Current Interventional Strategies for the Management of Atrial Fibrillation

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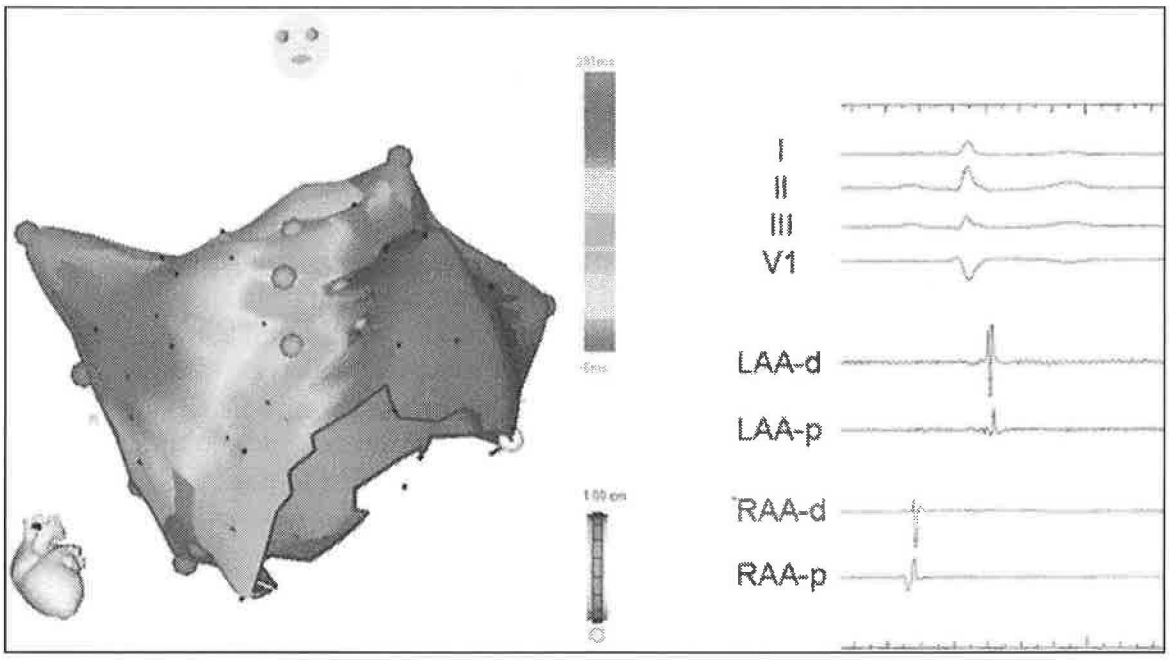

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INTRODUCTION

The field of interventional electrophysiology came of age in the early 1990s with the evolution of radiofrequency (RF) ablation for supraventricular and ventricular tachycardia, and implantable cardioverter-defibrillators for the prevention of sudden cardiac death. We are currently experiencing another period of groundbreaking innovation in electrophysiology. The advent of techniques for the ablation of atrial fibrillation (AF) has resulted in the ability to control this troublesome and common arrhythmia with unprecedented success. Techniques however remain challenging and imperfect, and many challenges remain. I will begin by reviewing the history, epidemiology, and sequelae of AF and current thoughts on its mechanism. I will then discuss current strategies for catheter-based ablative therapy of this arrhythmia. I will conclude by briefly discussing new surgical techniques that are in evolution, and look to the future, as new devices and treatment modalities become available.

The irregular pulse and its association with disease have been recognized since antiquity. In the mid-1700s, Jean Baptiste de Sénac correlated gross irregularities ("rebellious palpitation") with necropsy observation of mitral valve disease. He emphasized the origin of the heart's irregularity from the distended atrium consequent on distension or reflux of blood irritating the atrial wall. AF was first described electrocardiographically in 1874, when Edmé Vulpian observed the irregular atrial electrical behavior that he termed "fremissement fibrillaire" in dog hearts. Einthoven published the first EKG showing AF in 1906, although there was significant background interference, prohibiting accurate definition of fibrillatory atrial waves. In 1903 Hering was the first to publish a clear EKG of AF.

AF is the most frequently experienced arrhythmia, affecting 2.2 million people in the United States and is the commonest cause of embolic stroke.[1] In addition AF can cause palpitations, fatigue, reduced exercise capacity, and dyspnea although in an appreciable number of individuals, AF is asymptomatic. AF can precipitate heart failure, syncope, angina, myocardial infarction, and can trigger ventricular arrhythmias in susceptible individuals. AF is the sole cause of some cases of cardiac failure (tachycardia-induced cardiomyopathy), a proportion of which may be reversible with restoration of sinus rhythm. AF is a difficult arrhythmia to treat effectively, and unlike more organized arrhythmias such as atrial flutter and supraventricular tachycardia has, until recently, proved resistant to cure by catheter ablation.

EPIDEMIOLOGY

In the Framingham Study, approximately 7.2% of men and women aged between 30 and 62 developed AF when followed biennially for 30 years and in the Manitoba Follow-Up Study, 7.5% of male air crew recruits developed the arrhythmia when followed up for 44 years.[2] The overall prevalence of AF is 0.5%-1% and rises to over 10% in individuals aged over 80s.[1] The increasing age of Westernized populations, increasing prevalence of heart failure, and longer survival of those with AF means that the prevalence of AF is rising rapidly.[3] (Figure 1)

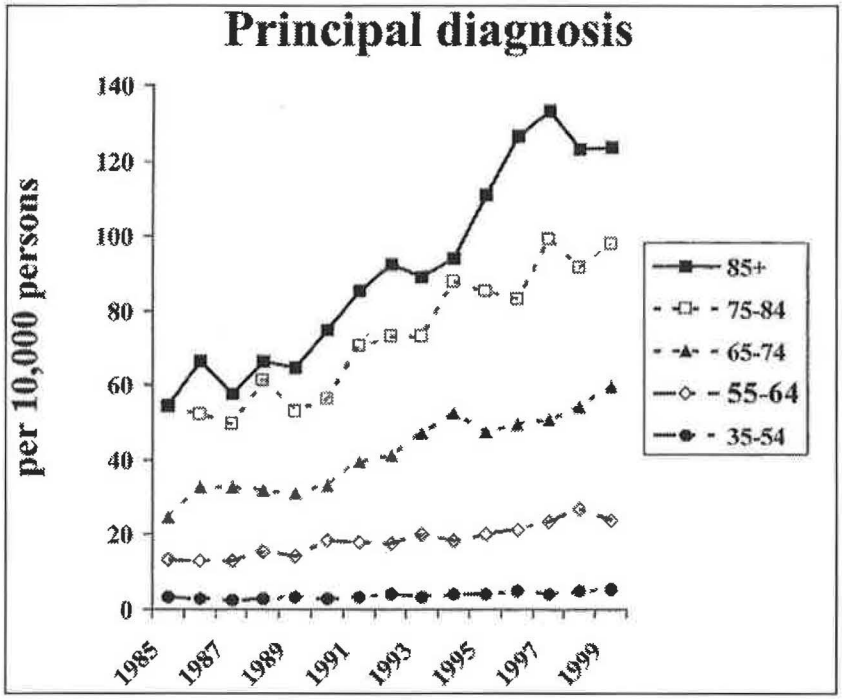

Figure 1: Age-specific prevalence (per 10 000 population) of hospitalizations for atrial fibrillation among adults 35 years of age or older by year, 1985 to 1999. (reference 6)

