Conduction Disturbances in Patients with Atrial Fibrillation

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ABSTRACT

Background: The electrophysiological mechanisms underlying atrial fibrillation (AF) are incompletely understood. Experimental studies have shown that remodelling of the atrial myocardium is linked to the occurrence and perpetuation of AF. Interatrial conduction disturbances and also delayed conduction at the posteroparaseptal region have also been reported as potential arrhythmogenic substrates. However, there is insufficient clinical evidence. Pulmonary vein (PV) potentials are invariably recordable at the PV ostia in patients with AF, and delayed conduction around the PV ostia may play a role in the initiation and maintenance of AF.

Objectives: 1) To find clinical evidence for the atrial remodelling in patients with chronic and paroxysmal AF; 2) to delineate the electrophysiological properties of transseptal conduction from the left to the right atrium in patients with paroxysmal AF; 3) to analyze the conduction velocities across the coronary sinus (CS) ostium (cross-CS ostium) and within the coronary sinus (intra-CS) in patients with and without paroxysmal AF; and 4) to investigate the presence and extent of PV potentials in patients without AF.

Methods: Study I: To estimate the refractoriness of the atrium during AF, monophasic action potentials (MAPs) were recorded during AF from 1–3 sites in the right atrium in 7 patients with chronic AF (CAF) and in 11 patients with paroxysmal AF (PAF). The fibrillatory (FF) interval between two consecutive upstrokes of the MAP was measured. The mean, median, 15th, 10th, and 5th percentile and the shortest FF intervals were calculated in each patient and used as estimates of the local atrial effective refractory period (AERP) during AF. In 9 patients, AERP was also tested using the extra stimulus technique during sinus rhythm. Study II: To evaluate the left-to-right transseptal conduction, right atrial mapping using the CARTO electroanatomic mapping system was performed at 111 ± 16 sites during pacing from the distal CS in 16 patients with paroxysmal AF. Activation maps of the right atrium were obtained from all patients and the

earliest breakthrough site was identified. The conduction times from the pacing site 1) to the earliest activation site of the septum, 2) to CS ostium, 3) to the presumed insertion of Bachmann's bundle, 4) the total septal activation time, and 5) the total right atrial activation time. Study III: To study the conduction delay across the CS ostium, the activation times and spatial distances of cross-CS ostium and intra-CS were measured between 5–11 paired sites, from which the activation velocities of cross-CS ostium and intra-CS were obtained in 13 patients with paroxysmal AF and 10 control patients with AV nodal re-entry tachycardia or ectopic atrial tachycardia, using the CARTO electroanatomic mapping system. Study IV: Circumferential catheter recordings at the PV ostia were obtained from 10 patients with paroxysmal AF and 9 with concealed WPW syndrome without any history of AF. Typical PV potential was defined as either rapid deflections that were separate from local atrial deflection with a time delay in between, or continuous, fractionated potentials that were not separate from the atrial deflection. The existence of PV potentials was verified during sinus rhythm and during atrial pacing at the distal CS for the left PVs or at the right atrial appendage for the right PVs. To quantify the extent to which the PV potentials were recordable, the number of PVs with typical PV potentials for each PV and for each patient was counted. The time interval from the onset to the end of the electrograms recordable at the PV ostium (A-PV interval) was measured, and the maximum and mean of these intervals were obtained.

Results: Study I: Thirty-eight MAP recordings were obtained. The shortest FF interval during AF was significantly shorter in patients with chronic AF than in patients with paroxysmal AF (50±13 vs. 72±31 ms, $p < 0.05$). Similar differences were seen in the mean, median, 15th, 10th and 5th percentile FF interval. The AERP during sinus rhythm was significantly longer than the estimated AERPs ($p < 0.05$ to $p < 0.01$). Study II: A single transseptal breakthrough near the CS ostium was observed in all patients. The activation time from the pacing site to the earliest septal activation site was 47±13 ms. The

total septal activation time (68±16 ms) was markedly longer than that in patients without AF in a previous observation, but the total RA activation time (118±17 ms) was similar. Study III: During sinus rhythm, the cross-CS ostium activation velocities in the AF group (1.2±0.2 m/s) were significantly slower than those in the control group (2.9±1.6m/s, $p < 0.05$). During distal CS pacing, the cross-CS ostium activation velocities in the AF group (1.0±0.5 m/s) also appeared slower than those in the control group (1.4±0.2m/s, $p = 0.07$). However, no difference was found in the intra-CS activation velocities between the two groups (2.8±1.9 m/s vs. 3.2±2.2 m/s and 1.5±0.3 m/s vs. 1.4±0.3 m/s, $p > 0.05$) during sinus rhythm and distal CS pacing. Study IV: Typical PV potentials were recorded in 31 of 34 PVs (91%) in patients with AF, but in 4 of 36 PVs (11.1%) in patients with concealed WPW syndrome. A simple, narrow potential was recorded in 3/34 PVs (9%) in patients with AF, but in 29/36 (81%) PVs in patients with concealed WPW syndrome. The maximal and mean A-PV intervals were significantly longer in patients with AF (71±24 and 49±13 ms, respectively) than in patients with concealed WPW syndrome (33±14 and 25±6 ms).

Conclusions: Electrical remodelling of the atrial myocardium is more marked in patients with chronic AF than in patients with paroxysmal AF. The AERP was significantly shortened during AF as compared to that during sinus rhythm, and the AERP shortening was more marked in patients with chronic AF than in patients with paroxysmal AF. These clinical findings support the connection between the electrical remodelling and the occurrence and/or perpetuation of the AF. The preferential site of transseptal conduction during distal CS pacing is near the CS ostium in patients with paroxysmal AF. This has clinical implications when surgical dissection or catheter ablation is considered to eliminate interatrial connection in patients with AF. Interatrial conduction at the postero-paraseptal region across the CS ostium was significantly slower in patients with paroxysmal AF than in control patients, further supporting the link between interatrial conduction deterioration and paroxysmal AF.

In patients with AF, typical PV potentials with marked conduction time delay were almost invariably recordable at the PV ostium; but in patients without any history of AF, merely simple, narrow potentials were found. These findings support the involvement of conduction delay and re-entrant activities around the PV ostia in the genesis and/or perpetuation of AF.

LIST OF PAPERS

This dissertation is based on the following studies, which are referred to in the text by their Roman numerals:

I. Hertervig E, Yuan S, Carlson J, Kongstad O, Olsson SB. Evidence for electrical remodelling of the atrial myocardium in patients with atrial fibrillation. A study using the monophasic action potential recording technique. Clin Physiol and Func Im 2002;22:8-12.

II. Hertervig E, Yuan S, Liu S, Kongstad O, Luo J, Olsson SB. Electroanatomic mapping of transseptal conduction during coronary sinus pacing in patients with paroxysmal atrial fibrillation. Scand Cardiovasc J 2003;37:340-343.

III. Xia Y, Hertervig E, Kongstad O, Ljungström E, Platonov P, Holm M, Olsson SB, Yuan S. Deterioration of interatrial conduction in patients with paroxysmal atrial fibrillation: Electroanatomic mapping of the right atrium and coronary sinus. Heart Rhythm 2004;1:548-553.

IV. Hertervig E, Kongstad O, Ljungström E, Olsson SB, Yuan S. Pulmonary vein potential recordings using a circumferential catheter in patients with and without atrial fibrillation. In manuscript.

ABBREVIATIONS

AF	atrial fibrillation
AP	action potential
CS	coronary sinus
ECG	electrocardiogram
ERP	effective refractory period
FF	fibrillatory interval during AF
LA	left atrium or left atrial
MAP	monophasic action potential
PV	pulmonary vein
RA	right atrium or right atrial
WPW syndrome	Wolf-Parkinson-White syndrome

INTRODUCTION

1. Clinical Aspects of Atrial Fibrillation

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterised by rapid uncoordinated electrical activation of the atrium with deterioration of atrial mechanical function. It is a common arrhythmia in the population and its incidence increases with age. AF has several clinical presentations, and classification of the different types is helpful in clinical management. The ACC/AHA/ESC recommend the following classification (1).

Paroxysmal AF: Episodes that start and stop by themselves, generally lasting less than 24 hours but sometimes lasting up to 7 days.

Persistent AF: Episodes lasting more than 7 days, or that require termination either pharmacologically or electrically.

Permanent AF: Long-standing continuous episodes where repeated attempts to terminate have either failed or have not been tried.

This is a time-based classification and it applies to episodes of AF lasting more than 30 seconds, and is unrelated to a reversible cause. Focal AF is a special form of AF, initiated or sometimes maintained by arrhythmogenic foci often within pulmonary veins (PVs). This type can be both paroxysmal and persistent.

There are different causes of AF, in patients with or without morphological cardiac abnormalities. Examples of the former are changes related to the pressure elevation in the atria such as valvular abnormalities and cardiomyopathies, coronary heart disease, inflammatory disease, atrial fibrosis (ageing), pericarditis and cardiac trauma (2). Examples of the latter are intoxications, increased sympathetic activity (hyperthyreosis, alcohol), increased parasympathetic activity and idiopathic (lone) AF (2). When there is a reversible cause such as cardiac surgery, myocardial infarction, pulmonary embolism, myocarditis or hyperthyroidism, treatment of the underlying cause and

management of the episode of AF will often eliminate the arrhythmia, and thus the need for long-term treatment.

Patients with lone AF have been reported to have infrastructural abnormalities of the atrial myocardium, verified with electron microscopy (3). In one-third of the patients, there is no concomitant disease or structural heart disease, and despite this, there is a risk of thromboembolic complications and a related increase in mortality (4). Paroxysmal AF accounts for 35–66% of all causes of AF, with prevalence peaking at 50–69 years of age (5, 6). The probability that lone AF will progress from paroxysmal to permanent is about 20%, and varies with population and duration of follow-up (6, 7).

Haemodynamic and prothrombotic effects (8)

AF has haemodynamic effects, not only related to the loss of atrial contraction and ventricular asynchrony, but also due to the accompanying irregular and rapid ventricular rhythm (9). These effects are especially relevant in patients with ventricular dysfunction and in those with diastolic dysfunction or mitral stenosis. In these conditions, the cardiac function depends on a longer diastole and more active ventricular filling than in a healthy heart (8). The loss of atrial contraction leads to stasis and this is more marked in the left atrium (LA), which is the common site of thrombus formation. Stasis is accompanied by hypercoagulability, increased concentration of fibrinogen, increased concentration of fibrin D-dimer, and endothelial dysfunction. All 3 of the components mentioned above probably contribute to the development of the prothrombotic state that accompanies AF (10).

Oral anticoagulation (11)

AF contributes to about 35% of strokes in an octogenarian population (12), increases the overall risk of stroke by a factor of 5, and is associated with

particularly severe strokes (13). Compared with age-matched controls, the relative risk of stroke is increased 2- to 7-fold in patients with non-rheumatic AF (14, 15, 16), and the absolute risk of stroke is between 1% and 5% per year, depending on clinical characteristics (12, 14, 17, 18). Oral anticoagulation with warfarin and other vitamin K antagonists reduces the risk of stroke related to AF by about 70% (19). Oral anticoagulants increase the risk of major bleeding from about 0.9% to 2.2% and of intracranial haemorrhages from about 0.2% to 0.4% (11). The protective effect of oral anticoagulation against strokes reaches a near-maximum at an international normalised ratio (INR) of 2 or more, whereas major bleeding events increase rapidly at INRs greater than 4 (11). These observations have led to a recommendation for an INR between 2.0 and 3.0. Maintenance of safe and effective INR is complicated by dose-response associations, drug interactions, diet interactions, intercurrent disease and other unidentifiable factors, and the therapy demands regular monitoring of the level of anticoagulation. Thus, only about half of all potentially eligible patients receive oral anticoagulation therapy (20).

In large randomised trials of stroke prevention in AF studies (21, 22), the main stroke factors were identified as advancing age, female gender, previous stroke or transient ischemic attack, hypertension, congestive heart failure, coronary heart disease, and diabetes. Most studies have been based on patients with persistent AF, who constituted about 88% of the first major trials (21). For patients with paroxysmal AF, there is insufficient information available. Retrospective analyses suggested that the paroxysmal AF could confer less risk than the persistent form (4). However, subsequent studies controlling for concomitant conditions suggested similar risks (21). Another issue is that episodes of paroxysmal AF are often asymptomatic. Current guidelines are assessed to present similar risk (1). A related issue is how to handle patients cardioverted from AF who remain in sinus rhythm for extended periods.

Presently, no support exists for the discontinuation of anticoagulation in such patients since the absence of anticoagulation is a strong predictor of stroke occurrence (11, 23, 24).

Maintenance of safe and effective oral anticoagulation is complicated by the following: unpredictable dose-response associations, many potential drug interactions and unpredictable effects of diet, intercurrent disease, and other unidentifiable factors, and the need for regular monitoring. To decide which patients with AF should undergo anticoagulation can be difficult. Factors that affect stroke and risk of bleeding include criteria related to patients and those related to the disorder (11). In the long term, direct-acting thrombin inhibitors in particular will replace vitamin K antagonists for prevention of thromboembolism in AF. At present, no drug other than vitamin K antagonist qualifies as a first line therapy against stroke in AF.

Anti-platelet drugs (11)

Platelets are important in coagulation, and anti-platelet drugs such as aspirin are valuable in preventing cerebral ischaemic events due to platelet-rich thromboemboli from carotid atherosclerotic lesions. Aspirin reduces the risk of stroke in patients by 22% compared to oral anticoagulant therapy, which reduces the risk of stroke by 36% (22).

The ACTIVE-W study (25) compared oral anticoagulant therapy with a combination of aspirin and clopidogrel in patients with AF who had one or more risk factors for stroke. The result showed that anticoagulation was better than dual anti-platelet therapy in the long-term prevention of major ischemic events (3.9% per year for warfarin and 5.6% for aspirin plus clopidogrel) without an increase in major bleeding (2.2% per year and 2.4% per year, respectively). The

patients without warfarin therapy still face an unacceptably high ischemic risk of nearly 6% a year with subsequent dual anti-platelet therapy.

The ACTIVE-A study is in progress, whereby clopidogrel is being compared with aspirin in patients ineligible for, or unwilling to take oral anticoagulation therapy. Warfarin remains the standard in antithrombotic care for eligible patients with AF. New developments are to be expected from orally administered direct thrombin blockers or oral factor-Xa inhibitors rather than from existing anti-platelet agents.

Rate or rhythm control (26)

Rate control

AF with uncontrolled ventricular rate leads to severe but reversible congestive heart failure. However, the prevention of excess resting tachycardia is not equivalent to the reproduction of physiological heart-rate control (11). Two major studies used different criteria for rate control: in AFFIRM (24), adequate rhythm control was defined as a resting rate of less than 80 beats per min and controlled rates (criteria left to the treating physician) during 6 min walk test or during Holter recordings, whereas in RACE (23) a resting rate of less than 100 beats per min was considered to be adequate. The adequacy of rate control is difficult to define, but heart rates of < 80 beats/min at rest with attainment of < 90% of the maximum at predicted heart rate with maximal exercise would be considered acceptable (26).

The first step in treatment of AF is control of the ventricular response. In elderly patients with conduction disease, rates may be controlled at the onset of AF; but for patients with intact AV nodal conduction rate, control medication is necessary. Which drug is used and how it is delivered depends on the urgency of the clinical situation, the patient's clinical stability, concomitant drug therapy, and medical conditions (27, 28).

In general, calcium channel blockers or beta-blockers are administered intravenously when a clinical effect is needed immediately. In most patients, a short-acting beta-blocker or calcium blocker gives an adequate ventricular response. Weaker AV-blockers, such as digitalis, are reserved for adjuvant therapy for patients with a diseased AV node, when single-drug treatment does not suffice, or for management of heart failure (29-31). In cases where conventional AV nodal blocking agents are ineffective such as in very ill patients, amiodarone may be useful because the drug's earliest effect, when administered intravenously, is negative dromotropism via its non-competitive beta-adrenergic and calcium channel blocking effect (31). Careful rate control is important because high rates over time may cause severe symptoms and also profound ventricular dysfunction in some individuals (32).
Optimum criteria for rate control are presently unknown. Resting tachycardia must be prevented and additional consideration of heart changes during exercise can be useful in some patients. More information is needed to best define rate-control criteria (11).

Rhythm control

The other strategy in AF treatment is maintenance of sinus rhythm (1). This approach has two parts: restoration of sinus rhythm for patients with persistent AF, and chronic treatment to prevent AF recurrence. Conversion of AF to sinus rhythm can be accomplished electrically or pharmacologically.

For electrical conversion, more than 95% of the patients can be shocked into sinus rhythm (33). Early recurrence of AF and late relapse are common and occur as a consequence of concomitant cardiac or electrical disease, and other factors such as duration of the antecedent arrhythmia (34). Prevention of early or

late relapse usually requires treatment with beta-blockers or antiarrhythmic drugs.

Pharmacological conversion is less effective. Drugs are more efficacious for converting AF of shorter rather than longer duration. Class IA and IC drugs have been used intravenously and orally with good success reported. The class IC drugs appear to be effective and safe for termination of AF with short duration in patients with normal hearts, and they can be used either orally or parenterally (35). However, drugs approved for this indication in Sweden are intravenous ibutilide, intravenous sotalol, and intravenous amiodarone, which are all class III antiarrhythmic drugs.

Chronic maintenance of sinus rhythm remains the challenge in this subject. Drug treatment is not curative. In most cases, the most we can expect is a reduction in the frequency, duration and severity of the events, which may be enough for some patients to have an improved quality of life (36). In addition, antiarrhythmic drugs have the potential to be toxic. It is important to distinguish between paroxysmal and persistent AF, because the former causes severe symptoms in young patients and the latter may become less noticed and more amendable to a conservative strategy of rate control. The guidelines have grouped patients by type of heart disease and presented what might be first-line and alternative drug therapy in the ACC/AHA/ESC guidelines (1). For example, in patients with congestive heart failure, the best studied drugs for efficacy and safety are dofetilide (not registered in Sweden) and amiodarone, which makes these drugs preferred therapy for patients with left ventricular dysfunction. Sotalol, amiodarone, and dofetilide are recommended for patients with ischemic heart disease (26). Many more drugs have been examined in patients with normal hearts, thus multiplying the therapeutic alternatives in these patients.

The currently available antiarrhythmic drugs are moderately effective in suppressing AF (by about 50% in 6–12 months) (1, 37). All the available antiarrhythmic drugs have adverse effects including organ toxicity, serious pro-arrhythmia or both (1). New approaches to sinus rhythm might improve the safety and effectiveness of rhythm control. Flecainide (38) and propafenone are more effective than placebo at suppressing symptomatic paroxysms in AF (39). Amiodarone is better than sotalol and class I drugs in sinus rhythm maintenance (40, 41), with improved quality of life and exercise capacity (41).

New pharmacological strategies that are based on the amiodarone model, on novel ionic targets, and on the notion of combatting the development of the AF substrate, promise new options for rhythm control (11, 31, 42). Novel I_{Na} blockers can stop AF by inhibiting the depolarising Na^+ current, and have frequency dependence so that substantial I_{Na} inhibition is mainly manifest at very rapid rates of the fibrillating atrium, with very little effect at rates of sinus rhythm and therefore low risk of pro-arrhythmia. I_{Kur} is important in repolarising the atrium but not the ventricle, and inhibition of this process is an interesting target for atrial selective antiarrhythmic substances. Inhibition of a pacemaker current (I_f) could suppress spontaneous automatic arrhythmogenic activity. Drugs with multiple channel-blocking actions are designed to suppress abnormal activity without causing pro-arrhythmia (based on the amiodarone model). These new drugs are promising new options for rhythm control.

