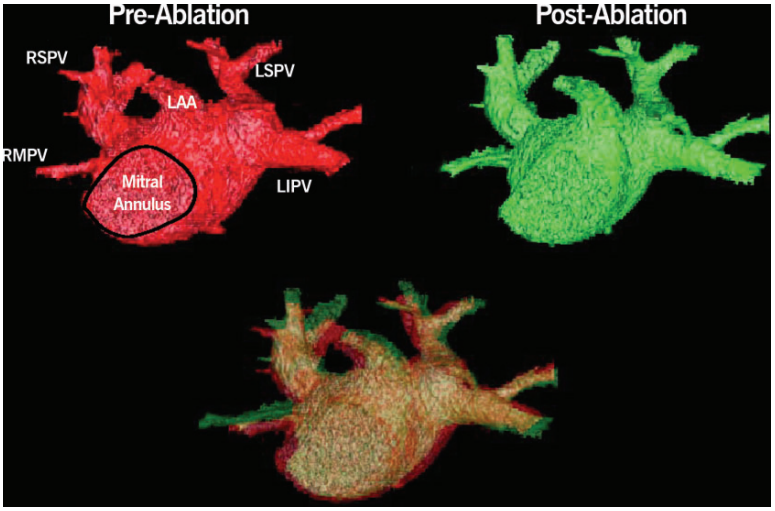

Figure 4 Decrease in left atrial volume and pulmonary vein (PV) ostial area after successful left atrial catheter ablation (LACA) in a patient with chronic atrial fibrillation (AF). Shown are the posteroanterior (**A**) and left anterior oblique (LAO) 40° (**B**) projections of the left atrium and the PVs before (red) and after (green) ablation. Pre- and postablation images are superimposed to better illustrate the changes in left atrial size (lower panels). The left atrial volume was 112 ml before ablation and 98 ml 4 months after ablation. There was no distortion of the PV geometry or any evidence of focal stenosis. *LAA* left atrial appendage, *LIPV* left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *RMPV* right middle pulmonary vein, *RSPV* right superior pulmonary vein. (Reproduced from ref. 22 with permission.)

merging CT images of the left atrium and esophagus acquired earlier. However, the esophagus is mobile, and it is unlikely that the position of the esophagus will be the same at the time of the ablation as during CT scanning performed before the procedure. As a matter of fact, a prior study demonstrated that both the position and the width of the esophagus often change even during an ablation procedure performed under conscious sedation.[7,8] The coronary sinus may also be in direct contact with the esophagus in approximately 50% of patients.[20] Therefore, caution should be exercised when ablation is performed within the coronary sinus.

Computed tomography has been helpful to assess the effects of ablation on left atrial size and geometry in three dimensions. Echocardiography has often been used to assess left atrial size; however, echocardiographic measurements are two dimensional and may not necessarily correlate well with more accurate volumetric information. A prior study demonstrated that maintenance of sinus rhythm 6 months after circumferential PV ablation is associated with a 15% decrease in left atrial volume (Figure 4).[21] There also was a 10% decrease in PV ostial area without any evidence of narrowing, suggesting that the larger PV ostial size in patients with AF probably is a passive phenomenon caused by left atrial dilation.[21]

A novel parameter to assess left atrial transport function is the left atrial ejection fraction as measured by volumetric analysis of the left atrial systole and diastole using dynamic CT imaging.[22] In a prior study, the mean left atrial ejection fraction was reported as 47% ± 5% in subjects without AF. At a mean of 5 months after circumferential PV ablation, there was an approximately

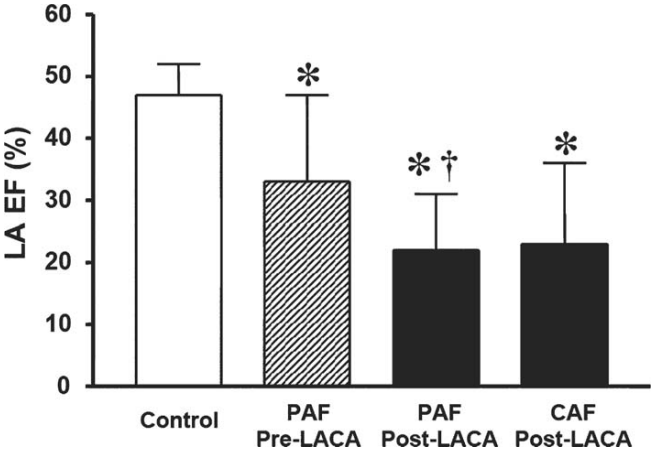

Figure 5 Left atrial (LA) ejection fraction (EF). Left atrial ejection fraction in control subjects (open bar) and in patients with paroxysmal atrial fibrillation (PAF) and chronic atrial fibrillation (CAF) before (hatched bar) and after (solid bar) circumferential pulmonary vein (PV) ablation. $^{*}p < 0.01$ compared to control; $^{\dagger}p < 0.01$ compared to before circumferential PV ablation. *LACA* left atrial catheter ablation. (Reproduced from ref. 22 with permission.)

30% decrease in the left atrial ejection fraction in patients with paroxysmal AF. Because there is no effective atrial contraction during AF, catheter ablation was associated with an improvement in ejection fraction in patients with chronic AF. After ablation, the left atrial ejection fraction was similar among patients with paroxysmal and chronic AF who remained in sinus rhythm but was significantly less than in control subjects without history of AF (Figure 5).[22]

Computed tomography is useful for identifying postablation PV narrowing, stenosis, or occlusion.[23–26] If necessary, CT scans may be repeated at regular intervals to determine the progression or regression of the stenosis and to monitor the results of venoplasty with or without stenting.[23,27,28] In contrast to conventional venography, the extent of stenosis can be assessed in three dimensions using virtual endoscopic 3-D reconstructions of the left atrium and the PVs. It has been reported that a focal PV stenosis larger than 50%, caused by compression by external structures or congenital narrowing, may preexist in 3% of patients prior to any left atrial ablation.[29] Therefore, a baseline study prior to ablation may be helpful to avoid misdiagnosis of acquired stenosis secondary to ablation.

Imaging of the chest by CT facilitates early diagnosis of atrioesophageal fistula and may prompt a timely intervention. The presence of air in the mediastinum and within the esophageal wall adjacent to the left atrium is a typical early finding on CT scans. Occasionally, a fistula tract can be observed between the left atrium and the esophageal lumen. The integrity of the posterior endocardial border and the esophageal musculature may be violated. It is important to alert the radiologist to the possibility of an atrioesophageal fistula so that the pertinent abnormalities are specifically sought. Ingestion of water-soluble contrast material during imaging may also be helpful.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has been used as an alternative to CT for imaging of the PVs and the left atrium.[16,17,30–32] Although acquisition of images may take longer during MRI compared to CT, radiation exposure and the risk of nephrotoxicity caused by radiocontrast agents are avoided. However, MRI usually is not feasible in patients who have implantable devices and is poorly tolerated in patients who are claustrophobic.

A unique potential application of gadolinium-enhanced MRI is assessment of the characteristics of ablation lesions in the heart. Magnetic resonance (MR) has been successfully used to image scars in the ventricular myocardium after myocardial infarction and catheter ablation.[33] However, imaging of the atrial myocardium is difficult because the myocardium is much thinner in the atrium than in the ventricle.

A novel application of MRI is real-time dynamic imaging of the heart during catheter ablation.[34] In an animal study, radio-frequency energy was delivered in the right ventricular apex using MR fluoroscopy.[34] Furthermore, lesion development was assessed in real time. However, catheters and recording systems have to be nonmagnetic and MR compatible during MR fluoroscopy. The feasibility of MR fluoroscopy to guide catheter ablation for AF remains to be determined.

Intracardiac Echocardiography

Intracardiac echocardiography (ICE) has been used to guide transeptal puncture, to better visualize the PVs and left atrium, and to guide power titration during radio-frequency ablation. There are two basic ICE systems available for use in the electrophysiology laboratory. One is a rotational ultrasound probe that has side view and is similar to conventional intracoronary ultrasound except for the larger diameter. This catheter is not steerable, requires a long sheath for positioning, and is useful only for guiding the transeptal puncture. In a recent study, this type of ultrasound probe was advanced into the left atrium and into the PVs to guide lesion delivery around the perimeter of the ostium.[35] The clinical efficacy was reported as 87% and 60% in patients with paroxysmal and chronic AF, respectively. There was a marked reduction in fluoroscopy duration. A major thromboembolic complication occurred in 1% of the patients.

The other ICE system is based on phased ultrasound. These probes are steerable and do not require a long sheath. Detailed 2-D imaging and Doppler data with color are also available. Phased ultrasound probes are helpful to guide the transeptal puncture and provide detailed imaging of the left atrium and PVs. The number of PVs and the location of the PV ostia and antrum can be identified. Although not yet validated against transesophageal echocardiography (TEE), phased ICE can be used to look for thrombi in the left atrial appendage.[36] Therefore, in patients who cannot tolerate a TEE or who have esophageal pathology precluding TEE, ICE can be used to rule out left atrial appendage thrombi. Development of thrombi over the catheters or sheaths has also been recognized with ICE.[37] Phased ultrasound can also be helpful to monitor for the development of pericardial effusion and tamponade, particularly in elderly patients, who may be at higher risk of perforation.

Phased ultrasound has been used to titrate power during applications of radio-frequency energy.[38,39] Based on the type of microbubbles generated as an effect of tissue heating, the power is titrated up or down. A rapid burst of bubbles visualized on ICE has been proposed to indicate overheating and an impending "tissue pop." Although it has been used successfully in a large number of patients, there may be two limitations of power titration based on microbubbles. First, the sensitivity of microbubbles to indicate tissue overheating has been demonstrated to be low in an animal experiment.[40] The absence of a burst of microbubbles does not necessarily confirm the absence of tissue overheating. Second, this approach cannot be utilized with open-irrigation catheters because infusion of saline by itself causes bubble formation.

Flow acceleration detected by Doppler ultrasound (available on phased-array systems) may indicate acute PV narrowing/stenosis during catheter ablation.[41] Left atrial mechanical function has also been assessed using ICE.[42,43] A novel approach is the development of integrated catheters that are capable of both ultrasound imaging and delivering radio-frequency energy.[44–46] A unique feature is that a 3-D reconstruction of the left atrium is also created using ultrasound imaging. These systems have been tested in animal models. Their clinical utility remains to be determined in patients with AF.

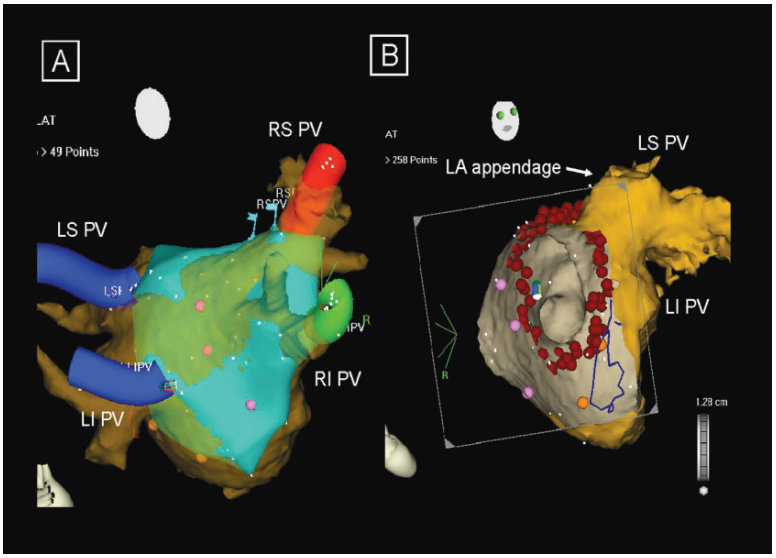

Figure 6 Image integration. An electroanatomical map created using the CARTO system is integrated with the three-dimensional (3-D) computerized tomographic image of the left atrium (LA) (**A**, posteroanterior projection). It is also possible to see the endocardial aspect of the integrated image (**B**). Radio-frequency energy (red tags) was delivered around the ostium of the left superior and inferior pulmonary veins. Opening of the left atrial appendage is also seen. *LS* left superior, *LI* left inferior, *PV* pulmonary vein, *RI* right inferior, *RS* right superior

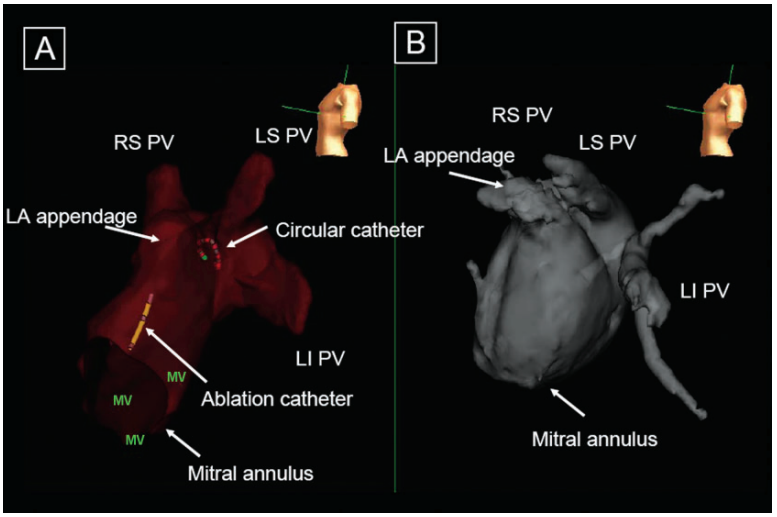

Figure 7 Left atrial three-dimensional (3-D) mapping and navigation. Left atrial geometry was constructed using the Navx system (**A**). It is also possible to visualize the representations of a circular mapping catheter and the ablation catheter in real time. **B** Corresponding computerized tomography of the left atrium with 3-D reconstruction. *LS* left superior, *LI* left inferior, *PV* pulmonary vein, *RI* right inferior, *RS* right superior, *MV* mitral valve

Nonfluoroscopic Three-Dimensional Catheter Navigation and Mapping

A major step in catheter ablation of complex arrhythmias has been development of nonfluoroscopic 3-D navigation and mapping systems. These sophisticated computer systems enable the creation of 3-D reconstructions of cardiac chambers with minimal fluoroscopic exposure. These systems also facilitate the acquisition and display of activation and propagation maps.

Two major 3-D mapping systems have been most commonly used: nonfluoroscopic electroanatomical mapping (CARTO), Biosense Webster; Figure 6) and nonfluoroscopic contact and noncontact mapping (Ensite NavX and Ensite, Endocardial Solutions; Figure 7). The CARTO system recognizes the position of a special magnetic tip in space utilizing a magnet placed underneath the patient and an external reference electrode. As the magnetic-tip catheter contacts the endocardial surface of the heart, data are acquired point by point. By triangulation of data points in space, a 3-D reconstruction of the left atrial endocardial surface is created. The reconstruction is a still image of the heart chamber. Vessels, particularly the PVs, the coronary sinus, and the vena cavae are represented by acquisition of data points during a pullback within the vessel. Subsequently, a fixed-diameter tube is created to represent the vessel mapped. However, this tube does not reflect the actual size of the vessel, and the location of the ostia of the PVs on the 3-D image may not be accurate. However, the position of the catheter within the cardiac chamber can be tracked in real time with minimal delay, and the catheter can be navigated without fluoroscopy. In addition to a color display of the results of point-by-point

activation mapping, the CARTO system allows for display of impedance maps and complex-fractionated electrogram maps.

The other nonfluoroscopic mapping and navigation systems are NavX and Ensite. The NavX system determines the position of an electrode in space by calculating the change in the impedance of a continuous high-frequency current emitted from the electrode among reference electrodes positioned on the back of the patient. Data points can be acquired from any catheter and from multiple electrodes at the same time. Hundreds to thousands of data points may be acquired in a very short time when a multielectrode catheter such as a ring catheter is used to map the PVs and the left atrium. A unique feature of the system is that multiple catheters and electrodes can be tracked in real time. This may be particularly helpful to minimize fluoroscopy when a multipolar ring catheter is used to guide PV isolation. As with the CARTO system, the NavX system is capable of providing activation and propagation maps.

The Ensite system utilizes a multielectrode balloon. An endocardial shell is created by moving a mapping catheter along the endocardial surface of the left atrium. Based on field theory and the inverse solution, isopotential mapping of arrhythmias is achieved by acquisition of a small number of tachycardia beats, and the need for point-by-point mapping is obviated. Ensite is most helpful for mapping of nonsustained focal arrhythmias. However, because of the thromboembolic risk associated with the presence of the balloon catheter in the left atrium, problems associated with movement of the balloon during the procedure, and the availability of the simpler NavX system, Ensite is infrequently used for catheter ablation of AF.

Image Integration

A recent development in imaging has been the integration of CT or MRI images of the heart with the electroanatomical maps created by a 3-D navigation system (Fig. 6).[47–52] If performed accurately, image integration may facilitate mapping and ablation. The location and number of the PVs and their ostia can easily be identified. The CT or MRI image integration facilitates identification of the true ostium and antrum and may avoid applications of energy within the PVs. The location of the atrial appendage and the configuration and thickness of the rim between the appendage and the left-side PVs can be identified. Variations in anatomy such as pouches in the roof can be recognized. The length and geometry of the mitral isthmus can also be recognized.

At present, there may be several limitations of the image integration technique. The CT or MRI images are often acquired days to weeks prior to the ablation. Left atrial geometry is affected by the loading conditions, heart rate, and rhythm and may vary with respiration. Therefore, the actual geometry in CT images and electroanatomical maps may not necessarily be exactly the same. A critically important step is the registration of two images. Because several points on the electroanatomical map are considered as fudicial points and are registered with the corresponding anatomical locations on the CT image, it is important to identify the anatomical sites precisely. In an animal study, the accuracy of registration was determined to be often less than 3 mm.[47]

Despite the potential benefits of image integration, no studies to date have demonstrated that image integration results in better clinical outcomes when

compared to electroanatomical mapping by itself. In a study that utilized image integration, complete PV isolation was achieved in 32% of all PVs in 16 patients who underwent circumferential PV ablation.[53] The mean total procedure and fluoroscopy times were 237 and 75 min, respectively. At 6-month follow-up, 80% of the patients with paroxysmal AF and 50% of the patients with persistent AF were free from AF. There was not a concurrent control group in this study, and the outcomes of catheter ablation of AF guided by image integration appear to be similar to those using more conventional approaches.

Conclusions

There has been much progress in imaging of the heart to facilitate catheter ablation. Each imaging modality may offer a unique feature that facilitates an ablation procedure. However, randomized studies are needed to demonstrate the relative value of the various imaging techniques in guiding catheter ablation of AF.

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Novel Balloon Catheter Technologies for Pulmonary Vein/Antrum Isolation

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Abstract: We describe novel balloon catheter technologies for pulmonary vein (PV)/antrum isolation using three different energy sources (high-intensity focused ultrasound, laser energy and cryothermia). 1) A High-intensity focused ultrasound (HIFU) balloon catheter is designed to focus HIFU energy circumferentially outside the PV (PV antrum). The catheter has two non-compliant balloons and a 9MHz ultrasound crystal is located with the distal balloon filled with contrast and water. The proximal balloon, filled with carbon dioxide, forma a parabolic reflecting interface to focus the ultrasound energy 2-6 mm in front of the distal balloon surface. 2) An endoscopic laser balloon catheter (ELBC) is designed to visualize the balloon-tissue interface using an endoscopic fiber in the balloon (filled with deuterium dioxide), combined with an adjustable focus for the laser energy (980 nm infrared diode laser) for PV ostial isolation. The laser application is delivered in 90 degree or 150 degree arcs and the arc is rotated in sequential laser applications to cover the entire circumference of the PV ostium. 3) A cryothermal balloon ablation system consists of a 10.5 Fr catheter shaft with double inner-outer cooling balloons to prevent refrigerant leakage (balloon diameter 23 mm or 28 mm), is advanced over a guidewire through a 12 Fr deflectable sheath. The refrigerant (N2O) is delivered under pressure from the console into the inner balloon chamber, where it undergoes a liquid-to gas phase change, resulting in balloon cooling to – 80 °C.

Keywords: Catheter ablation; atrial fibrillation; pulmonary vein; ultrasound energy; Laser; Cryothermia.

Electrical isolation of the pulmonary veins (PVs) or PV antrum by radiofrequency (RF) ablation is a primary component of many of the approaches for catheter ablation of atrial fibrillation (AF).[1–3] Isolation of the PVs at the ostia eliminated paroxysmal or persistent AF in approximately 50% to 65% of patients, with a 1% to 5% risk of pulmonary vein stenosis.[1–7] Pulmonary vein antrum ablation, placing the isolating lesions outside the PV ostia, increased ablation success to 70% to 90% and reduced the risk of PV stenosis to approximately 1%.[1–7] However, placing the RF ablation catheter around the

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PV ostium/antrum for point–point ablation is tedious, with the procedure time and results heavily dependent on the skill of the catheter operator. Electrical isolation is often incomplete or transient because of the difficulty in creating continuous transmural lesions in the left atrium using point-by-point RF applications.[2] There are several other limitations of RF ablation: (1) the requirement for stable contact between the ablation electrode and the left atrium; (2) the risk of thrombus formation when the electrode–tissue interface temperature exceeds 75 °C to 80 °C (while electrode temperature may be less than 55 °C to 60 °C)[8]; (3) the risks of perforation (associated with a steam pop); and (4) esophageal injury or the creation of a fistula between the left atrium and the esophagus with the use of RF power in the posterior left atrium.[9] Experimental and clinical studies have been performed to evaluate new devices with different energy sources to produce transmural circumferential ablation lesions around the PVs. In this chapter, we describe novel balloon catheter technologies for PV isolation using three different energy sources (high-intensity focused ultrasound, laser energy, and cryothermia).

High-Intensity Focused Ultrasound Balloon Catheter

A high-intensity focused ultrasound (HIFU) balloon catheter has been developed to isolate the pulmonary veins (PVs) outside the ostia (involving much of the PV antrum) with a lower risk of thrombus formation, PV stenosis, and left atrial perforation.[10,11] The HIFU balloon catheter (ProRhythm Inc., Ronkonkoma, NY) has two attached noncompliant balloons (Figure 1A). The larger distal balloon is filled with a mixture of water and contrast medium (4:1 ratio) and contains the 9-MHz ultrasound crystal. The small proximal balloon is filled with carbon dioxide, forming a parabolic surface at the base of the distal (water and contrast) balloon, which reflects the ultrasound in the forward direction, focusing a 360° ring of ultrasound energy (sonication ring) 2 to 6 mm in front of the distal balloon surface (Figure 1A). Three HIFU balloon sizes are available: a 24-mm diameter balloon (20-mm diameter sonication ring), a 27-mm diameter balloon (25-mm diameter sonication ring), and a 32-mm diameter balloon (30-mm diameter sonication ring).

Once the distal balloon is inflated, the water-and-contrast mixture is circulated continuously at 20 ml/min to cool the balloon and maintain balloon surface temperature at 42 °C or below during sonication. The pressure of the distal balloon is maintained at 8 psi to hold the parabolic shape. The pressure of the proximal carbon dioxide balloon is maintained at 1.2 psi.

The catheter has a central lumen for a guide wire, which is placed into the PV to guide the catheter over the PV orifice. The central lumen is also used for occlusive PV angiography (distal to the inflated balloon). A deflectable HIFU balloon catheter became available in a later study (Figure 1B).[12]

Preclinical Canine Studies

Canine Thigh Muscle Study

The potential advantages of ultrasound energy for ablation include the ability to focus the energy at various depths in the tissue; a low risk of thrombus formation because of the low absorption of ultrasound energy by the blood; and because of low blood absorption, elimination of the requirement for com-

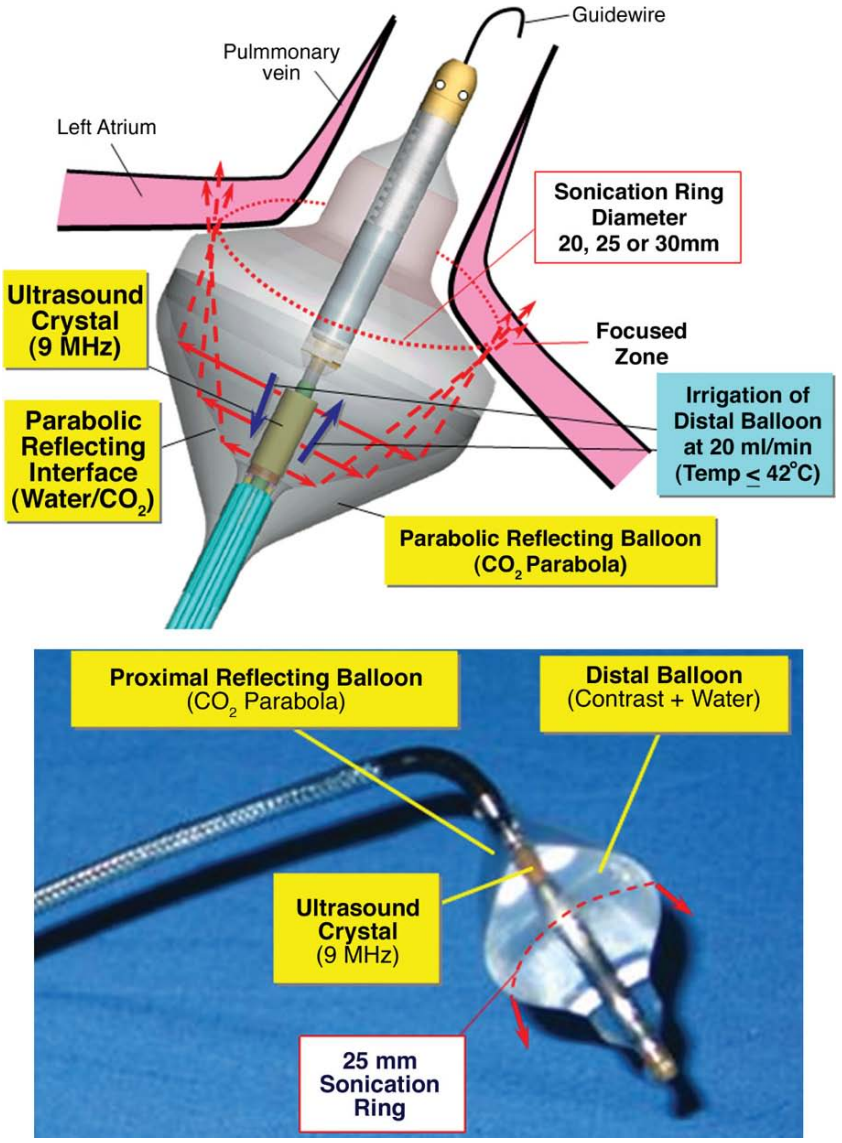

Figure 1 High-intensity focused ultrasound (HIFU) balloon catheter. **A** Schematic representation of the HIFU balloon catheter designed to focus high-intensity ultrasound circumferentially outside the pulmonary vein (PV) antrum. This system has two noncompliant balloons. The proximal balloon, filled with carbon dioxide, forms a parabolic interface with the distal balloon to reflect the ultrasound energy in the forward direction, focusing a 360° ring (sonicating ring) of ultrasound energy 2 to 6 mm in front of the distal balloon surface. The distal balloon has three sizes (24, 28, or 32 mm in diameter), producing sonicating rings of 20, 25, or 30 mm in diameter. A 9-MHz ultrasound crystal is located within the distal balloon. The acoustic power of the system is 35 W for all three distal balloon sizes, with negligible loss of power in the balloon. The distal balloon is irrigated internally with contrast and water at 20 ml/min during ablation to keep the balloon cool (≤42 °C). The catheter has a central lumen used for occlusion PV angiography (distal to the balloon) and for insertion of a guide wire (0.035 inch) supporting the navigation of the catheter. **B** Deflectable HIFU balloon catheter. The sonication ring diameter is 25 mm

plete circumferential balloon contact.[13–15] We examined the circumferential lesion characteristics and thrombogenic potential of HIFU applications using a canine thigh muscle preparation.[16]

In 12 dogs, the skin over the thigh muscle was incised and raised to form a cradle, which was superfused (350 ml/min) with heparinized canine blood (Activated clotting time (ACT) > 300 s) from the same animal at 37 °C to 38 °C.[17] A shallow cylinder of tissue was cored from the thigh muscle to simulate the PV–left atrial (LA) junction. A HIFU balloon catheter with a 20-, 25-, or 30-mm sonication ring was positioned over the cylinder, perpendicular to the thigh muscle, with the catheter tip in the blood field cylinder.