In industrialized countries, the number of affected individuals is projected to more than double over the next 50 years. There has been a doubling in the past 20 years of the rate of AF-related hospital admissions, and a 50% increase in direct health care costs due to AF over a recent 5-year period in the United Kingdom.[4-6]

CLINICAL CLASSIFICATION

The most useful clinical classification of AF is that in which AF is termed either paroxysmal, persistent, or permanent.[7] Paroxysmal AF (PAF) refers to episodes of AF which spontaneously terminate within 7 days (usually < 48 hours) without electrical or pharmacologic intervention. Persistent AF is that which terminates in over 7 days, and usually requires an intervention of some sort to do so. Permanent (or chronic) AF is that which does not respond to attempts at cardioversion, or recurs soon after cardioversion and is accepted, sometimes reluctantly, (by patient, physician or both) as a permanent state. The rate of progression from paroxysmal to permanent AF has been estimated to be 8% at one year with nearly 20% of cases progressing to permanent AF by 3 years. [8 9]

PREDICTORS AND RISK FACTORS

Established risk factors for AF include age, sex, heart disease, diabetes, and previous myocardial infarction. In the Framingham Study, hypertensive heart disease, particularly when accompanied by cardiomegaly on x-ray, or electocardiographic evidence of left ventricular hypertrophy emerged as the most common cardiac cause of AF. Cardiac failure is a consistent, powerful precursor of AF although the relationship is complex since heart disease may cause both AF and cardiac failure, furthermore AF and cardiac

failure perpetuate each other.[4,5] Valvular (particularly mitral) heart disease is an important cause of AF. The term 'lone AF' refers to that which occurs in the absence of hypertension or other underlying heart disease. In paroxysmal cases, lone AF accounts for a greater proportion of cases than in chronic AF. Congenital heart disease, pericarditis, pulmonary embolism and chronic pulmonary disease are known to cause AF. Noncardiac conditions such as hyperthyroidism (even when subclinical), phaeochromocytoma, and both acute and long-term alcohol abuse can present with AF. Obstructive sleep apnea is a recently described cause of AF. There is a relationship between elevated CRP levels and AF indicating a possible inflammatory contribution to the substrate.[10] In the Framingham study, men with the psychological traits of anger and hostility, but not those with type A behavior had significantly higher rates of AF.[11]

CONSEQUENCES OF AF

Symptoms

AF varies in its symptomatic impact. Some patients are apparently asymptomatic whilst others are significantly disabled by the arrhythmia. Women are more likely to experience symptoms of AF and have been reported to have higher heart rates during AF than men. AF has been shown to significantly reduce quality of life even when classic symptoms are absent.[12]

Thromboembolism

It is estimated that 15% of embolic stroke is directly attributable to AF. When AF complicates rheumatic heart disease, the risk of stroke is seventeen times that of patients in sinus rhythm.[13] However in the past 20 years it has become evident that the risk of stroke is increased even when AF occurs in the absence of valvular heart disease, so-called nonvalvular AF (NVAF). In the Framingham Study, the incidence of stroke increased nearly 5-fold in the presence of NVAF.[14] AF is also an important cause of peripheral thromboembolism.[15,16] The association of AF with stroke is complex since other major risk factors for stroke such as hypertension, heart failure, and cerebrovascular disease, are often present in patients with AF.

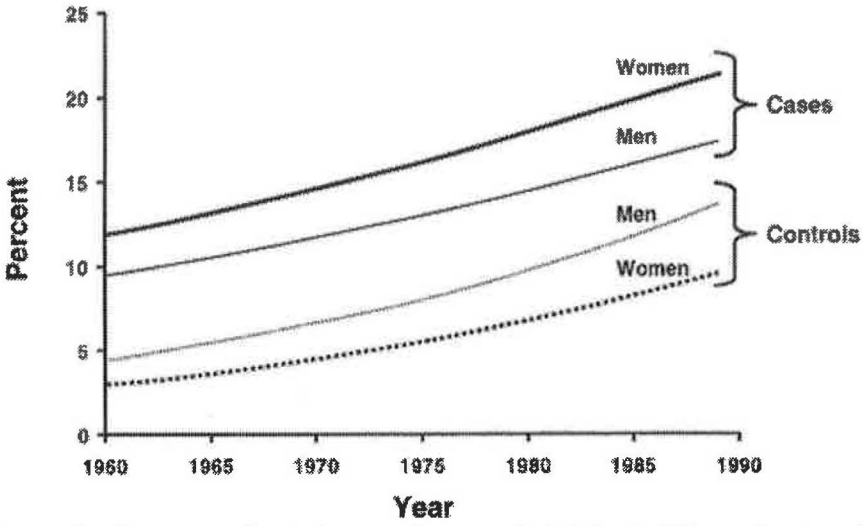

Figure 2: Trends for age-adjusted prevalence of AF in 1,871 patients with ischemic stroke and their age- and gender-matched controls, stratified by gender.[17]

AF is associated with increased stroke severity. 30-day mortality has been shown to be greater in strokes associated with AF than in those that are not (25% versus 14%).[18] In the Oxfordshire community stroke project the 30 day case fatality rate from stroke was significantly higher with AF (23%) than with sinus rhythm (8%).[19] It is likely that collateral circulation in the brain may be less developed in patients with a sudden interruption of blood flow caused by an embolus than in those who suffer a stroke as the result of an underlying long-standing arterial atherosclerotic process.[20]

Clinical risk of stroke in NVAF varies from 1% (similar to a sinus rhythm control group) to over 12%. Pooled data from five randomized controlled studies of anticoagulation (AFASAK, BAATAF, CAFA, SPAF, and SPINAF studies) have identified increasing age, a history of heart failure, previous stroke or TIA, a history of hypertension, and diabetes as clinical risk factors for stroke in AF.[21] Validated transthoracic and transesophageal echocardiographic markers of increased risk include left atrial enlargement, left ventricular dysfunction, reduced filling and emptying velocities of the left atrial appendage, spontaneous echo contrast (SEC; an echocardiographic appearance of a light grey swirling pattern seen inside cardiac chambers), and the presence of complex aortic plaque.[22]

AF and Mortality

AF is associated with an independent negative impact on mortality after adjustment for age, sex, and other cardiovascular risk factors.[23] The presence of AF independently predicts mortality when it occurs in association in acute coronary syndrome, congestive heart failure, and the peri-operative phase of coronary artery bypass surgery.[24] AF increases health care costs, for example direct costs attributable to AF in the United Kingdom are estimated at close to a billion dollars.[25]