Non-antiarrhythmic drugs may also play a role in rhythm control. For example, there are data showing that drugs that interfere with the renin-angiotensin system may limit atrial fibrosis and thereby reduce the frequency of AF after myocardial infarction.(43). These drugs are also used in hypertension, the most common cause of AF, and this treatment would be expected to reduce the disease burden (44).

Rate versus rhythm control (45)

A total of five randomised trials comparing rate control with rhythm control have been completed and published: PIAF, PAF2, AFFIRM, RACE, and STAF (23, 24, 46-48). The total number of patients studied was > 5,000 and both strategies used anticoagulation with warfarin. All five of these trials selected a relatively elderly population among those afflicted with AF. The therapies were predominantly pharmacological. In PIAF, amiodarone was the drug used. The other trials used a variety of antiarrhythmic drugs including amiodarone, sotalol, and class I antiarrhythmic drugs, although amiodarone was the most frequently used drug in all the studies. Electrical cardioversion was part of rhythm control in all trials, except in PAF2 where all patients had a DDDR pacemaker and were treated with radiofrequency ablation of the AV node. Patients in that trial were randomised to antiarrhythmic drug or no antiarrhythmic drug. In the other trials, beta-blockers, diltiazem, verapamil, and digitalis, alone or in combination, were used to achieve control of heart rate. All the trials used anticoagulation with warfarin following published guidelines.

In AFFIRM, the average follow-up of the 4,060 patients was 3.5 years. The number of patients enrolled in the other trials was smaller and the duration of follow-up was shorter. None of the above studies demonstrated the expected superiority of rhythm control. It seems quite clear that with respect to hospitalisation and adverse drug effect, rate control was superior to rhythm control. Several of the studies measured quality of life, and in all cases there was no difference between the strategies. There was a slight risk of excess death in the rhythm control approach. The absolute difference was 1.5% (rhythm control 15.0%, rate control 13.5%) (45). In the AFFIRM study the difference appeared after 2 years. The other studies were too short to contribute much to this endpoint. Pooled data from the studies showed in rate control group thrombotic

stroke, and major non-central nervous system haemorrhage were 3.4% and 4.9%, respectively, and in the rhythm control group the corresponding rates were 4.1% and 4.5%. The absolute differences were small and the risk ratios were not significant, but the risk ratio for thrombotic stroke favours the rate control approach (45). These findings reflect the differential use of warfarin in the two treatment strategies, in which warfarin was discontinued more frequently in the rhythm control strategy (23, 24, 48). In these trials, there were not many younger patients with little or no heart disease and few with congestive heart failure and poor ventricular function. The basic conclusion is that for the type of patient enrolled in these studies, rate control is acceptable primary therapy (45). Maintaining sinus rhythm and cure of AF is still important in some groups of patients with severe symptoms.

2. Non-pharmacological Treatment of Atrial Fibrillation

The following patient categories could be considered for non-pharmacological treatment:

a) patients with symptomatic AF who have failed to respond to conventional treatment, for example, antiarrhythmic drugs and/or cardioversion can be referred for catheter ablation. It is important that the patients are fully counselled as to the risks of ablation, and are prepared to take them.

b) patients with AF who are undergoing cardiothoracic surgery for other reasons can be considered to undergo surgical ablation (49).

Surgical ablation (49)

Cardiac surgeons were the pioneers of curative ablation of AF, and in 1992 Cox's Maze-III evolved from five years of accumulated worldwide surgical experience and carefully conducted animal and human mapping studies (50). Initially, the lesions were created by "cut and sew" method through a median sternotomy. This has the advantage of introducing lesions under direct vision, in which the transmurality of the lesions is certain. This technique is effective with maintenance of sinus rhythm, reported by Cox at greater than 97% (49, 51) and at 84.9% in a systematic review of 1,553 patients in all published series up to 2004 (52). In addition, both LA mechanical function (51, 53) and left ventricular function (54) have been shown to improve. The surgical approach includes the removal or closure of the LA appendage which leads to a low operative (0.5%) and follow-up stroke rate (0.3% at 12 years in one study) (52, 55).

The operation is technically difficult, and a few centres in the world have been able to replicate the original results of Cox. In addition, there is a mortality and morbidity associated with the procedure. In large series, the 30-day mortality rates have varied from 0% to 7.2% (mean 2.1%); however, many of these deaths occurred in patients undergoing concomitant surgery (52). Other complications

are sinus node dysfunction with requirements for permanent pacing (5.8%), bleeding caused by multiple lesions (4.9%), and stroke (0.5%) (52).

The Maze-III procedure was designed to interrupt all possible re-entry circuits that could exist in AF; however, it appears that the LA is usually the source of AF wavefronts with the right atrium (RA) as a bystander. A lesion set that isolates all PVs, a line that links the isolated PV line to the mitral valve annulus (and encircles the coronary sinus, CS, at that point), and an RA line across the tricuspid valve-inferior vena cava isthmus may be sufficient on its own to give high success rates in most patients. This is described by Cox as Minimaze (56).

New energy sources have been developed as an alternative to cut and sew. Cryoablation and radiofrequency energy are the most common, which use hand-held probes applied endocardially by direct vision. Newer energy sources such as laser, microwave (57) and ultrasound have the potential to produce transmural lesions even when applied epicardially. A further development from this is the use of a limited thoracic incision and a thorascopically-guided procedure (58). A comprehensive review of 2,279 patients who underwent these newer surgical methods found 78.3% maintenance in sinus rhythm at follow-up, with an operative mortality of 4.2% (52); 98.4% of these operations were performed alongside cardiac surgery, predominantly mitral valve surgery. Meta-analysis of surgical AF ablation studies has revealed that the results are very similar regardless of the technique used (49).

Pacemaker therapy

Pacing techniques that have been proposed as treatment for AF include standard pacing, alternative single-site pacing, multi-site atrial pacing, pacing algorithms to increase the amount of atrial pacing and to prevent atrial pauses, and antitachycardia atrial pacing to terminate AF. The role of permanent pacing to

prevent AF is controversial. For patients who have a bradycardia indication for pacing and also have AF, no consistent data from large randomised studies support the use of alternative single-site atrial pacing, multi-site RA pacing, biatrial pacing, overdrive pacing, or antitachycardia atrial pacing. Even fewer data support the use of atrial pacing in the management of AF in patients without symptomatic bradycardia. At present, permanent pacing to prevent AF in patients without a bradycardia indication for pacemaker should be considered unproven (59).

Catheter ablation of the AV junction

Despite therapy with drugs, it is estimated that more than 10% of patients with AF are refractory to medical treatment and may suffer intractable symptoms and diminished quality of life (60). Radiofrequency ablation of the atrioventricular (AV) junction in order to achieve complete AV-block followed by permanent pacemaker therapy is an accepted therapy in medically refractory patients. The overall success rate of AV junction ablation approaches 100%, and early complications are rare. The complication rate is low (3.2%), and most often secondary to catheterization technique (haematomas, thromboflebitis etc) (61). Severe complications such as pericardial effusion or ventricular arrhythmia are unusual, and death has been observed in < 0.1% of cases (61). Malignant ventricular arrhythmia and sudden death have been observed in the early phase after AV junction ablation (62-64). It is unclear whether the arrhythmia is related to the myocardial injury induced by the radiofrequency ablation, or to the underlying disease, or to the possible role of complete AV block and bradycardia. Most of the polymorphic ventricular tachycardias, ventricular fibrillation, or torsade de pointes that have been reported seem consistent with a pause or a bradycardia-dependent mechanism (62-64). In order to reduce the incidence of ventricular arrhythmia, pacing with a rapid rate of 90/min for 1–3 months has been proposed after ablation. Geelen et al. did not observe any

arrhythmia in patients in whom the pacemaker was set to a rate of 90/min (63). The treatment is controversial in paroxysmal AF where other types of ablation can cure the patient, but in the elderly population with medically refractory persistent AF, ablation of the AV junction followed by pacemaker implantation is a method to be considered.

Curative ablation strategies

A) Electrical isolation of the PVs and a stepwise ablation strategy –

The Bordeaux approach:

In the late 1990s, pioneer work by Haissaguerre et al. (65) demonstrated that ectopic beats or rapid firing of ectopic tachycardias from the PVs act as a trigger for the initiation of paroxysmal AF, and ablation of the focus abolished attacks of paroxysmal AF. That was the start of the era of curative ablation therapy of AF. This so-called focal ablation technique was later abandoned, due to the risk of PV stenosis and high recurrence rate, since the AF could be initiated by new foci from other PVs or by foci outside the PVs. With the development of a circumferential catheter technique (the Lasso catheter; Biosense-Webster), the ablation target was changed from the foci within the PVs to the preferential conduction sites at their ostia. The endpoint is electrical isolation of the conduction between the LA and the muscular sleeves within the PVs (66). This was called segmental PV ablation technique, which resulted in a success rate of 73% without antiarrhythmic drugs. To further improve the success rate and reduce the need for repeated procedures, segmental ablation strategy was later replaced by the PV encirclement strategy (67). This method is now still used in Bordeaux as a primary strategy for patients with paroxysmal AF.

For patients with persistent or permanent AF, it is thought that PV encirclement alone is not enough and a stepwise strategy has been established, that is, starting with PV isolation and followed by a stepwise strategy to achieve prolongation

and organization of atrial electrical activity until the conversion of sinus rhythm (68). The new strategy consists of the following steps: a) isolation of PVs; b) LA roof line; c) LA appendage (to avoid thrombus formation within the appendage, complete isolation of the appendage is avoided); d) isolation of the CS, including endocardial ablation along the posterior-inferior LA on the mitral annulus, radiofrequency applications within the CS, and around the CS ostium in the posteroseptal area of the RA; e) local ablation of atrial tissue with continuous electrical activity, complex fractionated potentials, and sites with a gradient of activation, or regions with a cycle lengths shorter than the mean LA appendage fibrillation cycle length, including septal area, the area of fossa ovalis and posterior LA; f) left-sided isthmus ablation, i.e. a linear ablation between the left-sided PV encircling line and the mitral annulus.

The step-wise ablation of the structures annexed to the LA such as the LA appendage, the CS and PVs, has the greatest impact on the prolongation of the AF cycle length, the conversion of AF to atrial tachycardia, and the termination of focal atrial tachycardias. It is important to note that it is believed that the disruption of a certain amount of myocardial mass is necessary to convert the AF into sinus rhythm. The success rate for a single stepwise procedure was 87% (68), while a repeated procedure increased the success rate substantially, up to 95% (69).

B) The double Lasso technique – The Hamburg approach:

The so-called double Lasso technique used by the Hamburg group is another alternative of the PV isolation strategy (70). It features: a) PV encircling ablation lines closer to the PV ostia; b) complete electrical PV isolation, as verified by recordings from 2 Lasso catheters in the ipsilateral PVs; and c) minimal myocardial disruption since they ablate strictly along the designed encircling lines and no additional lines are added.

Briefly, the ostia of the PVs are carefully identified through biplane PV angiography and the LA-PV junctions are tagged on 3-dimensional electroanatomic maps using the CARTO mapping system. Radiofrequency energy is applied at a distance of about 5 mm on the anterior aspect and 10 mm on the posterior aspect from the tagged LA-PV junction. At completion of the encircling lines, careful mapping and adding radiofrequency applications along the ablation line is performed until the sudden disappearance of all the PV spikes, which has been observed in all their cases. An important benefit of this alternative is a very clear endpoint, which consists of: a) all PV spikes within the ipsilateral PVs disappeared, or dissociated from the atrial activation in some patients, as documented by simultaneous recordings from the two Lasso catheters; and b) no recurrence of the PV spikes after intravenous administration of adenosine during sinus rhythm or CS pacing.

This technique affects the possible mechanisms of triggers in and around the PV ostium, micro re-entry in the PV antrum, and denervation of the parasympathetic inputs surrounding the PVs. The success rate using this method was found to be up to 95% in patients with paroxysmal AF and 80–85% in patients with permanent AF. Repeated procedures were required for 35–45% of patients (70, 71).

C) Circumferential PV ablation – The Milan approach:

The circumferential PV ablation strategy was first described by Pappone et al. 2000 (72). Another leading centre for this strategy is the Ann Arbor group in the United States (73, 74). The method can be referred to as an anatomical approach featuring wide-area circumferential linear lesions around the PV ostia, plus extra lines as guided by the CARTO mapping technique. Typically, the ablation starts from the left posterior mitral annulus and continues to the left-sided encircling lines, plus a line in-between the superior and inferior PVs. Then right-sided

encircling linear ablation is performed plus a line in-between the superior and inferior PV. Two additional lines are usually added, i.e. a roof-line and a posterior line both connecting the two encircling lines. These two additional lines and the annulus to the left-sided encirclement line are to prevent post-ablation atrial tachycardias. The encirclement in this approach is wider than with the Hamburg approach, about 1–2 cm from the PV ostium. The endpoint is voltage reduction of the local electrogram by 80–90% or to an amplitude < 0.2–0.5 mV. In patients with a history of typical atrial flutter, ablation is also performed in the cavotricuspid isthmus (75).

It is interesting to note that using this approach is not necessarily to achieve transmural lesions or complete electrical PV isolation. However, the success rate has been reported to be approximately 90% in patients with paroxysmal AF and 80% in those with permanent AF (75). The possible mechanisms of action of circumferential ablation strategy include: a) electrical PV isolation (to some degree); b) elimination of anchor points for the rotors, drivers, or re-entry at or near the PV-LA junction; c) ablation of potential sources on the posterior LA wall or in the vein of Marshall; d) ablation of RA-LA connections that may play a role in generating AF; e) atrial debulking to provide less space for circulating wavelets, and f) vagal denervation (75).In practice, PV encirclement performed in different centres varies greatly, i.e. smaller or bigger encirclement rings, with or without extra lines, etc. Generally speaking, the greater the distance from the ostia, the greater the number of applications required to achieve complete isolation. On the other hand, the greater the distance is from the ostia, the lower the risk of PV stenosis. It is also true that the larger the area is encircled, the more likely is the substrate in the posterior LA disrupted. Ideally, an individual mechanism-based ablation strategy should be adopted. However, such an individual strategy setting is not yet possible today, since our knowledge and techniques are still developing.

D) New approaches:

a) Ablation at sites with complex fractionated electrograms, i.e. mapping guided catheter ablation of the electrophysiological substrate.

Nademanee et al. (76) recently reported a novel concept for the treatment of AF, namely mapping guided catheter ablation of the electrophysiological substrate. This new approach targets only sites with complex fractionated atrial electrograms (CFAEs), which have been shown to be associated with areas of slow conduction and pivot points of re-entrant wavelets in previous human mapping studies (77, 78). The CFAEs were mapped using the CARTO mapping technique and they were found to be confined to the interatrial septum, PVs, the roof of the LA, the left posteroseptal mitral annulus, the CS ostium, and the septal areas. Their endpoint was the elimination of all the detectable complex fractionated electrograms, or the conversion to sinus rhythm, which was the case in 115/121 patients. At one-year follow-up, 76% of the patients were free from atrial arrhythmias. The success rate increased to 91% after a repeated procedure in 18/111 patients (76). The effectiveness of this new approach has also been verified by the Ann Arbor group (74) and the Bordeaux group (68, 69).

b) Ablation at sites with vagal response, i.e. ablation of ganglionated plexi.

Another new approach is to ablate the ganglionated plexi pioneered by Jackman's group (79, 80). Briefly, the ganglionated plexi were identified by severe vagal response, including marked bradycardia and/or high grade of AV block, during continuous high frequency stimulation to sites around the left and right PV antra. Radiofrequency ablation at these sites abolished the vagal response. In a group of 60 patients with paroxysmal or permanent AF at 12 months of follow-up, those with both PV isolation and ablation of the ganglionated plexi showed a success rate of 91% as compared to 76% for patients who had PV isolation alone (79). In another group of 26 patients with persistent or chronic AF, AF was not inducible after ablation of the ganglionated

plexi in 22 patients. At a mean of 6 months follow-up, all the 22 patients remained in sinus rhythm. Interestingly, none of the patients had PV isolation (80, 81).

Complications of catheter ablation (49)

For 9,000 patients reported to the worldwide survey of AF ablation, there was a mortality of 0.05% and an overall complication rate of 5.9% (82). Stroke and pericardial tamponade are risks of the treatment, but they can be minimised by improved technique and training. Iatrogenic PV stenosis became apparent as a result of delivering too much energy within the PVs. The development of an atrio-oesophageal fistula is a rare but lethal complication. Clinical manifestation is pericarditis, sepsis, or massive haematemesis (83).

3. Underlying Mechanisms of Atrial Fibrillation

AF can occur in patients without evidence of heart disease, but organic heart diseases such as congestive heart failure, mitral valve disease and coronary heart disease are major co-existing conditions that contribute to the occurrence and persistence of AF. The electrophysiological mechanisms behind the genesis and perpetuation of AF are still far from clear (84). There have been numerous reports about the correlation between conduction disturbances in the intra- and interatrial conduction in the development of AF, and it is also generally accepted that electrophysiological abnormalities around the ostia of the PVs are involved in the genesis and/or perpetuation of AF. With the improvements in technology, the development of animal models of AF, and new data from patient studies, several mechanisms have now been recognized as being behind the occurrence and perpetuation of AF.

Multiple wavelet hypothesis

In 1924, Garrey highlighted 3 competing theories of AF mechanisms: a) a hyperectopia according to which single or multiple rapidly firing atrial ectopic foci lead to fibrillation; b) a single rotor (mother wave) with fibrillatory conduction; and c) multiple circus re-entry (85). In 1959, Moe and Abildskov proposed the multiple re-entrant wavelet hypothesis (86-89) that AF was a result of random re-entry. It was postulated that AF consisted of a critical number of randomly distributed re-entrant wavelets; the greater the number of wavelets, the more likely that AF persists. The pathways of these wavelets were determined by the local refractoriness and excitability. This theory resembled the earlier theory, but replaced the notion of closed loop re-entry with the idea that AF is characterized by a large number of propagating wavefronts. A sufficient number of these wavefronts have to exist to be able to find excitable tissue for the arrhythmia to persist. This was verified in a computer model of atrial tissue,

which showed that AF could be sustained by multiple propagating wavefronts, and the presence of heterogeneous refractory properties in the atria (88).

Additional work by Allessie et al. (90) showed in rabbits that wavelength established the occurrence of re-entry, and in 1985 they (91) were able to map the spread of excitation in the atria of a dog heart during rapid atrial pacing-induced AF in the presence of acetylcholine This was the first experiment *in vivo* to demonstrate propagating wavelets giving rise to turbulent atrial activity. The maintenance of fibrillation in the canine atrium required a critical numbers of 4–6 wavelets (91).

Changes in autonomic tone, the use of antiarrhythmic drugs, and other factors modify the induction of AF due to their effect on the wavelength (90, 92). The existence of wavelets is determined by the wavelength, which is a product of the atrial effectory refractory period (ERP), and the conduction velocity. In other words, the wavelength is the distance travelled by the electrical impulse in one refractory period, refractory period × conduction velocity, according to Allesie's theory, i.e. the minimum path length for a re-entry circuit. Increased dispersion of atrial refractoriness and conduction disturbances favour shorter wavelengths and provide a substrate for greater numbers of circulating wavelets (92-94).

Re-entry that maintains AF requires an appropriate substrate and an initiating factor or trigger, generally in the form of a premature beat. Ectopic activity can provide the trigger for initiation, but if it is rapid and sustained, it may also maintain AF by itself (95). In normal human atria, it is believed that the wavelength is such that few re-entry circuits can be accommodated. When AF is initiated in normal human atria, it tends to terminate spontaneously when the underlying functional circuits die out. A decreased wavelength permits a larger number of re-entry circuits to be accommodated in a given mass of tissue, and in

this way promotes a multiple-circuit re-entry. Local conduction disturbances (for example, due to tissue fibrosis) can stabilise re-entry by producing conduction barriers, and without change in atrial refractory period, refractory heterogeneity or conduction velocity. This allows AF without a decrease in wavelength (96).