A single HIFU application (35 W acoustic power) was delivered for 20 to 60 s. Three to five individual HIFU applications were delivered to each thigh muscle, for a total of 82 HIFU applications. Seven of the 82 lesions were created while the surface of the balloon was intentionally held 2 mm above the surface of the thigh muscle (*noncontact ablation*). The blood within the skin cradle was removed after each HIFU application to examine the balloon and balloon–tissue interface for thrombus. After staining with triphenyl terazolium chloride (TTC) and fixation, the thigh muscles were sectioned parallel to the surface in 2-mm slices. The maximum diameter and the maximum depth of complete circumferential necrosis were measured.

The circumferential lesion depth increased with increasing HIFU application time (Figures 2 and 3). A single HIFU application for 40 s using a 20-mm sonication ring balloon produced continuous circumferential lesions at a depth of 4 mm in 10/14 lesions (71%). A single HIFU application for 60 s using a 25-mm or 30-mm sonication ring balloon produced continuous circumferential lesions at a depth of 4 mm in 9/13 (77%) and 14/16 (88%) lesions,

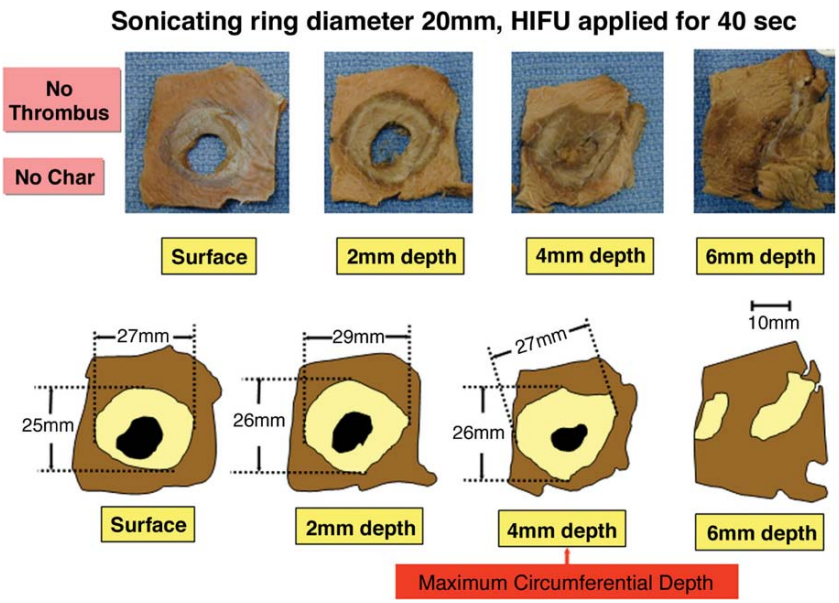

Figure 2 Circumferential lesion produced by a single high-intensity focused ultrasound (HIFU) application (35 W, 40 s) in the canine thigh muscle preparation. The maximum depth and maximum diameter of complete circumferential lesion were 4 and 29 mm, respectively. There is no thrombus or char at the surface of the thigh muscle

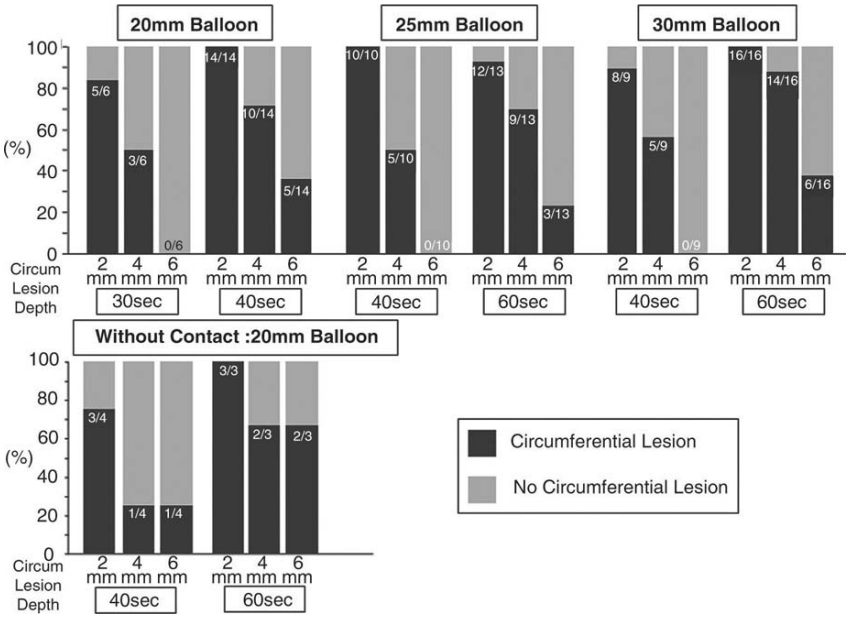

Figure 3 The depth of complete circumferential lesion after a single HIFU application (35 W) for 30 and 40 s with a 20-mm sonication ring; for 40 and 60 s with a 25-mm sonication ring; for 40 and 60 s with a 30-mm sonication ring; and for 40 and 60 s with a 20-mm balloon positioned 2 mm above the surface of the thigh muscle (noncontact ablation)

respectively. Without balloon–tissue contact (2 mm above the surface of the thigh muscle), circumferential lesions were produced at a depth of 4 mm in two of three single HIFU applications for 60 s using a 20-mm sonication ring balloon (Figure 3).[16]

Thrombus was not produced by any of the 82 HIFU applications (including noncontact applications) as a result of low absorption of ultrasound energy by blood (no direct heating of blood). These findings suggested that the HIFU balloon catheter would be a suitable PV/antrum isolation procedure.

In Vivo Canine Study

In a preclinical study, we utilized a canine model to test the safety and efficacy of the HIFU balloon catheter to produce circumferential transmural LA lesions, outside the PV orifice.[11] Thirty dogs were studied under closed chest conditions and pentobarbital anesthesia. After transeptal puncture, PV angiography was performed (Figure 4). A 20-Lole lasso catheter was positioned in the target PV before ablation to document the presence of PV potentials and after ablation to determine whether PV isolation was achieved, defined as elimination of all PV potentials (Figure 4). The PV antrum isolation was attempted in 32 PVs (21 right superior PVs [RSPVs] and 11 left superior PVs [LSPVs]) using the balloon with a 20-mm sonication ring. A single HIFU application was delivered to each PV antrum at an acoustic power of 35 W for 20 s in 12 PVs, 30 s in 5 PVs, 40 s in 13 PVs, and 60 s in 2 PVs.

A single HIFU application completely isolated 28 (88%) of the 32 PVs (10/12 PVs with 20-s sonication, 5/5 PVs with 30-s sonication, 11/13 PVs with 40-s sonication, and 2/2 PVs with 60-s sonication). For the 4 PVs not isolated by

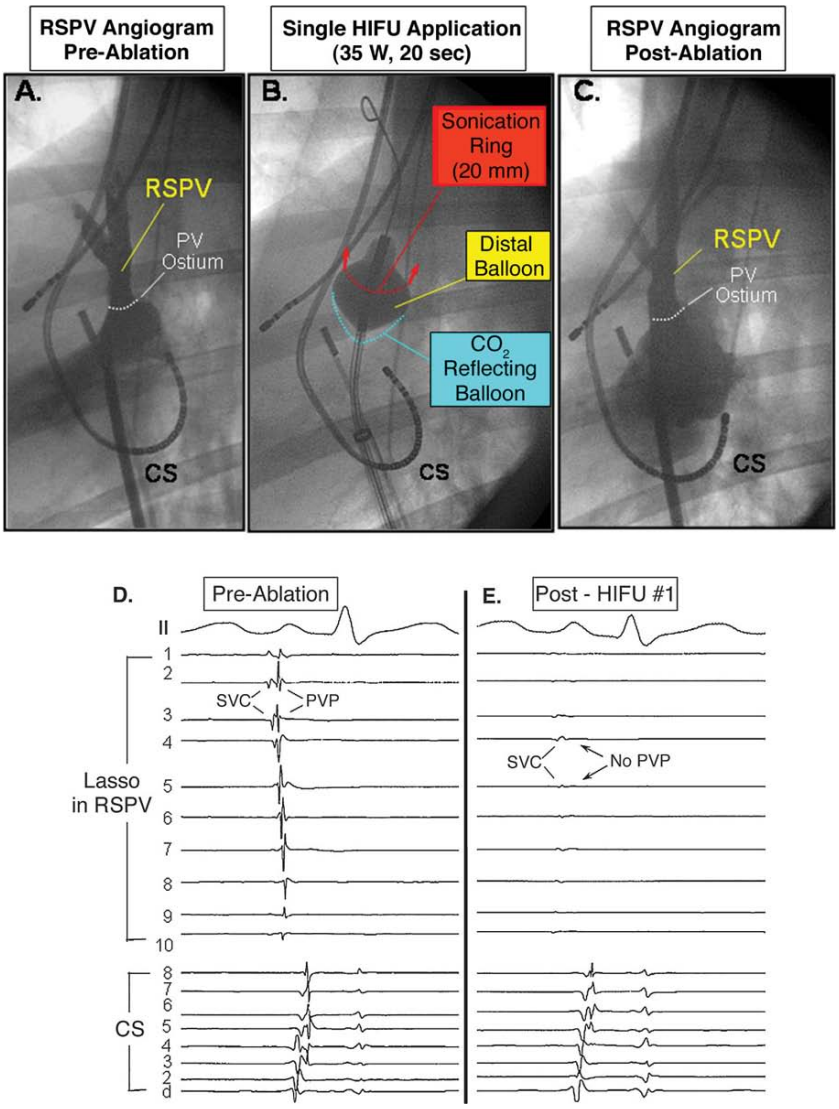

Figure 4 Successful isolation of the right superior pulmonary vein (RSPV) antrum with a single high-intensity focused ultrasound (HIFU) application in a canine model. **A** Angiography of the RSPV in the left anterior oblique projection showing the locations of PV ostium (white dotted line). **B An** HIFU balloon with a 20-mm sonicating ring was advanced over the guide wire and positioned with the catheter tip in the RSPV. The distal balloon was filled with water/contrast mixture. The proximal balloon (crescent shape outlined by blue dotted lines), filled with carbon dioxide, forms the parabolic reflecting surface, which focuses the ultrasound energy in the forward direction, producing a 360° sonicating ring around the RSPV antrum (red arrows and red dotted line). The HIFU energy (35 W acoustic power) was applied for 20 s. **C** Angiogram of the RSPV following the single HIFU application showing no narrowing of the PV ostium. **D** and **E** Recordings from the Lasso catheter in the RSPV during sinus rhythm before and after the HIFU application. **E** Before ablation, the Lasso catheter records discrete PV potentials (PVPs) from 10 close-bipolar electrodes (Lasso 1 to 10). The first potentials of Lasso 1 to 4 originated from the superior vena cava (SVC). **F** Following the single HIFU application, no PVPs were recorded, confirming complete PV isolation. In addition, there were no PV antrum potentials distal to the ablation site, confirming PV antrum isolation. *CS* coronary sinus

the single HIFU application, the balloon orientation was changed, and a second HIFU application was delivered, resulting in complete isolation of all 4 PVs. Fourteen dogs with 16 HIFU-targeted PVs were sacrificed 2 h after ablation. Gross examination (TTC staining) showed transmural circumferential lesions at all 16 PV antra.

The remaining 16 dogs, with one HIFU-targeted PV each, survived for 1 week to 3 months (median 1.5 months) following ablation. Mapping of the targeted PVs prior to sacrifice of these 16 dogs showed continued complete PV isolation in 14 of the 16 (88%) PVs. Histological examination showed a circumferential transmural lesion around 12 of the 14 isolated PVs. In the other 2 isolated PVs, the transmural lesion involved 80% of the PV circumference.

There was no narrowing of the PV orifice in any of the 32 PVs. However, there was narrowing of proximal PV branches, crossing the sonication ring very close to the surface of the balloon in 2 of the 32 PVs. In the dog that developed 90% narrowing of the PV branch with a 30-s HIFU application, the distance from the surface of the balloon to the PV branch was less than 1 mm. This dog was sacrificed acutely. In the other dog that developed 35% narrowing, the PV branch was located 2 mm from the surface of the balloon. The narrowing had resolved at 1 month. There was no phrenic nerve injury or esophageal lesion.

Clinical Feasibility Study

The initial feasibility testing was performed using a nondeflectable HIFU balloon catheter in patients undergoing catheter ablation of drug-resistant paroxysmal AF (19 patients) or persistent AF (8 patients).[10] The AF had occurred for 1 to 30 (median 6) years prior to enrollment in the study. Structural heart disease was present in 10 of the 27 patients, including hypertensive heart disease (3 patients), left ventricular hypertrophy without hypertension (3 patients), and coronary artery disease (4 patients). The LA diameter was 3.0 to 5.4 cm (median 3.9 cm).

Double transeptal puncture (8F sheaths) and angiography of the right and left PVs was performed. A 10- or 20-electrode circular mapping catheter (Lasso, Biosense-Webster Inc.) was used to document the location and depth of PV potentials prior to isolation. The other transeptal sheath was exchanged for a 16.5F sheath for the HIFU balloon catheter. The HIFU balloon catheter was advanced over a guide wire, positioning the catheter tip within the PV. The distal balloon was inflated, and contrast medium was injected through the lumen of the HIFU catheter to obtain an occlusion PV angiogram to identify the location of the sonicating ring relative to the PV ostium. The HIFU energy (35 W acoustic power) was applied for 40 s (20-mm sonicating ring) or 40 or 60 s (25- or 30-mm sonicating ring). If PV potentials were still present, the HIFU catheter was repositioned to cover the area of the residual PV potentials (manipulating the HIFU catheter to a different angle, placing the guide wire in a different branch of the PV, or changing balloon size), and HIFU applications were repeated. The PV angiography was repeated after the last HIFU application for each PV.

The PV antrum isolation was attempted for 77/103 PVs (25/27 RSPVs, all 23 LSPVs, 22/23 left inferior PVs [LIPVs], all 4 left common PV trunks, and 3/27 right inferior PVs [RIPVs]; Figure 5). The RSPV antrum was not targeted

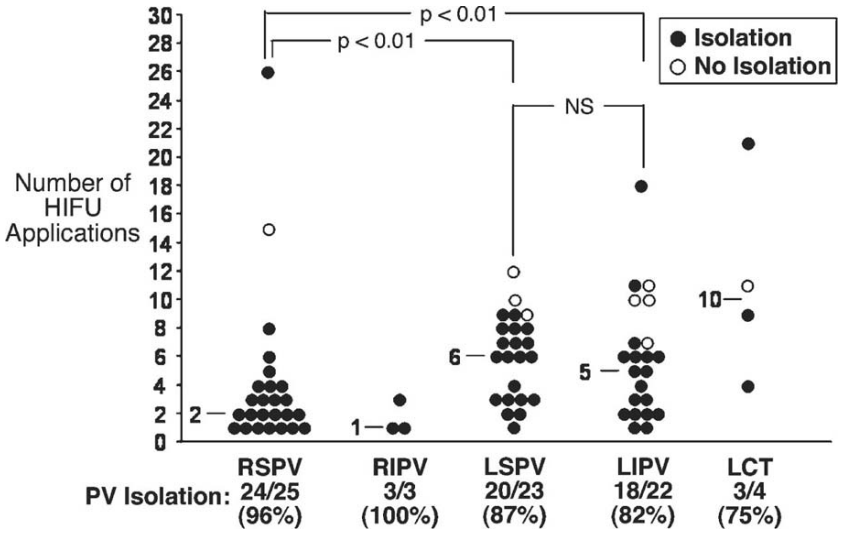

Figure 5 Number of high-intensity focused ultrasound (HIFU) applications required for isolation at the antra of the right superior pulmonary vein (RSPV), right inferior pulmonary vein (RIPV), left superior pulmonary vein (LSPV), left inferior pulmonary vein (LIPV), and left common PV trunk (LCT) in the 27 patients. Closed circles represent successful PV antrum isolation, and open circles represent unsuccessful PV antrum isolation. The median number of HIFU applications for each group is shown. *NS* not significant. (Modified from ref. 10 with permission.)

in two patients because, in one patient, a proximal branch of the RSPV was located just beyond the LA at the projected sonicating ring location (potential risk of stenosis), and PV potentials were absent in the other patient. The HIFU balloon could not be positioned around the LIPV in one patient. Only 3 RIPVs were targeted. Targeting the RIPV was optional because of difficulty positioning the balloon catheter to the RIPV over a guide wire.

Sonication with HIFU successfully isolated 68 (88%) of the 77 PV antra. A range of 1 to 26 (median 3) HIFU applications was used in the 68 successfully isolated PV antra, and 7 to 15 (median 10) HIFU applications were used in the 10 nonisolated PV antra (Figure 5). Isolation was achieved by only one sonication in 12 (16%) of the 77 PVs and by two or fewer sonications in 24 PVs (31%). One, two, three, or four PVs (counting the left common trunk as two PVs) were isolated in 1, 8, 15, and 3 patients, respectively.

Twenty-four (96%) of the 25 attempted RSPVs were isolated by 1 to 26 (median 2) HIFU applications (Figure 5). Isolation of 7 of the 25 RSPVs required only a single HIFU application (30-mm sonicating ring in 4 of the 7). Contact between the HIFU balloon and the LA endocardium was not required around the entire circumference for complete isolation with a single HIFU application. Flow around the balloon (incomplete contact) was present by occlusion angiography (Figure 6) or intracardiac echocardiography in approximately 40% of single HIFU applications, resulting in isolation of the RSPVs or left PVs.[10]

Isolation was not achieved in one RSPV, which was markedly larger than all other RSPVs (ostial dimensions of 40.3 × 38.4 mm). The HIFU balloon was positioned at the RIPV antrum in three patients (Figure 5). The three

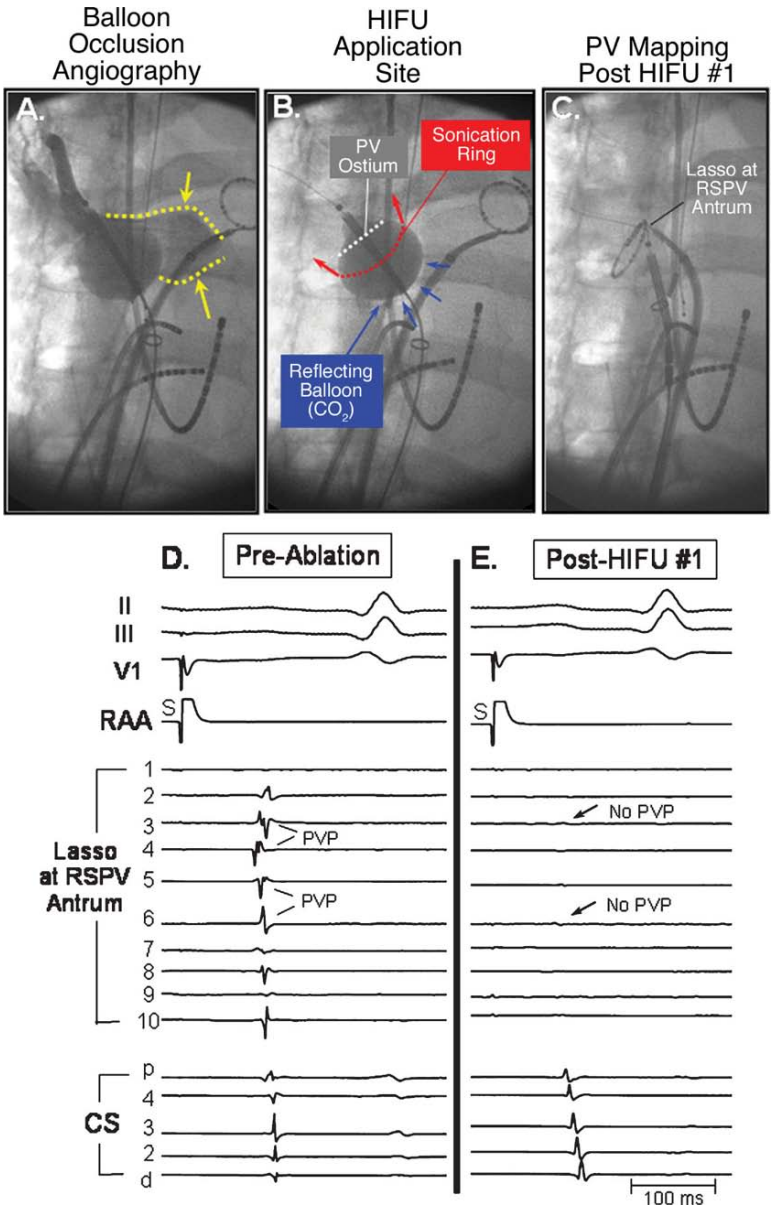

Figure 6 Successful isolation of right superior pulmonary vein (RSPV) antrum without circumferential balloon contact in a patient with paroxysmal atrial fibrillation (AF). **A** Balloon occlusion angiography of the RSPV before high-intensity focused ultrasound (HIFU) application shows flow of contrast (outlined by yellow dotted line and yellow arrows) around the HIFU balloon, indicating incomplete balloon contact with the left atrial endocardium. **B** A single HIFU application (35 W, 60 s) isolated the RSPV antrum despite the absence of circumferential balloon–atrial contact. **C** Radiogram (Right anterior oblique (RAO) projection) showing the Lasso catheter positioned in the RSPV antrum (outside the pulmonary vein [PV] ostium) following the HIFU application. **D** and **E** Lasso recordings from the RSPV antrum during right atrial appendage (RAA) pacing, before and after the single HIFU application. **D** Before ablation, PV antrum potentials were recorded from the Lasso close-bipolar electrodes (Lasso electrograms 2 to 10). **E** Following the single HIFU application, all PV antrum potentials were eliminated.

RIPVs were isolated using only one (two patients) or three (one patient) HIFU applications.

Antrum isolation was successful in 20 (87%) of the 23 LSPVs, 18 (81%) of the 22 LIPVs, and 3 of the 4 left common PV trunks (Figure 5), using a median of 6, 4.5, and 9 HIFU applications, respectively. The primary limitation for ablation of left PV antra using balloon technology is the prominent ridge between the left PVs and the left atrial appendage (LAA ridge). The initial HIFU applications usually eliminated the potentials at the posterior aspect of the LSPV or LIPV. Because the sonication ring was initially lying outside the LAA ridge, potentials were still present anteriorly along the LAA ridge. Ablation of the LAA ridge using the smaller (20-mm) HIFU balloon was required for completion of isolation in 15 of the 20 isolated LSPVs and 16 of the 18 isolated LIPVs (Figure 7). However, the combination of a prominent LAA ridge and lack of catheter deflection control prevented left PV antrum (LSPV or LIPV) isolation in 7 (26%) patients (Figure 5).[10] It is likely that the addition of another ablation catheter for targeting the remaining gaps in the ablation lines, rather than trying to reposition the balloon, would significantly reduce the number of HIFU applications and increase the number of successfully isolated PVs.

The 27 patients were followed for 15 to 31 (median 21) months after the single HIFU ablation procedure. At last follow-up, 15 of the 27 (56%) patients were free of symptomatic episodes of AF and atrial tachycardia (AT), and 5 of the remaining 12 patients had 50% or more reduction in the number of symptomatic AF/AT episodes.[10]

Examination of the HIFU balloon catheter following ablation showed no thrombus. There were no acute or late thromboembolic complications, including stroke or transient ischemic attack (TIA). Significant PV stenosis (≥50% narrowing) was not identified in any patient by PV angiography at the end of the ablation procedure or at 3 months by computed tomography (CT) or magnetic resonance (MR) angiogram. Pulmonary hemorrhage occurred in one patient because of perforation of the distal lingular branch of the LSPV during manipulation of the guide wire. No intervention or transfusion was required. The right phrenic nerve was injured in one patient with an unusually large RSPV (40.3 × 38.4 mm). Fifteen HIFU applications were delivered using both 20- and 30-mm balloons. After this complication, the phrenic nerve was localized by high-output pacing in the superior vena cava, right atrium, and RSPV antrum. None of the subsequent sonication sites was located close to the phrenic nerve, and there was no subsequent phrenic nerve injury.

A deflectable HIFU balloon catheter, introduced in later studies, allowed catheter access to all PVs, including the RIPVs. Schmidt et al. reported that a deflectable HIFU balloon could be accessed in all PVs in 12 patients with paroxysmal AF.[12] All 12 RSPVs were successfully isolated with 2 to 7 (median 4.5) HIFU applications, and 10 of the 12 RIPVs were successfully isolated with 3 to 11 (median 4.5) HIFU applications. Nine of the 10 LSPVs and 9 of the 10 LIPVs were successfully isolated with 3 to 20 (median 7) HIFU applications and 2 to 23 (median 6.5) HIFU applications, respectively. In 2 patients with left common trunk, successful isolation was achieved in 1 patient with 11 HIFU applications. With a follow-up period of 17 to 61 (median 55) weeks, 7 (58%) of the 12 patients were free of symptomatic episodes of AF and AT without antiarrhythmic medications, and another 2 patients had only 2 single episodes of AF within the 12 months following ablation.