The Role of the Left Atrial Appendage in Thromboembolism

In patients with NVAF, thrombus has a predilection to form within the left atrial appendage (LAA), a long, tubular, trabeculated pouch, with a narrow junction with the left atrium (LA). These anatomical features enhance stagnation of blood within the LAA, particularly when active contraction of the LAA is lost as occurs in AF. A study using transeshopahageal echocardiography (TEE) in 233 patients with persistent AF of more than 48 hours duration who were not on chronic anticoagulation revealed that 15% had evidence of left atrial thrombus, and all but one were located in the appendage (Figure 3). As has been mentioned, reduced (or absent) LAA inflow and outflow velocities are associated with LAA thrombus formation and a history of systemic embolism patients with AF. The cause of LAA dysfunction in patients with AF is likely to be related in part to a myopathic process which resulted in AF or which occurs as a result of the AF itself (an AF induced myopathy).

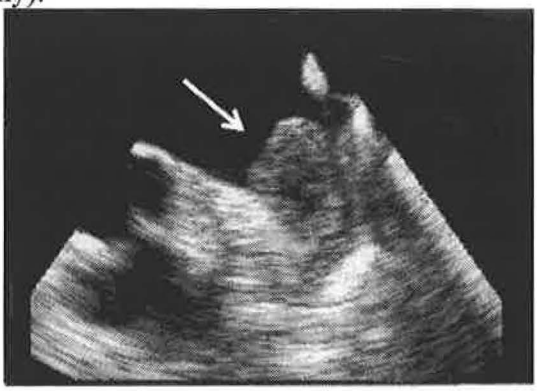

Figure 3: Thrombus (white arrow) occurring in the left atrial appendage (LAA) in a patient with AF.

PATHOPHYSIOLOGICAL MECHANISMS OF AF

Re-entry, increased automaticity, and triggered activity

A substantial proportion of tachyarrhythmias occur as a result of the phenomenon of re-entry or 'circus movement'. This occurs when an electrical impulse encounters an obstacle to conduction (such as scar tissue or a cardiac valve) and is split into two impulses (pathways) which may have distinctly different conduction properties. Under the right circumstances, as occurs following ectopic premature beats, the impulse may conduct exclusively down one pathway and may find that the other pathway is able to conducte in a retrograde direction resulting in a re-entrant loop (Figure 4A). Re-entry is often termed 'macro re-entry' if the circuit is relatively large and its perimeter can be viewed with the naked eye. 'Micro re-entry' refers to a circuit which is thought occur around a central obstacle on a microscopic level. A central anatomical obstacle need not be present in a re-entrant arrhythmia. The obstacle may be 'functional' i.e. an area of tissue that has been rendered refractory by electrical forces cancelling each other out. In the 'leading circle model' of re-entry described by Allesie and colleagues, sustained

tachycardia can occur in the pattern of a vortex whereby impulses spread centripetally from the circumference of a circulating wave towards the centre which acts as a functional obstacle for the circuit (Figure 4B).

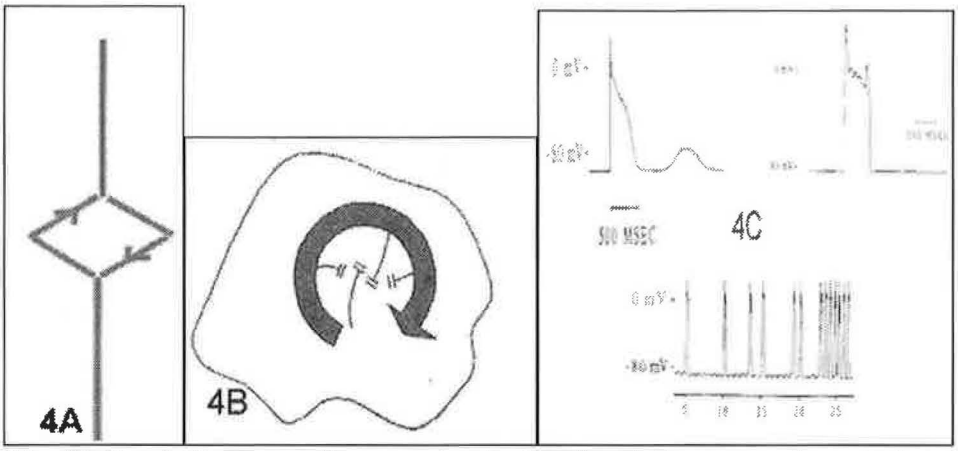

Figure 4A: Stylized diagram of a re-entrant circuit rotating around central anatomical obstacle; **4B** Leading circle re-entry theory which occurs around a functional, electronic obstacle; **4C** A normal action potential is shown above left. An afterdepolarizatrion causes excitation in the recovery period. This may cause repetitive firing to occur (bottom).

Abnormal automaticity arising from an ectopic focal intracardiac source is also an important cause of tachyarrhythmias. This occurs as a result of a rise in local intracellular Ca^{2+} which results in an abrupt depolarization at time that these cells are already partially depolarized This phenomenon is known as an 'afterdepolarization'. If these afterdepolarizations reach the threshold potential for re-excitation of the cell, spontaneous action potentials result, producing repetitive firing. (Figure 4C).

The multiple wavelet hypothesis

Theories as to the mechanism of AF date back to the early 1900s when the prevailing theory, first expounded by Sir Thomas Lewis was that AF was related to multiple randomly firing ectopic foci or "multiple heterotopous centers". His theory mixed electrical and mechanical phenomena and was the first credible explanation of the mechanism of AF. After the first demonstration of re-entry as a mechanism for arrhythmias in 1914, the various theories explaining the mechanism of AF included this concept too. In the early 1960s Moe and coworkers challenged the paradigm that AF had to be caused exclusively by either re-entry or abnormal automaticity. Their 'multiple wavelet hypothesis', developed using a mathematical model, describes AF as being maintained by the presence of numbers of wavelets of excitation wandering through the atrial myocardium around islets or strands of refractory tissue.[26 27] (Figure 5)

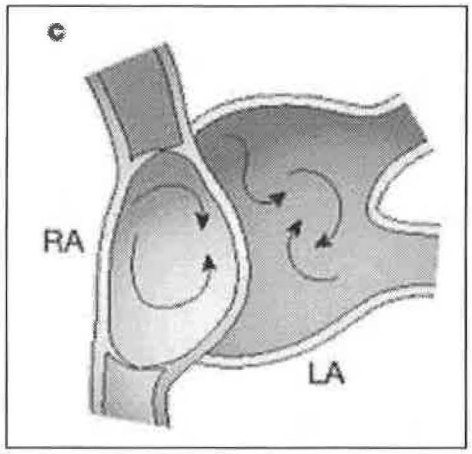

FIGURE 5: The multiple wavelet model of AF as described by Dr Gordon Moe

Allesie and co-workers mapped the spread of excitation during AF in the isolated blood perfused canine heart. They confirmed the presence of multiple extinguishing and dividing wavelets which exhibited fluctuations in size, and changes in direction of propagation.[28] They also encountered wavelets which appeared to enter one atrium from the neighboring atrium. These findings were then confirmed using high-density epicardial mapping of the free wall of the right atrium in patients in AF.[29] Key to the multiple wavelet theory is the concept of a critical atrial mass required to sustain the wavelets since it is thought that at least 3-5 separate wavelets are required for AF to persist. Thus the larger the atrium, the more likely AF will sustain itself and resist efforts aimed at its elimination. The multiple wavelet hypothesis which dictates that random re-entrant wavelets, circulating around anatomical and functional regions of block in the atria, perhaps driven by dominant rotors (see below) became broadly accepted as the mechanism underlying AF.