Thus, major issues of this hypothesis are that wavelets move randomly throughout the atria, which requires: a) a temporal dispersion of refractory periods; b) a sufficiently large area of tissue; and c) a relatively brief refractory period and/or relatively slow conduction. This hypothesis is widely accepted and forms the basis of surgical interventions, e.g. the MAZE procedure (97). Kottkamp et al. performed intraoperative radio-frequency linear ablation in patients with persistent and paroxysmal AF via a right anterolateral mini-thoracotomy, and at follow-up after 1 year, 95–97% of the patients were free of AF, although frequent extra beats or runs of atrial tachycardia from the PVs were observed. Thus, atrial compartmentalisation prevents the development of AF despite existing triggers/drivers. These findings may also support the multiple wavelet hypothesis (98).

The "Mother Rotor" hypothesis (99)

In 1978, Winfree et al. defined "rotor" as a stable rotating pattern of reaction and diffusion that surrounds a pivot point, also known as a phase "singularity" (100). From a rotor radiates a curved wavefront (i.e. a "spiral wave") into an adequate area of surrounding tissue. The definition of "rotor" here is the rotating engine that gives rise to the spiralling wavefronts that can often be observed during fibrillation. Although sustained rotating activity had been demonstrated in isolated rabbit atrial muscle by Allessie et al. in 1973 (90), rotors were not identified as possibly mechanisms underlying AF until later, when Schuessler et al. (101) and Skanes et al. (102) provided evidence for significant spatio-temporal periodicity during AF in the isolated heart. AF was induced by burst

pacing in the continuous presence of acetylcholine. In several episodes, sources of spatiotemporally periodic activity could be seen from the epicardium as stationary rotors on the anterior wall of the LA appendage. Based on these experiments, AF was proposed to depend on the periodic activity of discrete re-entrant sources (rotors). Both atria were capable of harbouring rotors of varying sizes and frequencies, but it was proposed that the rotors whose rotating period was shorter acted as the dominant frequency sources that maintained the overall activity (103).

In a canine model of chronic AF, Morillo et al. demonstrated that activation intervals during AF were not randomly distributed throughout the atria (104). A highly organized dispersion of cycle lengths was clearly apparent during sustained arrhythmia, with the shortest cycle length localized at the PV-LA junction, followed by LA free wall, LA appendage, RA free wall, and RA appendage. This contrasts with the theory of Moe, which is based on randomly wandering wavelets. Using isolated sheep heart, Mandapati et al. (105) demonstrated that AF was driven by micro re-entrant sources of the LA and that the PV region contained stable sources with the highest dominant frequency. Arora et al. also demonstrated re-entry at the PV-LA junction (106). These results from 3 independent laboratories (102, 105, 106) support the hypothesis that the maintenance of AF may depend on the periodic activity of a small number of rotors in the posterior LA-PV junctional region. Further experiments by Jalife et al. showed fibrillatory conduction through both atria and anatomical and/or functional obstacles leading to fragmentation and wavelet formation (99, 103), and according to this theory, wavefronts brake and initiate two counter-rotating vortices—and if stable enough, they become the engines that maintain AF. Sometimes only one of the vortices survives and keeps AF going (103).

Focal triggers and drivers from the PVs

Ectopic atrial activation, usually emerging from one or more foci located in the muscular sleeves of the proximal PVs, as a single beat or repetitive burst of activity, is an important contributor to the initiation of AF (65). Other parts of the RA and LA can give rise to ectopy, including the proximal superior vena cava (107) and the ligament of Marshall (108). Although this focal AF is usually paroxysmal in the early stages and can affect patients with structurally normal atria (109), a mechanism of focal initiation may underlie many cases of persistent AF with or without structural heart disease. In animal models, electroanatomic mapping (110) has demonstrated complex wavefronts within or emanating from the PVs. Thus, focal discharges may not simply be the triggers for multiple wavelet re-entries. A unifying theory is that focal tachycardia, which originates mostly in and around the PVs, promotes atrial remodelling and is required to trigger and maintain a substrate capable of multiple wavelet re-entry (111).

Thus, pioneer work by Haissaguerre and coworkers (65) highlighted the role of electrical activity within the PVs, and thereby started the era of AF ablation. AF may start by the trigger mechanism in one of the following ways: 1) ectopic beats as a trigger of AF; 2) rapid firing focus associated with the initiation of AF; or 3) driver tachycardia involving both the initiation and the perpetuation of AF. In fact, these are the basis of all the major ablation strategies, although other mechanisms have also been proposed.

Effects of autonomic innervation

Light and electron microscopic studies of PVs have demonstrated that they are innervated by adrenergic and cholinergic nerve fibres (112). Parasympathetic stimulation shortens the atrial ERP, increases its dispersion, and decreases the wavelength of re-entrant circuits that facilitate initiation and perpetuation of AF

(113, 114). Sympathetic activation affects sino-atrial and AV nodal conduction and automaticity, shortens atrial refractoriness, and can initiate action potential (AP) duration alternans (113, 115). Sympathetic neurotransmitters are known to increase atrial automaticity (115). Electrical stimulation of autonomic nerves on the heart itself can induce both atrial and ventricular arrhythmia (116). Clinical observation by Coumel et al. identified patients who developed AF during sleep ("vagal AF") and those who developed AF during exercise or motion (117, 118).

Schaurte et al. stimulated neural elements on the heart without exciting the adjacent myocardium in mongrel dogs, and evoked rapid ectopic beats from the PV area and superior vena cava, which showed variable degrees of conduction block to the atria and induced AF. In dogs with inducible AF, autonomic blockade was given with intravenous beta-receptor blockade and atropine. The response to high-frequency stimulation was blunted or prevented after beta-receptor blockade, and abolished by atropine. The probability of AF induction was highest in the left superior PV and lowest in the right inferior PV and RA appendage/LA appendage (119). These studies implicated local autonomic stimulation in the initiation of the PV trigger and the ability of the trigger to induce AF (79).

In anaesthetized dogs subjected to right and left thoracotomy, Scherlag et al. showed the influence of localized cardiac autonomic ganglia and the initiation and maintenance of AF (79). They found that high frequency stimulation applied to the fat pads induced AF and also caused AV-block due to a strong parasympathetic effect on the AV node. Radiofrequency ablation from the right and the left myocardium abolished the vagal response to high frequency stimulation delivered to the plaque electrodes close to the right superior PV and the left superior PV, respectively. Tan et al. showed in a post-mortem study (120) of 8 patients with no history of atrial arrhythmias and no history of

cardiovascular disease, that adrenergic and cholinergic nerves distributed equally and circumferentially along the PV ostium had the highest densities within 5 mm of the PV-LA junction, especially superior to the superior PVs and inferior to the inferior PVs. During stimulation or ablation, however, vagal response is more pronounced due to the relatively more rapid parasympathetic response.

There have been several clinical studies supporting the influence of the ganglionated plexi in the genesis of AF. Pappone et al. (121) showed a relationship between modification of autonomic nerve function and recurrent AF after circumferential PV ablation. In this study, 297 patients with paroxysmal AF were treated with circumferential PV ablation. Abolition of all evoked vagal reflexes around PV ostia was defined as complete vagal denervation, and this was obtained in 34.4% of the patients. Follow-up ended at 12 months, and the success rate in the denervated group was 99% as compared to 85% in the other group. In a study of 60 patients with paroxysmal or persistent AF, Scherlag et al. (79) showed a better outcome in patients with PV antrum isolation plus LA ganglionated plexi ablation than in patients with PV isolation alone, the success rate being 91% and 70%, respectively, for these two groups.

In summary, a) electrical stimulation of autonomic nerves facilitates the induction of AF at the entrances of PVs; b) beta-receptor blockade enhanced the induction of AF while atropine abolished it; c) ganglionated plexi at the PV entrance can be stimulated without capturing the atrium; d) under the stimulation of the ganglionated plexi, the induction of AF by extra beats from the PV was significantly enhanced; and e) ablation of these ganglionated plexi abolished the inducibility of AF. These findings support the hypothesis that local cardiac autonomic ganglia clustered in the fat pads at the margins of the PV

antra innervate myocardial sleeves and adjacent atrial myocardium, and can play a critical role in the initiation and maintenance of AF (79).

4. Other Factors that May Be Involved in the Genesis and/or Perpetuation of Atrial Fibrillation

Atrial remodelling

Atrial remodelling refers to change in atrial structure or function that promotes atrial arrhythmogenesis. Clinical experience is that paroxysmal AF often progresses to persistent AF, and the longer the AF persists, the more difficult it is to maintain sinus rhythm after cardioversion. Wiffels et al. observed in a chronically instrumented sheep model that artificial maintenance of AF led to a shortening of ERP, to a reversion of its physiological rate adaptation, and to an increase in rate, inducibility, and stability of AF. All these changes were reversible within 1 week of sinus rhythm (122). AF modifies the atrial properties so that it becomes self-maintaining (electrical remodelling), so-called "AF begets AF". Sustained atrial tachycardia produces a similar form of remodelling (atrial tachycardia remodelling), with time-dependent decreases in atrial ERP, reduction of physiological ERP, and reversion of rate adaptation (104). In dogs subjected to rapid atrial pacing, Gaspo et al. showed decrease in ERP, conduction velocity, and wavelength which—along with regional heterogeneity—provided a substrate for AF (123). This suggests that the rapid rate is the primary remodelling stimulus. The signal transduction leading to ERP abbreviation is still unclear; however, cellular Ca^{2+} is believed to play an important role (124).

Atrial tachycardia suppresses the contractility of atrial myocytes by altering the Ca^{2+} homeostasis (125), and thereby causes depressed atrial contraction which may contribute to the associated thromboembolic predisposition, and to perpetuation of AF (126). The ERP abbreviation caused by the atrial remodelling is due to abbreviation of AP duration (127, 128). Atrial tachycardia

remodelling is believed to contribute to several phenomena clinically, such as the tendency of paroxysmal AF to become persistent and the tendency for AF to recur soon after cardioversion.

Heart failure and atrial structural remodelling

Congestive heart failure is one of the most common causes of AF (129). Atrial ERP is unchanged or increased by heart failure, but local disturbance of atrial conduction occurs in and between atrial muscle bundles due to fibrosis (96). It is believed that these abnormalities in atrial structure and local conduction may stabilize atrial re-entry, allowing for AF-sustaining re-entry circuits that sometimes have a macro re-entry pattern (84, 130). In a canine heart failure model, despite the recovery of atrial electrical and structural remodelling, AF remained inducible and appeared to be related to persistent atrial fibrosis (131).

Electrical remodelling accounts for the self-promoting AF once it has begun, but other factors must add to the initial occurrence of AF. Patients with AF have upregulated levels of atrial extracellular signal-related kinase (ERK) and angiotensin-converting enzyme (ACE) (132), but a reduced density of angiotensin II type 1 receptors and an increased density of angiotensin II type 2 receptors (44). In experimental congestive heart failure, the promotion of AF is preceded by increased atrial concentrations of angiotensin II and by activation of mitogen activated protein kinases including ERK (133). In congestive heart failure atrial cell pathways are activated, followed by replacement of fibrosis which promotes intra-atrial re-entry. Inhibition of ACE reduces heart failure induced activation of ERK and fibrosis, and decreases the AF-promoting effects of heart failure (133). A study by Pedersen et al. showed that ACE inhibition reduces the incidence of AF after myocardial infarction (43).

Genetic factors in AF

Possible genes for triggering and maintenance of AF may include genes that affect automaticity, atrial refractory period, and conduction. In 1997, Brugada et al. were the first to identify linkage to a locus in chromosome 10q22-24 for familial AF in 3 different Spanish families (134). In these families, AF segregated as an autosomal dominant disease with high penetrance. In one of the families, 10 of the 26 members were affected. In the other 2 families, all 9 members who were affected had permanent AF and were asymptomatic with normal echocardiography. Darbar et al. could not confirm the linkage to chromosome 10 in 3 families with familial paroxysmal AF and rapid ventricular response, and in one family with a slow ventricular response (135). In contrast to the other 3 families, AF in the latter family was asymptomatic. Later, 4 of the 10 patients in this family developed a junctional rhythm and 5 of the patients developed left ventricular enlargement with reduced left ventricular function. This suggests that at least two different mechanisms (and possibly associated genes) were involved in AF in these families. In 2003, Chen et al. published data from a large Chinese family with autosomal dominantly inherited AF (136). The causative mutation was located in the *KCNQ1* gene on chromosome 11. This gene is involved in the cardiac I_{ks} potassium channel and two other potassium channels. The effect of this mutation is reduced AP and reduced ERP in atrial myocytes, which may in turn set the stage for initiation and maintenance of AF. Familial AF is clinically and genetically different. Different phenotypes may point to distinct mechanisms and genes underlying familial AF (137).

Conduction delay within the left atrium

Despite the predominant role of conduction disturbances around the PVs in the genesis of AF, there is evidence that delayed conduction in the LA, outside the PV area, contributes to the genesis and/or perpetuation of AF. It is quite common that in patients with AF the electrograms recorded from the posterior wall of the LA are low in amplitude and often fractionated, suggesting delayed conduction. Elimination of the fractionated electrograms by radiofrequency ablation leads to termination of AF (69, 76, 138). The current widely used PV encircling technique gives a high success rate in curing AF, not only through PV isolation but also due to the isolation of LA areas (72). Surgical approaches for AF treatment also include LA isolation and/or compartmentalisation, with good results (139). These clinical evidences support the involvement of conduction delay within the LA in the genesis and/or perpetuation of AF. However, the exact mechanisms are still unclear.

Conduction delay between the left and the right atrium

The zones of electrical conduction between the RA and the LA have been implicated in the initiation and maintenance of AF (140-142). Interatrial conduction block results in delayed activation of the atria, and such patients have a high incidence of atrial tachyarrhythmias (143). Interatrial transseptal conduction is non-uniform, but spreads using preferential zones of conduction, such as Bachmann's bundle, the CS ostium, and the superior border of the fossa ovalis (142). O'Donell et al. (144) measured the ERP and conduction times for Bachmann's bundle, CS ostium and the LA in patients with persistent AF, paroxysmal AF, and a control group. Pacing was performed from the upper quadrant of the right upper PV and the lower quadrant of the left upper PV. A lengthening of conduction times of > 100% between pacing at 600 ms and 220 ms at either Bachmann's bundle or the CS ostium was seen in 12/15 (80%) of the persistent AF group and 12/25 (47%) of the paroxysmal AF group, but only

in 1/15 (7%) of the control group. The dispersion of the ERP was significantly greater in the persistent AF group than in the paroxysmal AF group and the controls. This study showed the electrophysiological properties of the interatrial, transseptal conduction in response to PV. The main finding of the study was demonstration of longer ERPs, greater lengthening of conduction times, and increased conduction heterogeneity in response to premature PV impulses in patients with AF compared to controls, and the abnormalities were more pronounced in patients with persistent AF than in those with paroxysmal AF. AF was induced at a coupling interval close to the ERP of the preferential interatrial conduction. This supports the theory that both significant conduction disturbances and critically timed ectopic firing are necessary to allow re-entrant waveform to develop, leading to initiation of AF. Pacing at Bachmann's bundle has been shown to reduce the burden of AF in some patients, possibly by reducing the tendency of delayed or slowed conduction (145).

Interatrial conduction block with retrograde activation of the LA has been reported to be associated with a high incidence of atrial tachyarrhythmia (143). Daubert et al. reported that patients with advanced interatrial block and a demand for pacemaker therapy atrial activation could be re-synchronized with biatrial pacing and as a result of that, get a reduction of paroxysmal atrial tachycardia (atrial flutter and AF) (146). Saksena and colleagues reported that in a group of patients with AF and a demand for pacemaker therapy, 80% of the patients were in sinus rhythm after 13 ± 3 months when they had dual-site pacing with two electrodes placed at the high lateral RA and close to the CS orifice (147). Dual-site RA pacing reduces the activation times in all LA and RA regions, especially in areas of conduction delay. Multisite methods reduce the ability to initiate AF with atrial premature beats by reducing the window for AF induction and by minimizing the dispersion of atrial refractoriness (148).

Conduction delay within the right atrium

It has been reported that disturbances of atrial conduction are related to the genesis of AF (149-152). Individuals with clinical history of atrial flutter or AF have increased intraatrial conduction times in response to extra stimuli as compared to normal subjects (152), and atrial extra stimuli are more likely to induce AF when delivered from the high RA rather than from the CS (153). This phenomenon was studied by Papageorgiu et al. (150) who suggested that non-uniform anisotropic properties, required for re-entry and initiation of AF, exist in the triangle of Koch. In a study from our centre, Platonov et al. (151) provided further evidence for the role of atrial conduction disturbances in the genesis of lone AF. They showed a predominant prolongation of conduction time between the high lateral RA and the proximal CS, causing localized inferior-posterior interatrial conduction delay during sinus rhythm and during programmed stimulation from the distal CS in patients with paroxysmal AF.

The region of the proximal CS in induction of AF may be important, as shown by Saksena et al. (154) who demonstrated significant increases in conduction time in the proximal CS region accompanying the induction of AF. Similar findings were shown by Platonov et al. (155) in patients with lone AF, where induction of AF paroxysms was associated with increased conduction delay in the posterior septum and proximal CS region. Endocardial recordings suggest that the primary conduction disturbances within the proximal CS and the interatrial septum result in interatrial conduction disturbance, which may be an important factor for development of AF in a selected group of patients (151, 155). Elimination of the conduction delay in the region of the proximal CS made it impossible to induce AF (156), which indicates the importance of this region in the induction of AF.

In our centre, Luo et al. demonstrated with the electroanatomic mapping technique that there is no difference in the mean activation times and conduction velocities from the earliest activation site to the superior septum, His bundle area and CS ostium, or in the total activation time of the RA during sinus rhythm in AF patients compared to patients without AF (157). These findings suggest indirectly that the conduction delay in patients with AF is localised between the high RA and the proximal CS in the posterior interatrial septum.

5. Conduction of the Atrium

Anatomical aspects

Myocardial cells are striated muscle cells containing both myosin and actin filaments. Adjacent cells are joined end-to-end by structures called intercalated discs, which are actually cell membranes, and they facilitate propagation of impulses from one cell to another. The majority of myocardial cells are ordinary working cells that contract only upon stimulation from an external source. There are special cells, pacemaker cells, which are found in the conduction system. The conduction system is composed of the sinoatrial (SA) node, the atrioventricular (AV) node, the His bundle, the right bundle branch, the left bundle branch and its two fascicles, and the Purkinje fibres (Figure 1).

James (158) described the internodal conduction pathways in the RA in 1963. These sino-nodal connections course in the interatrial septum and they are organised into three bundles: anterior, median, and posterior. The posterior bundle, corresponding to the crista terminalis, is detached from the posterior end of the sinus node, drops vertically and forms the posterior edge of the interatrial septum, and ends at the posterior section of the AV node. The anterior and median bundles are situated anterior to the oval fossa. They leave from the sinus node in front of the lumen of the vena cava, circle the vena cava forward and backward, and reach the septum where they merge before penetrating the upper part of the AV node. These preferential conduction pathways are no different

from other septal tissues; it is just their architectal organisation into continuous bundles of parallel fibres that endows them with quicker and therefore preferential conduction properties (159).