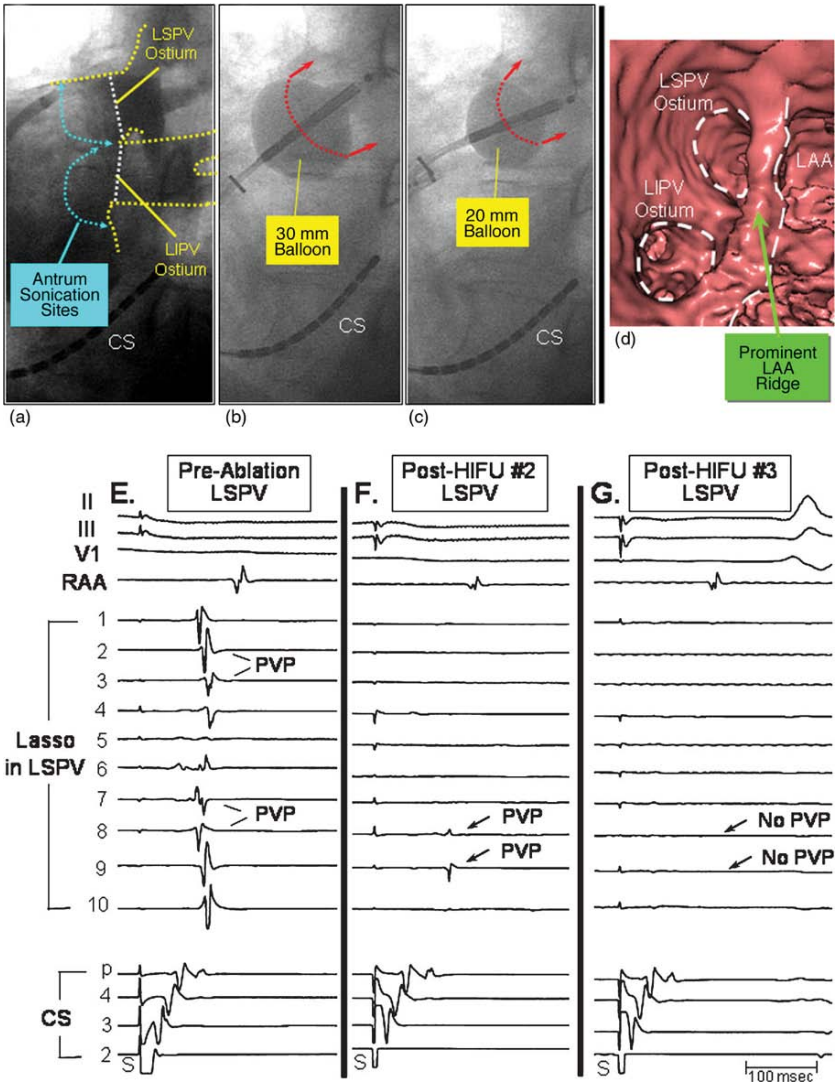

Figure 7 Isolation of the left superior pulmonary vein (LSPV) antrum with three high-intensity focused ultrasound (HIFU) applications in patients with paroxysmal atrial fibrillation (AF). **A** Angiogram in the left anterior oblique projection showing the locations of the LSPV and left inferior pulmonary vein (LIPV) ostia (white dotted line) and antra (blue dotted line). **B, E,** and **F** The HIFU balloon with a 30-mm sonicating ring was positioned at the LSPV antrum (**B**). Two HIFU applications at the LSPV antrum eliminated PV antrum potentials except at the left atrial appendage (LAA) ridge between the LSPV and the LAA (**E** before HIFU showing circumferential PV antrum potentials; **F** after the two HIFU applications showing potentials only in Lasso electrograms 8 and 9, located at the LAA ridge). **D** and **G** An HIFU balloon with a 20-mm sonication ring was used to target the LAA ridge (**C**). Complete LSPV isolation was achieved with a single HIFU application (HIFU 3) using the 20-mm HIFU balloon (**G** showing no PV potentials). **D** Endoscopic view of a magnetic resonance (MR) angiogram demonstrating a prominent LAA ridge that prevented isolation of the LSPV and LIPV antra in another patient. *CS* coronary sinus. (Modified from ref. 10 with permission.)

Phrenic nerve injury occurred in 2 of the 12 patients in Schmidt et al.'s study.[12] Following this experience, HIFU applications were not delivered when the phrenic nerve (localized by high-output pacing) was located within 1 cm of the sonication ring, and there was no subsequent phrenic nerve injury. A U.S. feasibility trial was performed at three centers in eight patients with paroxysmal AF. All four PVs were isolated in all patients. At 12-month follow-up, seven (88%) of eight patients were free of AT and AT without antiarrhythmic medications.

Esophageal perforation occurred in one patient in the U.S. feasibility trial using the deflectable balloon. Three HIFU applications were delivered to the RIPV, very close (within 3 mm) to the esophageal wall. The esophageal perforation healed with conservative therapy (without surgery) in 4 weeks. A canine model was created to identify the parameters of esophageal injury with HIFU.[18] Transmural esophageal injury (with esophageal ulcer) was associated with luminal esophageal temperature above 50 °C. This occurred with HIFU delivered with the LA (outside the PV) only when the sonication ring was located less than 3 mm from the luminal surface of the esophagus.

Endoscopic Laser Balloon Catheter

Laser energy applied directly into blood produces a thrombus because laser energy is absorbed by the blood (heating the blood).[19] Therefore, to prevent thrombus formation during laser ablation, the laser energy can be applied through a fluid-filled balloon positioned against the tissue to provide a bloodless interface for ablation. Endoscopic visualization can be incorporated into a balloon catheter to optically monitor for the intrusion of blood into the space between the balloon and the tissue.

An endoscopic laser balloon catheter (ELBC; CardioFocus Inc, Marlborough, MA, USA; Figure 8A) has been developed to visualize the balloon–tissue interface using an endoscopic fiber in the balloon combined with an adjustable focus for the laser energy (980-nm infrared diode laser) for PV isolation.[19–22] The laser balloon catheter is inserted through a 12F deflectable sheath. The noncompliant balloon has two sizes, with a diameter of 20 or 25 mm, and the forward firing of the focus diode laser beam. The balloon is filled with a mixture of contrast and deuterium dioxide (D_2O) and irrigated internally at 20 ml/min. The D_2O is used to minimize absorption of laser energy.

The laser fiber can be advanced and withdrawn to shift the site of lasing along the longitudinal axis of the catheter. The site of lasing is selected by looking through the endoscopic fiber, positioned just behind the laser fiber, and looking at the green laser aiming light. The laser application is delivered in 90° or 150° arcs. The arc is rotated in sequential laser applications to cover the entire circumference of the PV ostium (Figure 8B).

Preclinical Canine Studies

Canine Thigh Muscle Study

We used the canine thigh muscle preparation to examine the risk of thrombus formation during laser ablation when stagnant blood or pulsatile blood enters the space between the balloon and the tissue.[22] In seven dogs, ELBC (25-mm balloon diameter) was positioned along its side against the thigh muscle in the

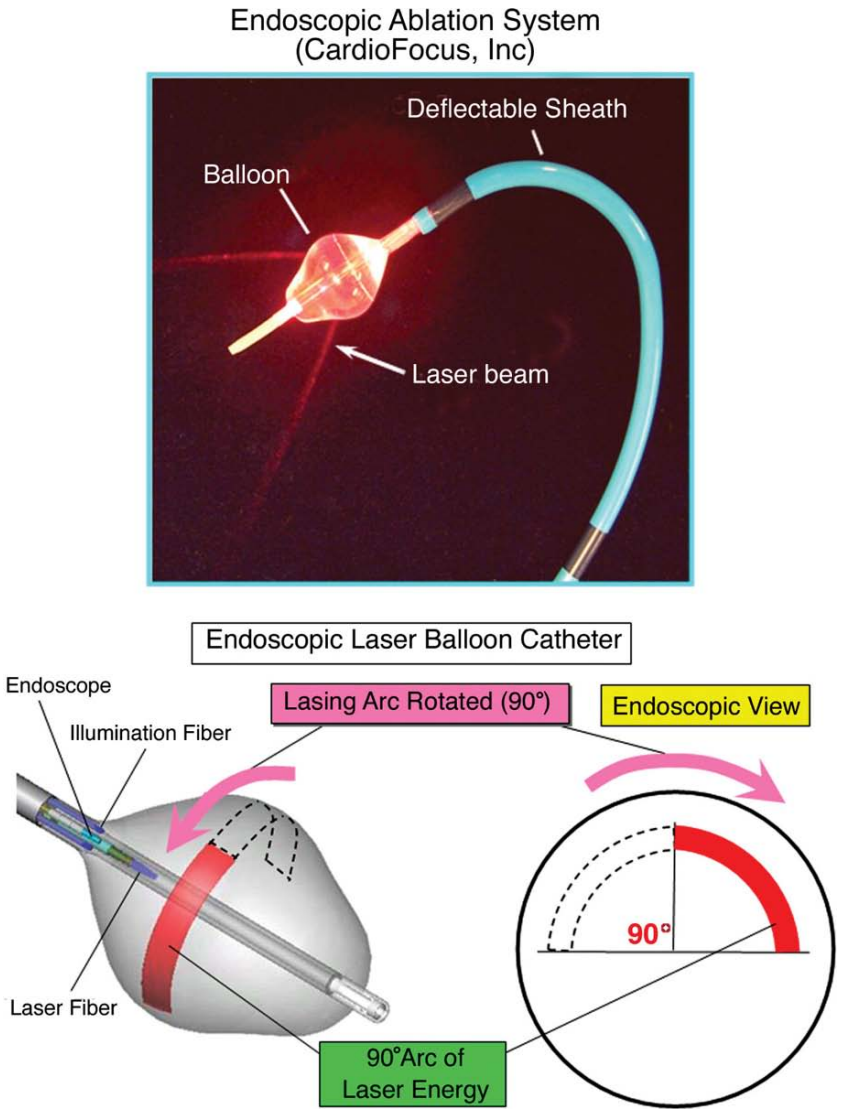

Figure 8 An endoscopic laser balloon catheter (ELBC; CardioFocus Inc). **A** The ELBC (20-mm diameter balloon) is inserted through a 12F deflectable sheath. The balloon is filled with a mixture of contrast and deuterium dioxide (D_2O) and irrigated internally at 20 ml/min. **B** The balloon contains an endoscopic fiber for visualization, a laser fiber, and an illumination fiber. The laser energy (980-nm infrared diode laser) is delivered in a 90° or 150° arc, which can be rotated in sequential laser applications to cover the entire pulmonary vein (PV) ostium

blood-filled cradle. The ELBC was filled with D_2O and irrigated internally at 20 ml/min. An endoscopic fiber within the ELBC was used to visualize each lasing arc (90° circumference) and determine the presence or absence of blood between the balloon and tissue (Figure 9A).

Sites were selected by endoscopy to lase with two thirds of the arc along a bloodless muscle field and one third of the arc into the blood. Five or 6 laser applications were delivered to each thigh muscle, for a total of 79 laser appli-

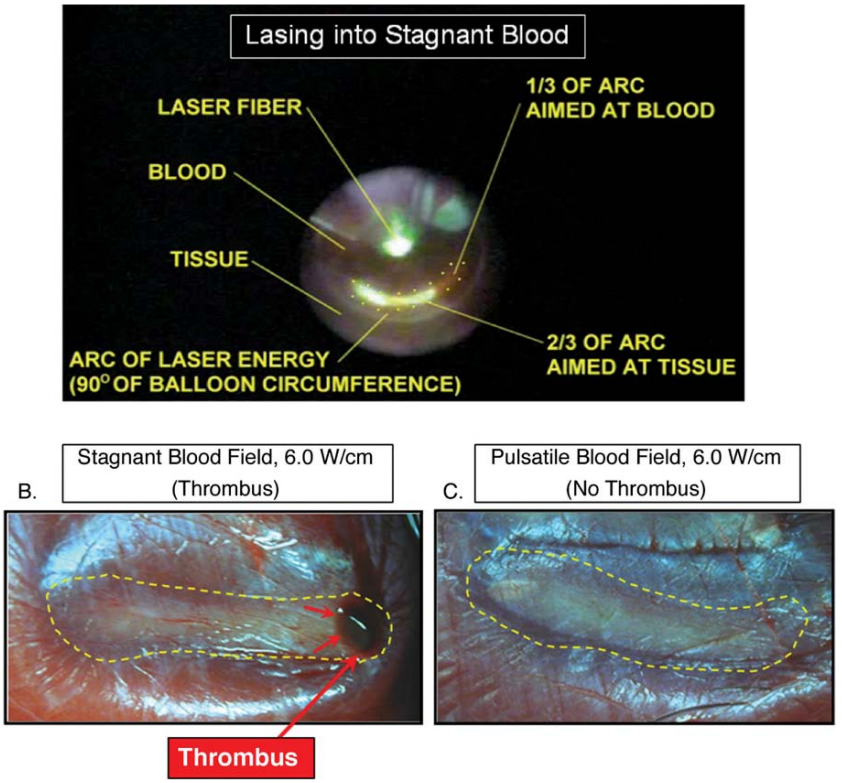

Figure 9 Laser energy application into stagnant blood in the canine thigh muscle preparation. **A** Laser energy (6.0 W/cm) was delivered for 60 s using a 90° arc. The ablation site was selected by endoscopic image to lase with two thirds of the arc along the bloodless muscle field and one third of the arc into stagnant blood. **B** Lasing into stagnant blood produced a thrombus. **C** Laser energy (6.0 W/ cm for 60 s) was delivered into pulsatile blood, and there was no thrombus formation

cations. Laser energy was applied at 6.0 W/cm (n = 55) or 7.2 W/cm (n = 24) for 60 s with either stagnant blood (constant balloon contact) or pulsatile blood (increasing/decreasing ELBC pressure once per second) under the ELBC. The blood within the skin cradle was removed after each laser application to examine the balloon and balloon–tissue interface for thrombus. Aspirin (80 mg by mouth) was administered at least 45 min before ablation.

There was no thrombus in any of the 37 laser applications into pulsatile blood at 6.0 W/cm for 60 s. However, thrombus occurred in 8 of the 18 (44%) when lasing into stagnant blood at 6.0 W/cm for 60 s (Figure 9). With a higher laser power application (7.2 W/cm for 60 s), thrombus occurred with lasing both into pulsatile blood (1 of the 25 applications, 5%) and into stagnant blood (1 of the 3 applications, 33%). These data indicate that the risk of thrombus can be minimized by avoiding lasing into stagnant blood and using a lasing power density of 6.0 W/cm. Lesion depth was 11.5 ± 1.5 mm. Importantly, endoscopic visualization effectively differentiates between stagnant and pulsatile blood in the lasing field, minimizing the risk of thrombus.[22]

In Vivo Canine Study

We utilized a canine model to test the safety and efficacy of the ELBC to produce circumferential transmural lesions at the PV orifice for PV isolation.[23] Twenty-two dogs were studied under a closed-chest condition and propofol anesthesia. After transeptal puncture, a 12F deflectable sheath was placed into the LA. The ELBC was inserted through the sheath and placed into the RSPVs (n = 22 dogs) or LSPVs (n = 13 dogs). The balloon was inflated and advanced against the PV ostium to obtain circumferential balloon contact (bloodless field). The aiming beam located the 150° lasing arc (Figure 10). The arc was rotated in sequential laser applications to cover the entire PV circumference, just inside the PV ostium. Laser applications were delivered for 60 s at a power density of 4.5, 5.5, or 6.0 W/cm. Testing for isolation, using a Lasso catheter, was performed after every 3 to 5 laser arc applications. A maximum of 12 laser arc applications per PV were delivered.

The ELBC was able to achieve a circumferential bloodless contact, confirmed by endoscopy, in all 22 RSPVs and in 10 of the 13 LSPVs. Ablation was not attempted in the 3 LSPVs where a circumferential bloodless field could not be achieved. Laser ablation successfully isolated 20 of the 22 RSPVs and all 10 LSPVs. Pulmonary vein isolation was achieved in all 16 PVs, 9 of 10 PVs, and 5 of 6 PVs ablated at 4.5, 5.5, and 6.0 W/cm, respectively. Of the 22 dogs, 19 survived for 1 to 12 (median 12) weeks following ablation. Mapping of the targeted PVs prior to sacrifice in these 19 dogs (26 PVs) showed continued complete PV isolation in 20 of the 26 (77%) targeted PVs. Histological examination showed a circumferential transmural lesion around the PV ostium in 17 of the 20 PVs that had continued complete PV isolation. The other 3 PVs had a transmural lesion encompassing 70% to 80% of the PV circumference.

There was no thrombus seen on the balloon following any of the laser applications. Acute stenosis of the PV ostium was not seen in any of the dogs. Mild narrowing (20% to 35%) was seen in 3 of the 32 PVs studied at the time of follow-up. Significant narrowing of a proximal PV branch located within 2 mm of the lasing site was seen acutely (PV angiography) in 2 of the 32 PVs (50% and 80% narrowing). At follow-up, there was only mild narrowing of these 2 proximal branches (25% and 33% narrowing, respectively). A right phrenic nerve injury was seen following ablation of the RSPV in 1 of 22 dogs. This occurred with ablation at a power density of 6 W/cm.

Clinical Feasibility Study

The initial feasibility study was performed using the ELBC in 30 patients undergoing ablation of drug-resistant paroxysmal AF (26 males and 4 females) at three centers (Italy, Czech Republic, Germany) for catheter ablation. Atrial fibrillation had been present in these individuals for 0.4 to 24 (mean 4.3) years. The LA diameter was 3.1 to 4.9 (mean 4.3) cm.

Laser applications were delivered to 116 PVs at a power density of 6.0 W/cm for 60 s using a 90° arc (Figure 11). Pulmonary vein isolation was achieved in 105 of the 116 (91%) PVs. A total of 2 to 40 (mean 14) laser arc applications were delivered in each PV. Twenty of the 30 patients have reached 12 months of follow-up, and 15 (75%) of the 20 patients are free of symptomatic episodes of AF and AT (2 of the 15 patients were receiving antiarrhythmic medications).[24]

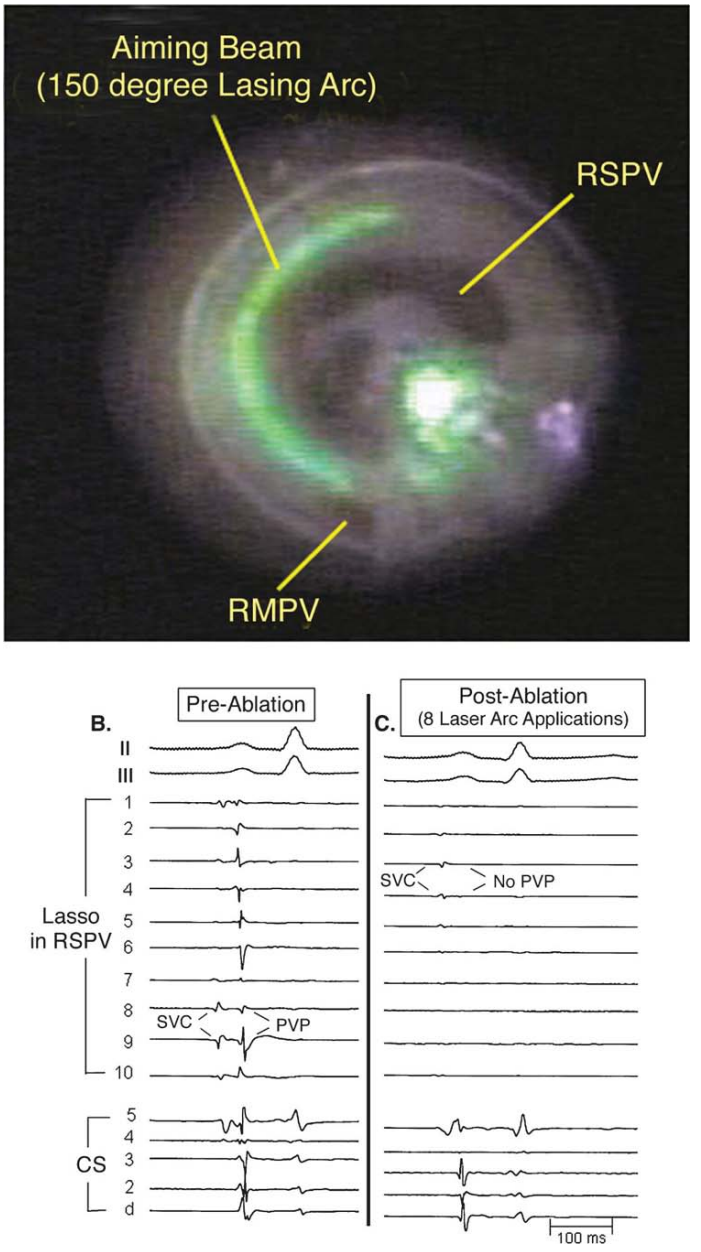

Figure 10 Successful isolation of the right superior pulmonary vein (RSPV) using the endoscopic laser balloon catheter (ELBC) in a canine model. **A** The ELBC was positioned into the RSPV, and the balloon was inflated and advanced against the ostium to obtain a circumferential bloodless field. The aiming beam (green arc) located the 150° lasing arc just inside the RSPV ostium. Eight sequential laser arc applications (4.5 W/cm for 60 s for each arch) were delivered around the ostium by rotating the lasing arc. **B** Before laser ablation, pulmonary vein potentials (PVPs) were recorded circumferentially in the RSPV. **C** After the eight laser arc applications, all PV potentials were eliminated. *CS* coronary sinus, *RMPV* right middle pulmonary vein, *SVC* superior vena cava

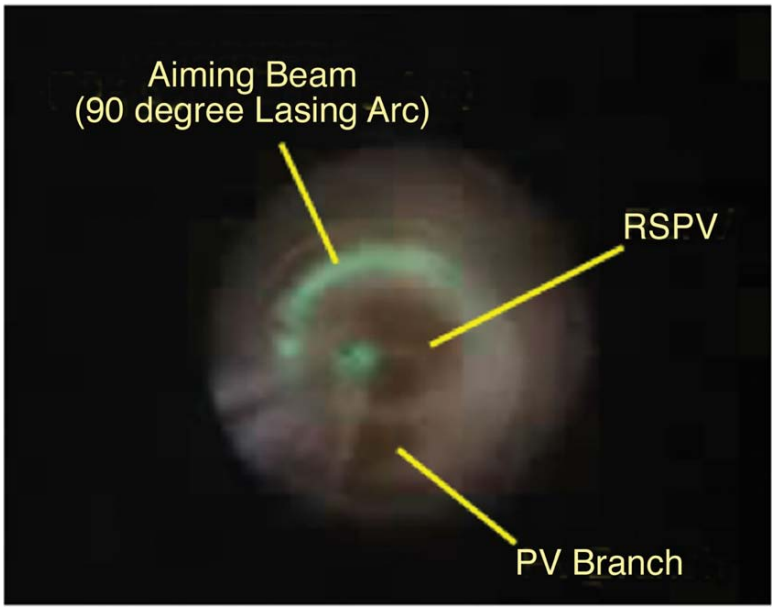

Figure 11 Endoscopic image of the right superior pulmonary vein (RSPV) in a patient with paroxysmal atrial fibrillation (AF). The aiming beam (green arc) located a 90° laser arc just inside the RSPV ostium. *PV* pulmonary vein

Significant PV stenosis (>50% narrowing) did not occur in any patient. Right phrenic nerve injury occurred in one patient. Stroke (reversible ischemic event) occurred in one patient. Pericardial tamponade occurred in one patient.

Cryothermal Balloon Catheter

Cryothermic ablation is associated with minimal risk of thrombus formation.[25] Cryoablation creates minimal endothelial/endocardial disruption and preserves the tissue architecture, suggesting a lower risk of vessel stenosis.[26] However, cryoablation lesions are heavily dependent on contact between the ablation catheter and the tissue and are decreased by warming blood flow.[27–29]

A novel cryothermal balloon catheter has been developed to improve the catheter–tissue contact and decrease the local blood flow at the PV ostium. The cryothermal balloon ablation system (Arctic Front, CryoCath Technologies Inc., Kirkland, Canada) consists of a 10 F catheter with double inner–outer cooling balloons to prevent refrigerant leakage (23- or 28-mm diameter; Figure 12) and is advanced over a guide wire through a 12F deflectable sheath. The refrigerant (N_2O) is delivered under pressure from the console into the inner balloon chamber, where it undergoes a liquid-to-gas phase change, resulting in balloon cooling to −80 °C.

Preclinical In Vivo Canine Study

Sarabanda et al. utilized a canine model to test the safety and efficacy of the cryothermal balloon catheter to produce circumferential transmural lesions at the PV orifice for isolation.[30] Eight dogs were studied via closed chest

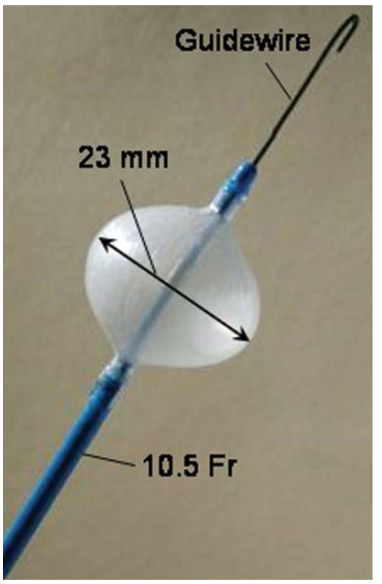

Figure 12 Cryothermal balloon ablation catheter. The balloon is 23 mm in diameter and the shaft size is 10.5 Fr and is compatible with a 12 Fr deflectable sheath. A guide wire (0.035 inch) within the central lumen of the catheter is utilized to position the balloon into the PV.

under ketamine and diazepam anesthesia. After transeptal puncture, the 12F deflectable sheath was placed into the LA. Selective PV angiography was performed before and after ablation. Intracardiac ultrasound imaging of the PV and LA was also performed for catheter placement.

The deflated cryothermal balloon catheter was advanced into the PV ostium, and the balloon was then inflated. Balloon–PV contact was verified by both Doppler flow examination and repeated contrast injection through the central lumen of the catheter (occlusion angiography). The location of any periballoon blood flow leakage was recorded and referenced to the position of the PV ostium. In all eight dogs, cryothermia was delivered to both the RSPV and LSPV with a balloon temperature of −80 °C. Ablation was performed one or two times for 4 or 8 min. Efficacy was defined as complete elimination of all PV potentials (confirmed by Lasso catheter mapping).

Complete PV isolation was achieved in 14 (88%) of the 16 PVs. Two dogs were sacrificed immediately after ablation, and the remaining six dogs (11 of the 12 PVs had complete isolation) were sacrificed 1 week after ablation. In the six chronic AF dogs, mapping of the targeted PVs prior to sacrifice at 1 week after ablation showed continued complete PV isolation in 10 of the 11 acutely isolated PVs. The success rate for chronic PV isolation was significantly higher in the absence of any periballoon blood flow leakage during ablation and with the achievement of lower balloon temperatures (10 of 10 PVs with temperature below −80 °C vs 0 of 2 PVs with balloon temperatures above −73 °C; $p = 0.015$). In the six chronic AF dogs, gross and histological examination showed a complete circumferential, transmural lesion at the PV orifice in all 10 PVs with successful PV isolation. In the two PVs with incomplete

isolation, a noncircumferential lesion with a gap at the inferior aspect of the PV was identified.[30]

There was no significant narrowing of the PV orifice in any dog. Right phrenic nerve palsy was seen in four of the eight dogs immediately and at 1 week after ablation. The ablation lesion extended to the right phrenic nerve in these four dogs. There was no evidence of injury to the esophagus.