Rotors and Spiral Waves in Atrial Fibrillation

A rotor has been defined as a stable rotating pattern of reaction and diffusion that surrounds a pivot point also known as a 'phase singularity'.[30] From this rotor a curved wavefront radiates into the surrounding tissue. In a series of experiments conducted on isolated sheets of perfused sheep atria, and using a technique known as optical mapping, Jaliffe and colleagues demonstrated that pacing at high but regular frequencies results in the breakdown of the direction of activation and resultant 'fibrillatory' conduction. This has resulted in the concept of a 'mother' or 'dominant' rotor as being responsible for the generation of multiple 'daughter' wavelets. Interestingly, the generation of such rotors is facilitated by the application of acetylcholine to such preparations. In isolated sheep hearts, such rotors have been described as occurring in the posterior LA, close to the ostia of the pulmonary veins.[31]

AF as a Self Perpetuating Arrhythmia

Elegant observations by Allesie and co-workers in the mid 1990s proved a mechanism whereby AF itself results in electrophysiological changes to the atria which encourage the perpetuation of AF and cause PAF to progress to persistent or permanent AF (''atrial fibrillation begets atrial fibrillation''). In a study on goats instrumented with multiple

electrodes sutured to the epicardium of both atria, AF was induced on an automatic repetitive basis by rapid pacing. The duration of the induced AF progressively increased and finally became persistent without the need for reinduction.[32] Interestingly, eighty-five years prior to Allessie's experiments, based just on circumstantial evidence, Sir Thomas Lewis had concluded that "the fibrillation itself aggravates the irritability of the auricular tissue. It is perhaps a factor of this nature which accounts for long continued auricular incoordination in patients who are affected with it."

Thus it appears that AF can be a self-perpetuating phenomenon, and its occurrence, initially in paroxysms, results in electrophysiological changes which encourage increasingly longer episodes of AF, and eventually its continuation as persistent or permanent AF. In addition to causing pure electrophysiological changes, AF has been shown in canine models to result in an atrial myopathy characterized by atria which, under the influence of AF, progressively enlarge in area.[33] [34] Microscopically, atrial myocytes in such remodeled atria contain increased numbers of enlarged mitochondria and a disrupted sarcoplasmic reticulum. In addition, sustained rapid ventricular rates may result in a tachycardia-related ventricular cardiomyopathy. The resultant increased left ventricular end-diastolic pressures result in further atrial stretch, atrial enlargement, and further perpetuation of the arrhythmia and the complications that arise from it.

EARLY ABLATIVE TECHNIQUES

Early ablative strategies were designed around the multiple wavelet hypothesis of AF. First described as an open-chested surgical procedure in 1991, the 'Maze' procedure aimed to disrupt these wavelets by creating scars by incising and re-suturing atrial tissue.[35] The resulting insulated corridors would allow conduction to proceed, unhindered, from sinus node to atrioventricular (AV) node. (Figure 6) success rates were impressive and there were few complications. The procedure is nevertheless an open-chested procedure performed on cardiopulmonary bypass with the attendant risks associated with such an approach, and is technically very demanding.

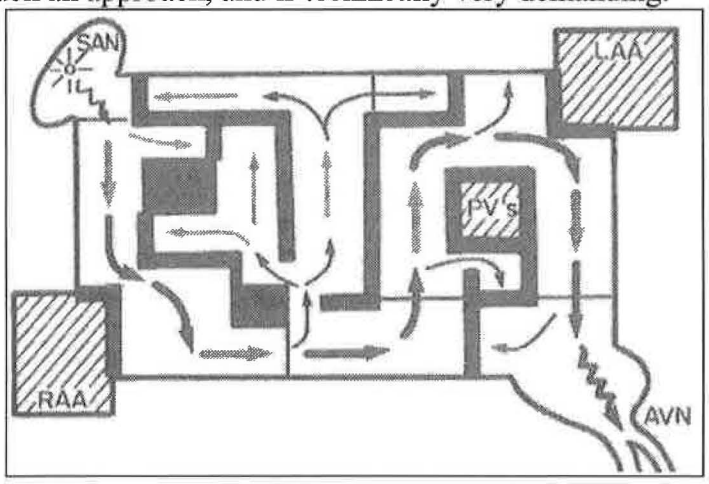

FIGURE 6: Schema of the original Maze concept. SAN – sinoatrial node; AVN – atrio-ventricular node. RAA – right atrial appendage, LAA – left atrial appendage

By the early 1990s, catheter-based radiofrequency (RF) ablation had become a widely-practiced modality for the successful cure of supraventricular tachycardia (SVT) and to a lesser extent ventricular tachycardia (VT). Complications rates for these procedures were low. Attempts to replicate the open-chested Maze model for the catheter-based treatment of AF however required prolonged (up to 18 hours), invasive procedures, ablating extensive areas of atrial myocardium. Cure rates for AF were modest at best and the risk of complications was high with these early procedures. Thus in the early to mid-1990s, catheter ablation did not appear to hold promise whatsoever as a therapeutic modality for AF.