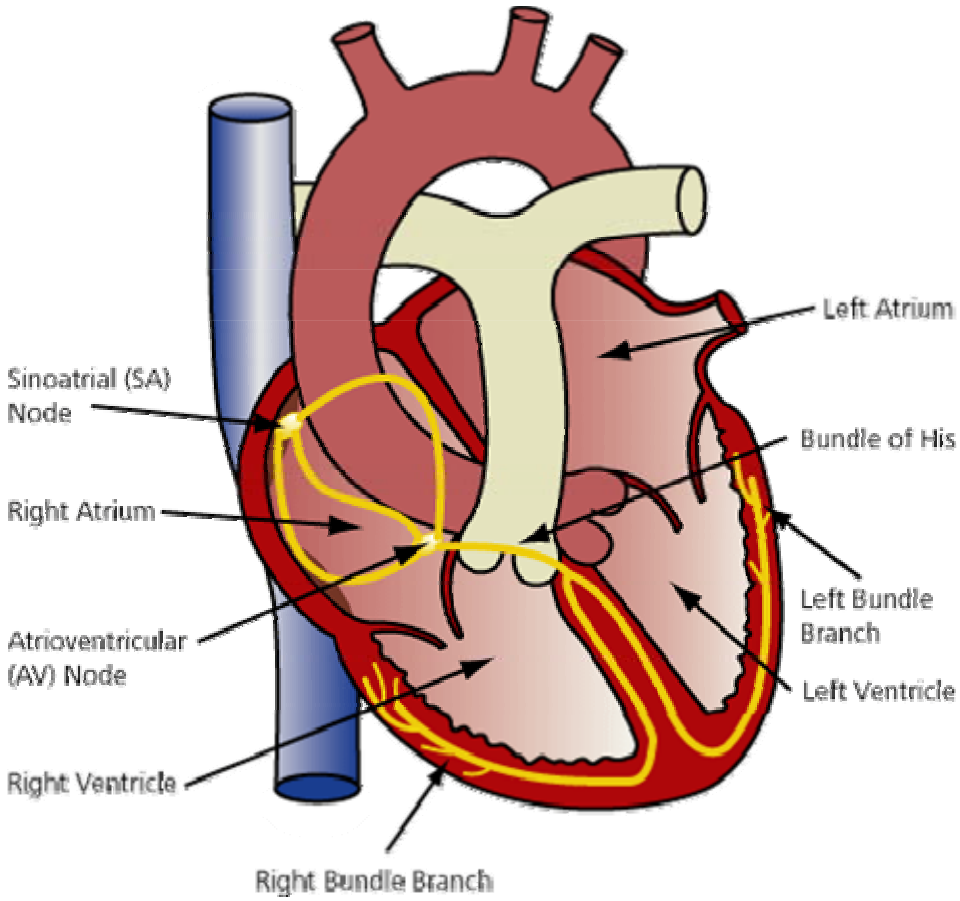

Figure 1. The electrical conduction system of the heart. An electrical stimulus is generated by the SA node, (localised in the upper right atrium) and generates an electrical stimulus periodically 60–100 times per minute under normal conditions. The electrical impulse travels from the SA node to the atrioventricular (AV) node, where it stops for a very short period, then continues down the conduction pathways via the bundle of His into the ventricles. The bundle of His divides into right and left pathways, to provide electrical stimulation to both ventricles. (Reproduced with permission from St Jude Medical, Inc., St Paul, USA).

There are multiple potential interatrial conduction pathways. The inner internodal bundle fibres divide in the anterosuperior part of the septum, into a vertical branch that connect the AV node, and a bundle that runs on the top of the atria—described by Bachmann in 1916 (160). Bachmann's bundle is close to the sinus node and is the preferential conduction route from the RA to the LA during sinus rhythm, as shown by electroanatomic mapping (161). However, other transseptal connections have been described in the regions of Koch's triangle with left posterior extensions of the AV node connections (158, 162, 163), connections at the septal level with fine muscular fibres (164), and at the CS level with connections between the CS level muscle cover and the LA (165). In an anatomical post-mortem study from our centre and St. Petersburg, Russia, Platonov et al. (166) studied hearts from patients with and without AF. A total of 27 patients were studied, and in 15 of them (7 patients with AF, 8 patients without AF) the interatrial septum was sliced for microscopic analysis. The results showed that the number of posterior interatrial bundles varied from 1 to 5 and that Bachmann's bundle was absent in 50% of the patients. There were no significant differences between the types and/or the numbers of posterior connections between the two groups. There was variability in the sizes and locations of the bundles, and some bundles were lying separately in the fatty tissues, which could be a substrate for arrhythmia (166).

Electrical activation of the atria

(A) Activation of the right atrium

De Ponti et al. (161) showed that during electroanatomic mapping of both atria, the earliest activation site in patients with normal hearts is in the upper part of the right lateral atrial wall. Two components with opposite direction originate from this site. The first component starts from the sinus node and splits early into two wavefronts, which simultaneously activate the lateral wall and the right side of the septum. These wavefronts show simultaneous progression along the

lateral wall, crista terminalis, and the septum. They rejoin in an area located in the medial part of the low RA, below the AV node-His bundle area and anterior to the CS orifice, where RA propagation ended in all the patients examined. The second component proceeds from the earliest activated area upwards towards the orifice of the superior caval vein, where it terminates. In a study from our centre of patients with and without paroxysmal AF, Luo et al. (157) identified the earliest activation in the upper part of the lateral RA corresponding to the sinus node. Two wavefronts with opposite directions originated from the sinus node area and propagated, the major one progressing along the lateral wall and the septum and the minor one activated upwards to the superior vena cava. In the AF group the activation ended at the low lateral RA in 2 patients and at the CS ostium in 4 patients, while in the control group the latest activation was at the CS ostium in 3 patients and at the low lateral area in 8 patients. In all patients, the sinus impulse propagated from the superior to the inferior septum.

(B) Interatrial activation

Anatomical examination of human and animal hearts has verified several atrial muscle connections between the RA and the LA, such as the Bachmann's bundle, by the rim of fossa ovalis, and at the ostium of the CS (164). These connections are functional, as shown by Roithinger et al. who used electroanatomic mapping of the RA during pacing from the distal CS (142). Three sites of early RA activation were found: on the anterosuperior part of the RA (the presumed insertion site of the Bachmann's bundle), around fossa ovalis, and in the CS region. De Ponti (161) showed two breakthroughs in humans during sinus rhythm, the anterior ones and the posterior ones. The anterior breakthrough was anatomically located at the insertion of Bachmann's bundle in the LA. The posterior breakthrough was located where commonly posteromedial interatrial connections are observed in humans, in the atrium around the orifices of the right PVs. Using a non-contact mapping system, Markides et al. (167)

showed that the earliest endocardial breakthrough was more frequently in the posteroseptal LA than in the anterosuperior LA (consistent with the position of Bachmann's bundle) during sinus rhythm, and the breakthrough varied very little during high rate atrial pacing or with isoproterenol. Sakamoto et al (168) evaluated the conduction endocardially and epicardially in dogs during pacing from the left superior and inferior PVs, the right PVs, the upper and lower RA, or the RA septum at various paced cycle lengths. They found four distinct electrical connections: the Bachmann's bundle, the CS, the antero-superior septum, and the postero-inferior septum. Bachmann's bundle was the most preferential connection during pacing from any epicardial site. The transseptal connections were only evident during pacing from the interatrial septum. The preference among the four connections was determined by the site of stimulation and the propagation of the activation was related to the myocardial architecture. The RA has a complexity of the myocardial architecture such as the crista terminalis and the pectinate muscles. There is a difference in the conduction velocity between the longitudinal and transverse propagation in inhomogeneous tissue, and there are anatomical barriers such as the crista terminalis, the Eustachian ridge, and the tendon of Todaro in the inferior septum of the RA. The different interatrial connections provide the possibility of re-entry and atrial tachycardias. These barriers could even exhibit a conduction delay or block during pacing from the inferior septum (169).

(C) Activation of the left atrium

Two different breakthroughs have been identified in the anterosuperior and posterosuperior LA during sinus rhythm (161). The anterior breakthrough is anatomically located at the insertion of Bachmann's bundle and the posterior breakthrough is located where posteromedial connections are commonly observed in humans, in the atrium around the orifices of PVs. From the anterior breakthrough, the propagating wavefront splits into two components, which

proceed simultaneously in a medial and lateral direction. The medial component, after having activated the medial area of the anterior wall and the left side of the septum, reaches the posterior wall and propagates with a medial to lateral orientation. The two components of the LA propagation meet at the posterolateral wall, where propagation of the sinus pulse ends. In a study by Markides et al. (167) in patients with AF, the activation pattern was found to depend on a principal line of functional block that is linked to the preferential orientation of the LA subendocardial fibres. These fibres run down from the top of the LA and travel between the PV ostia before turning septally to reach the mitral annulus in its anterior and septal parts. Endocardial activation is far more disorganised in the LA than in the RA, which gives the possibility for re-entry and initiation of arrhythmia.

(D) Conduction time and velocity

Atrial conduction times can be measured invasively between two or more leads (170, 171). The right intraatrial conduction is measured from the beginning of the P-wave or from the onset of the intracardiac signal recorded in the upper part of the RA to the onset of atrial depolarisation recorded in the para–His bundle region. The normal values of right intraatrial conduction are generally between 30 and 60 ms. Interatrial conduction time is measured from the beginning of the P wave or the intracardiac signal recorded in the upper part of the RA, to the onset of the LA depolarisation recorded at the level of the distal CS. It is normally between 60 and 85 ms. In the studies mentioned above, the interatrial conduction time reflects total atrial activation time, but not the conduction pattern in the various interatrial connections. In a study from our centre (157), there was found to be no difference in the conduction times in the RA between patients with and without AF. The conduction times measured in our study were consistent with those from the above studies.

The normal conduction velocity in atrial fibres is around 1 m/s (172). The electroanatomic mapping system allows precise correlation of an electrical signal with its anatomical origin, and accurate measurements of distance, activation time, and activation velocity between two recording sites. In the above study from our centre (157), the regional conduction velocity from the earliest activation site to the His bundle area, superior septum, and the CS ostium was found to be no different between patients with and without AF. However, the conduction velocity was not measured exactly along the direction of wavefront propagation. A novel algorithm has now been established in our laboratory so that conduction velocity can be measured exactly along the direction of propagation (173).

Ionic basis of action potential

The normal, regular beating of the heart is accompanied by cyclic changes in the membrane potential of cardiac cells. Intracellular microelectrodes can measure the membrane potential directly. Figure 2 illustrates a human atrial AP and the transmembrane ionic currents generating the AP (84).

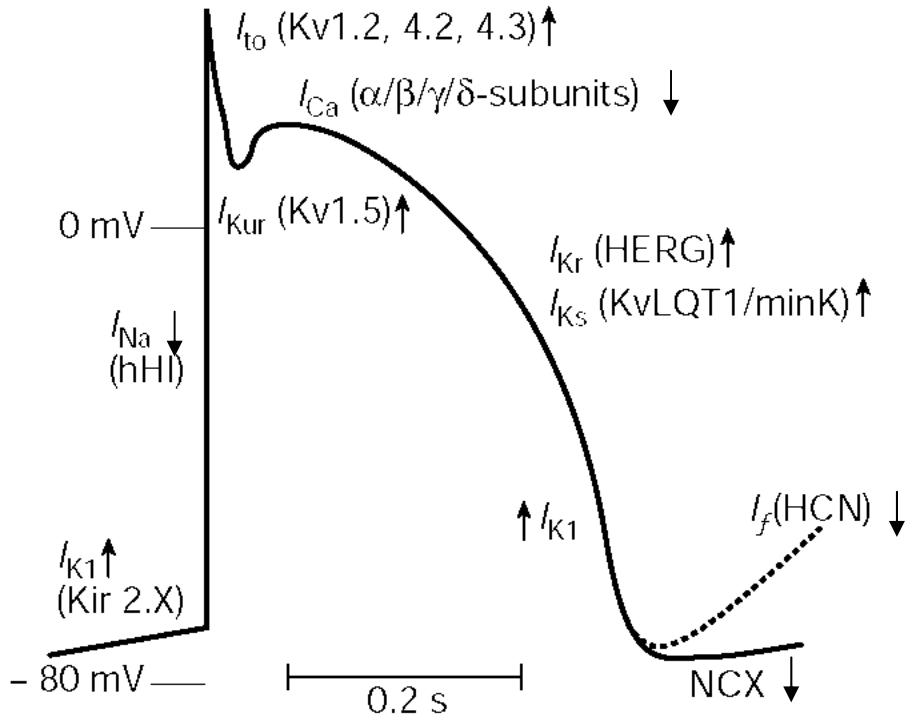

Figure 2. Human atrial action potential showing the principal currents that flow in each phase of the action potential. Inward currents are indicated by a downward arrow and outward currents by an upward arrow. (Modified with permission from reference (84) by Nattel et al. See text for details).

Transmembrane ionic currents are responsible for the depolarisation and repolarisation in the myocyte. I_{K1} is the background current responsible for the resting K^+ conductance that sets the resting potential in the atrial myocyte to between -70 and -80 mV (127, 174, 175). Cell firing is caused by rapid depolarisation (phase 0) through a large Na^+ current (I_{Na}) (176) that brings the cell from its resting potential to a value in the region of +40 mV, providing the electrical energy for cardiac conduction. The cell then partially repolarises (phase 1) through a transient outward K^+ current (I_{to}) (177), inactivation of which produces a notch in the AP. This is followed by a flat portion (phase 2) of the AP (the "plateau"), which is maintained by an inward L-type Ca^{2+} current (I_{Ca}) (178). A series of K^+ currents that activate in a time-dependent way and show little inactivation—the so-called "delayed rectifiers" (I_K)—leads to cellular

repolarisation (phase 3) (179, 180). In the human atrium, I_K has three components: an ultra-rapid component (I_{Kur}), a rapid component (I_{Kr}), and a slow component (I_{Ks}) (179, 180). Spontaneously automatic cells are depolarised by an inward pacemaker current (I_f) (181). The transmembrane Na^+/Ca^{2+} exchange (NCX) also carries an inward current during terminal repolarisation for a short time thereafter (84).

The balance between plateau inward and outward current determines the AP duration: increased inward current prolongs the AP and increased outward current abbreviates it. AP duration governs the time from cellular depolarisation to recovery of excitability at about -60 mV. The ionic current balance thus determines the refractory period and the likelihood of re-entry. For example, many clinically used drugs prolong AP duration and refractoriness by inhibiting I_{Kr} These drugs are effective in preventing AF, but can produce dangerous ventricular arrhythmias by interfering with ventricular repolarisation (182, 183).

Distribution of ion channels in the heart is not homogeneous, which is the basis of regional specialisation in electrical functions (84, 184). These conditions could make a possibility to develop more specific therapy against arrhythmia. I_{Kur} is carried by Kv1.5 channels that are expressed functionally in the human atrium but not in the ventricle; inhibiting these channels may provide a means of preventing AF without the risk of ventricular proarrhythmia (185-187).

Atrial action potential

The resting membrane potential is about -80mV in multicellular atrial preparations and about -70 mV in isolated atrial myocytes (127, 188). The atrial resting membrane potential is about 5–10 mV less negative than that of the ventricular myocytes, exhibits slower phase 3 repolarisation, and has little or no spontaneous phase 4 depolarisation. The amplitude of atrial APs of the right and

left canine atria is about 110 mV and 105 mV in single-cell preparations and 95 mV and 94 mV in multicellular preparations, respectively (127, 174, 175, 188). No significant difference has been found between the RA and the LA (188).

6. Methodological Aspects of Evaluating Conduction Disturbances in Atrial Fibrillation

Conduction disturbances are one of the most important factors involved in the genesis and/or maintenance of AF. Conventionally, conduction disturbances are evaluated using electrode catheter technique by recording multiple intracardiac electrograms from different areas within the cardiac chambers. Using these local electrograms, conduction times between different sites can be measured and compared. Based on these activation time measurements, a correlation between disturbances of atrial conduction and the genesis of AF has been repeatedly verified (149-152). The accuracy of these analyses was, however, limited by the variation of catheter placement under X-ray guidance, and thereby the variation of recording sites among different patients.

The development of the CARTO electroanatomic mapping technique (Biosense Webster, Diamond Bar, CA) have greatly improved the analysis of activation time (189, 190), since the system can accurately correlate the local activation time with its spatial location, with an accuracy of $\leq$ 1 mm (190, 191). The isochronal maps generated by the CARTO system give a detailed display of the activation pattern and sequence on the colour-coded 3-dimensional maps, and the isopotential maps (voltage maps) provide the possibility of confining scar or fibrous areas, and other anatomical conduction barriers. The system also allows the measurement of distance and activation time difference between two sampling sites, and in this way the activation velocity between these sites can be obtained (142). A limitation of the CARTO system is that only direct linear distance is provided for the calculation of conduction velocity. The distance

between two remote sites would then be shorter than the true distance over the endocardial surface, whereby conduction velocity is underestimated. To minimise the influence of the algorithm of distance measurement, the regional conduction velocity can be measured by summing the lengths of a series of short, straight linear distances, as done in the study of Luo et al.(157).

Evaluation of conduction disturbances during AF is difficult, since the above-mentioned activation time and velocity measurements are no longer possible. One indirect method is to measure the AF interval at different areas of the atria, in order to estimate the local excitability and refractoriness, based on the assumption that the atrial myocardium depolarises as soon as its excitability has recovered (192). Using a condensed electrode array, Holm et al. recorded 56 simultaneous bipolar electrograms from two different areas on the RA epicardium in patients with chronic AF, and found that during AF the RA activation ranges from disorganised to predominantly organised (193). Series work by the Jalife group using potentiometric dye and video imaging techniques to record the dynamics of transmembrane potentials at many sites during atrial fibrillation showed that at least some cases of paroxysmal and chronic AF are the result of the uninterrupted periodic activity of discrete re-entrant sites, i.e. the mother rotors (194, 195). This advanced technique extended our insight into the role of conduction disturbances in the genesis and maintenance of AF. The optical feature of the video imaging technique, however limit its application only in visual areas of the epicardium, and it is difficult to use in clinical settings.

AIMS

1. To obtain clinical evidence for electrical remodelling of the atrial myocardium in patients with chronic and paroxysmal AF using the monophasic action potential recording technique.

2. To determine the sites of activation breakthrough from the LA to the RA during distal CS pacing using the CARTO system in patients with paroxysmal AF.

3. To verify the deterioration of interatrial conduction at the posteroseptal area in patients with AF through analysis of the conduction velocities across the CS ostium and within the CS in patients with and without paroxysmal AF.

4. To investigate the presence and extent of PV potentials in patients with and without AF, in order to achieve a better understanding of the importance of PV potential and the electrical activity around the PV ostium in the genesis and perpetuation of AF.

MATERIALS AND METHODS

1. Patient Data

Patients in the studies were clinical patients who were referred for electrophysiological study and/or ablation to the Department of Cardiology, University Hospital, Lund, Sweden. All antiarrhythmic drugs had been withdrawn for at least five half-lives prior to the study. No patients were treated with amiodarone within 3 months prior to the study. The electrophysiology procedure was in accordance with the local institutional guidelines. Written informed consent was obtained from all patients, and the studies were approved by the local ethics committee and conformed to the principles outlined in the Declaration of Helsinki.

Study I

Eighteen patients (14 men, 4 women; mean age 59 ± 13 years) were included. Seven of them had chronic AF and were referred for radiofrequency ablation of the His bundle. Eleven patients had paroxysmal AF and were referred for invasive electrophysiology study to find possible triggering arrhythmias which might be eliminated by radiofrequency ablation or treatment with biatrial pacing.

Study II

Sixteen consecutive patients with paroxysmal AF and no structural heart disease (11 men, 5 women; mean age 56 ± 8 years, duration of arrhythmia 13 ± 7 years) were included. Echocardiogram was normal for all the patients, with the dimension of the LA measured in the parasternal long-axis view being 40 ± 6 mm, and 20 ± 4 mm/m^2 normalized to the body surface area.