Clinical Feasibility Study

The initial feasibility study using the cryothermal balloon catheter was performed in Germany in 49 (36 males and 13 females, mean age 59 ± 11 years) patients undergoing catheter ablation of drug-resistant AF.[31] Forty-two patients had paroxysmal AF, and 7 patients had persistent AF. The LA size was 42 ± 5 mm.

Cryoablation was performed by using a 28- or 23-mm balloon (Arctic Front). After transeptal puncture, PV angiography was performed to measure PV ostial diameter (mean 18.8 ± 4 mm). The cryothermal balloon catheter was advanced to the PV ostium over a guide wire though a 12F sheath. A mean of 2.4 ± 0.6 cryothermia applications (8 min for each application) were delivered to each PV. The mean balloon temperatures were −48 °C ± 19 °C. Using the cryoballoon, PV isolation was achieved in 72% of the left PVs, 73% of the RSPVs, and 59% of the RIPVs. In all PVs with residual PV potentials, cryoablation using the 9F cryocatheter eliminated all PV potentials in all patients. During a short-term follow-up of 3 to 6 months, 24 of 31 (77%) patients (including 5 patients with repeat ablation) had no recurrence of AF on Holter monitor.

There was no significant PV stenosis. Right phrenic nerve palsy occurred in 3 of the 49 patients.

Summary

This chapter describes new balloon ablation technology for PV isolation using three non-RF energy sources (HIFU, laser energy, and cryothermia). All three systems are promising for the elimination of the difficulty of point-by-point ablation for PV isolation. The principal limitations for all balloon technologies are (1) a prominent LAA ridge for isolation outside the PV ostium (presently HIFU) and (2) the potential for collateral injury, including right phrenic nerve injury during right PV isolation and esophageal injury. To prevent phrenic nerve injury, it may be helpful to maintain balloon positions outside the RSPV ostium and limit pushing the balloon against the RSPV. For HIFU, circumferential balloon contact is not required to produce a circumferential transmural lesion. To prevent esophageal injury, it may be helpful to avoid ablation within a few millimeters of the esophagus.[18]

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28

Remote Catheter Navigation

Walid Saliba, Sabine Ernst, Vivek Reddy, and Karl-Heinz Kuck

Abstract: Percutaneous catheter ablation has emerged as a promising curative modality for the treatment of atrial fibrillation (AF). However, the safety and success of this procedure are operator dependent and require precise catheter manipulation and stable contact during ablation. Remote catheter navigation has the potential to remove some of the barriers traditionally associated with percutaneous catheter ablation, such as the need for manual dexterity and long radiation exposure times, thus enabling more physicians to perform these procedures. Initial experience with the remote magnetic navigation system (MNS) shows the safety and feasibility of mapping and ablation of various arrhythmias, including successful ablation of AV Nodal Re-entrant Tachycardia (AVNRT), atrial flutter, and fibrillation as well as ventricular tachycardia. An initial learning curve is suggested, with eventual benefits including decrease in fluoroscopy and ablation time, mainly related to those hard to reach areas. Remote robotic navigation has been assessed predominantly for atrial ablation. In a preclinical animal study, target sites were accurately attained, and radio-frequency (RF) ablation was performed with no complications in both atria. In human trials, remote robotic navigation was shown to be safe and effective for mapping and ablation of atrial fibrillation and flutter as well as atrioventricular (AV) nodal reentrant tachycardias. These preliminary results regarding remote catheter navigation appear promising. Their added advantage over the current conventional approach in terms of improving the success rate while minimizing risk for both the patient and the operator remain to be proven in large-scale clinical trials.

Keywords: AF catheter ablation; Remote magnetic navigation; Remote robotic navigation; 3-D mapping systems.

Background

Catheter ablation is an established curative modality for various arrhythmias. Both navigation and precise positioning and stability of the ablation catheter are crucial for the overall success of the procedure. Some of the potential difficulties include difficulty in reaching certain areas within the cardiac

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chambers, the inability to hold a catheter in a steady location while therapy is performed, and percutaneous catheters with insufficient bend radii and limited degrees of freedom. Therefore, the need for catheter navigation systems that would aid in removal of these barriers has become apparent. The goal of such systems is to remove the need for manual dexterity, which lessens the physician experience curve for complex arrhythmia ablation, thus enabling more physicians to perform these procedures in a safe and effective manner.

Remote Magnetic Navigation

Baseline Concept of Magnetic Navigation

The principle of the MNS (Niobe®, Stereotaxis Inc.) has been described in detail.[1] In brief, it consists of two computer-controlled permanent magnets positioned, relative to each other, on either side of the fluoroscopy table (Axiom Artis®, Siemens, Germany) (Figure 1). While positioned in "navigate" position, a uniform magnetic field (0.08 T) of about 15-cm diameter is created inside the chest of the patient. The soft mapping and ablation catheter is also equipped with small permanent magnets embedded at the tip and that align parallel to the externally controlled magnetic field direction. By changing the orientation of the outer magnets relative to each other, the orientation of the magnetic field changes and thereby leads to a deflection of the catheter. All magnetic field vectors can be stored and if necessary reapplied—navigating the magnetic catheter automatically back to the selected site. In addition, a computer-controlled catheter advancer system (Cardiodrive® unit, Stereotaxis Inc.) is used to allow truly remote catheter navigation without the need for manual advancement/retraction.[2] The video workstation (Navigant II®, Stereotaxis Inc.) unit allows precise orientation of the catheter by joystick or mouse from the control room (Figure 2).

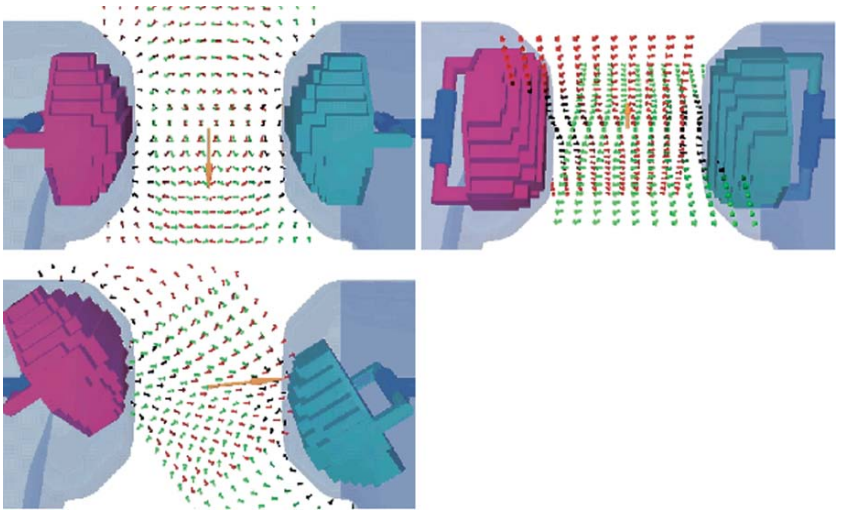

Figure 1 Schematic of the outer magnetic field (0.08 T) with different magnetic field lines (small red and green arrows). Magnetic device is depicted as a yellow arrow that aligns parallel to the magnetic field direction

Figure 2 **A** The examination room with magnets in "navigate" position. **B** Control room with Navigant workstation, foot switch for radiation (arrow), remote control of C-arm (asterisk), and foot switch of the radio-frequency generator (cross)

Clinical Experience

Since the orientation of the magnetic catheter tip is completely performed using the outer permanent magnets, the shaft of the catheter is very soft to allow all degrees of freedom. Therefore, the risk of perforation is extremely low. No such complication has been reported. The available catheters are equipped with a 4-mm solid tip to allow conventional radio-frequency (RF) current application using standard RF generators. Over the last 3 years, three generations of ablation catheters have been made available for clinical practice

in Europe; the initial catheter consisted of a 4-mm solid tip and a ring electrode together with a single magnet embedded in the tip. The next generation of catheters consisted of the same electrode configuration but a total of three miniaturized magnets in the tip. The most recent catheter has a total of three ring electrodes, thereby allowing the recording of two bipolar electrograms as in standard RF ablation catheters.

The initial experience of a multicenter mapping trial in the United States proved that the MNS allows safe and efficient mapping in all cardiac chambers.[3] Successful remote catheter ablation was published on patients with atrioventricular (AV) nodal reentrant tachycardia.[2,4,5] Regarding accessory pathway ablation, several iterations (especially in catheter design) and a primarily transseptal access improved the success rate in these patient cohorts to match the results of conventional ablation.[6,7]

Entering the field of ventricular tachycardia (VT), a first report has been published meanwhile on idiopathic VT originating in the right ventricular outflow tract.[8] Success rates matched the conventional ablation technique as expected.

Combination with Three-Dimensional Mapping Systems

The next necessary step in the development of the MNS to address more complex arrhythmias is the combination with a three-dimensional (3-D) mapping system. The first compatible 3-D system was the NavX (St. Jude Medical). Using irrigated-tip, custom-made catheters, successful 3-D mapping of the left atrium (LA) in a total of four patients was performed. Subsequently, long linear lesions were applied completely remote controlled around the ipsilateral pulmonary veins (PVs) according to the "double-Lasso" technique. All patients were successfully treated, and three of four patients had no recurrences during a follow-up of more than 1 year. The remaining patient underwent a second ablation procedure demonstrating single conduction gaps in both the septal and lateral PV isolation line, which were successfully eliminated using conventional irrigated-tip ablation.

Meanwhile, a compatible electroanatomical system is available for clinical use (CARTO RMT, Biosense Webster Europe) (Figure 3). The initial experience demonstrated good clinical results with regard to mapping accuracy; however, since there are no prospective "head-to-head" comparisons, no conclusion can be made yet about efficacy. Table 1 summarizes the 3-D mapping experience in our center with regard to mapping time and radiation exposure for the investigator.[9]

There is only one report on experience using a solid 4-mm tip catheter and the CARTO RMT system for catheter ablation of atrial fibrillation (AF) in a total of 40 patients.[10] In all patients, mapping of the LA was remote controlled. Subsequently, the investigators applied RF current for 15 s for a given site to ablate around the PVs and LA linear lesions (mitral and posterior). No information is given about line completeness and results of follow-up. Compared to the conventional ablation approach (using irrigated-tip standard catheters), the authors reported a significant reduction of ablation time for the septal PVs.

Another center has also reported their experience using the solid 4-mm tip catheter and the CARTO RMT system for catheter mapping and ablation of scar-related VT in a total of 24 patients.[11] The ventricular scar substrate in this patient cohort included remote myocardial infarction, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, and sarcoidosis in one patient. Electroanatomical mapping of the left ventricular,

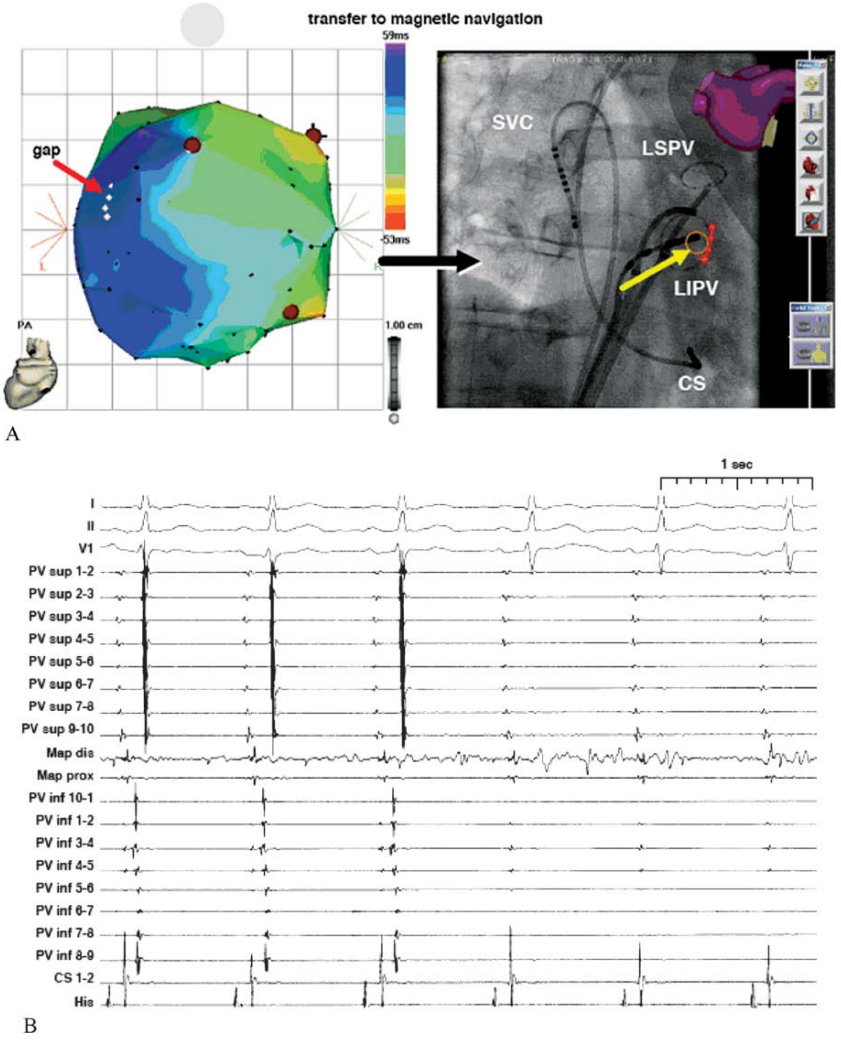

Figure 3 **A**Three-dimensional reconstruction of the left atrium using the magnetic navigation system in conjunction with the CARTO RMT system (*left panel*). The corresponding fluoroscopic image (*right panel*) depicts in Right anterior oblique (RAO) projection the Lasso catheters in both lateral pulmonary veins (PVs). Marked in red is the area where the conduction gap of a previously applied PV isolation line around the ipsilateral PVs is located. Transfer of the design line from the CARTO RMT is performed to automatically calculate the magnetic field vector. **B** Intracardiac recordings during radio-frequency delivery at this site eliminating the typical PV spike potential on both superior and inferior Lasso catheters, thereby proving a single gap along the ablation line. *CS* coronary sinus, *dis* distal, *His* His bundle recording, *LIPV* left inferior pulmonary vein, *LSPV* left superior pulmonary vein, *Map* ablation catheter, *prox* proximal, *PA* pulmonary artery, *PV inf* inferior pulmonary vein, *PV sup* superior pulmonary vein

right ventricular, and ventricular epicardial surfaces was constructed in 24, 10, and 12 patients, respectively (see Figure 4 for example). Complete chamber VT activation maps were created in four patients. A total of 77 VTs were inducible, of which 21 were targeted during VT using the remotely navigated RF ablation catheter alone (the remainder of the VTs were targeted using a substrate-based approach during sinus rhythm). With a combination of

Table 1 Results of single-center three-dimensional mapping using either the CARTO RMT or the NavX system.

Remote navigation success	13/13 (100%)
Reconstructed chamber	Left atrium in 6 patients
	Right atrium in 7 patients
Required mapping time (min)	NAVx: 81.7 (65.3–110.7)
	CARTO-RMT: 46.2 (45.6–49.3)
Total fluoroscopy (min)	17.2 (16.2–42.0)
	Applied from exam room: 14.3 (6.3–22.0)
	Applied from control room: 6.7 (3.1–10.3)

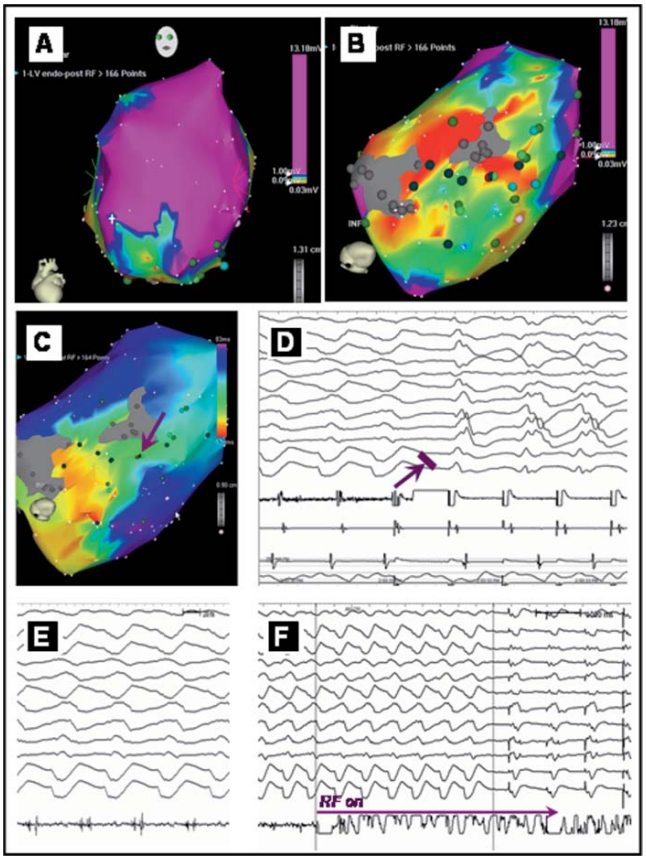

Figure 4 Ablation of post-myocardial infarction (MI) ventricular tachycardia (VT) with remote magnetic navigation. Bipolar voltage maps of the left ventricle (LV) endocardium are shown in anteroposterior (AP) (**A**) and inferior (**B**) views. **C** An activation map of the monomorphic VT in the inferior view. **D** An entrainment attempt at an inferior site (noted by the arrow) revealed termination of the VT by a nonpropagated impulse. **E** The beat-to-beat stability of the diastolic potential electrograms. The VT was eliminated after approximately 4 s on delivery of radio-frequency energy to this site (F)

entrainment and activation mapping, 17/21 VTs (81%) were successfully terminated in a mean of 8.4 ± 8.2 s; for the remainder, a manual irrigated RF ablation catheter was necessary. The mean fluoroscopy times for endocardial and epicardial mapping were 27 ± 23 s (range 0 to 105) and 18 ± 18 s (range

0 to 49), respectively. In concert with a manually navigated irrigated ablation catheter, 75/77 VTs (97%) were ultimately ablated. Four patients underwent a second procedure for recurrent VT, three using the MNS. After 1.2 procedures/patient, VT did not recur during a mean follow-up of 7 ± 3 months.

This study provided clinical evidence for the safety and feasibility of remote catheter navigation in performing ventricular substrate mapping in a wide range of disease pathologies. Remote magnetic navigation proved capable of performing each of the three major components of substrate-based VT ablation: (1) delineating and identifying endocardial and epicardial scar tissue, (2) performing the necessary electrophysiological maneuvers to identify those arrhythmogenic zones critical for maintaining tachycardia, and (3) delivering RF energy to terminate both endocardial and epicardial VT. Also, the "soft touch" of the remotely guided catheter permitted detailed endocardial and epicardial ventricular mapping with minimal fluoroscopy use.

Benefits

Besides the obvious reduction of the radiation exposure for the investigator, a significant reduction in total radiation exposure has been demonstrated in supraventricular tachycardia (SVT) ablation (AVNRT and accessory pathway ablation).

Impact on Future Ablation Procedures

Automatization of the sequential mapping process could possibly result in further reduction of procedure duration. Finally, improvement of the ablation catheter maneuverability and addition of different ablation techniques (such as irrigation) and energy sources (e.g., cryothermia) will undoubtedly extend the accessible arrhythmias using this novel platform technology.

Summary

Remote catheter ablation of mostly SVT using the new MNS Niobe has been reported to be highly effective. Using the cardiac advancer system (Cardiodrive, Stereotaxis Inc.) in conjunction with the MNS, mapping and ablation can be performed completely by remote control from the control room, therefore avoiding exposure of the investigator to scattered radiation from the patient during the ablation process.

Remote Robotic Navigation

Baseline Concept of Robotic Navigation

The Hansen robotic system integrates robotic technology with computed movement. The key aspect is an electromechanical manipulator that is designed to provide physicians with precise catheter control and 3-D navigation within the heart from the workstation, while the operator is away from the operating table.

The Sensei system has three main components: physician workstation, instinctive motion controller, and setup joint (Figure 5). The Sensei system is designed to operate in conjunction with the Artisan control catheter (Figure 6), which consists of a steerable guide catheter (SGC) and sheath (SGS). This contains a through lumen to accommodate the percutaneous catheters.

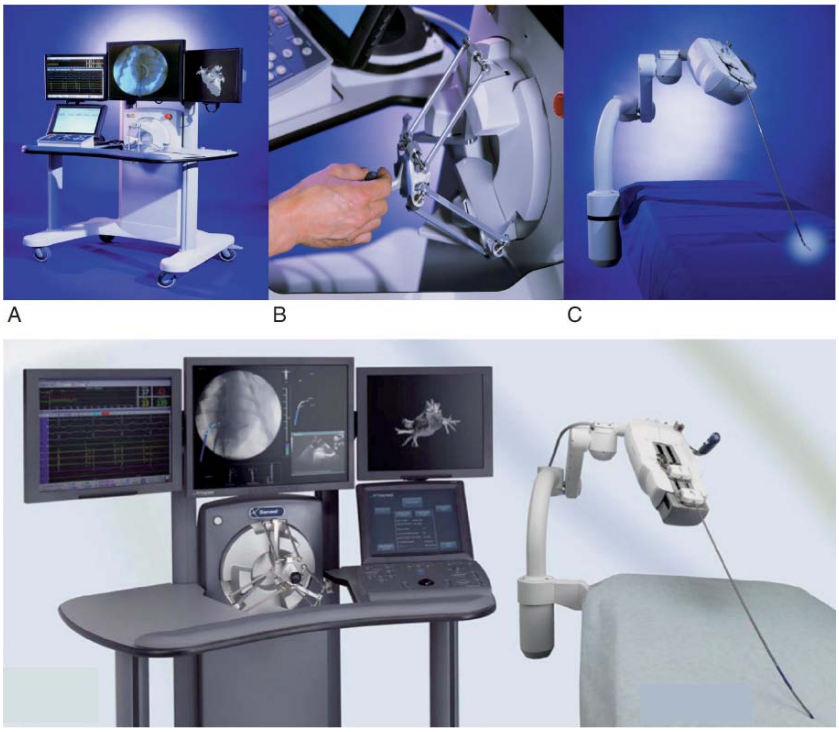

Figure 5 Hansen robotic system: **A** Physician workstation. **B** Instinctive motion controller. **C** Remote catheter manipulator

Figure 6 Steerable guide catheter inside a steerable sheath that **A** consists of an 8.5F through lumen. It mounts on portable robotic catheter manipulator (**B**) and has 6° of freedom (**C**)

The physician workstation consists of three monitors and a control console. The center monitor has real-time fluoroscopy imaging together with a synchronized ghost catheter. The other monitors are compatible with other 3-D mapping technology (CARTO, NavX), fluoroscopy, intracardiac echocardiography (ICE), and other recording systems.

The instinctive motion controller allows precise and direct catheter movement irrespective of image orientation. Hand movement corresponds to the particular view selected.

The robotic catheter manipulator is attached at the fluoroscopy table bedside rail via a setup joint and the Artisan control catheter is mounted on it. This unit responds to the commands input from the physician through the instinctive motion controller at the workstation.

The Artisan control catheter (RCM) consists of an outer sheath with unidirectional steerability that is mainly used for support and an 8F SGC. A set of four pull wires direct the tip of the sheath in various directions. As the physician's hand moves at the motion controller, this computed position is updated over 1,000 times each second and articulates the pull wires constantly to move the tip of the guide catheter with the mapping catheter through it. This allows the physician to access hard-to-reach areas in a precise and controlled manner and to maintain stability during interventional procedures. Unlike the stereotaxis system, in which the mapping or ablation catheter is custom designed to have embedded magnets that allow their use with that system, the robotic system allows any available (8F) catheter to be used through the SGS.

The force applied from the catheter onto the tissue can be estimated via a new technology (Intellisense) that is currently under study.

Clinical Experience

This system has been evaluated so far in two phases. In a preclinical phase, the safety and feasibility of catheter navigation, including LA instrumentation and transseptal puncture, were evaluated in the animal lab with the objective of evaluating the ability to remotely navigate to a series of 20 anatomical targets in the right atrial (RA) and LA and ventricles. During this preclinical evaluation, all of the anatomical targets were reached in all animals. The RF ablation and 3-D surface mapping were performed in four animals. Gross and histological pathology showed no evidence of perforation or other trauma. This preclinical study indicated feasibility of using the Sensei system for accurate control of the mapping and RF catheters and their stability at the target points.[12]

The second phase involved a human clinical trial with the objective to determine whether the improved control and placement of cardiac catheters using the Sensei system and Artisan catheter experienced during the preclinical study would transfer to human patients. The system was used to perform LA and RA mapping and RF ablation of AF and atrial flutter (AFL). A total of 39 patients with antiarrhythmic drug (AAD) refractory atrial arrhythmias were studied. In all patients, 3-D reconstruction of the corresponding atrial chamber anatomy was performed using the CARTO electroanatomical mapping system (Biosense Webster, Diamond Bar, CA) or the EnSite NavX system (St. Jude Medical, Minneapolis, MN). In patients undergoing AF ablation, two transseptal punctures (TSPs) were performed under ICE guidance, with one of the TSPs performed using the Sensei system. Pulmonary vein antrum isolation (PVAI) was performed using a 3.5-mm NaviStar ThermoCool® catheter (Biosense Webster) steered via the Artisan catheter and electrical isolation verified by circular mapping (see Figs. 7 and 8). All PVs as well as the superior vena cava (SVC) were successfully isolated. In nine patients, AFL was mapped and ablated, with bidirectional block obtained.

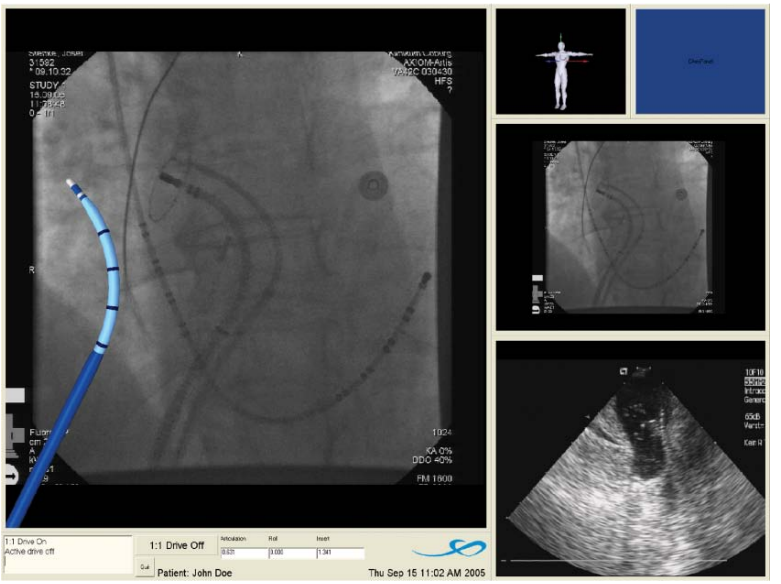

Figure 7 Main display showing the circular mapping catheter at the os of the right superior pulmonary vein (RSPV) with the ablation catheter through the steerable guide catheter (SGC) during mapping. The virtual catheter is seen on the left side of the screen and follows the same direction and orientation as the true catheter. Inserts displayed in the main screen show live intracardiac echocardiography (ICE) (lower right corner) where the mapping catheter is seen at the os of the RSPV

Two patients developed pericardial tamponade requiring pericardiocentesis with no further sequelae. The tamponade in one patient was the result of the manual TSP and unrelated to the use of the Sensei system; the procedure was aborted in this patient.