CURRENT ABLATION STRATEGIES FOR OF AF

The revival of the concept of AF as a focal arrhythmia

In a seminal paper in 1998, Haissaguerre et al described ablation of paroxysmal AF in 45 patients by targeting ectopic beats that were seen to initiate AF.[36] 94% of these foci were in the pulmonary veins (PV), particularly the left PV (Figure7). Unlike the Maze procedure, this technique involved ablation of very limited areas of sleeves of myocardium extending into the PVs. During a mean follow-up period of 8±6 months (median, 7), AF was eliminated completely in 28 patients (62%) without the use of drug therapy. No serious side effects were observed during these procedures. These findings, subsequently reproduced by others, required a complete reappraisal of the prevailing multiple wavelet theory of AF as being the sole mechanism underlying AF and revived Lewis' original concept of ectopy as a cause of AF. The predilection for the pulmonary veins as the sources for rapid focal tachcycardias may relate to the proximity of key intracardiac ganglia to the PVs. Atrial myocytes extending into the PVs exhibit relatively short action potentials, and hence may be more prone to the effects of autonomic alteration (see below). Several investigators have confirmed the findings of Haissaguerre, demonstrating that effective electrical isolation of PVs exhibiting foci of tachycardia can result in cure of PAF. Up to 20% of such patients will exhibit foci outside the PVs. In a series of 240 patients with a total of 358 ectopic foci initiating PAF, Lin and colleagues identified the posterior LA, the superior vena cava (at its junction with the right atrium), the crista terminalis (a ridge of tissue in the lateral right atrium), the coronary sinus (CS) ostium, and interatrial septum as being sources from which PAF can arise.[37]

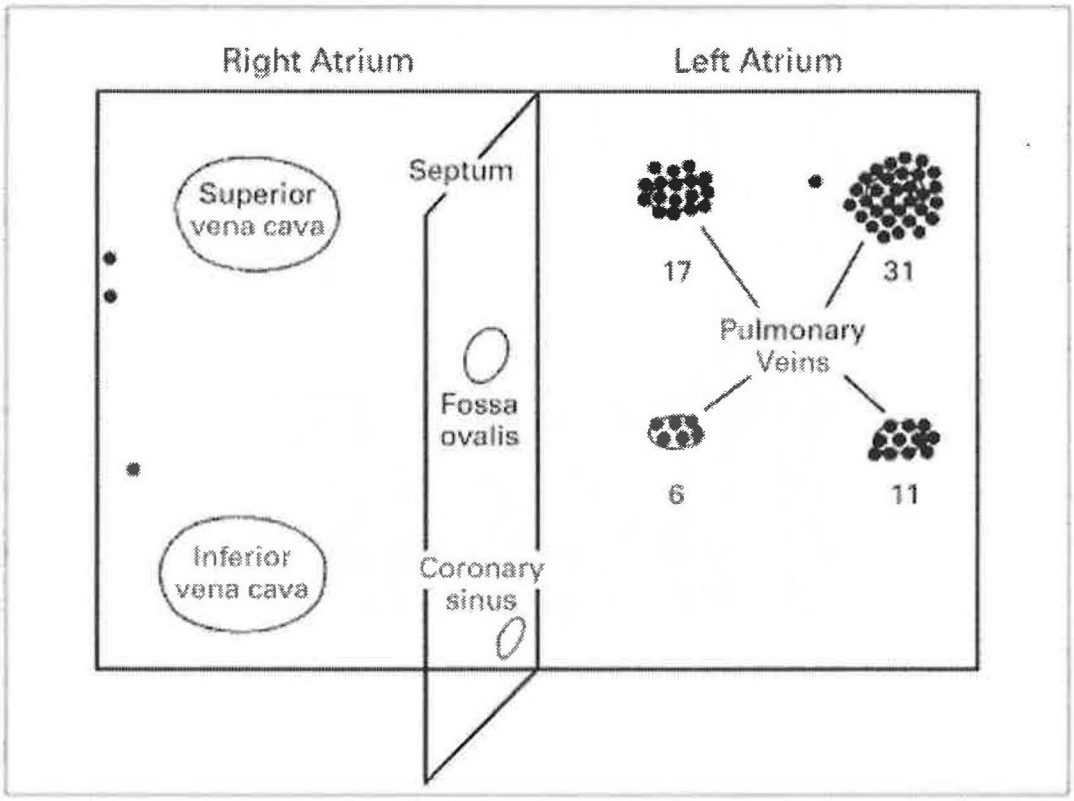

Figure 7: Location of initiating ectopic foci in 45 patients with AF. Note that the majority arose in the pulmonary veins (PVs), although non-PV sources exist.[36]

Electrical isolation of the pulmonary vein ostia by catheter ablation

As RF catheter ablation aimed at electrically isolating the PV focus responsible for AF became widespread, two important facts became apparent. The first was that ablation within an individual putative PV was unlikely to be very successful since as this PV was electrically isolated, tachycardia would be noted to be arising from a different PV. Thus it became apparent that ideally, all 4 PVs should be isolated from the atrial tissue. The second important fact that emerged was that ablation within the veins themselves could result in PV stenosis, which could be avoided if ablation took place further back within the atrial tissue in the antrum of the PV i.e. the flask-shaped LA tissue bordering the PV ostia. These two facts resulted in the design of ablation procedures targeting all four PVs, creating antral ablation lesions. Wide-area catheter ablation (WACA) creates empiric continuous circular lines of ablation around all 4 PV antral regions.[38] (Figure 8) WACA has become a widely practised approach to the ablation of AF, and is used in many centers, both as the sole procedure, or incorporated as part of a broader ablation strategy. The large area of atrial tissue ablated in such procedures may have the added advantage of 'debulking' the atrium thus reducing the available area for wavelets to circulate. Other operators practice more selective antral ablation (segmental ablation) targeting only the isolated sleeves of myocardial tissue extending into the PVs.

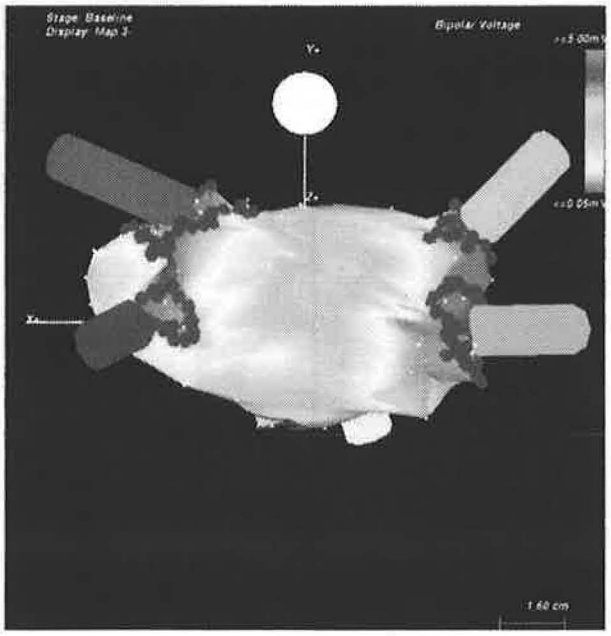

Figure 8: Electroanatomical image representing the left atrium from its posterior aspect in a patient undergoing wide area catheter ablation (WACA) of all 4 PV ostia in the antral regions of the veins. The dots represent ablation points, the tubes attached to the chamber represent the pulmonary veins.[38]

A survey in 92 physicians in the United States, involving almost 6000 AF ablations from 2000 to 2003, confirmed the widespread adoption of such empiric techniques aimed at the elimination of AF. During this time period the number of ablation procedures for AF increased four-fold. Self-reported short and long-term success rates of AF ablation were reported to be 71% and 66% at one and two years respectively.[39]

Targeting Areas of Complex Fractionated Electrograms

In 2004 Nademanee reported a completely unique approach for the ablation of AF.[40] The sole target for ablation in this approach is the targeting of complex and fractionated intracardiac electrograms (EGMs) (Figure 9).

a) **b)**

Figure 9: a) An example of complex fractionated electrograms (EGMs) recorded from the tip of an ablation catheter in contact with the left atrial myocardium in a patient in AF. b) EGMs exhibiting an organized pattern recorded from the tip of an ablation catheter in the left atrium in a patient with AF.