Study III

The study included 23 randomly selected patients, 13 with paroxysmal AF (mean age 54 ± 8 years and duration of arrhythmia 8 ± 4 years) and 10 patients (mean age 52 ± 12) with atrioventricular nodal re-entrant tachycardia (n = 7) or ectopic atrial tachycardia (n = 3) but without previous history of AF. Patients with organic heart disease and systemic disorders were excluded.

Study IV

The AF group consisted of 10 patients with lone AF (8 males, 2 females), mean age 50 ± 12 years and scheduled for AF ablation. Paroxysmal AF was clinically documented with ECG and/or Holter ECG recording. The duration of AF arrhythmia was 11 ± 9 years. The control group included 9 patients with concealed WPW syndrome without any history of AF (4 males, 5 females; mean age 51 ± 12 years) and scheduled for ablation of accessory pathways.

2. Endocardial Electrogram and MAP Recording (Study I)

A 7F quadripolar Ag-AgCl MAP recording-pacing combination catheter (EP Technologies, Sunnyvale, CA) was introduced percutaneously into the RA via the right femoral vein for recording monophasic action potential (MAP) signals and unipolar electrograms. The MAP signals were recorded from 1–3 sites using a computerised electrophysiology recording system (Bard Lab System; Bard, NJ) at a sampling rate of 1 kHz and a filter bandwidth from 0.01 to 1300 Hz. Unipolar electrogram was also simultaneously recorded from the tip-electrode of the same catheter at a filter bandwidth of 0.1 to 500 Hz.

In 3 patients, 2 with chronic AF and 1 with paroxysmal AF, burst pacing at 400 and 500 beats/min was performed 20 seconds during AF via the MAP catheter at the recording site, in order to evaluate the potential change of the AF interval.

The pacing impulse was 4 mA in amplitude and 0.2 ms in pulse width. In these 3 patients, MAP signals were recorded before and after burst pacing. In 7 patients with paroxysmal AF, the atrial ERP was measured during sinus rhythm using the extra stimulus technique at drive cycle lengths of 400 and/or 500 ms. In 2 patients with chronic AF, the atrial ERP was measured during sinus rhythm after successful cardioversion.

3. AF Interval Measurement (Study I)

The digitised MAP recordings were transferred to a PC computer system for analysis. The length of the recordings was 59 ± 40 s. The fibrillatory (FF) intervals during AF, defined as the distance between two consecutive MAP upstrokes on the MAP and between two consecutive intrinsic deflections on the unipolar electrogram, were measured using a custom-made software under a commercial program (Matlab). The upstroke of the MAP was identified by a pre-set threshold, and a beat-to-beat on-screen visual inspection and manual correction were made to ensure the accuracy of the computerised determination.

From each recording, the mean, median, 15th percentile, 10th percentile, 5th percentile, and the shortest FF intervals were obtained as estimations of the local atrial ERP. In patients who had more than one recording, the mean of each parameter in all the recordings was used for group comparison. These estimated atrial ERP parameters were compared between the patients with chronic AF and those with paroxysmal AF. The atrial ERP measured during sinus rhythm in the 9 patients was compared with the estimated atrial ERP in these patients during AF.

4. CARTO Mapping of the Right Atrium and the CS (Studies II and III)

The CARTO system (142, 189) was used for RA and CS mapping during sinus rhythm and/or distal CS pacing. A 6F decapolar catheter was placed in the CS and advanced to a distal position with the proximal electrode at the CS ostium, as judged by fluoroscopic and catheter techniques. Mapping was performed with a 7 F Navistar catheter (Biosense-Webster, Waterloo, Belgien) with the location reference fixed externally to the patient's back. Pacing was conducted at twice diastolic threshold from the distal CS bipole. Mapping started under fluoroscopy and then continued under the guidance of real-time 3-dimensional maps on the screen of the CARTO system. The timing annotation was set as the maximum value or the maximal slope for bipolar electrograms and as maximal slope for unipolar electrograms.

In study II, mapping of the RA was conducted during pacing at a cycle length 100 ms shorter than the sinus cycle length. The RA was mapped and anatomical landmarks of the superior and inferior vena cava, the ostium of the CS, the bundle of His, and the tricuspid annulus were identified. In order to clearly delineate the breakthrough of the transseptal conduction from the LA to the RA in these patients, high-density mapping was attempted on the interatrial septum, especially around the area of earliest activation.

In study III, mapping of the RA and CS was performed during sinus rhythm and/or distal coronary pacing at a cycle length of 600 ms. Bipolar electrograms were recorded via the mapping catheter. At least one recording in a 2-cm^2 area was obtained from the RA. High density maps around the CS ostium were acquired, in which at least two recordings were obtained in a 1 cm^2 area by mapping the anterior, posterior, superior, and inferior parts at each side of the

CS ostium. Similarly, within the CS, at least five mapping points around the CS wall were taken in each of the proximal, middle, and distal CS.

5. Pulmonary Vein Potential Recordings (Study IV)

In both groups, standard catheters were inserted via the right femoral vein: a bipolar catheter to the right ventricular apex for pacing, a 10-polar catheter to the CS for pacing and recording, and a 4-polar catheter to record the His bundle electrogram. Via a transseptal access, a 10- or 20-polar circumferential catheter (Lasso, 10-polar with 15 mm loop, or 20-polar 15–25 mm expandable loop; Biosense-Webster, Waterloo, Belgium) was inserted into the LA and was placed at the PV ostium.The PV ostia were verified by PV angiography and catheter manipulation under fluoroscopy. The circumferential catheter was then placed at the PV ostium and the distal loop of the circumferential catheter was expanded to get good tissue contact. Careful adjustment of the catheter position was attempted so that the distal loop was parallel to the PV ostium, and to simultaneously record both the local atrial deflection and the PV potentials if possible.

The left PVs were explored during sinus rhythm and during atrial pacing from the distal CS at a pacing cycle length of 500–700 ms, and the right PVs were explored during sinus rhythm and during pacing from the RA appendage using the His catheter with a pacing cycle length of 500–700 ms. The recordings were performed before ablation in the AF group. In the control group, the recordings were performed after ablation of the accessory pathway.

All the recordings were recorded as bipolar electrograms using a multi-channel electrophysiology recorder (Bard Lab System; Bard, NJ) with a frequency response of 30–500 Hz and at a sampling rate of 1 kHz. Each recording lasted 30 s and was stored on optical disc for off-line analysis. All recordings were

reviewed off-line on the screen of the Bard system and documented by printout at a paper speed of 100 mm/s.

Typical PV potentials were defined as rapid deflections a) separated from the local atrial deflection with a conduction delay in-between, or b) continuous, fractionated potentials that did not separate from the atrial deflection. When a sharp, distinct potential was recorded at the PV ostium without simultaneously recordable atrial deflection and the potential did not move closer to the pacing artefact during atrial pacing as specified above, it was taken as atypical PV potential. In patients with AF, it was observed that the sequence of the atrial deflection and the PV potentials reversed during pacing or spontaneous ectopic beats within the PV and the PV potential disappeared at the completion of electrical PV isolation. In recording channels where no rapid local potential was recordable but only low frequency, low amplitude (< 0.1 mV) far-field signals, we defined that channel as no PV potential.

To quantify the degree to which PV potentials were recordable, the number of recording channels with typical PV potentials was calculated for each PV and for all the PVs in each individual patient. In patients with a 10-polar Lasso catheter, the recordings were collected from channels 1–2, 2–3, 3–4 etc., while in patients in whom a 20-polar catheter was used, the recordings were collected from channels 1–2, 3–4, 5–6 etc. In this way, all patients would have totally 10 channels of recording for analysis.

To evaluate the conduction time delay across the PV ostium, the time interval between the onset of the local atrial deflection (A) and the end of the PV potential, A-PV interval, was also measured. We did not use the onset of the PV potential because it was difficult to measure when the PV potential was double, fractionated or continuous. When there was only a simple narrow potential

recordable at the PV ostium, the interval from the onset to the end of the potential was measured as A-PV interval. The maximal and mean A-PV intervals for each PV and for all 4 PVs were calculated.

6. Analysis of the CARTO Maps (Studies II and III)

In study II, the pacing artefact on the bipolar electrogram was taken as time reference to calculate the local activation times. Sites with unfavourable signal quality or unreliable beat-to-beat atrial capture were deleted. After visual inspection and manual correction of the annotation lines, the activation maps of the RA were obtained from all the patients. The earliest activation breakthrough site of the RA was identified on each of the maps. More than one RA breakthrough would be considered if a distinct site that activated within 15 ms from the earliest site existed and there was a clearly later activated area between these two early sites (142). Otherwise, a single breakthrough was defined.

In addition to the identification of the breakthrough points, the following parameters (142) were also measured: a) the activation time from the pacing site to the earliest activation site of the septum; b) the activation time from the pacing site to the CS ostium; c) the activation time from the pacing site to the earliest activation site on the high RA septum at the presumed insertion area of Bachmann's bundle; d) the distance between the CS ostium and the earliest activation site on the above-mentioned high septal area; e) the total septal activation time, defined as the time from the earliest to the latest septal activation site; and f) the total RA activation time, defined as the time from the earliest septal activation to the latest RA activation.

To analyse the activation velocity in study III**,** bipolar atrial electrogram from the CS with the maximum deflection was taken as time reference to calculate local activation time. Manual correction of the activation time at each point was

performed if necessary. Recordings of premature beats were excluded. Local activation was defined as the time point of the maximal slope on bipolar electrograms. Colour-coded, 3-dimensional activation sequence maps were reconstructed, with red colour identifying the earliest activation area and purple the latest.

For quantitative analysis, the following regional conduction times and linear distances along the long axis of the CS were measured between at least 5 paired sites using the CARTO system during sinus rhythm and/or distal CS pacing: 1) from the posteroparaseptal RA around the CS ostium to the proximal CS (cross-CS ostium), representing interatrial conduction across the ostium of the CS, and 2) between paired adjacent sites within the CS (intra-CS). Activation velocity between each paired measurement sites was calculated. To minimize the influence of using linear distance rather than the real distance over the endocardial surface of the CARTO system, we 1) limited the distance of the paired measurement sites to ≤ 30 mm, and 2) measured the distance between recording sites on the same plane of the RA and the CS, and between recording sites inside the CS, i.e. avoiding measurement along oblique lines. Additionally, mean velocity of cross-CS ostium and that of intra-CS were obtained in each patient by averaging the activation velocities between multiple paired sites for final analysis.

7. Statistical Methods

Data presented in the Tables and in the main text are mean ± 1 standard deviation in ms, if not otherwise specified. The Mann-Whitney test was used to check the statistical significance of FF-intervals between patients with chronic and paroxysmal AF (**Study I**) and the activation velocities between patients with AF and with AVNRT **(Study III)**. The Wilkoxon signed-rank analysis was used to compare the atrial ERP measured using programmed stimulus technique and that estimated from the FF intervals **(Study I)**. The Student *t*-test was used to compare the regional activation times in patients with paroxysmal AF **(Study II)**, and A-PV potential between patients with AF and with concealed WPW syndrome **(Study IV)**, A *p*-value of < 0.05 was considered statistically significant for all the statistical tests in this thesis.

MAIN RESULTS

1. FF Interval and atrial ERP Measurements in Patients with Chronic or Paroxysmal AF (Study I)

In total, 38 recordings were collected from 33 sites in these patients. The lengths of the recordings were 59 ± 40 s. On average, 342 ± 223 intervals were analyzed. Comparison of the MAP with the unipolar electrogram showed that the FF interval could be determined by the MAP upstroke in all recordings, but not by the intrinsic deflection on the unipolar electrogram due to the low amplitude of the signal and/or the contamination of the electrical activity in the neighbouring area (Figure 3).

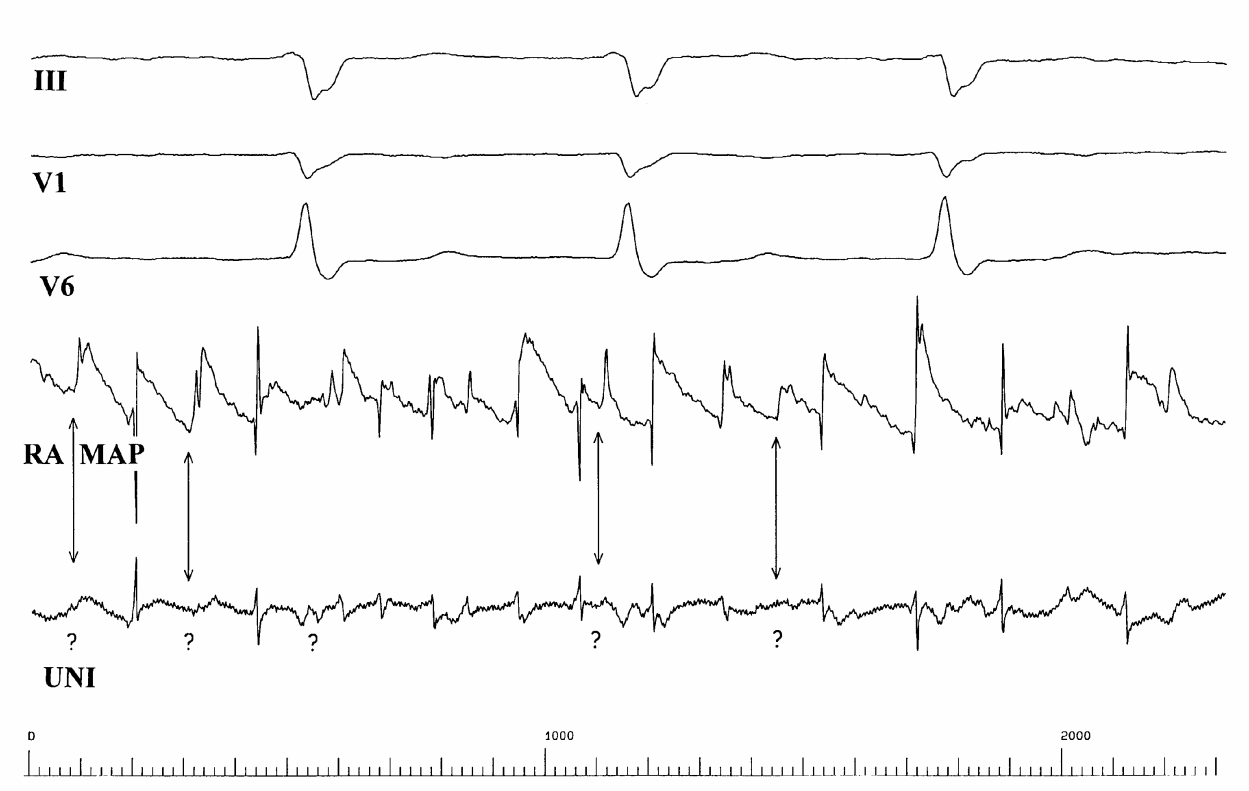

Figure 3. ECG lead III, V1, V6, right atrial MAP (RA MAP) and unipolar electrogram (UNI) from the MAP recording tip-electrode in the RA in a patient during AF, showing that the FF intervals can be determined more accurately in the MAP recording than in the unipolar electrograms. Note the local activations marked with arrows were not detectable in the unipolar electrogram, but were clearly identified in the MAP recording.

The atrial ERP in patients with paroxysmal AF measured using the extra stimulus technique during sinus rhythm was 212 ± 33 ms. The estimated atrial ERP during AF in the same group was 152 ± 31, 154 ± 30, 126 ± 37, 118 ± 41, 107 ± 43, and 69 ± 37 ms for the mean, median, 15th, 10th, 5th percentile, and shortest FF intervals respectively. The atrial ERP during sinus rhythm was significantly longer than the estimated atrial ERPs ($p < 0.05$ to $p < 0.01$).

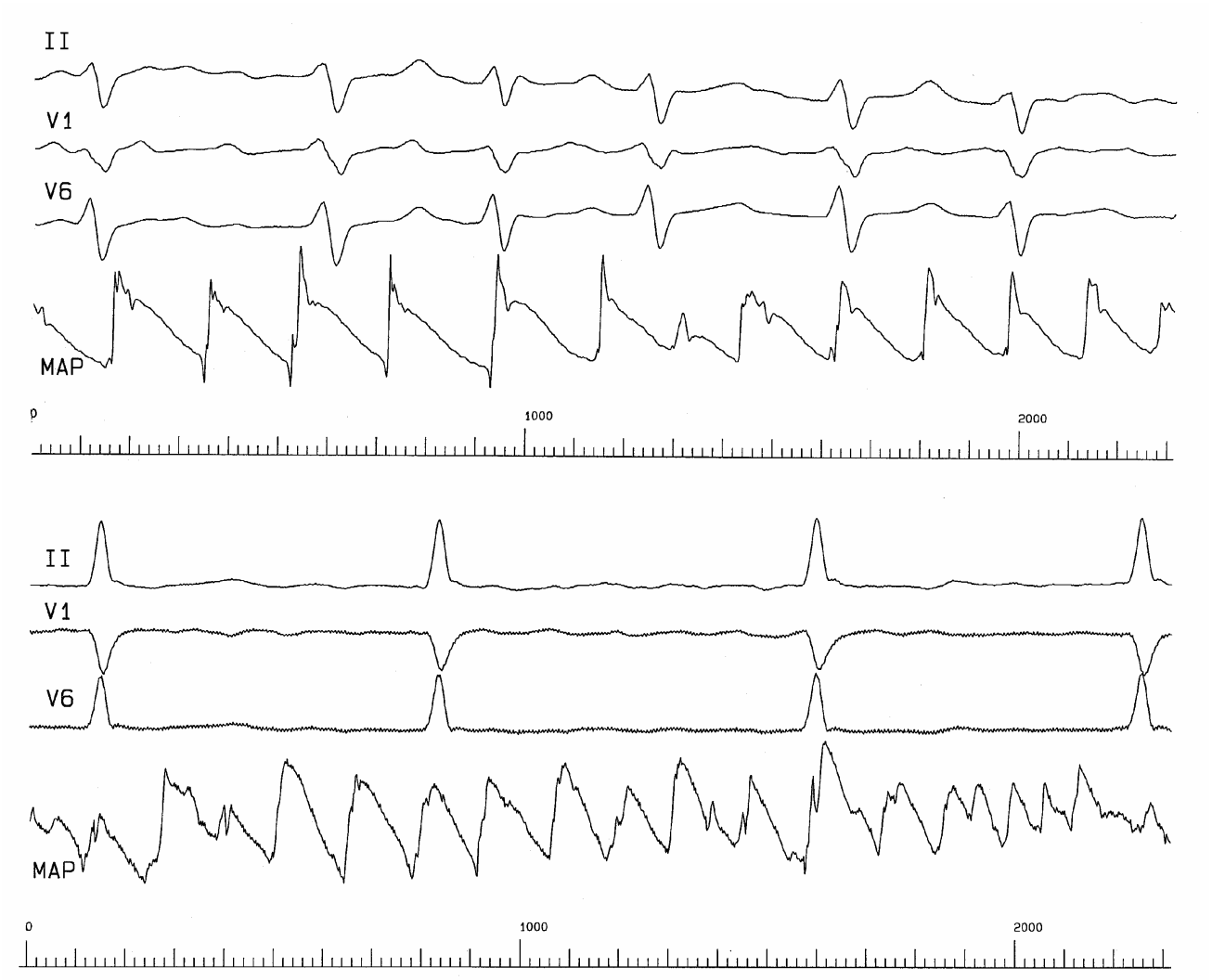

Figure 4. MAP recordings during AF in a patient with paroxysmal AF (upper panel) and in a patient with chronic AF (lower panel), showing that the electrical activity was relatively slower and more regular in the patient with paroxysmal AF than in that with chronic AF.