At 90-day follow-up, 31 patients were free from atrial arrhythmia, including 5 patients off AADs. Two patients developed a recurrent atrial arrhythmia, one AF patient required another procedure for AFL.[13]

The system has been used to a limited extent in other arrhythmias. Electrophysiological testing and RF ablation of the slow pathway was performed successfully in two patients with AVNRT with no complication reported. To date, there have not been any studies to evaluate the performance of the system in ventricular navigation and ablation of VT.

Advantages

Because of the remote location of the workstation from the fluoroscopy, radiation exposure to the physician is significantly reduced. Early experience showed an average of 12-fold reduction in radiation dosage between a bedside dosimeter and one located at the workstation, 3 to 4 meters away. Potentially, because of better catheter stability and easier navigation, total radiation exposure should be reduced; however, further head-to-head studies are needed to be able to answer this question. Furthermore, better access to hard-to-reach areas, precise control of the catheter tip, better stability and consistent contact, together with the potential for fine movement will lead to a reduced demand for manual skills.

In addition, the exquisite control afforded by the application of robotic technology to catheter manipulation together with the automatization of sequential mapping and ablation may allow for the emergence of a standardized approach to ablation and mapping of complex arrhythmias.

Conclusion

This initial human experience with remote catheter navigation suggests that mapping and ablation of various arrhythmias and more specifically AF are safe and feasible. The preliminary results with respect to long-term success are similar to those experienced using a conventional mapping-and-ablation approach. Further integration of this novel remote navigation tool with 3-D imaging and electrical mapping will provide a powerful tool for the mapping and ablation treatment of complex arrhythmias. With improved catheter stability and contacts with such systems, more investigation is needed to evaluate whether different energy output parameters are needed as compared to manual and conventional ablation catheters.

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Insight into the Pathophysiology of Atrial Flutter and Its Relationship to Atrial Fibrillation

Oussama Wazni and Andrea Natale

Abstract: Atrial flutter (AFL) and atrial fibrillation (AF) are frequently associated. Both are reentrant tachycardias; AFL is usually a stable macroentrant tachycardia with defined boundaries of areas with functional or anatomical block, whereas AF is a multiwavelet reentrant tachycardia with shifting activation. It has been reported that more than 50% of patients with one of them will at some point exhibit the other arrhythmia. This can be spontaneous, secondary to medications, after ablation, or after surgical procedures. Triggers that can initiate AF, whether the pulmonary veins or other extrapulmonary foci, also trigger AFL in the setting of lines of block. These lines of block can be functional as a result of antiarrhythmic drug therapy or anatomical lines, which can be native, as in typical AFL or iatrogenic anatomical lines of block after surgery or previous ablation.

Keywords: Atrial fibrillation; Atrial flutter; Catheter ablation; Macroentrant tachycardia.

Introduction

Atrial fibrillation (AF) and atrial flutter (AFL) are known to be related to each other. [1–3] However the relationship has not been definitively elucidated yet. This chapter addresses some issues about the arrhythmia mechanism and the relationship between AF and AFL.

Atrial flutter and AF are frequently associated with each other. Both are reentrant tachycardias. Atrial flutter is usually a stable macroentrant tachycardia with defined boundaries of areas with functional or anatomical block, whereas AF is a multiwavelet reentrant tachycardia with shifting activation. It has been reported that more than 50 % of patients with one of them will at some point exhibit the other arrhythmia. This can be spontaneous, secondary to medications, after ablation, or after surgical procedures.

From: *Contemporary Cardiology: Atrial Fibrillation, From Bench to Bedside*
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Spontaneous Conversion

Ambulatory monitoring frequently documents the coexistence of AF and AFL. In the analysis of incidence and predictors of AFL in the general population presented by Granada et al.,[3] 58% of patient with new onset AFL also had at least one episode of spontaneous AF. It is recognized that conversion of AF to AFL is a more common phenomenon. Roithinger et al.[4] identified a transitional period of organized activation they termed *streaming* along the lateral and inferior annulus. They found that the occurrence of this streaming reliably predicted the onset of AFL.

Watson and Josephson[5] also reported that AF is a frequent transitional rhythm during induction of AFL.

Ortiz et al.,[6] in a sterile pericarditis dog model, showed that although 50% of AFL transformed into AF without intervention, this was brief, and that in all dogs AF converted to AFL spontaneously. In the other 50%, adenosine triphosphate (ATP) had to be administered for conversion of AFL to AF. In the study, it was shown that AFL results from the formation of a long line of functional block followed by stable reentrant circuits with subsequent appearance of areas of slow conduction.

Atrial flutter degenerated to AF with decreasing cycle length because of ATP administration or was spontaneously followed by a decrease in the length of functional block and finally the development of unstable reentrant circuits, which changed location, shape, and cycle lengths. The same group[6] also showed that, in the sterile pericarditis model, that AFL does not start without first having a transitional rhythm that is very close to AF. This transitional rhythm then becomes AFL once the lines of block are established.

In clinical practice, it has also been shown that conversion of AF to AFL is much more common, whether spontaneous or induced by medications or invasive procedure such as ablation.

As a Result of Medications

The conversion of AF to AFL is well described in clinical practice. Class IC antiarrhythmic medications are known to cause increased AFL in patient with AF. This is exemplified by flecainide, which is used to treat AF. As a result, AFL with 1:1 conduction occurs. This is thought to be caused by the development of functional block, therefore forcing the activation front through local anatomical barriers, resulting in stable AFL.

In such patients, there is a high rate of postablation AF after cavotricuspid isthmus ablation for medication-induced AFL. This has been studied further by Kumagai et al.,[7] who showed that pulmonary vein (PV) triggers actually result in AFL. Reithmann et al.[8] also reported that in such patients there was still a high incidence of AF. Our group[9] has also shown that, in patients with both AFL and AF, pulmonary vein isolation (PVI) results in suppression of both AF and AFL without the need for isthmus ablation.

As a Result of Ablation or Surgery

Atrial flutter is also known to be a complication of ablation of AF. Early postablation atypical AFL has been shown to abate after lesion maturation after AF ablation. This implies that once the triggers of AF are ablated, then most iatrogenic AFL can be avoided[10–12].

Our group has shown that atypical AFL that occurs late after AF ablation can usually be treated with repeat PVI except patients with significant scar. In the latter group, defining the AFL circuit and ablating a critical isthmus is beneficial.

In addition, our group and others have shown that a significant proportion of postmaze arrhythmias are incisional flutters, and that to fully treat this subset of patients, reisolation of veins and flutter isthmus ablation are essential[12–13]. As mentioned, our group demonstrated that pulmonary vein antrum isolation with no history of cardiac surgery[9]. This is in contradistinction to those with previous cardiac surgery, for whom there was a higher recurrence of AFL and a need for further AFL ablation. This implies that once the triggers of AF are ablated, then most iatrogenic AFL can be avoided.[10–12]

Common Triggers

Hsieh et al.[14] identified triggers of transition of AFL to AF. They found that ectopic beats from the PVs (85%), crista terminalis (two foci, 10%), and superior vena cava (one focus, 5%) were responsible for conversion of AFL to AF. After successful ablation of these foci, no spontaneous transition was observed.

Kumagai et al.[15] suggested that focal activation originating from the PVs may trigger AFL and concluded that cavotricuspid isthmus (CTI) ablation combined with PVI should be considered in such patients.

Conclusion

It is possible to conclude that triggers that can initiate AF, whether the PVs or other extrapulmonary foci, also trigger AFL in the setting of lines of block. These lines of block can be functional as a result of antiarrhythmic drug therapy or anatomical lines, which can be native as in typical AFL or iatrogenic anatomical lines of block after surgery or previous ablation.

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Ablation Strategies for Left Atrial Flutter

Sumeet K. Mainigi, Edward P. Gerstenfeld, and David J. Callans

Abstract: Focal atrial tachycardia and macroreentrant left atrial (LA) flutter are proarrhythmic complications of atrial fibrillation ablation, occurring with varying incidence from 2% to 30%. We describe an organized approach to the diagnosis and treatment of these troublesome arrhythmias. Practical management options for treating these arrhythmias are discussed, including conservative therapy, pharmacologic options, and repeat ablative therapy. Diagnostic approaches to localizing focal tachycardias and macroreentrant flutters using the surface electrocardiogram and electrophysiological maneuvers such as entrainment and electroanatomic activation mapping are discussed. Approaches to ablation of focal and macroreentrant tachycardias are described. Data on prognosis and complications are also presented. Recommendations are given to avoid developing this proarrhythmic complication following the initial atrial fibrillation ablation procedure.

Keywords: Ablation; Atrial fibrillation; Atrial tachycardia; Flutter; Left atrial flutter; Left atrial tachycardia; Proarrhythmia.

Introduction

Radio-frequency (RF) ablation of the pulmonary veins (PVs) through segmental[1–3] or wide circumferential[4,5] isolation has become an effective treatment for patients with refractory atrial fibrillation (AF). Despite the success rate, reported to be in excess of 60% to 85%,[2,3,6–8] a number of postprocedural complications have been reported, including early and late recurrence of AF, cardiac tamponade, atrioesophageal fistula,[9,10] and PV stenosis. In addition, in select patients the procedure can be proarrhythmic, leading to subsequent development of an organized focal or macroreentrant left atrial (LA) flutter or tachycardia.[11–14] Different strategies have been employed to prevent the occurrence of these arrhythmias during the index procedure with mixed results. As the volume of AF procedures increases, addressing the consequent arrhythmias will become a growing challenge. In this chapter, we briefly outline the incidence and mechanisms of LA flutter postablation and discuss a strategy to treat this arrhythmia.

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Definition of Left Atrial Flutter

Confusion has abounded in the literature regarding the distinction between atrial tachycardias and atrial flutters. Based on surface electrocardiograms (ECGs), *atrial flutters* have been loosely defined as regular atrial arrhythmias faster than 240 to 250 beats/min without evidence of isoelectric baselines between atrial deflections. The Working Group of Arrhythmias of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology in 2001 published a position paper defining atypical atrial flutter as an atrial tachycardia with an ECG pattern of continuous undulation of the atrial complex, different from typical counterclockwise or clockwise flutter encircling the tricuspid valve, with a rate of 250 beats/min or higher. The group cautioned that true diagnosis is dependent on understanding of the mechanism through electrophysiological study.[15] This definition has been prospectively used in clinical trials evaluating LA flutter post-AF ablation.[15–17] In this chapter, we use the term *LA flutter* to refer primarily to macroreentrant tachycardias originating in the LA and use the term *LA tachycardia* to refer primarily to focal tachycardias originating from the PVs or ablation lines.

Incidence

Left atrial flutter occurs rarely in those without previous ablative or surgical procedures, and the exact incidence is unknown, although most occur in the setting of structural heart disease. Jais et al. reported concerning a series of 22 patients with LA flutter for a mean of 5 years. Of these patients, 77% (17/22) had evidence of structural heart disease, including 3 with mitral valve repair or replacement, 1 with aortic valve replacement, and 2 with previous typical flutter ablation. The remaining patients had evidence of valvular disease without previous intervention or ischemic, dilated, or hypertrophic cardiomyopathies. Two of the 5 patients without evidence of overt structural heart disease demonstrated evidence of electrically silent areas, potentially suggesting an underlying atrial myopathy.[18] The mechanisms in these cases were mainly macroreentrant circuits limited by native or functional barriers.

Most cases described in the literature and in our experience, however, involve patients who had previously undergone atriotomy for valve or other cardiac surgery or following percutaneous or surgical ablative procedures for AF. Left atrial flutter has been demonstrated to occur following percutaneous, catheter-based segmental PV ostial ablation[12,19] or wide circumferential ablation,[14,17,20,21] with or without additional linear lesion sets; operative RF ablation with wide line encircling of the PVs with a mitral isthmus line under direct visualization[22]; and following a surgical maze procedure.[23]

Table 1 shows the reported incidence of LA flutter following these various procedures. There is evidence that some LA flutters may resolve in the weeks to months following the initial procedure, which has an impact on management (discussed in the management section).[16,17,21] Occurrence of LA flutter during the initial ablation procedure or inducibility of LA flutter at the conclusion of the initial AF procedure does not necessarily correlate with long-term recurrence.[16,17,24]

Table 1 Incidence of left atrial flutter following various surgical and percutaneous procedures

Authors	Technique	Additional lesions	Incidence (%)	Time postprocedure (approximate)
Gerstenfeld et al.[12]	Segmental PV isolation	None	2.9	5.7 ± 2.8 months
Daoud et al.[16]	Two encircling lines around ipsilateral right and left PV ostia	Posterior wall line (or roof line)	8.9	4.2 ± 0.6 months
		Mitral isthmus line		
Ernst et al.[20]	Circular lesion around all PV ostia	Mitral isthmus line	9.5	32 ± 13 months
Ernst et al.[20]	Roof line	Middle of roof line to anterior mitral annulus	10	27 ± 11 months
		Roof line to posterior mitral annulus		
Ernst et al.[20]	Two encircling lines around ipsilateral right and left PV ostia	Posterior wall line	14	17 ± 5 months
		Mitral isthmus line		
Ernst et al.[20]	Two encircling lines around ipsilateral right and left PV ostia	None	0	13 ± 4 months 11 ± 5 months
Pappone et al.[21]	Two encircling lines around ipsilateral right and left PV ostia	None	10	After 6 weeks
Pappone et al.[21]	Two encircling lines around ipsilateral right and left PV ostia	Two posterior wall lines	3.9	After 6 weeks
		Mitral isthmus line		
Oral et al.[4]	Segmental PV isolation	None	0	5.4 ± 3.0 months
Oral et al.[4]	Two encircling lines around ipsilateral right and left PV ostia	Posterior wall line	2.5	5.4 ± 3.0 months
		Mitral isthmus line		
Chugh et al.[17]	Two encircling lines around ipsilateral right and left PV ostia	1 or 2 posterior wall line(s)	16	After 3 to 6 months
		Mitral isthmus line		
Villacastin et al.[44]	Focal PV isolation	None	6.6	2 months
Kobza et al.[28]	Two encircling lines around ipsilateral right and left PV ostia	Posterior wall line (or roof line)	6.7–11.3 (4.6% did not undergo repeat study)	5.3 ± 3.2 months
		Mitral isthmus line		
Ouyang et al.[48]	Two encircling lines around ipsilateral right and left PV ostia	None	24.3	178 days
Cummings et al.[30]	Segmental PV isolation	None	3.1	3 to 12 months
Mesas et al.[14]	Two encircling lines around ipsilateral right and left PV ostia	Posterior wall line	4.7	2.6 ± 1.6 months
		Mitral isthmus line		
Ouyang et al.[40]	Two encircling lines around ipsilateral right and left PV ostia	None	29	8 months

(continued)

Table 1 (continued)

Authors	Technique	Additional lesions	Incidence (%)	Time postprocedure (approximate)
Oral et al.[49]	Two encircling lines around ipsilateral right and left PV ostia	Posterior wall line	19	6 months
		Mitral isthmus line		
Oral et al.[49]	Two encircling lines around ipsilateral right and left PV ostia	Posterior wall line	27	6 months
		Mitral isthmus line		
		Left atrial septal line		
		Roof line		
		Posterior mitral annulus line or anterior wall line		
Sanders et al.[50]	Individual PV isolation	Cavotricuspid isthmus ablation	29	28 ± 4 months
		Roof line		
		Roof line to anterior mitral annulus		
Golovchiner et al.[51]	Maze III surgical procedure	None	14.9	15 ± 7 months

PV pulmonary vein.

As can be seen from the table, the incidence of postprocedural LA organized tachyarrhythmias ranged between 2% and 30%.[48–51] The wide range is likely a result of the variation in techniques used for the initial AF ablative procedure. As discussed in the mechanisms section, a higher volume of lesions through the use of "anatomic" PV isolation with accompanying ablation lines such as posterior wall, roof, mitral isthmus, or other lines may lead to a higher incidence of LA tachycardia postprocedure than in cases in which segmental PV isolation is performed.[25]

Identification of Left Atrial Flutter

As with all arrhythmias, analysis of a possible LA flutter begins with careful inspection of the surface ECG. Tachycardias originating from reconnected PV ostia typically have a small isoelectric baseline between atrial depolarizations and a morphology similar to those previously described for pace mapping or atrial premature beats originating from the PVs.[26] Tachycardias originating from the right PV typically have a positive component in lead I, are flat in avL, and have monophasic positive flutter waves in V1 and across the precordium (Figure 1). In contrast, left PV tachycardias tend to have an isoelectric lead I, have a negative component in avL, and have an "M"-shape pattern in V1 that becomes flat across the lateral precordium. Tachycardias originating from the inferior PV tend to have lower amplitude notched atrial waves in the inferior leads, occasionally with an initial negative component when originating from the bottom of the PV.

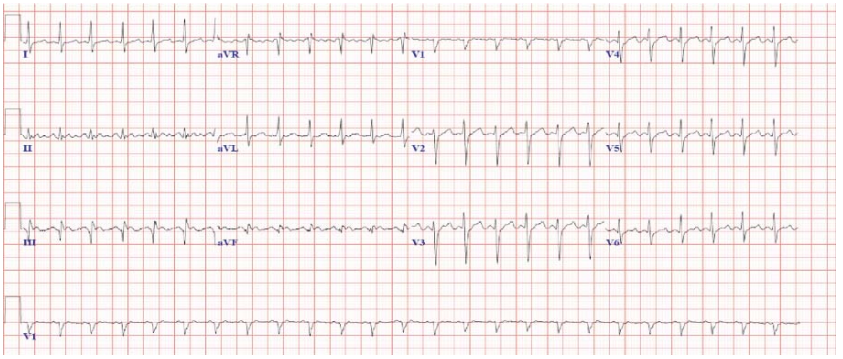

Figure 1 Electrocardiogram of left atrial flutter. This electrocardiogram is from a 46-year-old man with paroxysmal atrial fibrillation who underwent complete pulmonary vein isolation complicated by recurrent, symptomatic atrial tachycardia. Note the positive atrial activity in lead I, V1, and across the precordium. Subsequent electrophysiological study demonstrated a focal tachycardia originating near from the right superior pulmonary vein

Macroreentrant counterclockwise LA flutters encircling the mitral annulus typically have positive flutter waves in the inferior leads, with an amplitude in lead III greater than leads II and F, a negative component in lead I, and a deeply negative flutter wave in avL (Figure 2). These last characteristics are particularly useful in distinguishing counterclockwise mitral annulus flutter from left PV focal tachycardia. In contrast, clockwise mitral annular flutters typically have negative flutter waves in the inferior leads with lead III less than leads II and F and positive flutter waves in leads I and avL. The flutter waves in clockwise mitral annular flutter tend to be positive in lead I and the lateral precordial leads (Figure 1).[27]

Mechanisms of Left Atrial Flutter Postprocedure

Both macroreentrant[14] and focal tachycardias[11,12] have been reported after AF ablation. Focal atrial tachycardias typically originate from incomplete lines of ablation or reconnected segments of ablation related to slow conduction and unidirectional block from the index procedure. Macroreentry typically occurs as a result of one or more complete lines of block acting alone or in concert with native barriers (mitral valve annulus, coronary sinus [CS] ostium, or PV ostia) creating a protected critical isthmus for reentry.[11,12,14,28–30] Areas of incomplete ablation, frequently near the previously ablated PV ostia, may also create the substrate for automatic or triggered arrhythmias. Overall, the ablative approaches typical for AF procedures tend to prohibit or minimize fibrillatory conduction, leading to the development of more organized atrial flutter or tachycardia.

Different methods can be used to distinguish macroreentrant and focal arrhythmias. Classically, macroreentrant circuits demonstrate a continuous propagation sequence with adjacent early and late activation areas and an activation time encompassing most (>90%) of the tachycardia cycle length.[29] In contrast, focal tachycardias typically demonstrate radial spread of activation,

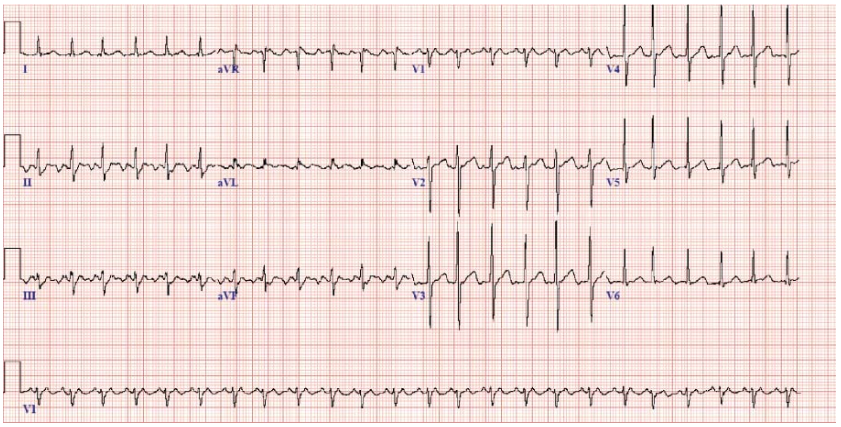

Figure 2 Electrocardiogram of left atrial flutter. This electrocardiogram is from a 60-year-old man with paroxysmal atrial fibrillation who underwent complete pulmonary vein isolation complicated by recurrent, symptomatic atrial tachycardia. Note the positive atrial activity in the inferior leads and negative atrial activity in the lateral leads. Subsequent electrophysiological study demonstrated a macroreentrant tachycardia encircling the mitral annulus

with the mapped activation not covering most of the tachycardia cycle length, with ablation of the focus interrupting the tachycardia.[14]

Careful evaluation of the baseline ablative procedure is necessary as the site of previous lesions frequently can localize the arrhythmia location. During a segmental PV ostial ablation, the lesions may vary between the venous or atrial side, creating a noncontiguous or nontransmural lesion, resulting in a zone of conducting tissue surrounded by scar.[19] Wide circular isolation or isolation using additional posterior wall, roof, or empiric mitral isthmus lines tends to cover a large area of atrial tissue, and both are fraught with the risk of gaps, particularly with the challenges of mitral isthmus ablation (see additional lines).

The long lesions intended to prevent AF create new fixed obstacles to propagation, and eventual discontinuities represent an ideal substrate for large gap-related reentrant circuits. Surgical experience has similarly shown that even ablation lines created under direct visualization during surgical procedures for AF may harbor gaps and promote LA flutter.[17,22,31] Given that gaps are a major culprit in the arrhythmic complications of AF ablation, a general rule of thumb for the baseline AF ablation procedure is to pursue the minimum number of lesions necessary to treat the underlying disorder, while ensuring that the lesions delivered are transmural and, if necessary, continuous.

Last, confirmation of PV isolation is necessary to rule out acute reconnectivity and minimize the likelihood of subsequent reentrant arrhythmias. This lack of confirmed conduction block may be responsible for some of the differences in reported postablation arrhythmias despite seemingly similar initial ablative strategies.[17,21]

Gaps are not the only explanation for occurrence of LA flutter after AF ablation. Atrial flutter and AF have long been recognized to be related arrhythmias, with each occurring commonly in the same patients.[28,32,33] The slow conduction created by class IC and III (particularly amiodarone) antiarrhythmic

drugs, used to suppress AF postablation, may promote regular atrial arrhythmias when used after AF ablation.[33–35]

Management/Approach to the Patient with Suspected Left Atrial Flutter

A careful, systematic approach to the patient with suspected LA flutter is important to confirm the appropriate diagnosis and treatment plan. One of the most common mistakes is misclassification of the patient with palpitations, shortness of breath, and other presenting symptoms as having AF rather than atrial flutter. Careful analysis of the presenting ECG is necessary, understanding that LA flutter may be mistaken for other atrial arrhythmias on the left and right side of the heart (see Identification of Left Atrial Flutter), including coarse AF. Central to the early management are the tenets of ventricular rate control and anticoagulation. The β-blockers, calcium channel blockers, and digoxin can be used effectively for rate control, although achieving adequate rate control may be more difficult than for AF. Anticoagulation with warfarin, as appropriate, should be continued, with a target international normalized ratio of 2 to 3. Class I or III agents can be used to control the arrhythmia. Electrical cardioversion is often necessary to restore sinus rhythm; however, if the arrhythmia quickly recurs, ventricular rate control should be used for several weeks before attempting further cardioversions to allow healing after the initial ablation procedure.

Inducibility of LA flutter at the conclusion of the AF ablation procedure is not a predictor of subsequent clinical arrhythmic events. Daoud et al. found that the incidence of inducible LA flutter at the conclusion of an AF ablation was 38% (43/112) following a procedure in which the right and left PV ostia were encircled and connected with additional ablation lines on the posterior wall or roof and mitral isthmus line. However, the clinical incidence of LA flutter 4 months following the procedure was 8.9%, with only 8% undergoing a second ablation procedure to treat the arrhythmia.[16]

Our findings are similar, and we believe a blanking period similar to that used for short-term AF recurrence following ablation should also be applied to LA flutter and other organized tachycardias. Spontaneous resolution of LA flutter during follow-up may be caused by progression of fibrosis, scar formation, coalescence of lesions, and elimination of gaps in the ablation lines. Alternatively, inflammation and premature atrial depolarizations may resolve, leading to quiescence. Maturation and remodeling of these lines may be a slow process, requiring months.[17]

Several authors have reported that patients with LA flutter post-AF ablation tend to have more significant symptoms.[28] Although not statistically significant, it has been shown that patients with this arrhythmia tend to require more frequent electrical cardioversions than had previously been necessary prior to the AF ablation. Daoud et al. found that electrical cardioversion was required 39 times for 28 patients with clinical arrhythmia (1.6 ± 0.6 episodes per patient).[16] In comparison to episodes of AF occurring before circumferential ablation, LA flutter was associated with a faster ventricular rate (124 ± 19 beats/min vs 91 ± 16 beats/min; $p < 0.001$) and was more likely to be persistent, requiring cardioversion (86% vs 32%; $p = 0.01$). An aggressive strategy of symptomatic relief with rate control using atrioventricular (AV) nodal blocking agents and

rhythm control using cardioversion and antiarrhythmic drugs should be used while sufficient time for spontaneous resolution is allowed to pass.