The author reported a 91% success rate for long-term freedom from AF, nearly 20% of patients required a second procedure. Many patients in persistent AF were noted to convert to sinus rhythm during the procedure. Although this landmark paper seemed to be a shift from techniques aimed at electrical isolation of the PVs, the authors did note that complex fractionated EGMs (CFE) tended to occur, amongst other locations, in close proximity to the PVs. The precise origin of CFEs are not fully understood, and it may be that they represent more than one phenomenon. It is likely that at least in some instances they represent points in proximity to dominant rotors which may maintain persistent AF. Some investigators believe that these regions may represent insertion points of ganglionic plexi in the posterior LA. Many have confirmed that targeting CFEs has a beneficial effect at least as a part of an ablative strategy, and this approach is now frequently incorporated, particularly in the ablation of persistent AF.[41 42]

Current Theories on the Evolution of AF and its Relevance to Ablation Strategies: The Trigger and the Substrate

The demonstration in the late 1990s of the ability of focal ectopy to result in the generation of AF and the ability of localized catheter ablation to result in long-term cure of paroxysmal AF has lead us full circle to the early 20th Century and Sir Thomas Lewis' original theories of the focal nature of AF. These observations along with the demonstration by Allessie that 'AF begets AF' has resulted in a more clear understanding of the pathophysiology of AF and is resulting in ablation strategies which can be tailored to individual patients, depending on where they fit in the pathophysiological spectrum of this disorder (Figure 10). In many patients AF arises initially as an episodic phenomenon and over time, becomes more sustained. During this time, the atria remodel both electrophysiologically and pathologically. Through direct and indirect mechanisms, AF causes the atria to enlarge, and results in microscopic ultrastructural changes. These changes have the effect of inducing multiple wavelet re-entry, and AF becomes a self-sustaining phenomenon.

Thus, patients who present with paroxysmal AF and who are found to have relatively normal-sized atria are likely to have rapidly firing focal triggers (usually but not exclusively in the PVs) which conduct to the remainder of the atria by fibrillatory conduction, hence manifesting as AF. Ablation in such patients is performed by targeting only the trigger.

In those patients with persistent AF, the atria have remodelled and AF is a self-propagating process consisting of multiple re-entrant wavelets. The relevance of the original trigger in such circumstances is unknown however, as discussed, wavelets do appear to be sustained by mother rotors which may anchor themselves to fixed anatomical structures such as the base of the LAA, and in the posterior atrium.[43] Ablation in such instances aims to eliminate both triggers and rotors, and modifies the substrate, aiming to prevent wavelet re-entry.

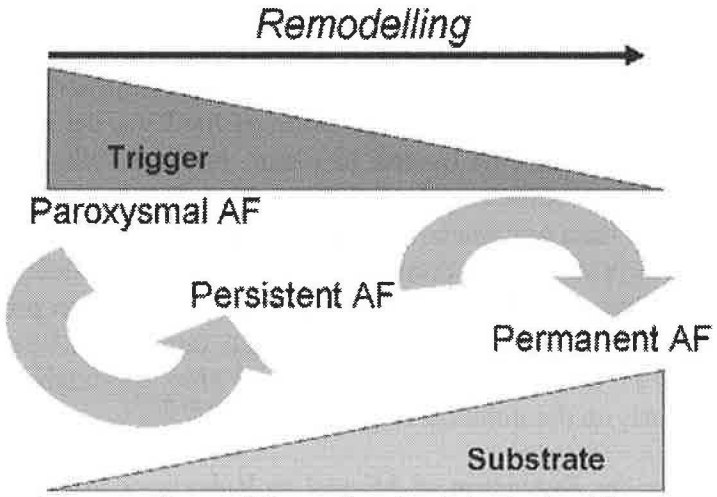

Figure 10: The modern paradigm of the pathophysiological self-propogation of AF from a trigger-driven, paroxysmal arrhythmia to a substrate-dependant permanent state, independent of the original trigger.

Linear Ablation in AF

Linear ablation is often performed for patients with persistent AF as part of a substrate-modification strategy. Linear lesions are continuous lesion sets which are placed across a potential isthmus i.e. a corridor which can serve as an area of conduction in a macro-re-entrant atrial tachyarrhythmia, and thus usually aim to connect 2 fixed, electrically inert anatomical points (such as scars, and valvular annuli). Commonly placed ablation sets include: a) Linear ablation at the roof of the LA.[44] In this situation a linear lesion is positioned to connect the left upper PV to the right upper PV; b) Linear ablation from the left inferior PV (LIPV) to the mitral annulus;[45] c) A linear lesion in the posterior LA connecting the 2 encircling lesion sets around the right and left PVs. This latter linear lesion has been largely abandoned with the avoidance of the posterior LA and its proximity to the esophagus (Figure 11) (see below).

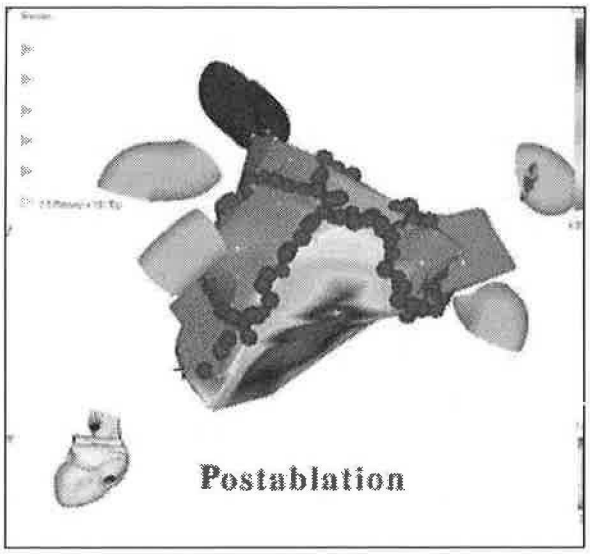

Figure 11: Linear lesions are frequently placed in the ablation of persistent and permanent AF. In this example a roof line connecting the left inferior pulmonary vein to the mitral annulus are seen in conjunction with wide-area lines encircling the pulmonary veins.