A trend was found that the FF intervals were markedly shorter in the chronic AF group than in the paroxysmal AF group (Figures 4 and 5). The difference was statistically significant for the shortest FF interval ($p < 0.05$). The mean, median, 15th, 10th, and 5th percentile of the FF interval also appeared markedly shorter in patients with chronic AF than in the patients with paroxysmal AF. However, the differences were not statistically significant (Table 1, Figure 5).

No significant difference in the FF interval was found before and after the burst pacing at cycle length of 400 and 500 beats/min in the 3 patients in whom burst pacing during AF was performed.

Table 1. The FF intervals during AF measured from MAP recordings

	n	Site	Mean	Median	15th percentile	10th percentile	5th percentile	Shortest
Paroxysmal AF	11	20	162±34	162±33	134±38	126±41	116±43	72±31*
Chronic AF	7	13	135±19	136±20	108±27	100±28	87±27	50±13

Data are presented as mean ± 1SD in ms. *$p < 0.05$ compared to that in the chronic AF group.

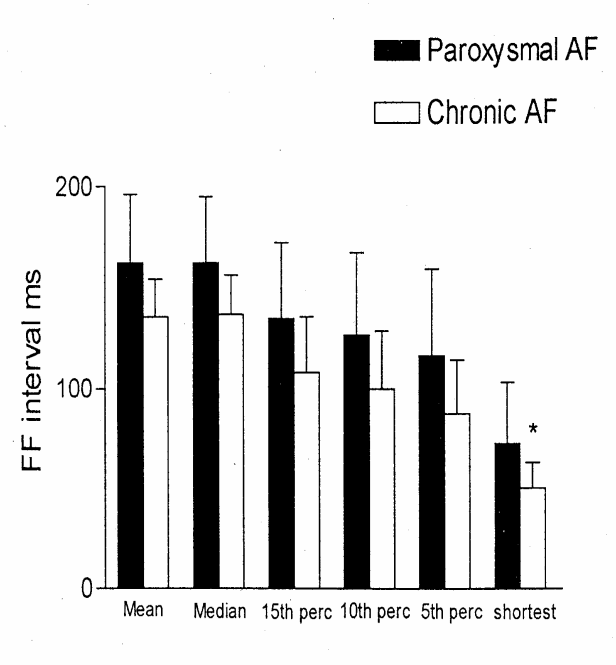

Figure 5. FF intervals in patients with paroxysmal AF (black bars) and with chronic AF (white bars), showing that the FF intervals tended to be shorter in patients with chronic AF than in patients with paroxysmal AF. *$p < 0.05$.

2. The Preferential Site of Transseptal Conduction, Regional Activation Times and Activation Sequences during Distal CS Pacing in patients with Paroxysmal AF (Study II)

During distal CS pacing, CARTO mapping of the RA was performed at 111 ± 16 sites in the 16 patients. A single transseptal breakthrough was observed in all of these patients, immediately by the CS ostium in 11 patients, about 10 mm caudal to the CS in 2 patients, 10 mm posterior to the CS in 1 patient, and 15 mm anterocranial to the CS in 1 patient (Table 2, Figure 6 and Figure 7). In patient 11, an additional breakthrough at the fossa ovalis was also observed, which was 2 ms later than the earliest activation at the CS ostium. The distance between breakthrough at the CS ostium and that at the fossa ovalis was 35 mm.

The activation times from the pacing site to the earliest septal activation were 47 ± 13 ms (range 33–73 ms) and to the CS ostium were 57 ± 15 ms (range 34–87 ms). The total septal activation time was 68 ± 16 ms (range 48–116 ms), and the total RA activation time was 118 ± 17 ms (range 98–159 ms). The shortest total atrial septal and total RA activation time was observed in a patient in whom a transseptal breakthrough was located anterosuperiorly to the CS ostium (patient 9, Table 2).

The activation ended at a single site of the RA in 12 patients, 8 in the high lateral RA, 1 in the midlateral RA, and 3 in the low lateral RA. In the remaining 4 patients, the activation ended at two distinct areas, in the high lateral and the midlateral RA in 3 patients and in the midlateral and the low lateral areas in one patient.

Table 2. Transseptal activation times during pacing from the distal CS in 16 patients with paroxysmal AF

Patient No.	Breakthrough	CS-d to break-through	CS-d to CS ostium	CS-d to Bachmann's	Total septal	Total RA
1	CS ostium	67	67	127	60	100
2	CS ostium	37	37	95	58	137
3	CS ostium	34	34	150	116	131
4	CS ostium	62	62	127	65	139
5	CS ostium	60	60	130	70	107
6	Inferior to CS	73	87	141	71	129
7	Inferior to CS	36	53	95	59	98
8	CS ostium	47	47	127	80	116
9	Ant.super. to CS	59	85	107	48	98
10	Posterior to CS	33	59	92	59	110
11	CS ostium + FO	46	48	103	67	119
12	CS ostium	38	40	63	60	111
13	CS ostium	48	53	77	70	118
14	CS ostium	39	65	107	68	113
15	CS ostium	41	61	117	90	159
16	CS ostium	36	46	62	54	101
Mean		47±13	57±15	108±26	68±16	118± 17

Values are mean ± 1SD in ms. Bachmann's = Bachmann's bundle; CS = coronary sinus; CSd = pacing site at distal coronary sinus; RA = right atrium; Ant.super. = anterosuperior; FO = fossa ovalis.

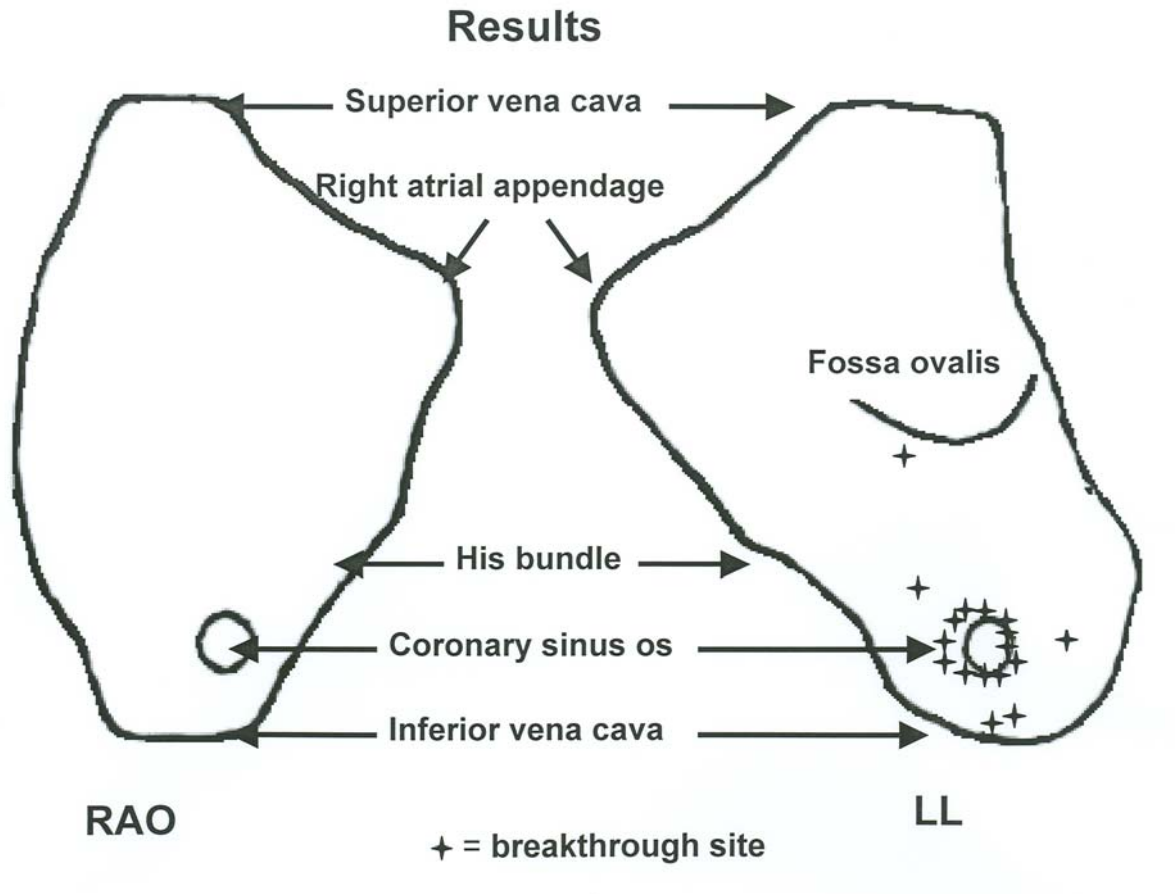

Figure 6. Schematic presentation of breakthrough sites to the RA during pacing from the distal CS in patients with paroxysmal AF.

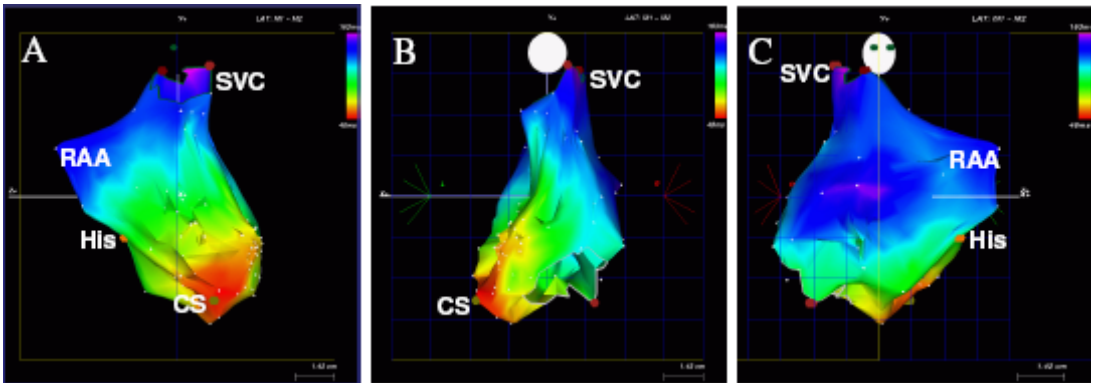

Figure 7. Activation map of the RA during pacing from the distal CS in patient 8 in left lateral view (panel A), posteroanterior view (panel B) and 45° right anterior oblique view (panel C). Colour-coded activation sequences are shown with red identifying the earliest activations and purple the latest. White cross markers depict positions of 116 mapping points. The head on top of the vertical line marks the *y* axis and represents map orientation. A single area of earliest activation (red) is in the region of the CS ostium (green dot, panels A and B), from where activation spreads quickly to the rest of the septum and eccentrically over the entire atrium. Two sites of latest activation are in the high and midlateral RA (panel C). SVC = superior vena cava; His = His bundle; RAA = right atrial appendage.

3. Activation Velocities across the CS Ostium and within the CS in Patients with and without AF (Study III)

General Data

CARTO mapping of the RA and CS was successful in all patients. In the AF group, the RA and CS mapping were performed at 88 ± 21 and 93 ± 22 sites during sinus rhythm and distal CS pacing, respectively. Altogether, 17 three-dimensional maps were obtained: 7 during sinus rhythm and 10 during distal CS pacing, i.e. 4 of the 13 patients were mapped both during sinus rhythm and distal CS pacing (Figure 8). During sinus rhythm, the mean velocities of cross-CS ostium activation were measured between 9 ± 2 paired sites and those of intra-CS activation between 6 ± 1 paired sites. During distal CS pacing, the mean velocities of cross-CS ostium and intra-CS activation were measured between 8 ± 2 paired sites and 6 ± 1 paired sites, respectively (Table 3).

In the control group, the RA and CS mapping were performed at 92 ± 22 and 98 ± 23 sites during sinus rhythm (Figure 9) and distal CS pacing, respectively. There were 8 maps acquired during sinus rhythm and 4 during distal CS pacing, i.e. 2 of the 10 patients were mapped during both sinus rhythm and distal CS pacing. The mean velocities of cross-CS ostium activation were measured between 8 ± 2 paired sites and those of intra-CS activation between 6 ± 1 paired sites during sinus rhythm. During distal CS pacing, the mean velocities of cross-CS ostium and intra-CS activation were measured between 8 ± 2 paired sites and 7 ± 2 paired sites, respectively (Table 3).

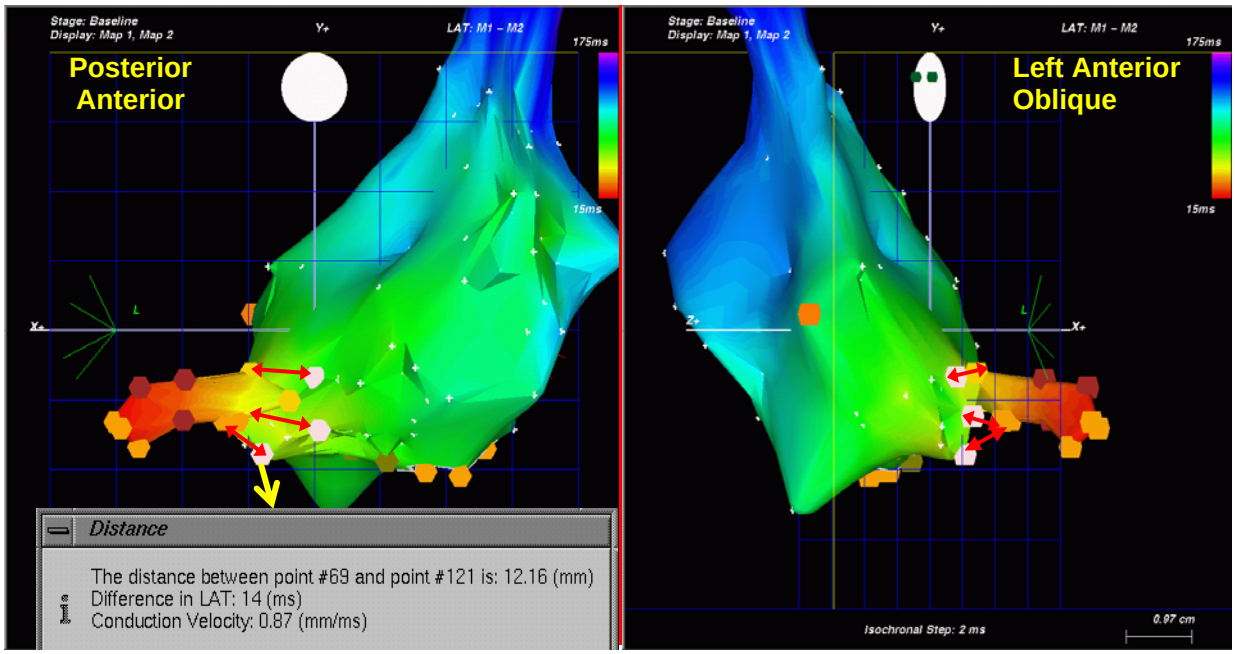

Figure 8. RA and CS maps during distal CS pacing in a patient with paroxysmal AF. The mean activation velocity across the CS ostium is 0.7 m/s, which was calculated from 8 paired sites between the posteroparaseptal RA and proximal CS. **Left:** Posterioranterior view, showing 3 paired sites (double-arrow lines) between the posteroparaseptal RA and posteroinferior proximal CS. The distance, conduction time, and velocity between one of the paired sites were automatically measured to be 12.16 mm, 14 ms and 0.87 mm/ms, respectively, using the CARTO system. **Right:** Left anterior oblique view, showing additional paired sites across the CS ostium.

Table 3. Distances and activation velocities of cross-CS ostium and intra-CS measured during sinus rhythm and distal CS pacing in AF group and control group

		Cross-CSo		Intra-CS	
		AF	Control	AF	Control
Sinus rhythm	Paired sites (n)	9±2	8±2	6±1	6±1
	Distance (mm)	23.0±2.8	20.4±3.2	15.8±3.9	15.1±3.9
	Velocity (m/s)	1.2±0.2*	2.9±1.6	2.8±1.9	3.2±2.2
CSd pacing	Paired sites (n)	8±2	8±2	6±1	7±2
	Distance (mm)	19.8±3.1	17.5±2.1	15.7±4.0	21.6±2.6
	Velocity (m/s)	1.0±0.5†	1.4±0.2	1.5±0.3	1.4±0.3

Values are given as mean ± 1 SD. AF = atrial fibrillation; CS = coronary sinus; CSd = distal CS; Cross-CSo and Intra-CS = across the CS ostium and within the CS.
*$p < 0.05$, comparing AF group and control group; †$p = 0.07$, comparing AF group and control group; $p > 0.05$ in all the other comparisons between the two groups.

Difference in activation velocity between patients with and without AF

On maps during sinus rhythm, the distances of the paired sites between the AF and the control group were not significantly different ($p > 0.05$). The activation velocities of intra-CS between the two groups were not significantly different either (2.8 ± 1.9 vs. 3.2 ± 2.2 m/s, $p > 0.05$). However, the activation velocities of cross-CS ostium in the AF group (1.2 ± 0.2 m/s) were significantly slower than those in the control group (2.9 ± 1.6 m/s, $p < 0.05$) (Table 3).

On maps during distal CS pacing, the distances between the paired sites were not significantly different between the two groups either ($p > 0.05$). The

activation velocities of intra-CS between the two groups showed no significant difference (1.5 ± 0.3 vs. 1.4 ± 0.3 m/s, $p > 0.05$). For conduction across the CS ostium, the activation velocities appeared slower in the AF group (1.0 ± 0.5 m/s) than in control group (1.4 ± 0.2m/s), but the difference was not statistically significant ($p = 0.07$) (Table 3).

Difference in activation velocity between sinus rhythm and distal CS pacing

In the AF group, the cross-CS ostium activation velocities during sinus rhythm were similar to those during distal CS pacing ($p > 0.05$). The intra-CS activation velocities during sinus rhythm showed a wide range (1.1–5.8 m/s) with a tendency to be faster (2.9 ± 1.6 m/s) than those during distal CS pacing (1.4 ± 0.2m/s, range 1.0–1.6 m/s), but the difference was not statistically significant.

In the control group, the cross-CS ostium and intra-CS activation velocities during sinus rhythm both displayed a higher variation, and tended to be faster than those during distal CS pacing (1.4–5.8 vs. 1.1–1.6 m/s and 1.1–6.0 vs. 1.1–1.7 m/s). However, neither the cross-CS ostium nor the intra-CS activation velocities during sinus rhythm were significantly different from those during distal CS pacing (Table 3).