Antiarrhythmic drugs may contribute to atrial tachycardias in some cases. A study from our institution found that a subset of patients with atrial tachycardia following AF ablation has resolution of their arrhythmia following cessation of antiarrhythmic drugs; however, no clinical or electrophysiological characteristic appeared to reliably identify the group. A trial of antiarrhythmic drug discontinuation should be attempted in patients with post-AF ablation atrial tachycardia, particularly if a IC agent is used.[36]

After a significant waiting period has passed following AF ablation without resolution of the LA flutter despite changes to antiarrhythmic drug therapy and cardioversion, it is reasonable to attempt a targeted ablation to treat the new arrhythmia. We typically wait at least 6 to 8 weeks after ablation before considering bringing a patient back to the electrophysiology laboratory.

Ablative Procedure for Post-Atrial Flutter Ablation Tachycardias

When the decision has been made to pursue an ablative strategy, it is important to review the prior ablation procedure as this may have direct impact on the location of the arrhythmia during the subsequent procedure. We typically discontinue antiarrhythmic medications five half-lives prior to the procedure.

The general principles governing other ablative procedures typically apply to post-AF LA flutter ablations as well. Necessary techniques in this procedure include activation mapping, entrainment mapping, and electroanatomical mapping in isolation or combination. The initial focus should be on localizing the arrhythmia to the right atrium (RA) or LA. Detailed activation and entrainment mapping should be performed to determine the arrhythmia mechanism and course. Last, delivery of targeted ablation lesions in the gap area or along the critical isthmus is performed. Termination of the arrhythmia after ablation at the gap or isthmus followed by confirmation of bilateral linear block on both sides of the line are the goal.[37] In patients presenting in sinus rhythm, programmed electrical stimulation with or without isoproterenol infusion is usually performed to induce the tachyarrhythmia. If tachycardia cannot be initiated, a systematic approach reisolating the PV if reconnected followed by targeting of previous ablation lines and possibly empiric lesions.

Exclusion of Right Atrial Origin

The first step in the ablative procedure is to exclude RA flutter, either typical or atypical. Since isthmus-dependent RA flutter may occasionally have an atypical appearance on the surface ECG, entrainment from the inferior vena cava/tricuspid valve isthmus should always be performed prior to transseptal puncture to exclude isthmus-dependent RA flutter. Entrainment maneuvers from the RA and CS should particularly focus on the postpacing interval. When the return cycle length exceeds the tachycardia cycle length by less than 30 ms, the pacing site is considered to be part of the circuit.[37] Entrainment can also be attempted from the right lateral, right isthmus, and right septal regions. An RA arrhythmia is less likely if these regions are not in the circuit.[37]

In addition, a focal RA septal source or LA source is more likely if the site of earliest RA activation is located in the Bachmann bundle area, near the CS, or fossa ovalis, as demonstrated by electroanatomical mapping, as these areas are typical RA breakthrough sites of LA activation.[29] Further supporting an LA origin is distal-to-proximal activation of the CS catheter during tachycardia. Of note, proximal-to-distal activation of the CS does not necessarily indicate an RA origin as an LA septal or perimitral origin or circuit could lead to a similar result. Last, significant variations in the RA cycle length suggest an LA source, particularly if the LA cycle length is fixed.

Transseptal Puncture and Evaluation of Left Atrial Source

After excluding the presence of an RA arrhythmia, we perform two transseptal punctures under echocardiographic or fluoroscopic guidance to map the LA. A mapping/ablation catheter and circular mapping catheter are typically advanced into the LA. Sufficient anticoagulation to prevent thrombosis, as is typically performed for the initial ablation procedure, should be maintained. Intravenous heparin should be administered to maintain an activated clotting time longer than 350 s.

Next, we usually create a detailed three-dimensional (3-D) electroanatomical activation map of the LA to determine if activation of the entire tachycardia cycle length can be recorded within the LA. Visualization of more than 90% of the tachycardia cycle length and the finding of adjacent areas of early and late activation tend to indicate macroreentrant circuits. We then combine electroanatomical mapping with entrainment mapping to better localize the circuit (Figure 3). Concealed entrainment with a postpacing interval no more than 30 ms greater than the tachycardia cycle length confirms sites within the circuit (Figure 4). Activation mapping can be performed along previous lesions to search for gaps. The finding of double potentials typically identifies intact lines of block, while narrowing of these double potentials often points toward gaps that may be involved in the circuit or be the source of focal activation.

Assessment and Targeting of the Pulmonary Veins

Using the general strategies discussed, our initial focus begins with an assessment of the PV for reconnectivity or presence of gaps. In our experience, atypical flutters following AF ablation are usually caused by recovery of PV conduction or gaps in linear lesions with the circuit propagating through the gap. In patients for whom the previous ablation was limited to PV isolation alone, the two dominant macroreentrant circuits are either around the mitral annulus or around the PVs, particularly in those with larger atria. Focal reentrant rhythms are typically located on one aspect of the PV, frequently the septal segments for right-side PVs. Careful analysis of local potentials, in conjunction with entrainment mapping and postpacing interval analysis, is necessary to avoid targeting bystander areas.[37]

After creation of a 3-D electroanatomical map, we usually begin with interrogation of each PV with a circular mapping catheter. This technique can be helpful for identifying reconnected PV ostia and for identifying middiastolic or long-fractionated electrograms that may suggest a critical isthmus of slow conduction. We attempt entrainment from the site of middiastolic potentials, the roof, posterior wall, anterior wall, septum, and lateral wall. In our previous

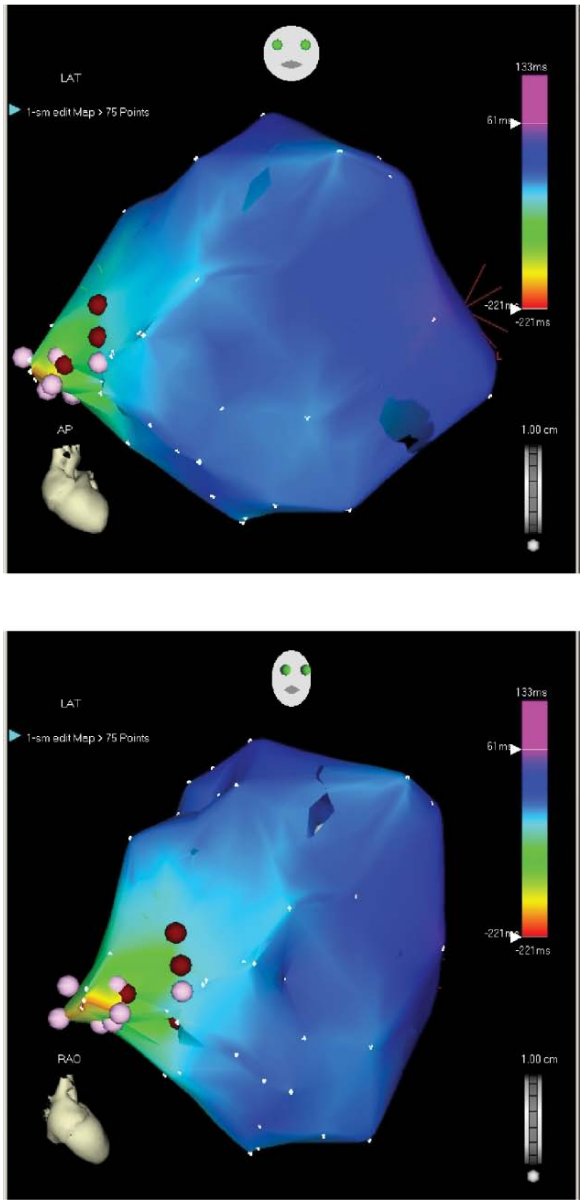

Figure 3 Activation maps from 48-year-old man with previous pulmonary vein isolation for paroxysmal atrial fibrillation with subsequent development of atrial tachycardia. The patient presented to the laboratory in the tachycardia. Activation mapping demonstrated earliest activation in the inferoseptal aspect of the right inferior pulmonary vein. **A** Activation mapping in an anterior-posterior view demonstrates earliest activation in the right inferior pulmonary vein. **B** Activation mapping in the right anterior oblique view. Focal ablation was delivered to the area of earliest activation and demonstrated termination of the tachycardia. Evaluation of the pulmonary vein during sinus rhythm demonstrated reconnection, and additional ablation lesions were performed to reisolate the pulmonary vein. Red dots represent 70-W lesions, and pink dots represent 50-Wlesions

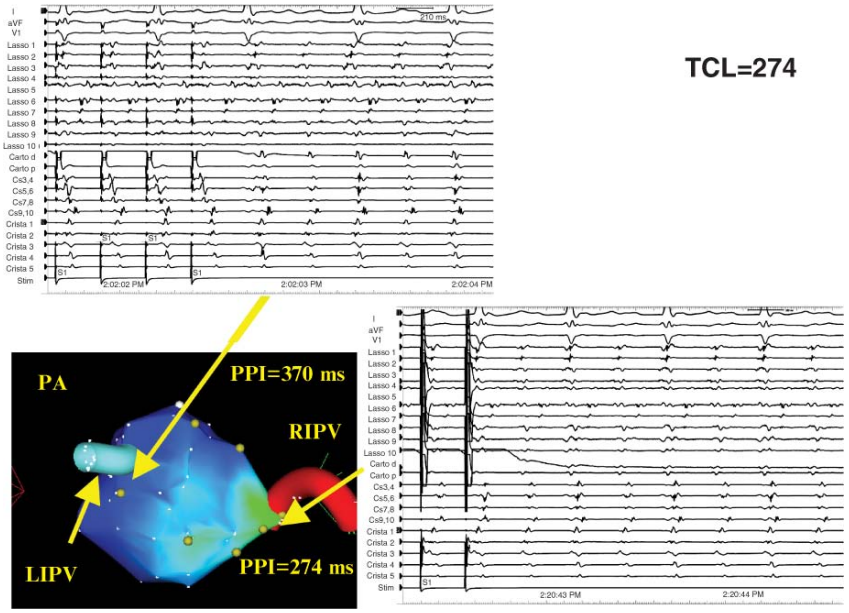

Figure 4 Entrainment mapping of the patient shown in Figure 2 confirmed the presence of a reentrant circuit within the right inferior pulmonary vein. The lasso catheter was placed at the ostium of the right inferior pulmonary vein. A postpacing interval (PPI) equivalent to the tachycardia cycle length was found in the inferoaspect of the right inferior pulmonary vein. A single radio-frequency lesion was delivered at this site and terminated the arrhythmia. *LIPV* left inferior pulmonary vein, *RIPV* right inferior pulmonary vein

reports, we have found that nine of ten patients with LA tachycardia following AF ablation had focal tachycardias originating near the PV ostia previously targeted for ablation. The remaining patient developed a macroreentrant tachycardia around the right PVs.[12] Most of the tachycardias in our previous studies have mainly originated near the septal aspect of the right PVs, particularly near the right inferior PV (Figure 3).[11,12]

The right inferior vein is the most technically challenging and often the last vein to be isolated. Consequently, acute reconnectivity may not be noticed during the baseline procedure. In addition, a high density of complex fractionated electrograms and autonomic ganglia have been reported to exist in this area, which may contribute to the substrate (short refractory period and unidirectional block) necessary for development of reentrant atrial tachycardias.[11,38,39]

During ablation, therefore, complete isolation of the inferoseptal aspect of the right PVs should be carefully performed during the initial PV isolation procedure. We have found that ablation at the PV segment with a postpacing interval approximating the tachycardia cycle length and long-fractionated or mid-diastolic electrograms usually terminated tachycardias involving the septal aspect (Figure 4).[11] When ablating PV tachycardias, moving the circular mapping catheter systematically to each PV ostium and searching for middiastolic or fractionated potentials often can suggest critical areas of the reentrant circuit. Entrainment mapping can confirm the location of a critical tachycardia isthmus that can be focally ablated.

Linear lesions between PVs and other anatomic obstacles during either the initial or subsequent ablation session typically are not warranted unless the PVs are addressed and a macroreentrant circuit around the mitral annulus or posterior wall is demonstrated.[11] Circuits around the left PVs tend to be less common than those circuits around the right. Left-side macroreentrant circuits typically can be treated with a linear lesion joining the vein to the mitral annulus or a roof line connecting both superior veins.[37] Circuits propagating around the right veins typically demonstrate a postpacing interval during entrainment that is much longer at the mitral isthmus than at the roof or posterior LA. A linear lesion connecting both superior veins may abolish this arrhythmia or may convert it to mitral annular flutter. The endpoint of ablation typically includes termination of the tachycardia with ablation across the critical isthmus and confirmation of block with reduction of the local electrograms and development of persistent double potentials.

Focused ablation in the area of PV reconnectivity with subsequent disappearance of PV potentials without reinducibility usually resolves focal arrhythmias originating from reconnected PVs in most patients.[40] Ablation at the site of earliest endocardial activation with a postpacing interval approximating the tachycardia cycle length often results in termination of the tachycardia. In our experience, all cases of focal tachycardia terminated abruptly or slowed and terminated during application of RF energy at the site of earliest activation. Typically, the PV of origin demonstrated reconnection, and these vessels were reisolated.[12] If focal ablation at this site is unsuccessful, reisolation of all reconnected PVs will successfully treat the tachycardia in most cases.

Isolation of reconnected PVs alone has been demonstrated to be very effective in treating atrial arrhythmias following post-AF ablation, with 83% of patients arrhythmia free (61% off and 23% on antiarrhythmic drugs) a mean of 486 days postprocedure.[30] These findings may be limited in those with significant preexisting scar, defined as areas with no atrial electrograms and voltage less than 0.05 mV.

Cummings et al. provided early evidence demonstrating that retargeting PV reconnectivity is a critical element in the occurrence of LA flutter following PV isolation. However, in patients with preexisting LA scar, simple reisolation of the PV may not be sufficient and may require targeting other areas or additional linear lesions.[30] During some ablative cases, the tachycardia will change activation or morphology during entrainment or degenerate into AF, limiting further investigation. As with patients who present in sinus rhythm in whom the tachycardia cannot be induced or is not tolerated, empiric PV isolation is generally effective in treating the arrhythmia.

Perimitral Flutter

Following evaluation of the PVs, attention should then be directed toward mapping around the mitral annulus. Perimitral flutter has a consistent proximal-to-distal or distal-to-proximal activation sequence of the CS and a postpacing interval that is within 30 ms of the tachycardia cycle length at the mitral isthmus and longer at the posterior LA. This arrhythmia can be approached by linear ablation of the mitral isthmus, connecting the lateral mitral isthmus and left inferior PV.[37] Occasionally, multiple lines are necessary to achieve endocardial block.

The mitral isthmus contains variable topography, and complete block may be difficult to achieve. If flutter is not terminated with endocardial ablation, ablation epicardially in the CS opposite the endocardial line is necessary in up to 80% of cases. An irrigated-tip catheter may be required to achieve adequate power to terminate flutter. When flutter does terminate, complete mitral isthmus block is frequently not present. Whether complete isthmus block is necessary to prevent flutter recurrence is not clear (Figure 5).[17,41]

Pseudomacroreentry

If activation recorded at different positions does not cover most of the tachycardia cycle length, two possibilities must be considered. First, it could be a focal, nonreentrant arrhythmia rather than a macroreentrant arrhythmia. Second, it could be that a focal, localized, reentrant circuit is present in an area of slowed conduction (pseudomacroreentry).[18,37,42] These small circuits require much more detailed activation mapping to be identified, with entrainment attempts at numerous sites in the LA. When entrainment does not localize the circuit in either the LA or RA, a nonreentrant or small reentrant arrhythmia should be considered. The most significant limitation of this mapping strategy in patients with atypical flutter is the frequent conversion of the clinical arrhythmia AF or different atrial tachycardia.[37,42]

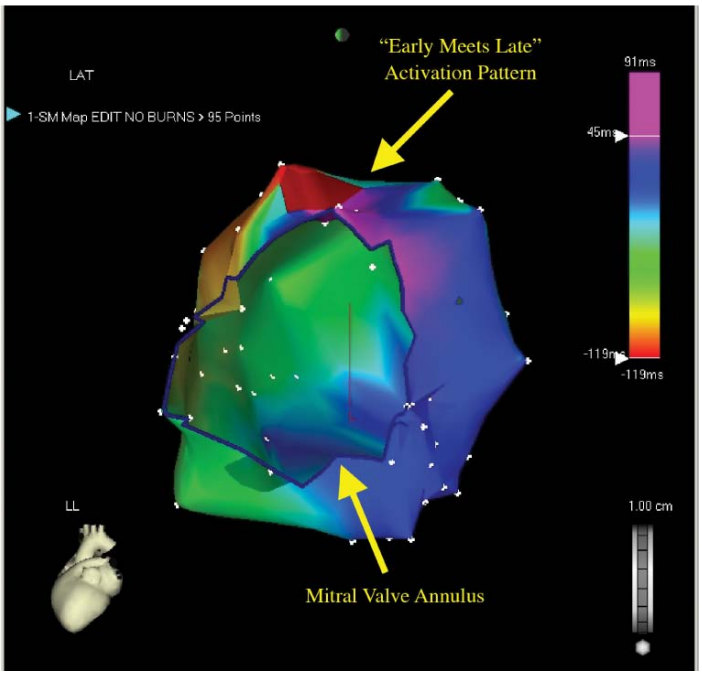

Figure 5 Activation maps from 57-year-old woman with previous pulmonary vein isolation for paroxysmal atrial fibrillation with subsequent development of atrial tachycardia. The patient presented to the laboratory in the tachycardia. Activation mapping demonstrated a macroreentrant rhythm around the mitral valve with demonstration of "early-meets-late" (arrow) activation pattern in the superior aspect of the valve. The tachycardia terminated with a linear lesion between the anterolateral aspect of the mitral annulus and the left inferior pulmonary vein (mitral isthmus line)

Additional Lines

Patients who have undergone additional lines during the index procedure, such as posterior wall or roof lines, may require additional mapping and ablation to terminate the arrhythmia or confirm noninducibility after the previous steps.[40] As with other lesions, reconnection along linear ablation lines usually manifests with low-amplitude fractionated signals with unipolar recordings demonstrating a negative QS pattern with sharp initial deflection in areas of focal activation. Detailed mapping should be performed with the goal to identify potential gaps in the line, which allows propagation of the circuit. Gaps are usually easier to identify in sinus rhythm, although pacing maneuvers (namely, assessment of the postpacing interval) during arrhythmia can be helpful. Entrainment mapping should be performed to identify the reentrant circuit and its critical isthmus.

Some authors advocate the use of empiric mitral-isthmus lines because of the frequency with which atrial tachycardias use the isthmus between the mitral annulus and the left inferior PV. However, complete block along this line can be difficult to achieve, and an incomplete line may facilitate macroreentry by creating a zone of slow conduction. In a randomized comparison of PV isolation with PV isolation with mitral isthmus ablation for treating AF, an 18% increase in success rate was reported with addition of mitral isthmus ablation. However, complete conduction block could only be achieved in 76% of patients, and there was a higher incidence of complications in the group undergoing mitral isthmus ablation.[43]

Empiric Ablation Lines

After achieving electrical isolation of the PVs, addressing focal activation or pseudomacroreentry, and achieving complete linear block along additional, previously placed lines, if the arrhythmia still persists, consideration of empiric lines should be made. The concern with this strategy is the potential introduction of proarrhythmic scar in the LA. Rather than performing completely empiric ablation lines, one can often get a sense of the path of the circuit through sites where activation during entrainment is similar to that of the tachycardia and where the postpacing interval is reasonable. For example, if the exact circuit cannot be delineated by postpacing intervals along the anterior septum, a right superior PV to mitral annulus line transecting the septum might be considered. On the other hand, if the postpacing intervals are better in the area of the LA roof or mitral isthmus, lines through these areas may be performed. Any slowing of the tachycardia cycle length during ablation should encourage continued ablation along this course.

Prognosis

The long-term success rate of ablation for post-AF arrhythmias is high. In our and other's experience, the arrhythmia success rate after 6 months post-repeat procedure is 90% or greater.[12,16,28,44] Pappone et al. found that between 14% and 18% of patients had transient symptomatic recurrences of atrial tachycardia early after ablation, with clinical improvement and no further recurrence between 6 and 8 months after the repeat procedure.[21] For this reason, we typically keep all

patients on antiarrhythmic therapy for at least 6 weeks after the repeat procedure, although the majority do not require long-term treatment.

Complications

In our experience, the complications for an LA flutter procedure are similar to those reported for the baseline AF ablation procedure. Expected complications associated with all ablative procedures include vascular complications associated with venous and arterial access (hematoma, major bleeding requiring transfusion, pseudoaneurysm), pneumothorax from jugular venous access, or cardiac tamponade or perforation associated with catheter manipulation. More severe complications associated with left-side procedures include air embolism, pericardial tamponade or perforation from improper transseptal puncture, mitral valve injury requiring repair or replacement (typically because of entanglement of the circular mapping catheter in the mitral apparatus), transient complete AV block or hypotension during RF energy delivery, and stroke or other thromboembolic complications. Pericardial tamponade appears to occur more frequently with the addition of a mitral isthmus line in addition to PV isolation.[41] Careful monitoring with fluoroscopy or intracardiac echocardiography as well as minimization of additional lesions can help decrease these complications or provide early detection to limit the consequences.

Right phrenic nerve injury can occur, particularly during ablation of the anterior aspect of the right PVs, superior vena cava (SVC), and lateral RA can occur. Left phrenic nerve injury occurs less commonly but can occur with RF energy delivery to the anterior LA or base of the left appendage. Typical symptoms include coughing or hiccups, as well as reduction in diaphragmatic respiratory motion.[37]

Two of the most feared complications associated with ablation near the PV include PV stenosis and atrioesophageal injury. Mild PV stenosis has been reported to occur in 6% to 8% of patients undergoing AF ablation.[45,46] Severe PV stenosis has been reported to vary from 1.7% to 5%.[45–47] Reported symptoms of severe PV stenosis include shortness of breath, cough, and hemoptysis. Chest computed tomographic (CT) scanning and ventilation-perfusion scanning have both been demonstrated to identify cases of severe PV stenosis.[45,46] Limiting RF power delivery, avoiding ablation inside or proximal to the PVs, and serial monitoring of blood velocities from the PVs during the procedure using intracardiac echocardiography can help avoid this complication.

Another, more critical, complication is the development of an atrioesophageal fistula, typically caused by aggressive ablation in the posterior wall near the esophagus. Patients presenting with this complication have typically demonstrated focal neurologic and other deficits from multiple septic or gaseous emboli, infectious manifestations, or chest pain within several days to a week following the ablation.[9] Diagnosis should be rapidly attempted with CT or magnetic resonance imaging (MRI), and emergent surgical consultation for treatment is necessary. Endoscopy should be avoided. Prevention during baseline and subsequent procedures should be aggressively attempted with use of intracardiac echocardiography to better provide real-time imaging of the

esophagus and minimization of posterior wall lesions with a decrease in RF energy delivery to the posterior wall.

Conclusion

Left atrial flutter is an infrequent but significant complication of AF ablative procedures. Careful attention during the follow-up of patients post-AF ablation is necessary so that this arrhythmic complication is not missed. Once diagnosis of an atypical atrial flutter is made, an initial conservative management strategy should be followed as most cases resolve spontaneously. If additional ablation is necessary, a systematic approach using the baseline ablative procedure as a guide should be used. While more than 90% of cases of both focal and macroreentrant atrial tachycardias following AF ablation can be effectively treated, the best treatment strategy for targeting LA flutter is prevention.

While much debate exists regarding the overall best technique for successful AF ablation, it is evident that the protocol needs to be tailored to the individual patient. Empiric lines in addition to PV isolation (segmental or complete) may increase the risk of proarrhythmic gaps. During the baseline ablation procedure, careful attention to the creation of continuous, transmural lesions without gaps should be followed with a goal of delivering the minimal number of lesions to treat the condition.

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Ablation Strategies for Left Atrial Flutter

Case 1

A 48-year-old man with previous pulmonary vein isolation for paroxysmal atrial fibrillation with subsequent development of symptomatic atrial tachycardia presents to the electrophysiology laboratory for repeat ablation.