Autonomic Potentiation of AF and its Relevance to Ablation Strategies

The autonomic nervous system has been extensively studied in relation to mechanism of AF. The heart and blood vessels are supplied by both afferent and efferent autonomic nerve fibers which through both sympathetic and parasympathetic mechanisms have profound effects on the genesis, perpetuation and rate of many arrhythmias. The sympathetic and parasympathetic systems generally have opposite effects on atrial tissue, and their interaction and anatomical distribution is incompletely understood. Autonomic factors involved in the mechanisms of PAF were first examined in depth by Coumel and coworkers who postulated two different patterns of AF induction and vulnerability, one with a predominantly vagal etiology, and another in which adrenergic mechanisms induce AF.[46 47] However this distinction is oversimplified and recent investigations suggest a more complex interplay between parasympathetic and sympathetic triggers. For example, competing sympathetic and parasympathetic mechanisms are seen to occur prior to the onset of postoperative AF.[48] There is extensive evidence that direct vagal stimulation of the atrium facilitates spontaneous atrial ectopy and renders the myocardium vulnerable to fibrillatory conduction. It has been reported that ablation can result in atrial vagal denervation and that this improves the success rate of ablation. Further clinical investigation in this area is ongoing.

Summary of Current Ablation Strategies

Although some operators perform empiric wide-area extra-ostial PV ablation with the addition of linear lesions in all patients who present for AF ablation, most employ an approach tailored to the individual. For patients with paroxysmal AF, isolation of the PVs is the first step, either by selectively targeting myocardial sleeves that extend into the

PVs, or by empirically encircling the veins. Some operators will then attempt to induce AF and search for triggers other than the PVs.

Ablation for persistent and permanent AF has only recently come to the forefront as a therapeutic modality.[41 49] Techniques for such undertakings vary widely. PV isolation is still frequently performed as an initial manoeuvre, followed by linear ablation, often at the roof of the LA and from the LIPV to the mitral annulus. Many will search for complex fractionated EGMs as ablation targets during such procedures. Recently, it has become apparent that targeting rapidly firing signals, even when these signals are organized can lead to success and that these signals may represent the pivot points of dominant rotors. The inter-relationship between AF and atrial flutter is complex, and whilst there is some understanding of the relationship, many intricacies remain unclear. Most operators will perform an atrial flutter ablation (which takes place in the right-atrium, and is relatively simple) in all cases with persistent AF. Others will only do so if atrial flutter has been documented in the past.

It is important to note that up to 20% of patients will require a second procedure since AF may recur, and patients may develop macro re-entrant atrial tachycardia and atypical left atrial flutter following the procedure. Many of these arrhythmias will spontaneously resolve, and most operators will wait for at least 2 months for this to occur. If this is not the case, a second procedure is indicated.

Hybrid Therapy for AF

It has been noted that certain individuals with AF, when administered antiarrhythmic drugs will exhibit typical atrial flutter. In such cases, optimal management is usually an atrial flutter ablation since most patients will maintain long-term sinus rhythm following such a procedure, provided the antiarrhythmic medication is continued. Some have advocated a trial of intravenous flecainide during an episode of AF in order to see whether this converts to atrial flutter, and if so, perform a flutter ablation and continue long-term oral flecainide.[50] Long-term maintenance of sinus rhythm was achieved in 53% of patients with this method.

Complications of AF Ablation

Major complications of AF ablation include; access complications such as groin hematoma, stroke, pulmonary vein stenosis, phrenic nerve injury (particularly when ablation is performed in the region of the right upper pulmonary vein), cardiac tamponade, atypical left atrial flutter (as discussed), and rarely atrio-esophageal fistula. Access complications can be avoided by careful placement of femoral venous and arterial catheters and close observation of the patient post-operatively. The intense anticoagulation regimen used to avoid thromboembolic complications can increase the severity of such complications if they arise. Stroke risk (currently approximately 2%) can be minimized by attempting to minimize the period of time that intervention takes place with the left atrium, and by maintaining an activated clotting time of between 350-400 seconds intraprocedurally.[51] Pulmonary vein stenosis is a serious complication of AF ablation. It was more common in the early days of the procedure and appears to be becoming far less common with avoidance of the veins themselves by ablating in the

antrum of the vein. Phrenic nerve injury can be avoided by pacing at high output from the ablation catheter and observing for diaphragmatic stimulation prior to ablation. Cardiac tamponade is avoided by mechanical means, and by maintaining a high index of suspicion for perforation intra-operatively particularly when ablation takes place in the isthmus between the mitral valve and the left inferior pulmonary vein. The complication of atrio-esophageal fistula has been reported in at least 30 cases worldwide. Avoidance of high energy, prolonged ablation in the posterior left atrium and the use of an esophageal temperature probe appears to be significantly impacting the incidence of this almost uniformly fatal complication of AF ablation.

Who Should be Considered for an AF Ablation?

Success rates for ablation of AF is in the order of 70% (Table 1). Presently AF ablation is recommended for patients with highly symptomatic AF despite optimal medical management. Those with paroxysmal AF who fit into this category are the ideal candidates for this therapy. Current guidelines advocate AF ablation in this setting after the failure of one antiarrhythmic drug, and before the introduction of amiodarone. Ablation of persistent and permanent AF is more complex, and currently success rates are not as high. Nevertheless, two recent publications have highlighted the feasibility and method of ablation for this form of AF, and many practitioners are performing ablations for sustained forms of AF.[41 49] Again, only patients with severe symptoms should be considered. Patients who request AF ablation from a desire to cease taking warfarin should be informed that anticoagulation will be continued after ablation, in many cases indefinitely, and this is not a reason to recommend AF ablation. In skilled hands, AF ablation can be performed in patients who have significant underlying conditions such as congestive heart failure and hypertrophic cardiomyoapthy. [52 53] Most practitioners avoid AF ablation in those aged over 65 years, in those with dilated atria (>5.5cm diameter), in patients who are more than moderately obese, and in the presence of various other significant morbidities.

Author	Patients	% Parox	Endpoint	Success rate	Mean Follow-up
Haissaguerre[36]	45	100	PVI, focal	62%	8
Haissaguerre[54]	90	100	PVI, focal	86%	6
Oral[55]	40	100	WACA/PVI	88%	12
Mansour[56]	40	80	WACA	75%	11
Ouyang[57]	41	100	PVI	76%	8
Marrouche[58]	259	51	PVI	87%	12
Kanagaratnam[59]	71	72	PVI	68%	29

TABLE 1 – Reported Success Rates of AF ablation

%Parox: % Patients with paroxysmal AF; **Success rate:** Refers to freedom from AF off antiarrhythmic drugs

AV NODE ABLATION WITH PACEMAKER IMPLANTATION

First performed in the 1908s, AV node ablation was in fact the first ablation ever done for a cardiac arrhythmia, and initially employed DC energy as a modality.[60] By creating complete heart block, both the rapidity and irregularity of the ventricular response subtended by AF are completely ameliorated. Permanent pacemaker implantation is necessary following the procedure. Used predominantly in symptomatic cases of permanent AF, the procedure combination remains a highly effective therapy for AF and reliably results in improvements in quality of life and exercise duration in the majority of patients. Randomized studies comparing this strategy to medical AV nodal blockade have confirmed improvements in palpitations, effort dyspnea, and exercise tolerance, however have failed to consistently demonstrate an improvement in LV function.[61] This is likely to arise as a result of the deleterious effects of chronic right ventricular (RV) pacing which results in iatrogenic left bundle branch block and dysynchonous ventricular function. This issue has been addressed by the recently published PAVE study which compared RV pacing to biventricular pacing after AV node ablation and found that the latter resulted in improved LV ejection fraction, and 6-minute walk distance, particularly when the ejection fraction is less than 45%.[62] These benefits are likely to become more pronounced after longer follow-up. Pacing the RV outflow tract in proximity to the His-Purkinje system (as opposed to the apex) may similarly achieve more synchronous biventricular

activation in such circumstances, and studies are currently underway to test this hypothesis.