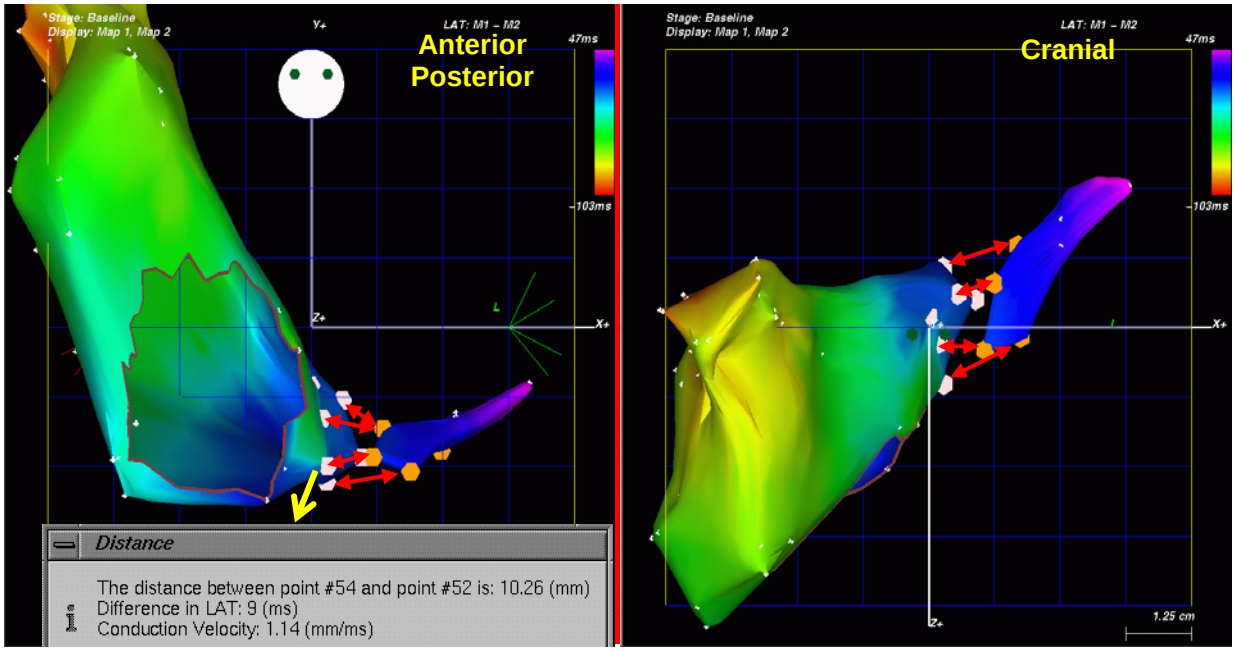

Figure 9. RA and CS maps during sinus rhythm in a patient with atrioventricular nodal re-entrant tachycardia. The mean velocity across the CS ostium is 1.5 m/s, calculated from 8 paired sites between posteroparaseptal RA and proximal CS. **Left:** Anteriorposterior view, showing 3 paired sites (double-arrow lines). The distance, conduction time and activation velocity between one of the paired sites were 10.26 mm, 9 ms and 1.14 mm/ms, respectively. **Right:** Cranial view, showing additional paired sites across the CS ostium.

4. Pulmonary Vein Potential Recordings in Patients with and without Atrial Fbrillation (Study IV)

In the AF group totally 34 of the 40 PVs were included in the data analysis, i.e. in 3 patients the right inferior PV was not catheterised due to clinical or technical reasons, in one patient the recording at the LIPV was performed during AF when it was not possible to identify the PV potentials, and in 2 additional patients recordings from one of the 4 PVs were missing due to technical errors. In 3 PVs, a simple, narrow potential was recorded. Thus, typical PV potentials were recorded in 31 of the remaining 34 PVs (91%) (Table 4, Figure 10).

In the nine patients with concealed WPW syndrome, all the 36 PVs were explored. Typical PV potentials were recorded in 4 of the 36 PVs (11%) (Figure 11 C), i.e. in 2 of the 10 recording channels in the left superior PV in 2 patients and in 2 and 5 recording channels, respectively, in the left inferior PV in 2 other patients. In 3 PVs, no electrical signal was recordable (8%). Thus, in 29 of the 36 PVs (81%), only a simple, biphasic, or triphasic, narrow potential was recorded, i.e. no separate local atrial deflection was recordable at the PV ostium (Table 4, Figures 11 A and B).

Table 4. Patient data and recording channels with typical PV potential recorded from the ostia of the PVs

nr	Diagn	Age (y)	Sex	Dur.arr (y)	Recording channels	LSPV no.	LIPV no.	RSPV no.	RIPV no.
1	cWPW	48	m	28	10	0	0	0	0
2		61	f	26	10	0	0	0	0
3		60	f	20	10	0	0	0	0
4		49	m	8	10	2	0	0	0
5		52	f	42	10	2	0	0	0
6		55	f	20	10	0	2	0	0
7		25	m	13	10	0	5	0	0
8		46	f	10	10	0	0	0	0
9		65	m	45	10	0	0	0	0
10	PAF	66	m	15	10	5	5	2	-
11		38	m	10	8*	4	8	7	-
12		53	f	2	10	4	-	5	3
13		39	m	4	10	8	5	5	-
14		60	m	2	10	5	-	0	3
15		46	m	15	10	10	8	5	6
16		62	m	28	10	7	5	7	10
17		41	f	23	10	10	8	4	-
18		30	m	4	10	8	1	7	3
19		60	m	9	10	6	1	0	0

*Only 8 channels were recorded.
- No data available due to AF, signals not recorded, or PV not accessed.

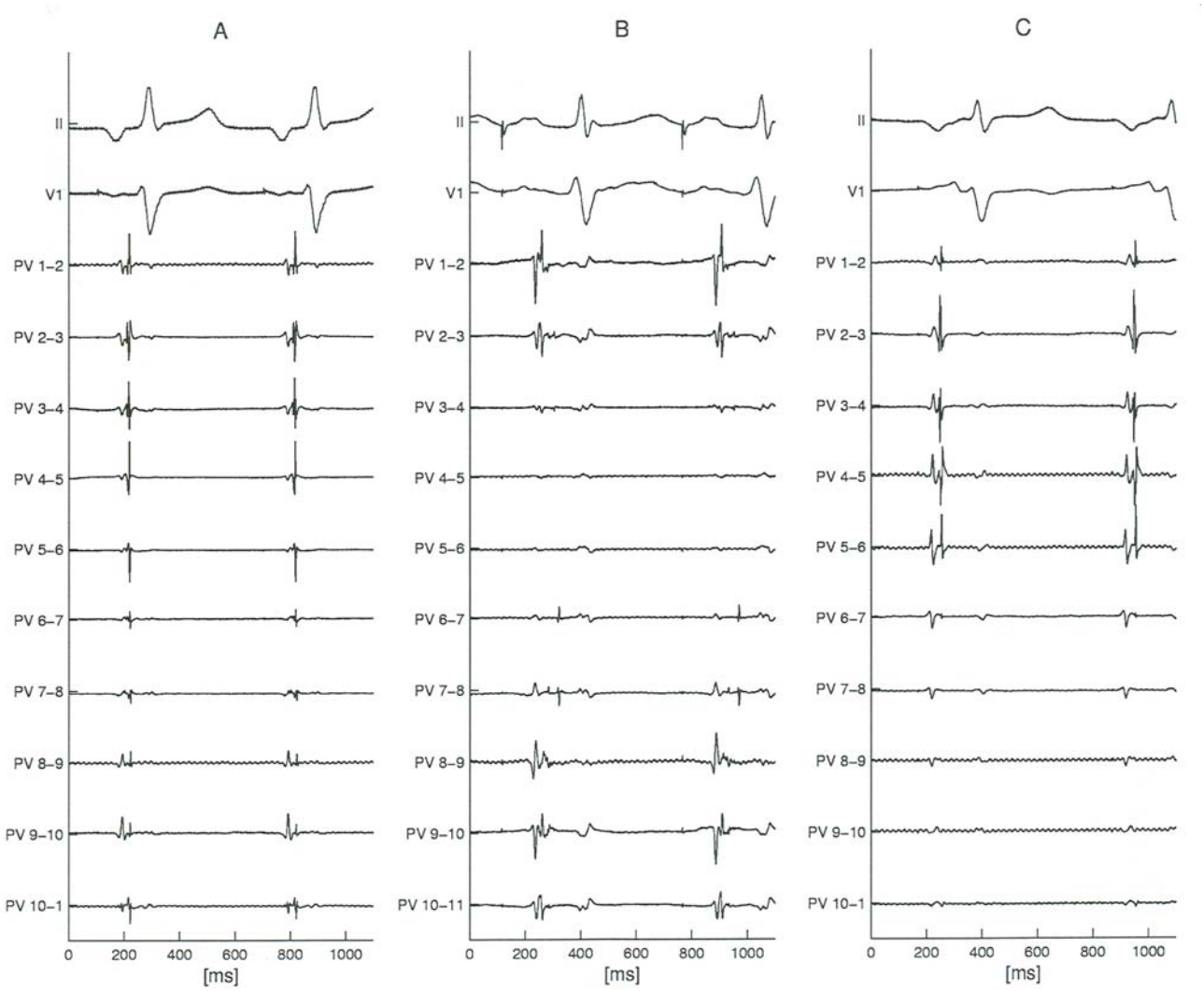

Figure 10. Recordings at the ostium of the left superior PV during distal CS pacing from patients 15 (A), 16 (B), and 14 (C) with AF, showing separate, distinct PV potentials, e.g. patient 14, channels PV3–4, 4–5 and 5–6, or multiphasic, fractionated potentials that are not clearly separated from the atrial deflection, e.g. patient 15, channels PV1–2, 2–3, 8–9 and 9–10. Note in patient 16, channels PV 3–4, 4–5 and 5–6 and in patient 14, channels PV 7–8, 8–9, 9–10 and 10–1 were counted as no PV potential.

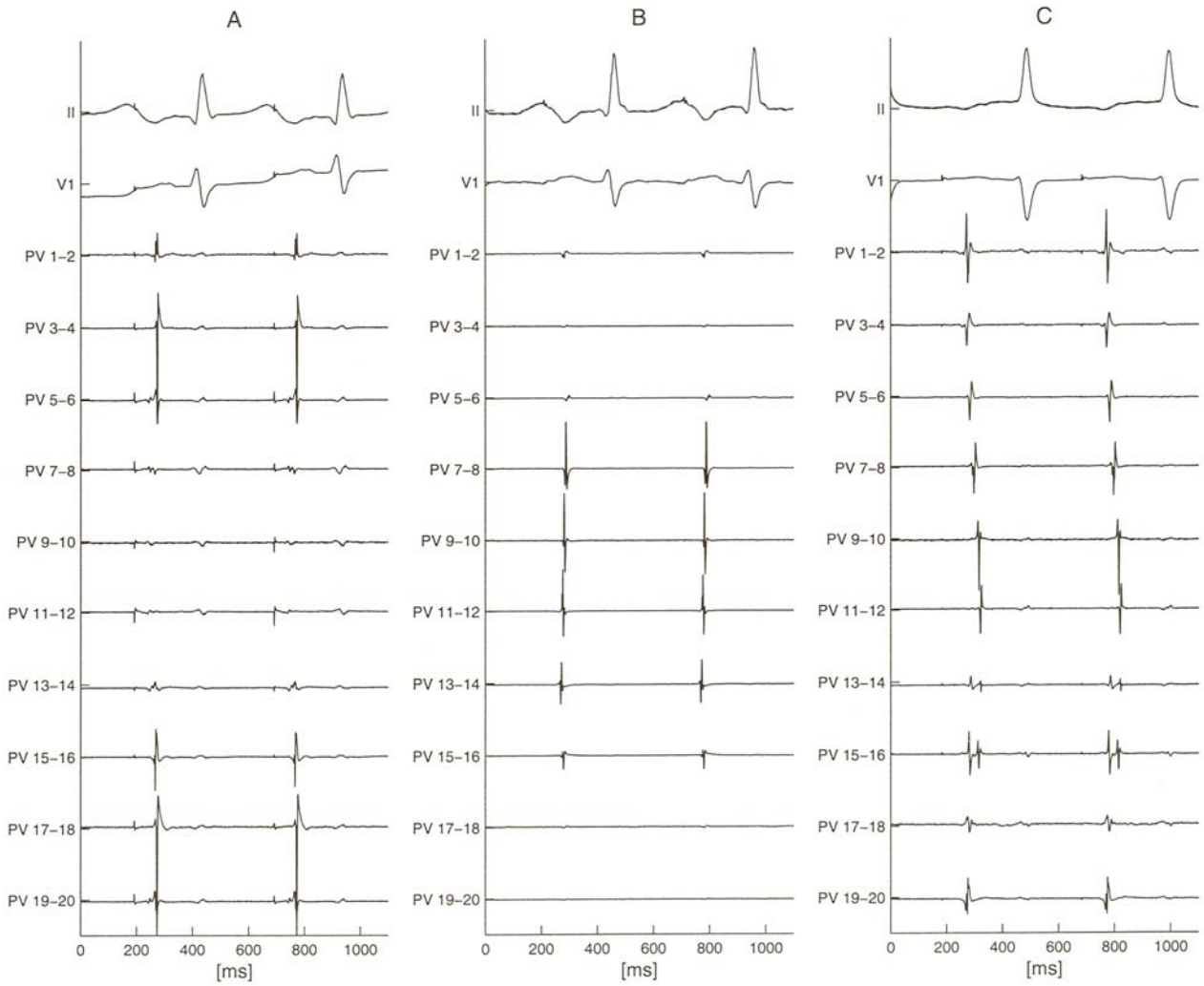

Figure 11. Recordings at the ostium of the left superior PV during distal CS pacing from patients 1 (A), 3 (B), and 4 (C) with concealed WPW syndrome, showing in majority of the recording channels merely simple, narrow potentials were recordable, with rare exceptions where separate PV potentials were recorded in a limited number of channels (e.g. in channels PV 13–14 and 15–16, panel C). Note in patient 1, channels PV 9–10 and 11–12 and in patient 3, channels PV 3–4, 5–6, 17–18 and 19–20 were counted as no PV potential.

The time interval from the onset of the local atrial deflection and the end of the PV potential, A-PV interval, was significantly longer in patients with AF than in patients with concealed WPW syndrome, i.e. not only for each of the PV, but also for all the 4 PVs, and not only for the maximal A-PV interval, but also for the mean A-PV interval between the two groups (Tables 5 and 6).

Table 5. Maximal time from the beginning of the local atrial electrogram to the end (A-PV interval) recorded at the ostia of the PVs

	LSPV	LIPV	RSPV	RIPV	Total
AF	n=10	n=8	n=10	n=6	n=10
	65.5±20.6*	84.4±21.8**	63.0±19.5*	77.5±33.1*	71.3±23.8**
Control	n=9	n=9	n=9	n=9	n=9
	35.6±16.5	35.6±15.7	30.6±16.5	30.0±6.1	32.9±14.0

Data presented are mean ± 1SD in ms. *p < 0.005, ** p < 0.0001 as compared to that in the control group.

Table 6. Mean time from the beginning of the local atrial electrogram to the end (A-PV interval) recorded at the ostia of the PVs

	LSPV	LIPV	RSPV	RIPV	Total
AF	n=10	n=8	n=10	n=6	n=10
	49.5±15.5*	56.6±9.2**	44.2±12.2**	45.6.6±11.4*	48.9±12.9**
Control	n=9	n=9	n=9	n=9	n=9
	23.7±9.3	26.3±11.7	19.4±8.3	22.6±4.9	24.8±5.5

Data presented are mean ± 1SD in ms. *p < 0.005, ** p < 0.0001 as compared to that in the control group.

GENERAL DISCUSSION

1. Methodological Aspects of the Evaluation of Atrial Refractoriness during AF (Study I)

During AF, it is not possible to measure atrial ERP with the extra stimulus technique. In most of the earlier studies, the atrial ERP during AF was estimated from two consecutive local activations on intracardiac electrograms based on the assumption that the atrial myocardium depolarises as soon as its excitability has recovered (192). In isolated canine atria, Kim et al. demonstrated a close correlation between the local atrial ERP and the minimal FF interval (196). In patients with lone AF, Capucci et al. measured the atrial ERP and the functional refractory period during sinus rhythm. They found a correlation between the mean FF interval during AF and the functional refractory period, and between the 5th percentile FF interval and the atrial ERP (197).

A non-invasive method known as frequency analysis of fibrillatory ECG has also been developed to estimate atrial ERP during AF from body surface recordings (198-200). Measurement of the FF interval from the intracardiac or surface electrograms is limited by the low amplitude and especially the contamination of the electrical activities in the neighbouring areas, as observed in our earlier studies and in Study I. The sharp upstroke of the MAP signal is a reliable parameter representing the local activation of the myocardial tissue underneath the catheter tip-electrode. Compared to the electrograms, the MAP is much less contaminated by signals from the surrounding areas (201). For these reasons, we used the MAP recordings instead of the electrograms for the FF interval measurement. Our results have further verified that the MAP is a better choice for the measurement of FF intervals and for estimation of the local refractoriness during AF.

2. Role of Myocardial Remodelling in the Occurrence and/or Perpetuation of AF (Study I)

The multiple wavelet hypothesis is one of the widely accepted underlying mechanisms for AF. Findings in several experimental studies have suggested that perpetuation of the AF may depend on continuous micro re-entry (122, 197). The fibrillatory wavelength is determined by conduction velocity and tissue refractoriness (77, 86, 87).

In 1971, Olsson et al. recorded MAPs in patients with chronic AF immediately after cardioversion. They found that the patients with a normal MAP duration did not have recurrence of AF, but those with a significantly shorter MAP duration had recurrence of AF in a few weeks (202). This may be one of the earliest observations on the shortening of refractoriness in relation to the recurrence of AF. Cotoi et al. later reported similar findings (203). Wijffels et al. (122) used a goat model in which continuous AF was induced by burst pacing, and they found that the maintenance of AF was followed by a marked shortening of atrial ERP, a reversion of physiological rate adaptation, and an increase in the atrial rate. These changes were reversible within one week in sinus rhythm.

The decrease in atrial refractoriness favours the occurrence and perpetuation of AF, which has also been shown in humans in several studies (197, 204, 205). This electrophysiological phenomenon is termed electrical remodelling, and is a progressive process that takes 1–3 weeks. It was also found that the remodelling was not influenced by the autonomic tone or atrial stretch, but verapamil infusion could prevent the phenomenon, which suggests that cytosolic calcium overload is an important mediator of the remodelling (206, 207). Thus, the available data suggest that the occurrence of AF is linked to a shortening of the atrial ERP/MAP duration. On the other hand, during an ongoing AF, the atrial ERP/MAP duration will be further shortened, which in turn facilitates the perpetuation of the AF.

In Study I, we found that the estimated atrial ERPs during AF were markedly shorter than those measured during sinus rhythm, and they were even shorter in patients with chronic AF than in patients with paroxysmal AF. In other words, the atrial ERP was further shortened during the perpetuation of the AF in the chronic AF group. These findings are consistent with the earlier observations in patients with paroxysmal AF using the electrogram technique (197) and support the above mentioned remodelling theory—and thereby add clinical evidence for the mechanism underlying the occurrence and perpetuation of the AF. We did not find significant changes in FF interval after atrial burst pacing, however, as did a previous study (197). This could be due to the limited number of patients in our study, but could also be explained by the fact that the remodelling is a long-term process, which may not be achieved immediately after burst pacing. Further study is clearly needed to clarify the mechanism behind these different findings.

3. Preferential Routes for Interatrial conduction (Studies II and III)

Anatomical and electrophysiological examination of human and animal hearts suggested that atrial muscle bundles, such as Bachmann's bundle (160, 208), the rim of the fossa ovalis (209), and the CS (165) form preferential conduction routes between the RA and the LA. In addition to Bachmann's bundle, the media layer of the CS and great cardiac vein, as well as muscle bundles extended from the right of the superior vena cava transversally to the anterior wall of the LA (160, 208), form other muscular connections between the RA and the LA, as suggested by recent anatomical and electrophysiological studies in both dogs (141, 210) and humans (165, 211). These two major interatrial connections have also been verified by electroanatomic mapping in patients with arrhythmias other than AF (142, 212). However, our knowledge of the exact location and function of interatrial conduction routes is still incomplete, and the preferential conduction routes seem to vary with different original pacing sites

(142, 144, 161, 167, 213, 214). The pattern of transseptal conduction in patients with AF has not been reported before, although the deterioration in interatrial conduction has been considered an important factor associated with the genesis and perpetuation of AF (151, 215). In addition, previous studies have repeatedly reported that the inter- and intraatrial conduction disturbances, especially the delayed interatrial conduction, are linked to the occurrence and/or perpetuation of AF, including AF of focal origin (143, 144, 150, 216, 217). Nevertheless, the exact deteriorated conduction areas are still not clear. Fibre connections between the two atria around the CS ostium have been highlighted to play an important role for interatrial conduction (142, 144, 218).