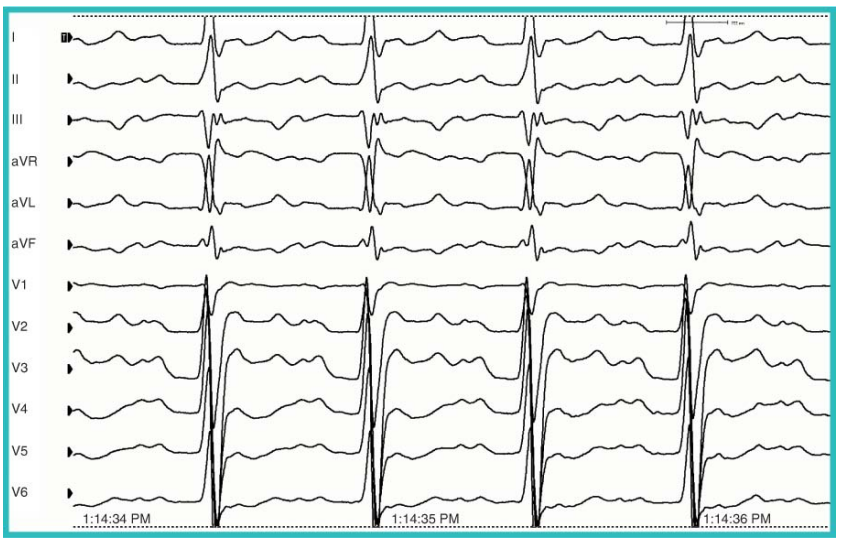

Figure 1 The patient presented to the laboratory in tachycardia. The 12-lead electrocardiogram on presentation is shown. Note the positive atrial activity in leads I and V1

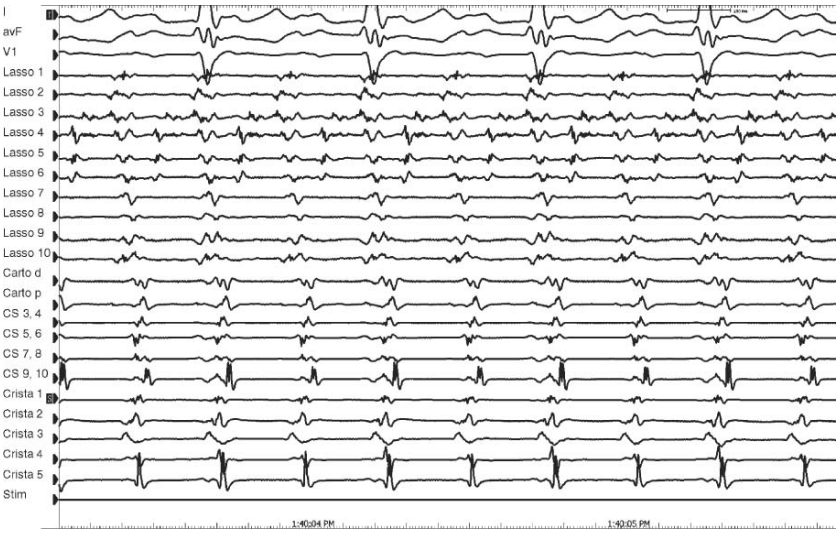

Figure 2 Placement of the circular mapping catheter in the ostium of each pulmonary vein demonstrated a source in the right inferior pulmonary vein with a tachycardia cycle length of 274 ms. With the Lasso catheter positioned at the ostium of the right inferior pulmonary vein, nearly continuous activity is evident in Lasso 3, suggesting a focal source. Lasso 10, CS 9, 10, and Crista 5 are proximal poles of catheter

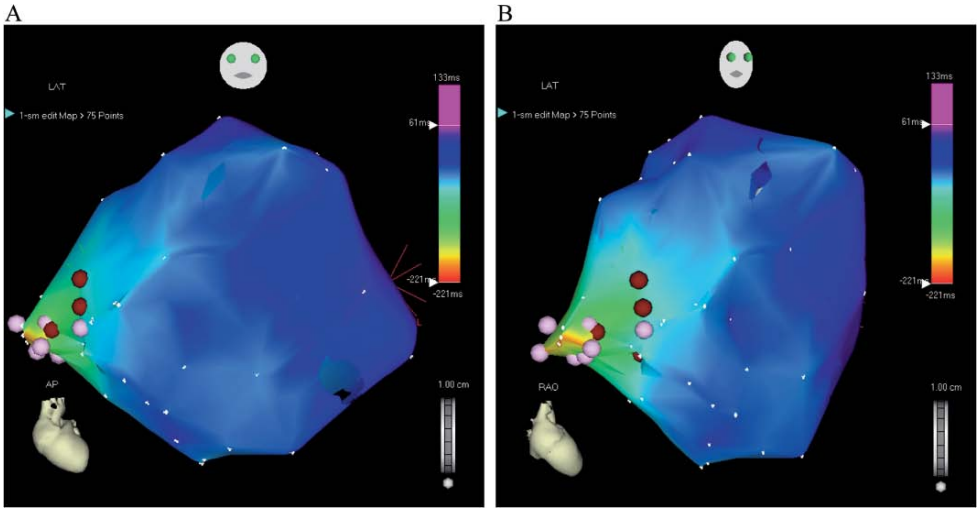

Figure 3 Activation mapping was performed and demonstrated earliest activation in the inferoseptal aspect of the right inferior pulmonary vein. **A** Anterior-posterior view of the left atrium. **B** Right anterior oblique view of the left atrium. **C** Right lateral view of the left atrium. A single radio-frequency ablation lesion (see Figs. 4 to 6) at the site of earliest activation with a postpacing interval approximately the same as the tachycardia cycle length terminated the arrhythmia. The right inferior pulmonary vein demonstrated reconnectivity and was reisolated. (Pink tag markers represent 50-W ablation lesions; red tag markers represent 70-W ablation lesions.)

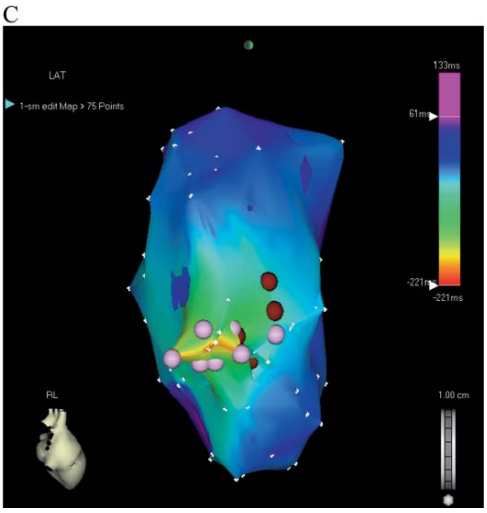

Figure 3 (continued)

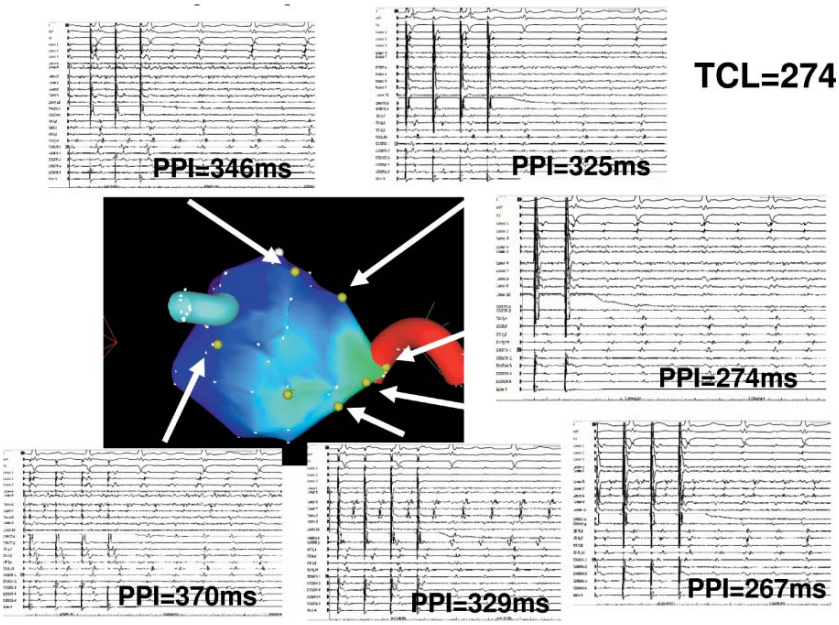

Figure 4 Entrainment mapping confirmed the presence of a reentrant circuit within the right inferior pulmonary vein. A postpacing interval equivalent to the tachycardia cycle length was found in the inferior aspect of the right inferior pulmonary vein. (Lasso 10, CS 9, 10, Crista 5 are the proximal poles of catheter; left inferior pulmonary vein shown in light blue, and right inferior pulmonary vein shown in red.)

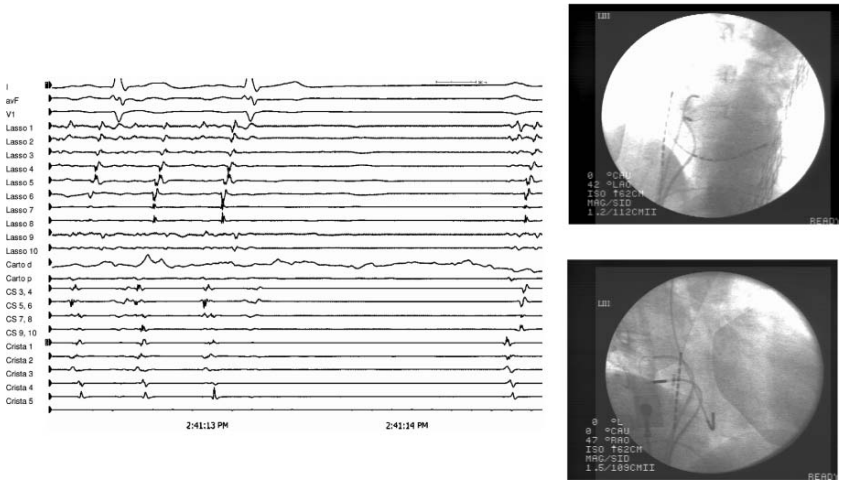

Figure 5 A single radio-frequency lesion was delivered at the site with postpacing interval approximately the same as the tachycardia cycle length with resultant termination of the arrhythmia. Left anterior oblique and right anterior oblique fluoroscopic images illustrate catheter positions at the site of successful ablation. Lasso and CARTO catheters were both positioned at ostium of right inferior pulmonary vein. (Lasso 10, CS 9, 10, Crista 5 are the proximal poles of the catheter.)

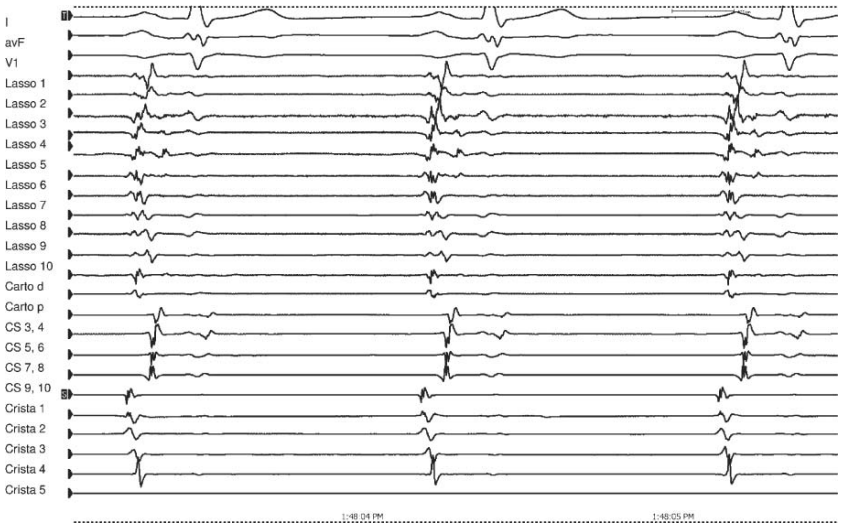

Figure 6 Evaluation of the pulmonary vein during sinus rhythm demonstrated reconnection, and additional ablation lesions were performed to reisolate the pulmonary vein. Lasso and CARTO catheters were both positioned at ostium of right inferior pulmonary vein. (Lasso 10, CS 9, 10, Crista 5 are the proximal poles of the catheter.)

Case 2

A 57-year-old woman with previous pulmonary vein isolation for paroxysmal atrial fibrillation with subsequent development of atrial tachycardia presents to the electrophysiology laboratory for repeat ablation

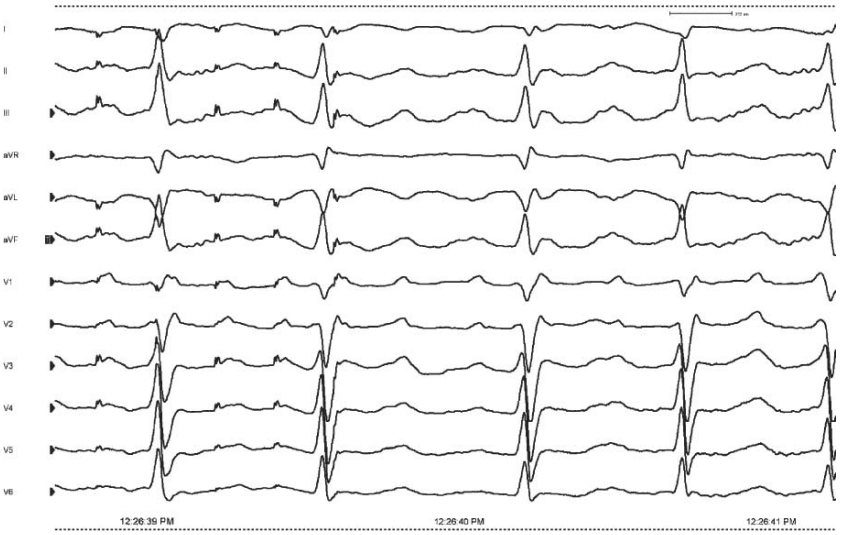

Figure 1 The patient presented to the laboratory in tachycardia. The 12-lead electrocardiogram on presentation is shown. Note the positive atrial activity in the inferior leads and negative activity in lead I and avL.

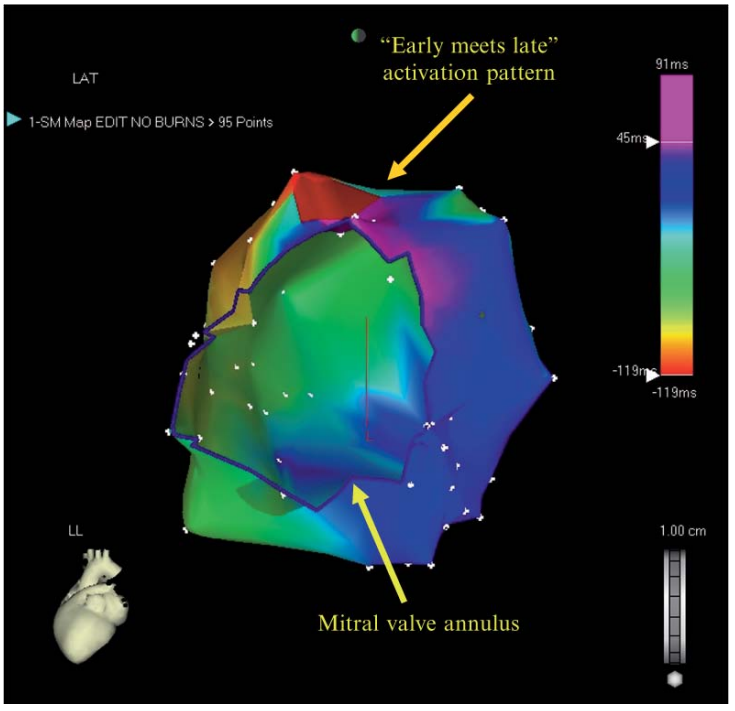

Figure 2 Activation mapping demonstrated a macroreentrant rhythm around the mitral valve with demonstration of "early-meets-late" activation pattern in the superior aspect of the valve

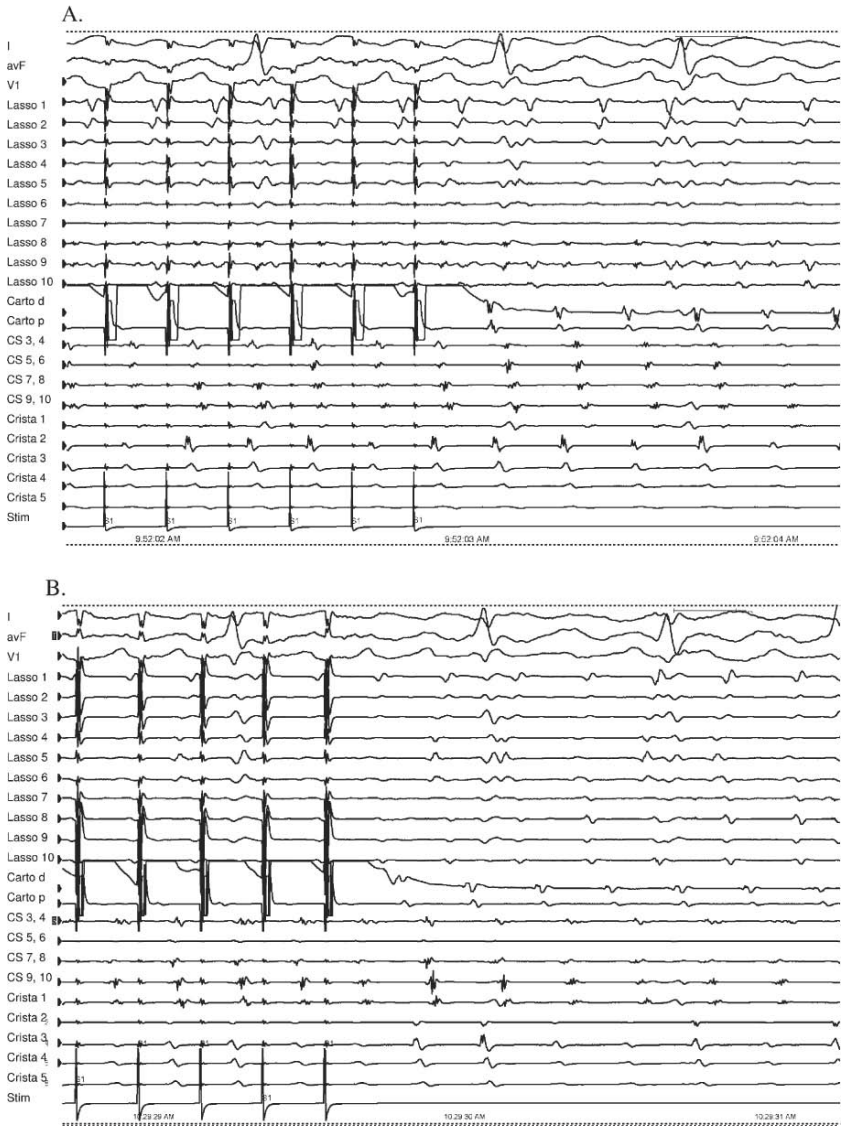

Figure 3 Pacing from around the mitral annulus. **A** Pacing from the septal aspect of the mitral annulus demonstrated a postpacing interval approximating the tachycardia cycle length with atrial activity demonstrating concealed entrainment. **B** Pacing from the superior aspect of the mitral annulus demonstrated a postpacing interval approximating the tachycardia cycle length. (Lasso 10, CS 9, 10, Crista 5 are the proximal poles of the catheter.)

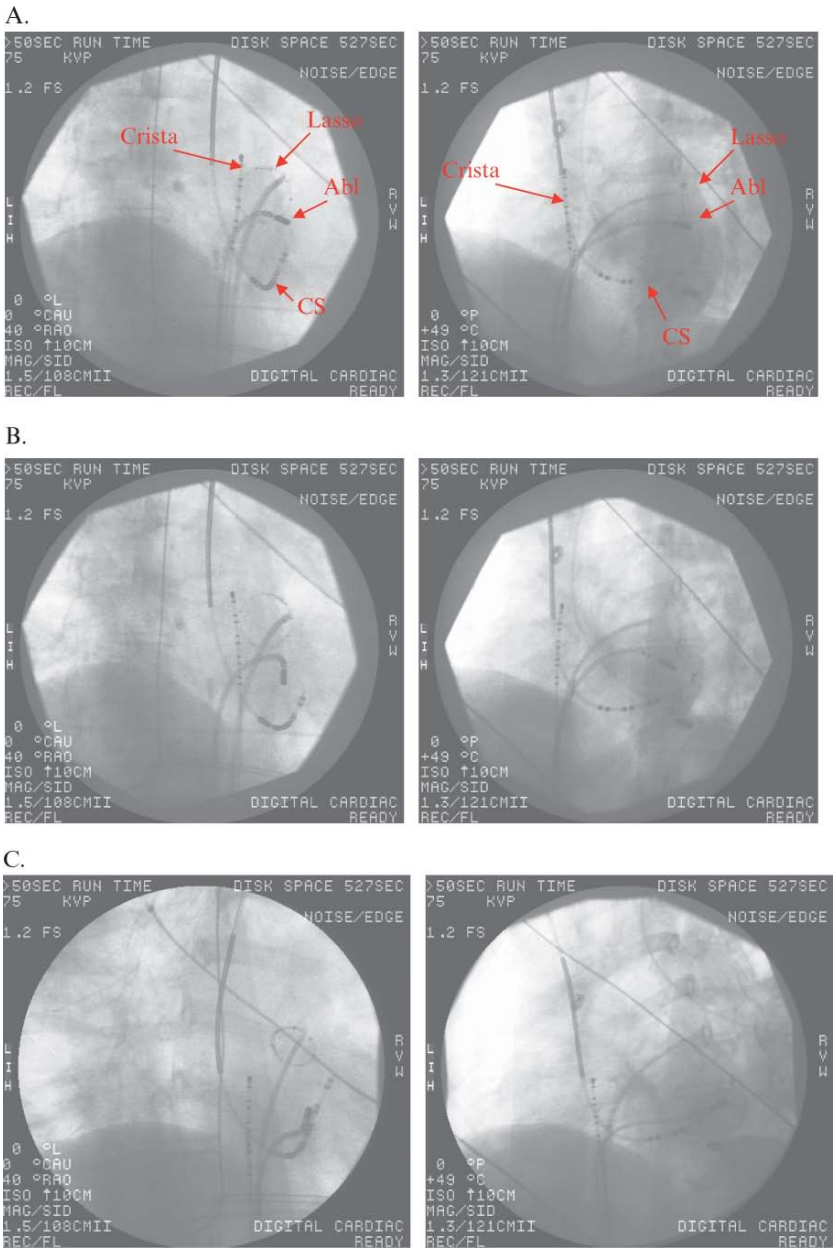

Figure 4 Fluoroscopic images demonstrating the **A** initial and **B** final left atrial locations of ablation for creation of a mitral isthmus line. **C** Subsequent ablation inside the coronary sinus was required to complete the line. *Abl* ablation catheter, *CS* coronary sinus catheter.

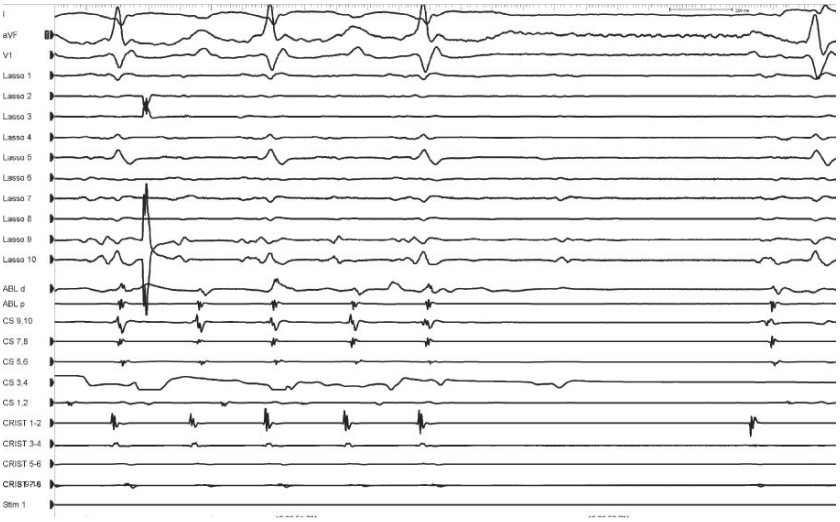

Figure 5 Termination of the tachycardia occurred with ablation. (Lasso 10, CS 9, 10, Crista 5 are the proximal poles of the catheter.)

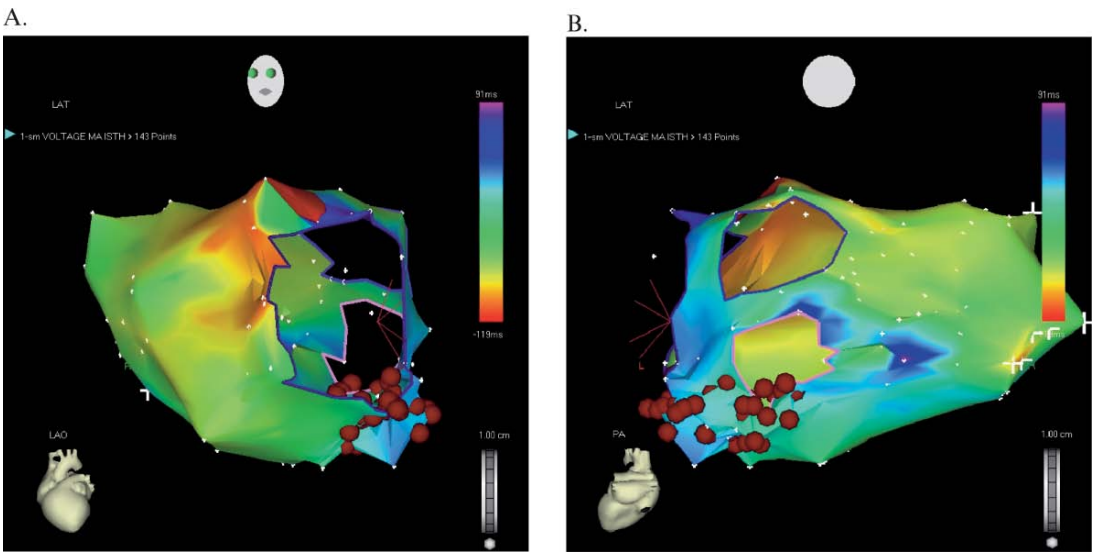

Figure 6 Activation map in **A** left anterior oblique view and **B** posterior-anterior view demonstrating the mitral isthmus line from the mitral annulus to the left inferior pulmonary vein (outlined in pink)

Section VII

Future Directions in Atrial Fibrillation

31

Atrial Fibrillation: Future Directions

Mithilesh K. Das, Anil V. Yadav, and Douglas P. Zipes

Abstract: Atrial fibrillation (AF) remains the most common sustained cardiac rhythm disorder, affecting more than 2 million Americans. Successful treatment and possible cure of this rhythm will require continued research into the mechanisms of AF, including the role of the autonomic nervous system. Further studies will also be required into the potential role of genetics as it pertains to identifying those at greatest risk of AF, as well as for the development of genetically directed pharmacotherapy. Other new drug approaches include those that are atrial selective and those that prevent atrial fibrosis, clearly a trigger for AF. Nonpharmacological management of AF will continue to have a rapid expansion of novel technologies for mapping and ablation, including cryoablation, high-frequency ultrasound, and laser ablation. These innovations will improve treatment and create cures for AF.

Keywords: Ablation; Antifibrosis; Atrial-selective agents; Autonomic nervous system; Endocardial mapping; Genetics; Pharmacotherapy.