SURGICAL OPTIONS FOR THE ABLATION OF AF

Pioneered by James Cox, the Maze procedure (as discussed) was introduced in the late 1980s.[63] This required a 'cut-and-sew' technique whereby the left atrium was divided in a manner aimed at interrupting all potential macro-reentrant circuits that could result in AF or flutter, and 'guide' the sinus impulse to reach the AV node and result in ventricular activation. The original Maze-I was modified to the Maze-II in order to avoid the sinus node damage that occurred as a result of this technique, however the Maze-II was too technically demanding and was again modified to the Maze-III procedure. Cox himself however rated the technical difficulty of this procedure at '9.5/10', and his high success rates (97%), were not reproduced by others in the field. Haissaiguerres seminal work describing the PVs as the source of triggers of PAF has led to the incorporation of surgically placed lesion sets which encircle the PVs. Placing these lesions alone will not be effective for cases of persistent or permanent AF since as discussed, in such cases, AF is a self-propogating problem independent of the original trigger. Thus, in addition to lesions encircling the PVs, many will place additional linear lesions, often very similar to those placed in catheter-based procedures i.e. connecting the mitral annulus to the left inferior PV, isolation of the coronary sinus, and incorporation of a cavo-tricuspid isthmus line to prevent the onset of typical atrial flutter (Figure 12). This simplification of the Maze-III technique ('Minimaze') and the advent of alternatives to 'cut-and-sew' as ablative techniques has resulted in the emergence of minimally invasive procedures utilizing thoracoscopy, and in some instances, robotic assistance. One potential advantage of all current surgical techniques is the inherent ability to include amputation of the atrial appendages (particularly the left), which are the main source of thrombi in AF patients. Currently, several modalities including a 'radiofrequency clamp' (which is clamped across the exterior of the PV antra and RF energy is delivered between the two poles), cryoablation, and the application of high-frequency ultrasound are all being intensively evaluated in the minimally invasive setting.[64] Patients with AF undergoing cardiac surgery for other reasons such as coronary artery bypass, and valvular (predominantly mitral) surgery should strongly be considered for a concomitant Minimaze procedure aimed at eliminating AF.

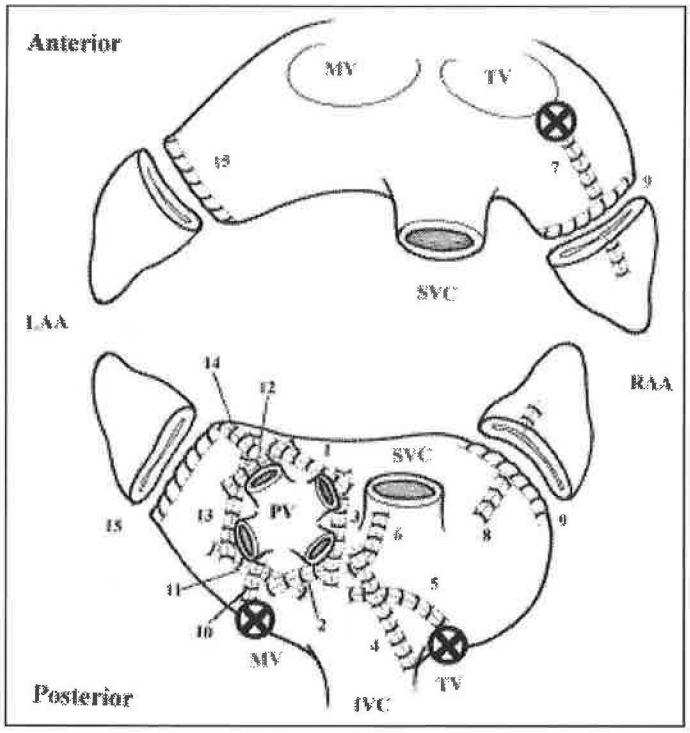

Figure 12: An example of a Minimaze procedure. Note the concomitant amputation of the atrial appendages, the lines encircling the pulmonary veins, and linear lesions.

LEFT ATRIAL APPENDAGE OCCLUSION FOR THE PREVENTION OF STROKE

In view of the fact that an estimated 90% of thrombi in patients with nonvalvular AF form in the LAA, devices have been designed to occlude the orifice of the LAA in order to prevent the embolization of thrombi. These devices are placed transvenously and require that a transpetal puncture is performed. The earliest device, the PLAATO device, has been studied in two multi-center nonrandomized trials in patients with AF deemed to be in a high risk subgroup for stroke and in whom anticoagulation was contraindicated. In a combined analysis of these two trials, implantation was successful in 108 of 111 patients who underwent a total of 113 procedures. One patient died after implantation, 3 experienced hemopericardium, there were 2 strokes (2.2%) after an average follow-up of 10 months.[65] The estimated annual stroke risk in this cohort was 6.3%. A new device, the 'Watchman' is currently being prospectively compared with warfarin therapy in a prospective, randomized trial.

FUTURE DIRECTIONS

Invasive therapy for AF has progressed to the point where improved control and in many instances, permanent cure is now within reach for selected patient groups. Ablation for AF is currently undergoing exponential growth. Increasingly, patients with symptomatic persistent and permanent AF are being effectively treated with ablation. Complication

rates are falling and operators are beginning to perform more uniform procedures as details regarding the underlying mechanisms of AF become clearer, partly as a result of these procedures themselves. Some term this process 'learning while burning'. Intense interest in improving these techniques exists. Several balloon devices aimed at isolating the PVs are in trial presently. The most promising of these is the 'cryoballoon' which is placed in the PV so that the PV is occluded. Refrigerant (liquid nitrogen) is then infused into the balloon which creates a circular lesion in the antrum of the PV. The risk of stroke and PV stenosis may well be lower with this technique than with RF-based systems. Similar designs with laser, microwave, and high intensity ultrasound are being evaluated. Minimally invasive surgical techniques also hold promise as potentially highly effective therapies.

It is likely that as techniques continue to evolve, improved success rates and lower complication rates will be seen, and what was formerly seen as an impossible arrhythmia to cure will join the list of those arrhythmias that can be reliably eliminated.

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