In study II, a single RA breakthrough during distal CS pacing was identified around the CS ostium in all the patients, which provides further evidence supporting the existence of a preferential pathway near the CS ostium for interatrial conduction. We did not find breakthrough near the insertion area of Bachmann's bundle in this group, probably due to the fact that our pacing site was closer to the CS ostium than to Bachmann's bundle. This is largely consistent with findings reported by Roithinger et al. (142). They found that during CS distal pacing, the transseptal activation was earliest at the CS ostium in 9 of their 11 patients, while during pacing at the posterior wall of the LA, 5 patients had breakthrough at Bachmann's bundle and 4 at the fossa ovalis (142).

The total RA activation times in our patients with paroxysmal AF were 117 ± 16 ms, similar to those observed in patients without AF (117 ± 49 ms) (142). However, the total septal activation time observed in this series, 69 ± 19 ms, was markedly longer than those in patients without AF, 41 ± 16 ms as reported by Roithinger et al. (142), which may suggest that local conduction delay, e.g. at the posteroseptal region, exists in patients with AF—as reported by Platonov et al. (151).

4. Clinical Implications of the Preferential Pathway for Interatrial Conduction (Studies II and III)

Previous studies have shown that focal or re-entrant activities in the LA are primarily responsible for the occurrence or perpetuation of AF (219), while the RA is passive, and radiofrequency ablation at the Bachmann's bundle insertion or the midseptum could terminate AF in dogs (220). Cryoablation around the CS is important for the success of the Maze procedure as a surgical therapy for AF (97), and the abolishment of interatrial conduction along the CS and at the CS orifice is critical for the conversion of long-lasting persistent AF to sinus rhythm by catheter ablation (69). All of these findings suggest that interruption of a preferential electrical connection between the LA and the RA may reduce the degree of wavelet-to-wavelet interaction that is critical for perpetuation of AF (92). In this respect, the identification of preferential pathway for transseptal conduction has clinical implications in patients with AF. Furthermore, we found in Study II that the interatrial connection around the CS is a consistent electrical pathway between the LA and the RA in patients with paroxysmal AF, which is in accordance with the pathoanatomical observations by Platonov et al. (166). This is important when elimination of interatrial connection is considered. Ablation at the orifice has been performed routinely by the Bordeaux group as one of the steps that convert permanent AF into sinus rhythm (68).

5. Activation Velocity as a Parameter of Interatrial Conduction (Study III)

Most of the previous studies have evaluated the inter- and intraatrial conduction properties using conduction times between remote sites. The accuracy of these evaluations must therefore have been influenced by the inter-individual variance of measurement sites. Velocity should be a better parameter of conduction properties than conduction times. However, activation velocity has scarcely been used, probably due to difficulties in measuring the distance between recording sites accurately.

Electroanatomic mapping techniques have been used to delineate the propagation of intra-atrial and interatrial conductions (142, 161, 167, 213, 214). These techniques allow precise correlation of electrical signal with its anatomical origin on 3-dimensional maps of the cardiac chambers, and thus allow accurate measurements of distance, activation time, and activation velocity between two recording sites. Compared to conduction times, activation velocity is a more precise parameter of conduction properties. Using the CARTO system, Luo et al. measured the conduction velocities of different areas of the RA and compared them in patients with and without paroxysmal AF (157). However, to our knowledge, no data of conduction velocity across the CS ostium have been reported. In Study III, we constructed the activation maps of the RA and the CS both during sinus rhythm and distal CS pacing, and used activation velocity instead of activation time to evaluate the interatrial conduction across the CS ostium.

6. Deterioration of Interatrial Conduction during Distal CS Pacing in AF patients (Study III)

Interatrial conductions have been conventionally evaluated through RA mapping during CS or LA pacing. This is partially due to the technical and ethical limitations for mapping in the LA, and also due to the recent finding that electrophysiological disturbances in the LA are important factors for the development of AF. Using the CARTO mapping system, different activation patterns of the RA during pacing from the distal CS have been observed previously, with most RA presenting a single transseptal breakthrough near the CS ostium (142, 218). In addition, using the Ensite 3000 noncontact mapping system, O'Donnell et al. observed similar preferential interatrial conduction route during pacing in the left upper PV (144). These findings suggested that the preferential conduction route during distal CS pacing should mostly be through the posterior region near the CS ostium.

In Study III, the activation velocities of cross-CS ostium and intra-CS during distal CS pacing were measured. These measurements should represent the actual conduction velocities since the preferential conduction route during distal CS pacing is along the long axis of the CS, as observed previously (142, 218) (Figure 12). We found that the activation velocities of intra-CS were similar in the two groups, whereas the cross-CS ostium activation velocities in the AF group appeared to be slower than those in the control group. These data support the previous finding that the interatrial conduction delay in patients with paroxysmal AF is located in the posteroparaseptal region around the CS ostium (151, 157).

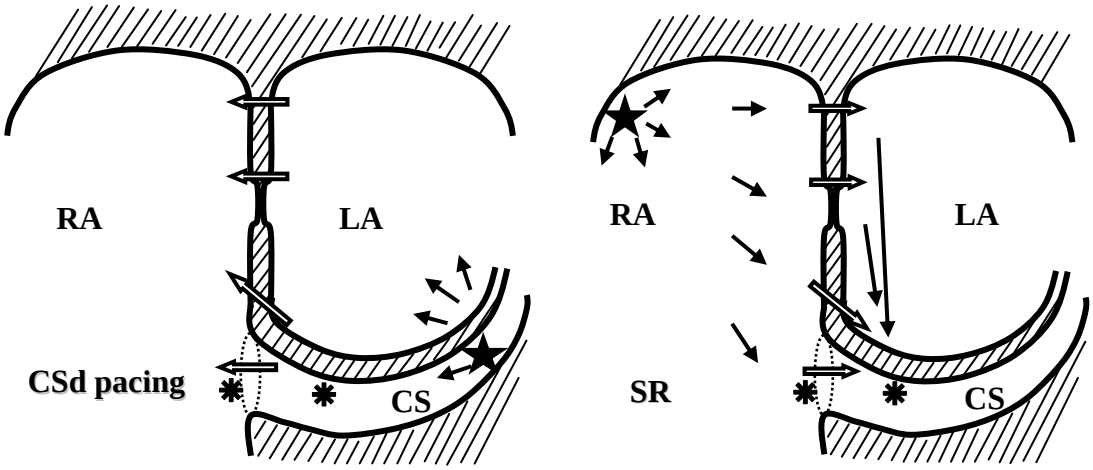

Figure 12. Schematic diagram of activation velocity measurements. *Open arrows* indicate possible interatrial conduction routes. *Solid arrows* indicate propagation of activation wavefronts. **Left:** During distal CS pacing, conduction across the CS ostium is along the long axis of the CS. Thus, the calculated activation velocity between the two stars (*)—with the left one indicating an RA site and the right one indicating a proximal CS site—may represent true conduction velocity across the CS ostium. **Right:** During sinus rhythm, when conduction is across the CS ostium along the long axis of the CS, the measured activation velocity between the two stars (*)—with the left one indicating an RA site and the right one indicating a proximal CS site—represents true interatrial conduction through the CS ostium. However, when the interatrial conduction is via other routes, the conduction route across the CS ostium is then not a preferential route. As a result, the RA site by the CS ostium and the site at the proximal CS are activated by different wavefronts. Thus, the calculated activation velocity would be over-estimated, as seen in some control patients in Study III (see text for details).

7. Deterioration of Interatrial Conduction during Sinus Rhythm in AF Patients (Study III)

Compared to the relatively clear interatrial conduction routes during distal CS pacing, the routes during sinus rhythm are more complicated. In the majority of published data, the dominant role of Bachmann's bundle for interatrial conduction has been emphasized. Conduction through other connections between the RA and the LA, such as posterior interatrial conduction, was thought to be limited to the local region and not to contribute significantly to LA activation in canine models (141), or in normal human atria (161). However, technical limitations for mapping the LA may have diminished the accuracy of mapping in the posteroparaseptum of the LA (221). Some anatomical studies have shown that there have been variable connections between the RA and the LA, and the importance of Bachmann's bundle as interatrial conduction may be questionable (166, 211). Furthermore, a recent study has shown that multiple connections capable of RA–LA conduction exist, and that the posterior communications appear to play a major role (167).

In Study III, the cross-CS ostium activation velocities during sinus rhythm were significantly slower in the AF patients than those in the control group. The interpretation of this finding is more complicated compared to that during distal CS pacing. The activation velocity represents the speed of interatrial conduction, provided the conduction crosses the CS ostium along the long axis of the CS. When the interatrial conduction is through other preferential routes, however, the activation time used to calculate the activation velocity across the CS ostium is actually the activation time difference between the posteroparaseptal RA and the proximal CS, with the former activated by wavefront from the lateral wall and the latter by that from other interatrial connections (Figure 12).

In Study III, the markedly slower cross-CS ostium activation velocities during sinus rhythm in the AF patients may suggest that either the cross-CS ostium conduction is delayed, or more probably that the conduction through other preferential routes is delayed, as suggested by earlier studies in patients with AF (144, 222). As a result, the proximal CS of AF patients is activated later than that of the control patients. In other words, the relatively slow cross-CS ostium activation velocities during sinus rhythm in patients with AF may represent true conduction velocities across the CS ostium, whereas the faster cross-CS ostium activation velocities in the control group may be a result of almost concurrent activations of the posteroparaseptal RA and the proximal CS through two different conduction routes (Figure 12). A similar postulation can be used to explain the faster intra-CS activation velocities during sinus rhythm. The fact that the activation velocities measured during sinus rhythm are all, except the cross-CS ostium activation velocities in patients with AF, faster than those during distal CS pacing (Table 3)—they even are faster than the normal conduction velocities of atrial fibres, which is around 1 m/s (172)—lends further support to this hypothesis. The greater range of activation velocities from 1 to 6 m/s also suggests more complex interatrial conduction routes during sinus rhythm, in contrast to the relatively clear interatrial conduction route during distal CS pacing.

8. PV Potentials and the Occurrence of AF (Study IV)

PV potentials are almost invariably recordable at the PV ostium in patients with AF. Segmental ablation (66), circumferential PV ablation (223), or electrically complete PV isolation (70) all lead to curative results in patients with paroxysmal, persistent or even permanent AF. This indicates that the electrical activities around the PV ostium, as manifested by the PV potential, are of clinical importance. PV potentials typically appear as rapid local potentials following an atrial deflection with a clear time delay in-between. Sometimes

they are rapid, continuous, fractionated potentials without clear time delay from the atrial deflection (224). It is generally accepted that PV potentials are generated from electrical activities of the myocardial sleeves within the PV. The time interval from the atrial deflection to the PV potential may represent conduction time across the PV ostium. There are also occasions when only a rapid but simple, biphasic, or triphasic potential is recorded at the PV ostium, without clear simultaneously recordable atrial deflection. Although referencing to the atrial deflection in other simultaneously recorded channels of electrograms and pacing from neighbouring area can help to verify if it is a PV potential or electrogram from atrial muscles nearby, it is sometimes difficult to identify the nature of the signal exactly. It could be a merged signal from both the atrial deflection and the PV potential, but we cannot not exclude the possibility that it is generated purely from myocardial tissue outside or inside the PV. However, recent results of catheter ablation have shown that electrically complete PV isolation is invariably accompanied by sudden disappearance of all the PV potentials, including this kind of simple, narrow potential (70), suggesting that these signals are also generated from myocardial tissue within the PV ostium or at least in the near vicinity of the PV ostium.

Thus, in the current study we took these kinds of signals as atypical PV potentials and calculated their interval to compare them with the A-PV intervals measured from recordings with typical PV potentials. Further study is certainly needed to clarify whether this narrow potential reflects only electrical activity of the muscle sleeves within the PV, or more likely, whether it generates from myocardial tissues both within and outside the PV. However, it is obvious that the signal clearly differs from the typical PV potentials that represent marked conduction delay across the PV ostium. It should therefore be understandable to refer the simple, narrow potential as representing less conduction delay than the wide, typical PV potentials.

We found in the current study that typical PV potentials were almost invariably recordable in all the PVs (91%) in patients with AF, but they were only found in a few recording channels in 11% of PVs in patients without AF (Table 4). Quantitatively, we found that the A-PV interval, the time interval between the local atrial deflection and the end of the PV potential, was clearly longer in patients with AF than in patients with concealed WPW syndrome (Tables 5 and 6, and Figures 10 and 11). In other words, in our patients with concealed WPW syndrome the local potentials recorded at the PV ostium were merely simple, biphasic, or triphasic narrow signals without clear separation from the local atrial activation. This may suggest that conduction delay between the LA tissue surrounding the PV ostium and the myocardium within the PV does not exist, or is minimal in patients without AF, while it is obvious and extensive in patients with AF. These findings suggest that conduction delay around and/or across the PV ostium may be an important electrophysiological substrate for the development and/or maintenance of AF, and strongly support the involvement of re-entrant activities around the PV ostium in the genesis/perpetuation of AF. Our postulation is also supported by an earlier clinical study by Jais et al. (224). They found that patients with AF were associated with longer PV-LA conduction time and shorter venous refractory period as compared to patients without AF, which favours re-entry within and around the ostium of the PVs. Similar findings were also reported by Tada et al. (225). The anatomical variations of the atrial myocardium extending into the PVs were found to be more complex in patients with AF than in patients without, which facilitates the re-entrant activities around the ostium of the PVs (226). Thus, the ostia of PVs may be important both for the initiation and maintenance of AF, as evidenced by the fact that PV potentials are present in almost all patients with AF, and radiofrequency ablations to the ostial region of the PVs can eliminate AF (66, 227-229).

9. Catheter Ablation around the PV Ostium and the Elimination of AF (Study IV)

In 2000, Haissaguerre et al. (66) described a technique to cure AF by delivering radiofrequency energy under the guidance of a circular mapping catheter until the conduction of atrial impulses into the PVs was abolished. The success rate for a single procedure is about 56–70% without antiarrhythmic drugs (66), while a repeat procedure increases the success rate substantially (69). With the accumulation of clinical experience, the AF ablation technique has been modified continuously (69, 70, 121) and the success rate has reached up to 95%, even in patients with persistent and permanent AF (68, 70).

Currently, three major ablation strategies are used clinically worldwide: a stepwise strategy as used by the Bordeaux group (68), PV encircling plus linear ablation as used by the Milan group (121), and the double Lasso technique or electrically complete isolation of the PVs without extra lines as used by the Hamburg group (70). It is interesting to note that in all of the 3 major strategies, PV isolation or encircling is taken as an important component of the curative treatment of AF (223, 228). Although there is evidence that parasympathetic nerve denervation during AF ablation (79) is important for the elimination of AF, the abolishment of delayed conduction and subsequent re-entrant activity at the PV ostium is certainly an important factor for the result of AF ablation.

10. Limitations of the Present Studies

In Study I, MAPs were recorded from randomly selected recording sites and therefore the result may have been influenced by site-specified differences in atrial ERP and/or FF intervals. However, we recorded MAPs from two or three sites in most of the patients and the mean value for each patient was taken for analysis, which may have minimised the site-related difference. Furthermore, the statistically significant difference between patient groups suggests the objective nature of our findings.

Our mapping was performed only during pacing at distal CS in Study II. Transseptal conduction patterns during pacing or spontaneous rhythms from other sites of the LA were not obtained. Consequently, the preferential pathway of transseptal conduction observed in Study II may not necessarily be preferential in clinical situations such as ectopic activities from the upper part of the LA, or in the upper PVs. Another limitation of Study II is that we had only 16 patients with paroxysmal AF. It would have been preferable to include a control group without history of AF, to reveal potential differences in transseptal conduction between the groups. However, referencing to the consistent findings in RA mapping in patients with unspecified arrhythmias (142) and LA mapping in patients with supraventricular tachycardia without history of AF (212), we have reason to believe that the posteroseptal connection is nevertheless one of the important pathways for interatrial conduction in patients with paroxysmal AF.

In Study III, the activation of the LA has only been evaluated within the CS. Ideally, detailed RA and LA mapping including the CS could provide clear evidence on the propagation routes and the area of conduction delay. Such data are difficult to obtain from patients, for clinical and ethical reasons. Therefore

we concentrated on the activation velocities across the CS ostium and on the differences in these parameters between patients with and without paroxysmal AF. In addition, the CARTO system only measures direct linear distance between two sites. As a result, the distance between two remote sites is shorter than the true distance over the endocardial surface; therefore, activation velocity is underestimated.

To minimize the influence of the CARTO algorithm of distance measurement, we measured the distance longitudinally along the CS and between adjacent sites over the surface of the RA endocardium in the same plane, and calculated each regional activation velocity by averaging multiple measurements. Moreover, the activation velocity was calculated using the same algorithm for both groups. We therefore believe that the significant differences in activation velocities between the two patient groups were objective findings and that they have important clinical implications.

Patients with WPW syndrome have a tendency to get paroxysmal AF, which is observed in about one-third of all patients (230). Little is known about the incidence of AF in concealed WPW syndrome, but according to Della Bella et al. (231) it may be about 3%. The control group in Study IV had no clinical history of AF, but this does not exclude asymptomatic episodes of AF and the tendency of AF to occur later in these patients. In this sense, patients with concealed WPW syndrome are not ideal as controls for AF. However, a significant difference in PV potential recordings was found between the groups. Besides, it is clear that pathological and pathophysiological changes can be found in the atrium of patients with AF, while patients with concealed WPW syndrome have an otherwise healthy heart. This gives us good reason to regard concealed WPW syndrome patients as a valid control group in this particular study.

In Study IV, when only a simple potential was recorded at the PV ostium without simultaneously recordable atrial deflection, it was taken as atypical PV potential in this study—although we could not verify that the potential is generated from the myocardial tissue inside the PV ostium, outside the PV ostium, or from both. We aimed, however, to evaluate the conduction time delay across the PV ostium and it was clear that typical PV potentials represent such a conduction delay. Therefore, it is reasonable to assume that the simple, narrow potentials recordable at the PV ostium, mostly in patients without any history of AF, reflect less conduction time delay than the wide, typical PV potentials.

CONCLUSIONS

Electrical remodelling of the atrial myocardium occurs during AF, and it is more marked in patients with chronic AF than in patients with paroxysmal AF (Study I).

The atrial ERP was significantly shortened during AF, as compared to that during sinus rhythm, and the atrial ERP shortening was more marked in patients with chronic AF than in patients with paroxysmal AF. These clinical findings support the connection between the electrical remodelling and the occurrence and/or perpetuation of theAF.

The preferential site of transseptal conduction during CS pacing in patients with paroxysmal AF is near the CS ostium (Study II).

In patients with paroxysmal AF, a preferential site of transseptal conduction was demonstrated to be near the CS ostium. This is consistent with previous anatomical and electroanatomic findings in animals and in patients without AF, and has clinical implications when surgical dissection or catheter ablation is considered to eliminate interatrial connection in patients with AF.

The interatrial conduction across the CS ostium is deteriorated in patients with paroxysmal AF (Study III).

Deterioration of interatrial conduction across the CS ostium during distal CS pacing in patients with paroxysmal AF is presented in Study III. Conduction delay at the posteroparaseptal region across the CS ostium and/or over other conduction routes during sinus rhythm in AF patients is indirectly suggested by our findings. These data support the link between interatrial conduction deterioration at the posteroparaseptal region and the genesis and/or perpetuation of paroxysmal AF.

The delayed conduction and re-entrant activities around the PV ostium may be involved in the genesis of AF (Study IV).

Patients without AF merely have simple, narrow potentials recordable at the PV ostium, as compared to patients with AF, in whom excessive, separate or continuous PV potentials invariably exist. The time interval between the local atrial deflection and the end of the PV potential was significantly longer in patients with AF than in patients with concealed WPW syndrome. These findings support the involvement of conduction delay and re-entrant activities around the PV ostium in the genesis and/or perpetuation of AF.

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