Atrial fibrillation (AF) is the most common cardiac arrhythmia associated with significant mortality and morbidity. It occurs in approximately 6% of the population over the age of 60. It is estimated to be present in over 3 million people with persistent AF in the United States and by 2050 is projected to increase further to 5.6 million.[1,2] At present, it has an enormous economic impact on our health care system, which will only continue to grow in the future. Less than a decade ago, the management of AF was limited to rate control, anticoagulation, antiarrhythmic drug (AAD) therapy, or atrioventricular (AV) node ablation with a pacemaker implant. Although ventricular rate control has been shown to be as good as rhythm control regarding mortality, these studies did not include the socioeconomic impact that AF has on several parameters, such as inadequate ventricular rate control, poor quality of life, or side effects of antiarrhythmic as well as anticoagulation therapies.[3,4] However, recent development of a potential cure of AF with catheter-based ablation and surgical techniques is revolutionizing AF management.[5,6]

Radio-frequency (RF) ablation therapy of AF continues to evolve because the pathophysiology of AF is incompletely understood but certainly appears to be

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Edited by A. Natale and J. Jalife © Humana Press, Totowa, NJ

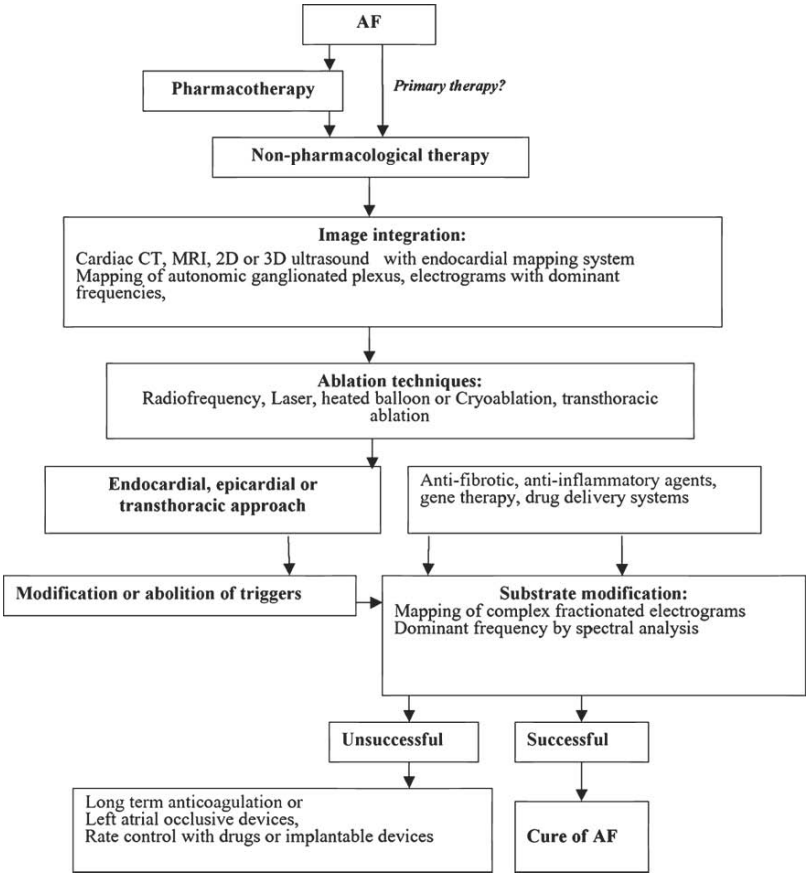

Figure 1 Pharmacological and non-pharmacological management of atrial fibrillation. AF=atrial fibrillation, CT=comuterized tomography, MRI=Magnetic resonence imaging, 2D=2 dimensional

multifactorial. Animal and human studies have provided initial understanding of the mechanisms that trigger and maintain AF, findings certain to contribute to better therapy. These factors include the role of autonomic modulation and genetic factors as well as development of newer pharmacological agents and nonpharmacological methods of rhythm as well as rate control (Figure 1). In this chapter, we focus on prevailing technologies involved in understanding the mechanism and therapy of AF, which are expected to improve in the near future. We have also tried to envision innovative tools that may have potential utility in the future.

Better Understanding the Mechanism of Atrial Fibrillation

In many, probably the majority, of patients, paroxysmal AF appears to originate from a focal source in thoracic veins and atria that can be targeted by ablation with a moderate success rate.[6] It is hoped further understanding of the AF mechanism, especially in persistent and permanent AF, will lead to a higher cure rate.

Triggers and Drivers

Present understanding delineates initiators of AF caused by a focal source (triggers) from factors perpetuating the arrhythmia (drivers). For example, optical mapping studies of AF in sheep hearts demonstrated a primary localized source as either an ectopic focus or a small reentry circuit.[7] The focally initiated wave front encounters areas of slow conduction recorded as complex fractionated electrograms that serve to maintain (drive) the AF. Persistent or permanent AF occurs because of perpetuation of either multiple wavelets or a single mother rotor in the atria influenced by chronic remodeling.[8,9] For example, acute atrial stretch increases atrial heterogeneity,[10] while chronic atrial stretch in a goat model of AF induces activation of numerous signaling pathways, leading to cellular hypertrophy, fibroblast proliferation, and tissue fibrosis.[11] The resulting electroanatomical substrate is characterized by increased nonuniform anisotropy and macroscopic slowing of conduction, promoting reentrant circuits in the atria. In addition, atrial remodeling demonstrated in transgenic mice models includes increased hypertrophy of myocytes, fibrosis, heterogeneity of conduction, and enhanced atrial repolarization.[12] With this background, prevention of electroanatomical remodeling by blockade of pathways activated by perpetuation of AF and chronic atrial stretch such as prevention of myocardial hypertrophy and dilation with medications (e.g., antifibrotic and anti-inflammatory agents described in the pharmacotherapy section) provides a promising strategy for future AF therapy.

Defining the Role of the Autonomic Nervous System in the Future

The autonomic nervous system (ANS) plays an important role in initiation, maintenance, and termination of AF. One potential mechanism of vagal initiation of focal AF appears related to heterogeneous abbreviation of the action potential duration in atria or pulmonary veins (PVs) that outlasts the calcium transient, which can then initiate triggered activity or focal microreentry.[13] The ganglionated plexus in the left atrium (LA) can be mapped endocardially using high-frequency stimulation or during AF by demonstrating a vagal response.[14] These areas are also associated with complex fractionated electrograms that serve as a substrate for reentry. Sympathetic heterogeneity produced by denervation[15] or by atrial remodeling can also contribute to AF.[16] Imaging atrial and PV parasympathetic and sympathetic innervation may facilitate targeted autonomic ablation approaches in the future.

Genetics of Atrial Fibrillation and Its Clinical Utility in the Future

Genetic research is aimed at identifying genes predisposing to AF in the hopes of identifying novel molecular targets as potential substrates for intervention. An inherited form of familial AF has been identified.[17] The Framingham Heart Study demonstrated that 30% of all patients with AF, with or without structural heart disease, had a family history of AF.[18] The relative risk of AF was increased by 85% in individuals with at least one parent with a history of AF. Currently, four gene mutations (*KCNQ1, KCNE2, KCNJ2*, and *KCNH2*) and two gene loci (10 q22–24 and 6q14–16) have been identified for autosomal dominant AF, as has a locus at 5p13 for an autosomal recessive AF.[19] These mutations result in gain of function of potassium channels, resulting in shortening of atrial action potential duration and effective refractory period, which support reentry. Genes are yet to be identified for other known inherited AF.

Studies demonstrated that polymorphism in human genes, and also gene–environment and gene–gene interactions, can influence the occurrence and phenotype of AF.[20] Atrial fibrillation is also associated with several rare channelopathies, such as *SCN5A* gene mutations of the Na^+ channel in the Brugada syndrome and familial cardiomyopathy as well as the ryanodine receptor gene mutation (Ca^+ channel) associated with exercise-induced polymorphic ventricular tachycardia (VT) and the short QT syndrome (K^+ channel).[21–24] Studies have demonstrated the association of AF with genetic polymorphism in *KCNE1* and connexin40 gene promoter renin–angiotensin system and angiotensin receptor blocker (ARB) genes.[25,26]

These observations suggest that AF can be a genetically heterogeneous disease. Therefore, AF can occur because of autosomal inheritance and by inherited DNA polymorphisms in patients with structurally normal hearts.[27] Development of novel drug targets rests with further identification of genetic factors responsible for triggering and maintaining AF, including genes that affect automaticity, atrial refractory period duration, and conduction. Future studies will focus on alterations in gene expression of ion channels to understand its pathophysiology, and determination of genetic defects will provide more information about the triggering and perpetuation of AF. The development over the next few years of chips with numerous single-nucleotide polymorphisms to perform genomewide scans will aid in risk stratification of those predisposed to AF. It will also help in development of therapies on the basis of individuals' genomic profiles.

Rhythm Control of Atrial Fibrillation

New developments in pharmacological and nonpharmacological therapy are expected to improve the future management of AF patients.

Pharmacotherapy

At present, the long-term results of antiarrhythmic medications for AF are suboptimal because fewer than 50% of patients remain in sinus rhythm; also, serious side effects limit the use of these drugs. Hence, several pharmacological agents are in development to improve the cardioversion and maintenance of sinus rhythm while minimizing adverse effects.[28]

Potassium Blockers

Azimilide dihydrochloride, an investigational selective class III AAD that blocks both the rapid (I_{Kr}) and slow (I_{ks}) components of the delayed rectifier channel, has been shown to be effective in AF and awaits Food and Drug Administration (FDA) approval for use in the United States. Dronedarone presents a viable alternative for amiodarone as it lacks the iodine moiety responsible for some of the toxicity seen with amiodarone. However, it is notable in that the Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) dronedarone was discontinued prematurely because of a statistically insignificant increased risk of death in the dronedarone group. The ATHENA (A Placebo-controlled Double Arm Trial to Asses the Efficacy of Dronaderone 400 mg bid for Prevention of Cardiovascular Hospitalization or Death from any cause in Patients with Atrial fibrillation/Atrial flutter) trial (currently ongoing) will assess the risk of dronedarone in high-risk heart failure patients to determine the future utility of this

medication. Tedisamil is a potential intravenous antiarrhythmic used as an alternative to ibutilide for acute chemical cardioversion with similar efficacy.[29]

Atrial-Selective Agents

There are several atrial-selective investigational drugs with potential for future use in AF. These drugs are potassium channel blockers in atria with a minimum effect on the ventricles, thereby minimizing the risk of torsade de pointes. These include RSD 1235, AZD7009, and AZD7009. RSD 1235 is a novel mixed frequency-dependent Na^+ channel blocker and atrial-preferential K^+ channel blocker with minimal ventricular effects. Initial phase II results coupled with positive results for two phase III clinical trials, Arrhythmia Conversion Trials 1 and 3 (ACT 1 and ACT 3), which were completed in December 2004 and September 2005, respectively, give this drug great promise.[30,31] Both ACT 2 and ACT 4 are currently ongoing. AZD7009 blocks I_{Kr}, I_{Na}, and I_{Kur} and has been studied in a canine sterile pericarditis model of AF and atrial flutter. AZD7009 was effective in terminating 100% of induced sustained AF or atrial flutter and was 95% effective in preventing their reinduction in this model. AVE0118 is another atrial-selective potassium channel blocker that blocks early atrial repolarizing currents I_{Kur} (present only in the atria) and I_{to} (found in greater density in the atria). The electrophysiological effects of AVE0118 have been studied in a rapid atrial pacing goat model by Blaauw et al.[32] Future studies are required to further evaluate the safety and efficacy of AVE0118.

5-Hydroxytryptamine Receptor Antagonists

5-Hydroxytryptamine ($5\text{-}HT_4$) receptor antagonists may play a role in preventing AF in the future. Early studies using 5-HT infusions resulted in sinus tachycardia and AF. The mechanism of proarrhythmia of 5-HT is postulated to be L-type calcium current enhancement, leading to calcium overload, resulting in increased triggered activity and decreased effective refractory period of the atria. Furthermore, perpetuation of AF may occur via platelet activation, which may act as positive feedback on the 5-HT receptor. Initial studies with 5-HT receptor antagonists have been intriguing. One study with compound RS-100302 in a swine model demonstrated successful termination of six of eight (75%) of episodes of induced AFL and eight of nine (89%) of AF episodes and prevented reinduction of sustained AF/atrial flutter in all cases.[33] A second 5-HT receptor antagonist (SB207266) is also in early development. This unique class of drugs that targets the hormonal axis of AF may prove to be an exciting new pharmacological approach to the treatment of AF.

Anti-inflammation and Antifibrosis Agents: Angiotensin-Converting Enzyme

Angiotensin-converting enzyme (ACE) inhibitors have demonstrated clear effects in several retrospective analyses; they reduced the development of AF by reducing atrial fibrosis, which plays a significant role in the initiation and maintenance of AF. Large-scale randomized clinical trials have not yet confirmed these findings; however, small prospective analyses have demonstrated the benefit of ACE inhibition in conjunction with amiodarone in maintaining sinus rhythm (84%) vs amiodarone alone (61%) after electrical cardioversion.[34] The ARBs have not demonstrated the same degree of benefit provided by ACE-I in retrospective analyses for the prevention of AF. In the Valsartan Heart Failure Trial (Val-HeFT), AF was reported in 5.3% of valsartan-treated patients compared with 7.9% of patients receiving placebo during 23 months

of follow-up.[35] The prospective randomized trial, the AF Clopidogrel Trial with Irbesartan for the Prevention of Vascular Events (ACTIVE), is planned to include a study arm (ACTIVE 1) to evaluate whether irbesartan is superior to placebo in preventing vascular events in patients with AF.

Aldosterone Blockers

Aldosterone excess has been demonstrated to promote adverse cardiac remodeling. However, to date no formal clinical trial demonstrating the beneficial effects of aldosterone in AF has been completed. Recent studies in a canine model with eplerenone have demonstrated reduced atrial tachyarrhythmia inducibility vs ACE inhibition with benazapril in a heart failure model.[36]

Statins

Similarly, statins have demonstrated anti-inflammatory effects by reducing AF associated with C-reactive protein (CRP) and inflammation. No prospective trials have been conducted at this point, but retrospective analyses in patients after coronary artery surgery have demonstrated a 50% reduction in postoperative AF in those patients receiving statin therapy. Statins have also been shown to prevent AF recurrence in patients with lone AF after successful cardioversion.[37,38] Furthermore, a decline in CRP after successful ablation of long-lasting persistent AF has also been demonstrated.[39]

Nonpharmacological Therapy of Atrial Fibrillation

At present, nonpharmacological treatments of AF include endocardial/epicardial ablation for cure or palliative therapy by elimination of triggers or drivers and ventricular rate control by AV node ablation. But, present methods of electrogram mapping and ablation are not optimum; therefore, the endpoint of ablation is not well understood, and the results of these procedures are still far from desired.

Endocardial Mapping and Ablation

There are three major approaches to endocardial AF ablation: isolation of PVs, wide circumferential ablation of the LA, and elimination of complex fractionated electrograms.[6,40,41] However, most electrophysiologists combine these techniques, especially in patients with persistent or permanent AF.[42] This is because substrate mapping requires extensive mapping of both atria, and it is often technically difficult to recognize the abnormal substrate (although it is relatively easy to locate the focal trigger if AF initiates repeatedly) in the electrophysiology laboratory. Mapping during AF is frequently difficult to interpret, and the development of new techniques for endocardial imaging and mapping for AF ablation is under way. Spectral analysis and frequency mapping to identify localized sites of high-frequency activity (dominant frequencies) during AF has led to ablation at these sites, which results in prolongation of the AF cycle length and termination of AF.[43–45] Therefore, mapping atrial wave fronts, dominant frequencies, and ganglionated plexuses in the atria and localization of potential sites for successful ablation will limit the number of RF applications in the future,[14,46] limit the complications related to extensive energy application in the atria, and shorten future procedure time.

The next-generation mapping technique appears dependent on a magnetically guided Stereotaxis system (St. Louis, MO) or a mechanical system (Hansen Technology, Mountain view, CA). The advantage is twofold; catheters or

sheaths will have greater maneuverability than is afforded by current operators, and radiation exposure to both patients and operators will be minimized. Automatic mapping of the cardiac chambers will be an added benefit to better delineate atrial anatomy and localize the areas of interest for ablation. A retrograde approach to access the LA by the magnetically guided catheters in the future may minimize the complications related to transseptal atrial puncture.

Epicardial Mapping and Ablation

At present, the maze procedure is limited to patients undergoing cardiac surgery for valve replacement or coronary artery bypass graft surgery, but it requires at least 40 to 45 min of cardiopulmonary bypass. New technologies employ a minithoracotomy (thus avoiding a sternotomy) and robotically guided (Da Vinci Medical System, Intuitive Surgical Inc.) epicardial or endocardial ablation with microwave energy.[47] Use of minimally invasive surgery to map ganglionated plexuses epicardially and ablation with bipolar ablation (Atricure, West Chester, OH) has shown promise, but the procedure time is still longer than routine endocardial ablation.[48] However, it may be one of the procedures of choice in patients undergoing minimally invasive surgery for mitral valve disease or coronary artery bypass surgery. The recent development of epicardial mapping and ablation of VT with a subxiphoid approach has opened the way for epicardial ablation of AF. If developed, it may effectively map ganglionated plexuses and eliminate the need for anticoagulation during the procedure. However, care must be taken to minimize the risk of injury to myocardium and coronary arteries and to reduce the risk for pericarditis.

A potential-based electrocardiographic imaging system developed by Intini et al. has been used to noninvasively compute epicardial potentials from measured body surface electrocardiographic data and construct epicardial electrograms and isochrones (activation sequences) as well as repolarization patterns on the heart.[49] Further development of noninvasive imaging and mapping of atrial electrical activities in AF patients by this method has a potential role in targeting specific sites for energy delivery, potentially by a transthoracic approach.[50]

Novel Energy Sources for Atrial Fibrillation Ablation

At present, RF energy is used in the majority of AF ablations. However, it is associated with risks such as cardiac perforation, thromboembolism, and PV stenosis. Furthermore, nonuniform myocardial damage is caused by inconsistent catheter–tissue contact, and the damage is nonreversible if vital structures such as the AV node are accidentally injured. Therefore, studies are under way for an ideal energy source that will be effective, user friendly, and less time consuming and possess minimal complications. Animal and human studies have shown that the following methods hold promise for the future: cryoablation, high-intensity focused ultrasound (HIFU), laser ablation, and magnetic-based navigation and ablation.

Cryoablation: Among the catheter-based technologies for cryoablation is the Artic Front catheter from Cryocath. The balloon-based technology utilizes nitrous oxide to cool the surface diameter of the balloon to deliver circumferential lesions within a minute. The device has been approved for use in Europe and is undergoing clinical trials in North America. Initial results using the 21-mm balloon resulted in moderate success, which improved by upgrading the balloon to 23- and 28-mm sizes to afford complete ostial

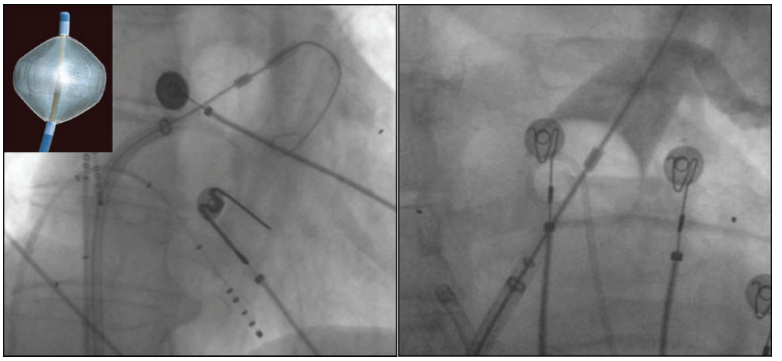

Figure 2 Pulmonary vein isolation in a patient with atrial fibrillation using a balloon cryoablation catheter (inset). The balloon is wedged in the left superior pulmonary vein with a guide wire advanced into the pulmonary vein (left) and pulmonary venogram revealing complete occlusion of the pulmonary vein (right). (Courtesy of J. Vogt, Herz-Und Diabeteszentrum.)

PV occlusion which resulted in greater success in PV isolation (Figure 2). In one study in a canine model, acute success of PV isolation was achieved in 87.5%. Successful isolation was associated with the absence of any periballon flow leak as seen by intracardiac echo (ICE) and with balloon temperatures less than −80 °C. Cryoablation is associated with intact endothelium at the veno–atrial junction of the PV and has a very low incidence of PV stenosis or thrombus formation. However, right phrenic nerve injury has been noted frequently, which can be avoided with pacing prior to lesion formation to establish phrenic nerve location. In the future, a balloon with an adjustable circumference will aid in dealing with larger PVs and those PVs with common ostia that currently require supplemental RF therapy when cryoablation is unsuccessful.

High-Intensity Focused Ultrasound: The technology for HIFU has been utilized both in open heart-based procedures and as an investigational balloon ablation catheter. A circumferential ultrasound (US) beam is delivered to electrically isolate the PVs. Initial results have been moderately successful. Complete tissue contact is not required, and there is a low incidence of PV stenosis as a result. Of note, HIFU creates significant artifact when used in conjunction with intracavitary echocardiography.

Laser Ablation: Laser-based technology to ablate AF continues to undergo early clinical trials in Europe and the United States. This promising technology utilizes a focused beam of energy to target specific PV ostial or atrial sites (Figure 3). Advantages include the ability to directly visualize the region ablated to ensure accuracy of lesion formation. Studies with a novel laser balloon endoscopic ablation system (EAS; CardioFocus Inc.) in patients with paroxysmal AF have demonstrated an initial success rate of 75% to 78% with a low incidence of PV stenosis. Early data demonstrated that the technique is feasible and has encouraging safety data. Further studies will be required in larger clinical trials to assess the long-term efficacy and safety of this novel therapy.

Figure 3 The low-power diode laser. It is housed in a balloon and introduced into the pulmonary veins via a catheter. It produces a radial (360°) lesion. (Courtesy of Vivek Reddy, Massachusetts General Hospital Web site.)

Magnetic-Based Navigation and Ablation: A promising and exciting technology that has now begun to receive widespread attention is the magnetic-based mapping and ablation system. The leader in this arena is Sterotaxis, which has received FDA approval for its ablation catheters. From a remote console, the system utilizes a powerful magnetic field to move the catheter tip for mapping and ablation. This is in contrast to most mapping and ablation systems, which currently utilize force at the base of the catheter to "push and pull" the catheter to appropriate locale rather than "guide" the mapping/ablation tip to the region of interest. This system allows for increased freedom and maneuverability through complex anatomy. The system is also "sheathless," which reduces the risk of thrombus formation and embolism. In addition, the risk of cardiac perforation and tamponade is extremely low, which minimizes morbidity as the catheters essentially bend and loop if an inappropriate amount of tension or force is detected. This technology has been used to treat all forms of supraventricular tachycardia (SVT), including AF, with very good results.[51]

Non-Catheter-Based Treatments

A novel technology from Exablate (Insightec, USA) utilizes magnetic resonance-guided focused ultrasound surgery (MRgFUS) to create lesions noninvasively. Akin to a magnifying glass focusing light, MRgFUS directs US energy to a pinpoint to create lesions. This technology has been employed successfully in the treatment of uterine fibroids and other solid tumors. Clinical trials are now utilizing MRgFUS in the treatment of breast, liver, and brain tumors. Ideally, this technology could be transferred to cardiac electrophysiology to deliver endocardial or epicardial lesions noninvasively. Appropriate technology would need to be employed to account for cardiac movement through gated imaging systems. Magnetic resonance-guided focused ultrasound surgery has the capability to provide "incisionless" nonthermal ablation, direct visualization

of lesions, no exposure to ionized radiation, and decreased morbidity and hospital stay. Potential differences from conventional endocardial ablation would be the inability to determine the effect on electrogram amplitude and lack of direct endocardial stimulation of cardiac tissue.

Cardiac surgeons are increasingly using novel technologies to treat AF. Epicardial and endocardial lesions are usually performed during concomitant cardiac procedures (e.g., coronary artery bypass grafting, valvular replacement) involving RF, microwave and laser and cryoablation. In the last approach, a new two-in-one device from Cryocath, the FrostByte, uses a clamp to secure and freeze the PVs epicardially. The clamp improves adhesion of the probe and aids in the precision of the cryo lesion delivery. This technology is increasingly versatile as it may be used to create epicardial as well as endocardial lesions in open or closed approaches and may be used in minimally invasive procedures in the future as well.

Success thus far has been very good, with 88.5% freedom from AF at 1 year follow-up during concomitant open procedures.[52] Initial animal studies examining the use of this technology from an epicardial approach are promising.[53] However, further confirmatory studies will be required in clinical trials and with minimally invasive techniques.

Rate Control of Atrial Fibrillation (Drugs and Implantable Devices)

Trials have shown that mortality and quality-of-life scores are similar in patients with rate control of AF as compared to rhythm control.[54] Therefore, a large population of AF patients is currently treated with AV nodal-blocking agents. The search for newer cardioselective adenosine receptor blockers (Tecadenoson, SDW-WAG994, and CVT 500) may provide new agents for the future.[55,56]

Sigg et al. showed the feasibility of ventricular rate control with focal acetylcholine delivery into the AV node via an implantable catheter in a canine model of AF.[57] Various drug delivery systems (e.g., transvascular, intramyocardial, and epicardial) to deliver embolic substances, cytotoxic agents, ethanol, antiarrhythmic agents, autonomic modulators, antibody-bound agents, biological agents, and nanoparticles are envisioned to achieve ablative or cellular alteration in patients with AF.[58] Genetic alteration of AV nodal conduction has been used to help control the ventricular rate during AF.[59]

Control of rapid ventricular rate in AF patients may be a challenge, and a substantial number of these patents have to undergo RF ablation of the AV node with a permanent pacemaker implant. This procedure makes them pacemaker dependent and therefore vulnerable to the risks of long-term right ventricular (RV) pacing. Pacing-related left ventricular (LV) dysfunction may potentially be avoided by AV node ablation with newer technologies such as cryoablation without damaging the proximal His bundle, which can be paced permanently.

Another invasive method of rate control is AV nodal modification by RF ablation. However, the results of this procedure have not been encouraging because of failure of rate control during follow-up in a substantial number of these patients, and therefore it has fallen out of favor in clinical practice.[60]

Bunch et al. demonstrated that AV nodal modification (without creating complete AV nodal block) in dogs could be achieved by injecting fibroblasts

in the AV node. This effect was substantially enhanced by pretreatment of fibroblasts with transforming growth factor β1 (TGF-β1).[61] These data promise a new line of therapy for management of rapid ventricular rate during AF without pacemaker implant.

Prevention of Thromboembolism

Cerebrovascular accidents and peripheral embolism account for the major morbidity from AF. The mainstay for long-term anticoagulation is warfarin and related compounds. However, warfarin requires frequent monitoring of international normalized ratio (INR) and is associated with significant bleeding risk. The quest for ideal anticoagulants with high efficacy-to-safety index, predictable dose response, and minimal drug interactions is under way. These anticoagulants include (1) inhibitors of the factor VIIa/tissue factor pathway; (2) factor Xa inhibitors, both indirect and direct; (3) activated protein C and soluble thrombomodulin; and (4) direct thrombin inhibitors. However, clinical development of these therapies often starts with studies for prevention of venous thrombosis and later for the prevention of thromboembolism in patients with AF.[62] At present, the greatest clinical need is for an oral anticoagulant to replace warfarin for long-term prevention and treatment of patients with venous and arterial thrombosis. Ximelagatran, an oral direct thrombin inhibitor, is the first of a series of promising new agents that might fulfill this need. Large phase III trials evaluating ximelagatran for the secondary prevention of venous thromboembolism and prevention of cardioembolic events in patients with AF have been completed. While the results are comparable to warfarin, ximelagatran did not fair well because of its side-effect profile, mainly because of liver toxicity. However, development of new compounds related to ximelagatran may eliminate its major side effects and be used as a better alternative to warfarin subsequently.

Left Atrial Occlusion or Exclusion Devices

The LA appendage is the source of embolism in 90% of patients with AF. Left atrial appendage occlusion devices may be an alternative therapy in the future, especially in patients who are not candidates for oral anticoagulation and RF ablation AF. Two types of investigational devices to occlude the LA appendage undergoing randomized control trial hold promise. The Watchman Left Atrial Appendage System (Atritech Inc., Plymouth, MN) and PLAATO (ev3 Inc., Plymouth, MN) are novel devices designed to prevent the embolization of thrombi that may form in the LA appendage. These devices are implanted via a catheter-based delivery system with a transseptal approach.[63,64] Certain types of LA stapling devices with a minithoracotomy also hold promise.[65]

Conclusion

Continued progress in basic research into the mechanisms of AF, coupled with rapidly developing technologies, will drive the basis for current and future therapies. Novel and innovative ideas reviewed here will continue to pave the way for future advancements yet to be discovered and implemented in the continued quest for a cure for AF.

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